EXHIBIT 293

Grant Final Report

Grant ID: R18 HS 017045

Electronic Support for Public Health–Vaccine Adverse Event Reporting System (ESP:VAERS)

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Exhibit 293

Abstract

Purpose: To develop and disseminate HIT evidence and evidence-based tools to improve healthcare decision making through the use of integrated data and knowledge management.

Scope: To create a generalizable system to facilitate detection and clinician reporting of vaccine adverse events, in order to improve the safety of national vaccination programs.

Methods: Electronic medical records available from all ambulatory care encounters in a large multi-specialty practice were used. Every patient receiving a vaccine was automatically identified, and for the next 30 days, their health care diagnostic codes, laboratory tests, and medication prescriptions were evaluated for values suggestive of an adverse event.

Results: Restructuring at CDC and consequent delays in terms of decision making have made it challenging despite best efforts to move forward with discussions regarding the evaluation of ESP:VAERS performance in a randomized trial and comparison of ESP:VAERS performance to existing VAERS and Vaccine Safety Datalink data. However, Preliminary data were collected and analyzed and this initiative has been presented at a number of national symposia.

Key Words: electronic health records, vaccinations, adverse event reporting

Final Report

Purpose

This research project was funded to improve the quality of vaccination programs by improving the quality of physician adverse vaccine event detection and reporting to the national Vaccine Adverse Event Reporting System (VAERS), via the following aims:

Aim 1. Identify required data elements, and develop systems to monitor ambulatory care electronic medical records for adverse events following vaccine administration.

Aim 2. Prepare, and securely submit clinician approved, electronic reports to the national Vaccine Adverse Event Reporting System (VAERS).

Aim 3. Comprehensively evaluate ESP:VAERS performance in a randomized trial, and in comparison to existing VAERS and Vaccine Safety Datalink data.

Aim 4. Distribute documentation and application software developed and refined in Aims 1 and 2 that are portable to other ambulatory care settings and to other EMR systems.

Scope

Public and professional confidence in vaccination depends on reliable postmarketing surveillance systems to ensure that rare and unexpected adverse effects are rapidly identified. The goal of this project is to improve the quality of vaccination programs by improving the quality of physician adverse vaccine event detection and reporting to the national Vaccine Adverse Event Reporting System (VAERS). This project is serving as an extension of the Electronic Support for Public Health (ESP) project, an automated system using electronic health record (EHR) data to detect and securely report cases of certain diseases to a local public health authority. ESP provides a ready-made platform for automatically converting clinical, laboratory, prescription, and demographic data from almost any EHR system into database tables on a completely independent server, physically located and secured by the same logical and physical security as the EHR data itself. The ESP:VAERS project developed criteria and algorithms to identify important adverse events related to vaccinations in ambulatory care EHR data, and made attempts at formatting and securely sending electronic VAERS reports directly to the Centers for Disease Control and Prevention (CDC).

Patient data were available from Epic System's Certification Commission for Health Information Technology-certified EpicCare system at all ambulatory care encounters within Atrius Health, a large multispecialty group practice with over 35 facilities. Every patient receiving a vaccine was automatically identified, and for the next 30 days, their health care diagnostic codes, laboratory tests, and medication prescriptions are evaluated for values

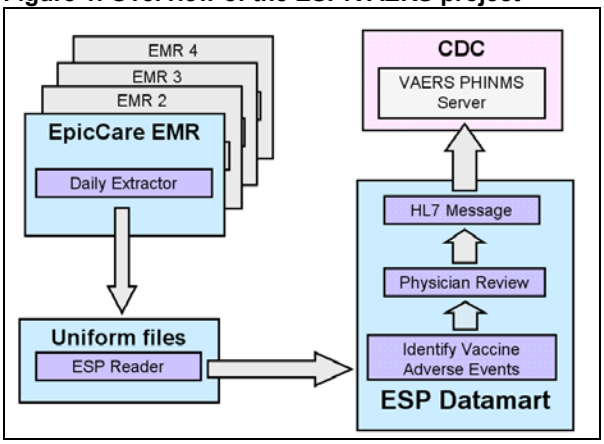
suggestive of an adverse vaccine event. When a possible adverse event was detected, it was recorded, and the appropriate clinician was to be notified electronically.

Clinicians in-basket messaging was designed to provide a preview a pre-populated report with information from the EHR about the patient, including vaccine type, lot number, and possible adverse effect, to inform their clinical judgment regarding whether they wish to send a report to VAERS. Clinicians would then have the option of adding free-text comments to pre-populated VAERS reports or to document their decision not to send a report. The CDC's Public Health Information Network Messaging System (PHIN-MS) software was installed within the facilities so that the approved reports could be securely transferred to VAERS as electronic messages in an interoperable health data exchange format using Health Level 7 (HL7).

Methods

The goal of Aim 1: *Identify required data elements, and develop systems to monitor ambulatory care electronic medical records for adverse events following vaccine administration*, and Aim 2: *Prepare, and securely submit clinician approved, electronic reports to the national Vaccine Adverse Event Reporting System (VAERS)*, was to construct the below flow of data in order to support the first two Aims:

Figure 1. Overview of the ESP:VAERS project



Existing and functioning ESP components are shown on the left, and Aims 1 and 2 on the right. ESP:VAERS flags every vaccinated patient, and prospectively accumulate that patient's diagnostic codes, laboratory tests, allergy lists, vital signs, and medication prescriptions. A main component of Aim 1 was to *Develop AE criteria to assess these parameters for new or abnormal values that might be suggestive of an adverse effect.* A reporting protocol & corresponding algorithms were developed to detect potential adverse event cases using diagnostic codes, and methods were tested to identify prescriptions or abnormal laboratory values that might be suggestive of an adverse effect. These algorithms were designed to seek both expected and unexpected adverse effects.

This reporting protocol was approved by both internal & external partners. We initially prepared a draft document describing the elements, algorithms, interval of interest after vaccination, and actions for broad classes of post-vaccination events, including those to be reported immediately without delay (such as acute anaphylactic reaction following vaccination), those never to be reported (such as routine check-ups following vaccination) and those to be reported at the discretion and with additional information from the attending physician through a feedback mechanism. The draft was then widely circulated as an initial / working draft for comment by relevant staff in the CDC and among our clinical colleagues at Atrius. In addition to review by the internal CDC Brighton Collaboration liaison, this protocol has also received review & comment via the CDC's Clinical Immunization Safety Assessment (CISA) Network.

The goal of Aim 2 was the *Development of HL7 messages code for ESP:VAERS to ensure secure transmission to CDC via PHIN-MS*. The HL7 specification describing the elements for an electronic message to be submitted to Constella, the consultants engaged by CDC for this project was implemented. Synthetic and real test data was been generated and transmitted between Harvard and Constella. However, real data transmissions of non-physician approved reports to the CDC was unable to commence, as by the end of this project, the CDC had yet to respond to multiple requests to partner for this activity.

The goal of Aim 3 was to *Comprehensively evaluate ESP:VAERS performance in a randomized trial, and in comparison to existing VAERS and Vaccine Safety Datalink data.*

We had initially planned to evaluate the system by comparing adverse event findings to those in the Vaccine Safety Datalink project—a collaborative effort between CDC's Immunization Safety Office and eight large managed care organizations. Through a randomized trial, we would also test the hypothesis that the combination of secure, computer-assisted, clinician-approved, adverse event detection, and automated electronic reporting will substantially increase the number, completeness, validity, and timeliness of physician-approved case reports to VAERS compared to the existing spontaneous reporting system; however, due to restructuring at CDC and consequent delays in terms of decision making, it became impossible to move forward with discussions regarding the evaluation of ESP:VAERS performance in a randomized trial, and compare ESP:VAERS performance to existing VAERS and Vaccine Safety Datalink data. Therefore, the components under this particular Aim were not achieved.

Aim 4 *Distribution of documentation and application software developed and refined in Aims 1 and 2 that are portable to other ambulatory care settings and to other EMR systems* has been successfully completed. Functioning source code is available to share under an approved open source license. ESP:VAERS source code is available as part of the ESP source code distribution. It is licensed under the LGPL, an open source license compatible with commercial use. We have added the ESP:VAERS code, HL7 and other specifications and documentation to the existing ESP web documentation and distribution resource center http://esphealth.org, specifically, the Subversion repository available at:
http://esphealth.org/trac/ESP/wiki/ESPVAERS.

Results

Preliminary data were collected from June 2006 through October 2009 on 715,000 patients, and 1.4 million doses (of 45 different vaccines) were given to 376,452 individuals. Of these doses, 35,570 possible reactions (2.6 percent of vaccinations) were identified. This is an average of 890 possible events, an average of 1.3 events per clinician, per month. These data were presented at the 2009 AMIA conference.

In addition, ESP:VAERS investigators participated on a panel to explore the perspective of clinicians, electronic health record (EHR) vendors, the pharmaceutical industry, and the FDA towards systems that use proactive, automated adverse event reporting.

Adverse events from drugs and vaccines are common, but underreported. Although 25% of ambulatory patients experience an adverse drug event, less than 0.3% of all adverse drug events and 1-13% of serious events are reported to the Food and Drug Administration (FDA). Likewise, fewer than 1% of vaccine adverse events are reported. Low reporting rates preclude or slow the identification of "problem" drugs and vaccines that endanger public health. New surveillance methods for drug and vaccine adverse effects are needed. Barriers to reporting include a lack of clinician awareness, uncertainty about when and what to report, as well as the burdens of reporting: reporting is not part of clinicians' usual workflow, takes time, and is duplicative. Proactive, spontaneous, automated adverse event reporting imbedded within EHRs and other information systems has the potential to speed the identification of problems with new drugs and more careful quantification of the risks of older drugs.

Unfortunately, there was never an opportunity to perform system performance assessments because the necessary CDC contacts were no longer available and the CDC consultants responsible for receiving data were no longer responsive to our multiple requests to proceed with testing and evaluation.

Inclusion of AHRQ Priority Populations

The focus of our project was the Atrius Health (formerly HealthOne) provider & patient community. This community serves several AHRQ inclusion populations, specifically low-income and minority populations in primarily urban settings.

Atruis currently employs approximately 700 physicians to serve 500,000 patients at more than 18 office sites spread throughout the greater Metropolitan Boston area. The majority of Atruis physicians are primary care internal medicine physicians or pediatricians but the network also includes physicians from every major specialty.

The entire adult and pediatric population served by Atruis was included in our adverse event surveillance system (ESP:VAERS). Atruis serves a full spectrum of patients that reflects the broad diversity of Eastern Massachusetts. A recent analysis suggests that the population served by Atruis is 56% female, 16.6% African American, 4% Hispanic. The prevalence of type 2 diabetes in the adult population is 5.7%. About a quarter of the Atruis population is under age 18.

List of Publications and Products

ESP:VAERS [source code available as part of the ESP source code distribution]. Licensed under the GNU Lesser General Public License (LGPL), an open source license compatible with commercial use. Freely available under an approved open source license at: http://esphealth.org.

Lazarus, R, Klompas M, Hou X, Campion FX, Dunn J, Platt R. Automated Electronic Detection & Reporting of Adverse Events Following Vaccination: ESP:VAERS. The CDC Vaccine Safety Datalink (VSD) Annual Meeting. Atlanta, GA; April, 2008.

Lazarus R, Klompas M Automated vaccine adverse event detection and reporting from electronic medical records. CDC Public Health Informatics Network (PHIN) Conference August 27, 2008.

Klompas M, Lazarus R ESP:VAERS Presented at the American Medical Informatics Association Annual Symposium; 2009 November 17th.

Lazarus R, Klompas M, Kruskal B, Platt R Temporal patterns of fever following immunization in ambulatory care data identified by ESP:VAERS Presented at the American Medical Informatics Association Annual Symposium; 2009 November 14–18: San Francisco, CA.

Linder J, Klompas M, Cass B, et al. Spontaneous Electronic Adverse Event Reporting: Perspectives from Clinicians, EHR Vendors, Biopharma, and the FDA. Presented at the American Medical Informatics Association Annual Symposium; 2009 November 14–18: San Francisco, CA.

EXHIBIT 294

Guidance for Industry

Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products — Content and Format

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
January 2006
Labeling

Guidance for Industry

Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products — Content and Format

Additional copies are available from:

Office of Training and Communications
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or

Office of Communication, Training and
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Center for Biologics Evaluation and Research
Food and Drug Administration
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(Internet) http://www.fda.gov/cber/guidelines.htm

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
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Labeling

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Contains Nonbinding Recommendations

Guidance for Industry[1]
Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products — Content and Format[2]

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance is intended to help applicants and reviewers in drafting the ADVERSE REACTIONS section of prescription drug labeling as required by 21 CFR 201.57(c)(7). Its primary purpose is to aid in (1) selecting information for inclusion in the section, (2) characterizing adverse reactions selected for inclusion, (3) organizing and presenting the information within the section, and (4) updating adverse reaction information. The goal of this guidance is to assist applicants in designing ADVERSE REACTIONS sections that contain the drug safety information important to patient management decisions and that convey the information in a clear and accessible format.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

As this guidance seeks to bring greater consistency to the content and format of the ADVERSE REACTIONS section, the Agency emphasizes that reviewer and applicant judgment remain critical in assessing how or whether to present information on an adverse reaction. FDA reviewers and applicants should assess such factors as seriousness, severity, frequency, and

[1] This guidance has been prepared by the Medical Policy Coordinating Committee in the Center for Drug Evaluation and Research (CDER) in conjunction with the Center for Biologics Evaluation and Research (CBER).

[2] This guidance applies to drugs, including biological drug products. For the purposes of this guidance, drug product or drug will be used to refer to human prescription drug and biological products that are regulated as drugs.

strength of causal association in determining which adverse reactions to include in the ADVERSE REACTIONS section and in characterizing those reactions. In general, the ADVERSE REACTIONS section includes only information that would be useful to health care practitioners making treatment decisions and monitoring and advising patients. Exhaustive lists of every reported adverse event, including those that are infrequent and minor, commonly observed in the absence of drug therapy or not plausibly related to drug therapy should be avoided (see § 201.57(c)(7) and the Glossary at the end of this guidance for a definition of Adverse Reaction). Such lists are not informative and tend to obscure the more clinically meaningful information.

III. ADVERSE REACTIONS SECTION — CONTENT AND FORMAT

The ADVERSE REACTIONS section is required to list the adverse reactions that occur with the drug and with drugs in the same pharmacologically active and chemically related class, if applicable (§ 201.57(c)(7)(i)). Separate lists are required for adverse reactions identified from clinical trials (§ 201.57(c)(7)(ii)(A)) and those identified from spontaneous reports after a drug has been marketed (§ 201.57(c)(7)(ii)(B)). This section of the guidance provides recommendations for ensuring that information about the most clinically important adverse reactions is readily accessible (see III.A), and for organizing the information on adverse reactions from clinical trials (see III.B) and from postmarketing safety reports (see III.C).

A. Making the Most Clinically Important Information Accessible

Typically, adverse reactions for a given drug will have varying clinical significance (ranging from serious to minor) and certain adverse reactions that have relatively serious clinical implications will be discussed, often in greater detail, in other sections of labeling (e.g., WARNINGS AND PRECAUTIONS, CONTRAINDICATIONS, and BOXED WARNING). The ADVERSE REACTIONS section should make it easier for health care practitioners to recognize and retain the adverse reactions information that is most important to prescribing decisions. The beginning of the ADVERSE REACTIONS section should identify the most clinically significant adverse reactions and direct practitioners to more detailed information about those reactions, if any. For example, the section should first:

- Identify and cross-reference all serious and otherwise important adverse reactions described in greater detail in other labeling sections, especially BOXED WARNING or WARNINGS AND PRECAUTIONS (e.g., see WARNINGS AND PRECAUTIONS (5.1)).

- Identify the most commonly occurring adverse reactions (e.g., all adverse reactions occurring at a rate of 10 percent or greater in the treatment group and at a rate at least twice the placebo rate).

- Identify adverse reactions, if any, that resulted in a significant rate of discontinuation or other clinical intervention (e.g., dosage adjustment, need for other therapy to treat an adverse reaction) in clinical trials.

B. Adverse Reactions From Clinical Trials

The presentation of adverse reactions identified from clinical trials is the major component of the ADVERSE REACTIONS section. The ADVERSE REACTIONS section must include a listing of all such reactions that occurred at or above a specified rate that is appropriate to the drug's safety database (see III.B.3), a separate listing of those adverse reactions that occurred below the specified rate, but for which there is some basis to believe there is a causal relationship between the drug and the event (see III.B.4), and, to the extent information is available and relevant, additional detail about the nature, frequency, severity, duration, dose-response, and demographic characteristics of those adverse reactions with significant clinical implications (§ 201.57(c)(7)(ii)(A)). The following is the recommended organization of adverse reactions identified from clinical trials.

1. Description of Data Sources

The presentation of adverse reactions information identified from clinical trials must be preceded by information necessary to interpret the adverse reactions (§ 201.57(c)(7)(i)). This information would ordinarily include a description of the overall clinical trial database from which adverse reaction data have been drawn, including a discussion of overall exposure (number of patients, dose, schedule, duration), demographics of the exposed population, designs of the trials in which exposure occurred (e.g., placebo-controlled, active-controlled), and any critical exclusions from the safety database.

Sample Database Description

The data described below reflect exposure to drug X in [n][3] patients, including [n] exposed for 6 months and [n] exposed for greater than one year. Drug X was studied primarily in placebo- and active-controlled trials (n = __, and n = ___, respectively), and in long-term follow up studies. The population was [age range], [gender distribution], [race distribution] and had [diseases/conditions]. Most patients received doses [describe range, route of administration, frequency, duration, as appropriate].

2. Statement on the Significance of Adverse Reaction Data Obtained From Clinical Trials

To help place in perspective the significance of adverse reaction data obtained from clinical trials, the following statement, or an appropriate modification, should precede the presentation of adverse reactions from clinical trials:

[3] All n's refer to those exposed to drug and not control.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

3. Presentation of Common Adverse Reactions (the Adverse Reactions Table)

The ADVERSE REACTIONS section next should list the adverse reactions identified from clinical trials that occurred at or above a specified rate appropriate to the database (for purposes of this guidance, "common" adverse reactions). The listing must include the rate of occurrence of an adverse reaction for the drug and any comparators (active- or placebo-controls), unless such data cannot be determined or presenting the rates for a comparator would be misleading (§ 201.57(c)(7)(ii)(A)). To permit side-by-side comparison of adverse reaction rates, common adverse reactions are typically presented in a table.[4]

a. Use Best Available Data

The data in the listing of common adverse reactions should be derived from placebo-controlled and/or dose-response studies if these data are available and the databases are sufficiently large to be informative. If these data are unavailable or not sufficiently informative, the primary table should be based on active-controlled data. If concurrently controlled data are unavailable, overall rates from well-monitored, single-arm databases can be used to provide some indication of what was observed in treated patients. In general, only the most informative data should be presented in the table. For example, if placebo-controlled data were available and sufficiently informative, there would usually be no need to present in a table active-controlled data, single-arm trial data, or the overall safety data, even if they are from larger databases. If a data source is not used in the development of a table, but provides important information about adverse reactions listed in the table that is not found in the trials used in the development of the table (e.g., information about prolonged duration of therapy), that information can be discussed in the commentary following the table (see III.B.5).

b. Description of Data Sources for the Table

The table should be accompanied by a description of the data sources reflected in the table, the basis for including adverse reactions in the table

[4] A table can include less common, even rare, important events when the database is large enough to provide a meaningful comparison to a control group.

(e.g., all reactions occurring at > n% in the treated group and for which the rate for drug exceeds the rate for placebo), and the way in which adverse reaction rates were derived (e.g., for a given adverse reaction, was the rate derived from all reported adverse events of that type not present at baseline or from a subset of reported events deemed by investigators to be drug-related). The description of data sources should indicate the types of studies from which the information in the table was derived and whether the study data were pooled. This information can be provided in text preceding the table, in a footnote to the table, in the title to the table, or some combination of these.

c. How Many Tables?

A single adverse reaction table will usually be adequate. However, it may be more informative to present data in more than one table when a drug's adverse reaction profile differs substantially from one setting or population to another, the adverse reactions that differ are clearly drug related, and the data have important implications for use (or nonuse) and monitoring. Situations in which there may be important differences between rates include different indications, formulations, demographic subgroups, study durations, dosing regimens, and types of studies (e.g., intensely monitored small studies vs. a large outcome study). In these situations, the content of the additional table or tables should be limited to only those adverse reactions for which there were meaningful differences in rates.

4. Presentation of Less Common Adverse Reactions

The ADVERSE REACTIONS section next should present those adverse reactions that occurred below the specified rate for inclusion in the common adverse reactions table or listing, but for which there is some basis to believe there is a causal relationship between the drug and the event (for purposes of this guidance, "less common" adverse reactions). It is difficult to establish that very low frequency adverse events are caused by a drug, and there will often be large numbers of these events reported, most of them not caused by the drug. Lengthy lists of adverse events unlikely to have been caused by the drug are of little or no value to prescribers, and are therefore inappropriate for inclusion in labeling.

Serious, low-frequency adverse events generally will be listed when there is reason to suspect that the drug may have caused the event. Typical reasons to suspect causality for an event include (1) timing of onset or termination with respect to drug use, (2) plausibility in light of the drug's known pharmacology, (3) occurrence at a frequency above that expected in the treated population, and (4) occurrence of an event typical of drug-induced adverse reactions (e.g., liver necrosis, agranulocytosis, Stevens-Johnson syndrome). For serious events that are typical of drug-induced adverse reactions, the occurrence of even a single

event could be a basis for inclusion in the list. When none of these reasons exist, however, an event should be excluded from the list. For example, in a large study of a non-cardiovascular drug in elderly patients, a certain number of acute myocardial infarctions might be expected unrelated to the study drug. If the rate in the study does not exceed the expected rate, those adverse events should be excluded from the ADVERSE REACTIONS section.

Non-serious, low-frequency adverse events should be listed only when there is strong evidence that the drug caused the event. Such evidence may include, for example, positive challenge/dechallenge tests or rate of occurrence in a large controlled trial that, although low, is markedly imbalanced between drug and control arms.

5. Commentary on Listings of Common and Less Common Adverse Reactions

For adverse reactions with significant clinical implications (e.g., those that are most commonly occurring, that result in discontinuation or dose modification, or that require monitoring), the listings of common and less common adverse reactions must be supplemented with additional details about the nature, frequency, severity, dose-response, and demographic characteristics of the adverse reaction, to the extent data are available and important (§ 201.57(c)(7)(ii)(A)). It is more likely that supplemental information will be needed for the more commonly occurring adverse reactions.

a. Information on Nature, Frequency, and Severity

To the extent information is available and important and bears on the nature, frequency, and severity of clinically important adverse reactions, the commentary must discuss applicable factors (§ 201.57(c)(7)(ii)(A)). Examples include:

- Concomitant therapy
- Time course of the reaction
- Steps that can diminish the likelihood or severity of, or prevent, adverse reactions
- Changes in adverse reaction rates as a function of duration of therapy (e.g., increasing or decreasing (tolerance) rates with increasing duration of therapy, adverse reactions that emerge only with long-term use)

b. Dose-Response Information

The commentary must identify clinically significant adverse reactions that exhibit a dose response (§ 201.57(c)(7)(ii)(A)). It may be helpful to

include a small table showing the dose response for adverse reactions for which dose response would be expected to influence dose selection.

c. Demographic and Other Subgroups

The commentary must include clinically important information about observed differences, or lack of observed differences, in adverse reactions in various demographic groups (e.g., age, racial, gender) (§ 201.57(c)(7)(ii)(A)). If information is available and important, the commentary should also discuss observed differences, or lack of observed differences, for other subgroups (e.g., renal failure, liver failure, different severity levels of same disease). Where there is no reliable information on differences or similarities in adverse reaction profiles among demographic subgroups, that fact should be disclosed, along with an explanation of why such information is unavailable (e.g., clinical trials were not designed or powered to detect differences in these populations).

d. Multiple Indications

The commentary should summarize any important differences or similarities in the adverse reactions profiles for different indications. If there are substantial and clinically important differences in adverse reaction profiles between indications, and the differences cannot be adequately summarized in the commentary, there should be separate listings of adverse reactions for each indication. When warranted, clinically important differences or similarities in adverse reaction profiles for multiple indications can also be identified in a more prominent location in the ADVERSE REACTIONS section (e.g., at the beginning of the section).

e. Multiple Formulations

If a drug has multiple formulations and a certain formulation or formulations present unique adverse reaction concerns, the commentary should identify clinically important concerns.

C. Presentation of Adverse Reaction Information From Spontaneous Reports

The ADVERSE REACTIONS section must list adverse reactions identified from domestic and foreign spontaneous reports (§ 201.57(c)(7)(ii)(B)). This listing must be separate from the listing of adverse reactions identified in clinical trials (§ 201.57(c)(7)(ii)(B)) and must also be preceded by information necessary to interpret the adverse reactions (§201.57(c)(7)(i)). To help practitioners interpret the significance of data obtained from postmarketing spontaneous reports, the following statement, or an appropriate modification, should precede these data:

The following adverse reactions have been identified during postapproval use of drug X. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Decisions about whether to include an adverse event from spontaneous reports in labeling are typically based on one or more of the following factors: (1) seriousness of the event, (2) number of reports, or (3) strength of causal relationship to the drug. When an adverse reaction identified from spontaneous reporting is included in the labeling, the number of spontaneous reports ordinarily is not cited, because the number can quickly become outdated. If the number of reports is cited, the period of observation should be stated.

IV. GENERAL PRINCIPLES FOR SELECTING AND CHARACTERIZING DATA IN THE ADVERSE REACTIONS SECTION

A. Selecting Adverse Events for Inclusion

The definition of adverse reactions does not include all adverse events observed during use of a drug. It is limited to those events for which there is some basis to believe there is a causal relationship between occurrence of an adverse event and the use of a drug (§ 201.57(c)(7)). Decisions on whether there is some basis to believe there is a causal relationship are a matter of judgment and are based on factors such as: (1) the frequency of reporting, (2) whether the adverse event rate for the drug exceeds the placebo rate, (3) the extent of dose-response, (4) the extent to which the adverse event is consistent with the pharmacology of the drug, (5) the timing of the event relative to the time of drug exposure, (6) existence of challenge and dechallenge experience, and (7) whether the adverse event is known to be caused by related drugs.

B. Rare, Serious Reactions

For serious adverse events that are unusual in the absence of drug therapy (e.g., liver failure, agranulocytosis, rhabdomyolysis, idiopathic thrombocytopenic purpura, intussusception), there is a basis to believe there is a causal relationship between the event and the drug at a very low rate of occurrence. Therefore, these events are generally listed in the adverse reactions section even if there are only one or two reported events, unless it is clear that a causal relationship can be excluded.

C. Determining Adverse Reaction Rates

The rate of an identified adverse reaction is ordinarily derived from all reported adverse events of that type in the database used. Determining a rate based on a subset of reported events that individual investigators believe to be causally related to drug exposure is discouraged. Excluding events from the rate calculation based on the judgment of individual investigators introduces bias and inconsistency in rate determinations.

D. Avoiding Nonspecific Terms

In characterizing overall adverse reaction experience, nonspecific terms that lack a commonly understood or precise meaning are discouraged, as use of such terms can be misleading. For example, the phrase *well-tolerated* is a vague and subjective judgment about a drug's adverse reaction profile for which there are no commonly understood parameters. In addition, the terms *rare*, *infrequent*, and *frequent* do not provide meaningful information about the frequency of occurrence of adverse reactions. Specific frequency ranges (e.g., adverse reactions occurring in < 1/500) provide more precise information about incidence.

E. Comparative Safety Claims

Comparative safety claims for drugs in terms of frequency, severity, or character of adverse reaction must be based on data from adequate and well-controlled studies (as defined in 21 CFR 314.126), unless this requirement is waived (§ 201.57(c)(7)(iii)).[5] Details of studies that are the basis for comparative safety claims would ordinarily be discussed in the CLINICAL STUDIES section of the labeling. Care should be taken to avoid inclusion of comparator rates that would imply a comparative safety claim that is unsubstantiated or otherwise misleading (e.g., if an excessive dose of an active comparator was used). If the requirement that claims be based on adequate and well-controlled studies is waived to permit inclusion of comparative rates (e.g., because the identity and rates of adverse reactions for the active comparator are important to understanding the significance of the information), the comparator rates should be qualified by a disclaimer indicating that the data are not an adequate basis for comparison of rates between the study drug and the active control.[6]

F. Negative Findings

A negative finding can be reported if the absence of the reaction is convincingly demonstrated in a trial of adequate design and power.

V. GENERAL PRINCIPLES FOR PRESENTING ADVERSE REACTIONS DATA IN A TABLE OR LIST

A. Pooling Data

If there are no major study-to-study differences in study design, study population, and adverse reaction rates, an overall pooling of safety data from multiple studies may increase the precision of adverse reaction rates and provide a more clinically useful representation of a drug's adverse reaction profile.

[5] The requirement can be waived under 21 CFR 201.58, or 21 CFR 314.126(c), if applicable.
[6] Also see the discussion of comparative data in the guidance for industry on *Clinical Studies Section of Labeling for Human Prescription Drug and Biological Products—Content and Format*.

B. Classifying Adverse Reactions

Adverse reactions should be classified using meaningful and specific terms that best communicate the nature and significance of the reaction. There should ordinarily be a common classification scheme across all studies in the safety database. Events that are reported under different terms in the database, but that represent the same phenomenon (e.g., sedation, somnolence, drowsiness) should ordinarily be grouped together as a single adverse reaction to avoid diluting or obscuring the true effect. Similarly, adverse events reported in more than one body system that appear to represent a common pathophysiologic event should be grouped together to better characterize the reaction. For example, an allergic-type adverse event that has respiratory (wheezing) and dermatologic (rash, urticaria) manifestations should be classified as a single adverse reaction (e.g., hypersensitivity).

C. Categorizing Adverse Reactions

Within a listing, adverse reactions must be categorized by body system, by severity of reaction, in order of decreasing frequency, or by a combination of these, as appropriate. Within a category, adverse reactions must be listed in decreasing order of frequency. If frequency cannot be reliably determined, adverse reactions must be listed in decreasing order of severity (§ 201.57(c)(7)(ii)).

D. Frequency Cutoff

The frequency cutoff for the listing of common adverse reactions identified from clinical trials (usually the adverse reactions table) must be appropriate to the safety database (§ 201.57(c)(7)(ii)(A)). Factors that could influence selection of a frequency cut-off include the size of the safety database, the designs of the trials in the database, and the nature of the indication. The frequency cutoff should be noted in the listing or table header, in the text accompanying the listing or table, or in a footnote.

E. Quantitative Data

For quantitative data (e.g., abnormal laboratory values, vital signs, ECGs), it is usually preferable to present rates of abnormal values and to specify the cutoff value for inclusion (e.g., five times the upper limit of normal) than to refer to a grading system.

F. Denominator

The denominator (N = number of patients) should be provided for each column in a table or listing, except for the listing of adverse reactions identified from postmarketing spontaneous reports (see III.C).

G. Subgroup Rates

The rates for reactions that are specific to a subgroup (e.g., gender-specific reactions such as menstrual irregularity) should be determined using the appropriate denominator, and that denominator should be identified in a footnote. If rates of specific adverse reactions were gathered for only a subgroup of patients or studies (e.g., an adverse effect on a laboratory test), that fact should be disclosed in a footnote.

H. Percentages

Adverse reaction rates expressed in percentages should ordinarily be rounded to the nearest integer. An exception would be for particularly serious adverse reactions (e.g., stroke, intracranial hemorrhage, agranulocytosis) occurring at low rates in a large study where fractions of a percent may be meaningful.

I. Adverse Reaction Rates for Drug Less Than for Placebo

Adverse reactions for which the placebo rate equals or exceeds the rate for the drug (after rounding) should not be included in the ADVERSE REACTIONS section unless there is some compelling factor (e.g., timing) that suggests that the event is caused by the drug. In that case, the adverse reaction should be discussed in the commentary following the table.

J. Significance Testing

Results of significance testing should be omitted unless they provide useful information and are based on a prespecified hypothesis in an adequately designed and powered study.

VI. UPDATING THE ADVERSE REACTIONS SECTION

A. Sources of Information

Sources of information to be considered when updating the ADVERSE REACTIONS section of labeling include controlled trials or epidemiologic studies conducted after marketing approval, manufacturer's safety-related labeling supplements, and other analyses of postmarketing adverse events, including single cases or case series from the literature or from spontaneous reporting.

B. New or Outdated Information

Applicants are urged to review at least annually the content of the ADVERSE REACTIONS section to ensure that the information remains current. We expect the labeling to be consistent with newly acquired information from controlled trials or spontaneous reports and with the evolution of labeling in the pertinent drug class. Conversely, when there is reliable new adverse reaction information (either overall information or information relevant to a particular adverse reaction) that is inconsistent with the information in the ADVERSE REACTIONS section, we expect the outdated information to be deleted from all affected sections of the labeling or appropriately

modified, and the new information incorporated in all relevant parts of the labeling. The applicant must update the labeling when new information becomes available that causes the labeling to become inaccurate, false, or misleading (21 CFR 201.56(a)(2)).

GLOSSARY

Adverse Reaction (21 CFR 201.57(c)(7)): For purposes of prescription drug labeling and this guidance, an *adverse reaction* is an undesirable effect, reasonably associated with the use of a drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence. This definition does not include all adverse events observed during use of a drug, only those for which there is some basis to believe there is a causal relationship between the drug and the occurrence of the adverse event.

Adverse reactions may include signs and symptoms, changes in laboratory parameters, and changes in other measures of critical body function, such as vital signs and ECG.

Adverse Event (or adverse experience): For the purposes of this guidance, the term *adverse event* refers to any untoward medical event associated with the use of a drug in humans, whether or not considered drug-related.

Serious Adverse Reaction: For purposes of this guidance, the term *serious adverse reaction* refers to any reaction occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability or incapacity, or a congenital anomaly or birth defect. Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious adverse reactions when, based upon appropriate medical judgment, they may jeopardize the patient or subject, and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

EXHIBIT 295

Chapter 21: Surveillance for Adverse Events Following Immunization Using the Vaccine Adverse Event Reporting System (VAERS)

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I. Public Health Importance

Vaccination is one of the ten great public health achievements of the 20th century.[1] Vaccines have reduced the incidence of many vaccine-preventable diseases in the United States by more than 98% compared to the pre-vaccine era.[2,3] This historic decrease in disease rates is shown in Table 1.

Table 1. Decline in vaccine-preventable disease morbidity in the United States during the 20th century[2,3]

Disease	Baseline 20th century annual morbidity	2014 reported cases	% Decrease
Smallpox	48,164*	0	100
Diphtheria	175,885†	1	>99
Pertussis	147,271‡	32,971	>77
Tetanus	1,314§	25	>98
Poliomyelitis (paralytic)	16,316¶	0	100
Measles	503,282#	667	>99
Mumps	152,209**	1,223	>99
Rubella	47,745††	6	>99
Congenital rubella	823 (estimated)‡‡	1	>99
Haemophilus influenzae, type b	20,000 (estimated)§§	306 (serotype b or unknown serotype, age <5 years)	>98

* *Average annual number of cases during 1900–1904.*

† *Average annual number of reported cases during 1920–1922, 3 years before vaccine development.*

‡ *Average annual number of reported cases during 1922–1925, 4 years before vaccine development.*

§ *Estimated number of cases based on reported number of deaths during 1922–1926 assuming a case-fatality rate of 90%.*

¶ *Average annual number of reported cases during 1951–1954, 4 years before vaccine licensure.*

Average annual number of reported cases during 1958–1962, 5 years before vaccine licensure.

** *Number of reported cases in 1968, the first year reporting began and the first year after vaccine licensure.*

†† *Average annual number of reported cases during 1966–1968, 3 years before vaccine licensure.*

§§ *Estimated number of cases from population-based surveillance studies before vaccine licensure in 1985.*

Vaccinations are usually administered to healthy persons and often are mandated by states as a condition for school attendance (with certain exemptions allowed); therefore, they are held to a higher standard of safety than other medical products.[4] However, as with all medical products, no vaccine is perfectly safe or effective. Vaccines can cause minor adverse events (AEs) such as fever or local reactions at the injection site. Rarely, they can cause serious AEs such as anaphylaxis. Adverse events can also occur coincidentally after vaccines (i.e. they would have occurred in the absence of vaccination). Improving our understanding of vaccine safety is important to reduce the occurrence of vaccine AEs and maintain public confidence in vaccine. One way to enhance our understanding of vaccine safety is to improve surveillance for vaccine AEs. Robust vaccine safety monitoring may foster the discovery of adverse events associated with vaccination, and thus the development and use of safer vaccines and recommendations to minimize the risk of AE after vaccination (e.g., creating new recommendations, contraindications, and precautions).[5]

II. Background

Vaccines, like other pharmaceutical products, undergo extensive testing and review for safety, immunogenicity, and efficacy in trials with animals and humans before they are licensed in the United States. Because these trials generally include a placebo control or comparison group, it is possible to ascertain which local or systemic reactions were actually caused by the vaccine. However, prelicensure trials are relatively small—usually limited to a few thousand subjects— and usually last no longer than a few years. In addition, they may be conducted in populations less demographically, racially, and ethnically diverse than those in which the vaccine is ultimately used. Persons with certain health conditions, such as pregnancy, may be excluded from the trials. Prelicensure trials usually do not have the ability to detect rare AE or an AE with delayed onset. The continuous monitoring of vaccine safety in the general population after licensure (known as post-licensure or postmarketing surveillance) is needed to identify and evaluate risk for such AEs after vaccination.[4]

The National Childhood Vaccine Injury Act of 1986 (NCVIA) mandates that healthcare providers who administer vaccines and vaccine manufacturers report certain AEs following specific vaccination.[6] The NCVIA's purposes were to compensate persons who may have
been injured by vaccines and to reduce threats to the stability of the immunization program (e.g., liability concerns, inadequate supply of vaccine, rising vaccine costs).[7] The NCVIA requires that healthcare providers report to VAERS specific AEs which are listed on the Vaccine Adverse Event Reporting System (VAERS) Table of Reportable Events Following Vaccination. (Note that this table was revised as of March, 2017 and is available at https://vaers.hhs.gov/docs/VAERS_Table_of_Reportable_Events_Following_Vaccination.pdf.)[8] VAERS, co-managed by the Centers for Disease Control (CDC) and Prevention and the U.S. Food and Drug Administration (FDA), was established in 1990 for the collection and analysis of reports of AEs following vaccination.[9] Spontaneous reporting systems for AEs similar to VAERS exist in many countries; some monitor vaccines separately from other drug products, but many are joint programs. These programs form the cornerstone of drug and vaccine safety monitoring efforts around the world.

III. Objectives of VAERS

The objectives of VAERS are to:

- monitor increases in known side effects, like arm soreness where a shot was given
- identify potential patient risk factors for particular types of health problems related to vaccines
- assess the safety of newly licensed vaccines
- watch for unexpected or unusual patterns in adverse event reports, and
- serve as a monitoring system for vaccinations administered in public health emergencies

Scope of reports sought

Anyone can report any vaccine AEs to VAERS. Reports are accepted from health care providers, vaccine manufacturers, patients, parents and anyone else who cares to report. Persons who are not healthcare providers are encouraged to consult with a healthcare provider to ensure that information is complete and accurate and that their provider is aware of the AE. Manufacturers are required to report to VAERS all AEs made known to them for any US-licensed vaccine. Reports of vaccination errors are also accepted by VAERS.

The VAERS Table of Reportable Events Following Vaccination (available at https://vaers.hhs.gov/docs/VAERS_Table_of_Reportable_Events_Following_Vaccination.pdf) lists the events mandated for healthcare providers to report to VAERS. In addition, healthcare providers should submit reports to VAERS for all clinically significant AEs occurring after vaccination, in all age groups, even if the causal relationship to vaccination is uncertain. Such events include (but may not be limited to) all deaths, any life-threatening illness; an illness requiring a hospitalization, prolongation of a hospital stay, or any illness resulting in a permanent disability; and congenital anomalies, as well as less serious AEs of concern. The VAERS form requests information about the AE, the vaccine(s) received, the timing of vaccination before the AE, demographic information about the recipient, concurrent medical illness or medications, and prior medical history and history of prior AEs. The VAERS form allows description of the AE in a narrative format by the reporter. The VAERS form has been updated, and the new form (VAERS-2.0), has been in use since

June 2017. The VAERS-2.0 form is available on the VAERS website at https://vaers.hhs.gov/index. The AE should be described on the VAERS form as clearly as possible, with accurate timing with respect to vaccination. Additional medical records or discharge summaries are requested by the VAERS staff during follow-up for reports of a serious AE.

Reporting to VAERS
Reporting to VAERS online (i.e., web-based reporting) is strongly encouraged since it allows for quicker receipt and processing of the information. The option to report on a downloadable pdf was made available in June 2017. If someone is unable to report online or via the writable pdf, they can contact VAERS by phone at 1-800-822-7967 or email at info@vaers.org for assistance.

A VAERS reporting form, which can be copied for reporting purposes, is available online at https://vaers.hhs.gov/pdf/vaers_form.pdf. The Vaccine Information Statements (http://www.cdc.gov/vaccines/hcp/vis/index.html) developed by CDC for all US-licensed vaccines and given to patients at the time of vaccination also contain instructions on how to report an AE to VAERS. Detailed instructions for completing the reporting form are provided below. Local health departments should follow the reporting instructions provided by their State Immunization Program.

Completion of VAERS form and submission of reports

Instructions for completing the VAERS form are on the VAERS website (https://vaers.hhs.gov/index).

Note: *Report AEs associated with vaccines on the VAERS form. Do not use the FDA's MEDWATCH forms to report vaccine AEs.*

Do not report events associated with tuberculosis screening tests (Tine, PPD, or Mantoux), immune globulins, or other non-vaccine medical products to VAERS. These events should be reported to the 1-MedWatch program http://www.fda.gov/Safety/MedWatch/ or by calling 800-FDA-1088 (800-332-1088).

Reporting responsibilities
Clinic staff at the local level are responsible for completing a VAERS report when an AE is suspected or occurs following immunization. As much of the requested information as possible should be included. Although reporting priority may be given to serious or unexpected events or unusual patterns of expected non serious events, all clinically significant AEs should be reported. Each report should be reviewed for completeness and accuracy before it is sent to VAERS with specific attention to the following sections.

- *Dates*—All dates should make chronological sense. For example, the vaccine date cannot precede the birth date, or the report date cannot precede the vaccine date. All date fields should include the month, day, and year.
- *Patient name*—Verify that the patient's first and last names are correct. This check assists in identification of duplicate reports.
- *Reporter information*—The reporter name and complete mailing address are requested *(upper right corner of form)*. Verification letters and requests for missing or follow-up information are sent to this address. VAERS sends any reporter other than a manufacturer or State Immunization Program staff member (see below) a letter or email (based on the reporter's preference) verifying receipt of the form and requesting any critical information that was missing from the VAERS report (if necessary).
- *Critical boxes*—Certain items on the VAERS form are crucial to the analysis of VAERS data and have been designated as critical boxes (data fields). Persons reporting will be asked to supply this information later if it is missing. Critical boxes are differentiated by a square around their respective item numbers on the form as follows and are highlighted on the pdf:

Critical boxes	VAERS 2.0 Form box number
Date of birth	Box 2
Age of patient at the time of vaccination	Box 6
Sex	Box 3
Date of vaccination (and time if known)	Box 4
Date of onset of AE (and time, if known)	Box 5
Narrative description of AE, symptoms, etc.	Box 18
Indicates whether a report is regarded as serious or non-serious, and identifies the serious reports for follow-up Serious (serious status is based on the Code of Federal regulations) • Patient died and date of death • Life-threatening illness (based on the judgment of the reporter) • Required hospitalization and number of days hospitalized • Resulted in prolongation of hospitalization • Resulted in permanent disability Non-serious • Required emergency department or doctor visit • None of the above	Box 21
All vaccines given on the date listed in box 4 of the VAERS-2.0 form, including name of vaccine, manufacturer, vaccine lot number, route and site of administration and number of previous doses given.	Box 17

- *Timely reporting*—Reporters are encouraged to send reports to VAERS as AEs occur, especially reports of any serious event. Programs are discouraged from sending batches of reports Timely reporting is essential for rapid assessment of vaccine safety concerns and follow-up investigation.

  States may have VAERS reports sent directly to VAERS from providers without being sent to the State Immunization Program Staff first. If VAERS reports are sent directly from healthcare providers and do not include an immunization project number [box 24 or 26 completed on the VAERS report-see below], the provider will be contacted for notification of report receipt and for follow-up information instead of the State Immunization Program Staff.

State Immunization Program staff activities

The State Immunization Program staff member designates a VAERS Coordinator or Vaccine Safety Coordinator with overall responsibility for VAERS-related activities including the following specific responsibilities:

- Serving as CDC's main point-of-contact for vaccine safety in the awardee's jurisdiction.
- Alerting CDC to vaccine safety concerns in awardee's jurisdiction and responding to vaccine safety emergencies.
- Reporting vaccine safety emergencies and events of concern requiring vaccine safety responses to the CDC Immunization Safety Office (404-498-0680) or the CDC Emergency Operations Center (770-488-7100).
- Collaborating with CDC and other partners (e.g., FDA, local health departments, healthcare facilities, providers) to respond to and investigate reports of serious adverse events in accordance with state health department policy.
- Identifying and responding to vaccine safety issues of concern in respective jurisdiction.

Activities required of state immunization program staff who chose to submit reports from local health departments or immunization projects

The State Immunization Program staff member (VAERS coordinator or Vaccine Safety Coordinator) who chooses to submit VAERS reports from local health departments or immunization projects (rather than having the healthcare provider caring for the patient submit it) is responsible for the following activities:

- Registering with Epi-X—CDC's secure communications network for public health professionals (https://www.cdc.gov/epix/) at the email address: epiXhelp@cdc.gov so that they can receive quarterly report summaries of the VAERS reports that they submitted.
- Reviewing each report for completeness (especially the critical boxes), obtaining any other necessary information, and clarifying any questions about the report.
- Assigning an identifying immunization project number using the 2-letter state postal abbreviation, 2- or 4-digit representation for year, and the state numbering sequence. For example, the 57th report received in Arizona in 2016 begins with AZ, followed by 16, followed by 057, and should look like this: AZ16057. This number is entered into box 26 of the VAERS 2.0 form.
- Uploading or sending the original report with the identifying number to VAERS and keeping a copy. As with local reporting, the cases should be forwarded rapidly to VAERS and not sent in a batch. Any further correspondence about a report must include the 6-digit VAERS ID number, which is assigned by the VAERS system. Reports are entered into the VAERS database under this number. It is also helpful to have the patient's name and date of birth, if available, to help identify the specific report. VAERS maintains the confidentiality of patients' personal identifying information, consistent with the requirements of the NCVIA.
- Completing the quarterly update report that is sent by VAERS via Epi-X (https://www.cdc.gov/epix/). (Although these follow-up requests are sent quarterly, the case reports are scanned upon receipt at VAERS and available to CDC and FDA for evaluation in near real time upon request.) This quarterly report contains a list of all initial reports received during the quarter, by VAERS ID number and state immunization project number, and serves as an acknowledgment of those reports. Specific missing or incomplete information for these reports is noted and completed in the appropriate boxes. The quarterly update report also lists reports for which VAERS requests recovery status at 60 days postvaccination and at 1 year postvaccination. The State Immunization Program staff submits to VAERS any requested missing information, as well as follow-up recovery status information for each listed report at 60 days and 1 year postvaccination. The State Immunization Program staff may update any other pertinent information about these individuals, such as vaccination information or date of birth. Reponses to quarterly report questions can be submitted to VAERS by mail, fax, or email.

States are asked to update VAERS with any personnel, fax, phone, or address changes. This is done by means of a quarterly e-mail request from VAERS to the state health department.

IV. Evaluation of VAERS Data

VAERS reports are received and processed by staff at the VAERS contract site. Upon receipt by VAERS, reports are entered into a database, and staff use a standard set of coding terms from the Medical Dictionary for Regulatory Affairs (MedDRA) to code the AEs; a report may include more than one AE. FDA and CDC medical officers and vaccine safety experts review reports of deaths and other serious events and conduct other analyses to address specific safety concerns and to evaluate trends in reporting. Although all serious reports are reviewed, it is primarily by analyzing all reports in aggregate that possible safety concerns (or "signals") between vaccines and AEs can be properly detected and assessed.[10] When vaccine safety concerns are detected in VAERS they almost always require further assessment such as the Vaccine Safety Datalink (VSD) (see below).

Approximately 40,588 U.S. reports of AEs following immunization are now received by VAERS each year (CDC, unpublished data). All reports are accepted and entered without case-by-case determination of whether the AEs could have been caused by the vaccine in question. To put the number of reports of AEs in perspective, it should be noted that each year over 317 million doses of vaccine are distributed in the United States (CDC unpublished data). Additionally, the type and severity of events reported vary from minor local reactions to death. Of the U.S. primary reports received between 2012 and 2016, 0.4% reported death as the outcome; 5% reported a serious nonfatal adverse event (as defined above), and 94.6% reported non-serious events (CDC unpublished data).

From 2012 through 2016, vaccine providers submitted 32% of U.S. VAERS reports, vaccine manufacturers submitted 41%; patients or parents submitted 13%, and 14% came from other or unknown sources (CDC unpublished data).

Direct reporting to VAERS by healthcare providers or by state immunization program staff is strongly encouraged, as these reports usually arrive on a timelier basis than those submitted first to manufacturers. Manufacturers are not required to provide these reports to VAERS immediately upon receipt unless serious or unexpected events have occurred. As a result, evaluation of non-serious vaccine-associated events may be delayed.

Usefulness

The data from VAERS have been used by FDA, CDC, and the National Vaccine Injury Compensation Program at the Health Resources and Services Administration (HRSA), vaccine policy bodies, including the Advisory Committee on Immunization Practices (https://www.cdc.gov/vaccines/acip/), and other stakeholders. Below are some recent examples of how VAERS data have contributed to public health, listed by some of the major objectives of VAERS:

Detect new or rare AEs. The classic example is when VAERS detected an unexpected number of intussusception reports after the introduction of the first rotavirus vaccine Rotashield®.[11] Further investigation in other systems verified this association and the Rotashield® vaccine is no longer licensed in the United States.[12–14]

A more recent example is that VAERS found a small increased risk for febrile seizures among young children after influenza vaccine (Fluzone®) during the 2010–2011 season.[15] Additional studies covering influenza seasons from 2006–2007 through 2011–2012 confirmed this signal that simultaneous administration of flu vaccine with certain other vaccines (PCV and/or DTaP) appears to be associated with an increased risk for febrile seizures in young children on the day of and day after vaccination.[16, 17] However, this finding did not change the ACIP recommendations to give flu vaccine with other recommended vaccines since the benefits of on-time vaccinations outweigh the risk of febrile seizures[18] and most children who have febrile seizures recover quickly and have no long-term adverse effects.[19]

Assess the safety of newly licensed vaccines. VAERS has been used to assess the safety profile of the high-dose trivalent inactivated influenza vaccine; these findings have supported the vaccine's indications and recommendations.[20]

Identify potential risk factors in vaccinees for particular types of AEs. VAERS contributed data to support severe combined immunodeficiency syndrome (SCID) as a new contraindication for rotavirus vaccine.[21, 22]

Rapidly respond to vaccine safety concerns or public health emergencies. VAERS provided the first national data during 2009–10 H1N1 pandemic response. The first 2 months of data were published 3 months after the start of the program.[23] VAERS has also identified a number of preventable vaccination errors that once brought to attention of the public health community have been incorporated into training materials and other prevention strategies.[24–27]

VAERS data have also been used by the Institute of Medicine (IOM) Vaccine Safety Committee in an extensive assessment of the causal relations between common childhood vaccines and AE. IOM established an independent expert committee that conducted comprehensive reviews of 158 vaccine-AE pairs to study existing and emerging immunization safety concerns among eight different vaccines. In 2012, Adverse Effects of Vaccines: Evidence and Causality was published and includes causality conclusions for each vaccine-AE pair addressed.[28] The IOM report summarizes the current epidemiologic evidence (including information obtained from VAERS) for causality between an immunization and a hypothesized health effect, the biologic mechanisms relevant to the adverse event hypothesis, and the significance of the issue in a broader societal context. The entire report can be downloaded free of charge or purchased at https://www.nap.edu/catalog/13164/adverse-effects-of-vaccines-evidence-and-causality. This reference may be useful to providers or public health officials who are called on to answer the public's questions on vaccine safety and the occurrence of AEs.

Reporting sensitivity

Like all passive surveillance systems, VAERS is subject to varying degrees of underreporting. The sensitivity of VAERS is affected by the likelihood that parents and/or vaccinees detect an AE; that parents and/or vaccinees bring the event to the attention of their health-care provider(s); that parents and/or healthcare providers suspect an event is related to prior vaccination; that parents and/or healthcare

providers are aware of VAERS; and that parents and/or health-care providers report the event. The completeness of reporting of AEs associated with certain vaccines varies according to the severity of the event and the specificity of the clinical syndrome to the vaccine.[29, 30] Reporting can also be stimulated by media attention on specific AEs.[31]

VAERS major strengths are:

- Its scale: VAERS is national in scope and can therefore be used during public health emergencies
- Its timeliness
- Its capacity to detect new AEs in addition to monitoring pre-specified AEs found in pre licensure trials
- Its accessibility; anyone can submit a report.

V. Limitations of VAERS

The limitations of VAERS, which are common to many passive reporting systems, should be considered in interpreting VAERS data.

Dose distribution data. Vaccine dose distribution data are used to calculate reporting rates. However, these data are not age or state-specific. In addition, dose distribution information, derived from biologics surveillance data provided by vaccine manufacturers, also does not track the amount of vaccine actually administered. This biologics surveillance data is proprietary and is not available to the public. The only exception is for annual influenza vaccine. Data on the number of doses of influenza vaccine distributed are calculated by CDC and made available to the public, but are not product specific by brand or manufacturer.

Quality of information. Since all reports, even incomplete ones, are accepted by VAERS, and because anyone may submit reports to VAERS, the accuracy and amount of information vary significantly between reports.

Underreporting. Underreporting may occur for several reasons. These include limitations in detection of an event, lack of recognition of association between vaccine and event, or failure to submit a report. Underreporting can affect the ability of VAERS to detect very rare events, although this may less of a concern for clinically serious events as they are more likely to be reported than non-serious events.[29]

Biased and stimulated reporting. Reports to VAERS may not be representative of all AEs that occur. Events that occur within a few days to weeks of vaccine administration are more likely to be submitted to VAERS than events with a longer onset interval. Media attention to particular types of medical outcomes can stimulate reporting.[31]

Confounding by drug and disease. Many reports to VAERS describe events that may have been caused by medications or underlying disease processes. Other reports to VAERS encompass clinical syndromes that are poorly defined, not clearly understood, or represent diagnoses of exclusion (e.g., sudden infant death syndrome).

Inability to determine causation. VAERS reports are usually not helpful in assessing whether a vaccine actually caused the reported AEs because they lack either unique laboratory findings or other information necessary to draw such conclusions. Often multiple vaccines are administered at the same visit, making attribution of causation to a single vaccine or antigen difficult. Additionally, there is lack of an unvaccinated group for comparison in VAERS. Therefore, reports to VAERS are useful for generating hypotheses, but studies with vaccinated and unvaccinated subjects are necessary to confirm any hypotheses generated by VAERS observations.[5]

VI. Enhancing surveillance

Several activities can be undertaken to improve the quality of VAERS as a surveillance system.

Improving quality of information reported

At the state and local levels, VAERS forms (including the web-based reporting form) should be reviewed prior to submission for completeness and accuracy. The reporter should be contacted if any information is missing. For death and serious outcomes after vaccination, the VAERS staff will attempt to obtain

additional documentation (e.g., hospital discharge summaries, laboratory reports, death certificates, autopsy reports). The VAERS staff routinely contacts reporters—health care providers and parents or vaccine recipients—to obtain missing information or to correct inaccurate information for all reports of deaths, serious AEs, and other selected clinically significant events.

Evaluation of system attributes

A survey was conducted in 2005 to assess the knowledge, attitudes, and practices among healthcare providers about reporting to VAERS.[32] Data indicated that although 71% of respondents were familiar with VAERS, only 17% said they were very familiar with it. Approximately 37% of healthcare providers had identified at least one adverse event after immunization, but only 17% stated that they had ever reported to VAERS. Vaccine Information Statements (VIS) were the most common source used to learn about VAERS. CDC is continuing to support efforts to further evaluate providers' perceptions and behaviors about VAERS and about reporting AEs after vaccination.

Promoting awareness

Current outreach and education efforts to promote VAERS include online print and web material, and general information brochures in English and Spanish at https://www.cdc.gov/vaccinesafety/ensuringsafety/monitoring/vaers/print-material.html and CDC vaccine safety publications available at https://www.cdc.gov/vaccinesafety/ensuringsafety/monitoring/vaers/publications.html

VAERS contact information is provided on all VISs, which are required to be handed out at each vaccination visit to persons receiving a vaccine that is covered by the Vaccine Injury Compensation Program (VCIP)—i.e., a vaccine listed available at https://www.hrsa.gov/vaccinecompensation/vaccineinjurytable.pdf). VIS use is strongly encouraged for all vaccines, including those not covered by the VICP

VAERS data, without patient identifying information, are available to the public through the VAERS website for downloading raw data files or via search engine on the CDC WONDER site (https://wonder.cdc.gov/vaers.html) and are updated monthly.

Despite its limitations, VAERS is useful in that it generates signals that trigger further investigations. VAERS can detect unusual increases in previously reported events. As noted earlier, the sentinel role of VAERS is particularly significant for newly licensed vaccines, as evidenced in 2009 by the VAERS publication of the first summary of post-licensure H1N1 pandemic influenza safety data®.[23] Although manufacturers are now routinely asked to conduct or sponsor post-licensure studies designed to collect additional safety data for large numbers of vaccine recipients, the need for a national post-licensure surveillance system remains. Like pre-licensure studies, post-licensure studies may not be large enough to detect novel very rare AEs, or may take several years to accumulate enough data to assess a rare occurrence.

VII. The National Vaccine Injury Compensation Program

The National Childhood Vaccine Injury Act of 1986 established the National VICP to provide compensation for AEs following immunization. VICP is a "no-fault" system to compensate individuals whose injuries may have been caused by covered vaccines. VICP is separate from VAERS and managed by HRSA. Reporting an event to VAERS does not result in the filing of a claim to the VICP. A claim for compensation must be filed directly with VICP. Any individual, of any age, who received a covered vaccine and believes he or she was injured as a result, can file a petition with VICP. The VCIP website lists specific injuries or conditions and time frames following vaccination that may be compensated under the VICP. If an injury and/or condition does not meet the requirements in the vaccine injury table, a petitioner must prove through evidence such as expert witness testimony, medical records, or medical opinion that the vaccine caused the injury and/or condition.[6, 33]

The toll-free number for the VCIP is 800-338-2382. Further information can be obtained by visiting their VICP website (https://www.hrsa.gov/vaccinecompensation/ or by writing to National Vaccine Injury Compensation Program, Parklawn Building, 5600 Fishers Lane, 8N146B, Rockville, MD 20857.

VIII. Other Vaccine Safety Monitoring Activities

In addition to VAERS, several other systems exist to monitor the safety of vaccines. The systems maintained by CDC are listed below.

The Vaccine Safety Datalink project (http://www.cdc.gov/vaccinesafety/activities/vsd.html) is a collaborative effort between CDC's Immunization Safety Office and several integrated healthcare systems to monitor immunization safety and address the gaps in scientific knowledge about AEs following immunization.[34] The VSD links computerized vaccination and medical records for approximately 10 million persons (3% of the total U.S. population) enabling evaluation of less frequent AEs. Denominator data and control groups are also readily available. The VSD thus provides a way of testing hypotheses related to vaccine safety. VSD has also implemented a system to conduct near real-time monitoring for specific AEs after vaccines in the VSD population.

The Clinical Immunization Safety Assessment (CISA) Network (http://www.cdc.gov/vaccinesafety/Activities/CISA.html), consists of six academic centers with vaccine safety expertise that are working in partnership with CDC. The CISA Network is designed to improve scientific understanding of vaccine safety issues at the individual patient level. Its goals are to study mechanisms of vaccine AEs, study individual risk factors for AEs, serve as a resource to provide consultation for difficult vaccine safety issues, and to assist in developing vaccine safety guidance.

In summary, ongoing post-licensure safety monitoring is necessary for all U.S. licensed vaccines. Well-established systems are in places to accomplish that monitoring and State Immunization Program staff have a key role to play in helping to keep vaccines safe.

References

1. CDC. Ten great public health achievements—United States, 1900–1999. *MMWR Morb Mortal Wkly Rep* 1999;48(12): 241–3. https://www.cdc.gov/mmwr/preview/mmwrhtml/00056796.htm
2. CDC. Achievements in public health, 1900–1999. Impact of vaccines universally recommended for children—United States, 1990–1998. *MMWR Morb Mortal Wkly Rep* 1999;48(12):243–8. https://www.cdc.gov/mmwr/preview/mmwrhtml/00056803.htm
3. Adams DA, Thomas KR, Jajosky R, et al. Summary of notifiable infectious diseases and conditions—United States, 2014. *MMWR Morb Mortal Wkly Rep* 2016;63(54):1–152. doi: 10.15585/mmwr.mm6354a1
4. Chen RT. Davis RL, Rhodes PH. Special methodological issues in pharmacoepidemiology studies of vaccine safety. In: Strom BL, editor. Pharmacoepidemiology 4th ed. Sussex: John Wiley & Sons; 2005.
5. Chen RT, Rastogi SC, Mullen JR, et al. The Vaccine Adverse Event Reporting System (VAERS). *Vaccine* 1994;12(6): 542–550. doi: 10.1016/0264-410X(94)90315-8
6. National Childhood Vaccine Injury Act of 1986, at Section 2125 of the Public Health Service Act as codified at 42 U.S.C. Section 300aa.
7. Brink EW, Hinman AR. The Vaccine Injury Compensation Act: The new law and you. *Contemp Pediatr* 1989;6(3):28–42.
8. HRSA. National Vaccine Injury Compensation Program: revisions to the Vaccine Injury Table 80 Federal Register. 45132–54. 2015. Codified at 42 CFR §100. https://www.federalregister.gov/documents/2015/07/29/2015-17503/national-vaccine-injury-compensation-program-revisions-to-the-vaccine-injury-table.
9. CDC. Current Trends Vaccine Adverse Event Reporting System—United States. *MMWR Morb Mortal Wkly Rep* 1990;39(41):730–3. https://www.cdc.gov/mmwr/preview/mmwrhtml/00001804.htm.
10. Shimabukuro TT, Nguyen M, Martin D, DeStefano F. Safety monitoring in the Vaccine Adverse Event Reporting System (VAERS). *Vaccine* 2015;33(36):4398–405. doi: 10.1016/j.vaccine.2015.07.035
11. CDC. Intussusception among recipients of rotavirus vaccine—United States, 1998–1999. *MMWR Morb Mortal Wkly Rep* 1999;48(27):577–81. https://www.cdc.gov/mmwr/preview/mmwrhtml/mm4827a1.htm.

12. Murphy TV, Gargiullo PM, Massoudi MS, et al. Rotavirus Intussusception Investigation Team. Intussusception among infants given an oral rotavirus vaccine. *N Engl J Med* 2001;344(8):564–72. doi: 10.1056/NEJM200102223440804
13. Zanardi LR, Haber P, Mootrey GT, Niu MT, Wharton M. Intussusception among recipients of rotavirus vaccine: reports to the Vaccine Adverse Event Reporting System. *Pediatrics* 2001;107(6):E97. doi: 10.1542/peds.107.6.e97
14. Kramarz P, France EK, DeStefano F, et al. Population-based study of rotavirus vaccination and intussusception. *Pediatr Infect Dis J* 2001;20(4):410–16.
15. Leroy Z, Broder K, Menschik D. Febrile seizures after 2010–2011 influenza vaccine in young children, United States: a vaccine safety signal from the Vaccine Adverse Event Reporting System. *Vaccine*. 2012;30(11):2020–3. doi: 10.1016/j.vaccine.2011.12.042
16. Tse A, Tseng HF, Greene SK,Vellozzi C, Lee GM; VSD Rapid Cycle Analysis Influenza Working Group. Signal identification and evaluation for risk of febrile seizures in children following trivalent inactivated influenza vaccine in the Vaccine Safety Datalink Project, 2010–2011. *Vaccine* 2012;30:2024–31. doi: 10.1016/j.vaccine.2012.01.027
17. Duffy J, Weintraub E, Hambidge SJ, et al. Vaccine Safety Datalink. Febrile seizure risk after vaccination in children 6 to 23 months. *Pediatrics* 2016;138(1). doi: 10.1542/peds.2016-0320
18. CDC. Prevention and control of influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP)—United States, 2012–13 influenza season. *MMWR Morb Mortal Wkly Rep* 2011;61 (32):613–18. https://www.cdc.gov/mmWr/preview/mmwrhtml/mm6132a3.htm
19. Steering Committee on Quality Improvement and Management, Subcommittee on Febrile Seizures, American Academy of Pediatrics. Febrile seizures: clinical practice guideline for the long-term management of the child with simple febrile seizures. *Pediatrics* 2008;121(6):1281–6. doi: 10.1542/peds.2008-0939
20. Moro PL, Arana J, Cano M, et al. Postlicensure safety surveillance for high-dose trivalent inactivated influenza vaccine in the Vaccine Adverse Event Reporting System, 1 July 2010–31 December 2010.*Clin Infect Dis* 2012;54(11):1608–14. doi: 10.1093/cid/cis256
21. CDC. Addition of severe combined immunodeficiency as a contraindication for administration of rotavirus vaccine. *MMWR Morb Mortal Wkly Rep* 2010; 59(22):687–8. (https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5922a3.htm).
22. Bakare N, Menschik D, Tiernan R, Hua W, Martin D. Severe combined immunodeficiency (SCID) and rotavirus vaccination: reports to the Vaccine Adverse Events Reporting System (VAERS). *Vaccine*. 2010; 28(40):6609–12.
23. CDC. Safety of influenza A (H1N1) 2009 monovalent vaccines—United States, Oct. 1–Nov. 24, 2009 *MMWR Morb Mortal Wkly Rep* 2009; 58(48):1351–56. https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5848a4.htm
24. Hibbs BF, Moro PL, Lewis P, Miller ER, Shimabukuro TT. Vaccination errors reported to the Vaccine Adverse Event Reporting System, (VAERS) United States, 2000–2013. *Vaccine*. 2015;33(28):3171–8. doi: 10.1016/j.vaccine.2015.05.006
25. Haber P, Schembri CP, Lewis P, et al. Notes from the field: reports of expired live attenuated influenza vaccine being administered—United States, 2007–2014. *MMWR Morb Mortal Wkly Rep* 2014; 63(35):773. https://www.cdc.gov/Mmwr/preview/mmwrhtml/mm6335a3.htm
26. Hibbs BF, Miller ER, Shimabukuro T. Notes from the field: rotavirus vaccine administration errors—United States, 2006–2013. *MMWR Morb Mortal Wkly Rep* 2014;63(4):81. https://www.cdc.gov/Mmwr/preview/mmwrhtml/mm6304a4.htm
27. Su JR, Miller ER, Duffy J, Baer BM, Cano MV. Notes from the field: Administration Error Involving a Meningococcal Conjugate Vaccine—United States, March 1, 2010–September 22, 2015. *MMWR Morb Mortal Wkly Rep* 2016;65(6):161–2. https://www.cdc.gov/mmwr/volumes/65/wr/mm6506a4.htm

28. Institute of Medicine. Adverse effects of vaccines: evidence and causality. Stratton K, Ford A, Rusch E, Clayton EW, editors. Washington, DC: National Academies Press: 2011.
29. Rosenthal S, Chen R. The reporting sensitivities of two passive surveillance systems for vaccine adverse events. *Am J Public Health* 1995;85(12):1706–09. doi: 10.2105/AJPH.85.12.1706
30. Verstraeten T, Baughman AL, Cadwell B, Zanardi L, Haber P, Chen RT, Vaccine Adverse Event Reporting System Team. Enhancing vaccine safety surveillance: a capture-recapture analysis of intussusception after rotavirus vaccination. *Am J Epidemiol* 2001;154(11):1006–12. doi: 10.1093/aje/154.11.1006
31. Eberth JM, Kline KN, Moskowitz DA, Montealegre JR, Scheurer ME. The role of media and the Internet on vaccine adverse event reporting: a case study of human papillomavirus vaccination. *J Adolesc Health* 2014;54(3):289–95. doi: 10.1016/j.jadohealth.2013.09.005
32. McNeil MM, Li R, Pickering S, Real TM, Smith PJ, Pemberton MR. Who is unlikely to report adverse events after vaccinations to the Vaccine Adverse Event Reporting System (VAERS)? *Vaccine* 2013;31(24):2673–79.
33. Evans G. National Childhood Vaccine Injury Act: revision of the vaccine injury table. *Pediatrics* 1996;98(6):1179–81. doi: 10.1016/j.vaccine.2013.04.009
34. McNeil MM, Gee J, Weintraub ES, et al. The Vaccine Safety Datalink: successes and challenges monitoring vaccine safety. *Vaccine* 2014;32(42):5390–98. doi: 10.1016/j.vaccine.2014.07.073

This document can be found at: www.cdc.gov/vaccines/pubs/surv-manual/chpt21-surv-adverse-events.html

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EXHIBIT 296

Perspectives in Clinical Research

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Phase IV of Drug Development

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Abstract

Not all Phase IV studies are post-marketing surveillance (PMS) studies but every PMS study is a phase IV study. Phase IV is also an important phase of drug development. In particular, the real world effectiveness of a drug as evaluated in an observational, non-interventional trial in a naturalistic setting which complements the efficacy data that emanates from a pre-marketing randomized controlled trial (RCT). No matter how many patients are studied pre-marketing in a controlled environment, the true safety profile of a drug is characterized only by continuing safety surveillance through a spontaneous adverse event monitoring system and a post-marketing surveillance/non-interventional study. Prevalent practice patterns can generate leads that could result in further evaluation of a new indication via the RCT route or even a signal that may necessitate regulatory action (change in labeling, risk management/minimization action plan). Disease registries are another option as are the large simple hybrid trials. Surveillance of spontaneously reported adverse events continues as long as a product is marketed. And so Phase IV in that sense never ends.

Keywords: Non-interventional/observational, post-marketing safety surveillance, generalizability, effectiveness, real world

JUST as Phase I is sometimes referred to as the acid test of drug development (where the rubber meets the road), since it is the first time that the drug is being tested in humans, Phase IV may be considered as the real test since for the first time that the drug is tested in the real world.

Drug products are launched after regulatory authorities have scrutinized a vast amount of data from animal and clinical studies and found it to show that the drug is sufficiently effective and adequately safe in specified indications. The popular notion is that drugs are thoroughly studied before they are marketed, so that everything about the drug is known the time of launch. Few realize that while enough is known the time of launch to avoid calamities, catastrophes and disasters, a lot of the thorough knowledge that we

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have about well-established products is obtained after the drug has been marketed and hundreds of thousands of patients have been exposed to the product through commercial sales. This is so because of 3 primary reasons:

- It is not possible to study more than a few thousand patients in clinical trials. The economics of the pharmaceutical industry does not allow for more money and time to be spent on pre-launch development than is done currently. Anymore pre-launch spending would make drugs even more expensive than they are today and render them unmarketable and also delay its reach to patients.
- A lot of the additional knowledge about drugs comes from scientific, rather than commercial interest, through research done by individual workers in universities and research institutions and by groups of investigators with academic interest in the drug or in therapeutics. Generally, such studies are possible only after the drug receives regulatory approval and becomes commercially available.
- Some of the new knowledge about a drug is obtained by serendipity when doctors all over the world use the drug in a wide spectrum of patients, with varied ethnicity, various underlying diseases, and a range of concomitant medication.

RCTs are essential to prove efficacy or the fact that a drug works but are inevitably limited in generalizability as extrapolation of the results from RCTs can only be to patients included in the RCTs under controlled conditions (strict inclusion and exclusion criteria, drug provided free of cost, compliance monitored, etc). In the real world no patient can be excluded; even pregnant and lactating women, those with hepato-renal dysfunction, on multiple concomitant medications for concomitant clinical conditions must be treated. How the drug performs in such real world conditions is a test of its effectiveness. All studies conducted in a phase IV setting, i.e., after marketing authorization approval per label are called phase IV studies. Of these, those mandated by the regulatory authority to be conducted as observational studies in a naturalistic setting per label are called PMS studies.

Non-Interventional Studies (NIS)

By definition, an NIS is a study conducted to assess safety, tolerability and effectiveness of marketed medicines in clinical practice, i.e., in a naturalistic setting where choice of therapy is consistent with approved prescribing information (no study drug to be supplied) and in line with current practice at the study site; other aspects of patient-care, including clinical examinations, laboratory investigations, and the use of instrumentation, other invasive and non-invasive procedures are in consonance with current practice at the study site. The drug is prescribed per routine practice per label, the doctor's decision to prescribe precedes decision to enroll preferably by at least a month, there is no systematic assignment of treatment, there is no protocol (it is called an observational plan), informed consent essentially comprises a data privacy clause, there is no investigator indemnity, and there are no additional diagnostic tests or visits beyond what would anyway be done per usual practice. In the current scenario, NIS do not need regulatory approval but it is a good practice to register it on the Clinical Trials Registry of India (CTRI) website.

There is a mistaken perception that such studies are done only to increase sales. In fact since one is merely capturing actual use of the product there should be no real increase in sales. There is a debate on whether off-label use should be captured. If a company were to do such a study it may be wrongly perceived that company is trying to promote off- label prescribing. However the point is that it is only through knowledge of real world practice that sometimes new ways of using the product are discerned, e.g., a new route

(nimesulide per rectal as reported in Nise-PMS study), or new indication, e.g., low dose aspirin as an anti-platelet agent. The company should not use this data but instead apply to the regulator to do a formal study in this new indication. Thus medicine advances.

NIS thus allow information to be collected on the actual use of a particular drug. Usual clinical practice must always be adhered to in these studies and no additional diagnostic or monitoring procedures (i.e., additional visits) can be applied to the patients. Besides providing greater knowledge about drug effects, non-interventional studies can also be a good way of further mapping risks in the real world.

Large simple trial (LST)

It is a hybrid between a randomized clinical trial and an observational study (e.g., cohort study). A large number of participants are randomized to treatment groups, with follow-up per routine practice. Simple refers to the effort of enrolling physicians and participants and the objective is to interfere with routine practice as little as possible (Table 1). One example of such a study was the VOLUME study on Exubera (inhaled insulin) which was a requirement of US FDA as part of a risk management plan. In fact there is a school of thought that going forward regulators may insist on sponsors doing pre-marketing studies (phase III) that closely mimic the real world (instead of the typical RCTs which would be done in phase IIb – robust proof of efficacy) so that there is greater confidence of the drug's effectiveness prior to approval. This could minimize drug withdrawals but has the potential to delay launch of the drug. While an RCT maximizes validity but has limited generalizability, and an observational study has limited validity (depends on appropriateness of design and control for bias) but maximizes generalizability, a large simple trial maximizes validity and generalizability.

Post-Marketing Surveillance (PMS) Studies

Adverse reactions that occur in fewer than 1 in 3,000 – 5,000 patients are unlikely to be detected in Phase I – III investigational clinical trials, and may be unknown at the time a drug is approved. These rare adverse reactions are more likely to be detected when large numbers of patients are exposed to a drug after it has been approved and marketed.

Safety monitoring, nevertheless, is just one form of Post-PMS. Another is the planned collection of clinical data relating to the use of a drug through the conduct of PMS studies. These could be general, open studies where unlike pre-marketing studies, the selection of patients is not strictly defined by stringent inclusion and exclusion criteria, but governed by the permissible indications and contra-indications of the drug as stated in the text of prescribing information. This ensures that information is collected in a varied spectrum of patients, and makes it likely that the study will yield data that may not have been captured in Phase III studies.

PMS studies exemplify the difference between efficacy and effectiveness. Efficacy is judged within the controlled environment of a clinical trial with strict inclusion and exclusion criteria and close monitoring and ensured compliance. Effectiveness is the real test of a drug when it is used in a much larger population, with varied organ system function, concomitant drugs and where monitoring and compliance are not always ensured. In other words, a PMS study is a non-interventional study requested by regulatory authorities to verify the safety, tolerability and effectiveness of a marketed drug in a particular population per the locally approved label.

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Conducting such general, open-label PMS studies is a regulatory requirement in countries such as Japan and the Philippines. In India, PMS data used to be submitted to the Drugs Controller General of India (DCGI) within 2 years of launch. Now Periodic Safety Update Reports (PSURs) are filed at regular intervals as specified in the revised Schedule Y of the Drugs and Cosmetics Act. Most, other regulatory authorities, however, do not insist on PMS studies. Instead, in countries such as Germany, regulators may require a company to conduct controlled clinical studies under precisely defined enrollment criteria, to investigate specific concerns and gather information about the drug under specific conditions of use when there is a suspected problem.

The outcomes of such studies could be signals, pharmacoepidemiological information, need for controlled studies, labeling changes with modified undesirable effects section, indications and dosing schedules, and regulatory action (boxed warning, risk minimization action plan, withdrawal). Other phase IV studies could be RCTs, *in vitro* studies, outcomes research (burden of illness) and pharmacoeconomic studies, drug utilization studies, practical clinical trials, and investigator-initiated research in practice.

Adverse event monitoring

The number of patients one would need to observe to have a 95% chance of detecting 1, 2, or 3 cases of an adverse reaction at a given incidence of the reaction can be gauged from this table:[1]

It is evident from this that rare, but fatal side effects such as aplastic anaemia seen with chloramphenicol, or retinal damage with high dose chloroquine therapy can only be detected if there is a system of collecting adverse event information from customers once a drug has been marketed.

Safety monitoring continues for the life of a drug. Pharmaceutical companies with worldwide operations have established large global systems to track, investigate, and evaluate adverse drug events (Aes) for their products on a continuing basis and report them to regulatory authorities around the world. When a doctor fills up adverse event report (AER) form s/he is playing a vital role in this global endeavor. S/he is in effect a continuing surveillance source for products and shoulders responsibility for the safety of patients. The reporting of Aes helps the company evaluate them for relatedness and accordingly this may lead to change in labeling, if required.

Serious and unexpected suspected adverse reactions (SUSARs) are reported to regulatory authorities on a continual basis and non-serious ones are compiled and reported periodically.[2] Changes in prescribing information are undertaken by the company on the basis of these reports, either at the behest of regulatory authorities or, often, voluntarily. On occasion the drug may be withdrawn from the market.

Case-Control Studies

PMS studies conducted after the launch of a product are part of Phase IV development of the drug. Some of these studies may be retrospective case-control evaluations. These are done to evaluate rare suspected side effects. For example, when there was a suspicion that use of oral contraceptives may be associated with an increased incidence of thrombophlebitis (clotting of blood in the deep veins) and thromboembolism (blockage of smaller arteries due to detached blood clots) case-control studies were carried out. A group of cases of thromboembolism were compared with age matched controls that were as similar to the cases as possible, but without the disease. The fact that the rate of oral contraceptive

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consumption among the two groups did show a statistical difference indicated that oral contraceptive use is in fact associated with a 2-4 fold increase in incidence of embolic phenomena. Cohort and cross-sectional studies may also be done as part of comparative observational studies in pharmacovigilance planning.

Drug Utilisation Studies (DUS)[2]

Such studies describe how a drug is marketed, prescribed, and used in a population, and how these factors influence outcomes, including clinical, social, and economic outcomes.[3] These studies provide data on specific populations, such as the elderly, children, or patients with hepatic or renal dysfunction, often stratified by age, gender, concomitant medication, and other characteristics. DUS can be used to determine if a product is being used in these populations. From these studies denominator data can be developed for use in determining rates of adverse drug reactions. DUS have been used to describe the effect of regulatory actions and media attention on the use of drugs, as well as to develop estimates of the economic burden of the cost of drugs. DUS can be used to examine the relationship between recommended and actual clinical practice. These studies can help to determine whether a drug has the potential for drug abuse by examining whether patients are taking escalating dose regimens or whether there is evidence of inappropriate repeat prescribing. Important limitations of these studies can include a lack of clinical outcome data or information of the indication for use of a product.

Registry

A prospective observational study of patients with certain shared characteristics (e.g., particular disease, exposure, or risk factor) that collects ongoing and supporting data over time on well-defined outcomes of interest for analysis and reporting. Properly designed and executed, registries can provide a real-world view of clinical practice, patient outcomes, safety, and comparative effectiveness.

Conclusion

Thus, we find that product launch is merely a milestone in drug development, albeit an important one, rather than a mark of the end of the development process. Inevitably, however, the investments made late in Phase IV, usually a declining phase of the product life-cycle, are much smaller than commitments during the early growth phase. Not only have most of the important questions been answered but also the commercial interest in answering residual or newly emergent questions is low towards the end of the patent period and the potential commercial gains from use of new data are small in the face of emerging new therapies that have been designed to surpass the older agents. Commercial development of a drug in fact only ends with, or close to, the end of patent life. But surveillance of spontaneously reported AE continues as long as a product is marketed. And so Phase IV in that sense never ends.

References

1. Grahame-Smith DG, Aronson JK, editors. Oxford Textbook of Clinical Pharmacology. 2nd ed. Oxford University Press; 2004. p. 117. (reprinted), Chapter 9.

2. International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use (ICH) Guideline on Pharmacovigilance Planning, E2E. 2004 Nov 18th;

3. Strom BL, editor. Pharmacoepidemiology. 3rd ed. New York, NY: John Wiley and Sons, Ltd; 2002.

Figures and Tables

Table 1

Large Simple Trial

Open in a separate window

EXHIBIT 297

Morbidity and Mortality Weekly Report

Vaccination Coverage Among Children Aged 19–35 Months — United States, 2017

Holly A. Hill, MD, PhD[1]; Laurie D. Elam-Evans, PhD[1]; David Yankey, PhD[1]; James A. Singleton, PhD[1]; Yoonjae Kang, MPH[1]

The Advisory Committee on Immunization Practices (ACIP) recommends routine vaccination by age 24 months against 14 potentially serious illnesses (*1*). CDC used data from the 2017 National Immunization Survey-Child (NIS-Child) to assess vaccination coverage at national, state, territorial, and selected local levels among children aged 19–35 months in the United States. Coverage remained high and stable overall, exceeding 90% for ≥3 doses of poliovirus vaccine, ≥1 dose of measles, mumps, and rubella vaccine (MMR), ≥3 doses of hepatitis B vaccine (HepB), and ≥1 dose of varicella vaccine. Although the proportion of children who received no vaccine doses by age 24 months was low, this proportion increased gradually from 0.9% for children born in 2011 to 1.3% for children born in 2015. Coverage was lower for most vaccines among uninsured children and those insured by Medicaid, compared with those having private health insurance, and for children living outside of metropolitan statistical areas* (MSAs), compared with those living in MSA principal cities. These disparities could be reduced with greater awareness and use of the Vaccines for Children† (VFC) program, eliminating missed opportunities to vaccinate children during visits to health care providers, and minimizing interruptions in health insurance coverage.

The NIS-Child is a random-digit–dialed telephone (cellular and landline) survey of parents/guardians of children aged 19–35 months in the 50 states, the District of Columbia, selected local areas, and U.S. territories.§ NIS-Child coverage estimates are based on a provider-reported vaccination history. Interviewers request contact information for all the child's vaccination providers and permission to contact each provider to obtain vaccination records for that child. All identified providers are mailed an immunization history questionnaire to record dates and types of vaccines administered; data from responding providers are combined to create a synthesized vaccination history for each child. NIS-Child methods, including weighting procedures, have been described.¶ In 2017, the overall response rate** to the telephone interview portion of the survey was 26.1%. Adequate provider-reported vaccination data†† were available for 53.9% of children with a completed household interview, resulting in a sample size of 15,333 children. T-tests on weighted data were used to evaluate differences in coverage estimates by sociodemographic characteristics; differences were considered statistically significant for p-values <0.05. CDC assessed changes in survey accuracy, estimated components of difference between the 2016 and 2017 NIS-Child estimates, and estimated linear trends in vaccination coverage by month and year of birth using weighted linear regression.§§ No evidence for change in survey accuracy from 2016 to 2017 was detected (*2*).

2017 Vaccination Coverage

Coverage was >90% for vaccination with ≥3 doses of poliovirus vaccine (92.7%), ≥1 dose of MMR (91.5%), ≥3 doses of HepB (91.4%), and ≥1 dose of varicella vaccine (91.0%) (Table 1). Children were least likely to be up-to-date with ≥2 doses of hepatitis A vaccine (HepA) (59.7%), the combined 7-vaccine series¶¶ (70.4%), and rotavirus vaccination (73.2%). Coverage with HepB birth dose was also low (73.6%).

* MSA status was determined on the basis of household-reported city and county of residence and was grouped into three categories: MSA principal city, MSA nonprincipal city, and non-MSA. MSAs and principal cities were as defined by the U.S. Census Bureau (https://www.census.gov/geo/reference/gtc/gtc_cbsa.html). Non-MSA areas include urban populations not located within an MSA as well as completely rural areas.

† https://www.cdc.gov/vaccines/programs/vfc/index.html.

§ Estimates for states, selected local areas, and the territory of Guam are available online (https://www.cdc.gov/vaccines/imz-managers/coverage/childvaxview/data-reports/index.html). The local areas sampled separately for the 2017 NIS included areas that receive federal Section 317 immunization funds and are included in the NIS sample every year (Chicago, Illinois; New York, New York; Philadelphia County, Pennsylvania; Bexar County, Texas; and Houston, Texas) and three additional sample areas (El Paso County, Texas; Dallas County, Texas; and Travis County, Texas). The 2017 NIS-Child was also conducted in Guam, Puerto Rico, and U.S. Virgin Islands; however, data collection in Puerto Rico and U.S. Virgin Islands was suspended because of the severity of the 2017 hurricane season, resulting in insufficient data for estimation of vaccination coverage. National estimates in this report exclude all territories.

¶ Details regarding the statistical methodology of NIS-Child are available in the NIS-Child Data User's Guide 2016. https://www.cdc.gov/vaccines/imz-managers/nis/datasets.html.

** The Council of American Survey Research Organizations (CASRO) household response rate is calculated as the product of the resolution rate (percentage of the total telephone numbers called that were classified as nonworking, nonresidential, or residential), screening completion rate (percentage of known households that were successfully screened for the presence of age-eligible children), and the interview completion rate (percentage of households with one or more age-eligible children that completed the household survey). The CASRO household response rate is equivalent to the American Association for Public Opinion Research type 3 response rate. http://www.aapor.org/AAPOR_Main/media/publications/Standard-Definitions20169theditionfinal.pdf.

†† Children with at least one vaccination reported by a provider and those who had received no vaccinations were considered to have adequate provider data.

§§ https://www.cdc.gov/vaccines/imz-managers/coverage/childvaxview/pubs-presentations/NIS-vax-trends-2012-2016.html.

¶¶ The combined 7-vaccine series (4:3:1:3*:3:1:4) includes ≥4 doses of DTaP; ≥3 doses of poliovirus vaccine; ≥1 dose of measles-containing vaccine; ≥3 or ≥4 doses (depending upon product type) of Hib; ≥3 doses of Hep-B; ≥1 dose of varicella vaccine; and ≥4 doses of PCV.

TABLE 1. Estimated vaccination coverage among children aged 19–35 months, by selected vaccines and doses — National Immunization Survey-Child, United States, 2013–2017*

Vaccine/Dose	Survey year % (95% CI)				
	2013	2014	2015	2016	2017
DTaP†					
≥3 doses	94.1 (93.2–95.0)	94.7 (94.0–95.4)	95.0 (94.4–95.5)	93.7 (92.8–94.5)§	94.0 (93.3–94.7)
≥4 doses	83.1 (81.8–84.3)	84.2 (83.0–85.4)	84.6 (83.5–85.7)	83.4 (82.1–84.6)	83.2 (82.0–84.3)
Poliovirus (≥3 doses)	92.7 (91.6–93.6)	93.3 (92.5–94.1)	93.7 (93.0–94.3)	91.9 (90.9–92.9)§	92.7 (91.9–93.5)
MMR (≥1 dose)¶	91.9 (90.9–92.7)	91.5 (90.6–92.4)	91.9 (91.0–92.7)	91.1 (90.1–92.0)	91.5 (90.6–92.3)
Hib					
Primary series**	93.7 (92.7–94.5)	93.3 (92.5–94.1)	94.3 (93.7–94.9)	92.8 (91.8–93.6)§	92.8 (91.9–93.6)
Full series**	82.0 (80.7–83.3)	82.0 (80.7–83.2)	82.7 (81.5–83.8)	81.8 (80.5–83.0)	80.7 (79.4–82.0)
HepB					
≥3 doses	90.8 (89.7–91.7)	91.6 (90.7–92.4)	92.6 (91.9–93.3)	90.5 (89.3–91.5)§	91.4 (90.5–92.3)
Birth dose††	74.2 (72.8–75.7)§	72.4 (70.9–73.9)	72.4 (71.0–73.7)	71.1 (69.5–72.7)	73.6 (72.0–75.2)§
Varicella (≥1 dose)¶	91.2 (90.2–92.1)	91.0 (90.1–91.9)	91.8 (91.0–92.5)	90.6 (89.6–91.5)	91.0 (90.1–91.8)
PCV					
≥3 doses	92.4 (91.4–93.3)	92.6 (91.8–93.4)	93.3 (92.5–94.0)	91.8 (90.8–92.7)§	91.9 (90.9–92.8)
≥4 doses	82.0 (80.6–83.3)	82.9 (81.6–84.2)	84.1 (83.0–85.2)	81.8 (80.4–83.1)§	82.4 (81.1–83.6)
HepA					
≥1 dose	83.1 (81.9–84.3)§	85.1 (84.0–86.2)§	85.8 (84.7–86.8)	86.1 (84.9–87.2)	86.0 (84.8–87.1)
≥2 doses§§	54.7 (53.1–56.3)	57.5 (55.9–59.1)§	59.6 (58.1–61.0)	60.6 (59.1–62.2)	59.7 (58.2–61.3)
Rotavirus¶¶	72.6 (71.1–74.0)§	71.7 (70.1–73.2)	73.2 (71.8–74.6)	74.1 (72.6–75.5)	73.2 (71.6–74.7)
Combined 7-vaccine series***	70.4 (68.8–71.9)	71.6 (70.2–73.1)	72.2 (70.9–73.6)	70.7 (69.2–72.2)	70.4 (68.9–71.9)
No vaccinations	0.7 (0.5–1.1)	0.8 (0.6–1.0)	0.8 (0.6–1.0)	0.8 (0.6–1.0)	1.1 (0.9–1.4)§

Abbreviations: CI = confidence interval; DTaP = diphtheria, tetanus toxoids, and acellular pertussis vaccine; HepA = hepatitis A vaccine; HepB = hepatitis B vaccine; Hib = *Haemophilus influenzae* type b conjugate vaccine; MMR = measles, mumps, and rubella vaccine; PCV = pneumococcal conjugate vaccine.

* For 2013, children born during January 2010–May 2012; for 2014, children born during January 2011–May 2013; for 2015, children born during January 2012–May 2014; for 2016, children born during January 2013–May 2015; and for 2017, children born during January 2014–May 2016.

† Includes children who might have been vaccinated with diphtheria and tetanus toxoids vaccine or diphtheria, tetanus toxoids, and pertussis vaccine.

§ Statistically significant ($p<0.05$) change in coverage compared with previous survey year.

¶ Includes children who might have been vaccinated with measles, mumps, rubella, and varicella vaccine.

** Hib primary series: ≥2 or ≥3 doses, depending on product type received; full series includes primary series and booster dose, which includes receipt of ≥3 or ≥4 doses, depending on product type received.

†† One dose of HepB administered from birth through age 3 days.

§§ Estimates of ≥2 doses of HepA are likely underestimates because a child could be on schedule but not receive a second dose of HepA until age 41 months. This dose would not be collected by NIS-Child, which includes children aged 19–35 months only.

¶¶ Includes ≥2 doses of Rotarix monovalent rotavirus vaccine (RV1), or ≥3 doses of RotaTeq pentavalent rotavirus vaccine (RV5). The maximum age for the final rotavirus dose is 8 months, 0 days.

*** The combined 7-vaccine series (4:3:1:3*:3:1:4) includes ≥4 doses of DTaP, ≥3 doses of poliovirus vaccine, ≥1 dose of measles-containing vaccine, the full series of Hib (≥3 or ≥4 doses, depending on product type), ≥3 doses of HepB, ≥1 dose of varicella vaccine, and ≥4 doses of PCV.

Vaccination Coverage by Selected Characteristics

Coverage was lower (range = 2.6–6.9 percentage points) for children living in non-MSAs than among those living in MSA principal cities for most vaccines (Table 2). Children living in non-MSAs had a higher prevalence of having received no vaccinations (1.9%) compared with children in MSA principal cities (1.0%).

Coverage among children insured by Medicaid was lower (2.5–15.0 percentage points, depending on vaccine) than that among those with private insurance for all vaccines assessed except the HepB birth dose (Table 2). The same pattern was observed among uninsured children: coverage was substantially lower (14.7–30.3 percentage points) than that among those privately insured. Prevalence of uninsured children in the 2017 NIS-Child was 2.8%. This lower vaccination coverage among the uninsured, Medicaid-insured, and those living outside of MSAs was especially evident for diphtheria and tetanus toxoids and acellular pertussis vaccine (DTaP), the full series of *Haemophilus influenzae* type b conjugate vaccine (Hib), and pneumococcal conjugate vaccine (PCV), that require a booster dose in the second year of life. In addition, the proportion of uninsured children who had received no vaccinations (7.1%) was higher than that among those with private insurance (0.8%). The proportion of unvaccinated children was similar among children insured by Medicaid and those with private insurance. Among unvaccinated children in the 2017 NIS-Child, 17.2% were uninsured.

Differences in vaccination coverage by race/ethnicity and poverty status in 2017 were similar to those observed in previous years (Supplementary Table 1, https://stacks.cdc.gov/view/cdc/59414) (*3*). Vaccination coverage also varied by state (Supplementary Table 2, https://stacks.cdc.gov/view/

TABLE 2. Estimated vaccination coverage among children aged 19–35 months, by selected vaccines and doses, metropolitan statistical area (MSA) status,* and health insurance status† — National Immunization Survey-Child, United States, 2017§

	MSA status % (95% CI)			Health insurance status % (95% CI)			
Vaccine/Dose	MSA, principal city (referent) (n = 6,689)	MSA, non-principal city (n = 5,846)	Non-MSA (n = 2,798)	Private only (referent) (n = 8,536)	Any Medicaid (n = 5,714)	Other insurance (n = 644)	Uninsured (n = 439)
DTaP¶							
≥3 doses	94.6 (93.4–95.6)	94.1 (92.9–95.0)	91.6 (89.1–93.6)**	96.5 (95.7–97.2)	92.6 (91.2–93.8)**	93.7 (90.7–95.8)**	78.2 (71.3–83.8)**
≥4 doses	85.0 (83.3–86.5)	82.6 (80.6–84.5)	78.1 (74.9–80.9)**	86.9 (85.2–88.5)	80.8 (78.9–82.5)**	83.6 (79.3–87.2)	62.4 (55.0–69.1)**
Poliovirus (≥3 doses)	93.2 (91.9–94.4)	92.9 (91.7–93.9)	90.1 (87.4–92.2)**	95.2 (94.3–96.0)	91.2 (89.6–92.5)**	92.7 (89.5–95.0)	77.9 (71.0–83.6)**
MMR†† (≥1 dose)	92.5 (91.2–93.6)	90.9 (89.3–92.3)	89.9 (88.0–91.6)**	93.7 (92.3–94.8)	90.4 (89.1–91.6)**	91.0 (87.5–93.6)	74.6 (67.5–80.6)**
Hib							
Primary series§§	93.4 (92.2–94.5)	92.6 (91.1–93.9)	91.2 (88.7–93.2)	95.5 (94.6–96.2)	91.1 (89.5–92.5)**	92.2 (88.8–94.7)**	78.0 (71.1–83.7)**
Full series§§	81.6 (79.6–83.4)	80.7 (78.6–82.7)	77.3 (74.1–80.2)**	85.1 (83.2–86.9)	77.7 (75.6–79.7)**	78.8 (73.8–83.1)**	62.0 (54.6–68.9)**
HepB							
≥3 doses	92.6 (91.3–93.7)	90.4 (88.7–91.9)**	90.7 (88.8–92.3)	93.3 (91.9–94.4)	90.4 (88.8–91.7)**	92.5 (89.4–94.7)	78.6 (71.8–84.1)**
Birth dose¶¶	73.6 (71.1–76.0)	72.8 (70.3–75.1)	76.6 (73.6–79.3)	73.0 (70.9–75.0)	74.7 (72.0–77.2)	71.8 (66.2–76.8)	68.7 (61.9–74.8)
Varicella†† (≥1 dose)	92.3 (91.0–93.4)	90.4 (88.7–91.8)	88.3 (86.2–90.1)**	92.9 (91.5–94.1)	90.4 (89.1–91.6)**	91.3 (88.0–93.8)	69.5 (62.2–76.0)**
PCV							
≥3 doses	92.2 (90.5–93.6)	91.9 (90.4–93.2)	90.6 (88.0–92.6)	94.5 (92.9–95.7)	90.5 (88.9–91.8)**	91.0 (87.6–93.5)**	75.2 (67.9–81.2)**
≥4 doses	83.6 (81.7–85.4)	82.0 (79.9–84.0)	79.1 (75.9–81.9)**	87.6 (85.8–89.3)	78.9 (76.8–80.8)**	81.3 (76.8–85.2)**	59.0 (51.6–66.1)**
HepA							
≥1 dose	87.2 (85.3–88.9)	85.7 (83.9–87.4)	82.5 (80.1–84.6)**	88.1 (86.5–89.6)	85.3 (83.5–87.0)**	86.1 (81.7–89.5)	63.3 (55.7–70.3)**
≥2 doses	61.1 (58.7–63.4)	59.2 (56.7–61.6)	56.5 (53.3–59.7)**	63.2 (61.0–65.2)	57.7 (55.2–60.2)**	61.1 (55.2–66.7)	35.7 (29.1–42.9)**
Rotavirus* **	73.8 (71.3–76.2)	73.3 (70.7–75.7)	70.5 (67.3–73.6)	81.8 (79.8–83.6)	66.8 (64.2–69.4)**	67.4 (61.0–73.3)**	51.5 (44.2–58.7)**
**Combined 7-vaccine series††† **	71.9 (69.7–74.1)	69.8 (67.4–72.2)	66.8 (63.6–69.9)**	76.0 (73.9–77.9)	66.5 (64.1–68.9)**	69.2 (63.6–74.2)**	48.5 (41.2–55.8)**
No vaccinations	1.0 (0.7–1.3)	1.1 (0.8–1.5)	1.9 (1.3–2.7)**	0.8 (0.6–1.1)	1.0 (0.7–1.4)	—§§§	7.1 (4.6–10.8)**

Abbreviations: CI = confidence interval; DTaP = diphtheria and tetanus toxoids and acellular pertussis vaccine; HepA = hepatitis A vaccine; HepB = hepatitis B vaccine; Hib = *Haemophilus influenzae* type b conjugate vaccine; MMR = measles, mumps, and rubella vaccine; PCV = pneumococcal conjugate vaccine.

* MSA status was determined on the basis of household-reported county and city of residence and was grouped into three categories: MSA principal city, MSA nonprincipal city, and non-MSA. MSA and principal city were as defined by the U.S. Census Bureau (https://www.census.gov/geo/reference/gtc/gtc_cbsa.html). Non-MSA areas include urban populations not located within an MSA as well as completely rural areas.

† Children's health insurance status was reported by parent or guardian. "Other insurance" includes the Children's Health Insurance Program, military insurance, coverage via the Indian Health Service, and any other type of health insurance not mentioned elsewhere.

§ Children in the 2017 National Immunization Survey-Child were born during January 2014–May 2016.

¶ Includes children who might have been vaccinated with diphtheria and tetanus toxoids vaccine or diphtheria, tetanus toxoids, and pertussis vaccine.

** Statistically significant ($p<0.05$) difference compared with the referent group.

†† Includes children who might have been vaccinated with measles, mumps, rubella, and varicella vaccine.

§§ Hib primary series: ≥2 or ≥3 doses, depending on product type received; full series includes primary series and booster dose, which includes receipt of ≥3 or ≥4 doses, depending on product type received.

¶¶ One dose of HepB administered from birth through age 3 days.

*** Includes ≥2 or ≥3 doses, depending on product type received (≥2 doses for Rotarix [RV1] or ≥3 doses for RotaTeq [RV5]).

††† The combined 7-vaccine series (4:3:1:3*:3:1:4) includes ≥4 doses of DTaP, ≥3 doses of poliovirus vaccine, ≥1 dose of measles-containing vaccine, the full series of Hib (≥3 or ≥4 doses, depending on product type of vaccine), ≥3 doses of HepB, ≥1 dose of varicella, and ≥4 doses of PCV.

§§§ Estimate not available because the 95% CI was ≥20.

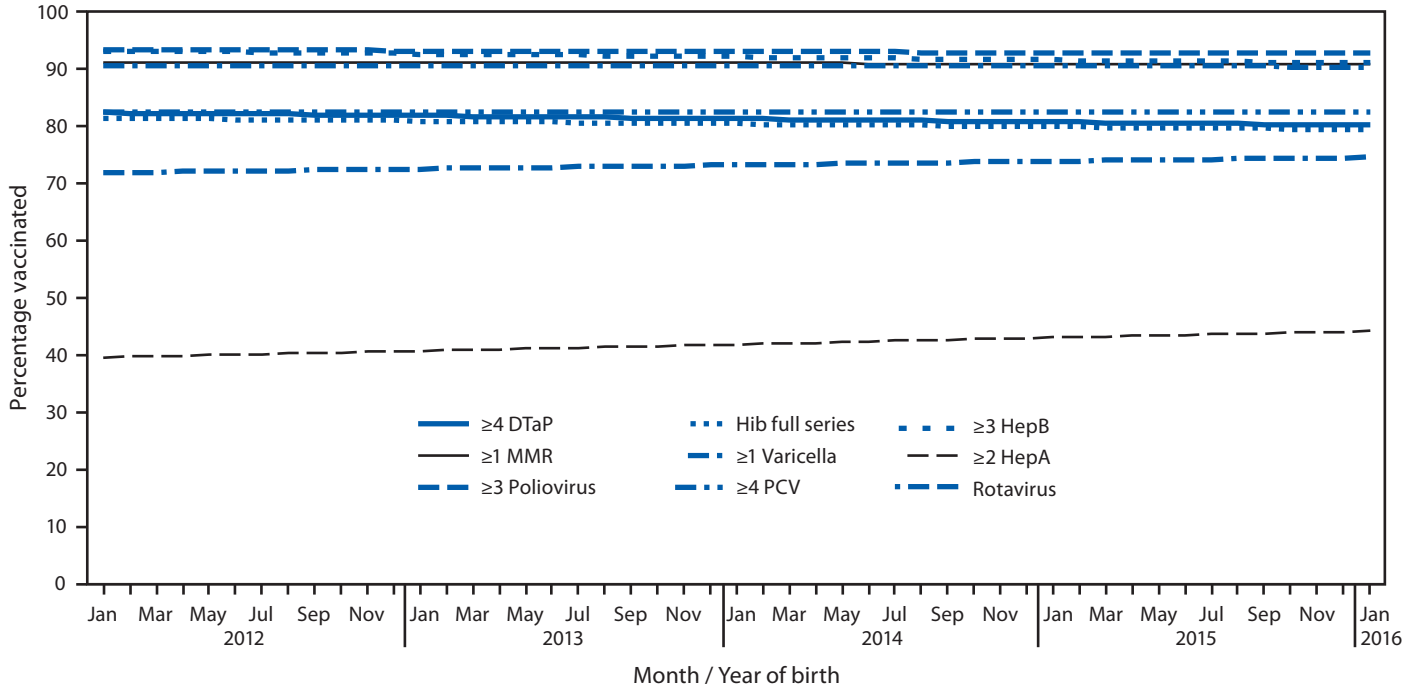
cdc/59415). For example, estimated rotavirus coverage ranged from 64.7% in California to 85.1% in Rhode Island. Coverage with MMR ranged from 85.8% in Missouri to 98.3% in Massachusetts; MMR coverage was <90% for 11 states in 2017.

Trends in Vaccination Coverage

Coverage by month and year of birth remained stable during January 2012–January 2016 for most vaccines (Figure) (*2*). Coverage by age 2 years over 12 consecutive birth months declined by 0.5 percentage points for ≥3 HepB doses and increased by 1.1 percentage points for ≥2 HepA doses (*2*). Coverage with ≥2 HepA doses was higher by age 35 months than by age 24 months (e.g., 75.3% versus 39.6% for children born January 2012) (*2*).

HepB birth dose coverage was higher in 2017 (73.6%) than in 2016 (71.1%) (Table 1). Analysis of trends in HepB birth dose coverage by month and year of birth during January 2012–May 2016 indicated no change in coverage, although an increasing trend was estimated for more recent births (January 2014–May 2016) (*2*). The percentage of unvaccinated

FIGURE. Estimated linear trend in coverage with selected vaccines* by age 24 months,† by month and year of birth§ — National Immunization Survey-Child, United States, 2013–2017



Abbreviations: CI = confidence interval; DTaP = diphtheria, tetanus toxoids, and acellular pertussis vaccine; HepA = hepatitis A vaccine; HepB = hepatitis B vaccine; Hib = *Haemophilus influenzae* type b conjugate vaccine; MMR = measles, mumps, and rubella vaccine; PCV = pneumococcal conjugate vaccine.

* Hib full series: ≥3 or ≥4 doses, depending on product type received (primary series and booster dose). Rotavirus: ≥2 or ≥3 doses, depending on product type received (≥2 doses for Rotarix [RV1] or ≥3 doses for RotaTeq [RV5]).

† Except for rotavirus, vaccination coverage was assessed before the child reached his/her 24-month birthday. The Kaplan-Meier method was used to account for censoring vaccination status for children assessed before age 24 months. Rotavirus vaccination was assessed before the child reached his/her 8-month birthday.

§ Estimated linear relationship between month and year of birth and vaccination coverage, based on weighted linear regression analysis using the inverse of the estimated variance of each point estimate to construct the weights. Estimated percentage point change over 12 birth months: ≥4 DTaP -0.55 (95% CI = -1.20 to 0.10); ≥3 poliovirus -0.17 (-0.52 to 0.18); ≥1 MMR -0.11 (-0.58 to 0.35); Hib full series -0.51 (-1.13 to 0.11); ≥3 HepB -0.53 (-0.97 to -0.09); ≥1 varicella -0.05 (-0.53 to 0.42); ≥4 PCV 0.0 (-0.69 to 0.68); ≥2 HepA 1.13 (0.30 to 1.97); rotavirus 0.68 (-0.09 to 1.45).

children increased from 0.8% in 2016 to 1.1% in 2017. By annual birth cohort, the percentage of children with no vaccinations by age 2 years increased from 0.9% for children born in 2011 to 1.3% (47,700 children) for those born in 2015 (Supplementary Figure, https://stacks.cdc.gov/view/cdc/59413), representing an additional 18,400 unvaccinated children.

Discussion

Overall vaccination coverage among young children remained high and stable in the United States in 2017. However, the findings from this survey highlight several opportunities for improvement. Coverage was lower for most vaccines among uninsured and Medicaid-insured children and among children living outside of MSAs. These disparities were larger for vaccines that require a booster dose in the second year of life (e.g., DTaP, Hib, and PCV). Although the number of children who have received no vaccinations by age 24 months has been gradually increasing, most children are still routinely vaccinated. Continued evaluation of prevalence and reasons for nonvaccination is needed, as are improvements in access to and delivery of age-appropriate vaccinations to all children. CDC continues to examine barriers to early childhood vaccination, including assessing obstacles to and parents' experiences with accessing vaccination services.

Vaccination coverage differences by insurance status are concerning, given that children insured by Medicaid and uninsured children are eligible for the VFC program, which was designed to remove financial barriers by providing free vaccines to program participants. However, other issues, such as unfamiliarity with the VFC program and how to access it, transportation, child care, and convenience of clinic hours might also need to be addressed if the goals of this important element of the immunization safety net are to be fully realized. Lack of geographic proximity to vaccination providers, including those who participate in the VFC program, can be a barrier to vaccination. The shortage of health care providers, especially pediatricians, might partially explain the lower coverage among children living in rural areas (*4*).

Vaccination coverage could be increased and sociodemographic and geographic disparities reduced with increased administration of all recommended vaccines during provider visits. A study of potentially achievable coverage estimated that 90% coverage would have been attained many years ago for the recommended number of doses of DTaP, PCV, and Hib for children aged 19–35 months if missed opportunities for administration of the final doses of these vaccines had been eliminated (*5*). Reducing missed opportunities would promote timely receipt of all recommended vaccine doses and decrease the amount of time that children remain vulnerable to vaccine-preventable diseases.

The percentage of children who have received no vaccines has increased, reaching 1.3% for children born in 2015, compared with 0.3% among those 19–35 months when surveyed in 2001 (*6*). Some children might be unvaccinated because of choices made by parents, whereas for others, lack of access to health care or health insurance might be factors. Unvaccinated children in the 2017 NIS-Child were disproportionately uninsured: 17.2% of unvaccinated children were uninsured, compared with 2.8% of all children. Evidence-informed strategies addressing parents' decisions about vaccinating their children could focus on both programs and individual patients, such as vaccine delivery through school programs, strong recommendations by providers to parents to vaccinate their children, and reinforcement of the importance of community protection through vaccination (*7*).

Variation in coverage by health insurance and MSA status and the increasing percentage of unvaccinated children raise concerns about possible pockets of susceptibility in which children are not as well protected as national coverage estimates might indicate. Measles was declared eliminated from the United States in 2000, yet outbreaks caused by imported cases continue to occur each year; 118 measles cases were reported in 2017 (https://www.cdc.gov/measles/cases-outbreaks.html) (*8*). The continued occurrence of measles outbreaks in the United States underscores the need to ensure high MMR coverage among all young children.

The findings in this report are subject to at least two limitations. First, low response rates and lack of access to phoneless households could result in selection bias, which might persist even with application of survey weights designed to minimize such bias. Second, vaccination histories might be incomplete if not all providers were identified or some of those identified chose not to participate. Bias in vaccination coverage estimates has been evaluated in a sensitivity analysis accounting for these potential errors, with results indicating underestimation of actual vaccination coverage by 4 to 5 percentage points (*9*).

Vaccination coverage among young children could be improved through higher participation by both children and providers in the Vaccines for Children program. Consistent access to health insurance is another important element of the immunization safety net. Barriers to participation in the VFC program should be identified and eliminated so that all eligible children have the opportunity to access recommended vaccines. A number of evidence-based strategies have also been described that could enhance these efforts to increase vaccination coverage, such as notifying parents when children are due for a vaccination, establishing standing orders or policies that allow nonphysician personnel to administer vaccines, and enhancing computerized immunization information systems for tracking vaccinations (https://www.thecommunityguide.org/topic/vaccination) (*10*). Continued vaccination coverage assessment using the NIS-Child can guide efforts to improve vaccination coverage and protect children from vaccine-preventable diseases and better understand the low but increasing prevalence of nonvaccination.

Summary

What is already known about this topic?

The Advisory Committee on Immunization Practices recommends routine vaccination by age 24 months against 14 potentially serious illnesses.

What is added by this report?

In 2017, coverage with most recommended vaccines among children aged 19–35 months remained stable and high but was lower in more rural areas and among uninsured or Medicaid-insured children. A small but increasing proportion of children received no vaccines by age 24 months.

What are the implications for public health practice?

Collaboration with state immunization programs, eliminating missed immunization opportunities, and minimizing interruptions in insurance coverage are important to understand and address coverage disparities among children eligible for the Vaccines for Children program and those in rural areas.

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References

1. Robinson CL, Romero JR, Kempe A, Pellegrini C; Advisory Committee on Immunization Practices (ACIP) Child/Adolescent Immunization Work Group. Advisory Committee on Immunization Practices recommended immunization schedule for children and adolescents aged 18 years or younger—United States, 2017. MMWR Morb Mortal Wkly Rep 2017;66:134–5. PubMed https://doi.org/10.15585/mmwr.mm6605e1

2. CDC. Evaluating vaccination coverage trends with the National Immunization Survey-Child (NIS-Child), 2013–2017, United States. Atlanta, GA: US Department of Health and Human Services, CDC; 2018. https://www.cdc.gov/vaccines/imz-managers/coverage/childvaxview/pubs-presentations/NIS-vax-trends-2013-2017.html
3. Hill HA, Elam-Evans LD, Yankey D, Singleton JA, Kang Y. Vaccination coverage among children age 19–35 months—United States, 2016. MMWR Morb Mortal Wkly Rep 2017;66:1171–7. PubMed https://doi.org/10.15585/mmwr.mm6643a3
4. Shipman SA, Lan J, Chang CH, Goodman DC. Geographic maldistribution of primary care for children. Pediatrics 2011;127:19–27. PubMed https://doi.org/10.1542/peds.2010-0150
5. Zhao Z, Smith PJ, Hill HA. Evaluation of potentially achievable vaccination coverage with simultaneous administration of vaccines among children in the United States. Vaccine 2016;34:3030–6. PubMed https://doi.org/10.1016/j.vaccine.2016.04.097
6. Smith PJ, Chu SY, Barker LE. Children who have received no vaccines: who are they and where do they live? Pediatrics 2004;114:187–95. PubMed https://doi.org/10.1542/peds.114.1.187
7. MacDonald NE, Butler R, Dubé E. Addressing barriers to vaccine acceptance: an overview. Hum Vaccin Immunother 2018;14:218–24. PubMed https://doi.org/10.1080/21645515.2017.1394533
8. Hall V, Banerjee E, Kenyon C, et al. Measles outbreak—Minnesota April–May 2017. MMWR Morb Mortal Wkly Rep 2017;66:713–7. PubMed https://doi.org/10.15585/mmwr.mm6627a1
9. Wolter KM, Pineau VJ, Skalland B, et al. Total survey error assessment for sociodemographic subgroups in the 2012 U.S. National Immunization Survey. In: Biemer PP, de Leew E, Eckman S, Edwards B, Kreuter F, Lyberg LE, eds. Total survey error in practice. New York, NY: John Wiley and Sons; 2017.
10. Murthy N, Rodgers L, Pabst L, Fiebelkorn AP, Ng T. Progress in childhood vaccination data in immunization information systems—United States, 2013–2016. MMWR Morb Mortal Wkly Rep 2017;66:1178–81. PubMed https://doi.org/10.15585/mmwr.mm6643a4

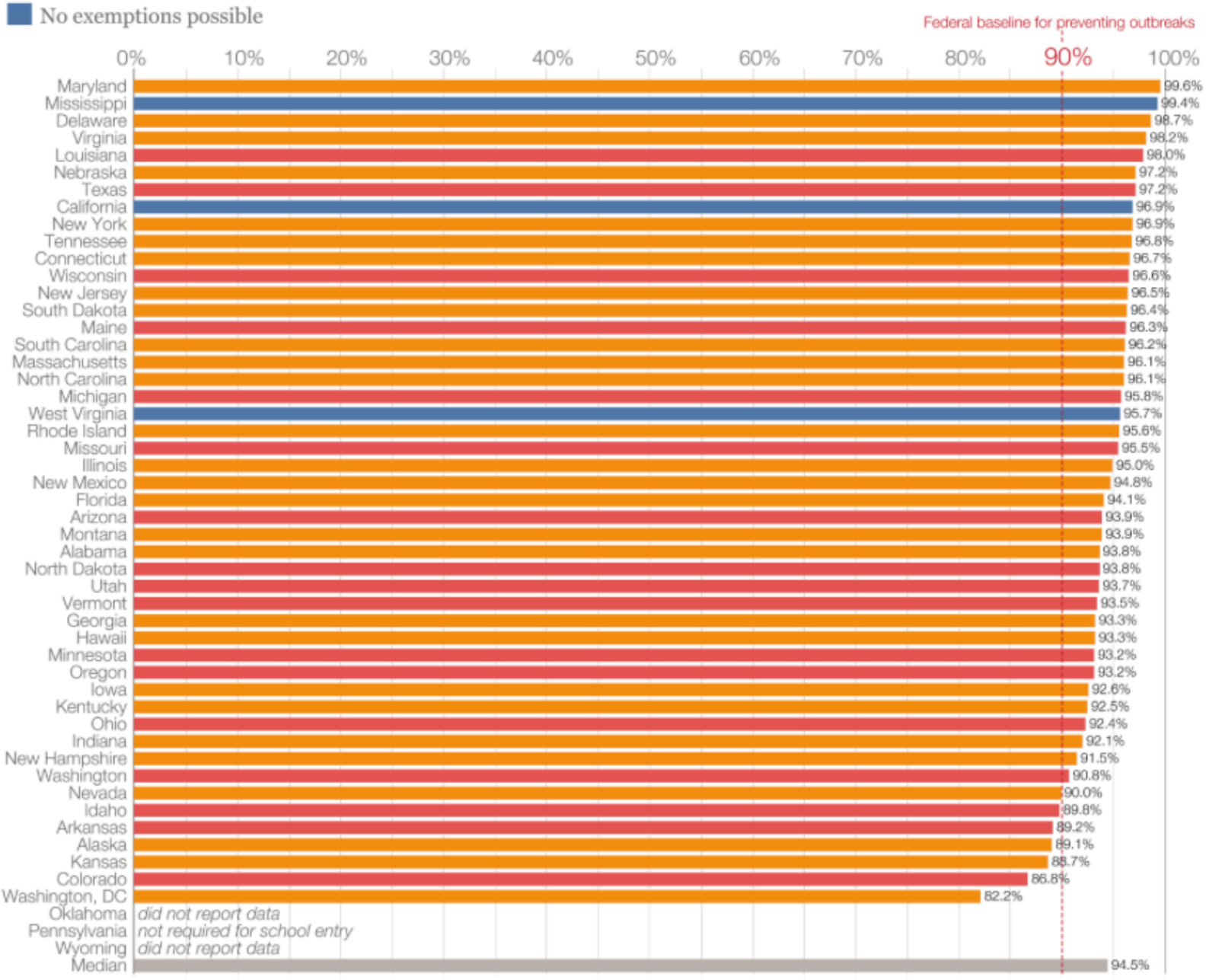
EXHIBIT 298

Vaccination coverage of children, by US state in 2016/17

Our World in Data

Share of kindergarten children covered with five doses against Diphtheria Tetanus, and Pertussis.
The color of the bar indicates which exemptions from the required vaccination are possible:

- Religious and philosophical exemptions possible
- Only religious exemption possible
- No exemptions possible



Data: Vaccination coverage: *School Vaccination Assessment Report*, 2016-17 school year; National Center for Immunization and Respiratory Diseases. Estimated vaccination coverage with five doses of Childhood Diphtheria toxoid, Tetanus toxoid, acellular Pertussis (DTaP) vaccination for kindergartners (typical age range: 4–6 years).
Exemptions: Immunization Action Coalition – *Exemptions Permitted for State Immunization Requirements*; LexisNexis; StateNet 2017

The data visualization is available at OurWorldinData.org. There you find research and more visualizations on this topic.

EXHIBIT 299

WebMD

Most Parents Confident About Vaccine Safety

A Few Rely on Vaccine Advice From Celebrities, Study Shows

By Denise Mann

FROM THE WEBMD ARCHIVES

April 18, 2011 -- Two new studies seek to better understand parents' attitudes about vaccine safety and analyze potential barriers to routine childhood vaccination. The new reports appear in a special vaccine safety supplement in journal *Pediatrics*.

There has been some concern about vaccine safety and risks in recent years due in part to the increasing number of recommended vaccines, conflicting safety information, and a widely publicized study suggesting that certain vaccines may increase risk for autism. This study was publically refuted, but it has had lasting repercussions on some parent's attitudes about vaccine safety. As a result, there has been some concern about a possible resurgence of vaccine-preventable diseases such as measles.

In one report, the majority of parents with at least one child aged 6 or younger believe that vaccines are important for their children's health and they were "confident" or "very confident" in vaccine safety. Overall, 93.4% said that their youngest child had received or would receive all the recommended vaccines. But parents did express some concerns about pain from the shots, too many vaccines during one visit, and fever.

About one in five parents were not confident about the safety and importance of childhood vaccines.

"In general, the study results are very reassuring," says study author Allison Kennedy, MPH, an epidemiologist at the CDC in Atlanta. "Overall, parents had high confidence in vaccine safety and most plan to fully vaccinate their child, but we also saw that parents did have questions and some concerns even if they were planning to fully vaccinate their children."

The main source of information on childhood immunization and vaccine safety in this study was the pediatrician and/or nurse.

1 2 View All < > NEXT PAGE

WebMD

Most Parents Confident About Vaccine Safety

CONTINUED

A Few Rely on Vaccine Advice From Celebrities, Study Shows

FROM THE WEBMD ARCHIVES

Discuss Concerns With Pediatrician

Doctors can help ease some of these concerns by explaining to parents why vaccines are bunched together, as well providing information on vaccine-preventable illnesses, she says.

“They can also tell parents what to look for after the shots and how to manage those issues as well,” she says.

“Pain is a concern, and we can’t tell if it is a deal breaker or not, but there are comfort measures that parents can take,” says another of the study's researchers, Kristine Sheedy, MPH, associate director of communication science for the CDC’s National Center for Immunization and Respiratory Diseases.

For example, breastfeeding, sweet-tasting liquid, pacifiers, distraction, and the use of local numbing agents may reduce pain and crying among infants getting vaccinated.

Despite some backlash, “at a national level, we have maintained record-high immunization rates and the number of children who are completely unvaccinated remains below 1%,” Sheedy says. “There are challenges in various pockets, but we are fortunately doing OK nationwide.”

Parents Take Celebrities' Advice on Vaccine Safety

In a second study, researchers found that while parents tend to place a lot of trust in their child's doctor when it comes to vaccine safety information; they sometimes also give credence non-health professionals, including celebrities.

Celebrities were trusted a lot for vaccine safety information by 2% of study participants and not at all by 76% of the participants.

“Ideally, physicians should have the best and most reliable vaccine information for parents, and they have an obligation to have the facts about vaccine safety at their disposal,” says study author Gary Freed, MD, MPH, a pediatrician at the University of Michigan Health System in Ann Arbor.

Importantly, “celebrities discuss their own anecdotal experiences and should not be viewed as credible, true scientific sources,” he says. “It is dangerous when people who are not experts in a field are seen as experts."

“Parents will get misinformation, disinformation, and incorrect information, which may result in them making bad decisions for their children and leaving them unprotected against life-threatening but preventable diseases,” he says.

WebMD Health News | Reviewed by Laura J. Martin, MD on April 18, 2011

Sources
SOURCES:
Allison Kennedy, MPH, epidemiologist, CDC, Atlanta, Ga.
Kristine Sheedy, MPH, associate director, communication science, National Center for Immunization and Respiratory Diseases, CDC, Atlanta.
Gary Freed, MD, MPH, pediatrician, University of Michigan Hearth System, Ann Arbor.
Freed, G. *Pediatrics supplement*, 2011.
Kennedy, A. *Pediatrics supplement*, 2011.

EXHIBIT 300

ftp.cdc.gov - /pub/Health_Statistics/NCHS/Datasets/nis/

[To Parent Directory]

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CDC Centers for Disease Control and Prevention

National Immunization Surveys

Datasets and Related Documentation for the National Immunization Survey - Child, 2009 and Prior

2009

- Readme File [TXT – 9 KB]
- Data User's Guide [PDF – 2.1 MB]
- Household Interview Questionnaire [PDF – 706 KB]
- Provider-Immunization History Questionnaire [PDF – 229 KB]
- Data Documentation, Codebook and Frequencies [PDF – 1.6 MB]
- Dataset [DAT – 21.9 MB]
- SAS Input Statements [SAS – 70 KB]
- R Input Statements [R – 91 KB]

2008

- Readme File [TXT – 8 KB]
- Data User's Guide [PDF – 8.5 MB]
- Data Documentation, Codebook and Frequencies [PDF – 7 MB]
- Dataset [DAT – 21.5 MB]
- SAS Input Statements [SAS – 65 KB]
- R Input Statements [R – 84 KB]

2007

- Readme File [TXT – 9 KB]
- Data User's Guide [PDF – 12 MB]
- Data Documentation, Codebook and Frequencies [PDF – 11 MB]
- Dataset [ZIP – 3.3 MB]
- SAS Input Statements [SAS – 63 KB]
- R Input Statements [R – 74 KB]

2006

- Readme File [TXT – 8 KB]
- Data User's Guide [PDF – 2.7 MB]
- Data Documentation, Codebook and Frequencies [PDF – 7.4 MB]

- Dataset [ZIP – 4.7 MB]
- SAS Input Statements [SAS – 60 KB]

2005

- Readme File [TXT – 8 KB]
- Data User's Guide [PDF – 3.7 MB]
- Data Documentation, Codebook and Frequencies [PDF – 595 KB]
- Dataset [ZIP – 3.3 MB]
- SAS Input Statements [SAS – 57 KB]

2004

- Readme File [TXT – 16 KB]
- Data User's Guide [PDF – 669 KB]
- Data Documentation, Codebook and Frequencies [PDF – 352 KB]
- Dataset [ZIP – 2.8 MB]
- SAS Input Statements [SAS – 49 KB]

2003

- Readme File [TXT – 16 KB]
- Data User's Guide [PDF – 2.6 MB]
- Data Documentation, Codebook and Frequencies [PDF – 3.2 MB]
- Dataset [ZIP – 2.7 MB]
- SAS Input Statements [SAS – 49 KB]

2002

- Readme File [TXT – 16 KB]
- Data User's Guide [PDF – 2.1 MB]
- Data Documentation, Codebook and Frequencies [PDF – 1.2 MB]
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- SAS Input Statements [SAS – 45 KB]

2001

- Readme File [TXT – 16 KB]
- Data User's Guide [PDF – 455 KB]
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2000

- Readme File [TXT – 15 KB]
- Data User's Guide [PDF – 588 KB]
- Data Documentation, Codebook and Frequencies [PDF – 242 KB]
- Dataset [ZIP – 2.6 MB]
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1999

- Readme File [TXT – 15 KB]
- Data User's Guide [PDF – 789 KB]
- Data Documentation, Codebook and Frequencies [PDF – 841 KB]
- Dataset [ZIP – 3.4 MB]
- SAS Input Statements [SAS – 62 KB]

1998

- Readme File [TXT – 15 KB]
- Data User's Guide [PDF – 518 KB]
- Data Documentation, Codebook and Frequencies [PDF – 421 KB]
- Dataset [ZIP – 2.9 MB]
- SAS Input Statements [SAS – 51 KB]

1997

- Readme File [TXT – 15 KB]
- Data User's Guide [PDF – 741 KB]
- Data Documentation, Codebook and Frequencies [PDF – 323 KB]
- Dataset [ZIP – 2.8 MB]
- SAS Input Statements [SAS – 57 KB]

1996

- Readme File [TXT – 15 KB]
- Data User's Guide [PDF – 384 KB]
- Data Documentation, Codebook and Frequencies [PDF – 233 KB]
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1995

- Readme File [TXT – 15 KB]
- Data User's Guide [PDF – 325 KB]
- Data Documentation, Codebook and Frequencies [PDF – 221 KB]
- SAS Input Statements [SAS – 35 KB]

EXHIBIT 301

MMWR Weekly
September 5, 2008 / 57(35);961-966

National, State, and Local Area Vaccination Coverage Among Children Aged 19--35 Months --- United States, 2007

The National Immunization Survey (NIS) provides vaccination coverage estimates among children aged 19--35 months for each of the 50 states and selected urban areas.* This report describes the results of the 2007 NIS, which provided coverage estimates among children born during January 2004--July 2006. *Healthy People 2010* established vaccination coverage targets of 90% for each of the vaccines included in the combined 4:3:1:3:3:1† vaccine series and a target of 80% for the combined series (*1*). Findings from the 2007 NIS indicated that ≥90% coverage was achieved for most of the routinely recommended vaccines (*2*). The majority of parents were vaccinating their children, with less than 1% of children receiving no vaccines by age 19--35 months. The coverage level for the 4:3:1:3:3:1 series remained steady at 77.4%, compared with 76.9% in 2006. Among states and local areas, substantial variability continued, with estimated vaccination coverage ranging from 63.1% to 91.3%. Coverage remained high across all racial/ethnic groups and was not significantly different among racial/ethnic groups after adjusting for poverty status. However, for some vaccines, coverage remained lower among children living below the poverty level compared with children living at or above the poverty level. Maintaining high vaccination coverage and continued attention to reducing current poverty disparities is needed to limit the spread -preventable diseases and ensure that children are protected.

To collect vaccination information on age-eligible children (i.e., those aged 19--35 months), NIS uses a quarterly, random-digit--dialing sample of telephone numbers for each survey area. When respondents grant permission to contact providers, the telephone interview is followed by a mail survey of the children's vaccination providers to validate immunization information. NIS methodology, including how the responses are weighted to represent the population of children aged 19--35 months, has been described previously (*3*). During 2007, the household response rate (*4*) was 64.9%; a total of 17,017 children with provider-verified vaccination records were included in this report, representing 68.6% of all children with completed household interviews. Statistical analyses were conducted using t-tests. Differences were considered statistically significant at $p<0.05$. A poverty status variable§ was added to the logistic regression models to control for racial/ethnic differences among children living at or above the poverty level and children living

below the poverty level. This report describes coverage levels for vaccines that have been included in the routine childhood vaccination schedule recommended by the Advisory Committee on Immunization Practices (ACIP) since 2000 or before (*2*).

In 2007, national coverage with the 4:3:1:3:3:1 series was 77.4%; this coverage has been stable since 2004. Coverage with the combined 4:3:1:3:3:1:4 vaccine series (i.e., the 4:3:1:3:3:1 series plus ≥4 doses of 7-valent pneumococcal conjugate vaccine [PCV7]) is being reported for the first time and was 66.5%. National coverage was ≥90% for each of the vaccines included in the 4:3:1:3:3:1 series except for ≥4 doses of DTaP (84.5%); coverage with ≥3 doses of DTaP was 95.5% (Table 1). Coverage with ≥1 dose of varicella vaccine (VAR) reached 90% for the first time. VAR coverage among American Indian/Alaska Native (AI/AN)[¶] children increased significantly, from 85.4% in 2006 to 94.9% in 2007. National vaccination coverage estimates for PCV7 continued to increase, from 86.9% in 2006 to 90.0% in 2007 for ≥3 doses and from 68.4% to 75.3% for ≥4 doses. Among AI/AN children, coverage with the fourth dose of PCV7 increased significantly, from 62.7% to 80.4%.

Substantial differences were observed in vaccination coverage among states and local areas (Table 2). Estimated coverage for the 4:3:1:3:3:1 series ranged from 91.3% in Maryland to 63.1% in Nevada. Among the 14 local areas included in the 2007 NIS, coverage with the 4:3:1:3:3:1 series ranged from 82.2% in Philadelphia, Pennsylvania, to 69.6% in San Bernardino, California.

Vaccination coverage levels were higher among AI/ANs compared with whites for measles, mumps, and rubella (MMR) vaccine, hepatitis B (HepB) vaccine, and VAR (Table 3). Coverage with the fourth dose of DTaP and the fourth dose of PCV7 among black children was not significantly lower than white children after controlling for poverty status. Vaccination coverage with the fourth dose of DTaP and the fourth dose of PCV7 was lower among children living below the poverty level compared with children living at or above the poverty level, but this difference declined from 6.1% in 2006 to 4.8% in 2007 for ≥4 doses of DTaP and from 9.4% in 2006 to 3.5% in 2007 for ≥4 doses of PCV7. Vaccination coverage levels were similar across all racial/ethnic groups for the 4:3:1:3:3:1 series. Coverage differed for this series among children living at or above the poverty level compared with children living below the poverty level, but this difference declined from 4.9% in 2006 to 3.2% in 2007. Coverage between white and black children with the 4:3:1:3:3:1:4 series was not significantly different after controlling for poverty status.

Reported by: *N Darling, MPH, M Kolasa, MPH, KG Wooten, MA, Immunization Svcs Div, National Center for Immunization and Respiratory Diseases, CDC.*

Editorial Note:

NIS is the only population-based, provider-verified survey to provide national, state, and local area estimates of vaccination coverage among children aged 19--35 months. The results of the 2007 survey indicate that vaccination coverage for vaccines recommended routinely by ACIP since 2000 and before (*2*) reached record high levels. Improvements in vaccination coverage for VAR meant that national coverage estimates for all individual vaccines in the 4:3:1:3:3:1 series were ≥90%, except coverage with ≥4 doses of DTaP. Coverage with ≥4 doses of PCV7 also was <90%. However, 3-dose coverage for both DTaP and PCV7 remained high. Coverage with ≥4 doses of PCV7 increased significantly to 75.3% in 2007, a substantial increase since PCV7 was first recommended in 2000 (*5*). However, coverage with ≥4 doses of DTaP has not changed during the past 5 years. Increasing coverage for the fourth dose of DTaP and the fourth dose of PCV7 would improve national coverage for the 4:3:1:3:3:1 series and the 4:3:1:3:3:1:4 series, which will be used to

monitor the *Healthy People 2010* immunization objectives beginning with 2009 NIS data. The vaccine shortage that ended in September 2004 (*6*) might have reduced coverage with the fourth dose of PCV7 among children in the 2007 NIS cohort (i.e., those born during January 2004--July 2006). Use of effective interventions, such as parent and provider reminder/recall, reducing out-of-pocket costs, increasing access to vaccination, and multicomponent interventions that include education might further improve overall coverage in areas where coverage is low (*7*). In addition, closing the coverage gap between areas with the highest and lowest coverage remains a priority. To achieve this, further collaborative efforts among CDC, state immunization coordinators, immunization programs, and other entities are essential.

Vaccination coverage among AI/AN children for VAR, MMR vaccine, and the fourth dose of PCV7 increased significantly in 2007 compared with 2006; in 2007, coverage levels among AI/AN children were higher for two of these vaccines (VAR and MMR vaccine) compared with white children. Improved exchange of data between the Indian Health Service information system and state immunization information systems and implementation of evidence-based strategies such as reminder/recall at Indian Health Service and tribal facilities, might have contributed to these increases in vaccination coverage (A. Groom, CDC, personal communication, August 2008). However, further monitoring is needed to determine whether these levels will be sustained.

As in 2006, the results of the 2007 NIS indicate that differences in poverty status accounted for the observed differences in coverage between white and black children for the fourth dose of DTaP and fourth dose of PCV7. In 2007, these differences in coverage between children living at or above the poverty level compared with children living below the poverty level were reduced by one percentage point for DTaP and by nearly six percentage points for PCV7. Continued efforts are needed to improve vaccination coverage among children of all racial and ethnic groups living below the poverty level.

The 2007 NIS results confirm that the majority of parents are vaccinating their children, with less than 1% of children receiving no vaccines by age 19--35 months. Although vaccination coverage in this age group remains high, recent outbreaks of measles have occurred in certain communities (*8*). Several factors might explain this apparent paradox. Despite record high coverage with MMR vaccine, nearly 8% of children aged 19--35 months surveyed for the 2007 NIS remained unvaccinated. Measles is highly contagious, and clustering of unimmunized children within geographic areas can increase risk for measles and other vaccine-preventable disease transmission. Clusters of unimmunized children might not be detected by NIS methods and might not be visible in national and state rates. Furthermore, any changes in vaccination behaviors among parents of children born after July 2006 would not have been detected by the 2007 survey. Increased attention to parental concerns about vaccine safety has become apparent in recent years (*9*). The 2008 NIS is collecting information on parental concerns about vaccine safety to better assess parental attitudes and beliefs about vaccines. In addition, CDC and its partners are developing new educational materials that can assist parents in making fully informed decisions about immunizing their children.**

The findings in this report are subject to at least three limitations. First, NIS is a telephone survey, and statistical adjustments might not compensate fully for nonresponse and households without landline telephones. Second, underestimates of vaccination coverage might have resulted from the exclusive use of provider-verified vaccination histories because completeness of these records is unknown. Finally, although national coverage estimates are precise, annual estimates and trends for state and local areas should be interpreted with caution because of smaller sample sizes and wider confidence intervals.

Achieving and maintaining high vaccination coverage levels is important to further reduce the burden of vaccine-preventable diseases and prevent a resurgence of measles and other diseases that have been

eliminated in the United States (*10*). Although vaccination coverage estimates were at record highs and above the *Healthy People 2010* target for most of the routinely recommended vaccines in 2007, ongoing efforts through partnerships among national, state, local, private, and public entities are needed to sustain these levels and ensure that vaccination programs in the United States remain strong.

Acknowledgments

The findings in this report are based, in part, on contributions by PJ Smith, PhD, Immunization Svcs Div, and BP Bell, MD, Office of the Director, National Center for Immunization and Respiratory Diseases, CDC.

References

1. US Department of Health and Human Services. Healthy people 2010 (conference ed, in 2 vols). Washington, DC: US Department of Health and Human Services; 2000. Available at http://www.healthypeople.gov/document/html/objectives/14-24.htm.
2. CDC. Recommendations and guidelines: 2008 child & adolescent immunization schedules for persons aged 0--6 years, 7--18 years, and catch-up schedule. Atlanta, GA: US Department of Health and Human Services, CDC; 2008. Available at http://www.cdc.gov/vaccines/recs/schedules/child-schedule.htm.
3. CDC. Statistical methodology of the National Immunization Survey, 1994--2002. Vital Health Stat 2005;2(138). Available at http://www.cdc.gov/nchs/data/series/sr_02/sr02_138.pdf.
4. Ezzati-Rice TM, Frankel MR, Hoaglin DC, Loft JD, Coronado VG, Wright RA. An alternative measure of response rate in random-digit-dialing surveys that screen for eligible subpopulations. J Econ Soc Meas 2000;26:99--109.
5. CDC. Preventing pneumococcal disease among infants and young children: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2000;49(No. RR-9).
6. CDC. Pneumococcal conjugate vaccine shortage resolved. MMWR 2004; 53:851--2.
7. Briss PA, Rodewald LE, Hinman AR, et al. Reviews of evidence regarding interventions to improve vaccination coverage in children, adolescents, and adults. The Task Force on Community Preventive Services. Am J Prev Med 2000;18:97--140.
8. CDC. Update: measles---United States, January--July 2008. MMWR 2008;57:893--6.
9. Cooper LZ, Larsen HJ, Katz SL. Protecting public trust in immunization. Pediatrics 2008;122:149--53.
10. CDC. Measles---United States, January 1--April 25, 2008. MMWR 2008; 57:494--8.

* Fourteen local areas were sampled separately for the 2007 NIS. These included six areas that receive federal immunization grant funds and are included in the NIS sample every year (District of Columbia; Chicago, Illinois; New York, New York; Philadelphia County, Pennsylvania; Bexar County, Texas; and Houston, Texas); seven previously sampled areas (Alameda County, California; Los Angeles County, California; San Bernardino County, California; Miami-Dade County, Florida; Marion County, Indiana; Dallas County, Texas; and El Paso County, Texas); and one area sampled for the first time (western Washington). Local areas sampled in the NIS might change yearly as state immunization programs target local assessments where they are most needed.

† ≥4 doses of diphtheria, tetanus toxoid, and any acellular pertussis vaccine, which can include diphtheria and tetanus toxoid vaccine or diphtheria, tetanus toxoid, and pertussis vaccine (DTaP); ≥3 doses of poliovirus vaccine; ≥1 dose of measles, mumps, and rubella vaccine; ≥3 doses of *Haemophilus influenzae* type b vaccine; ≥3 doses of hepatitis B vaccine; and ≥1 dose of varicella vaccine).

§ Poverty status was based on 2006 U.S. Census poverty thresholds (available at http://www.census.gov/hhes/www/poverty.html).

¶ For this report, persons identified as white, black, Asian, or American Indian/Alaska Native are all non-Hispanic. Persons identified as Hispanic might be of any race.

** Additional information available at http://www.cdc.gov/vaccines.

Table 1

TABLE 1. Estimated vaccination coverage among children aged 19–35 months, by selected vaccines and dosages — National Immunization Survey, United States, 2003–2007

Vaccine	2003* %	2003* (95% CI††)	2004† %	2004† (95% CI)	2005§ %	2005§ (95% CI)	2006¶ %	2006¶ (95% CI)	2007** %	2007** (95% CI)
DTP/DT/DTaP§§										
≥3 doses	96.0	(±0.5)	95.9	(±0.5)	96.1	(±0.5)	95.8	(±0.5)	95.5	(±0.5)
≥4 doses	84.8	(±0.8)	85.5	(±0.8)	85.7	(±0.9)	85.2	(±0.9)	84.5	(±0.9)
Poliovirus	91.6	(±0.7)	91.6	(±0.7)	91.7	(±0.7)	92.8	(±0.6)	92.6	(±0.7)
MMR¶¶ ≥1 dose	93.0	(±0.6)	93.0	(±0.6)	91.5	(±0.7)	92.3	(±0.6)	92.3	(±0.7)
Hib*** ≥3 doses	93.9	(±0.6)	93.5	(±0.6)	93.9	(±0.6)	93.4	(±0.6)	92.6	(±0.7)
Hepatitis B ≥3 doses	92.4	(±0.6)	92.4	(±0.6)	92.9	(±0.6)	93.3	(±0.6)	92.7	(±0.7)
Varicella ≥1 dose	84.8	(±0.8)	87.5	(±0.7)	87.9	(±0.8)	89.2	(±0.7)	90.0	(±0.7)
PCV7†††										
≥3 doses	68.1	(±1.0)	73.2	(±1.0)	82.8	(±1.0)	86.9	(±0.8)	90.0	(±0.8)
≥4 doses	35.8	(±1.0)	43.4	(±1.1)	53.7	(±1.3)	68.4	(±1.1)	75.3	(±1.2)
Combined series										
4:3:1§§§	82.2	(±0.9)	83.5	(±0.9)	83.1	(±1.0)	83.1	(±0.9)	82.8	(±1.0)
4:3:1:3¶¶¶	81.3	(±0.9)	82.5	(±0.9)	82.4	(±1.0)	82.1	(±1.0)	81.8	(±1.0)
4:3:1:3:3****	79.4	(±0.9)	80.9	(±0.9)	80.8	(±1.0)	80.5	(±1.0)	80.1	(±1.0)
4:3:1:3:3:1††††	72.5	(±1.0)	76.0	(±1.0)	76.1	(±1.1)	76.9	(±1.0)	77.4	(±1.1)
4:3:1:3:3:1:4§§§§	30.8	(±1.0)	38.4	(±1.1)	47.2	(±1.3)	60.1	(±1.2)	66.5	(±1.3)
Children who received no vaccinations	0.4	(±0.1)	0.4	(±0.2)	0.4	(±0.1)	0.4	(±0.1)	0.6	(±0.2)

* Born during January 2000–July 2002.
† Born during January 2001–July 2003.
§ Born during February 2002–July 2004.
¶ Born during January 2003–June 2005 (2006 estimates based on National Immunization Survey dataset, which was rereleased on February 25, 2008, after correcting for Hispanic overcount in nine states).
** Born during January 2004–July 2006.
†† Confidence interval.
§§ Diphtheria, tetanus toxoids and pertussis vaccines, diphtheria and tetanus toxoids, and diphtheria, tetanus toxoids, and any acellular pertussis vaccine.
¶¶ Measles, mumps, and rubella vaccine.
*** *Haemophilus influenzae* type b (Hib) vaccine.
††† 7-valent pneumococcal conjugate vaccine (PCV7).
§§§ ≥4 doses of DTaP, ≥3 doses of poliovirus vaccine, and ≥1 dose of any measles-containing vaccine.
¶¶¶ 4:3:1 plus ≥3 doses of Hib vaccine.
**** 4:3:1:3 plus ≥3 doses of hepatitis B vaccine.
†††† 4:3:1:3:3 plus ≥1 dose of varicella vaccine.
§§§§ 4:3:1:3:3:1: plus ≥4 doses of PCV7.

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Table 2

TABLE 2. Estimated vaccination coverage for the 4:3:1:3:3:1* and 4:3:1:3:3:1:4† vaccination series and selected individual vaccines among children aged 19–35 months, by state and selected local areas — National Immunization Survey, United States, 2007§

State/Area	≥4 DTaP¶		≥1 MMR**		≥1 VAR††		≥4 PCV7§§		4:3:1:3:3:1		4:3:1:3:3:1:4	
	%	(95% CI¶¶)	%	(95% CI)	%	(95% CI)	%	(95% CI)	%	(95% CI)	%	(95% CI)
United States	84.5	(±0.9)	92.3	(±0.7)	90.0	(±0.7)	75.3	(±1.2)	77.4	(±1.1)	66.5	(±1.3)
Alabama	85.4	(±5.2)	95.0	(±2.8)	92.0	(±4.5)	79.6	(±5.7)	78.2	(±6.3)	67.3	(±7.0)
Alaska	81.7	(±5.6)	89.7	(±4.1)	80.5	(±6.0)	80.9	(±6.0)	70.1	(±6.8)	64.4	(±7.3)
Arizona	85.4	(±5.7)	89.0	(±4.8)	86.0	(±5.4)	76.8	(±6.6)	75.2	(±6.7)	66.1	(±7.3)
Arkansas	78.8	(±5.8)	92.5	(±3.1)	89.2	(±4.2)	65.4	(±6.4)	72.3	(±6.2)	57.4	(±6.5)
California	84.9	(±4.0)	94.6	(±2.4)	93.2	(±2.6)	78.8	(±4.8)	77.1	(±4.7)	67.7	(±5.4)
Alameda County	83.1	(±5.4)	91.6	(±4.4)	89.6	(±4.5)	80.7	(±5.7)	76.3	(±5.8)	69.4	(±6.2)
Los Angeles County	84.0	(±5.3)	95.8	(±2.8)	93.9	(±3.3)	74.8	(±6.2)	78.0	(±5.9)	65.0	(±6.7)
San Bernardino County	74.8	(±6.2)	90.3	(±4.3)	89.8	(±4.4)	68.6	(±6.4)	69.6	(±6.5)	57.5	(±6.8)
Rest of state	86.4	(±5.8)	94.7	(±3.5)	93.5	(±3.8)	81.3	(±7.1)	77.4	(±7.0)	69.7	(±8.1)
Colorado	82.1	(±7.0)	91.2	(±4.5)	88.9	(±5.9)	70.7	(±8.7)	78.0	(±7.8)	64.3	(±9.1)
Connecticut	91.1	(±4.4)	95.3	(±2.8)	94.2	(±3.3)	88.8	(±4.9)	86.8	(±5.0)	81.2	(±5.9)
Delaware	86.9	(±4.5)	94.8	(±3.3)	92.1	(±3.8)	77.3	(±6.2)	80.3	(±5.7)	68.6	(±6.7)
District of Columbia	85.1	(±5.6)	95.2	(±3.3)	94.0	(±3.5)	77.5	(±6.2)	81.6	(±5.9)	71.0	(±6.7)
Florida	85.0	(±5.2)	92.3	(±4.1)	90.2	(±4.4)	66.1	(±6.7)	80.3	(±5.5)	61.8	(±6.8)
Miami-Dade County	86.0	(±5.0)	95.4	(±3.0)	90.8	(±4.5)	61.2	(±7.3)	76.1	(±6.3)	53.8	(±7.4)
Rest of state	84.9	(±6.0)	91.8	(±4.8)	90.1	(±5.1)	67.0	(±7.8)	81.0	(±6.4)	63.2	(±7.9)
Georgia	85.5	(±5.2)	91.4	(±4.2)	91.6	(±4.1)	75.5	(±6.7)	79.6	(±6.0)	65.9	(±7.2)
Hawaii	90.6	(±3.8)	93.8	(±3.7)	95.5	(±2.6)	80.7	(±5.8)	87.5	(±4.5)	77.4	(±6.1)
Idaho	77.2	(±6.3)	86.1	(±5.2)	75.5	(±6.4)	66.6	(±7.2)	65.6	(±7.2)	52.9	(±7.6)
Illinois	81.6	(±4.2)	93.1	(±2.7)	88.7	(±3.4)	76.0	(±4.5)	73.5	(±4.8)	65.8	(±5.0)
City of Chicago	78.2	(±6.4)	89.5	(±4.7)	88.8	(±4.2)	69.0	(±6.7)	71.0	(±6.7)	60.6	(±6.8)
Rest of state	82.7	(±5.2)	94.4	(±3.2)	88.7	(±4.4)	78.5	(±5.6)	74.4	(±6.0)	67.6	(±6.3)
Indiana	80.3	(±4.4)	90.4	(±3.3)	88.3	(±3.5)	70.4	(±5.2)	74.0	(±4.6)	61.8	(±5.3)
Marion County	80.8	(±5.2)	87.5	(±4.6)	86.0	(±4.6)	75.0	(±5.7)	71.4	(±5.9)	63.2	(±6.3)
Rest of state	80.2	(±5.2)	91.0	(±3.9)	88.8	(±4.2)	69.4	(±6.1)	74.5	(±5.4)	61.5	(±6.3)
Iowa	83.0	(±5.9)	93.0	(±3.8)	88.2	(±4.6)	72.3	(±6.6)	75.9	(±6.3)	64.2	(±6.9)
Kansas	87.0	(±4.9)	93.1	(±3.5)	88.7	(±4.1)	75.0	(±6.2)	76.0	(±6.0)	64.8	(±6.8)
Kentucky	85.2	(±5.8)	90.8	(±4.6)	87.9	(±5.1)	69.7	(±6.5)	78.2	(±6.2)	63.3	(±6.7)
Louisiana	80.1	(±5.9)	92.9	(±3.4)	91.5	(±3.7)	76.0	(±6.0)	77.0	(±6.1)	66.9	(±6.9)
Maine	86.7	(±5.4)	90.2	(±4.8)	85.5	(±5.3)	82.5	(±5.6)	72.9	(±6.9)	67.0	(±7.2)
Maryland	94.8	(±2.4)	97.1	(±2.0)	96.8	(±1.9)	84.4	(±5.9)	91.3	(±3.1)	79.9	(±6.2)
Massachusetts	90.0	(±5.0)	93.3	(±4.6)	87.4	(±5.6)	85.1	(±6.3)	77.9	(±7.3)	76.0	(±7.4)
Michigan	84.3	(±6.1)	89.5	(±5.3)	89.5	(±5.3)	71.1	(±7.4)	78.8	(±6.7)	66.9	(±7.5)
Minnesota	88.9	(±4.7)	94.9	(±2.8)	89.1	(±4.7)	82.1	(±6.2)	80.5	(±6.1)	72.8	(±6.9)
Mississippi	81.0	(±6.8)	87.2	(±5.8)	88.4	(±5.6)	65.8	(±7.8)	77.1	(±7.0)	61.2	(±7.9)
Missouri	80.6	(±6.5)	89.0	(±5.2)	89.4	(±5.0)	73.7	(±7.0)	76.1	(±6.9)	64.7	(±7.5)
Montana	79.1	(±5.8)	89.6	(±4.0)	78.5	(±5.8)	70.7	(±6.7)	65.3	(±6.9)	58.0	(±7.0)
Nebraska	87.8	(±5.3)	94.0	(±3.7)	93.8	(±3.8)	80.5	(±6.5)	82.9	(±6.0)	74.4	(±7.1)
Nevada	71.4	(±7.3)	86.3	(±4.9)	83.3	(±5.5)	61.7	(±7.5)	63.1	(±7.6)	50.7	(±7.5)
New Hampshire	94.4	(±3.5)	96.6	(±2.6)	95.2	(±3.1)	87.3	(±5.3)	90.6	(±4.3)	80.5	(±6.2)
New Jersey	85.3	(±5.9)	91.2	(±5.5)	92.5	(±4.8)	69.3	(±7.8)	80.5	(±6.4)	62.3	(±7.9)
New Mexico	81.6	(±7.0)	90.6	(±3.6)	88.8	(±3.9)	72.0	(±7.6)	76.0	(±7.2)	65.4	(±7.7)
New York	88.9	(±2.9)	93.6	(±2.1)	88.4	(±3.2)	75.1	(±4.5)	77.8	(±4.1)	65.2	(±4.9)
City of New York	84.7	(±4.5)	91.9	(±3.2)	89.0	(±3.9)	73.4	(±5.4)	76.3	(±5.3)	64.4	(±6.0)
Rest of state	92.8	(±3.8)	95.2	(±2.6)	87.8	(±5.1)	76.7	(±7.2)	79.1	(±6.3)	65.9	(±7.6)
North Carolina	85.8	(±5.0)	96.9	(±2.0)	93.3	(±4.1)	81.7	(±5.6)	77.3	(±6.5)	70.1	(±7.0)
North Dakota	85.5	(±4.9)	95.2	(±2.9)	91.5	(±3.8)	81.4	(±5.5)	77.2	(±5.7)	68.9	(±6.3)
Ohio	86.6	(±4.9)	90.7	(±3.7)	89.1	(±4.1)	74.7	(±6.0)	77.7	(±5.8)	64.5	(±6.5)
Oklahoma	82.7	(±6.0)	89.9	(±5.0)	89.7	(±5.0)	58.3	(±7.8)	78.5	(±6.3)	53.3	(±7.7)
Oregon	77.8	(±7.3)	88.9	(±5.3)	84.2	(±6.3)	70.1	(±7.5)	70.5	(±7.6)	62.7	(±7.8)
Pennsylvania	86.4	(±3.6)	93.8	(±2.5)	91.9	(±2.8)	79.1	(±4.4)	78.8	(±4.3)	68.3	(±4.9)
Philadelphia County	88.3	(±5.4)	92.2	(±4.5)	91.8	(±4.4)	81.2	(±6.5)	82.2	(±6.2)	73.0	(±7.3)
Rest of state	86.0	(±4.2)	94.1	(±2.8)	92.0	(±3.2)	78.8	(±5.1)	78.2	(±4.9)	67.5	(±5.7)
Rhode Island	84.9	(±6.1)	94.7	(±3.9)	92.1	(±4.1)	90.7	(±4.4)	75.0	(±7.0)	69.2	(±7.4)
South Carolina	84.2	(±4.5)	92.5	(±3.2)	91.5	(±3.3)	80.8	(±4.8)	79.5	(±5.0)	74.9	(±5.3)
South Dakota	88.7	(±4.5)	95.0	(±2.4)	85.3	(±5.2)	54.3	(±7.4)	76.9	(±6.1)	45.8	(±7.4)

* Includes ≥4 doses of diphtheria, tetanus toxoid, and any acellular pertussis vaccine (DTaP) (also can include diphtheria and tetanus toxoid vaccine or diphtheria, tetanus toxoid, and pertussis vaccine); ≥3 doses of poliovirus vaccine; ≥1 dose of any measles-containing vaccine; ≥3 doses of *Haemophilus influenzae* type b vaccine; ≥3 doses of hepatitis B vaccine; and ≥1 dose of varicella vaccine.
† 4:3:1:3:3:1 plus ≥4 doses of 7-valent pneumococcal conjugate vaccine (PCV7).
§ Children in the 2007 National Immunization Survey were born during January 2004–July 2006.
¶ ≥4 doses of DTaP.
** ≥1 dose of measles, mumps, and rubella vaccine.
†† ≥1 dose of varicella vaccine at or after child's first birthday.
§§ ≥3 doses of PCV7.
¶¶ Confidence interval.

TABLE 2. (*Continued*) Estimated vaccination coverage for the 4:3:1:3:3:1* and 4:3:1:3:3:1:4† vaccination series and selected individual vaccines among children aged 19–35 months, by state and selected local areas — National Immunization Survey, United States, 2007§

State/Area	≥4 DTaP¶ %	(95% CI¶¶)	≥1 MMR** %	(95% CI)	≥1 VAR†† %	(95% CI)	≥4 PCV7§§ %	(95% CI)	4:3:1:3:3:1 %	(95% CI)	4:3:1:3:3:1:4 %	(95% CI)
Tennessee	84.8	(±6.0)	94.5	(±4.3)	92.3	(±4.7)	72.6	(±7.5)	78.7	(±6.7)	64.3	(±7.7)
Texas	82.1	(±3.5)	90.4	(±2.6)	90.0	(±2.6)	75.7	(±4.0)	77.3	(±3.8)	68.5	(±4.4)
Bexar County	85.5	(±4.8)	90.9	(±3.9)	88.8	(±4.3)	79.1	(±5.5)	80.1	(±5.3)	74.0	(±5.8)
City of Houston	77.9	(±5.6)	89.4	(±3.8)	89.6	(±3.8)	71.6	(±5.9)	73.0	(±5.7)	64.1	(±6.2)
Dallas County	77.0	(±6.0)	89.9	(±4.1)	90.0	(±4.1)	70.8	(±6.3)	71.9	(±6.2)	61.0	(±6.8)
El Paso County	81.8	(±5.7)	90.3	(±4.8)	91.1	(±4.7)	69.3	(±6.9)	77.4	(±6.2)	63.1	(±7.1)
Rest of state	83.4	(±5.1)	90.6	(±3.8)	90.2	(±3.8)	77.4	(±5.8)	78.7	(±5.6)	70.4	(±6.4)
Utah	82.2	(±5.3)	90.9	(±4.0)	86.6	(±4.8)	70.7	(±6.4)	73.6	(±6.1)	61.4	(±6.8)
Vermont	81.9	(±7.5)	93.6	(±5.2)	77.6	(±7.8)	84.2	(±7.0)	67.3	(±8.3)	62.7	(±8.5)
Virginia	84.1	(±4.8)	90.9	(±3.8)	87.8	(±4.5)	79.1	(±5.1)	75.5	(±5.7)	67.9	(±6.1)
Washington	80.9	(±5.4)	90.5	(±3.9)	84.0	(±4.9)	73.8	(±6.0)	69.0	(±6.1)	64.6	(±6.2)
Western Washington	88.1	(±4.8)	91.9	(±3.9)	80.8	(±5.9)	82.3	(±5.8)	71.3	(±6.7)	66.8	(±7.0)
Rest of state	79.3	(±6.4)	90.2	(±4.6)	84.8	(±5.8)	71.9	(±7.2)	68.4	(±7.3)	64.1	(±7.4)
West Virginia	84.5	(±4.9)	96.2	(±2.1)	89.2	(±3.8)	75.8	(±5.7)	75.5	(±5.6)	64.9	(±6.2)
Wisconsin	82.0	(±6.1)	91.4	(±4.6)	86.7	(±5.4)	78.7	(±6.5)	77.1	(±6.6)	69.6	(±7.2)
Wyoming	78.7	(±6.1)	87.5	(±5.2)	78.5	(±6.3)	68.0	(±6.7)	70.2	(±6.8)	58.7	(±7.1)

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Table 3

TABLE 3. Estimated vaccination coverage among children aged 19–35 months, by selected vaccines and dosages, race/ethnicity,* and poverty level† — National Immunization Survey, United States, 2007§

Vaccine	White %	(95% CI¶)	Black %	(95% CI)	Hispanic %	(95% CI)	American Indian/ Alaska Native %	(95% CI)	Asian %	(95% CI)	Below poverty level %	(95% CI)	At or above poverty level %	(95% CI)
DTaP**														
≥3 doses	95.5	(±0.7)	93.9	(±1.8)	96.1	(±1.1)	97.3	(±2.9)	96.4	(±2.4)	94.1	(±1.2)	96.0	(±0.6)
≥4 doses	85.3	(±1.2)	82.3	(±2.7)	83.8	(±2.2)	86.4	(±7.1)	87.5	(±4.0)	81.1	(±2.1)	85.9	(±1.1)
Poliovirus	92.6	(±0.9)	91.1	(±2.1)	93.0	(±1.6)	94.8	(±5.5)	95.0	(±2.6)	91.9	(±1.3)	92.8	(±0.9)
MMR†† ≥1 dose	92.1	(±0.8)	91.5	(±2.0)	92.6	(±1.6)	96.2	(±3.2)	93.9	(±3.5)	91.3	(±1.4)	92.6	(±0.8)
Hib§§ ≥3 doses	92.9	(±0.9)	90.8	(±2.2)	93.5	(±1.4)	95.0	(±4.1)	91.0	(±3.4)	91.0	(±1.5)	93.1	(±0.8)
Hepatitis B ≥3 doses	92.5	(±0.9)	91.2	(±2.1)	93.6	(±1.6)	96.7	(±3.0)	93.8	(±2.9)	92.1	(±1.4)	92.9	(±0.9)
Varicella ≥1 dose	89.2	(±1.0)	89.8	(±2.2)	90.6	(±1.7)	94.9	(±3.5)	93.7	(±2.9)	89.2	(±1.6)	90.1	(±0.9)
PCV7¶¶														
≥3 doses	89.8	(±0.9)	89.5	(±2.2)	91.0	(±1.7)	94.0	(±4.3)	86.8	(±4.7)	89.0	(±1.6)	90.3	(±0.9)
≥4 doses	76.6	(±1.4)	70.3	(±3.4)	75.4	(±2.6)	80.4	(±7.1)	75.0	(±5.9)	72.8	(±2.4)	76.3	(±1.4)
Combined series														
4:3:1:3***	82.6	(±1.2)	79.5	(±2.9)	81.5	(±2.3)	85.3	(±7.2)	81.9	(±5.1)	78.8	(±2.2)	82.9	(±1.2)
4:3:1:3:3†††	81.0	(±1.3)	77.5	(±3.1)	79.8	(±2.4)	85.1	(±7.3)	80.7	(±5.2)	76.9	(±2.3)	81.4	(±1.2)
4:3:1:3:3:1§§§	77.5	(±1.3)	75.3	(±3.2)	78.0	(±2.5)	82.7	(±7.5)	79.4	(±5.3)	75.0	(±2.3)	78.2	(±1.3)
4:3:1:3:3:1:4¶¶¶	67.0	(±1.6)	62.0	(±3.6)	67.0	(±2.8)	74.6	(±8.4)	68.6	(±6.5)	64.7	(±2.7)	66.9	(±1.5)

* Persons identified as white, black, Asian, or American Indian/Alaska Native are all non-Hispanic. Persons identified as Hispanic might be of any race. Native Hawaiian or other Pacific Islanders and multiple races were not included because of small sample sizes.
† Poverty status was based on 2006 U.S. Census poverty thresholds (available at http://www.census.gov/hhes/www/poverty.html).
§ Children in the 2007 National Immunization Survey were born during January 2004–July 2006.
¶ Confidence interval.
** Diphtheria, tetanus toxoid, and any acellular pertussis vaccine, which can include diphtheria and tetanus toxoid vaccine or diphtheria, tetanus toxoid, and pertussis vaccine.
†† Measles, mumps, and rubella vaccine.
§§ *Haemophilus influenzae* type b (Hib) vaccine.
¶¶ 7-valent pneumococcal conjugate vaccine (PCV7).
*** ≥4 doses of DTP/DT/DTaP, ≥3 doses of poliovirus vaccine, and ≥1 dose of any measles-containing vaccine, and ≥3 doses of Hib vaccine.
††† 4:3:1:3 plus ≥3 doses of hepatitis B vaccine.
§§§ 4:3:1:3:3 plus ≥1 dose of varicella vaccine.
¶¶¶ 4:3:1:3:3:1 plus ≥4 doses of PCV7.

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National, State, and Local Area Vaccination Coverage Among Children Aged 19–35 Months — United States, 2012

The National Immunization Survey (NIS) is a random-digit–dialed telephone survey used to monitor vaccination coverage among U.S. children aged 19–35 months. This report describes national, state, and selected local area vaccination coverage estimates for children born during January 2009–May 2011, based on results from the 2012 NIS. *Healthy People 2020** objectives set childhood vaccination targets of 90% for ≥1 doses of measles, mumps, and rubella vaccine (MMR); ≥3 doses of hepatitis B vaccine (HepB); ≥3 doses of poliovirus vaccine; ≥1 doses of varicella vaccine; ≥4 doses of diphtheria, tetanus, and pertussis vaccine (DTaP); ≥4 doses of pneumococcal conjugate vaccine (PCV); and the full series of *Haemophilus influenzae* type b vaccine (Hib). Vaccination coverage remained near or above the national *Healthy People 2020* target for ≥1 doses of MMR (90.8%), ≥3 doses of poliovirus vaccine (92.8%), ≥3 doses of HepB (89.7%), and ≥1 doses of varicella vaccine (90.2%). Coverage increased from 68.6% in 2011 to 71.6% in 2012 for the birth dose of HepB.† Coverage was below the *Healthy People 2020* target and either decreased or remained stable relative to 2011 for ≥4 doses of DTaP (82.5%), the full series of Hib (80.9%), and ≥4 doses of PCV (81.9%). Coverage also remained stable relative to 2011 and below the *Healthy People 2020* targets of 85% and 80%, respectively, for ≥2 doses of hepatitis A vaccine (HepA) (53.0%), and rotavirus vaccine (68.6%). The percentage of children who had not received any vaccinations remained <1.0%. Although disparities in coverage were not observed for most racial/ethnic groups, children living in families with incomes below the federal poverty level had lower coverage than children living in families at or above the poverty level for ≥4 doses of DTaP (by 6.5 percentage points), the full Hib series (by 7.6 percentage points), ≥4 doses of PCV (by 8.6 percentage points), ≥2 doses of HepA (by 6.0 percentage points), and rotavirus vaccine (by 9.5 percentage points). Maintaining high coverage levels is important to maintain the current low burden of vaccine-preventable diseases in the United States and prevent their resurgence (*1*).

NIS uses a quarterly, random-digit–dialed sample of telephone numbers to reach households with children aged 19–35 months in the 50 states and selected local areas and territories,§

*Additional information available at http://healthypeople.gov/2020/topicsobjectives2020/objectiveslist.aspx?topicid=23. The *Healthy People 2020* targets for children aged 19–35 months are 90%, except for rotavirus vaccine (80%) and ≥2 doses of HepA (85%).

†The *Healthy People 2020* target for the birth dose (0–3 days) of HepB is 85%, measured by annual birth cohort. In the two most recent complete birth cohorts captured by NIS, coverage with the birth dose of HepB was 65.0% for children born in 2008 and 70.6% for children born in 2009.

§The eight local areas separately sampled for the 2012 NIS included six areas that receive federal Section 317 immunization funds and are included in the NIS sample every year (District of Columbia; Chicago, Illinois; New York, New York; Philadelphia County, Pennsylvania; Bexar County, Texas; and Houston, Texas) and two additional sampled areas (Dallas County, Texas, and El Paso County, Texas). The territory of the U.S. Virgin Islands (including St. Croix, St. Thomas, and St. John) was included in the 2012 NIS landline sample, but data from the U.S. Virgin Islands are excluded from national coverage estimates.

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followed by a mail survey sent to the children's vaccination providers to collect vaccination information. Data were weighted to represent the population of children aged 19–35 months, with adjustments for households with multiple telephone lines and mixed telephone use (landline and cellular), household nonresponse, and exclusion of households without telephone service.[¶] Beginning in 2011, NIS changed from sampling only landline telephones to a dual-frame sampling scheme, with interviews conducted via landline or cellular telephone. The response rate[**] for the 2012 NIS was 64.7% for the landline telephone sample (including the U.S. Virgin Islands) and 30.6% for the cellular telephone sample. Providers returned vaccination records for 67.6% of the 12,727 children with completed household interviews from the landline sample and 63.9% of the 13,009 children with completed household interviews from the cellular telephone sample, for a total of 16,916 children with provider-reported vaccination records included in this report. Of this total, 8,313 (49%) were from the cellular telephone sample, of whom 5,281 were from households with only cellular telephone service. Because the number of Hib[††] and rotavirus vaccine[§§] doses required differs according to manufacturer, coverage estimates for these vaccines take into account the type of vaccine used. Logistic regression was used to examine differences among racial/ethnic groups, controlling for poverty status. Statistical analyses were conducted using t-tests based on weighted data and accounting for the complex survey design. A p-value of <0.05 was considered statistically significant.

In 2012, national vaccination coverage among children aged 19–35 months was 82.5% for ≥4 doses of DTaP, 92.8% for ≥3 doses of poliovirus vaccine, 90.8% for ≥1 doses of MMR, 89.7% for ≥3 doses of HepB, and 90.2% for ≥1 doses of varicella vaccine (Table 1). Although this represents a decline in coverage from 2011 of 1–2 percentage points for DTaP,

¶ A description of the statistical methodology of the NIS is available at http://www.cdc.gov/nchs/data/series/sr_02/sr02_138.pdf and ftp://ftp.cdc.gov/pub/health_statistics/nchs/dataset_documentation/nis/nispuf11_dug.pdf.

** The Council of American Survey Research Organization (CASRO) household response rate, calculated as the product of the resolution rate (percentage of the total telephone numbers called that were classified as nonworking, nonresidential, or residential), screening completion rate (percentage of known households that were successfully screened for the presence of age-eligible children), and the interview completion rate (percentage of households with one or more age-eligible children that completed the household survey). Additional information is available at http://casro.org. The CASRO response rate is equivalent to the American Association for Public Opinion Research (AAPOR) type 3 response rate. Information about AAPOR response rates is available at http://www.aapor.org/am/template.cfm?section=standard_definitions1&template=/cm/contentdisplay.cfm&contentid=1814.

†† Coverage for the primary Hib series was based on receipt of ≥2 or ≥3 doses, depending on product type received. The PRP-OMB Hib products require a 2-dose primary series with doses at ages 2 months and 4 months. All other Hib products require a 3-dose primary series with doses at ages 2, 4, and 6 months. Coverage for the full series, which includes the primary series and a booster dose, was based on receipt of ≥3 or ≥4 doses, depending on product type received. All Hib products require a booster dose at age 12–15 months.

§§ Coverage for rotavirus vaccine was based on ≥2 or ≥3 doses, depending on product type received (≥2 doses for Rotarix [RV1], licensed in April 2008, and ≥3 doses for RotaTeq [RV5], licensed in February 2006).

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TABLE 1. Estimated vaccination coverage among children aged 19–35 months, by selected vaccines and dosages — National Immunization Survey, United States, 2008–2012*

Vaccine and dosage	2008 %	2008 (95% CI)	2009 %	2009 (95% CI)	2010 %	2010 (95% CI)	2011 %	2011 (95% CI)	2012 %	2012 (95% CI)
DTaP										
≥3 doses	96.2	(±0.5)	95.0	(±0.6)	95.0	(±0.6)	95.5	(±0.5)	94.3	(±0.7)†
≥4 doses	84.6	(±1.0)	83.9	(±1.0)	84.4	(±1.0)	84.6	(±1.0)	82.5	(±1.2)†
Poliovirus (≥3 doses)	93.6	(±0.6)	92.8	(±0.7)	93.3	(±0.7)	93.9	(±0.6)	92.8	(±0.7)†
MMR (≥1 doses)	92.1	(±0.7)	90.0	(±0.8)	91.5	(±0.7)	91.6	(±0.8)	90.8	(±0.8)
Hib§										
Primary series	N/A		92.1	(±0.8)	92.2	(±0.8)	94.2	(±0.6)	93.3	(±0.7)
Full series	N/A		54.8	(±1.4)	66.8	(±1.3)	80.4	(±1.1)	80.9	(±1.2)
HepB										
≥3 doses	93.5	(±0.7)	92.4	(±0.7)	91.8	(±0.7)	91.1	(±0.7)	89.7	(±0.9)†
1 dose by 3 days (birth)¶	55.3	(±1.3)	60.8	(±1.3)	64.1	(±1.3)	68.6	(±1.3)	71.6	(±1.4)†
Varicella (≥1 doses)	90.7	(±0.7)	89.6	(±0.8)	90.4	(±0.8)	90.8	(±0.7)	90.2	(±0.8)
PCV										
≥3 doses	92.8	(±0.6)	92.6	(±0.7)	92.6	(±0.8)	93.6	(±0.6)	92.3	(±0.8)†
≥4 doses	80.1	(±1.1)	80.4	(±1.2)	83.3	(±1.0)	84.4	(±1.0)	81.9	(±1.1)†
HepA**										
≥1 doses	70.5	(±1.1)	75.0	(±1.1)	78.3	(±1.1)	81.2	(±1.0)	81.5	(±1.1)
≥2 doses	40.4	(±1.2)	46.6	(±1.4)	49.7	(±1.4)	52.2	(±1.4)	53.0	(±1.5)
Rotavirus††	N/A		43.9	(±1.4)	59.2	(±1.4)	67.3	(±1.3)	68.6	(±1.4)
Combined series										
4:3:1:3*:3:1:4§§	N/A		44.3	(±1.4)	56.6	(±1.3)	68.5	(±1.3)	68.4	(±1.4)
Children who received no vaccinations	0.6	(±0.2)	0.6	(±0.1)	0.7	(±0.2)	0.8	(±0.2)	0.8	(±0.1)

Abbreviations: CI = confidence interval; DTaP = diphtheria and tetanus toxoids and acellular pertussis vaccine (includes children who might have been vaccinated with diphtheria and tetanus toxoids and pertussis vaccine or diphtheria and tetanus toxoids vaccine); MMR = measles, mumps, and rubella vaccine; Hib = *Haemophilus influenzae* type b vaccine; N/A = not available (estimate not available if the unweighted sample size for the denominator was <30 or 95% CI half width / estimate >0.588 or 95% CI half width >10); HepB = hepatitis B vaccine; HepA = hepatitis A vaccine; PCV = pneumococcal conjugate vaccine.

* For 2008, includes children born during January 2005–June 2007; for 2009, children born during January 2006–July 2008; for 2010, children born during January 2007–July 2009; for 2011, children born during January 2008–May 2010; and for 2012, children born during January 2009–May 2011.

† Statistically significant change in coverage compared with 2011 (p<0.05).

§ Hib primary series: receipt of ≥2 or ≥3 doses, depending on product received. Full series: receipt of ≥3 or ≥4 doses, depending on product received (primary series and booster dose). Hib coverage for primary or full series not available until 2009.

¶ HepB administered from birth through age 3 days.

** HepA coverage not available before 2008.

†† Rotavirus vaccine includes ≥2 or ≥3 doses, depending on the product received (≥2 doses for Rotarix [RV1] or ≥3 doses for RotaTeq [RV5]). Estimates of rotavirus vaccine coverage not available before 2009.

§§ 4:3:1:3*:3:1:4 series, referred to as routine, includes ≥4 doses of DTaP, ≥3 doses of poliovirus vaccine, ≥1 doses of measles vaccine, full series of Hib (3 or 4 doses, depending on product), ≥3 doses of HepB, ≥1 doses of varicella vaccine, and ≥4 doses of PCV.

poliovirus, and HepB, coverage for these vaccines has remained high and stable for at least the past decade.¶¶ Coverage with ≥4 doses of PCV decreased from 84.4% in 2011 to 81.9% in 2012. Coverage with the birth dose of HepB increased from 68.6% in 2011 to 71.6% in 2012. Coverage with the full series of Hib, which steadily increased during 2009–2011 after a vaccine shortage that occurred from December 2007 to September 2009 (*2*), was similar in 2012 at 80.9% compared with 2011. Similarly, coverage with ≥2 doses of HepA and rotavirus vaccine remained similar to 2011 levels at 53.0% and 68.6% in 2012, respectively.

Coverage with the combined vaccine series (4:3:1:3*:3:1:4)*** was 68.4% in 2012, also similar to coverage in 2011.

Children in families with incomes below the federal poverty level††† had lower coverage than children in families at or above the poverty level for ≥3 and ≥4 doses of DTaP, primary and full series of Hib, ≥3 and ≥4 doses of PCV, ≥2 doses of HepA, rotavirus vaccine, and the combined vaccine series (Table 2).

¶¶ Information on coverage with individual vaccines since the inception of NIS in 1994 through 2012 is available at http://www.cdc.gov/vaccines/stats-surv/nis/figures/2012_map.htm.

*** The 4:3:1:3*:3:1:4 vaccine series includes ≥4 doses of DTaP/diphtheria and tetanus toxoids vaccine/diphtheria and tetanus toxoids and pertussis vaccine, ≥3 doses of poliovirus vaccine, ≥1 doses of measles vaccine, ≥3 or ≥4 doses of Hib (depending on product type of vaccine), ≥3 doses of HepB, ≥1 doses of varicella vaccine, and ≥4 doses of PCV.

††† Poverty level uses income and family size to categorize households into 1) at or above the poverty level and 2) below the poverty level. Poverty level was based on 2011 U.S. Census poverty thresholds, available at http://www.census.gov/hhes/www/poverty/data/threshld.

TABLE 2. Estimated vaccination coverage among children aged 19–35 months, by selected vaccines and dosages, race/ethnicity,* and poverty level† — National Immunization Survey, United States, 2012§

	Race/Ethnicity												Poverty level			
	White, non-Hispanic		Black, non-Hispanic		Hispanic		American Indian/ Alaska Native		Asian		Multiracial, non-Hispanic		At or above		Below	
Vaccine and dosage	%	(95% CI)	%	(95% CI)	%	(95% CI)	%	(95% CI)	%	(95% CI)	%	(95% CI)	%	(95% CI)	%	(95% CI)
DTaP																
≥3 doses	94.8	(±0.8)	94.0	(±1.6)	93.5	(±1.9)	95.6	(±3.3)	96.1	(±2.1)	95.1	(±2.0)	95.0	(±0.9)	93.4	(±1.3)**
≥4 doses	83.6	(±1.5)	79.6	(±3.1)¶	80.8	(±2.9)	88.2	(±5.9)	88.1	(±4.3)	85.6	(±3.6)	85.0	(±1.4)	78.5	(±2.3)**
Poliovirus (≥3 doses)	93.0	(±0.9)	92.9	(±1.8)	92.5	(±1.8)	95.2	(±3.4)	92.3	(±3.6)	93.3	(±2.3)	93.4	(±0.9)	91.8	(±1.4)
MMR (≥1 doses)	90.9	(±1.0)	90.9	(±2.1)	90.7	(±2.0)	92.0	(±5.0)	89.8	(±5.2)	92.3	(±2.6)	91.4	(±1.0)	89.9	(±1.6)
Hib††																
Primary series	93.7	(±0.9)	91.1	(±2.2)	93.5	(±1.7)	94.5	(±3.9)	94.9	(±2.2)	94.0	(±2.2)	94.3	(±0.8)	91.9	(±1.4)**
Full series	82.2	(±1.4)	77.5	(±3.3)¶	79.5	(±2.8)	84.7	(±7.1)	86.1	(±4.4)	82.5	(±3.9)	84.0	(±1.4)	76.4	(±2.2)**
HepB																
≥3 doses	89.3	(±1.1)	89.7	(±2.2)	89.4	(±2.1)	94.0	(±3.9)¶	93.2	(±2.7)¶	92.2	(±2.6)	89.8	(±1.1)	89.4	(±1.5)
1 dose by 3 days (birth)§§	69.2	(±1.6)	74.9	(±3.6)¶	73.9	(±3.4)¶	NA		71.6	(±6.6)	75.9	(±4.8)¶	69.4	(±1.7)	75.8	(±2.5)**
Varicella (≥1 doses)	89.8	(±1.0)	90.4	(±2.1)	90.9	(±2.1)	92.5	(±4.5)	91.9	(±3.2)	90.9	(±2.9)	90.6	(±1.0)	89.7	(±1.7)
PCV																
≥3 doses	92.7	(±1.0)	91.2	(±2.0)	92.4	(±1.8)	94.0	(±4.0)	90.7	(±3.3)	94.0	(±2.2)	93.4	(±0.9)	90.7	(±1.5)**
≥4 doses	83.5	(±1.4)	77.1	(±3.5)¶	82.1	(±2.5)	NA		80.7	(±5.1)	84.1	(±3.7)	85.3	(±1.2)	76.7	(±2.3)**
HepA (≥2 doses)	52.6	(±1.8)	52.0	(±3.9)	54.4	(±3.4)	NA		57.5	(±7.7)	49.4	(±5.7)	55.4	(±1.8)	49.4	(±2.7)**
Rotavirus¶¶	70.5	(±1.6)	60.4	(±4.0)¶	70.0	(±3.1)	NA		69.9	(±7.1)	69.3	(±5.4)	72.5	(±1.6)	63.0	(±2.5)**
Combined series																
4:3:1:3*:3:1:4***	69.3	(±1.7)	64.8	(±3.8)¶	67.8	(±3.2)	NA		71.6	(±6.6)	71.5	(±4.8)	71.6	(±1.6)	63.4	(±2.7)**

Abbreviations: CI = confidence interval; DTaP = diphtheria and tetanus toxoids and acellular pertussis vaccine (includes children who might have been vaccinated with diphtheria and tetanus toxoids and pertussis vaccine or diphtheria and tetanus toxoids vaccine); Hib = *Haemophilus influenzae* type b vaccine; MMR = measles, mumps, and rubella vaccine; N/A = not available (estimate not available if the unweighted sample size for the denominator was <30 or 95% CI half width / estimate >0.588 or 95% CI half width >10); HepB = hepatitis B vaccine; HepA = hepatitis A vaccine; PCV = pneumococcal conjugate vaccine.

* Native Hawaiian or other Pacific Islanders not included because of small sample sizes.

† Poverty level was determined for all children. Children were classified as below poverty if their total family income was less than the poverty threshold specified for the applicable family size and number of children aged <18 years. All others were classified as at or above poverty. Poverty thresholds reflect yearly changes in the Consumer Price Index. Thresholds and guidelines available at http://www.census.gov/hhes/www/poverty.html.

§ Children in the 2012 National Immunization Survey were born during January 2009–May 2011.

¶ Estimates are statistically significant at p<0.05. Children identified as non-Hispanic white were the reference group.

** Estimates are statistically significant at p<0.05. Children living at or above poverty were the reference group.

†† Hib primary series: receipt of ≥2 or ≥3 doses, depending on product received; full series: primary series and booster dose includes receipt of ≥3 or ≥4 doses, depending on product received.

§§ HepB (≥1 doses) administered from birth through age 3 days.

¶¶ Includes ≥2 or ≥3 doses, depending on product received (≥2 doses for Rotarix [RV1] or ≥3 doses for RotaTeq [RV5]).

*** 4:3:1:3:3:1:4 series includes ≥4 doses of DTaP, ≥3 doses of poliovirus vaccine, ≥1 doses of measles vaccine, full series of Hib (3 or 4 doses, depending on type), ≥3 doses of HepB, ≥1 doses of varicella vaccine, and ≥4 doses of PCV.

Children in families below the poverty level had higher HepB birth dose coverage than children living at or above the poverty level. No differences by poverty status were observed for poliovirus vaccine, MMR, ≥3 doses of HepB, or varicella vaccine.

Compared with white children,§§§ black children had lower coverage for ≥4 doses of DTaP, the full series of Hib, ≥4 doses of PCV, rotavirus vaccine, and the combined 4:3:1:3*:3:1:4 series (Table 2). After adjustment for poverty status, black race was not associated with coverage with any of these vaccines except for rotavirus. American Indian/Alaska Native (AI/AN) children and Asian children had higher coverage for ≥3 doses of HepB compared with white children. Black, Hispanic, and multiracial children had higher coverage for the birth dose of HepB compared with white children. With the exception of the difference in HepB birth dose coverage between Hispanic and white children, all of these associations with ≥3 doses of HepB and the birth dose of HepB remained statistically significant after adjustment for poverty status.

Vaccination coverage varied by state, with coverage for the combined vaccine series ranging from 59.5% in Alaska to 80.2% in Hawaii (Table 3). Fifteen states had point estimates of MMR coverage below the *Healthy People 2020* target of 90%, and only Connecticut, Delaware, and the District of Columbia had coverage ≥90% for ≥4 doses of DTaP. Variations in coverage were widest for the birth dose of HepB (ranging from 36.0%

§§§ Child's race/ethnicity was reported by their parent or guardian. Children categorized in this report as white, black, Asian, American Indian/Alaska Native, or multiracial were identified as non-Hispanic by their parent or guardian. Children identified as multiracial had more than one race category selected. Persons identified as Hispanic might be of any race.

TABLE 3. Estimated vaccination coverage among children aged 19–35 months, by selected individual vaccines and vaccination series* and state/local area — National Immunization Survey, United States, 2012†

State/Area	MMR (≥1 doses)		DTaP (≥4 doses)		HepB (birth)§		HepA (≥2 doses)¶		Rotavirus**		Combined series*	
	%	(95% CI)	%	(95% CI)	%	(95% CI)	%	(95% CI)	%	(95% CI)	%	(95% CI)
United States	**90.8**	**(±0.8)**	**82.5**	**(±1.2)** §§	**71.6**	**(±1.4)**††	**53.0**	**(±1.5)**	**68.6**	**(±1.4)**	**68.4**	**(±1.4)**
Alabama	93.1	(±3.5)	84.8	(±5.9)	83.8	(±4.9)††	49.2	(±7.4)	66.0	(±7.4)§§	71.3	(±6.8)
Alaska	86.2	(±5.1)	79.4	(±5.8)	56.8	(±6.9)	50.1	(±6.9)	60.3	(±6.8)	59.5	(±6.8)
Arizona	88.3	(±4.9)	82.7	(±5.8)	83.0	(±5.3)††	55.2	(±6.9)	71.6	(±6.7)	67.5	(±7.5)
Arkansas	92.3	(±4.0)	79.8	(±6.4)	81.7	(±6.5)	40.1	(±7.5)	56.3	(±8.0)	66.4	(±7.6)
California	91.5	(±4.3)	81.6	(±6.6)	61.5	(±7.5)	54.6	(±7.8)	71.0	(±6.8)	66.8	(±7.5)
Colorado	91.5	(±4.5)	82.8	(±6.7)	64.0	(±8.4)	56.2	(±8.6)	73.5	(±7.7)	71.7	(±7.9)
Connecticut	94.8	(±2.9)	91.3	(±3.8)	75.7	(±5.7)	65.5	(±6.3)††	72.5	(±6.4)	77.1	(±5.7)
Delaware	94.4	(±3.4)	90.9	(±4.3)	72.3	(±6.7)	65.7	(±7.1)††	76.5	(±6.5)	72.6	(±6.7)
District of Columbia	93.0	(±3.7)	90.7	(±4.0)	78.2	(±5.4)	62.3	(±6.6)	54.2	(±6.8)	73.4	(±6.2)
Florida	91.0	(±4.8)	83.3	(±6.5)	62.6	(±7.6)	51.9	(±8.1)	66.0	(±7.9)	68.6	(±7.5)
Georgia	91.9	(±4.2)	86.7	(±5.2)	87.6	(±5.1)	65.9	(±7.6)	71.8	(±7.2)	74.7	(±6.8)
Hawaii	95.0	(±2.7)	87.9	(±4.6)	82.7	(±5.2)††	58.1	(±7.1)	70.6	(±6.5)††	80.2	(±5.5)
Idaho	93.3	(±3.6)	76.6	(±6.7)	70.1	(±7.8)	52.8	(±8.6)	68.2	(±7.2)	63.0	(±8.2)
Illinois	91.6	(±2.7)	85.3	(±2.6)	71.3	(±5.0)	48.2	(±5.4)	67.2	(±5.2)	68.5	(±4.9)
City of Chicago	86.8	(±6.1)	79.4	(±7.6)	70.3	(±8.4)	45.2	(±8.7)	69.5	(±8.7)	60.4	(±8.8)§§
Rest of state	93.2	(±2.9)	87.4	(±4.1)	71.7	(±6.0)	49.3	(±6.6)	66.4	(±6.3)	71.4	(±5.8)
Indiana	90.0	(±4.5)	76.8	(±6.5)	78.2	(±6.0)	48.0	(±7.5)	63.9	(±7.4)	61.4	(±7.4)
Iowa	93.3	(±3.4)††	88.2	(±4.4)	68.3	(±7.5)	59.3	(±7.2)††	70.2	(±7.5)	74.8	(±6.3)
Kansas	88.5	(±4.6)	79.0	(±6.0)§§	78.3	(±5.4)	58.5	(±6.9)	59.9	(±7.0)	65.0	(±6.7)
Kentucky	89.2	(±4.4)	83.0	(±5.4)	80.8	(±5.6)	48.4	(±7.0)	69.0	(±6.4)	68.2	(±6.6)
Louisiana	90.5	(±4.0)	77.8	(±6.6)	76.6	(±6.8)	46.9	(±7.3)	65.0	(±7.4)	68.5	(±7.1)
Maine	91.2	(±4.2)	87.9	(±5.1)	74.2	(±5.8)	52.5	(±7.4)††	64.7	(±7.0)	72.6	(±6.6)
Maryland	92.5	(±4.8)	83.2	(±6.2)	73.3	(±6.6)	53.1	(±7.3)	71.2	(±6.9)	67.1	(±7.1)
Massachusetts	93.7	(±3.4)	88.2	(±4.5)	74.0	(±6.2)	57.5	(±6.9)	82.4	(±5.6)	73.5	(±6.2)
Michigan	91.4	(±4.4)	81.5	(±6.7)	78.9	(±6.1)	40.9	(±7.4)§§	64.3	(±7.4)	70.5	(±7.3)
Minnesota	90.1	(±5.6)	84.2	(±5.6)	62.8	(±7.4)	55.4	(±7.7)	76.6	(±6.4)	66.2	(±7.6)
Mississippi	93.4	(±4.3)	83.6	(±6.4)	81.6	(±6.5)	39.7	(±8.2)	63.8	(±8.0)	77.5	(±7.0)
Missouri	92.7	(±4.1)	81.9	(±7.0)	78.7	(±6.2)	56.3	(±7.9)	69.3	(±7.8)	63.9	(±8.0)
Montana	91.5	(±4.0)	86.6	(±4.4)††	64.5	(±6.8)§§	50.5	(±7.3)	61.3	(±7.4)	66.5	(±7.1)
Nebraska	89.0	(±4.4)§§	84.5	(±5.2)§§	79.4	(±5.8)	60.6	(±7.0)	74.2	(±6.2)	72.6	(±6.5)
Nevada	89.8	(±4.1)	81.0	(±5.5)	70.5	(±6.3)	52.2	(±7.0)	62.7	(±6.7)	65.3	(±6.6)
New Hampshire	93.7	(±3.4)	88.7	(±4.7)	72.2	(±6.6)	57.0	(±7.0)	83.0	(±5.8)	80.1	(±5.7)††
New Jersey	94.8	(±2.7)	84.7	(±5.1)	52.6	(±6.9)	45.9	(±6.9)	68.0	(±6.6)††	71.5	(±6.4)
New Mexico	88.8	(±4.4)	87.0	(±4.9)	68.9	(±7.0)	51.9	(±7.6)	78.4	(±5.8)	71.6	(±6.6)
New York	90.2	(±2.9)	83.8	(±3.5)	61.5	(±4.7)††	45.9	(±4.7)	65.5	(±4.5)	63.7	(±4.6)
City of New York	90.3	(±3.9)	82.9	(±5.3)	60.5	(±6.4)††	44.4	(±6.6)	56.8	(±6.8)	62.8	(±6.5)
Rest of state	90.0	(±4.2)	84.6	(±4.7)	62.4	(±6.8)	47.5	(±6.7)	74.1	(±5.9)††	64.6	(±6.5)

See table footnotes on page 738.

in Vermont to 87.6% in Georgia), ≥2 doses of HepA (ranging from 32.3% in Wyoming to 65.9% in Georgia), and rotavirus vaccine (ranging from 54.2% in the District of Columbia to 83.0% in New Hampshire).

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Editorial Note

The results of the 2012 NIS indicate that vaccination coverage among children aged 19–35 months continues to be near or above the *Healthy People 2020* target of 90% for MMR, poliovirus vaccine, HepB, and varicella vaccine. Although coverage estimates for many vaccines had small but statistically significant decreases compared with 2011, estimates are not directly comparable between years because NIS methods were changed. The number of interviews conducted via cellular telephone increased in 2012, such that approximately half of the 2012 NIS unweighted sample came from the cellular telephone sampling frame, compared with 11% of the 2011 unweighted sample. In 2012, an estimated 45% of U.S. children aged <18 years lived in households with cellular telephones only (*3*). The proportion of children aged 19–35 months living in households with only cellular telephone service estimated from the weighted 2012 NIS sample was 52.7%. Thus, the NIS sample now more closely resembles the U.S. population with respect to telephone service, and these 2012 vaccination

TABLE 3. (*Continued*) Estimated vaccination coverage among children aged 19–35 months, by selected individual vaccines and vaccination series* and state/local area — National Immunization Survey, United States, 2012†

	MMR (≥1 doses)		DTaP (≥4 doses)		HepB (birth)§		HepA (≥2 doses)¶		Rotavirus**		Combined series*	
State/Area	%	(95% CI)	%	(95% CI)	%	(95% CI)	%	(95% CI)	%	(95% CI)	%	(95% CI)
North Carolina	89.0	(±4.9)	85.9	(±5.4)	78.2	(±5.9)	48.5	(±7.3)	68.0	(±7.1)	75.4	(±6.5)
North Dakota	90.6	(±5.4)	85.1	(±6.2)	82.3	(±5.6)	59.8	(±7.5)	75.4	(±7.1)	72.2	(±7.2)
Ohio	90.3	(±4.9)	83.3	(±6.0)	77.8	(±6.2)	53.8	(±7.0)	67.4	(±7.5)	66.8	(±6.9)
Oklahoma	90.0	(±4.8)	79.1	(±6.0)	67.4	(±7.4)	56.1	(±7.4)	56.4	(±7.7)	61.0	(±7.6)
Oregon	87.3	(±4.7)	81.2	(±5.8)	65.4	(±6.6)	57.6	(±7.0)	66.1	(±6.7)	66.7	(±6.7)
Pennsylvania	87.0	(±4.6)§§	80.1	(±5.3)	83.2	(±4.3)††	58.5	(±6.1)	72.5	(±5.5)	68.3	(±5.9)
Philadelphia County	92.6	(±4.3)	85.4	(±5.7)	78.1	(±6.0)	58.1	(±7.6)	68.0	(±7.2)	73.8	(±7.1)
Rest of state	85.9	(±5.5)§§	79.1	(±6.2)	84.2	(±5.1)††	58.6	(±7.1)	73.4	(±6.4)	67.2	(±6.9)
Rhode Island	94.3	(±3.1)	89.0	(±4.9)	68.3	(±6.7)	57.3	(±6.9)	79.8	(±6.4)	72.5	(±6.5)
South Carolina	93.2	(±3.5)	80.9	(±6.0)	78.4	(±5.8)††	48.5	(±7.3)	70.6	(±6.7)††	71.8	(±6.7)
South Dakota	93.3	(±3.0)	79.2	(±5.5)	76.6	(±5.6)	45.3	(±6.8)††	59.5	(±7.0)	63.6	(±6.4)
Tennessee	92.2	(±4.0)	82.0	(±6.0)	68.8	(±7.0)	55.4	(±7.7)	64.3	(±7.6)	73.1	(±6.8)
Texas	89.7	(±2.4)§§	77.4	(±3.6)§§	74.6	(±3.7)	57.4	(±4.0)	67.5	(±3.9)	64.8	(±4.0)§§
Bexar County	90.9	(±4.0)	77.5	(±6.4)	76.4	(±6.4)††	62.6	(±7.6)	67.5	(±7.4)	65.7	(±7.5)
City of Houston	92.2	(±4.7)	83.4	(±6.8)	84.3	(±5.6)	64.4	(±8.4)	79.7	(±7.6)††	70.9	(±7.9)
Dallas County	86.5	(±5.6)	78.8	(±6.6)	72.3	(±7.0)§§	56.8	(±8.0)	72.0	(±7.2)	69.8	(±7.5)
El Paso County	87.1	(±4.7)	76.5	(±6.1)	77.9	(±5.6)	57.4	(±6.7)	68.4	(±6.7)	62.3	(±6.7)
Rest of state	89.7	(±3.3)§§	76.2	(±5.0)	72.8	(±5.2)	55.7	(±5.6)	64.5	(±5.4)§§	62.9	(±5.6)§§
Utah	87.3	(±5.5)	80.5	(±6.6)	78.6	(±6.3)	57.1	(±7.7)	74.5	(±6.8)	73.0	(±7.2)
Vermont	91.7	(±3.8)	86.0	(±5.0)	36.0	(±6.7)††	37.4	(±6.4)	64.2	(±6.6)	63.2	(±6.7)
Virginia	94.3	(±3.9)	82.7	(±6.6)	71.4	(±7.4)	50.0	(±8.3)	71.9	(±7.9)	69.8	(±7.7)
Washington	84.8	(±5.8)	84.0	(±5.5)	73.2	(±6.5)	51.0	(±7.4)	68.6	(±7.0)	65.2	(±7.2)
West Virginia	84.6	(±6.0)	79.1	(±6.8)	74.4	(±6.6)††	54.9	(±7.9)	62.6	(±7.8)	60.8	(±7.9)
Wisconsin	89.3	(±5.2)	87.8	(±5.3)	72.2	(±6.5)	55.6	(±7.4)	67.4	(±7.1)	75.2	(±6.5)
Wyoming	91.2	(±3.9)	79.4	(±6.0)	64.8	(±7.1)	32.3	(±6.8) §§	69.1	(±6.7)††	67.2	(±6.8)
U.S. Virgin Islands	63.7	(±7.4)§§	55.6	(±7.7)	72.8	(±7.0)	12.0	(±4.7)	15.6	(±5.7)	41.5	(±7.6)

Abbreviations: CI = confidence interval; DTaP = diphtheria and tetanus toxoids and acellular pertussis vaccine (includes children who might have been vaccinated with diphtheria and tetanus toxoids and pertussis vaccine or diphtheria and tetanus toxoids vaccine); HepB = hepatitis B vaccine; HepA = hepatitis A vaccine; Hib = *Haemophilus influenzae* type b vaccine; MMR = measles, mumps, and rubella vaccine; PCV = pneumococcal conjugate vaccine.

* Includes ≥4 doses of DTaP, ≥3 doses of poliovirus vaccine, ≥1 doses of measles vaccine, full series of Hib (3 or 4 doses, depending on product), ≥3 doses of HepB, ≥1 doses of varicella vaccine, and ≥4 doses of PCV.

† Children in the 2012 National Immunization Survey were born during January 2009–May 2011.

§ HepB administered from birth through age 3 days.

¶ ≥2 doses HepA and measured among children aged 19–35 months.

** ≥2 or ≥3 doses of rotavirus vaccine, depending on product received (≥2 doses for Rotarix [RV1] or ≥3 doses for RotaTeq [RV5]).

†† Statistically significant increase in coverage compared with 2011 (p<0.05).

§§ Statistically significant decrease in coverage compared with 2011 (p<0.05).

coverage estimates should be considered a baseline against which subsequent trends in coverage can be evaluated.

After a sustained increase from 2009 to 2011, likely attributable to recovery from a Hib vaccine shortage that occurred from December 2007 to June 2009 (*2*), coverage with the full series of Hib vaccine has reached levels in 2012 similar to those of DTaP and PCV, vaccines that also require a booster dose during the second year of life. Because the frequency of recommended well-child visits declines after age 12 months, fewer opportunities for catch-up doses with these vaccines exist when children fall behind schedule. CDC encourages the use of provider and system-based interventions aimed at encouraging adherence to well-child visits and facilitating delivery of vaccines at these visits. Examples include use of immunization information systems, provider assessment and feedback, provider reminders, standing orders, and provider education in conjunction with other interventions (*4*).

Coverage with HepA and rotavirus, the more recently recommended vaccines, also remained similar in 2012 compared with 2011, after several years of continued increase. Similar to Hib, DTaP, and PCV, the plateau in coverage for HepA might be attributable to fewer opportunities for catch-up doses, as the first dose of HepA is recommended during age 12–23 months. Children's vaccination status in NIS is determined up to age 19–35 months, so some children might have received their second dose, or might be due for the second dose, after the survey was conducted (the second dose is recommended 6–18 months after the first dose) (*5*). For rotavirus vaccine, the first dose should be given before age 14 weeks and 6 days because of insufficient evidence of safety in children aged >15 weeks, and the final dose should be given by age 8 months (*5*). These age restrictions might preclude infants from starting or completing the series. Health-care providers should make every

What is already known on this topic?

Healthy People 2020 set childhood vaccination targets of 90% for ≥1 doses of measles, mumps, rubella vaccine (MMR); ≥3 doses of hepatitis B vaccine (HepB); ≥3 doses of poliovirus vaccine; ≥1 doses of varicella vaccine; ≥4 doses of diphtheria, tetanus, and pertussis vaccine; ≥4 doses of pneumococcal conjugate vaccine; and the full series of *Haemophilus influenzae* type b vaccine. The National Immunization Survey estimates coverage among U.S. children aged 19–35 months for these and other vaccines.

What is added by this report?

In 2012, childhood vaccination coverage remains near or above national target levels for ≥1 doses of MMR (90.8%), ≥3 doses of HepB (89.7%), ≥3 doses of poliovirus vaccine (92.8%), and ≥1 doses of varicella vaccine (90.2%); however, coverage varied by state and tended to be lower among children in families with incomes below the federal poverty level.

What are the implications for public health practice?

Sustaining current coverage levels and increasing coverage for those vaccines below national target levels is needed to maintain the low levels of vaccine-preventable diseases and prevent a resurgence of these diseases in the United States. Ensuring systems such as client reminder/recall and vaccination programs are in place in settings such as Special Supplemental Nutrition Program for Women, Infants, and Children (WIC) clinics and child-care facilities can help support high vaccination coverage.

effort to start and complete administration of the rotavirus vaccine series on time.

Although few differences in coverage by racial/ethnic group were observed after adjustment for poverty status, differences in coverage by poverty level remained for many vaccines. The Vaccines For Children program[¶¶¶] has been successful in removing differences in coverage between children living above and below the poverty level that once existed for vaccines such as MMR, polio, and HepB (*6*); however, coverage among children living below the poverty level still lags behind coverage of children living at or above the poverty level for newer vaccines (HepA and rotavirus) and vaccines that require 4 doses to complete the series.

Vaccination coverage continues to vary across states. Clusters of unvaccinated children leave communities vulnerable to outbreaks of disease. The continued occurrence of measles outbreaks among unvaccinated persons in the United States (*7*) underscores the importance of maintaining uniformly high coverage to prevent transmission of imported disease. Recent budget cuts to state and local health departments (*8*) as well as differences by state in factors such as population characteristics, immunization program activities, vaccination requirements for child-care centers, and vaccine financing policies might contribute to variations in vaccination coverage.

The findings in this report are subject to at least four limitations. First, the proportion of the NIS sampled by cellular telephone in 2012 was about half compared with only 11% in 2011 and zero in earlier years. Living in a household with only cellular telephone service is associated with poverty and other demographic factors that might be related to vaccination status (*3*). Second, underestimates of vaccination coverage might have resulted from the exclusive use of provider-reported vaccination histories because completeness of these records is unknown. Third, bias resulting from nonresponse and exclusion of households without telephone service might persist after weighting adjustments, although estimated bias from these sources for the 2011 NIS was low for selected vaccines examined, ranging from 0.3 (for MMR) to 1.5 (for ≥4 DTaP) percentage points (*9*). The potential for nonresponse bias was increased in 2012 because of the lower response rate for the cellular telephone sample. However, a comparison of vaccination coverage estimates from the NIS from July 2011 through June 2012 with those from the National Health Interview Survey during the same period yielded similar results, both overall and for children living in cellular-only households, despite largely different response rates between the two surveys (Assessment Branch, Immunization Services Division, National Center for Immunization and Respiratory Diseases, and Survey Planning and Special Surveys Branch, Division of Health Interview Statistics, National Center for Health Statistics, CDC; unpublished data; 2013). Finally, although national coverage estimates are precise, estimates for state and local areas should be interpreted with caution because of smaller sample sizes and wider confidence intervals.

High vaccination coverage among preschool-aged children has resulted in historically low levels of most vaccine-preventable diseases in the United States (*1*). The results of the 2012 NIS indicate that vaccination coverage among young children remained relatively stable and the proportion of children who do not receive any vaccinations has remained low. Slight decreases in coverage for some vaccines relative to 2011 cannot be immediately explained but could be attributable to a change in NIS methods. The 2012 results should be considered a baseline against which future trends in coverage can be evaluated. Careful monitoring of coverage levels overall and in subpopulations (e.g., racial/ethnic and geographic) is important to ensure that all children remain adequately protected. Parents and health-care providers should work to sustain high coverage and improve coverage for the more recently recommended vaccines and those that require booster doses after age 12 months. In addition to health system–based

[¶¶¶] Additional information about the Vaccines for Children program is available at http://www.cdc.gov/vaccines/programs/vfc/default.htm.

interventions previously described, national, state and local immunization programs should continue to partner with providers to implement the *Guide to Community Preventive Services*–recommended interventions aimed at increasing community demand for vaccination, such as client reminder/recall and client or family incentives. Enhanced access to health services also is recommended, through reduced out-of-pocket costs, home visits, and vaccination programs in child-care centers, schools, and Special Supplemental Nutrition Program for Women, Infants, and Children (WIC) settings**** (*4*). Health insurance reforms of the Affordable Care Act require health plans to cover recommended immunizations without cost to the enrollee when administered by an in-network provider (*10*).††††

**** Additional information about WIC is available at http://www.fns.usda.gov/wic.

†††† Enrollment in the new Health Insurance Marketplace begins October 1, 2013. The Health Insurance Marketplace will offer individuals and small businesses a streamlined process to compare health plans, get answers to questions, find out if they are eligible for tax credits for private insurance or health programs like the Children's Health Insurance Program (CHIP), and enroll in a health plan that meets their needs. Consumers can learn more about the Marketplace at http://www.healthcare.gov or the Spanish-language site http://www.cuidadodesalud.gov or by calling the 24-hour consumer call center at 1-800-318-2596. Hearing impaired callers using TTY/TDD technology can call 1-855-889-4325 for assistance.

References

1. CDC. Vaccine-preventable diseases, immunizations, and MMWR—1961–2011. MMWR 2011;60(Suppl 4):49–57.
2. CDC. Updated recommendations for use of *Haemophilus influenzae* type b (Hib) vaccine: reinstatement of the booster dose at ages 12–15 months. MMWR 2009;58:673–4.
3. CDC. Wireless substitution: early release of estimates from the National Health Interview Survey, July–December 2012. Atlanta, GA: US Department of Health and Human Services, CDC; 2013. Available at http://www.cdc.gov/nchs/data/nhis/earlyrelease/wireless201306.pdf.
4. Community Preventive Services Task Force. Increasing appropriate vaccination: universally recommended vaccinations. In: The Guide to Community Preventive Services. Atlanta, GA: Community Preventive Services Task Force; 2013. Available at http://www.thecommunityguide.org/vaccines/index.html.
5. CDC. General recommendations on immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2011;60(No. RR-2).
6. CDC. Vaccination coverage by race/ethnicity and poverty level among children aged 19–35 months, United States, 1996. MMWR 1997;46:963–8.
7. CDC. Measles—United States, 2011. MMWR 2012;61:253–7.
8. Association of State and Territorial Health Officials. Budget cuts continue to affect the health of Americans: update March 2012. Arlington, VA: Association of State and Territorial Health Officials; 2012. Available at http://www.astho.org/display/assetdisplay.aspx?id=6907.
9. Pineau V, Wolter K, Skalland B, et al. Modeling total survey error in the 2011 National Immunization Survey (NIS): pre-school children and teens. Paper presented at 2013 Joint Statistical Meetings, August 3–8, 2013; Montreal, Quebec, Canada.
10. Patient Protection and Affordable Care Act. Pub. L. No. 111-48,124 Stat. 119 (2010).

Morbidity and Mortality Weekly Report

Measles — United States, January 1–August 24, 2013

Measles is a highly contagious, acute viral illness that can lead to complications and death. Although measles elimination (i.e., interruption of continuous transmission lasting ≥12 months) was declared in the United States in 2000 (*1*), importation of measles cases continues to occur. During 2001–2012, the median annual number of measles cases reported in the United States was 60 (range: 37–220), including 26 imported cases (range: 18–80). The median annual number of outbreaks reported to CDC was four (range: 2–16). Since elimination, the highest numbers of U.S. cases were reported in 2008 (140 cases) and 2011 (220) (Figure 1) (*2,3*). To update measles data, CDC evaluated cases reported by 16 states during January 1–August 24, 2013. A total of 159 cases of measles were reported during this period. Most cases were in persons who were unvaccinated (131 [82%]) or had unknown vaccination status (15 [9%]). Forty-two importations were reported, and 21(50%) were importations from the World Health Organization (WHO) European Region. Eight outbreaks accounted for 77% of the cases reported in 2013, including the largest outbreak reported in the United States since 1996 (58 cases) (*4*). These outbreaks demonstrate that unvaccinated persons place themselves and their communities at risk for measles and that high vaccination coverage is important to prevent the spread of measles after importation.

Confirmed measles cases in the United States are reported by state and local health departments to CDC using a standard case definition.* A measles case is confirmed in a person with febrile rash illness and laboratory confirmation or a direct epidemiologic link to a confirmed case. Laboratory confirmation involves serologic detection of measles-specific immunoglobulin M, a significant increase in measles immunoglobulin G level, isolation of measles virus, or detection of measles virus by nucleic acid amplification in a clinical specimen (e.g., nasopharyngeal or oropharyngeal swab, nasal aspirate, throat wash, or urine). Cases are considered imported if exposure to measles virus occurred outside the United States 7–21 days before rash onset and rash occurred within 21 days of entry into the United States, with no known exposure to measles in the United States during that period. Import-associated cases include 1) imported cases, 2) cases that are linked epidemiologically to imported cases, and 3) cases for which an epidemiologic link has not been identified but the viral genotype detected suggests recent importation.† An outbreak of measles is defined as a chain of transmission with three or more confirmed cases.

During January 1–August 24, 2013, a total of 159 cases were reported to CDC from 16 states and New York City (Figure 2). Patients ranged in age from 0 days to 61 years; 18 (11%) were aged <12 months, 40 (25%) were aged 1–4 years, 58 (36%) were aged 5–19 years, and 43 (27%) were aged ≥20 years. Among the 159 cases, 17 (11%) persons required hospitalization, including four patients diagnosed with pneumonia. No deaths were reported.

Among the 159 cases, 157 (99%) were import-associated, and two had an unknown source. Forty-two (26%) importations (23 returning U.S residents and 19 visitors to the United States) from 18 countries were reported, and 21 (50%) of the importations were from the WHO European Region. Genotypes identified to date are D8 (47 cases), B3 (six), H1 (four), D9 (three), and D4 (two).

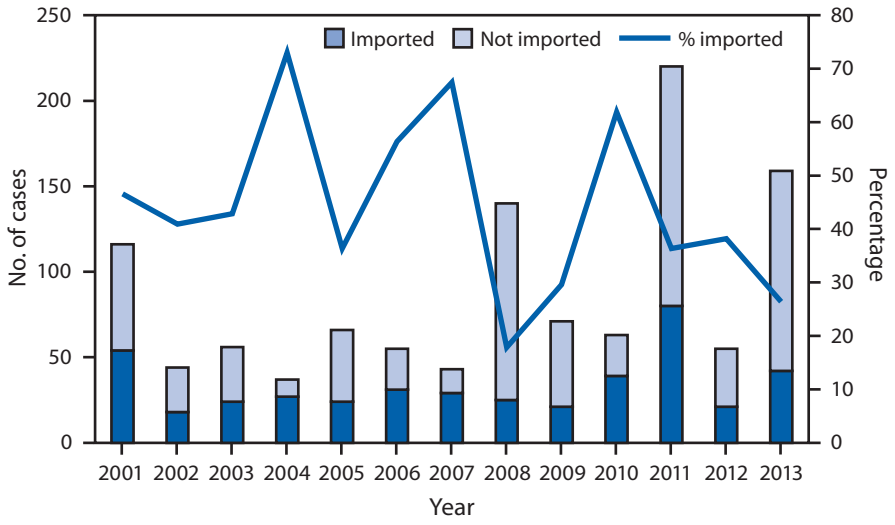
Most cases were in persons who were unvaccinated (131 [82%]) or had unknown vaccination status (15 [9%]). Thirteen (8%) of the patients had been vaccinated, of whom three had received 2 doses of measles, mumps, and rubella (MMR) vaccine. Among 140 U.S. residents who acquired measles, 117 (84%) were unvaccinated, and 11(8%) had unknown vaccination status. Of those who were unvaccinated, 92 (79%) had philosophical objections to vaccination, six (5%) had missed opportunities for vaccination, 15 (13%) occurred among infants aged <12 months who were not eligible for vaccination, and for four (3%) the reason for no vaccination was unknown (Figure 3). Among the 21 U.S resident patients who traveled abroad and were aged ≥6 months, 14 (67%) were unvaccinated, five (24%) had unknown vaccination status, and two had received 1 dose of MMR vaccine.

To date in 2013, eight outbreaks have accounted for 77% of the cases, and outbreaks have ranged from three to 58 cases. The largest outbreak occurred in New York City (*4*). None of these patients had documentation of vaccination at the time of exposure, including 12 (21%) who were aged <12 months. Of those who were eligible for vaccination, 31 (67%) had objected or had parental objection to vaccination because of religious or philosophical beliefs (*4*). The second largest outbreak, in North Carolina (23 cases, including a California resident), occurred mainly among persons not vaccinated because of personal belief exemptions (*5*). In an ongoing outbreak in Texas, 20 confirmed cases have been reported as of August 24 among members of a church community. Nineteen (95%) cases were in patients aged >12 months, and 17 (85%) of the patients were unvaccinated. The index patient was an adult with unknown measles vaccination history who traveled to Indonesia.

* Available at http://wwwn.cdc.gov/nndss/script/casedef.aspx?condyrid=908&datepub=1/1/2013%2012:00:00%20am.

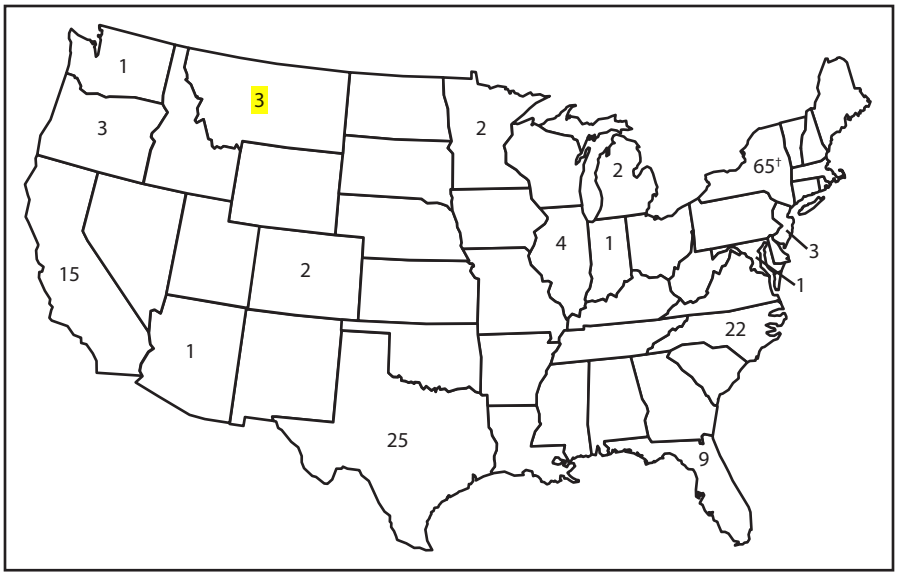
† Additional information available at http://www.cdc.gov/vaccines/pubs/surv-manual/chpt07-measles.html.

FIGURE 1. Number and percentage of measles cases that were directly imported and number of cases that were not directly imported* — United States, 2001–2013†



* Directly imported cases are those in patients who acquired measles outside the United States and brought their infection into the United States. Cases not directly imported include those that were acquired in the United States but linked to directly imported cases, imported virus, and cases with unknown sources.
† As of Aug 24, 2013.

FIGURE 2. Number of measles cases (N = 159), by state — United States, 2013*



* As of August 24, 2013.
† Includes New York City.

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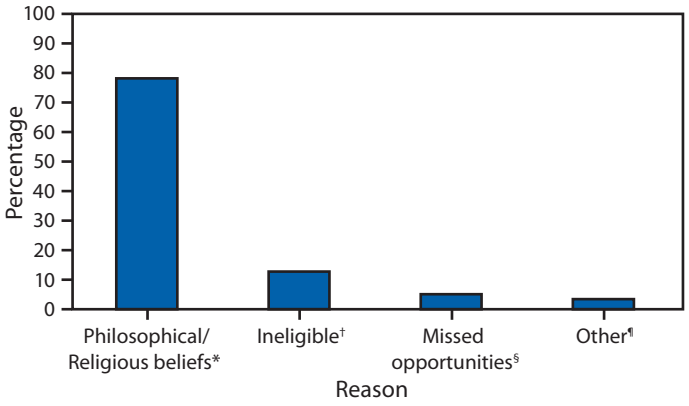
Editorial Note

Measles elimination has been maintained in the United States since it was declared in 2000. However, an estimated 20 million cases of measles occur each year worldwide, and cases continue to be imported into the United States. The increase in measles cases in the United States in 2013 serves as a reminder that imported measles cases can result in large outbreaks, particularly if introduced into areas with pockets of unvaccinated persons.

During 2013, nearly two thirds of the cases came from three outbreaks. In these outbreaks, transmission occurred after introduction of measles into communities with pockets of persons unvaccinated because of philosophical or religious beliefs. This allowed for spread to occur, mainly in households and community gatherings, before public health interventions could be implemented. Despite progress in global measles control and elimination, measles importations are likely to continue posing risks of measles outbreaks in unvaccinated communities. Maintaining high MMR vaccination coverage is essential to prevent measles outbreaks and sustain measles elimination in the United States.

To date in 2013, 23 measles importations have been reported by U.S. residents, most of whom were aged ≥6 months and unvaccinated. The source of imported cases continues to be most often the WHO European Region, a popular destination for U.S. travelers and an area where measles continues to circulate. All persons aged ≥6 months without evidence of measles immunity who travel outside the United States should be vaccinated before travel with 1 dose of MMR vaccine for infants aged 6–11 months and 2 doses for persons aged ≥12 months, at least 28 days apart. Routine MMR vaccination is recommended for all children at age 12–15 months, with a second dose at age 4–6 years. Two doses of MMR vaccine are also recommended for health-care personnel and students attending post–high school educational institutions, unless they have other evidence of immunity. Other adults without evidence of measles immunity should receive 1 dose of MMR vaccine. Health-care providers should encourage timely vaccination of all eligible patients and should remind parents

FIGURE 3. U.S residents with measles who were unvaccinated (n = 117), by reasons for not receiving measles vaccine — United States, January 1–July 13, 2013



* Includes persons who were unvaccinated because of their own or their parents' beliefs.
† Includes persons ineligible for measles vaccination, generally those aged <12 months.
§ Includes children aged 16 months–4 years who had not been vaccinated and international travelers aged ≥6 months who were unvaccinated but had no exemption.
¶ Includes persons who were known to be unvaccinated and the reason was unknown.

who plan to travel internationally with children of the increased risk for measles and the importance of vaccination (*6*).

Patients with measles often seek medical care; therefore, health-care providers should maintain a high awareness of measles and suspect measles in persons who have a febrile rash illness and clinically compatible symptoms and who have recently traveled abroad or have had contact with travelers. Providers should implement isolation precautions immediately, collect an appropriate laboratory specimen, and promptly report suspected measles case to their local health department (*7*). Early reporting and rapid control efforts by states and local public health agencies are essential to limit the spread of disease. Timely response plays an important role in limiting the size of outbreaks and preventing spread of measles, even in communities with large numbers of unvaccinated persons.

High MMR vaccine coverage in the United States (91% among children aged 19–35 months) limits the size of measles outbreaks; however, some states have coverage levels <90% (*8*). Additionally, unvaccinated children tend to cluster geographically and socially, increasing the risk for outbreaks (*9*). Increases in the proportion of persons declining vaccination for themselves or their children might lead to large-scale and sustained outbreaks, threatening the elimination of measles in the United States (*10*). Maintenance of high, 2-dose MMR vaccine coverage, early detection of cases, and rapid public health response to a case are the key factors that will lead to sustained elimination, despite the continued importation of cases into the United States.

What is already known on this topic?

Measles elimination has been maintained in the United States since it was declared in 2000. However, an estimated 20 million cases of measles occur each year worldwide, with continued importation of cases into the United States.

What is added by this report?

During January 1–August 24, 2013, a total of 159 cases of measles were reported to CDC, of which 146 (92%) were in persons who were unvaccinated or had unknown vaccination status and 42 (26%) cases were imported. Nearly two thirds of the cases were reported from three outbreaks that occurred after introduction of measles into communities with pockets of philosophical or religious exemptions.

What are the implications for public health practice?

Importation of measles into communities with unvaccinated persons can lead to large outbreaks and threaten the elimination of measles in the United States. Maintenance of high coverage with 2 doses of measles, mumps, and rubella vaccine, early detection of cases, and rapid public health response to reports of measles are key factors that will lead to sustained elimination.

References

1. Katz SL, Hinman AR. Summary and conclusions: measles elimination meeting, 16–17 March 2000. J Infect Dis 2004:189(Suppl 1):S43–7.
2. CDC. Summary of notifiable diseases—United States, 2008. MMWR 2010;57(54).
3. CDC. Summary of notifiable diseases—United States, 2011. MMWR 2013;60(53).
4. CDC. Notes from the field: measles outbreak among members of a religious community—Brooklyn, New York, March–June 2013. MMWR 2013;62:752–3.
5. CDC. Notes from the field: measles outbreak associated with a traveler returning from India—North Carolina. MMWR 2013;62:753.
6. CDC. Prevention of measles, rubella, congenital rubella syndrome, and mumps, 2013: summary recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2013;62(No. RR-4).
7. CDC. 2007 guideline for isolation precautions: preventing transmission of infectious agents in healthcare settings. Atlanta, GA: US Department of Health and Human Services, CDC; 2007. Available at http://www.cdc.gov/hicpac/2007ip/2007isolationprecautions.html.
8. CDC. National, state, and local area vaccination coverage among children aged 19–35 months— United States, 2012. MMWR 2013;62:733–40.
9. Smith PJ, Chu SY, Barker LE. Children who have received no vaccines: who are they and where do they live? Pediatrics 2004;114:187–95.
10. Omer SB, Salmon DA, Orenstein WA, deHart MP, Halsey N. Vaccine refusal, mandatory immunization, and the risks of vaccine-preventable diseases. N Engl J Med 2009;360:1981–8.

Morbidity and Mortality Weekly Report

Influenza Vaccination Practices of Physicians and Caregivers of Children with Neurologic and Neurodevelopmental Conditions — United States, 2011–12 Influenza Season

Cognitive dysfunction, seizure disorders (epilepsy), and other neurologic disorders are conditions associated with a high risk for complications of influenza virus infection (*1*–*3*). This risk was observed during the 2009 influenza pandemic; among 336 pediatric deaths, 146 occurred in children with underlying neurologic disorders, most commonly intellectual disability (76%) and epilepsy (51%) (*4*). Because little is known about influenza-related knowledge and practices among the families and health-care providers of children with neurologic or neurodevelopmental (NND) conditions, CDC worked with Family Voices and the American Academy of Pediatrics to survey parents and physicians during the 2011–12 influenza season to assess these factors. Among 1,005 children with NND conditions, parents reported that 50% of children were vaccinated or had a vaccine appointment scheduled. Vaccination rates were low for children with intellectual disability (52%) and epilepsy (59%). Physician recognition of high-risk conditions was low for intellectual disability (46%) and epilepsy (52%). Efforts to improve physician awareness are essential because physicians are in a key position to educate parents of children with NND conditions about their increased risk for influenza complications and the importance of prevention through vaccination. Further research also is needed to identify barriers to influenza vaccination among families and health-care providers of these children.

CDC collaborated with Family Voices, a national advocacy group for children with special health-care needs, to recruit via listservs parents of children with chronic medical conditions. An online survey was distributed to members of the Family Voices listservs and administered from September 6 through October 24, 2011. Parents or other caregivers were asked about their knowledge, attitudes, and practices related to having their children vaccinated with seasonal influenza vaccine.

This report focuses on vaccination behavior during the 2011–12 influenza season. For purposes of this study, vaccination rates were calculated by dividing the number of children reported to have been vaccinated or for whom a vaccination appointment was scheduled by the number of children for whom a response was obtained. Only children aged ≥6 months with high-risk conditions as defined by the Advisory Committee on Immunization Practices (*1*) were included in the analysis.

CDC also collaborated with the American Academy of Pediatrics to recruit primary-care and specialty physicians who provide care for children at high risk for influenza complications, specifically children with neurologic conditions. Physicians were recruited through American Academy of Pediatrics specialty listservs, including the Council on Children with Disabilities, the Committee on Practice and Ambulatory Medicine, and the Section on Neurology. An online survey was available from March 7 through May 15, 2011. This survey collected basic information regarding practice setting, specialty, and vaccination practices for various patient populations. Respondents also were asked which chronic medical conditions were associated with increased risk for severe illness from influenza.

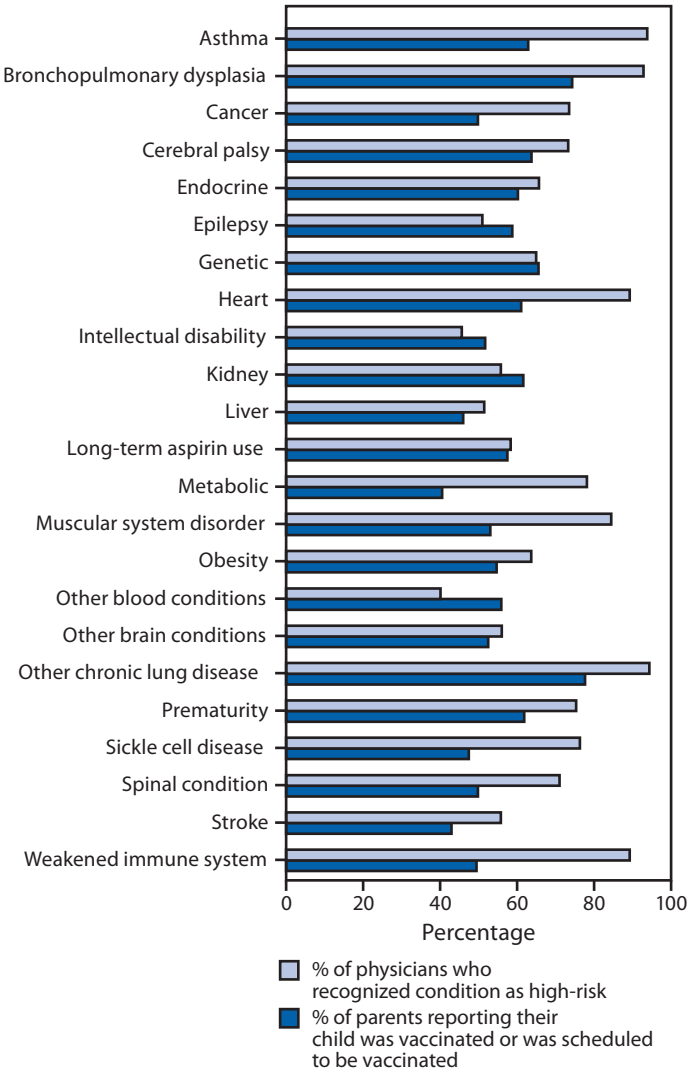
Descriptive statistics were summarized as percentages. Between-group differences were assessed using chi-square testing. A p-value of <0.05 was considered to be statistically significant.

A total of 1,940 surveys were completed by parents of children with a high-risk condition. Seasonal influenza vaccination rates categorized by high-risk condition ranged from 41% for children with metabolic conditions to 78% for children with chronic lung disease (Figure). Among 1,005 parents of children with NND conditions, 50% reported their child had received or had an appointment scheduled to receive influenza vaccine at the time of survey completion.

Among all respondents, health-care providers were reported most frequently (75%) as the source of information about vaccines in general, and influenza vaccine specifically. Parents of vaccinated children were more likely (80% versus 64% [$p<0.001$]) to report using health-care providers as a source of information. Use of the Internet (24%) and family support or disability advocacy organizations (22%) were less frequently reported as sources of information and did not differ between families of vaccinated and unvaccinated children.

A total of 412 physicians participated in the online survey. Of those, 183 (44%) respondents identified themselves as primary-care providers. Among the remaining physicians, the predominant specialties were neurology (65), emergency medicine (56), critical care (28) and genetics/metabolism (24). A total of 393 physicians completed the question about high-risk conditions (Figure). Intellectual disability and hematologic disorders other than sickle cell disease were considered to be high-risk conditions by a minority of respondents. Further analyses were performed on a subset of physicians most likely to provide outpatient medical care to children with NND conditions: primary-care pediatricians, neurologists, geneticists, developmental pediatricians, and physiatrists. These physicians caring for children with NND conditions were more likely than other pediatricians to

FIGURE. Influenza vaccination coverage among children at high risk for complications of influenza and physician recognition of high-risk conditions — United States, 2010–11 influenza season



indicate cerebral palsy (79% versus 63%), epilepsy (57% versus 39%), spinal cord conditions (76% versus 60%), stroke (63% versus 41%), and other brain conditions (62% versus 44%) as high-risk conditions ($p<0.05$ for all comparisons). They were not more likely to rate intellectual disability as a high-risk condition.

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What is already known on this topic?

Since 2005, the Advisory Committee on Immunization Practices has included cognitive dysfunction, spinal cord injuries, seizure disorders, and other neuromuscular disorders as high-risk conditions for complications associated with influenza virus infection. A review of pediatric influenza deaths during the 2009 H1N1 pandemic revealed that 146 (43%) of the 336 deaths occurred in children with an underlying neurologic condition.

What is added by this report?

Parents of children with neurologic or neurodevelopmental disorders and physicians caring for such children were surveyed by CDC during the 2011–12 influenza season. Parents responding to an online survey reported that 50% of 1,005 children with a neurologic disorder were vaccinated against influenza or had a vaccine appointment scheduled. Among the physicians, intellectual disability was recognized as a high-risk condition by 46% of respondents and epilepsy by 52%.

What are the implications for public health practice?

Vaccination coverage levels among children with neurologic conditions are comparable with those of healthy children, despite the fact that they are at increased risk for poor outcomes. Further research among families and health-care providers is needed to identify barriers to influenza immunization.

Editorial Note

Annual influenza vaccination is recommended for all children aged 6 months–18 years. Although they are at greater risk for poor outcomes related to infection with influenza viruses, influenza vaccination of children with NND conditions was similar to that observed in the general pediatric population. The results of this survey are consistent with 2011–12 national seasonal influenza vaccination coverage estimates of 52% among children aged 6 months–17 years in the general population (*5*). In contrast, the *Healthy People 2020* goal (IID-12) is to increase the percentage of children who are vaccinated annually to 80% (*6*). Parents and caregivers reported that health-care providers were the most important source of information about vaccines. Intellectual disability and epilepsy were the two most common NND conditions among children who died during the 2009 influenza pandemic (*2*) but were two of the three conditions least likely to be recognized as high-risk by physicians.

The findings in this report are subject to at least four limitations. First, selection bias likely affected the results. Both the health-care provider and caregiver surveys were distributed via listserv services that require a subscription, which might have led to the exclusion of non–American Academy of Pediatrics member physicians who treat children at high risk for influenza complications. In addition, physicians especially interested in influenza prevention and treatment might be overrepresented in the sample. Similarly, the caregiver survey excludes parents

and caregivers who are not on Family Voices listservs. Second, although it was not possible to calculate response rates because both surveys were distributed to multiple listservs, participation bias also likely affected the results. Third, the results of both surveys are based on self-report and might not reflect actual vaccination practices. Also, because this study assessed parental intent to vaccinate and parents were surveyed early in the influenza season, current vaccination and scheduled vaccination appointments were combined. However, parental intent to vaccinate a child might not have always resulted in vaccination. Finally, the physicians who participated in the health-care provider survey were not the same physicians who treated the patients in the parent survey. Therefore, their responses might not be representative of the experiences the caregivers had with their own health-care providers.

Despite these limitations, the results of these surveys demonstrate that children with NND conditions are no more likely to be vaccinated than healthy children, despite the fact that they are at increased risk for poor outcomes. Health-care providers remain the primary source of information regarding influenza vaccination. Increased outreach and communication efforts to both primary- and subspecialty-care providers might help reduce influenza-related morbidity and mortality among these children.

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References

1. CDC. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2005;54(No. RR-8).
2. Keren R, Zaoutis TE, Bridges CB, et al. Neurological and neuromuscular disease as a risk factor for respiratory failure in children hospitalized with influenza infection. JAMA 2005;294:2188–94.
3. CDC. Severe influenza among children and young adults with neurologic and neurodevelopmental conditions—Ohio, 2011. MMWR 2012;60:1729–33.
4. Blanton L, Peacock G, Cox C, Jhung M, Finelli L, Moore C. Neurologic disorders among pediatric deaths associated with the 2009 pandemic influenza. Pediatrics 2012;130:390–6.
5. CDC. Flu vaccination coverage, United States, 2011–12 influenza season. Atlanta, GA: US Department of Health and Human Services, CDC; 2013. Available at http://www.cdc.gov/flu/professionals/vaccination/coverage_1112estimates.htm#age-group-children.
6. US Department of Health and Human Services. Healthy people 2020. Washington, DC: US Department of Health and Human Services; 2013. Available at http://www.healthypeople.gov/2020/topicsobjectives2020/objectiveslist.aspx?topicid=23.

Comparison of Provisional with Final Notifiable Disease Case Counts — National Notifiable Diseases Surveillance System, 2009

States report notifiable disease cases to CDC through the National Notifiable Diseases Surveillance System (NNDSS). This allows CDC to assist with public health action and monitor infectious diseases across jurisdictional boundaries nationwide. The *Morbidity and Mortality Weekly Report* (*MMWR*) is used to disseminate these data on infectious disease incidence. The extent to which the weekly notifiable conditions are overreported or underreported can affect public health understanding of changes in the burden, distribution, and trends in disease, which is essential for control of communicable diseases (*1*). NNDSS encourages state health departments to notify CDC of a case when initially reported. These cases are included in the weekly provisional counts. The status of reported cases can change after further investigation by the states, resulting in differences between provisional and final counts. Increased knowledge of these differences can help in guiding the use of information from NNDSS. To quantify the extent to which final counts differ from provisional counts of notifiable infectious disease in the United States, CDC analyzed 2009 NNDSS data for 67 conditions. The results of this analysis demonstrate that for five conditions, final case counts were lower than provisional counts, but for 59 conditions, final counts were higher than provisional counts. The median difference between final and provisional counts was 16.7%; differences were ≤20% for 39 diseases but >50% for 12. These differences occur for various diseases and in all states. Provisional case counts should be interpreted with caution and an understanding of the reporting process.

Reporting of cases of certain diseases is mandated at the state or local level, and states, the Council of State and Territorial Epidemiologists (CSTE), and CDC establish policies and procedures for submitting data from these jurisdictions to NNDSS. Not all notifiable diseases are reportable at the state level, and although disease reporting is mandated by legislation or regulation, state reporting to CDC is voluntary. States send reports of cases of nationally notifiable diseases to CDC on a weekly basis in one of several standard formats. Amended reports can be sent, as well as new reports. Cases are reported by week of notification to CDC. Cases reported each week to CDC and published in *MMWR* are deemed provisional. The NNDSS database is open throughout the year, allowing states to update their records as new information becomes available. Annually, CDC provides each state epidemiologist with a cutoff date (usually 6 months after the end of the reporting year) by which all records must be reconciled and no additional updates are accepted for that reporting period. After the database is closed, final case counts, prepared after the states have reconciled the year-to-date data with local reporting units, are approved by state epidemiologists as accurate reflections of final case counts for the year and are published in the *MMWR Summary of Notifiable Diseases — United States.* Data for 2009 were published in 2011 (*2*).

CDC's publication schedule allows states time to complete case investigation tasks. To examine the extent that provisional counts of infectious diseases differ from final counts, CDC compared the cumulative case counts published for week 52 of 2009 in the *MMWR* of January 8, 2010 to the case counts published in the NNDSS final data set for 2009 (cutoff date of June 2010) published in *MMWR* on August 20, 2010. To assess whether discrepancies between provisional and final counts were more common in specific states or regions, or everywhere, reporting was examined, by state, of four diverse diseases: one sexually transmitted disease (*Chlamydia trachomatis*, genital infection), one vaccine-preventable disease (pertussis), one foodborne disease (salmonellosis), and one vectorborne disease (Lyme disease). Data are not presented for tuberculosis and human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome because these data are published quarterly rather than weekly in *MMWR*. Weekly reports of these conditions to the public health community are of limited value because of differences in reporting patterns for these diseases, and long-term variations in the number of cases are more important to public health practitioners than weekly variations (*3*).

Reported data for 67 notifiable diseases were reviewed. Final counts were lower than provisional counts for five diseases, the same as provisional counts for three, and higher for 59 (Table 1). The median difference between final and provisional counts was 16.7%; differences were ≤20% for 39 diseases but >50% for 12. Among diseases with ≥10 cases reported in 2009, final counts were lower than provisional counts for just four: invasive *Haemophilus influenzae* disease, ages <5 years, unknown serotype (final: 166, provisional: 218); acute hepatitis C (final: 782, provisional: 844); toxic-shock syndrome, other than streptococcal (final: 74, provisional: 76); and influenza-associated pediatric mortality (final: 358, provisional: 360). Final counts were higher than provisional counts for 51 diseases. The greatest percentage differences between provisional and final case counts were for arboviral disease, West Nile virus (neuro/nonneuro) (final: 720, provisional: 0); mumps (final: 1,991, provisional: 982); and Hansen disease (final: 103, provisional: 59).

TABLE 1. Comparison of provisional and finalized notifiable diseases data — National Notifiable Diseases Surveillance System, 2009

Disease	Final data	Provisional data	Absolute change	Change (%)
Anthrax	1	—	1	
Arboviral disease, California serogroup (neuro/nonneuro)	55	41	14	(34.1)
Arboviral disease, Eastern equine (neuro/nonneuro)	4	4	0	(0.0)
Arboviral disease, Powassan (neuro)	6	1	5	(500.0)
Arboviral disease, St. Louis encephalitis (neuro/nonneuro)	12	10	2	(20.0)
Arboviral disease, West Nile virus (neuro/nonneuro)	720	—	720	
Botulism, total	118	92	26	(28.3)
Brucellosis	115	100	15	(15.0)
Chancroid	28	25	3	(12.0)
Chlamydia trachomatis, genital infections	1,244,180	1,100,230	143,950	(13.1)
Cholera	10	8	2	(25.0)
Coccidioidomycosis	12,926	12,729	197	(1.5)
Cryptosporidiosis, total	7,654	6,652	1,002	(15.1)
Cyclosporiasis	141	123	18	(14.6)
Ehrlichiosis, *Ehrlichia chaffeen*	944	801	143	(17.9)
Ehrlichiosis, *Ehrlichia ewingii*	7	6	1	(16.6)
Ehrlichiosis, *Anaplasma phagocytophilum*	1,161	690	471	(68.3)
Ehrlichiosis, undetermined	155	122	33	(27.0)
Giardiasis	19,399	17,548	1,851	(10.6)
Gonorrhea	301,174	260,530	40,644	(15.6)
Haemophilus influenzae, invasive disease, all ages, both sexes	3,022	2,896	126	(4.4)
Haemophilus influenzae, invasive disease, ages <5 yrs, serotype b	38	25	13	(52.0)
Haemophilus influenzae, invasive disease, ages <5 yrs, nonserotype b	245	203	42	(20.7)
Haemophilus influenzae, invasive disease, ages <5 yrs, unknown serotype	166	218	−52	(−23.9)
Hansen disease	103	59	44	(74.6)
Hantavirus pulmonary syndrome	20	12	8	(66.7)
Hemolytic uremic syndrome postdiarrheal	242	210	32	(15.2)
Hepatitis A, viral, acute	1,987	1,849	138	(7.5)
Hepatitis B, viral, acute	3,405	3,020	385	(12.7)
Hepatitis C, viral, acute	782	844	−62	(−7.4)
Influenza-associated pediatric mortality	358	360	−2	(−0.6)
Legionellosis	3,522	3,145	377	(12.0)
Listeriosis	851	755	96	(12.7)
Lyme disease, total	38,468	29,780	8,688	(29.2)
Malaria	1,451	1,169	282	(24.1)
Measles, total	71	61	10	(16.4)
Meningococcal disease, all serogroups	980	887	93	(10.5)
Mumps	1,991	982	1,009	(102.8)
Pertussis	16,858	13,506	3,352	(24.8)
Plague	8	7	1	(14.3)
Polio	1	—	1	
Psittacosis	9	9	0	(0.0)
Q fever, total	113	95	18	(19.0)
Rabies, animal	5,343	3,581	1,762	(49.2)
Rabies, human	4	4	0	(0.0)
Rocky Mountain spotted fever, total	1,815	1,393	422	(30.3)
Rubella	3	4	−1	(−25.0)
Rubella, congenital syndrome	2	1	1	(100.0)
Salmonellosis	49,192	44,468	4,724	(10.6)
Shiga toxin-producing *Escherichia coli* (STEC)	4,643	4,323	320	(7.4)
Shigellosis	15,931	14,581	1,350	(9.3)
Streptococcal disease, invasive group A	5,279	4,861	418	(8.6)
Streptococcal toxic-shock syndrome	161	125	36	(28.8)
Streptococcus pneumoniae, invasive disease, drug resistant, all ages	3,370	2,823	547	(19.4)
Streptococcus pneumoniae, invasive disease, drug resistant, ages <5 yrs	583	464	119	(25.7)
Streptococcus pneumoniae, invasive disease, nondrug resistant, ages <5 yrs	1,988	1,768	220	(12.4)
Syphilis, congenital	427	257	170	(66.2)
Syphilis, primary and secondary	13,997	12,833	1,164	(9.1)
Tetanus	18	14	4	(28.6)
Toxic-shock syndrome (other than streptococcal)	74	76	−2	(−2.6)
Trichinellosis	13	12	1	(8.3)
Tularemia	93	79	14	(17.7)
Typhoid fever	397	324	73	(22.5)
Vancomycin-intermediate *Staphylococcus aureus* (VISA)	78	70	8	(11.4)
Vancomycin-resistant *Staphylococcus aureus* (VRSA)	1	—	1	
Varicella (chickenpox morbidity)	20,480	16,944	3,536	(20.9)
Vibriosis	789	593	196	(33.1)

Examining four diverse but commonly reported diseases in detail revealed no consistent association between state or region and the magnitude of the discrepancy between final and provisional counts (Table 2). For *Chlamydia trachomatis*, genital infections, the final case count was 13.1% higher than the provisional count nationally; it was <2% lower everywhere and ≥20% higher in six states. Two states, Arkansas and North Carolina, reported no cases provisionally, but reported final case counts of 14,354 and 41,045, respectively. For Lyme disease, the final case count was 29.2% higher than the provisional count nationally. Only 23 jurisdictions reported >100 cases, including 21 states, upstate New York, and New York City. Of these, four states reported a final count lower than their provisional count (range: 13.4%–29.2%) and eight jurisdictions reported final counts ≥20% higher. The greatest percentage differences between provisional and final case counts were in Connecticut (final: 4,156, provisional: none), Minnesota, (final: 1,543, provisional: 169), Texas (final: 276, provisional: 48), and New York City (final: 1,051, provisional: 262). For pertussis, the final case count was 24.8% higher than the provisional count nationally; it was <2% lower everywhere and ≥20% higher in 18 states and the District of Columbia (DC). Of the five states that reported >1,000 cases, the states with the greatest percentage differences between provisional and final counts were Minnesota (final: 1,121, provisional: 165) and Texas (final: 3,358, provisional: 2,437). For salmonellosis, the final case count was 10.6% higher than provisional count nationally. Six states reported a final count lower than their provisional count (range: 0.1%–2.9%) and nine states plus DC reported final counts ≥20% higher, the highest being DC (final: 100, provisional: 26), Louisiana (final: 1,180, provisional: 599), and Indiana (final: 629, provisional: 349).

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Editorial Note

The findings in this report corroborate previous observations that provisional NNDSS data should be interpreted with caution (*1,4,5*). The primary appeal of provisional counts is timeliness; in comparison, final counts are more complete and accurate. As additional information is collected during investigations, final case counts might be higher or lower than the provisional counts. Local and state health departments collect reportable surveillance data primarily to assist with disease control and prevention efforts (i.e., to monitor local outbreaks of infectious diseases), to measure disease burden among high-risk populations, and to assess effectiveness of local interventions. At the national level, these data can be compared with baseline data to detect unusual disease occurrences. Final data sets are useful in monitoring national trends and for determining the effectiveness of national intervention efforts. In 2009, final case counts did not differ from end-of-year provisional counts by >20% for two thirds of the 67 notifiable diseases examined. Understanding how provisional counts relate to final counts is essential for interpreting provisional data (*6,7*).

Final counts might be higher than provisional counts for several possible reasons: 1) as amended records are sent by states during the notification process, cases might be reclassified among confirmed, probable, suspected, and not-a-case categories; 2) states vary in their practices regarding when they report cases with incomplete data or that are under investigation, leading to variable delays; 3) allocation of cases to a state can be delayed; 4) laboratory testing, case investigation, and data entry can be delayed as a result of temporary staff absences (e.g., leave, furlough, or turnover); 5) states sometimes delay sending some reports to CDC until the end of the year; and 6) internal CDC data processing problems can cause a discrepancy.

The findings in this report are subject to at least one limitation. It was impossible to determine when final counts were known to the state and local jurisdictions so that they could take public health action. This report focuses only on counts published in *MMWR*. The jurisdictions might have been aware of final case counts sooner, and only notification to CDC was delayed. Although this study examined 1 year of data, previous research using multiple years of data for hepatitis A and B concluded that provisional data generally tend to underrepresent the final data counts for those conditions (*1*). The addition of

What is already known on this topic?

Provisional counts of notifiable diseases usually differ from final counts; they are most often lower.

What is added by this report?

In 2009, finalized case counts were higher than the provisional case counts for 59 of 67 notifiable diseases. The median difference between final and provisional counts was 16.7%; differences were ≤20% for 39 diseases but >50% for 12. These differences occur, to a greater or lesser extent, for a wide variety of diseases and in all states.

What are the implications for public health practice?

Notifiable disease data are subject to case reclassification leading to undernotification or overnotification. Provisional case counts should be interpreted with caution because of the reporting process. The primary appeal of provisional counts is timeliness; in comparison, final counts are more complete and accurate.

TABLE 2. Comparison of provisional and final reported cases of notifiable diseases for selected conditions, by state and area — National Notifiable Diseases Surveillance System, United States, 2009

Area	Chlamydia			Lyme disease			Pertussis			Salmonellosis		
	Final	Provisional	Change (%)	Final	Provisional	Change (%)	Final	Provisional	Change (%)	Final	Provisional	Change (%)
United States	**1,244,180**	**1,100,230**	**(13.1)**	**38,468**	**29,780**	**(29.2)**	**16,858**	**13,506**	**(24.8)**	**49,191**	**44,468**	**(10.6)**
New England	40,776	39,850	(2.3)	12,440	6,314	(97.0)	626	592	(5.7)	2,174	2,110	(3.0)
Connecticut	12,127	11,532	(5.2)	4,156	—		56	48	(16.7)	430	406	(5.9)
Maine	2,431	2,386	(1.9)	970	894	(8.5)	80	78	(2.6)	121	119	(1.7)
Massachusetts	19,315	19,538	(–1.2)	5,256	3,662	(43.5)	358	348	(2.9)	1,155	1,159	(–0.4)
New Hampshire	2,102	1,633	(28.7)	1,415	1,156	(22.4)	76	76	(0.0)	261	243	(7.4)
Rhode Island	3,615	3,614	(0.0)	235	212	(10.9)	45	31	(45.2)	144	122	(18.0)
Vermont	1,186	1,147	(3.4)	408	390	(4.6)	11	11	(0.0)	63	61	(3.3)
Mid-Atlantic	159,111	154,989	(2.7)	16,346	16,691	(–2.1)	1,222	1,101	(11.0)	5,514	5,001	(10.3)
New Jersey	23,974	21,181	(13.2)	4,973	4,163	(19.5)	244	158	(54.4)	1,132	802	(41.2)
New York (Upstate)	33,722	32,099	(5.1)	4,600	4,179	(10.1)	265	252	(5.2)	1,370	1,321	(3.7)
New York City	58,347	59,370	(–1.7)	1,051	262	(301.2)	98	92	(6.5)	1,253	1,171	(7.0)
Pennsylvania	43,068	42,339	(1.7)	5,722	8,087	(–29.2)	615	599	(2.7)	1,759	1,707	(3.1)
Eastern North Central	197,133	167,016	(18.0)	2,969	2,359	(25.9)	3,206	2,990	(7.2)	5,169	4,597	(12.4)
Illinois	60,542	48,929	(23.7)	136	126	(7.9)	648	570	(13.7)	1,484	1,294	(14.7)
Indiana	21,732	21,111	(2.9)	83	62	(33.9)	392	338	(16.0)	629	349	(80.2)
Michigan	45,714	44,873	(1.9)	103	99	(4.0)	900	854	(5.4)	960	911	(5.4)
Ohio	48,239	34,036	(41.7)	58	56	(3.6)	1,096	1,096	(0.0)	1,407	1,407	(0.0)
Wisconsin	20,906	18,067	(15.7)	2,589	2,016	(28.4)	170	132	(28.8)	689	636	(8.3)
Western North Central	70,396	66,205	(6.3)	1,693	303	(458.8)	2,840	1,678	(69.3)	2,679	2,472	(8.4)
Iowa	9,406	9,311	(1.0)	108	96	(12.5)	235	192	(22.4)	408	398	(2.5)
Kansas	10,510	9,798	(7.3)	18	14	(28.6)	240	146	(64.4)	398	269	(48.0)
Minnesota	14,197	12,222	(16.2)	1,543	169	(813.0)	1,121	165	(579.4)	575	572	(0.5)
Missouri	25,868	25,698	(0.7)	3	3	(0.0)	1,015	975	(4.1)	656	667	(–1.7)
Nebraska	5,443	5,262	(3.4)	5	20	(–75.0)	141	141	(0.0)	341	337	(1.2)
North Dakota	1,957	1,769	(10.6)	15	—		30	29	(3.5)	103	73	(41.1)
South Dakota	3,015	2,145	(40.6)	1	1	(0.0)	58	30	(93.3)	198	156	(26.9)
South Atlantic	249,979	194,409	(28.6)	4,466	3,778	(18.2)	1,632	1,551	(5.2)	14,478	13,488	(7.3)
Delaware	4,718	4,718	(0.0)	984	952	(3.4)	13	13	(0.0)	142	137	(3.7)
District of Columbia	6,549	6,414	(2.1)	61	20	(205.0)	7	3	(133.3)	100	26	(284.6)
Florida	72,931	71,731	(1.7)	110	127	(–13.4)	497	500	(–0.6)	6,741	6,749	(–0.1)
Georgia	39,828	29,934	(33.1)	40	53	(–24.5)	223	194	(15.0)	2,362	2,365	(–0.1)
Maryland	23,747	22,138	(7.3)	2,024	1,775	(14,0)	148	134	(10.5)	803	784	(2.4)
North Carolina	41,045	—		96	63	(52.4)	220	223	(–1.4)	1,810	1,053	(71.9)
South Carolina	26,654	25,014	(6.7)	42	39	(7.7)	262	252	(4.0)	1,195	1,153	(3.6)
Virginia	30,903	30,881	(0.1)	908	579	(56.8)	222	198	(12.1)	1,095	1,004	(9.1)
West Virginia	3,604	3,579	(0.7)	201	170	(18.2)	40	34	(17.7)	230	217	(6.0)
Eastern South Central	92,522	87,926	(5.2)	41	36	(13.9)	803	760	(5.7)	3,077	2,937	(4.8)
Alabama	25,929	22,833	(13.6)	3	3	(0.0)	305	285	(7.0)	932	850	(9.7)
Kentucky	13,293	13,166	(1.0)	1	1	(0.0)	226	219	(3.2)	453	451	(0.4)
Mississippi	23,589	22,146	(6.5)	—	—		75	66	(13.6)	899	853	(5.4)
Tennessee	29,711	29,781	(–0.2)	37	32	(15.6)	197	190	(3.7)	793	783	(1.3)
Western South Central	162,915	136,836	(19.1)	278	48	(479.2)	3,993	2,882	(38.6)	6,411	4,751	(34.9)
Arkansas	14,354	—		—	—		369	278	(32.7)	615	607	(1.3)
Louisiana	27,628	25,308	(9.2)	—	—		149	90	(65.6)	1,180	599	(97.0)
Oklahoma	15,023	12,959	(15.9)	2	—		117	77	(52.0)	652	615	(6.0)
Texas	105,910	98,569	(7.5)	276	48	(475.0)	3,358	2,437	(37.8)	3,964	2,930	(35.3)
Mountain	80,476	73,912	(8.9)	57	44	(30.0)	1,019	890	(14.5)	3,028	2,812	(7.7)
Arizona	26,002	25,110	(3.6)	7	6	(16.7)	277	224	(23.7)	1,086	1,051	(3.3)
Colorado	19,998	16,362	(22.2)	1	1	(0.0)	231	233	(–0.9)	619	621	(–0.3)
Idaho	3,842	3,501	(9.7)	16	15	(6.7)	99	99	(0.0)	174	172	(1.2)
Montana	2,988	2,913	(2.6)	3	3	(0.0)	61	57	(7.0)	110	99	(11.1)
Nevada	10,045	9,743	(3.1)	13	5	(160.0)	24	9	(166.7)	252	173	(45.7)
New Mexico	9,493	8,947	(6.1)	5	5	(0.0)	85	66	(28.8)	369	325	(13.5)
Utah	6,145	5,466	(12.4)	9	7	(28.6)	220	181	(21.6)	321	283	(13.4)
Wyoming	1,963	1,870	(5.0)	3	2	(50.0)	22	21	(4.8)	97	88	(10.2)
Pacific	190,872	179,087	(6.6)	178	207	(–14.0)	1,517	1,062	(42.8)	6,662	6,300	(5.8)
Alaska	5,166	4,412	(17.1)	7	3	(133.0)	59	49	(20.4)	68	70	(–2.9)
California	146,796	139,689	(5.1)	117	154	(–24.0)	869	473	(83.7)	5,003	4,757	(5.2)
Hawaii	6,026	5,610	(7.4)	—*	—*		46	29	(58.6)	338	297	(13.8)
Oregon	11,497	10,245	(12.2)	38	35	(8.6)	252	246	(2.4)	433	416	(4.1)
Washington	21,387	19,131	(11.8)	16	15	(6.7)	291	265	(9.8)	820	760	(7.9)

* Not notifiable in Hawaii.

more years to the current research, which examined multiple notifiable conditions and documents substantial differences across states, regions, and numerous conditions, would not be expected to change the overall results.

Interpreting weekly incidence data is complex because of surveillance system limitations. Nonetheless, health practitioners have to respond to public health threats based on preliminary surveillance information. In 2006, CDC and CSTE reconsidered data presentation formats and included additional information (e.g., 5-year weekly average, previous 52 weeks median, and maximum number of cases) to aid interpreting these data (*3*). However, the findings in this report illustrate that major challenges still exist in presenting and interpreting provisional data and highlights the need to examine specific factors that can contribute to late reporting of cases (e.g., late case reporting by providers to health departments or late reporting of cases by health departments to CDC) (*4*). Although information technology has improved notifiable disease reporting (*8*), NNDSS data remain subject to reporting artifacts. Understanding specific reasons for the variation between the provisional and final case counts for each condition can improve the use of provisional data for disease surveillance and notification.

Acknowledgments

Richard Hopkins, MD, Florida Dept of Health. John Davis-Cole, PhD, District of Columbia Dept of Health. Michael Landen, MD, New Mexico Dept of Health. Participating state health departments and reporting jurisdictions.

References

1. Smallman-Raynor M, Cliff AD, Haggett P, Stroup DF, Williamson GD. Spatial and temporal patterns in final amendments to provisional disease counts. J Public Health Manag Pract 1999;5:68–83.
2. CDC. Summary of notifiable diseases—United States, 2009. MMWR 2011;58(53).
3. CDC. Notice to readers: changes in presentation of data from the National Notifiable Diseases Surveillance System. MMWR 2006;55:13–4.
4. Stroup DF, Williamson GD, Herndon JL, Karon JM. Detection of aberrations in the occurrence of notifiable diseases surveillance data. Stat Med 1989;8:323–9.
5. Stroup DF, Wharton M, Kafadar K, Dean AG. Evaluation of a method for detecting aberrations in public health surveillance system data. Am J Epidemiol 1993;137:373–80.
6. Birkhead G, Chorba TL, Root S, Klaucke DN, Gibbs NJ. Timeliness of national reporting of communicable diseases: the experience of the National Electronic Telecommunications System for Surveillance. Am J Public Health 1991;81:1313–5.
7. Boehmer TK, Patnaik JL, Burnite SJ, Ghosh TS, Gershman K, Vogt RL. Use of hospital discharge data to evaluate notifiable disease reporting to Colorado's Electronic Disease Reporting System. Public Health Rep 2011;126:100–6.
8. Silk BJ, Berkelman RL. A review of strategies for enhancing the completeness of notifiable disease reporting. J Public Health Manag Pract 2005;11:191–200.

Notes from the Field

Measles Outbreak Among Members of a Religious Community — Brooklyn, New York, March–June 2013

On March 13, 2013, an intentionally unvaccinated adolescent aged 17 years returned to New York City from London, United Kingdom, while infectious with measles. This importation led to the largest outbreak of measles in the United States since 1996 (*1*).

Investigation of suspected cases included patient interviews, medical record reviews, and ascertainment of immunization records. Testing for measles immunoglobulin G (IgG) and immunoglobulin M (IgM) and testing for measles virus RNA by reverse-transcription polymerase chain reaction (RT-PCR) were performed, and measles genotype was determined. Cases were identified in residents of New York City and classified according to the Council of State and Territorial Epidemiologists clinical case definition (*2*). Exposed contacts were identified, and control measures were implemented.

A total of 58 cases* were identified, including six generations of measles infection in two neighborhoods of the borough of Brooklyn. All cases were in members of the orthodox Jewish community. No case was identified in a person who had documented measles vaccination at the time of exposure; 12 (21%) of the cases were in infants too young (aged <12 months) for routine immunization with measles, mumps, and rubella (MMR) vaccine. The outbreak was first recognized in Brooklyn's Borough Park neighborhood, where the median age of 28 infected persons was 10 years (range: 0–32 years), and 79% of cases in persons aged ≥12 months were in three extended families whose members declined use of measles vaccine. The outbreak spread to the Williamsburg neighborhood, where the median age of 30 infected persons was 19 months (range: 0 months–32 years), and the primary reasons for lack of vaccination were refusal (nine, 30%) and delay (eight, 27%). Forty-eight (83%) of all cases were confirmed by positive measles IgM or RT-PCR result and 10 (17%) by epidemiologic linkage (*2*). Genotype D8 was identified in 17 cases, consistent with known current circulation of this genotype in the United Kingdom. No other genotype was identified among the cases.

In 31% of cases, no medical care for rash illness had been sought and, therefore, the cases had not been reported to the New York City Department of Health and Mental Hygiene (DOHMH) by a medical provider. In 9% of cases, patients saw a medical provider at the time of rash illness but were not reported when the diagnosis of measles was first considered. In 52% of cases, measles was likely acquired from a relative. Complications included pneumonia in one child; two pregnant women required hospitalization, including one who miscarried. The last case onset occurred on June 9, 2013.

Approximately 3,500 contacts were identified in health-care, school, and home settings. Control measures included administration of immune globulin or MMR vaccine post-exposure prophylaxis; home isolation; alerts to medical providers; active recall of children in medical practices who were not up-to-date with measles vaccine; notifications to families, schools and day care providers through letters, flyers, and advertisements in newspapers; immunization audits of schools; and meetings with religious leaders and elected officials. DOHMH recommended that obstetricians in affected communities test for measles immunity during pregnancy and vaccinate women without evidence of measles immunity postpartum. Because infants were affected, vaccination recommendations during the outbreak period were expanded to include MMR vaccine for all children aged 6–11 months in the affected communities, with the second dose of MMR vaccine administered early, as soon as 4 weeks after the first dose of MMR vaccine.

Measles elimination was declared in the United States in 2000. However, importations of measles continue to present risks for outbreaks in the United States. This outbreak was propagated by a few extended families whose members declined MMR vaccine and by children with delays in receiving MMR vaccine in densely populated neighborhoods (*3*). High vaccination coverage within the Brooklyn orthodox Jewish community likely limited the scope of the outbreak. The insular nature of the affected community and high population-level vaccination coverage outside this community likely prevented further spread of measles.

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* Includes 57 confirmed cases and one case in a newborn who was culture-positive and born to an infected mother but did not have documentation of clinical symptoms.

Notes from the Field

References

1. CDC. Measles outbreak among school-aged children—Juneau, Alaska, 1996. MMWR 1996;45:777–80.
2. Council of State and Territorial Epidemiologists. Public health reporting and national notification for measles; 2012. Atlanta, GA: Council of State and Territorial Epidemiologists; 2012. Available at http://c.ymcdn.com/sites/www.cste.org/resource/resmgr/ps/12-id-07final.pdf.
3. New York City Department of Planning. Population: 2010 demographic maps. New York, NY: New York City Department of Planning; 2013. Available at http://www.nyc.gov/html/dcp/html/census/demo_maps_2010.shtml.

Measles Outbreak Associated with a Traveler Returning from India — North Carolina, April–May 2013

On April 14, 2013, public health officials in North Carolina were notified of suspected measles infections in two unvaccinated members of a family. Measles was confirmed by laboratory testing at the State Laboratory of Public Health on April 16, 2013. Investigators learned that a third unvaccinated member of the household had developed fever and rash 11 days earlier, after returning to the United States from a 3-month visit to India, but measles had not been suspected until household contacts sought evaluation for similar symptoms.

During April and May, direct and indirect transmission from the returning traveler resulted in 22 identified cases of measles (including the two cases first reported), for a total of 23 cases overall. Most cases were among residents of a largely unvaccinated religious community in rural North Carolina. Eighteen (78%) of the 23 patients were unvaccinated, three (13%) had been fully vaccinated with 2 doses of measles vaccine, and two (9%) had unknown vaccination status. The 23 patients ranged in age from 1 to 59 years. Measles was confirmed by laboratory testing of specimens from 16 patients (70%). Specimens collected from eight cases were sent to the Vaccine Preventable Disease Reference Center at the Wisconsin State Laboratory of Hygiene for molecular characterization. Genotype D8, the most commonly identified measles genotype in India (*1*), was identified in the specimens from all eight cases.

This outbreak required extensive resources from both state and local public health agencies. Estimates provided by local health departments indicated that approximately 2,200 hours were spent on control efforts. Isolation orders were issued to 30 persons with suspected or confirmed measles infection. Investigation of the contacts of these persons led to the identification of approximately 1,000 exposed persons from various settings, including health-care facilities, schools, and community events. Contacts without evidence of measles immunity were offered postexposure prophylaxis with measles vaccine or immune globulin as indicated (*2*). Written quarantine orders were issued to 72 (81%) of 89 susceptible contacts who did not receive measles vaccine within 72 hours of exposure, and oral quarantine orders were issued to the remaining 17 (19%).

Although measles is no longer endemic in the United States (*2*), importation of measles virus continues to occur. This outbreak consumed resources from state and local public health agencies for many weeks and resulted in restrictions on the movement, through isolation or quarantine measures, of approximately 115 persons in the community. Preventing future travel-associated outbreaks in North Carolina and the United States will require maintaining high rates of immunization (particularly among travelers to areas where measles is endemic), rapid identification of cases, and swift public health response.

Reported by

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References

1. Rota PA, Brown K, Mankertz A, et al. Global distribution of measles genotypes and measles molecular epidemiology. J Infect Dis 2011;204 (Suppl 1):S514–23.
2. CDC. Prevention of measles, rubella, congenital rubella syndrome, and mumps, 2013: summary recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2013;62(No. RR-4).

Announcements

National Child Passenger Safety Week — September 15–21, 2013

In the United States, motor vehicle–related injuries are a leading cause of death among children (*1*). In 2011, a total of 656 passenger vehicle occupants aged 0–12 years died as a result of a crash (*2*). During 1975–2011, child restraints saved an estimated 9,874 lives of children aged 0–4 years (*2*). Seating position also contributes to child passenger safety. To keep child passengers as safe as possible, drivers should properly restrain children aged <13 years in a back seat and follow the American Academy of Pediatrics' child passenger safety recommendations (*3*).

For 2013, National Child Passenger Safety Week is September 15–21. As part of the campaign, September 21 is designated as National Seat Check Saturday, when drivers with child passengers are encouraged to visit a child safety seat inspection station to have a certified technician inspect their car seat and give hands-on advice free of charge. Additional information and an inspection station locator are available from the National Highway Traffic Safety Administration at http://www.nhtsa.gov/Safety/CPS. Promotional materials (in English and Spanish) are available at http://www.trafficsafetymarketing.gov/cps.

References

1. CDC. Web-based Injury Statistics Query and Reporting System (WISQARS). Atlanta, GA: US Department of Health and Human Services, CDC; 2013. Available at http://www.cdc.gov/ncipc/wisqars.
2. National Highway Traffic Safety Administration. Traffic safety facts 2011 data—children. Washington, DC: US Department of Transportation, National Highway Traffic Safety Administration; 2013. Available at http://www-nrd.nhtsa.dot.gov/pubs/811767.pdf.
3. Durbin DR; Committee on Injury, Violence, and Poison Prevention. Child passenger safety. Pediatrics 2011;127:e1050–66.

CDC's New Healthy Aging Data Portfolio

The CDC Healthy Aging Program has released a Healthy Aging Data Portfolio (available at http://nccd.cdc.gov/dph_aging/default.aspx) that focuses on the health and well-being of older persons in the United States. Two factors will significantly affect health and social systems in the United States: longer adult life spans and a dramatic increase in the number of older adults, primarily because of the aging of "baby boomers" (persons born during 1946–1964). The population of U.S. residents aged ≥65 years is expected to double during the next 25 years, to about 72 million persons.

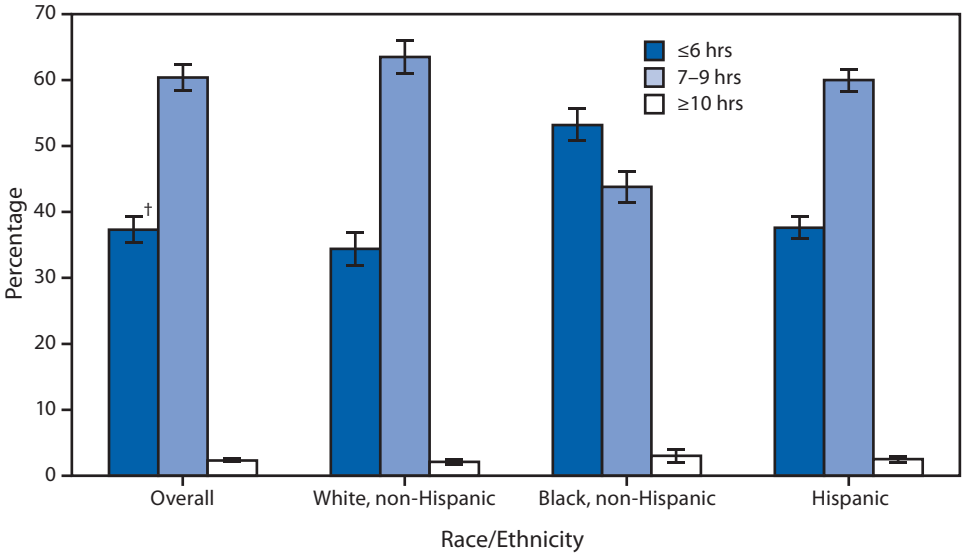
The portfolio is a compilation of previously published reports that focus on adults aged 50–64 years or ≥65 years, depending on the nature of the report. The portfolio includes the newly released report, *The State of Aging and Health in America 2013*, which provides data on key indicators and strategies to improve the health and quality of life for adults aged ≥65 years. National, state, and local public health and aging services network professionals, researchers, health-care providers, journalists, decision makers, and others interested in the health of older adults can use the portfolio to examine national, state, and selected local area data, create custom reports, learn about related expert recommendations and *Healthy People 2020* objectives, and find links to informational resources. Additional information about CDC's work on healthy aging is available at http://www.cdc.gov/aging.

Morbidity and Mortality Weekly Report

QuickStats

FROM THE NATIONAL CENTER FOR HEALTH STATISTICS

Sleep Duration* Among Adults Aged ≥20 Years, by Race/Ethnicity — National Health and Nutrition Examination Survey, United States, 2007–2010



* Data on sleep duration come from the question, "How much sleep do you usually get at night on weekdays or workdays?" All estimates are age-adjusted to the 2000 projected U.S. standard population using the age groups 20–39, 40–59, and ≥60 years.
† 95% confidence interval.

During 2007–2010, 60.4% of U.S. adults aged ≥20 years slept 7–9 hours at night, 37.3% slept 6 hours or less, and 2.3% slept 10 hours or more. Non-Hispanic black adults were less likely to report sleeping 7–9 hours and more likely to report sleeping 6 hours or less than non-Hispanic white and Hispanic adults.

Source: CDC. National Health and Nutrition Examination Survey. Hyattsville, MD: US Department of Health and Human Services, CDC, National Center for Health Statistics; 2007–2010. Available at http://www.cdc.gov/nchs/nhanes.htm.

Reported by: Steven M. Frenk, PhD, sfrenk@cdc.gov, 301-458-4096; Yinong Chong, PhD.

The *Morbidity and Mortality Weekly Report (MMWR)* Series is prepared by the Centers for Disease Control and Prevention (CDC) and is available free of charge in electronic format. To receive an electronic copy each week, visit *MMWR*'s free subscription page at *http://www.cdc.gov/mmwr/mmwrsubscribe.html*. Paper copy subscriptions are available through the Superintendent of Documents, U.S. Government Printing Office, Washington, DC 20402; telephone 202-512-1800.

Data presented by the Notifiable Disease Data Team and 122 Cities Mortality Data Team in the weekly *MMWR* are provisional, based on weekly reports to CDC by state health departments. Address all inquiries about the *MMWR* Series, including material to be considered for publication, to Editor, *MMWR* Series, Mailstop E-90, CDC, 1600 Clifton Rd., N.E., Atlanta, GA 30333 or to *mmwrq@cdc.gov.*

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EXHIBIT 303

Centers for Disease Control and Prevention

AdultVaxView

Vaccination Coverage Among Adults in the United States, National Health Interview Survey, 2016

Key Findings

- Compared with 2015 NHIS estimates, modest increases in vaccination coverage occurred for some vaccines and age groups but coverage decreased for one vaccine overall and in two age groups in one racial/ethnic category. Apart from these changes, vaccination coverage among adults in 2016 was similar to estimates from 2015.
  - Overall influenza vaccination decreased 3.1 percentage points to 70.4% among adults ≥65 years, and decreased among whites in all age groups except among adults 19-49 years (range: minus 2.2 – minus 3.5 percentage points).
  - Pneumococcal vaccination increased 3.3 percentage points to 66.9% among adults ≥ 65 years.
  - Vaccination of adults 19 years and older with tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine (Tdap) increased by 3.4 percentage points to 26.6% overall.
  - Hepatitis A vaccination increased by 14.8 percentage points to 23.7% among adults 19-49 years with chronic liver conditions.
  - Herpes Zoster (Shingles) vaccination increased 2.8 percentage points to 33.4% among adults 60 years and older and increased 3.1 percentage points to 37.4% among adults 65 years and older.
  - HPV vaccination (at least one dose) among females and males 19-26 years who had not received HPV vaccination prior to 19 years was 8.6% and 2.7%, respectively.
  - Coverage did not change for other vaccinations in other age groups and many adults remained unvaccinated with recommended vaccines.
- Racial and ethnic vaccination differences persisted for all vaccinations in this report with generally lower coverage for most vaccinations among non-Hispanic black, Hispanic, and non-Hispanic Asian adults compared with white adults. Vaccination differences widened for Tdap (blacks, all age groups) and herpes zoster (Asians, ≥65 years) (due primarily to increases among whites).

Conclusions/Recommendations:

- Many adults in the United States have not received recommended vaccinations and racial/ethnic vaccination differences persist.
- Influenza vaccination decreased among whites and overall among adults ≥65 years.
- While modest gains occurred in vaccination coverage for pneumococcal, Tdap, hepatitis A (persons with chronic liver conditions), herpes zoster, and HPV vaccination, coverage did not improve for other vaccinations and many adults remained unvaccinated with recommended vaccines.
  - Among adults 65 years and older:
    - Over one-third did not report pneumococcal or Td vaccination.

        - Approximately 4 out of 5 did not report Tdap vaccination.
        - Nearly two-thirds did not report a herpes zoster vaccination.
    - Among adults younger than 65 years with indications for pneumococcal vaccination, approximately 3 out of 4 did not report ever having been vaccinated.
    - Among adults 19-26 years recommended for HPV catch-up vaccination:
        - About 11 out of 12 females and 32 out of 33 males not vaccinated before 19 years did not report HPV vaccination (at least one dose).
- The recommendation of a health care provider can ensure vaccination.
    - Following the Standards for Adult Immunization Practice, all providers should routinely assess adults' vaccination status at every clinical encounter, strongly recommend needed vaccines, and either offer needed vaccines or refer their patients to another provider who can administer the recommended vaccine, and document the vaccines administered in their state's immunization information system (IIS).
    - Vaccination providers should ensure reporting of vaccinations to their state's IIS to support consolidation of adult patients' vaccination records (1, 2). Using their state's IIS can help providers access their patients' immunization records and improve the ability to routinely and accurately assess their patients' vaccination status.

Introduction

Adults are at risk of illness, hospitalization, disability, and, in some cases, death from vaccine-preventable diseases, particularly influenza (flu) and pneumococcal disease. CDC recommends vaccinations for adults based on age, health conditions, prior vaccinations, and other factors (3) to prevent vaccine-preventable diseases and related outcomes. Many adults are not fully vaccinated, leaving them vulnerable to preventable infectious diseases.

This report summarizes data on vaccination coverage for U.S. adults 19 years and older from the 2016 National Health Interview Survey (NHIS) (4). The NHIS is an in-person survey of eligible civilian non-institutionalized adults. Information on receipt of vaccinations, health and health care is self-reported and not verified through review of medical records or other means (5).

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Who Was Vaccinated?

- Influenza Vaccination
- Pneumococcal Vaccination
- Tetanus Vaccination
- Hepatitis A Vaccination
- Hepatitis B Vaccination
- Herpes Zoster Vaccination
- Human Papillomavirus Vaccination
- Trends in Adult Vaccination Coverage, 2010-2016
- Additional Vaccination Data

Influenza Vaccination

- Influenza vaccination coverage for the 2015-16 season overall among adults ≥19 years was 43.5%, similar to the estimate for the 2014-15 season.
- Compared with the 2014-15 season, influenza vaccination coverage decreased among whites ≥19 years (2.2 percentage points to 46.3%), 50-64 years (3.5 percentage points to 46.7%), and ≥65 years (3.1 percentage points to 72.0%).
- Influenza vaccination coverage among adults ≥65 years overall decreased by 3.1 percentage points to 70.4% for the 2015–16 season compared with the 2014–15 season estimate.
- In the 2015-16 season, coverage among whites ≥19 years (46.3%) was higher than that for blacks (39.5%) and Hispanics (33.1%).

TABLE 1. Estimated proportion of adults ≥19 years who received influenza vaccination, by age group, increased-risk status, and race/ethnicity*, National Health Interview Survey, United States, 2015-16 season [1 sheet]

Pneumococcal Vaccination

- Pneumococcal vaccination coverage among adults 19-64 years at increased risk for pneumococcal disease was 24.0% in 2016, similar to the estimate for 2015.
- Coverage among whites 19-64 years at increased risk was higher (24.5%) compared with Asians (16.2%), but did not differ for other racial/ethnic groups.
- Pneumococcal vaccination coverage among adults ≥65 years was 66.9% in 2016, a 3.3 percentage point increase compared with 2015.
- Coverage among whites ≥65 years (71.0%) was higher compared with blacks (55.5%), Hispanics (48.6%), and Asians (52.6%).

TABLE 2. Estimated proportion of adults ≥19 years who received pneumococcal vaccination, by age group, increased-risk status*, and race/ethnicity†, National Health Interview Survey, United States, 2016 [1 sheet]

Tetanus Vaccination

- In 2016, the proportion of adults reporting having received any tetanus toxoid-containing vaccination during the past 10 years was 62.2% for adults ≥19 years, 62.8% for adults 19-49 years, 64.2% for adults 50-64 years, and 58.0% for adults ≥65 years, all similar to estimates for 2015.
- Whites had higher coverage across all age groups compared with blacks, Hispanics, and Asians.
- Among adults for whom Tdap vaccination could be assessed, coverage in the past ten years was 26.6% among adults ≥19 years (a 3.4 percentage point increase compared with 2015), 28.0% among adults 19-64 years (a 3.3 percentage point increase compared with 2015), and 20.4% among adults ≥65 years (a 3.9 percentage point increase compared with 2015).
- Whites had higher Tdap coverage across all age groups compared with blacks, Hispanics, and Asians and these vaccination differences increased for blacks only compared with differences measured in 2015.

TABLE 3. Estimated proportion of adults ≥19 years who received tetanus vaccination, not including and including pertussis vaccine, by age group, increased-risk status, and race/ethnicity*, National Health Interview Survey, United States, 2016 [1 sheet]

Hepatitis A Vaccination

- In 2016, reported hepatitis A vaccination coverage (≥2 doses) was 9.5 % for adults ≥19 years, 13.4% for adults 19-49 years, and 5.4% for adults ≥50 years, similar to the estimates for 2015.
- Among adults 19-49 years, coverage for blacks (10.2%) was lower than that for whites (14.0%).
- Vaccination coverage was higher among adults who had traveled outside the United States to a country in which hepatitis A is of high or intermediate endemicity than among respondents who did not travel outside the United States or had traveled only to countries in which the disease is of low endemicity.
- Hepatitis A vaccination coverage among adults 19-49 years with chronic liver conditions was 23.7%, a 14.8 percentage point increase compared with the 2015 estimate.

TABLE 4. Estimated proportion of adults ≥19 years who received Hepatitis A vaccination, by age group, increased-risk status*, and race/ethnicity†, National Health Interview Survey, United States, 2016 [1 sheet]

Hepatitis B Vaccination

- In 2016, reported hepatitis B vaccination coverage (≥3 doses) was 24.8 % for adults ≥19 years, 32.9% for adults 19-49 years, and 15.9% for adults ≥50 years, similar to the estimates for 2015.
- Among adults 19-49 years, coverage for blacks (27.0%) and Hispanics (25.8%) was lower than that for whites (36.2%).
- Vaccination coverage was higher among adults who had traveled outside the United States to a country in which hepatitis B is of high or intermediate endemicity than among respondents who did not travel outside the United States or had traveled only to countries in which the disease is of low endemicity.

TABLE 5. Estimated proportion of adults ≥19 years who received Hepatitis B vaccination*, by age group, increased-risk status†, and race/ethnicity§, National Health Interview Survey, United States, 2016 [1 sheet]

Herpes Zoster Vaccination

- Among adults ≥60 years, 33.4% reported receiving herpes zoster vaccination, a 2.8 percentage point increase from 2015. Whites ≥60 years had higher herpes zoster vaccination coverage (37.7%) compared with blacks (15.7%), Hispanics (21.4%), and Asians (21.9%) and these vaccination differences increased compared with 2015 estimates.
- Among adults 60-64 years, 23.9% reported herpes zoster vaccination, similar to the estimate for 2015. Whites 60-64 years had higher herpes vaccination coverage (27.2%) compared with blacks (8.9%).
- Among adults ≥65 years, 37.4% reported herpes zoster vaccination, a 3.1 percentage point increase from 2015. Whites ≥65 years had higher herpes zoster vaccination coverage (41.7%) compared with blacks (19.6%), Hispanics (22.1%), and Asians (23.3%) and these vaccination differences increased for Asians only compared with differences measured in 2015.

TABLE 6. Estimated proportion of adults ≥60 years who received herpes zoster vaccination, by age group and race/ethnicity*, National Health Interview Survey, United States, 2016 [1 sheet]

Human Papillomavirus Vaccination

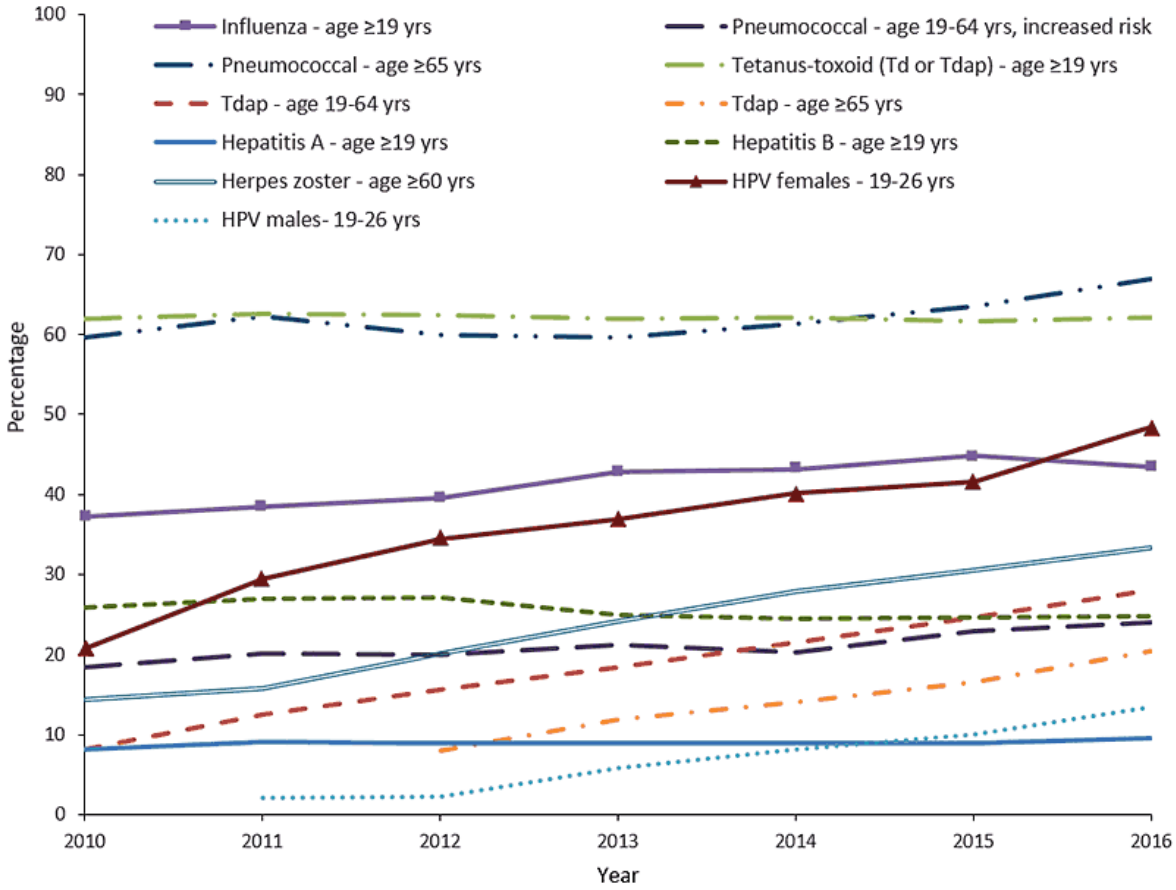
- In 2016, among females 19-26 years, 48.5% reported receipt of at least one dose of HPV vaccine, a 6.9 percentage point increase compared with the estimate reported for 2015. Blacks (41.5%) had lower coverage compared with whites (52.2%) and this vaccination difference increased compared with the difference measured in 2015.
- Among females 19-21 years, HPV vaccination coverage was 51.6%, a 9.6 percentage point increase compared with the estimate for 2015.
- Among females 22-26 years, HPV vaccination coverage was 46.6%, similar to the 2015 estimate.
- Among males 19-26 years and 19-21 years, HPV vaccination coverage (at least one doses) was 13.5% and 21.2%, increases of 3.4 and 5.5 percentage points, respectively.
- HPV vaccination (at least one dose) among females and males 19-26 years who had not received HPV vaccination prior to 19 years was 8.6% and 2.7%, similar to estimates for 2015.

TABLE 7. Estimated proportion of adults ≥19 years who received HPV vaccination, by age group, sex, and race/ethnicity*, National Health Interview Survey, United States, 2016 [1 sheet]

Trends in Adult Vaccination Coverage, 2010-2016

- Overall during 2010 through 2016, although point estimates for each year generally varied by only a few percentage points, linear trend tests indicated that vaccination coverage generally increased for all vaccines in this report, except for tetanus vaccination (Td or Tdap) among adults ≥19 years.
  - Influenza vaccination, ≥19 years—range: 37.2%–44.8%.
  - Pneumococcal vaccination, 19-64 years at increased risk—range: 18.5%–24.0%.
  - Pneumococcal vaccination, ≥65 years—range: 59.7%–66.9%.
  - Tdap vaccination, 19-64 years—range: 8.2%–28.0%.
  - Tdap vaccination, ≥65 years (2012-2016)—range: 8.0%–20.4%.
  - Hepatitis A vaccination, ≥19 years—range: 8.1%–9.5%.
  - Hepatitis B vaccination, ≥19 years—range: 24.5%–27.1%.
  - Herpes zoster vaccination, ≥60 years—range: 14.4%–33.4%.
  - HPV vaccination, females 19-26 years—range: 20.7%–48.5%.
  - HPV vaccination, males 19-26 years (2011-2016)—range: 2.1%–13.5%.
- During the 2009-10 through the 2015-16 influenza seasons, fewer than half of adults ≥19 years were vaccinated (range: 37.2%–44.8%).

FIGURE. Estimated proportion of adults ≥19 years who received selected vaccines, by age group and increased risk status — National Health Interview Survey, United States, 2010–2016. See data file [1 sheet].



Abbreviations: HPV = human papillomavirus; Td = tetanus and diphtheria toxoids; Tdap = tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine. See additional trend figures for select vaccines [4 sheets].

Additional Vaccination Coverage Information

- Vaccination coverage for selected vaccinations was estimated for adults ≥19 years who were healthcare personnel and proportions were estimated of adults ≥19 years by type of tetanus vaccine received, age at first dose of HPV vaccine, and racial/ethnic vaccination differences (See: Box 1).
- Estimates of proportions vaccinated were stratified by age group, health insurance status, having a usual place for health care, number of physician contacts, nativity, number of years living in the United States, and citizenship (See: Box 2).

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What Can Be Done? (Recommendations)

In 2016, adult vaccination coverage in the United States remained similar to 2015, except for modest increases in pneumococcal (adults ≥65 years), Tdap (adults ≥19 years), hepatitis A (adults 19-49 years with chronic liver conditions), herpes zoster (adults ≥60 years and adults ≥65 years), and HPV (females 19-21 and 19-26 years; males 19-21 years and 19-26 years) vaccination. Influenza vaccination decreased among adults ≥65 years overall and among whites in all age groups except adults 19-49 years. Many adults in the United States have not received recommended vaccinations and racial and ethnic vaccination differences persisted for all seven vaccines in this report, widening for pneumococcal (≥65 years, blacks, Hispanics, and Asians compared with whites), Tdap (all age groups, blacks, Hispanics, and Asians compared with whites), herpes zoster (≥60 years and ≥65 years, blacks, Hispanics, and Asians compared with whites), and HPV

(females 19-26 years, blacks compared with whites). Incorporating routine assessment of adult vaccination needs, recommendation, and offer of needed vaccinations into routine clinical care of adults can help improve vaccination rates and narrow racial and ethnic differences in vaccination coverage (1, 2, 5, 6).

To improve vaccination coverage, providers and provider organizations are encouraged to increase awareness and use of tools for implementing the Standards for Adult Immunization Practice. In addition, CDC encourages healthcare providers to consider immunization quality improvement projects that may result in measurable increases in adult immunization rates. Nationwide adoption of electronic health records, electronic patient portals, and patient-directed clinical decision support offer opportunities for improving adult vaccination rates (5). Some states are implementing innovative strategies to enhance vaccine access. For example, the Oregon Immunization Program has established a "mini-grant project" where annual funding announcements are issued and any group interested in providing or promoting immunizations can apply. This may include local health departments, clinics, or coalitions who are working with underserved populations within their own communities. The Massachusetts Department of Public Health has partnered with Center for Health Care Financing (CHCF) to implement a vaccination billing service for local health departments to ensure that the local health agencies are able to receive reimbursement for vaccines administered to patients with various health insurance plans, including Medicaid, Medicare part B and private health insurance plans. The Massachusetts Department of Public Health has also developed a strategy to help local health departments and other community health centers reach and vaccinate uninsured and disparate populations, which is highlighted in their guide to reaching and engaging diverse communities [61 pages].

Data Source and Methods

NHIS collects information about the health and health care of the noninstitutionalized U.S. civilian population using nationally representative samples. Face-to-face interviews are conducted by the U.S. Census Bureau for CDC's National Center for Health Statistics. Non-institutionalized adults 19 years and older with interviews conducted during August 2015-June 2016 (for influenza vaccination) and January–December 2016 (for pneumococcal, Td, Tdap, hepatitis A, hepatitis B, herpes zoster, and HPV vaccination) were included in this analysis. The total adult sample was 32,626 persons ≥19 years. The final sample adult component response rate for the 2016 NHIS was 54.3%. The final sample adult response rates for estimating influenza vaccination coverage for the 2015-16 influenza season were 55.2% for 2015 and 54.3% for 2016. NHIS methods have been previously published. Questions about receipt of vaccinations recommended for adults are asked of one randomly selected adult within each family in the household and have been described previously (5). Weighted data were used to produce national vaccination coverage estimates. For non-influenza adult vaccination coverage estimates, the weighted proportion of respondents who reported receiving selected vaccinations was calculated. To better assess influenza vaccination coverage for the 2015-16 season, the Kaplan-Meier survival analysis procedure was used. Point estimates and 95% confidence intervals (CIs) were calculated by using statistical software to account for the complex sample design. T tests were used for comparisons between 2016 and 2015 and, for comparisons of each level of each characteristic (e.g., race/ethnicity), to a chosen referent level (e.g., for race/ethnicity, non-Hispanic white was the reference group). Statistical significance was defined as $p<0.05$. Coverage estimates are not reported for small sample size ($n<30$) or relative standard error (standard error/estimates) >0.3. Influenza vaccination coverage estimates from NHIS (≥19 years) reported here differ by 1.8% from previously reported estimates from BRFSS (Behavioral Risk Factor Surveillance System) (≥18 years); however, vaccination trends were similar during the 2009-2010 through the 2015-2016 seasons; racial/ethnic vaccination differences were similar.

Limitations

- All data rely on self-report and were not validated with medical records. However, adult self-reported vaccination status has been shown to be ≥70% sensitive in one or more studies for pneumococcal, tetanus toxoid-containing, herpes zoster, and hepatitis B vaccines and ≥70% specific in one or more studies for all except tetanus and hepatitis

B vaccination (7, 8, 9, 10).

- Adults particularly might not be able to recall accurately vaccines received as infants or adolescents and hepatitis B vaccination coverage levels might be greatly underestimated. Additional study is needed for accuracy of recall by young adults of vaccinations they may have been received as children or adolescents. The findings for hepatitis B vaccination among younger adults 19-29 years should be viewed with caution, based on comparison with estimates based on provider-reported vaccinations from the NIS (National Immunization Survey)-Teen (11).
- The response rate was 54.3%. Nonresponse bias can result if respondents and nonrespondents differ in their vaccination rates, and if survey weighting does not fully correct for this.
- The NHIS excluded persons in the military and those residing in institutions, which might result in underestimation or overestimation of vaccination coverage levels.
- The Tdap vaccination estimate is subject to considerable uncertainty. Respondents who reported a tetanus vaccination but were unable to say whether Td or Tdap was used during 2005–2016 were excluded (38.7%) from estimations of Tdap coverage, creating a potential for bias.
- Due to small sample size, the increase in hepatitis A vaccination coverage among persons 19-49 years with chronic liver disease could be spurious.
- NHIS survey data methods and limitations.

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References:

1. National Vaccine Advisory Committee. Recommendations from the National Vaccine Advisory Committee: standards for adult immunization practice. Public Health Rep 2014;129:115–23.
2. CDC. Standards for Adult Immunization Practice.
3. CDC. Vaccine information for adults.
4. National Health Interview Survey public use data file.
5. Williams WW, Lu P-J, O'Halloran AO, et al. Surveillance of vaccination coverage among adult populations – United States, 2015. MMWR Surveill Summ 2017;66(No. SS-11):1-28.
6. Community Preventive Services Task Force. The guide to community preventive services. Increasing appropriate vaccination: universally recommended vaccinations . Atlanta, GA: US Department of Health and Human Services,

CDC; 2011.

7. Rolnick SJ, Parker ED, Nordin JD, Hedblom BD, Wei F, Kerby T, et al. Self-report compared to electronic medical record across eight adult vaccines: do results vary by demographic factors? Vaccine 2013;31(37):3928-3935.
8. Mangtani P, Shah A, Roberts JA. Validation of influenza and pneumococcal vaccine status in adults based on self-report. Epidemiol Infect 2007;135(1):139-143.
9. Donald RM, Baken L, Nelson A, Nichol KL. Validation of self-report of influenza and pneumococcal vaccination status in elderly outpatients. Am J Prev Med 1999;16:173-7.
10. Zimmerman RK, Raymund M, Janosky JE, et al. Sensitivity and specificity of patient self-report of influenza and pneumococcal polysaccharide vaccinations among elderly outpatients in diverse patient care strata. Vaccine 2003;21:1486-91.
11. Walker TY, Elam-Evans LD, Singleton JA, et al. National, Regional, State, and Selected Local Area Vaccination Coverage Among Adolescents Aged 13–17 Years — United States, 2016. MMWR Morb Mortal Wkly Rep 2017;66:874–882. DOI

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BOX 1-Tables. Vaccination coverage for adults ≥19 years who were healthcare personnel (HCP) and proportions of adults ≥19 years by type of tetanus vaccine received, age at first dose of human papillomavirus (HPV) vaccine, and racial/ethnic vaccination differences — National Health Interview Survey, United States, 2016*

Table	URL (hyperlinked)	Result summary
Proportion of Health Care Personnel Who Received Selected Vaccinations	Box 1/ Table 1 [1 sheet] Table 1 HCP	Overall, influenza, tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine (Tdap), and hepatitis B vaccination coverage for 2016 was similar to 2015 estimates among HCP ≥19 years. White HCP had higher vaccination coverage compared with black HCP or Hispanic HCP.
Proportion of Health Care Personnel with Direct Patient Care Who Received Selected Vaccinations	Box 1/ Table 2 [1 sheet] Table 2 HCP Direct Contact	Overall, influenza and Tdap vaccination coverage for 2016 was similar to 2015 estimates among HCP ≥19 years with and without direct patient care. In 2016, among HCP ≥19 years with direct patient care, hepatitis B vaccination coverage decreased 4.6 percentage points to 69.5% compared with the estimate for 2015. Tdap and hepatitis B vaccination coverage was higher among HCP with direct patient care compared with those without direct patient care.
Proportion of Adults Who Received Tdap Among Those	Box 1/ Table 3 [1 sheet] Table 3 Tdap type	Among adults ≥19 years, 41.5% reported they knew what type of tetanus vaccine they received, 44.6% reported they were not informed of the vaccination type, and 13.9% could not recall the type of tetanus vaccination received. Among those who reported they knew what type tetanus vaccine they

Reporting Tetanus Vaccination		received, 73.2% reported receiving Tdap. HCP reported receipt of Tdap more often than did non-HCP.
Age at First Dose of HPV Vaccination	Box 1/ Table 4 [1 sheet] Table 4 HPV Age at 1st dose	Among women 19-26 years, 10.6% reported receiving the first dose of HPV vaccine at 11-12 years, 67.0% at 13-17 years, and 10.9% at 19-26 years. Among males 19-26 years, 9.8% reported receiving the first dose of HPV vaccine at 11-12 years, 53.0% at 13-17 years, and 21.6% at 19-26 years. Among respondents 19–26 years, the difference between the age reported at the time of the interview and the age at which respondents indicated that the first dose of HPV vaccine was received was ≥12 years for 4.8% of women and for 6.2% of males. This would imply receipt of vaccination in 2004 or earlier, before HPV vaccine was licensed for use in 2006.
Racial/Ethnic Differences in Vaccination Coverage Among Adults	Box 1/ Table 5 [1 sheet] Table 5 Summary RE diff	Compared with 2015, racial/ethnic differences in vaccination coverage persisted for all seven vaccines in this report [7 sheets]. With whites as the reference group, there were differences in vaccination coverage for 48 of the 66 comparisons by vaccine and age/target groups (not including comparisons of the "other" race/ethnic group).

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BOX 2–Tables. Estimated proportion of adults ≥19 years who received selected vaccinations, by age group, risk status, health insurance status, having a usual place for health care, physician contacts, nativity, number of years living in the United States, and citizenship — National Health Interview Survey, United States, 2016*

Supplementary Table	URL (hyperlinked)	Result summary

† In 2011, the Advisory Committee on Immunization Practices (ACIP) recommended hepatitis B vaccination for persons with diabetes 19–59 years and stated that persons with diabetes aged 60 years and older should be considered for vaccination.

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Page last reviewed: February 8, 2018

EXHIBIT 304

Essay

Why Most Published Research Findings Are False

John P. A. Ioannidis

Summary

There is increasing concern that most current published research findings are false. The probability that a research claim is true may depend on study power and bias, the number of other studies on the same question, and, importantly, the ratio of true to no relationships among the relationships probed in each scientific field. In this framework, a research finding is less likely to be true when the studies conducted in a field are smaller; when effect sizes are smaller; when there is a greater number and lesser preselection of tested relationships; where there is greater flexibility in designs, definitions, outcomes, and analytical modes; when there is greater financial and other interest and prejudice; and when more teams are involved in a scientific field in chase of statistical significance. Simulations show that for most study designs and settings, it is more likely for a research claim to be false than true. Moreover, for many current scientific fields, claimed research findings may often be simply accurate measures of the prevailing bias. In this essay, I discuss the implications of these problems for the conduct and interpretation of research.

Published research findings are sometimes refuted by subsequent evidence, with ensuing confusion and disappointment. Refutation and controversy is seen across the range of research designs, from clinical trials and traditional epidemiological studies [1–3] to the most modern molecular research [4,5]. There is increasing concern that in modern research, false findings may be the majority or even the vast majority of published research claims [6–8]. However, this should not be surprising. It can be proven that most claimed research findings are false. Here I will examine the key factors that influence this problem and some corollaries thereof.

The Essay section contains opinion pieces on topics of broad interest to a general medical audience.

Modeling the Framework for False Positive Findings

Several methodologists have pointed out [9–11] that the high rate of nonreplication (lack of confirmation) of research discoveries is a consequence of the convenient, yet ill-founded strategy of claiming conclusive research findings solely on the basis of a single study assessed by formal statistical significance, typically for a *p*-value less than 0.05. Research is not most appropriately represented and summarized by *p*-values, but, unfortunately, there is a widespread notion that medical research articles

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should be interpreted based only on *p*-values. Research findings are defined here as any relationship reaching formal statistical significance, e.g., effective interventions, informative predictors, risk factors, or associations. "Negative" research is also very useful. "Negative" is actually a misnomer, and the misinterpretation is widespread. However, here we will target relationships that investigators claim exist, rather than null findings.

As has been shown previously, the probability that a research finding is indeed true depends on the prior probability of it being true (before doing the study), the statistical power of the study, and the level of statistical significance [10,11]. Consider a 2 × 2 table in which research findings are compared against the gold standard of true relationships in a scientific field. In a research field both true and false hypotheses can be made about the presence of relationships. Let R be the ratio of the number of "true relationships" to "no relationships" among those tested in the field. R is characteristic of the field and can vary a lot depending on whether the field targets highly likely relationships or searches for only one or a few true relationships among thousands and millions of hypotheses that may be postulated. Let us also consider, for computational simplicity, circumscribed fields where either there is only one true relationship (among many that can be hypothesized) or the power is similar to find any of the several existing true relationships. The pre-study probability of a relationship being true is $R/(R + 1)$. The probability of a study finding a true relationship reflects the power $1 - \beta$ (one minus the Type II error rate). The probability of claiming a relationship when none truly exists reflects the Type I error rate, α. Assuming that c relationships are being probed in the field, the expected values of the 2 × 2 table are given in Table 1. After a research finding has been claimed based on achieving formal statistical significance, the post-study probability that it is true is the positive predictive value, PPV. The PPV is also the complementary probability of what Wacholder et al. have called the false positive report probability [10]. According to the 2 × 2 table, one gets $PPV = (1 - \beta)R/(R - \beta R + \alpha)$. A research finding is thus

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Abbreviation: PPV, positive predictive value

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Table 1. Research Findings and True Relationships

Research Finding	True Relationship		
	Yes	No	Total
Yes	$c(1-\beta)R/(R+1)$	$c\alpha/(R+1)$	$c(R+\alpha-\beta R)/(R+1)$
No	$c\beta R/(R+1)$	$c(1-\alpha)/(R+1)$	$c(1-\alpha+\beta R)/(R+1)$
Total	$cR/(R+1)$	$c/(R+1)$	c

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more likely true than false if $(1-\beta)R > \alpha$. Since usually the vast majority of investigators depend on $\alpha = 0.05$, this means that a research finding is more likely true than false if $(1-\beta)R > 0.05$.

What is less well appreciated is that bias and the extent of repeated independent testing by different teams of investigators around the globe may further distort this picture and may lead to even smaller probabilities of the research findings being indeed true. We will try to model these two factors in the context of similar 2 × 2 tables.

Bias

First, let us define bias as the combination of various design, data, analysis, and presentation factors that tend to produce research findings when they should not be produced. Let u be the proportion of probed analyses that would not have been "research findings," but nevertheless end up presented and reported as such, because of bias. Bias should not be confused with chance variability that causes some findings to be false by chance even though the study design, data, analysis, and presentation are perfect. Bias can entail manipulation in the analysis or reporting of findings. Selective or distorted reporting is a typical form of such bias. We may assume that u does not depend on whether a true relationship exists or not. This is not an unreasonable assumption, since typically it is impossible to know which relationships are indeed true. In the presence of bias (Table 2), one gets PPV = $([1-\beta]R + u\beta R)/(R + \alpha - \beta R + u - u\alpha + u\beta R)$, and PPV decreases with increasing u, unless $1-\beta \leq \alpha$, i.e., $1-\beta \leq 0.05$ for most situations. Thus, with increasing bias, the chances that a research finding is true diminish considerably. This is shown for different levels of power and for different pre-study odds in Figure 1.

Conversely, true research findings may occasionally be annulled because of reverse bias. For example, with large measurement errors relationships are lost in noise [12], or investigators use data inefficiently or fail to notice statistically significant relationships, or there may be conflicts of interest that tend to "bury" significant findings [13]. There is no good large-scale empirical evidence on how frequently such reverse bias may occur across diverse research fields. However, it is probably fair to say that reverse bias is not as common. Moreover measurement errors and inefficient use of data are probably becoming less frequent problems, since measurement error has decreased with technological advances in the molecular era and investigators are becoming increasingly sophisticated about their data. Regardless, reverse bias may be modeled in the same way as bias above. Also reverse bias should not be confused with chance variability that may lead to missing a true relationship because of chance.

Testing by Several Independent Teams

Several independent teams may be addressing the same sets of research questions. As research efforts are globalized, it is practically the rule that several research teams, often dozens of them, may probe the same or similar questions. Unfortunately, in some areas, the prevailing mentality until now has been to focus on isolated discoveries by single teams and interpret research experiments in isolation. An increasing number of questions have at least one study claiming a research finding, and this receives unilateral attention. The probability that at least one study, among several done on the same question, claims a statistically significant research finding is easy to estimate. For n independent studies of equal power, the 2 × 2 table is shown in Table 3: PPV = $R(1-\beta^n)/(R+1-[1-\alpha]^n - R\beta^n)$ (not considering bias). With increasing number of independent studies, PPV tends to decrease, unless $1-\beta < \alpha$, i.e., typically $1-\beta < 0.05$. This is shown for different levels of power and for different pre-study odds in Figure 2. For n studies of different power, the term β^n is replaced by the product of the terms β_i for $i = 1$ to n, but inferences are similar.

Corollaries

A practical example is shown in Box 1. Based on the above considerations, one may deduce several interesting corollaries about the probability that a research finding is indeed true.

Corollary 1: The smaller the studies conducted in a scientific field, the less likely the research findings are to be true. Small sample size means smaller power and, for all functions above, the PPV for a true research finding decreases as power decreases towards $1-\beta = 0.05$. Thus, other factors being equal, research findings are more likely true in scientific fields that undertake large studies, such as randomized controlled trials in cardiology (several thousand subjects randomized) [14] than in scientific fields with small studies, such as most research of molecular predictors (sample sizes 100-fold smaller) [15].

Corollary 2: The smaller the effect sizes in a scientific field, the less likely the research findings are to be true. Power is also related to the effect size. Thus research findings are more likely true in scientific fields with large effects, such as the impact of smoking on cancer or cardiovascular disease (relative risks 3–20), than in scientific fields where postulated effects are small, such as genetic risk factors for multigenetic diseases (relative risks 1.1–1.5) [7]. Modern epidemiology is increasingly obliged to target smaller

Table 2. Research Findings and True Relationships in the Presence of Bias

Research Finding	True Relationship		
	Yes	No	Total
Yes	$(c[1-\beta]R + uc\beta R)/(R+1)$	$c\alpha + uc(1-\alpha)/(R+1)$	$c(R+\alpha-\beta R+u-u\alpha+u\beta R)/(R+1)$
No	$(1-u)c\beta R/(R+1)$	$(1-u)c(1-\alpha)/(R+1)$	$c(1-u)(1-\alpha+\beta R)/(R+1)$
Total	$cR/(R+1)$	$c/(R+1)$	c

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effect sizes [16]. Consequently, the proportion of true research findings is expected to decrease. In the same line of thinking, if the true effect sizes are very small in a scientific field, this field is likely to be plagued by almost ubiquitous false positive claims. For example, if the majority of true genetic or nutritional determinants of complex diseases confer relative risks less than 1.05, genetic or nutritional epidemiology would be largely utopian endeavors.

Corollary 3: The greater the number and the lesser the selection of tested relationships in a scientific field, the less likely the research findings are to be true. As shown above, the post-study probability that a finding is true (PPV) depends a lot on the pre-study odds (*R*). Thus, research findings are more likely true in confirmatory designs, such as large phase III randomized controlled trials, or meta-analyses thereof, than in hypothesis-generating experiments. Fields considered highly informative and creative given the wealth of the assembled and tested information, such as microarrays and other high-throughput discovery-oriented research [4,8,17], should have extremely low PPV.

Corollary 4: The greater the flexibility in designs, definitions, outcomes, and analytical modes in a scientific field, the less likely the research findings are to be true. Flexibility increases the potential for transforming what would be "negative" results into "positive" results, i.e., bias, *u*. For several research designs, e.g., randomized controlled trials [18–20] or meta-analyses [21,22], there have been efforts to standardize their conduct and reporting. Adherence to common standards is likely to increase the proportion of true findings. The same applies to outcomes. True findings may be more common when outcomes are unequivocal and universally agreed (e.g., death) rather than when multifarious outcomes are devised (e.g., scales for schizophrenia outcomes) [23]. Similarly, fields that use commonly agreed, stereotyped analytical methods (e.g., Kaplan-Meier plots and the log-rank test) [24] may yield a larger proportion of true findings than fields where analytical methods are still under experimentation (e.g., artificial intelligence methods) and only "best" results are reported. Regardless, even in the most stringent research designs, bias seems to be a major problem. For example, there is strong evidence that selective outcome reporting, with manipulation of the outcomes and analyses reported, is a common problem even for randomized trails [25]. Simply abolishing selective publication would not make this problem go away.

Corollary 5: The greater the financial and other interests and prejudices in a scientific field, the less likely the research findings are to be true. Conflicts of interest and prejudice may increase bias, *u*. Conflicts of interest are very common in biomedical research [26], and typically they are inadequately and sparsely reported [26,27]. Prejudice may not necessarily have financial roots. Scientists in a given field may be prejudiced purely because of their belief in a scientific theory or commitment to their own findings. Many otherwise seemingly independent, university-based studies may be conducted for no other reason than to give physicians and researchers qualifications for promotion or tenure. Such nonfinancial conflicts may also lead to distorted reported results and interpretations. Prestigious investigators may suppress via the peer review process the appearance and dissemination of findings that refute their findings, thus condemning their field to perpetuate false dogma. Empirical evidence on expert opinion shows that it is extremely unreliable [28].

Corollary 6: The hotter a scientific field (with more scientific teams involved), the less likely the research findings are to be true.

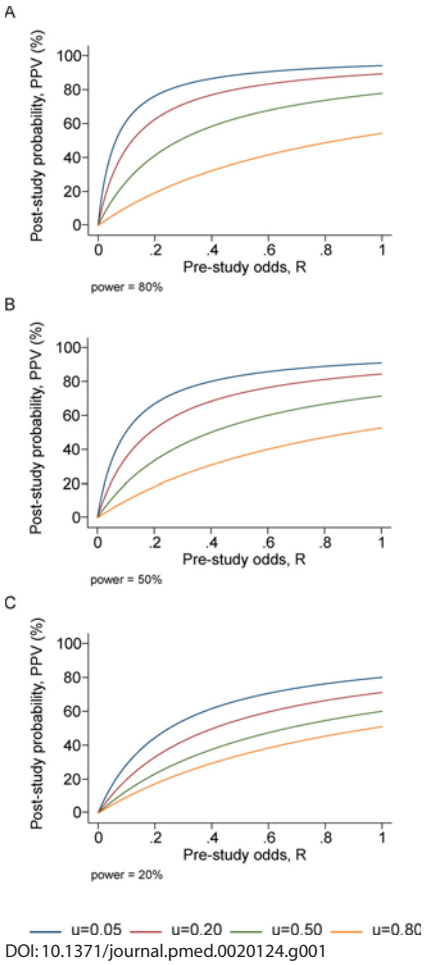

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Figure 1. PPV (Probability That a Research Finding Is True) as a Function of the Pre-Study Odds for Various Levels of Bias, *u*

Panels correspond to power of 0.20, 0.50, and 0.80.

This seemingly paradoxical corollary follows because, as stated above, the PPV of isolated findings decreases when many teams of investigators are involved in the same field. This may explain why we occasionally see major excitement followed rapidly by severe disappointments in fields that draw wide attention. With many teams working on the same field and with massive experimental data being produced, timing is of the essence in beating competition. Thus, each team may prioritize on pursuing and disseminating its most impressive "positive" results. "Negative" results may become attractive for dissemination only if some other team has found a "positive" association on the same question. In that case, it may be attractive to refute a claim made in some prestigious journal. The term Proteus phenomenon has been coined to describe this phenomenon of rapidly

Table 3. Research Findings and True Relationships in the Presence of Multiple Studies

Research Finding	True Relationship		
	Yes	No	Total
Yes	$cR(1-\beta^n)/(R+1)$	$c(1-[1-\alpha]^n)/(R+1)$	$c(R+1-[1-\alpha]^n-R\beta^n)/(R+1)$
No	$cR\beta^n/(R+1)$	$c(1-\alpha)^n/(R+1)$	$c([1-\alpha]^n+R\beta^n)/(R+1)$
Total	$cR/(R+1)$	$c/(R+1)$	c

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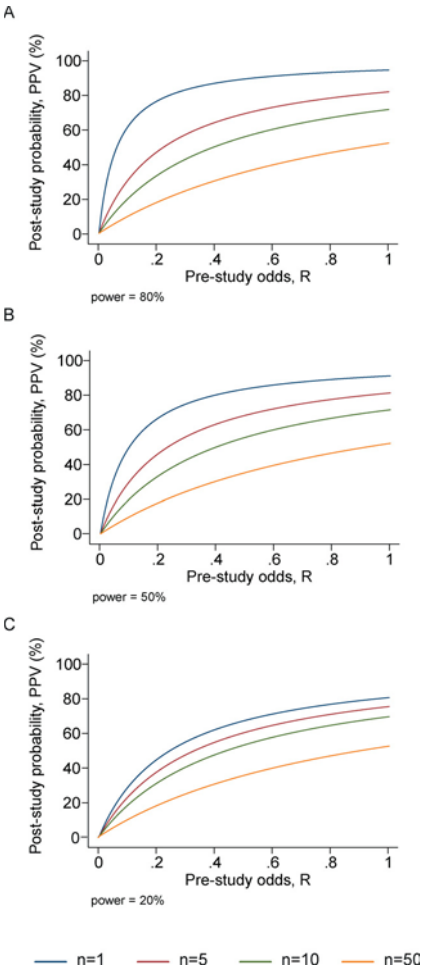

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Figure 2. PPV (Probability That a Research Finding Is True) as a Function of the Pre-Study Odds for Various Numbers of Conducted Studies, *n*

Panels correspond to power of 0.20, 0.50, and 0.80.

alternating extreme research claims and extremely opposite refutations [29]. Empirical evidence suggests that this sequence of extreme opposites is very common in molecular genetics [29].

These corollaries consider each factor separately, but these factors often influence each other. For example, investigators working in fields where true effect sizes are perceived to be small may be more likely to perform large studies than investigators working in fields where true effect sizes are perceived to be large. Or prejudice may prevail in a hot scientific field, further undermining the predictive value of its research findings. Highly prejudiced stakeholders may even create a barrier that aborts efforts at obtaining and disseminating opposing results. Conversely, the fact that a field is hot or has strong invested interests may sometimes promote larger studies and improved standards of research, enhancing the predictive value of its research findings. Or massive discovery-oriented testing may result in such a large yield of significant relationships that investigators have enough to report and search further and thus refrain from data dredging and manipulation.

Box 1. An Example: Science at Low Pre-Study Odds

Let us assume that a team of investigators performs a whole genome association study to test whether any of 100,000 gene polymorphisms are associated with susceptibility to schizophrenia. Based on what we know about the extent of heritability of the disease, it is reasonable to expect that probably around ten gene polymorphisms among those tested would be truly associated with schizophrenia, with relatively similar odds ratios around 1.3 for the ten or so polymorphisms and with a fairly similar power to identify any of them. Then $R = 10/100{,}000 = 10^{-4}$, and the pre-study probability for any polymorphism to be associated with schizophrenia is also $R/(R + 1) = 10^{-4}$. Let us also suppose that the study has 60% power to find an association with an odds ratio of 1.3 at $\alpha = 0.05$. Then it can be estimated that if a statistically significant association is found with the *p*-value barely crossing the 0.05 threshold, the post-study probability that this is true increases about 12-fold compared with the pre-study probability, but it is still only 12×10^{-4}.

Now let us suppose that the investigators manipulate their design, analyses, and reporting so as to make more relationships cross the $p = 0.05$ threshold even though this would not have been crossed with a perfectly adhered to design and analysis and with perfect comprehensive reporting of the results, strictly according to the original study plan. Such manipulation could be done, for example, with serendipitous inclusion or exclusion of certain patients or controls, post hoc subgroup analyses, investigation of genetic contrasts that were not originally specified, changes in the disease or control definitions, and various combinations of selective or distorted reporting of the results. Commercially available "data mining" packages actually are proud of their ability to yield statistically significant results through data dredging. In the presence of bias with $u = 0.10$, the post-study probability that a research finding is true is only 4.4×10^{-4}. Furthermore, even in the absence of any bias, when ten independent research teams perform similar experiments around the world, if one of them finds a formally statistically significant association, the probability that the research finding is true is only 1.5×10^{-4}, hardly any higher than the probability we had before any of this extensive research was undertaken!

Most Research Findings Are False for Most Research Designs and for Most Fields

In the described framework, a PPV exceeding 50% is quite difficult to get. Table 4 provides the results of simulations using the formulas developed for the influence of power, ratio of true to non-true relationships, and bias, for various types of situations that may be characteristic of specific study designs and settings. A finding from a well-conducted, adequately powered randomized controlled trial starting with a 50% pre-study chance that the intervention is effective is eventually true about 85% of the time. A fairly similar performance is expected of a confirmatory meta-analysis of good-quality randomized trials: potential bias probably increases, but power and pre-test chances are higher compared to a single randomized trial. Conversely, a meta-analytic finding from inconclusive studies where pooling is used to "correct" the low power of single studies, is probably false if $R \leq 1{:}3$. Research findings from underpowered, early-phase clinical trials would be true about one in four times, or even less frequently if bias is present. Epidemiological studies of an exploratory nature perform even worse, especially when underpowered, but even well-powered epidemiological studies may have only a one in five chance being true, if $R = 1{:}10$. Finally, in discovery-oriented research with massive testing, where tested relationships exceed true ones 1,000-fold (e.g., 30,000 genes tested, of which 30 may be the true culprits) [30,31], PPV for each claimed relationship is extremely low, even with considerable

standardization of laboratory and statistical methods, outcomes, and reporting thereof to minimize bias.

Claimed Research Findings May Often Be Simply Accurate Measures of the Prevailing Bias

As shown, the majority of modern biomedical research is operating in areas with very low pre- and post-study probability for true findings. Let us suppose that in a research field there are no true findings at all to be discovered. History of science teaches us that scientific endeavor has often in the past wasted effort in fields with absolutely no yield of true scientific information, at least based on our current understanding. In such a "null field," one would ideally expect all observed effect sizes to vary by chance around the null in the absence of bias. The extent that observed findings deviate from what is expected by chance alone would be simply a pure measure of the prevailing bias.

For example, let us suppose that no nutrients or dietary patterns are actually important determinants for the risk of developing a specific tumor. Let us also suppose that the scientific literature has examined 60 nutrients and claims all of them to be related to the risk of developing this tumor with relative risks in the range of 1.2 to 1.4 for the comparison of the upper to lower intake tertiles. Then the claimed effect sizes are simply measuring nothing else but the net bias that has been involved in the generation of this scientific literature. Claimed effect sizes are in fact the most accurate estimates of the net bias. It even follows that between "null fields," the fields that claim stronger effects (often with accompanying claims of medical or public health importance) are simply those that have sustained the worst biases.

For fields with very low PPV, the few true relationships would not distort this overall picture much. Even if a few relationships are true, the shape of the distribution of the observed effects would still yield a clear measure of the biases involved in the field. This concept totally reverses the way we view scientific results. Traditionally, investigators have viewed large and highly significant effects with excitement, as signs of important discoveries. Too large and too highly significant effects may actually be more likely to be signs of large bias in most fields of modern research. They should lead investigators to careful critical thinking about what might have gone wrong with their data, analyses, and results.

Of course, investigators working in any field are likely to resist accepting that the whole field in which they have spent their careers is a "null field." However, other lines of evidence, or advances in technology and experimentation, may lead eventually to the dismantling of a scientific field. Obtaining measures of the net bias in one field may also be useful for obtaining insight into what might be the range of bias operating in other fields where similar analytical methods, technologies, and conflicts may be operating.

How Can We Improve the Situation?

Is it unavoidable that most research findings are false, or can we improve the situation? A major problem is that it is impossible to know with 100% certainty what the truth is in any research question. In this regard, the pure "gold" standard is unattainable. However, there are several approaches to improve the post-study probability.

Better powered evidence, e.g., large studies or low-bias meta-analyses, may help, as it comes closer to the unknown "gold" standard. However, large studies may still have biases and these should be acknowledged and avoided. Moreover, large-scale evidence is impossible to obtain for all of the millions and trillions of research questions posed in current research. Large-scale evidence should be targeted for research questions where the pre-study probability is already considerably high, so that a significant research finding will lead to a post-test probability that would be considered quite definitive. Large-scale evidence is also particularly indicated when it can test major concepts rather than narrow, specific questions. A negative finding can then refute not only a specific proposed claim, but a whole field or considerable portion thereof. Selecting the performance of large-scale studies based on narrow-minded criteria, such as the marketing promotion of a specific drug, is largely wasted research. Moreover, one should be cautious that extremely large studies may be more likely to find a formally statistical significant difference for a trivial effect that is not really meaningfully different from the null [32–34].

Second, most research questions are addressed by many teams, and it is misleading to emphasize the statistically significant findings of any single team. What matters is the

Table 4. PPV of Research Findings for Various Combinations of Power (1 − β), Ratio of True to Not-True Relationships *(R)*, and Bias *(u)*

1 − β	*R*	*u*	Practical Example	PPV
0.80	1:1	0.10	Adequately powered RCT with little bias and 1:1 pre-study odds	0.85
0.95	2:1	0.30	Confirmatory meta-analysis of good-quality RCTs	0.85
0.80	1:3	0.40	Meta-analysis of small inconclusive studies	0.41
0.20	1:5	0.20	Underpowered, but well-performed phase I/II RCT	0.23
0.20	1:5	0.80	Underpowered, poorly performed phase I/II RCT	0.17
0.80	1:10	0.30	Adequately powered exploratory epidemiological study	0.20
0.20	1:10	0.30	Underpowered exploratory epidemiological study	0.12
0.20	1:1,000	0.80	Discovery-oriented exploratory research with massive testing	0.0010
0.20	1:1,000	0.20	As in previous example, but with more limited bias (more standardized)	0.0015

The estimated PPVs (positive predictive values) are derived assuming $\alpha = 0.05$ for a single study.
RCT, randomized controlled trial.
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totality of the evidence. Diminishing bias through enhanced research standards and curtailing of prejudices may also help. However, this may require a change in scientific mentality that might be difficult to achieve. In some research designs, efforts may also be more successful with upfront registration of studies, e.g., randomized trials [35]. Registration would pose a challenge for hypothesis-generating research. Some kind of registration or networking of data collections or investigators within fields may be more feasible than registration of each and every hypothesis-generating experiment. Regardless, even if we do not see a great deal of progress with registration of studies in other fields, the principles of developing and adhering to a protocol could be more widely borrowed from randomized controlled trials.

Finally, instead of chasing statistical significance, we should improve our understanding of the range of R values—the pre-study odds—where research efforts operate [10]. Before running an experiment, investigators should consider what they believe the chances are that they are testing a true rather than a non-true relationship. Speculated high R values may sometimes then be ascertained. As described above, whenever ethically acceptable, large studies with minimal bias should be performed on research findings that are considered relatively established, to see how often they are indeed confirmed. I suspect several established "classics" will fail the test [36].

Nevertheless, most new discoveries will continue to stem from hypothesis-generating research with low or very low pre-study odds. We should then acknowledge that statistical significance testing in the report of a single study gives only a partial picture, without knowing how much testing has been done outside the report and in the relevant field at large. Despite a large statistical literature for multiple testing corrections [37], usually it is impossible to decipher how much data dredging by the reporting authors or other research teams has preceded a reported research finding. Even if determining this were feasible, this would not inform us about the pre-study odds. Thus, it is unavoidable that one should make approximate assumptions on how many relationships are expected to be true among those probed across the relevant research fields and research designs. The wider field may yield some guidance for estimating this probability for the isolated research project. Experiences from biases detected in other neighboring fields would also be useful to draw upon. Even though these assumptions would be considerably subjective, they would still be very useful in interpreting research claims and putting them in context. ■

References

1. Ioannidis JP, Haidich AB, Lau J (2001) Any casualties in the clash of randomised and observational evidence? BMJ 322: 879–880.
2. Lawlor DA, Davey Smith G, Kundu D, Bruckdorfer KR, Ebrahim S (2004) Those confounded vitamins: What can we learn from the differences between observational versus randomised trial evidence? Lancet 363: 1724–1727.
3. Vandenbroucke JP (2004) When are observational studies as credible as randomised trials? Lancet 363: 1728–1731.
4. Michiels S, Koscielny S, Hill C (2005) Prediction of cancer outcome with microarrays: A multiple random validation strategy. Lancet 365: 488–492.
5. Ioannidis JPA, Ntzani EE, Trikalinos TA, Contopoulos-Ioannidis DG (2001) Replication validity of genetic association studies. Nat Genet 29: 306–309.
6. Colhoun HM, McKeigue PM, Davey Smith G (2003) Problems of reporting genetic associations with complex outcomes. Lancet 361: 865–872.
7. Ioannidis JP (2003) Genetic associations: False or true? Trends Mol Med 9: 135–138.
8. Ioannidis JPA (2005) Microarrays and molecular research: Noise discovery? Lancet 365: 454–455.
9. Sterne JA, Davey Smith G (2001) Sifting the evidence—What's wrong with significance tests. BMJ 322: 226–231.
10. Wacholder S, Chanock S, Garcia-Closas M, El ghormli L, Rothman N (2004) Assessing the probability that a positive report is false: An approach for molecular epidemiology studies. J Natl Cancer Inst 96: 434–442.
11. Risch NJ (2000) Searching for genetic determinants in the new millennium. Nature 405: 847–856.
12. Kelsey JL, Whittemore AS, Evans AS, Thompson WD (1996) Methods in observational epidemiology, 2nd ed. New York: Oxford U Press. 432 p.
13. Topol EJ (2004) Failing the public health—Rofecoxib, Merck, and the FDA. N Engl J Med 351: 1707–1709.
14. Yusuf S, Collins R, Peto R (1984) Why do we need some large, simple randomized trials? Stat Med 3: 409–422.
15. Altman DG, Royston P (2000) What do we mean by validating a prognostic model? Stat Med 19: 453–473.
16. Taubes G (1995) Epidemiology faces its limits. Science 269: 164–169.
17. Golub TR, Slonim DK, Tamayo P, Huard C, Gaasenbeek M, et al. (1999) Molecular classification of cancer: Class discovery and class prediction by gene expression monitoring. Science 286: 531–537.
18. Moher D, Schulz KF, Altman DG (2001) The CONSORT statement: Revised recommendations for improving the quality of reports of parallel-group randomised trials. Lancet 357: 1191–1194.
19. Ioannidis JP, Evans SJ, Gotzsche PC, O'Neill RT, Altman DG, et al. (2004) Better reporting of harms in randomized trials: An extension of the CONSORT statement. Ann Intern Med 141: 781–788.
20. International Conference on Harmonisation E9 Expert Working Group (1999) ICH Harmonised Tripartite Guideline. Statistical principles for clinical trials. Stat Med 18: 1905–1942.
21. Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, et al. (1999) Improving the quality of reports of meta-analyses of randomised controlled trials: The QUOROM statement. Quality of Reporting of Meta-analyses. Lancet 354: 1896–1900.
22. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, et al. (2000) Meta-analysis of observational studies in epidemiology: A proposal for reporting. Meta-analysis of Observational Studies in Epidemiology (MOOSE) group. JAMA 283: 2008–2012.
23. Marshall M, Lockwood A, Bradley C, Adams C, Joy C, et al. (2000) Unpublished rating scales: A major source of bias in randomised controlled trials of treatments for schizophrenia. Br J Psychiatry 176: 249–252.
24. Altman DG, Goodman SN (1994) Transfer of technology from statistical journals to the biomedical literature. Past trends and future predictions. JAMA 272: 129–132.
25. Chan AW, Hrobjartsson A, Haahr MT, Gotzsche PC, Altman DG (2004) Empirical evidence for selective reporting of outcomes in randomized trials: Comparison of protocols to published articles. JAMA 291: 2457–2465.
26. Krimsky S, Rothenberg LS, Stott P, Kyle G (1998) Scientific journals and their authors' financial interests: A pilot study. Psychother Psychosom 67: 194–201.
27. Papanikolaou GN, Baltogianni MS, Contopoulos-Ioannidis DG, Haidich AB, Giannakakis IA, et al. (2001) Reporting of conflicts of interest in guidelines of preventive and therapeutic interventions. BMC Med Res Methodol 1: 3.
28. Antman EM, Lau J, Kupelnick B, Mosteller F, Chalmers TC (1992) A comparison of results of meta-analyses of randomized control trials and recommendations of clinical experts. Treatments for myocardial infarction. JAMA 268: 240–248.
29. Ioannidis JP, Trikalinos TA (2005) Early extreme contradictory estimates may appear in published research: The Proteus phenomenon in molecular genetics research and randomized trials. J Clin Epidemiol 58: 543–549.
30. Ntzani EE, Ioannidis JP (2003) Predictive ability of DNA microarrays for cancer outcomes and correlates: An empirical assessment. Lancet 362: 1439–1444.
31. Ransohoff DF (2004) Rules of evidence for cancer molecular-marker discovery and validation. Nat Rev Cancer 4: 309–314.
32. Lindley DV (1957) A statistical paradox. Biometrika 44: 187–192.
33. Bartlett MS (1957) A comment on D.V. Lindley's statistical paradox. Biometrika 44: 533–534.
34. Senn SJ (2001) Two cheers for P-values. J Epidemiol Biostat 6: 193–204.
35. De Angelis C, Drazen JM, Frizelle FA, Haug C, Hoey J, et al. (2004) Clinical trial registration: A statement from the International Committee of Medical Journal Editors. N Engl J Med 351: 1250–1251.
36. Ioannidis JPA (2005) Contradicted and initially stronger effects in highly cited clinical research. JAMA 294: 218–228.
37. Hsueh HM, Chen JJ, Kodell RL (2003) Comparison of methods for estimating the number of true null hypotheses in multiplicity testing. J Biopharm Stat 13: 675–689.

EXHIBIT 305

PLOS ONE

How Many Scientists Fabricate and Falsify Research? A Systematic Review and Meta-Analysis of Survey Data

Daniele Fanelli

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Abstract

The frequency with which scientists fabricate and falsify data, or commit other forms of scientific misconduct is a matter of controversy. Many surveys have asked scientists directly whether they have committed or know of a colleague who committed research misconduct, but their results appeared difficult to compare and synthesize. This is the first meta-analysis of these surveys.

To standardize outcomes, the number of respondents who recalled at least one incident of misconduct was calculated for each question, and the analysis was limited to behaviours that distort scientific knowledge: fabrication, falsification, "cooking" of data, etc… Survey questions on plagiarism and other forms of professional misconduct were excluded. The final sample consisted of 21 surveys that were included in the systematic review, and 18 in the meta-analysis.

A pooled weighted average of 1.97% (N=7, 95%CI: 0.86–4.45) of scientists admitted to have fabricated, falsified or modified data or results at least once –a serious form of misconduct by any standard– and up to 33.7% admitted other questionable research practices. In surveys asking about the behaviour of colleagues, admission rates were 14.12% (N=12, 95% CI: 9.91–19.72) for falsification, and up to 72% for other questionable research practices. Meta-regression showed that self reports surveys, surveys using the words "falsification" or "fabrication", and mailed surveys yielded lower percentages of misconduct. When these factors were controlled for, misconduct was reported more frequently by medical/pharmacological researchers than others.

Considering that these surveys ask sensitive questions and have other limitations, it appears likely that this is a conservative estimate of the true prevalence of scientific misconduct.

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Introduction

The image of scientists as objective seekers of truth is periodically jeopardized by the discovery of a major scientific fraud. Recent scandals like Hwang Woo-Suk's fake stem-cell lines [1] or Jan Hendrik Schön's duplicated graphs [2] showed how easy it can be for a scientist to publish fabricated data in the most prestigious journals, and how this can cause a waste of financial and human resources and might pose a risk to human health. How frequent are scientific frauds? The question is obviously crucial, yet the answer is a matter of great debate [3], [4].

A popular view propagated by the media [5] and by many scientists (e.g. [6]) sees fraudsters as just a "few bad apples" [7]. This pristine image of science is based on the theory that the scientific community is guided by norms including disinterestedness and organized scepticism, which are incompatible with misconduct [8], [9]. Increasing evidence, however, suggests that known frauds

are just the “tip of the iceberg”, and that many cases are never discovered. The debate, therefore, has moved on to defining the forms, causes and frequency of scientific misconduct [4].

What constitutes scientific misconduct? Different definitions are adopted by different institutions, but they all agree that fabrication (invention of data or cases), falsification (wilful distortion of data or results) and plagiarism (copying of ideas, data, or words without attribution) are serious forms of scientific misconduct [7], [10]. Plagiarism is qualitatively different from the other two because it does not distort scientific knowledge, although it has important consequences for the careers of the people involved, and thus for the whole scientific enterprise [11].

There can be little doubt about the fraudulent nature of fabrication, but falsification is a more problematic category. Scientific results can be distorted in several ways, which can often be very subtle and/or elude researchers' conscious control. Data, for example, can be “cooked” (a process which mathematician Charles Babbage in 1830 defined as “an art of various forms, the object of which is to give to ordinary observations the appearance and character of those of the highest degree of accuracy”[12]); it can be “mined” to find a statistically significant relationship that is then presented as the original target of the study; it can be selectively published only when it supports one's expectations; it can conceal conflicts of interest, etc… [10], [11], [13], [14], [15]. Depending on factors specific to each case, these misbehaviours lie somewhere on a continuum between scientific fraud, bias, and simple carelessness, so their direct inclusion in the “falsification” category is debatable, although their negative impact on research can be dramatic [11], [14], [16]. Henceforth, these misbehaviours will be indicated as “questionable research practices” (QRP, but for a technical definition of the term see [11]).

Ultimately, it is impossible to draw clear boundaries for scientific misconduct, just as it is impossible to give a universal definition of professional malpractice [10]. However, the intention to deceive is a key element. Unwilling errors or honest differences in designing or interpreting a research are currently not considered scientific misconduct [10].

To measure the frequency of misconduct, different approaches have been employed, and they have produced a corresponding variety of estimates. Based on the number of government confirmed cases in the US, fraud is documented in about 1 every 100.000 scientists [11], or 1 every 10.000 according to a different counting [3]. Paper retractions from the PubMed library due to misconduct, on the other hand, have a frequency of 0.02%, which led to speculation that between 0.02 and 0.2% of papers in the literature are fraudulent [17]. Eight out of 800 papers submitted to *The Journal of Cell Biology* had digital images that had been improperly manipulated, suggesting a 1% frequency [11]. Finally, routine data audits conducted by the US Food and Drug Administration between 1977 and 1990 found deficiencies and flaws in 10–20% of studies, and led to 2% of clinical investigators being judged guilty of serious scientific misconduct [18].

All the above estimates are calculated on the number of frauds that have been discovered and have reached the public domain. This significantly underestimates the real frequency of misconduct, because data fabrication and falsification are rarely reported by whistleblowers (see Results), and are very hard to detect in the data [10]. Even when detected, misconduct is hard to prove, because the accused scientists could claim to have committed an innocent mistake. Distinguishing intentional bias from error is obviously difficult, particularly when the falsification has been subtle, or the original data destroyed. In many cases, therefore, only researchers know if they or their colleagues have wilfully distorted their data.

Over the years, a number of surveys have asked scientists directly about their behaviour. However, these studies have used different methods and asked different questions, so their results have been deemed inconclusive and/or difficult to compare (e.g. [19], [20]). A non-systematic review based on survey and non-survey data led to estimate that the frequency of “serious misconduct”, including plagiarism, is near 1% [11].

This study provides the first systematic review and meta-analysis of survey data on scientific misconduct. Direct comparison between studies was made possible by calculating, for each survey question, the percentage of respondents that admitted or observed misconduct at least once, and by limiting the analysis to qualitatively similar forms of misconduct -specifically on fabrication, falsification and any behaviour that can distort scientific data. Meta-analysis yielded mean pooled estimates that are higher than most previous estimates. Meta-regression analysis identified key methodological variables that might affect the accuracy of results, and suggests that misconduct is reported more frequently in medical research.

Methods

Searching

Electronic resources were searched during the first two weeks of August 2008. Publication and journal databases were searched in English, while the Internet and resources for unpublished and “grey” literature were searched using English, Italian, French and Spanish words.

Citation databases.

The Boolean string “research misconduct” OR “research integrity” OR “research malpractice” OR “scientific fraud” OR “fabrication, falsification” OR “falsification, fabrication” was used to search: Science Citation Index Expanded (SCI-EXPANDED), Social Sciences Citation Index (SSCI), Arts & Humanities Citation Index (A&HCI), Conference Proceedings Citation Index- Science (CPCI-S), BIOSIS Previews, MEDLINE, Business Source Premier, CINAHL Plus, SPORTDiscus, Library, Information Science & Technology Abstracts, International Bibliography of the Social Sciences, America: History & Life, Teacher Reference Center, Applied Social Sciences Index And Abstracts (ASSIA), ERIC, Index Islamicus, CSA linguistics and language behaviour, Physical Education Index, PILOTS, Social Services Abstracts, Sociological Abstracts, Proquest Dissertation & Theses, ECONLIT, Educational Research Abstracts (ERA) Online, Article First, Economic and Social Data Service, Francis, Geobase, Georefs, Global Health (CABI), Index to Theses, International Bibliography of the Social Sciences (IBSS), IEEE Xplore, INSPEC, JSTOR, Mathematical Sciences Net (MathSciNet), PubMEd, Russian Academy of Sciences bibliographies, Sciencedirect, Teacher Reference Center, EMBASE, EMBASE Classics, PSYCHINFO.

Scientific journals.

The Boolean string “research misconduct” OR “research integrity” OR “research malpractice” OR “scientific fraud” OR “fabrication, falsification” OR “falsification, fabrication” was used to search: Interdisciplinary Science Reviews, American Journal of Sociology, Annual Review of Sociology, PNAS, Issues in Science & Technology, Journal of Medical Ethics, PLoSONE, Science and Engineering Ethics, Sociology of Health & Illness, Minerva, The Scientific World Journal, Social Science Research, Social Studies of Science, Science in Context.

Grey literature databases.

The Boolean string “research misconduct” OR “research integrity” OR “research malpractice” OR “scientific fraud” OR “fabrication, falsification” OR “falsification, fabrication” was used to search: SIGLE, National Technical Information Service, British Library Collections, British Library Direct, Canadian Evaluation Society, Bioethics Literature Database.

The Italian string “etica AND ricerca” was used in: CNR database.

The French string “scientifique AND “ethique” OR “fraude” OR “faute” OR “enquete” OR “sondage” was used in: LARA -Libre acces aux rapports scientifiques et techiques

Internet search engines.

The Boolean string “research misconduct” OR “research integrity” OR “research malpractice” OR “scientific fraud” OR “fabrication, falsification” OR “falsification, fabrication”, the Spanish Boolean string “ética cientifica” OR “faltas éticas” the French Boolean string “faute scientifique” OR “éthique scientifique” were used to search: ScienceResearch.com, Scirus.

Titles and available abstracts of all records were examined, and the full text of all potentially relevant studies was retrieved. The references list of the retrieved studies and of other documents was also examined in search of potentially relevant papers.

Selection

Only quantitative survey data assessing how many researchers have committed or observed colleagues committing scientific misconduct in the past were included in this review. Surveys asking only opinions or perceptions about the frequency of misconduct were not included.

To allow direct quantitative comparison across data sets, studies were included only if they presented data in frequency or percentage categories, one of which was a “never” or “none” or “nobody” category - indicating that the respondent had never committed or observed the behaviour in question. Studies lacking such a category, or presenting results in statistical formats that prevented the retrieval of this information (e.g. mean and standard deviation) were excluded. Respondents of any professional position and scientific discipline were included, as long as they were actively conducting publishable research, or directly involved in it (e.g. research administrators). Surveys addressing misconduct in undergraduate students were excluded, because it was unclear if the misconduct affected publishable scientific data or only scholastic results.

This review focused on all and only behaviours that can falsify or bias scientific knowledge through the unjustified alteration of data, results or their interpretation (e.g. any form of fabrication and falsification, intentional non-publication of results, biased methodology, misleading reporting, etc…). Plagiarism and professional misconduct (e.g. withholding information from colleagues, guest authorship, exploitation of subordinates etc…) were excluded from this review. Surveys that made no clear distinction between the former and latter types of misconduct (e.g. that asked about fabrication, falsification and plagiarism in the same question) were excluded.

Any available data on scientists' reaction to alleged cases of misconduct was extracted from included studies. Since these data provided only additional information that was not the focus of the review, survey questions that did not distinguish between data manipulation and plagiarism were included in this section of the results, but clearly identified.

Validity assessment

Surveys that did not sample respondents at random, or that did not provide sufficient information on the sampling methods employed where given a quality score of zero and excluded from the meta-analysis. All remaining papers were included, and were not graded on a quality scale, because the validity and use of quality measures in meta-analysis is controversial [21], [22]. Instead of using an arbitrary measure of quality, the actual effect of methodological characteristics on results was tested and then controlled for with regression analysis. In the tables listing study characteristics, the actual words reported in the paper by the authors are quoted directly whenever possible. The few cases where a direct quotation could not be retrieved are clearly indicated.

Data abstraction

For each question, the percentage of respondents who recalled committing or who observed (i.e. had direct knowledge of) a colleague who committed one or more times the specified behaviour was calculated. In the majority of cases, this required summing up the responses in all categories except the “none” or “never” category, and the “don't know” category.

Some studies subdivided the sample of respondents according to a variety of demographic characteristics (e.g. gender, career level, professional position, academic discipline, etc…) and disaggregated the response data accordingly. In all these cases, the data was re-aggregated.

Given the objectivity of the information collected and the fact that all details affecting the quality of studies are reported in this paper, it was not necessary to have the data extracted/verified by more than one person.

Quantitative data synthesis

The main outcome of the meta-analysis was the percentage (proportion) of respondents that recalled committing or that knew of a colleague committing the specified behaviour at least once in the given recall period. This measure was not normally distributed (Kolmogorov-Smirnov test: 0.240, df=19, P=0.005) so it was *logit* transformed [23], and weighted by inverse variance of logit transformed proportion using the following equations for effect size, standard error and weight, respectively:

$$\mathrm{ES} = \mathrm{Log}_e\left[\frac{p}{(1-p)}\right]$$

$$\mathrm{SE} = \sqrt{\frac{1}{np} + \frac{1}{n(1-p)}}$$

$$\mathrm{W} = \frac{1}{SE^2} = np(1-p)$$

Where p is the proportion of respondents recalling at least one case of the specified behaviour, and n is the total number of respondents. The distribution of the logit-transformed effect sizes was not significantly different from normal (K-S: 0.109, df=19, P= 0.2). To facilitate their interpretation, the final logit results (ES and 95%CI) were back-transformed in percentages using the following equations for proportion and percentages, respectively:

$$p = \frac{e^x}{e^x + 1}$$

$$\% = 100p$$

Where x is either ES or each of the corresponding 95%CI values.

Mean pooled effect size was calculated assuming a random effects model, and homogeneity was tested with Chochran's Q test. Differences between groups of studies were tested using inverse variance weighted one-way ANOVA. The combined effect of independent variables on effect sizes was tested with inverse variance weighted regression assuming a random effects model and estimated via iterative maximum likelihood.

To avoid the biasing effect of multiple outcomes within the same study, all meta-analyses on the main outcome of interest (i.e. the prevalence of data fabrication, falsification and alteration) were conducted using only one outcome per study. For the same reason, in the regression analysis, which combined all available effect sizes on data fabrication, falsification and alteration, studies that had data both on self- and on non self- where used only for the former.

The regression model first tested the combined effect of three methodological factors measured by binary variables (self- vs non-self- reports, handed vs mailed questionnaire, questions using the word “falsification” or “fabrication” vs questions using “alteration”, “modification” etc…). Then, the effect of several study characteristics was tested (year when the survey was conducted, surveys

conducted in the USA vs anywhere else, surveys conducted exclusively on researchers vs any other, biomedical vs other types of research, social sciences vs natural sciences, medical consultants and practitioners vs other). To avoid over-fitting, each study characteristic was tested independently of the others.

Questions on behaviours of secondary interest (questionable research practices) where too diverse to allow meaningful meta-analysis, so they were combined in broad categories for which only crude unweighted parameters were calculated. All statistical analyses were run on SPSS software package. Meta-analyses were conducted using the “MeanES”, “MetaF” and “MetaReg” macros by David B. Wilson [24].

Publication bias-Sensitivity analysis

The popular funnel-plot-based methods to test for publication bias in meta-analysis are inappropriate and potentially misleading when the number of included studies is small and heterogeneity is large [25], [26]. However, the robustness of results was assessed with a sensitivity analysis. Pooled weighted estimates for effect size and regression parameters were calculated leaving out one study at a time, and then compared to identify influential studies. In addition, to further assess the robustness of conclusions, meta-analyses and meta-regression were run without logit transformation.

Results

Flow of included studies

Electronic search produced an initial list of 3276 references. Examination of titles and abstracts, and further examination of the references lists in the retrieved papers and in other sources led to a preliminary list of 69 potentially relevant studies. Of these, 61 were published in peer-reviewed journals, three were dissertations theses, three were published in non-peer reviewed popular science magazines, one was published in a book chapter, and one was published in a report. All studies were published in English except for one in Spanish.

After examination of full text, 33 studies were excluded because they did not have any relevant or original data, two because they presented data exclusively in a format that could not be used in this review (e.g. means and standard deviations), eight because their sample included non-researchers (e.g. students) and/or because they addressed forms of academic misconduct not directly related to research (e.g. cheating on school projects), five because they do not distinguish fabrication and falsification from types of misconduct not relevant to the scopes of this review (Table S1). Therefore, 21 studies were included in the review. Three of these did not match the quality requirements to be included in the meta-analysis. Data from these three studies was only used to estimate crude unweighted means for QRP and more generic questions, and not for analyzing the main outcome of interest (data fabrication, falsification, modification). Therefore, the meta-analysis was conducted on 18 studies (Figure 1).

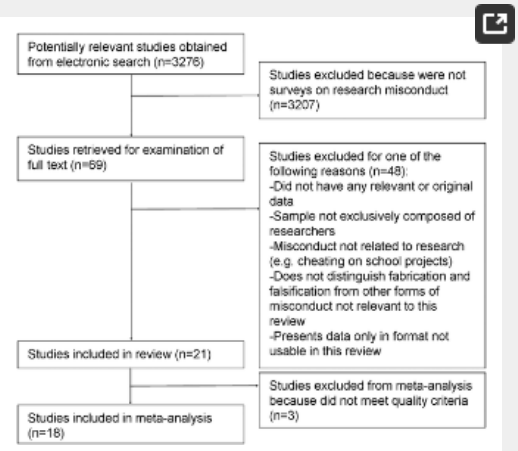


Figure 1. Study selection flow diagram.
https://doi.org/10.1371/journal.pone.0005738.g001

Study characteristics

Table 1 lists the characteristics of included studies and their quality score for inclusion in meta-analysis. Included surveys were published between 1987 and 2008, but had been conducted between 1986 ca and 2005. Respondents were based in the United States in 15 studies (71% ca of total), in the United Kingdom in 3 studies (14% ca), two studies had a multi-national sample (10%

ca) and one study was based in Australia. Six studies had been conducted among biomedical researchers, eight were more specifically targeted at researchers holding various positions in the medical/clinical sciences (including pharmacology, nursing, health education, clinical biostatistics, and addiction-studies), six surveys had multi-disciplinary samples, one surveyed economists.

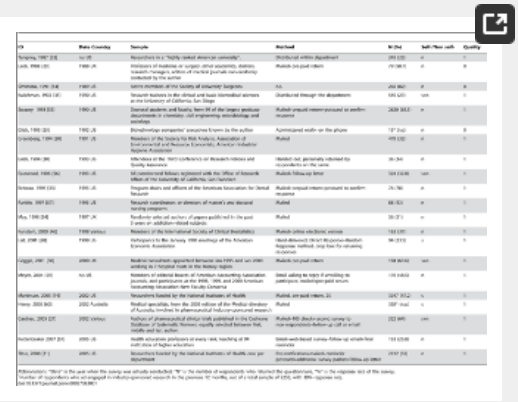


Table 1. Characteristics of studies included in the review.
https://doi.org/10.1371/journal.pone.0005738.t001

Quantitative data analysis

Scientists admitting misconduct.

When explicitly asked if they ever fabricated or falsified research data, or if they altered or modified results to improve the outcome (see Table S2, questions 1, 4, 6, 8, 10, 17, 26), between 0.3% and 4.9% of scientists replied affirmatively (N=7, crude unweighted mean: 2.59%, 95%CI=1.06–4.13). Meta-analysis yielded a pooled weighted estimate of 1.97% (95%CI: 0.86–4.45), with significant heterogeneity (Cochran's Q=61.7777, df=6, P<0.0001) (Figure 2). If only questions explicitly using the words “fabrication” or “falsification” were included (Table S2, questions 3, 6, 10, 26), the pooled weighted estimate was 1.06% (N=4, 95%CI: 0.31–3.51)

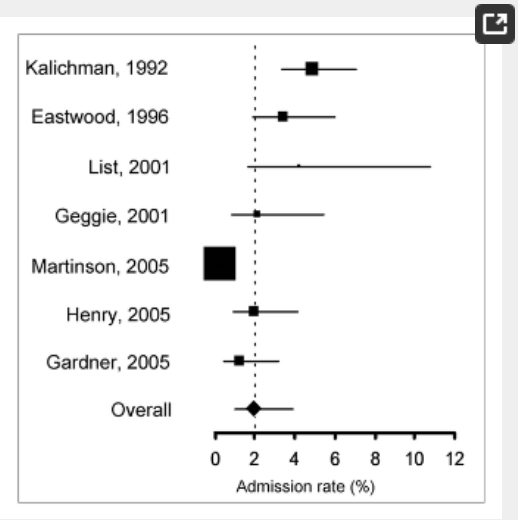


Figure 2. Forrest plot of admission rates of data fabrication, falsification and alteration in self reports.
Area of squares represents sample size, horizontal lines are 95% confidence interval, diamond and vertical dotted line show the pooled weighted estimate.
https://doi.org/10.1371/journal.pone.0005738.g002

Other questionable practices were admitted by up to 33.7% of respondents (Table S2) (Figure 3, N=20 (six studies), crude unweighted mean: 9.54%, 95%CI=5.15–13.94).

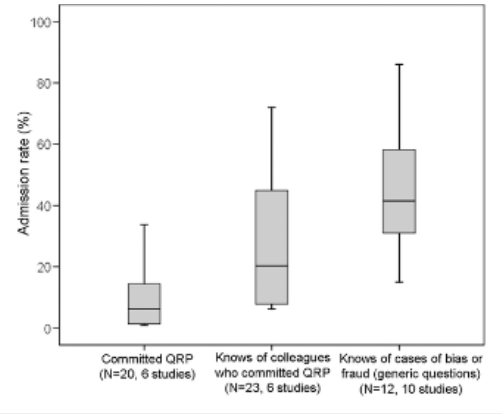


Figure 3. Admission rates of Questionable Research Practices (QRP) in self- and non-self-reports.
N indicates the number of survey questions. Boxplots show median and interquartiles.
https://doi.org/10.1371/journal.pone.0005738.g003

Consistently across studies, scientists admitted more frequently to have "modified research results" to improve the outcome than to have reported results they "knew to be untrue" (Inverse Variance Weighted Oneway ANOVA Q(1,4)=14.8627, P=0.011)

In discussing limitations of results, two studies [19], [27] suggested that their results were very conservative with respect to the actual occurrence of misconduct, while the other studies made no clear statement. Non-response bias was recognized as a limitation by most surveys. One study employed a Random-Response technique on part of its sample to control for non-response bias, and found no evidence for it [28] (see Discussion for further details).

Scientists observing misconduct.

When asked if they had personal knowledge of a colleague who fabricated or falsified research data, or who altered or modified research data (Table S3, questions, 1, 6, 7, 10, 20, 21, 29, 32, 34, 37, 45, 54) between 5.2% and 33.3% of respondents replied affirmatively (N=12, crude unweighted mean: 16.66%, 95%CI=9.91–23.40). Meta-analysis yielded a pooled weighted estimate of 14.12% (95% CI: 9.91–19.72) (Figure 4). If only questions explicitly using the words "fabrication" or "falsification" were included (Table S3, questions 1, 6, 7, 10, 17, 21, 29, 32, 37, 45, 54), the pooled weighted estimate was 12.34% (N=11, 95%CI: 8.43–17.71)

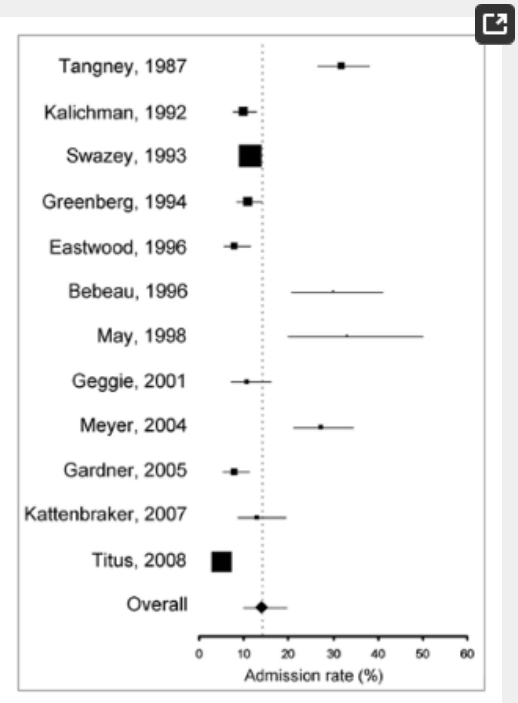


Figure 4. Forrest plot of admission rates of data fabrication, falsification and alteration in non-self reports.

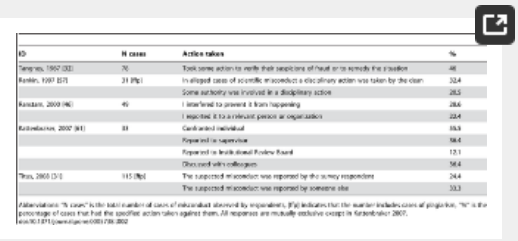
Area of squares represents sample size, horizontal lines are 95% confidence interval, diamond and vertical dotted line show the pooled weighted estimate.
https://doi.org/10.1371/journal.pone.0005738.g004

Between 6.2% and 72% of respondents had knowledge of various questionable research practices (Table S3) (Figure 3, N=23 (6 studies), crude unweighted mean: 28.53%, 95%CI=18.85–38.2). When surveys asked about more generic questions (e.g. "do you have knowledge of any cases of fraud?" [29], [30]) or defined misconduct in more comprehensive ways (e.g. "experimental deficiencies, reporting deficiencies, misrepresentation of data, falsification of data" [30]) between 12% and 92% replied affirmatively (Table S3) (N=10 (seven studies), crude unweighted mean: 46.24, 95%CI=16.53–75.95).

In discussing their results, three studies [27], [29], [31] considered them to be conservative, four [30], [32], [33], [34] suggested that they overestimated the actual occurrence of misconduct, and the remaining 13 made no clear statement.

Scientists reporting misconduct.

Five of the included studies asked respondents what they had done to correct or prevent the act of misconduct they had witnessed. Around half of the alleged cases of misconduct had any action taken against them (Table 2). No study asked if these actions had the expected outcome. One survey [27] found that 29% of the cases of misconduct known by respondents were never discovered.



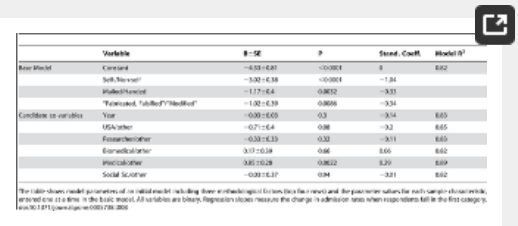
ID	N cases	Action taken	%
Tangney, 1987 [32]	70	Took some action to verify their suspicions of fraud or to remedy the situation	46
Konkin, 1997 [27]	31 (Bp)	In alleged cases of scientific misconduct a disciplinary action was taken by the dean	32.4
		Some authority was involved in a disciplinary action	26.5
Kandasamy, 2000 [46]	49	I interfered to prevent it from happening	28.6
		I reported it to a relevant person or organization	22.4
Kattenbraker, 2007 [61]	81	Coerced individual	18.5
		Reported to supervisor	58.4
		Reported to Institutional Review Board	12.1
		Discussed with colleagues	58.4
Titus, 2008 [31]	115 (Bp)	The suspected misconduct was reported by the survey respondent	24.4
		The suspected misconduct was reported by someone else	33.3

Abbreviations: "N cases" is the total number of cases of misconduct observed by respondents; "(Bp) indicates that the question includes cases of plagiarism; "%" is the percentage of cases that had the specified action taken against them. All responses are mutually exclusive except in Kattenbraker 2007.

Table 2. Actions taken against misconduct.
https://doi.org/10.1371/journal.pone.0005738.t002

Factors influencing responses.

Methodological differences between studies explained a large portion of the variance among effect sizes (N=15, one outcome per study, Table 3). Lower percentages of misconduct were reported in self reports, in surveys using the words "falsification" or "fabrication", and in mailed surveys. Mailed surveys had also higher response rates than handed-out surveys (Mean: 26.63% ±2.67SE and 48.53%±4.02SE respectively, t-test: t=−2.812, df=16, P=0.013), while no difference in response rates was observed between self- and non-self-reports (Mean: 42.44±6.24SE and 44.44±5.1SE respectively, t=−0.246, P=0.809) and between surveys using or not "fabrication or falsification" (Mean: 42.98%±6.0SE and 44.51±4.76SE respectively, t=−0.19, P=0.85). Excluding all surveys that were not mailed, were not self-reports and that did not use the words "falsification" or "fabrication" yielded a maximally conservative pooled weighted estimate of 0.64% (N=3, 95%CI: 0.25–1.63).



	Variable	B±SE	P	Sqrd. Coeff.	Model R^2
Base Model	Constant	−4.53±0.81	<0.0001	0	0.62
	Self/Normal	−3.00±0.38	<0.0001	−1.34	
	Mailed/Handed	−1.17±0.4	0.0032	−0.33	
	"Fabricated, Falsified"/"Modified"	−1.00±0.39	0.0098	−0.34	
Condition on variables	Year	−0.00±0.00	0.3	−0.14	0.65
	USA/other	−0.7±0.4	0.08	−0.2	0.65
	Researcher/other	−0.33±0.33	0.32	−0.11	0.65
	Biomedical/other	0.17±0.39	0.66	0.06	0.62
	Med/other	0.81±0.28	0.0022	0.29	0.69
	Social Sci/other	−0.03±0.37	0.94	−0.01	0.62

The table shows model parameters of six initial models including three methodological factors (face-to-face/mail and the questionnaire subjects for each sample characteristic, entered one at a time in the basic model. All variables are binary. Regression slopes measure the change in admission rates when respondents fall in the first category.

Table 3. Inverse variance-weighted regression on admission rates.
https://doi.org/10.1371/journal.pone.0005738.t003

When the three methodological factors above where controlled for, a significant effect was found for surveys targeted at medical and clinical researchers, who reported higher percentages of misconduct than respondents in biomedical research and other fields (Table 3). The effect of this parameter would remain significant if Bonferroni-corrected for multiple comparisons. If self- and non-self- reports were tested separately for the effect of study characteristics (one characteristic at a time), a significant effect was found only in self-reports for year when survey was conducted (k=7, b=−0.1425±0.0519, P=0.006) and a nearly significant effect was found again in self-reports for survey delivery method (k=7, b=−1.2496±0.6382, P=0.0502)

Sensitivity analysis

Self-report admission rates varied between 1.65% -following the removal of Kalichman and Friedman (1992) [35]- and 2.93% -following the removal of Martinson et al. (2005) [19] (Figure 5). Reports on colleagues' misconduct varied between 12.85% (when Tangney (1987) [32] was removed) and 15.41% (when Titus et al. (2008) [31] was removed (Figure 6). Weighted pooled estimates on non-logit-trasformed data yielded self- and non-self- admission rates of 2.33% (95%CI 0.94–3.73%) and 14.48% (95%CI: 11.14–17.81%) respectively, showing that the results are robust and conservative.

Figure 5. Sensitivity analysis of admission rates of data fabrication, falsification and alteration in self reports.
Plots show the weighted pooled estimate and 95% confidence interval obtained when the corresponding study was left out of the analysis.
https://doi.org/10.1371/journal.pone.0005738.g005

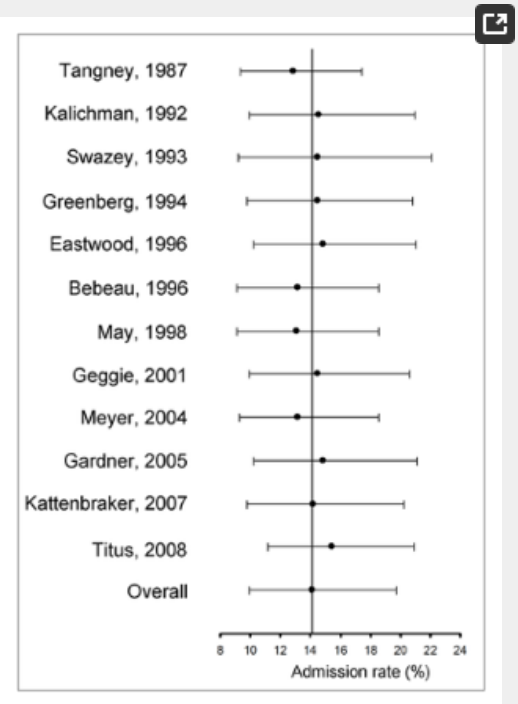


Figure 6. Sensitivity analysis of admission rates of data fabrication, falsification and alteration in non-self reports.
Plots show the weighted pooled estimate obtained when the corresponding study was left out of the analysis.
https://doi.org/10.1371/journal.pone.0005738.g006

Results of the regression analysis were robust to the leave-one-study-out test: the four significant variables remained statistically significant when anyone of the studies was excluded (Table S4). The largest portion of variance was explained when Titus et al. (2008) [31] was removed (R^2=0.9202). Meta-regression on non-transformed data showed similar trends to that on transformed data for all four parameters, but only two parameters remained statistically significant (self-/non-self- and delivery method, P<0.0001 and p=0.0083 respectively), and the overall portion of variance explained by the model was lower (R^2=0.6904).

Discussion

This is the first meta-analysis of surveys asking scientists about their experiences of misconduct. It found that, on average, about 2% of scientists admitted to have fabricated, falsified or modified data or results at least once –a serious form of misconduct my any standard [10], [36], [37]– and up to one third admitted a variety of other questionable research practices including "dropping data points based on a gut feeling", and "changing the design, methodology or results of a study in response to pressures from a funding source". In surveys asking about the behaviour of colleagues, fabrication, falsification and modification had been observed, on average, by over 14% of respondents, and other questionable practices by up to 72%. Over the years, the rate of admissions declined significantly in self-reports, but not in non-self-reports.

A large portion of the between-studies variance in effect size was explained by three basic methodological factors: whether the survey asked about self or not, whether it was mailed or handed out to respondents, and whether it explicitly used the words "fabrication" and "falsification". Once these factors were controlled for, surveys conducted among clinical, medical and pharmacological researchers appeared to yield higher rates of misconduct than surveys in other fields or in mixed samples.

All the above results were robust with respect to inclusion or exclusion of any particular study, with perhaps one exception: Martinson et al. (2005) [19], which is one of the largest and most frequently cited surveys on misconduct published to date. This study appears to be rather conservative, because without it the pooled average frequency with which scientists admit they have committed misconduct would jump to nearly 3%.

How reliable are these numbers? And what can they tell us on the actual frequency of research misconduct? Below it will be argued that, while surveys asking about colleagues are hard to interpret conclusively, self-reports systematically underestimate the real frequency of scientific misconduct. Therefore, it can be safely concluded that data fabrication and falsification –let alone other questionable research practices- are more prevalent than most previous estimates have suggested.

The procedure adopted to standardize data in the review clearly has limitations that affect the interpretation of results. In particular, the percentage of respondents that recall at least one incident of misconduct is a very rough measure of the frequency of misconduct, because some of the respondents might have committed several frauds, but others might have "sinned" only once. In this latter case, the frequencies reported in surveys would tend to overestimate the prevalence of biased or falsified data in the literature. The history of science, however, shows that those responsible of misconduct have usually committed it more than once [38], [39], so the latter case might not be as likely as the former. In any case, many of the included studies asked to recall at least one incident, so this limitation is intrinsic to large part of the raw data.

The distinction made in this review between "fabrication, falsification and alteration" of results and QRP is somewhat arbitrary. Not all alterations of data are acts of falsification, while "dropping data points based on a gut feeling" or "failing to publish data that contradicts one's previous research" (e.g. [19]) might often be. As explained in the introduction, any boundary defining misconduct will be arbitrary, but intention to deceive is the key aspect. Scientists who answered "yes" to questions asking if they ever fabricated or falsified data are clearly admitting their intention to misrepresent results. Questions about altering and modifying data "to improve the outcome" might be more ambiguously interpreted, which might explain why these questions yield higher admission rates. However, even if we limited the meta-analysis to the most restrictive types of questions in self-reports, we would still have an average admission rate above 1%, which is higher than previous estimates (e.g. [11]).

The accuracy of self-reports on scientific misconduct might be biased by the effect of social expectations. In self-reports on criminal behaviour, social expectations make many respondents less likely to admit a crime they committed (typically, females and older people) and make others likely to report a crime they have not really committed (typically, young males) [40]. In the case of scientists, however, social expectations should always lead to underreporting, because a reputation of honesty and objectivity is fundamental in any stage of a scientific career. Anyone who has ever falsified research is probably unwilling to reveal it and/or to respond to the survey despite all guarantees of anonymity [41]. The opposite (scientists admitting misconduct they didn't do) appears very unlikely. Indeed, there seems to be a large discrepancy between what researchers are willing to do and what they admit in a survey. In a sample of postdoctoral fellows at the University of California San Francisco, USA, only 3.4% said they had modified data in the past, but 17% said they were "willing to select or omit data to improve their results" [42]. Among research trainees in biomedical sciences at the University of California San Diego, 4.9% said they had modified research results in the past, but 81% were "willing to select, omit or fabricate data to win a grant or publish a paper" [35].

Mailed surveys yielded lower frequencies of misconduct than handed out surveys. Which of the two is more accurate? Mailed surveys were often combined with follow-up letters and other means of encouraging responses, which ensured higher response rates. However, the accuracy of responses to sensitive questions is often independent of response rates, and depends strongly on respondents' perception of anonymity and confidentiality [43], [44]. Questionnaires that are handed to, and returned directly by

respondents might better entrust anonymity than surveys that need to be mailed or emailed. Therefore, we cannot rule out the possibility that handed out surveys are more accurate despite the lower response rates. This latter interpretation would be supported by one of the included studies: a handed out survey that attempted to measure non-response bias using a Random-Response (RR) technique on part of its sample [28]. Differently from the usual Direct Response technique, in RR, respondents toss coins to determine whether they will respond to the question or just mark “yes”. This still allows admission rates to be calculated, yet it guarantees full anonymity to respondents because no one can tell whether an individual respondent answered “yes” to the question or because of chance. Contrary to author's expectations, response and admission rates were not higher with RR compared to DR, suggesting that in this handed out survey non-response bias was absent.

The effect of social expectations in surveys asking about colleagues is less clear, and could depend on the particular interests of respondents. In general, scientists might tend to protect the reputation of their field, by minimizing their knowledge of misconduct [27]. On the other hand, certain categories of respondents (e.g. participants at a Conference on Research Policies and Quality Assurance [30]) might have particular experience with misconduct and might be very motivated to report it.

Surveys on colleagues' behaviour might tend to inflate estimates of misconduct also because the same incident might be reported by many respondents. One study controlled for this factor by asking only one researcher per department to recall cases that he had observed in that department in the past three years [31]. It found that falsification and fabrication had been observed by 5.2% of respondents, which is lower than all previous non-self reports. However, since one individual will not be aware of all cases occurring around him/her, this is a conservative estimate [31]. In the sensitivity analysis run on the regression model, exclusion of this study caused the single largest increase in explained variance, which further suggests that findings of this study are unusual.

Another critical factor in interpreting survey results is the respondents' perception of what does and does not constitute research misconduct. As mentioned before, scientists were less likely to reply affirmatively to questions using the words “fabrication” and “falsification” rather than “alteration” or “modification”. Moreover, three surveys found that scientists admitted more frequently to have “modified” or “altered” research to “improve the outcome” than to have reported results they “knew to be untrue”. In other words, many did not think that the data they “improved” were falsified. To some extent, they were arguably right. But the fuzzy boundary between removing noise from results and biasing them towards a desired outcome might be unknowingly crossed by many researchers [10], [14], [45]. In a sample of biostatisticians, who are particularly well trained to see this boundary, more than half said they had personally witnessed false or deceptive research in the preceding 10 years [46].

The grey area between licit, questionable, and fraudulent practices is fertile ground for the “Mohammed Ali effect”, in which people perceive themselves as more honest than their peers. This effect was empirically proven in academic economists [28] and in a large sample of biomedical researchers (in a survey assessing their adherence to Mertonian norms [47]), and may help to explain the lower frequency with which misconduct is admitted in self-reports: researchers might be overindulgent with their behaviour and overzealous in judging their colleagues. In support of this, one study found that 24% of cases observed by respondents did not meet the US federal definition of research misconduct [31].

The decrease in admission rates observed over the years in self-reports but not in non-self-reports could be explained by a combination of the Mohammed Ali effect and social expectations. The level and quality of research and training in scientific integrity has expanded in the last decades, raising awareness among scientists and the public [11]. However, there is little evidence that researchers trained in recognizing and dealing with scientific misconduct have a lower propensity to commit it [47], [48], [49]. Therefore, these trends might suggest that scientists are no less likely to commit misconduct or to report what they see their colleagues doing, but have become less likely to admit it for themselves.

Once methodological differences were controlled for, cross-study comparisons indicated that samples drawn exclusively from medical (including clinical and pharmacological) research reported misconduct more frequently than respondents in other fields or in mixed samples. To the author's knowledge, this is the first cross-disciplinary evidence of this kind, and it suggests that misconduct in clinical, pharmacological and medical research is more widespread than in other fields. This would support growing fears that the large financial interests that often drive medical research are severely biasing it [50], [51], [52]. However, as all survey-based data, this finding is open to the alternative interpretation that respondents in the medical profession are simply more aware of the problem and more willing to report it. This could indeed be the case, because medical research is a preferred target of research and training programs in scientific integrity, and because the severe social and legal consequences of misconduct in medical research might motivate respondents to report it. However, the effect of this parameter was not robust to one of the sensitivity analyses, so it would need to be confirmed by independent studies before being conclusively accepted.

The lack of statistical significance for the effect of country, professional position and other sample characteristics is not strong evidence against their relevance, because the high between-study variance caused by methodological factors limited the power of the analysis (the regression had to control for three methodological factors before testing any other effect). However, it suggests that such differences need to be explored at the study level, with large surveys designed specifically to compare groups. A few of the included studies had done so and found, for example, that admission rates tend to be higher in males compared to females [42] and in mid-career compared to early career scientists [19], and that they tend to differ between disciplines [41], [53]. If more studies attempted to replicate these results, possibly using standardized methodologies, then a meta-analysis could reveal important correlates of scientific misconduct.

In conclusion, several surveys asking scientists about misconduct have been conducted to date, and the differences in their results are largely due to differences in methods. Only by controlling for these latter can the effects of country, discipline, and other demographic characteristics be studied in detail. Therefore, there appears to be little scope for conducting more small descriptive surveys, unless they adopted standard methodologies. On the other hand, there is ample scope for surveys aimed at identifying sociological factors associated with scientific misconduct. Overall, admission rates are consistent with the highest estimates of misconduct obtained using other sources of data, in particular FDA data audits [11], [18]. However, it is likely that, if on average 2% of scientists admit to have falsified research at least once and up to 34% admit other questionable research practices, the actual frequencies of misconduct could be higher than this.

Supporting Information

Table S1.
Studies excluded from the review.
https://doi.org/10.1371/journal.pone.0005738.s001
(0.14 MB DOC)

Table S2.
Self-report questions included in review, and responses.
https://doi.org/10.1371/journal.pone.0005738.s002
(0.07 MB DOC)

Table S3.
Non-self report questions included in the review, and responses.
https://doi.org/10.1371/journal.pone.0005738.s003
(0.11 MB DOC)

Table S4.
Sensitivity analysis for meta-regression model.
https://doi.org/10.1371/journal.pone.0005738.s004
(0.07 MB DOC)

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Author Contributions

Conceived and designed the experiments: DF. Performed the experiments: DF. Analyzed the data: DF. Wrote the paper: DF.

References

1. Saunders R, Savulescu J (2008) Research ethics and lessons from Hwanggate: what can we learn from the Korean cloning fraud? Journal of Medical Ethics 34: 214–221.
View Article • Google Scholar

2. Service RF (2003) Scientific misconduct - More of Bell Labs physicist's papers retracted. Science 299: 31–31.
View Article • Google Scholar

3. Marshall E (2000) Scientific misconduct - How prevalent is fraud? That's a million-dollar question. Science 290: 1662–1663.
View Article • Google Scholar

4. Sovacool BK (2008) Exploring scientific misconduct: isolated individuals, impure institutions, or an inevitable idiom of modern science? Journal of Bioethical Inquiry 5: 271–282.
View Article • Google Scholar

5. Bogner A, Menz W (2006) Science crime: the Korean cloning scandal and the role of ethics. Science & Public Policy 33: 601–612.
View Article • Google Scholar

6. Koshland DE (1987) Fraud in Science. Science 235: 141.
View Article • Google Scholar

7. La Follette MC (2000) The evolution of the “scientific misconduct” issues: an historical overview. Procedings of the Society for Experimental Biology and Medicine 224: 211–215.
View Article • Google Scholar

8. Merton RK (1942) The normative structure of science. In: Merton RK, editor. The Sociology of Science: Theoretical and Empirical Investigations. Chicago, IL: University of Chicago Press.

9. Sismondo S (2004) An introduction to science and technology studies. Malden, Mass.: Blackwell.

10. Smith R (2000) What is research misconduct? The COPE Report 2000: the Committee on Publication Ethics.

11. Steneck NH (2006) Fostering integrity in research: definitions, current knowledge, and future directions. Science and Engineering Ethics 12: 53–74.
View Article • Google Scholar

12. Babbage C (1830) Reflections on the decline of science in England and on some of its causes. In: Campbell-Kelly M, editor. The Works of Charles Babbage. London Pickering.

13. Krimsky S (2007) When conflict-of-interest is a factor in scientific misconduct. Medicine and Law 26: 447–463.
View Article • Google Scholar

14. De Vries R, Anderson MS, Martinson BC (2006) Normal misbehaviour: scientists talk about the ethics of research. Journal of Empirical Research on Human Research Ethics 1: 43–50.
View Article • Google Scholar

15. Guston DH (1999) Changing explanatory frameworks in the US government's attempt to define research misconduct. Science and Engineering Ethics 5: 137–154.
View Article • Google Scholar

16. Steneck NH (2003) The role of professional societies in promoting integrity in research. American Journal of Health Behaviour 27: S239–S247.
View Article • Google Scholar

17. Claxton LD (2005) Scientific authorship Part 1. A window into scientific fraud? Mutation Research-Reviews in Mutation Research 589: 17–30.
View Article • Google Scholar

18. Glick JL (1992) Scientific data audit -a key management tool. Accountability in Research 2: 153–168.
View Article • Google Scholar

19. Martinson BC, Anderson MS, de Vries R (2005) Scientists behaving badly. Nature 435: 737–738.
View Article • Google Scholar

20. Greenberg M, Goldberg L (1994) Ethical challenges to risk scientists: an exploratory analysis of survey data. Science, Technology, and Human Values 19: 223–241.
View Article • Google Scholar

21. Greenland S (1994) Quality scores are useless and potentially misleading - Reply to Re - a Critical-Look at Some Popular Analytic Methods. American Journal of Epidemiology 140: 300–301.
View Article • Google Scholar

22. Juni P, Witschi A, Bloch R, Egger M (1999) The hazards of scoring the quality of clinical trials for meta-analysis. Jama-Journal of the American Medical Association 282: 1054–1060.
View Article • Google Scholar

23. Lipsey M, Wilson DB (2001) Practical meta-analysis. California: Sage Publications.

24. Wilson DB (2005) SPSS Macros for Meta-analysis, Available at: http://mason.gmu.edu/~dwilsonb/ma.html.

25. Terrin N, Schmid CH, Lau J, Olkin I (2003) Adjusting for publication bias in the presence of heterogeneity. Statistics in Medicine 22: 2113–2126.
View Article • Google Scholar

26. Macaskill P, Walter SD, Irwig L (2001) A comparison of methods to detect publication bias in meta-analysis. Statistics in Medicine 20: 641–654.
View Article • Google Scholar

27. Gardner W, Lidz CW, Hartwig KC (2005) Authors' reports about research integrity problems in clinical trials. Contemporary Clinical Trials 26: 244–251.
View Article • Google Scholar

28. List JA, et al. (2001) Academic economists behaving badly? A survey on three areas of unethical behaviour. Economic Inquiry 39: 162–170.
View Article • Google Scholar

29. Lock S (1988) Misconduct in medical research: does it exist in Britain? British Medical Journal 297: 1531–1535.
View Article • Google Scholar

30. Glick LJ, Shamoo AE (1994) Results of a survey on research practices, completed by attendees at the third conference on research policies and quality assurance. Accountability in Research 3: 275–280.
View Article • Google Scholar

31. Titus SL, Wells JA, Rhoades LJ (2008) Repairing research integrity. Nature 453: 980–982.
View Article • Google Scholar

32. Tangney JP (1987) Fraud will out ? Or will it? New Scientist 115: 62–63.
View Article • Google Scholar

33. Bebeau MJ, Davis EL (1996) Survey of ethical issues in dental research. Journal of Dental Research 75: 845–855.
View Article • Google Scholar

34. May C, Campbell S, Doyle H (1998) Research misconduct: A pilot study of British addiction researchers. Addiction Research 6: 371–373.
View Article • Google Scholar

35. Kalichman MW, Friedman PJ (1992) A pilot study of biomedical trainees' perceptions concerning research ethics. Academic Medicine 67: 769–775.
View Article • Google Scholar

36. COPE (2000) The COPE report 2000. Committee on Publication Ethics.

37. Berk RA, Korenman SG, Wenger NS (2000) Measuring consensus about scientific research norms. Science and Engineering Ethics 6: 315–340.
View Article • Google Scholar

38. Judson HF (2004) The Great Betrayal: Fraud in Science. Orlando, Florida: Harcourt.

39. Grant J (2007) Corrupted Science: Fraud, Ideology and Politics in Science. Wisley, UK: Facts, Figures and Fun (AAPPL).

40. Farrington DP (2003) What has been learned from self-reports about criminal careers and the causes of offending. London: Home Office.

41. Martinson BC, Anderson MS, Crain LA, De Vries R (2006) Scientists' perceptions of organizational justice and self-reported misbehaviours. Journal of Empirical Research on Human Research Ethics 1: 51–66.
View Article • Google Scholar

42. Eastwood S, Derish P, Leash E, Ordway S (1996) Ethical issues in biomedical research: Perceptions and practices of postdoctoral research fellows responding to a survey. Science and Engineering Ethics 2: 89–114.
View Article • Google Scholar

43. Tourangeau R, Smith TW (1996) Asking sensitive questions - The impact of data collection mode, question format, and question context. Public Opinion Quarterly 60: 275–304.
View Article • Google Scholar

44. Bates SC, Cox JM (2008) The impact of computer versus paper-pencil survey, and individual versus group administration, on self-reports of sensitive

behaviours. Computers in Human Behaviour 24: 903–916.
View Article • Google Scholar

45. Lynöe N, Jacobsson L, Lundgren E (1999) Fraud, misconduct or normal science in medical research - an empirical study of demarcation. Journal of Medical Ethics 25: 501–506.
View Article • Google Scholar

46. Ranstam J, Buyse M, George SL, Evans S, Geller NL, et al. (2000) Fraud in medical research: An international survey of biostatisticians. Controlled Clinical Trials 21: 415–427.
View Article • Google Scholar

47. Anderson MS, Martinson BC, De Vries R (2007) Normative dissonance in science: results from a national survey of US scientists. Journal of Empirical Research on Human Research Ethics 2: 3–14.
View Article • Google Scholar

48. Plemmons DK, Brody SA, Kalichman MW (2006) Student perceptions of the effectiveness of education in the responsible conduct of research. Science and Engineering Ethics 12: 571–582.
View Article • Google Scholar

49. Turrens JF (2005) Teaching research integrity and bioethics to science undergraduates. Cell Biol Educ 4: 330–334.
View Article • Google Scholar

50. Angell M (2000) Is academic medicine for sale? New England Journal of Medicine 342: 1516–1518.
View Article • Google Scholar

51. Bekelman JE, Li Y, Gross CP (2003) Scope and impact of financial conflicts of interest in biomedical research - A systematic review. Jama-Journal of the American Medical Association 289: 454–465.
View Article • Google Scholar

52. Sismondo S (2008) Pharmaceutical company funding and its consequences: a qualitative systematic review. Contemporary Clinical Trials 29: 109–113.
View Article • Google Scholar

53. Swazey J, Anderson M, Karen L (1993) Ethical problems in academic research. American Scientist 81: 542–553.
View Article • Google Scholar

54. Simmons RL, Polk HCJ, Williams B, Mavroudis C (1991) Misconduct and fraud in research: social and legislative issues symposium of the Society of University Surgeons. Surgery 110: 1–7.
View Article • Google Scholar

55. Glick JL (1993) Perceptions concerning research integrity and the practice of data audit in the biotechnology industry. Account Res 3: 187–195.
View Article • Google Scholar

56. Eastwood S, Derish P, Leash E, Ordway S (1996) Ethical issues in biomedical research: perceptions and practices of postdoctoral research fellows responding to a survey. Science and Engineering Ethics 2: 89–114.
View Article • Google Scholar

57. Rankin M, Esteves MD (1997) Perceptions of scientific misconduct in nursing. Nursing Research 46: 270–276.
View Article • Google Scholar

58. Geggie D (2001) A survey of newly appointed consultants' attitudes towards research fraud. Journal of Medical Ethics 27: 344–346.
View Article • Google Scholar

59. Meyer MJ, McMahon D (2004) An examination of ethical research conduct by experienced and novice accounting academics. Issues in Accounting Education 19: 413–442.
View Article • Google Scholar

60. Henry DA, Kerridge IH, Hill SR, McNeill PM, Doran E, et al. (2005) Medical specialists and pharmaceutical industry-sponsored research: a survey of the Australian experience. Medical Journal of Australia 182: 557–560.
View Article • Google Scholar

61. Kattenbraker MS (2007) Health education research and publication: ethical considerations and the response of health educators. Carbondale: Southern Illinois University.Doctoral dissertation.

EXHIBIT 306

COMMENTARY

Scientists behaving badly

To protect the integrity of science, we must look beyond falsification, fabrication and plagiarism, to a wider range of questionable research practices, argue **Brian C. Martinson, Melissa S. Anderson** and **Raymond de Vries**.

Serious misbehaviour in research is important for many reasons, not least because it damages the reputation of, and undermines public support for, science. Historically, professionals and the public have focused on headline-grabbing cases of scientific misconduct, but we believe that researchers can no longer afford to ignore a wider range of questionable behaviour that threatens the integrity of science.

We surveyed several thousand early- and mid-career scientists, who are based in the United States and funded by the National Institutes of Health (NIH), and asked them to report their own behaviours. Our findings reveal a range of questionable practices that are striking in their breadth and prevalence (Table 1). This is the first time such behaviours have been analysed quantitatively, so we cannot know whether the current situation has always been the case or whether the challenges of doing science today create new stresses. Nevertheless, our evidence suggests that mundane 'regular' misbehaviours present greater threats to the scientific enterprise than those caused by high-profile misconduct cases such as fraud.

Table 1 | Percentage of scientists who say that they engaged in the behaviour listed within the previous three years ($n = 3,247$)

Top ten behaviours	All	Mid-career	Early-career
1. Falsifying or 'cooking' research data	0.3	0.2	0.5
2. Ignoring major aspects of human-subject requirements	0.3	0.3	0.4
3. Not properly disclosing involvement in firms whose products are based on one's own research	0.3	0.4	0.3
4. Relationships with students, research subjects or clients that may be interpreted as questionable	1.4	1.3	1.4
5. Using another's ideas without obtaining permission or giving due credit	1.4	1.7	1.0
6. Unauthorized use of confidential information in connection with one's own research	1.7	2.4	0.8 ***
7. Failing to present data that contradict one's own previous research	6.0	6.5	5.3
8. Circumventing certain minor aspects of human-subject requirements	7.6	9.0	6.0 **
9. Overlooking others' use of flawed data or questionable interpretation of data	12.5	12.2	12.8
10. Changing the design, methodology or results of a study in response to pressure from a funding source	15.5	20.6	9.5 ***
Other behaviours			
11. Publishing the same data or results in two or more publications	4.7	5.9	3.4 **
12. Inappropriately assigning authorship credit	10.0	12.3	7.4 ***
13. Withholding details of methodology or results in papers or proposals	10.8	12.4	8.9 **
14. Using inadequate or inappropriate research designs	13.5	14.6	12.2
15. Dropping observations or data points from analyses based on a gut feeling that they were inaccurate	15.3	14.3	16.5
16. Inadequate record keeping related to research projects	27.5	27.7	27.3

Note: significance of χ^2 tests of differences between mid- and early-career scientists are noted by ** ($P < 0.01$) and *** ($P < 0.001$).

As recently as December 2000, the US Office of Science and Technology Policy (OSTP) defined research misconduct as "fabrication, falsification, or plagiarism (FFP) in proposing, performing, or reviewing research, or in reporting research results"[1]. In 2002, the Federation of American Societies for Experimental Biology and the Association of American Medical Colleges objected to a proposal by the US Office of Research Integrity (ORI) to conduct a survey that would collect empirical evidence of behaviours that can undermine research integrity, but which fall outside the OSTP's narrow definition of misconduct[2,3]. We believe that a valuable opportunity was wasted as a result.

"Our findings suggest that US scientists engage in a range of behaviours extending far beyond falsification, fabrication and plagiarism."

A proper understanding of misbehaviour requires that attention be given to the negative aspects of the research environment. The modern scientist faces intense competition, and is further burdened by difficult, sometimes unreasonable, regulatory, social, and managerial demands[4]. This mix of pressures creates many possibilities for the compromise of scientific integrity that extend well beyond FFP.

We are not the first to call attention to these issues — debates have been ongoing since questionable research practices and scientific integrity were linked in 1992 report by the National Academy of Sciences[5]. But we are the first to provide empirical evidence based on self reports from large and representative samples of US scientists that document the occurrence of a broad range of misbehaviours.

The few empirical studies that have explored misbehaviour among scientists rely on confirmed cases of misconduct[6] or on scientists' perceptions of colleagues' behaviour[7–9], or have used small, non-representative samples of respondents[8,9]. Although inconclusive, previous estimates of the prevalence of FFP range from 1% to 2%. Our 2002 survey was based on large, random samples of scientists drawn from two databases that are maintained by the NIH Office of Extramural Research. The mid-career sample of 3,600 scientists received their first research-project (R01) grant between 1999 and 2001. The early-career sample of 4,160 NIH-supported postdoctoral trainees received either individual (F32) or institutional (T32) postdoctoral training during 2000 or 2001.

Getting data

To assure anonymity, the survey responses were never linked to respondents' identities. Of the 3,600 surveys mailed to mid-career scientists, 3,409 were deliverable and 1,768 yielded usable data, giving a 52% response rate. Of the 4,160 surveys sent to early-career scientists, 3,475 were deliverable, yielding 1,479 usable responses, a response rate of 43%.

Our response rates are comparable to those of other mail-based surveys of professional populations (such as a 54% mean response rate from physicians[10]). But our approach certainly leaves room for potential non-response bias; misbehaving scientists may have been less likely than others to respond to our survey, perhaps for fear of discovery and potential sanction. This, combined with the fact that there is

probably some under-reporting of misbehaviours among respondents, would suggest that our estimates of misbehaviour are conservative.

Our survey was carried out independently of, but at around the same time as, the ORI proposal. The specific behaviours we chose to examine arose from six focus-group discussions held with 51 scientists from several top-tier research universities, who told us which misbehaviours were of greatest concern to them. The scientists expressed concern about a broad range of specific, sanctionable conducts that may affect the integrity of research.

To affirm the serious nature of the behaviours included in the survey, and to separate potentially sanctionable offences from less serious behaviours, we consulted six compliance officers at five major research universities and one independent research organization in the United States. We asked these compliance officers to assess the likelihood that each behaviour, if discovered, would get a scientist into trouble at the institutional or federal level. The first ten behaviours listed in Table 1 were seen as the most serious: all the officers judged them as likely to be sanctionable, and at least four of the six officers judged them as very likely to be sanctionable. Among the other behaviours are several that may best be classified as carelessness (behaviours 14 to 16).

Admitting to misconduct

Survey respondents were asked to report in each case whether or not ('yes' or 'no') they themselves had engaged in the specified behaviour during the past three years. Table 1 reports the percentages of respondents who said they had engaged in each behaviour. For six of the behaviours, reported frequencies are under 2%, including falsification (behaviour 1) and plagiarism (behaviour 5). This finding is consistent with previous estimates derived from less robust evidence about misconduct. However, the frequencies for the remaining behaviours are 5% or above; most exceed 10%. Overall, 33% of the respondents said they had engaged in at least one of the top ten behaviours during the previous three years. Among mid-career respondents, this proportion was 38%; in the early-career group, it was 28%. This is a significant difference ($\chi^2 = 36.34$, d.f. = 1, $P < 0.001$). For each behaviour where mid- and early-career scientists' percentages differ significantly, the former are higher than the latter.

Although we can only speculate about the observed sub-group differences, several explanations are plausible. For example, opportunities to misbehave, and perceptions of the likelihood or consequences of being caught, may change during a scientist's career. Or it may be that these groups received their education, training, and work experience in eras that had different behavioural standards. The mid-career respondents are, on average, nine years older than their early-career counterparts (44 compared with 35 years) and have held doctoral degrees for nine years longer.

Another possible explanation for sub-group differences is the under-reporting of misbehaviours by those in relatively tenuous, early-career positions. Over half (51%) of the mid-career respondents have positions at the associate-professor level or above, whereas 58% of our early-career sample are post-doctoral fellows.

Addressing the problem

Our findings suggest that US scientists engage in a range of behaviours extending far beyond FFP that can damage the integrity of science. Attempts to foster integrity that focus only on FFP therefore miss a great deal. We assume that our reliance on self reports of behaviour is likely to lead to under-reporting and therefore to conservative estimates, despite assurances of anonymity. With as many as 33% of our survey respondents admitting to one or more of the top-ten behaviours, the scientific community can no longer remain complacent about such misbehaviour.

Early approaches to scientific misconduct focused on 'bad apples'. Consequently, analyses of misbehaviour were limited to discussions of individual traits and local (laboratory and departmental) contexts as the most likely determinants. The 1992 academy report[5] helped shift attention from individuals with 'bad traits' towards general scientific integrity and the 'responsible conduct of research.'

Over the past decade, government agencies and professional associations interested in promoting integrity have focused on responsible conduct in research[5,11,12]. However, these efforts still prioritize the immediate laboratory and departmental contexts of scientists' work, and are typically confined to 'fixing' the behaviour of individuals.

"Certain features of the working environment of science may have unexpected and potentially detrimental effects on the ethical dimensions of scientists' work."

Missing from current analyses of scientific integrity is a consideration of the wider research environment, including institutional and systemic structures. A 2002 report from the Institute of Medicine directed attention to the environments in which scientists work, and recommended an institutional (primarily university-level) approach to promoting responsible research[13]. The institute's report also noted the potential importance of the broader scientific environment, including regulatory and funding agencies, and the peer-review system, in fostering or hindering integrity, but remained mostly silent on this issue owing to a dearth of evidence.

In our view, certain features of the research working environment may have unexpected and potentially detrimental effects on the ethical dimensions of scientists' work. In particular, we are concerned about scientists' perceptions of the functioning of resource distribution processes. These processes are embodied in professional societies, through peer-review systems and other features of the funding and publishing environment, and through markets for research positions, graduate students, journal pages and grants. In ongoing analyses, not yet published, we find significant associations between scientific misbehaviour and perceptions of inequities in the resource distribution processes in science. We believe that acknowledging the existence of such perceptions and recognizing that they may negatively affect scientists' behaviours will help in the search for new ways to promote integrity in science.

Little attention has so far been paid to the role of the broader research environment in compromising scientific integrity. It is now time for the scientific community to consider what aspects of this environment are most salient to research integrity, which aspects are most amenable to change, and what changes are likely to be the most fruitful in ensuring integrity in science. ■

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1. OSTP *Federal Policy on Research Misconduct* http://www.ostp.gov/html/001207_3.html (2005).
2. Teitelbaum, S. L. *Nature* **420**, 739–740 (2002).
3. Korn, D. *Nature* **420**, 739 (2002).
4. Freeman, R., Weinstein, E., Marincola, E., Rosenbaum, J. & Solomon, F. *Science* **294**, 2293–2294 (2001).
5. *Panel on Scientific Responsibility and the Conduct of Research* (Natl Acad., Washington DC, 1992).
6. Steneck, N. H. *ORI Introduction to the Responsible Conduct of Research* (US Government Printing Office, Washington DC, 2004).
7. Swazey, J. M., Anderson, M. S. & Louis, K. S. *Am. Sci.* **81**, 542–553 (1993).
8. Ranstam, J. *et al. Control Clin. Trials* **21**, 415–427 (2000).
9. Geggie, D. *J. Med. Ethics* **27**, 344–346 (2001).
10. Asch, D. A., Jedrziewski, M. K. & Christakis, N. A. *J. Clin Epidemiol.* **50**, 1129–1136 (1997).
11. *Committee on Science Engineering and Public Policy On Being a Scientist: Responsible Conduct in Research* (Natl Acad., Washington DC, 1995).
12. *Panel on Scientific Responsibility and the Conduct of Research* (Natl Acad., Washington DC, 1993).
13. Institute of Medicine and National Research Council Committee on Assessing Integrity in Research Environments *Integrity in Scientific Research: Creating an Environment that Promotes Responsible Conduct* (Natl Acad., Washington DC, 2002).

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EXHIBIT 307

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FEATURE

COMPETING INTERESTS

Centers for Disease Control and Prevention: protecting the private good?

After revelations that the CDC is receiving some funding from industry, **Jeanne Lenzer** investigates how it might have affected the organisation's decisions

Jeanne Lenzer *associate editor, The BMJ, USA*

The Centers for Disease Control and Prevention (CDC) includes the following disclaimer with its recommendations: "CDC, our planners, and our content experts wish to disclose they have no financial interests or other relationships with the manufacturers of commercial products . . . CDC does not accept commercial support."[1]

The CDC's image as an independent watchdog over the public health has given it enormous prestige, and its recommendations are occasionally enforced by law.

Despite the agency's disclaimer, the CDC does receive millions of dollars in industry gifts and funding, both directly and indirectly, and several recent CDC actions and recommendations have raised questions about the science it cites, the clinical guidelines it promotes, and the money it is taking.

Marcia Angell, former editor in chief of the *New England Journal of Medicine,* told *The BMJ,* "The CDC has enormous credibility among physicians, in no small part because the agency is generally thought to be free of industry bias. Financial dealings with biopharmaceutical companies threaten that reputation."[2]

Industry funding of the CDC has taken many doctors, even some who worked for CDC, by surprise. Philip Lederer, an infectious diseases fellow at Massachusetts General Hospital and Brigham and Women's Hospital in Boston, Massachusetts, and a former CDC epidemic intelligence service officer, told *The BMJ* he was "saddened" to learn of industry funding.

The CDC's director, Tom Frieden, did not respond to a question about the disclaimer. He told *The BMJ* by email, "Public-private partnerships allow CDC to do more, faster. The agency's core values of accountability, respect, and integrity guide the way CDC spends the funds entrusted to it. When possible conflicts of interests arise, we take a hard, close look to ensure that proper policies and guidelines are followed before accepting outside donations."

Since its inception in 1946, the CDC has had a pivotal role not only in the prevention of infectious diseases but in reducing workplace hazards, motor vehicle injuries, and tobacco related deaths and in ensuring food safety.

One of the CDC's most important contributions, with an estimated eight million lives saved to date,[3] has been its work to educate the public about the dangers of tobacco. CDC spokesperson Thomas Skinner says the surgeon general's first report on smoking in 1964 was a "tipping point," when tobacco was first clearly identified as a health hazard by the US government. Skinner said the CDC's anti-tobacco campaign "serves as an important counter to the more than $950 000 [£630 000; €860 00] that the tobacco industry spends each hour—more than $23m a day—on cigarette advertising and promotion."

Opening up to private money

Funding of CDC took a turn in 1983, when the CDC was authorised to accept external "gifts" from industry and other private parties. In 1992, Congress passed legislation to encourage relationships between industry and the CDC by creating the non-profit CDC Foundation, which began operations in 1995.

The CDC Foundation raised $52m in fiscal year 2014, of which $12m was from corporations. The CDC itself in fiscal year 2014 received $16m in conditional funding from sources such as corporations, individuals, and philanthropy, including the CDC Foundation. Conditional donations are earmarked for specific projects. For example, in 2012, Genentech earmarked $600 000 in donations to the CDC Foundation for CDC's efforts to promote expanded testing and treatment of viral hepatitis. Genentech and its parent company, Roche, manufacture test kits and treatments for hepatitis C.

Numerous manufacturers give donations to the CDC Foundation. Janssen also contributed $1.5m in 2012-13,[1] and in 2011-12 contributors included Merck ($915 149), Genzyme ($762 000), Sanofi-Aventis ($600 000), and Abbott Laboratories ($550 000).

The CDC has recently issued controversial recommendations for screening tests and drugs,[2 4] and is currently overseeing several equally controversial studies.[5] Some of these are

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Exhibit 307

associated with "conditional" industry funding, as the three examples below show.

Cohort screening for hepatitis C

The CDC issued guidelines in August 2012 recommending expanded (cohort) screening of everyone born from 1945 to 1965 for hepatitis C virus.[1] The agency cited new direct acting antiviral drugs and protease inhibitors to treat hepatitis C as part of its rationale for cohort screening, saying the drugs "can halt disease progression and provide a virologic cure (ie, sustained viral clearance following completion of treatment) in most persons."

The science behind cohort screening has been challenged[4] and is said to be "the subject of major debate."[6] The scientific debate along with the price tags of the newer drugs (over $84 000 per treatment course for the new drug sofosbuvir), raise questions about CDC's industry funding.

In 2010, the CDC, in conjunction with the CDC Foundation, formed the Viral Hepatitis Action Coalition, which supports research and promotes expanded testing and treatment of hepatitis C in the United States and globally. Industry has donated over $26m to the coalition through the CDC Foundation since 2010. Corporate members of the coalition include Abbott Laboratories, AbbVie, Gilead, Janssen, Merck, OraSure Technologies, Quest Diagnostics, and Siemens—each of which produces products to test for or treat hepatitis C infection.

Conflict of interest forms filed by the 34 members of the external working group that wrote and reviewed the new CDC recommendation in 2012 show that nine had financial ties to the manufacturers.[1]

A report by the Office of the Inspector General in December 2009 found that external advisors to the CDC "play an influential role in decision making for the federal government." The inspector general evaluated conflicts of interest of advisors and concluded, "CDC has a systemic lack of oversight of the ethics program": 97% of disclosure forms filed by advisors were incomplete, and 13% of advisors participated in meetings without filing any disclosure at all.[7]

Although the CDC states it has addressed all of the deficiencies cited in the report, the agency did not restrict participation of the nine conflicted external advisors in the recommendation to broaden hepatitis C screening.[1] However, the CDC told *The BMJ* that external advisors acted in an "individual capacity" and are not designated as "special government employees." It said that their financial ties to industry didn't comprise a conflict of interest as the participants "had no relationships directly related to the task-reviewing evidence as a basis for an HCV testing guideline. The reported financial activities represent activities not directly related to this work but involving commercial and non-commercial entities that could be perceived to influence involvement in the task."

Oseltamivir for flu

Following criticism of the CDC and its foundation for accepting a directed donation from Roche for the agency's Take 3 flu campaign (Step 3 tells the public to "take antiviral medicine if your doctor prescribes it"),[2] the CDC posted an article on its website entitled, "Why CDC Recommends Influenza Antiviral Drugs."[8] The agency cited multiple observational and industry funded studies, including the recent meta-analysis by Dobson and colleagues,[9] which it described as an "independent" study. However, the study was sponsored by Roche, and all four authors had financial ties to Roche, Genentech, or Gilead (the first two sell oseltamivir and Gilead holds the patent).[10]

Despite its extensive list of studies, the CDC did not cite the systematic review and meta-analysis by the Cochrane Collaboration.[11]

The CDC told *The BMJ* that it didn't include the Cochrane review because Cochrane "did not consider any data from uncontrolled observational studies of oseltamivir treatment. While such studies have inherent design limitations, they can inform clinical practice and public health, especially when data from RCTs [randomized controlled trials] are unavailable or have not been conducted among high-risk groups or hospitalized influenza patients, or because having a placebo group would be unethical since antiviral treatment is recommended for these groups."

The US Food and Drug Administration issued a warning to Roche that it could not claim that oseltamivir reduces pneumonia or deaths since it has never provided evidence to the FDA to support that claim.[2] Manufacturers are prohibited by law from making off-label claims about their drugs. However, doctors can legally recommend drugs for off-label uses. By funding the CDC's Take 3 campaign, Roche and other companies are not claiming their antivirals will reduce pneumonia or death. CDC director, Frieden, however, did make the off-label claim, telling the public that it could "save your life."[2]

Shannon Brownlee, senior vice president of the Lown Institute and former journalist covering the CDC, told *The BMJ*, "This looks like classic stealth marketing, in which industry puts their message in the mouths of a trusted third party, such as an academic or a professional organization."

CDC and the sugar industry

The CDC has also been criticised for its role in a series of studies into an epidemic of chronic kidney disease among men working in the sugar fields of central America.[5] The sugar industry is paying $1.7m to fund the studies, and critics say the fact the research is being funded by the men's employers raises concerns about how far it will probe industry's role in the disease outbreak. The CDC states it will provide "technical assistance and subject matter expertise," for the studies, with the foundation serving as the "grant administrator overseeing the donor funding and facilitating the research activities."

Researchers think that the epidemic, which has killed over 20 000 mostly young men,[12] is most likely to be caused by "two interdependent factors: the misuse of agrochemicals and the working conditions of the labor force."[13] The men are exposed to banned and dangerous pesticides, some of which are known to be nephrotoxic, and the working conditions cited include "regular exposure to very hot temperatures and extreme physical effort, lead[ing] to heat stress and dehydration."[13]

Daniel Brooks, associate professor of epidemiology at the Boston University School of Public Health, will lead the CDC research, which includes several observational studies examining genetics and biomarkers in children and a longitudinal study of the sugarcane workers and their families for an as yet undetermined time period. He defends the CDC's involvement, saying it provides two main benefits, creating a "firewall between donors and researchers" and enlisting the expertise of the CDC.

The sugar industry has trumpeted Brooks' earlier research into the epidemic as proof that conditions in the fields are not the cause of the men's deaths; Mario Amador, general manager of Nicaragua's National Committee of Sugar Producers, dismissed

the idea that the disease has an occupational origin, telling a reporter with the International Consortium of Investigative Journalists, "We are fully convinced that there is no direct relationship between [chronic kidney disease] and the activities conducted in the sugarcane industry."[5]

The Pan American Health Organization has called the outbreak, "a serious public health problem that requires urgent, effective, and concerted multisectoral action."

Jerome R Hoffman, a methodologist and emeritus professor of medicine at UCLA, told *The BMJ*, the study was asking the wrong questions. "Epidemiologic studies can of course be tremendously useful in cases like this, but given the human suffering involved, we need to devise and test interventions that have a chance to prevent or ameliorate this substantial harm, as quickly as possible. It's inappropriate to focus on things that cannot protect these workers, such as identifying an unusual genetic predisposition to kidney failure, or evaluating a biomarker to follow the disease, while ignoring modifiable factors."

Not just the carrot—but the stick

Corporations have not only been offering gifts to the CDC; they have also used a heavy stick—with consequences that continue to hobble critical research. In 1996, the National Rifle Association, which is underwritten in large part by gun manufacturers, mounted an offensive against CDC's research into gun violence. The association lobbied Congress, and pro-gun representatives slashed $2.6m from the CDC budget—the exact amount the agency had spent in the previous year on firearm injury research. The funding was later restored, but the bill prohibited any of the restored funds from being used to "advocate or promote gun control."

Frederick Rivara, one of the team members who conducted gun research for the CDC before the cuts, told *The BMJ* that firearms research has "plummeted dramatically," and that gun violence remains a major public health concern in the US, where nearly half a million people have died from gunshot wounds since the funding cuts.

After multiple mass murders, including the shooting of 20 first grade children at the Sandy Hook Elementary School in Newton, Connecticut in 2012, President Obama asked Congress for $10m to fund research into preventing gun violence; however, Congress has not approved the funds to date. The president renewed this request for the 2016 budget.

Professional reaction

Neil Calman, president and chief executive of the Institute for Family Health in New York, a large community health center network in 31 locations with over half a million patient visits a year, says the institute has relied on CDC guidance largely because of its prestige as an independent agency, free of industry relationships. Calman told *The BMJ,* "Industry funding undermines trust and introduces a bias in the presentation of results and treatment recommendations that is deplorable for a government agency. If the allegations of industry funding and influence are true, we will have to look very carefully at recommendations we are following now and those made in the future by the CDC."

Calman said, "Industry claims their scientific methodology ensures their studies are unbiased—just as the CDC claims money doesn't affect their recommendations. Yet multiple studies clearly—and repeatedly—show that who sponsors a study, or issues a guideline, makes a difference."

Hoffman said, "Most of us were shocked to learn the CDC takes funding from industry. Of course it is outrageous that industry apparently is allowed to punish the CDC if the agency conducts research that has the potential to cut into profits. But it was our government that made this very bad arrangement, so the way to fix it is not to ask the CDC to 'pretty please be more ethical, and avoid conflicts of interest'; rather, as a society, we have to get the government to reject this devil's bargain, by changing the rules so this can no longer happen."

John Mandrola, a cardiologist in Louisville, Kentucky, reacted to the news of industry funding, saying that the CDC "must have the highest of moral ground. For if we are to believe them about public health matters, there can be no conflicts of interest. The public good, pure evidence, that is all."[14]

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1 Recommendations for the identification of chronic hepatitis C virus infection among persons born during 1945-1965. *Morbid Mortal Wkly Rep* 2012;61:1-36. www.cdc.gov/mmwr/pdf/rr/rr6104.pdf.
2 Lenzer J. Why aren't the US Centers for Disease Control and Food and Drug Administration speaking with one voice on flu? *BMJ* 2015;350:h658.
3 Holford TR, Meza R, Warner KE, et al. Tobacco control and the reduction in smoking-related premature deaths in the United States, 1964-2012. *JAMA* 2014;311:164-71.
4 Koretz R, Lin K, Ioannidis JPA, Lenzer J. Is widespread screening for hepatitis C justified? *BMJ* 2014;350:g7809.
5 Chavkin S. CDC launches industry-funded study of mystery kidney ailment. *Global Muckraker.* 2014 Dec 2. www.icij.org/blog/2014/02/cdc-launches-industry-funded-study-mystery-kidney-ailment.
6 European Association for Study of the Liver. EASL clinical practice guidelines: management of hepatitis C virus infection. *J Hepatol* 2014;60:392-420.
7 Levinson DR. CDC'S ethics program for special government employees on federal advisory committees. 2009. https://oig.hhs.gov/oei/reports/oei-04-07-00260.pdf.
8 CDC. Why CDC Recommends Influenza Antiviral Drugs. 2015. www.cdc.gov/media/haveyouheard/hyh-antiviraldrugs.html.
9 Dobson J, Whitley RJ, Pocock S, Monto AS. Oseltamivir treatment for influenza in adults: a meta-analysis of randomised controlled trials. *Lancet* 2015;385:1729-37.
10 Lenzer J. CDC, conflicting (conflicted?) info, Tamiflu & unquestioning news reporting. *HealthNewsReview* 2015 Feb 10. www.healthnewsreview.org/2015/02/conflicting-study-reports-tamiflu-and-unquestioning-news-reporting/.
11 Jefferson T, Jones M, Doshi P, et al. Oseltamivir for influenza in adults and children: systematic review of clinical study reports and summary of regulatory comments. *BMJ* 2014;348:g2545.
12 Ramirez-Rubio O, McClean MD, Amador JJ, Brooks DR. An epidemic of chronic kidney disease in Central America: an overview. *Postgrad Med J* 2013;89:123-5.
13 Ordunez P, Martinez R, Reveiz L, et al. Chronic kidney disease epidemic in central America: urgent public health action is needed amid causal uncertainty. *PLoS Negl Trop Dis* 2014;8:e3019.
14 Mandrola J. Public trust, the CDC and Tamiflu. *Dr John M* 2015. Feb 13. www.drjohnm.org/2015/02/public-trust-the-cdc-and-tamiflu/#comments.

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PREVALENCE OF INDUSTRY SUPPORT AND ITS RELATIONSHIP TO RESEARCH INTEGRITY

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Abstract

Most U.S. clinical trials are funded by industry. Opportunities exist for sponsors to influence research in ways that jeopardize research objectivity. The purpose of this study was to survey U.S. medical school faculty to assess financial arrangements between investigators and industry to learn about investigators' first hand knowledge of the effects of industry sponsorship on research.

Here we show first-hand knowledge that compromises occurred in: research participants' well-being (9%), research initiatives (35%), publication of results (28%), interpretation of research data (25%), and scientific advancement (20%) because of industry support. Financial relationships with industry were prevalent and considered important to conducting respondents' research.

Keywords

financial conflict of interest; industry sponsorship; research integrity

Introduction

Comparison of individual studies and the results of meta-analyses have raised concerns about the undue influence industry funding may have on research integrity (Tereskerz, 2007; Bero and Rennie, 1996; Kjaergard and Als-Nielsen, 2002; Stelfox et al., 1998; Davidson, 1986; Friedberg et al., 1999; and Bekelman et al., 2003). Research demonstrates that financial entanglements between investigators and industry sponsors are associated with an adverse

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affect on assessments of research credibility (Chaudhry et al., 2002; Schroter et al., 2004; and Kim et al., 2004). In spite of these concerns, most clinical trials are financed by pharmaceutical companies (Kaplan and Brownlee, 1999; and Maatz, 1993). Circumstances such as adverse research reports or delays in getting drugs to market can translate into millions in lost revenue (Tereskerz, 2007), producing incentives for sponsors to influence research to advance their interests. They may also produce conflicts of interest (COI's) for investigators that can compromise scientific objectivity (Rochon et al., 1998; Bodenheimer, 2000; and Reed and Camargo, 1999).

A challenge faced by those developing policies/regulations to manage financial COI's is the lack of empirical data on financial arrangements between industry and investigators at academic research institutions (Tereskerz and Moreno, 2005). There have been institution-specific studies describing the nature of university faculty researchers' personal financial relationships with industry sponsors (Tereskerz, 2007). Estimates of such arrangements have also been made by others (Bekelman et al., 2003). Whether these data represent national experience is generally unknown.

The objective of this study was to examine the prevalence of various financial arrangements between industry and investigators at top U.S. research institutions and to investigate researcher practices that relate to research integrity regarding industry-sponsored research. We asked respondents to report question-able research integrity practices in their institutions and departments, about which they had first-hand knowledge. We tested to see if those with greater amounts of industry support, or those employed in departments that have industry support, are more likely to report that they know of such practices. We also examined disclosure practices and assessed the importance of industry support to investigators' careers.

Methods

Sample[1]

We purposely targeted the 33 universities in the United States which received the most research funding. Using sample selection methods from similar studies (Blumenthal et al., 1996), we used medical school catalogs and *Peterson's Guide to Graduate Programs in the Biological and Agricultural Science* (Peterson's Guide 1997) to identify all life science departments and graduate programs at the selected institutions. Departments were classified as clinical or nonclinical, depending on whether their names designated a clinical discipline. From each school, we randomly selected one department of medicine (internal medicine or other medicine subspecialties), another clinical department, and two nonclinical departments (N = 132). Faculty in departments of medicine and their subspecialties were thus over-sampled, because they often receive more extramural research funds than other departments. To focus on active researchers, clinical faculty were included in the sample only if they had published at least one article listed in the National Library of Medicine's MEDLINE database during a five year period preceding the study.[2]

Instrument Design

Study variables were identified from the literature and other sources (Boyd and Bero, 2000; Public Health Service, 2001; 42 CFR; and National Institutes of Health, 2000), and a survey instrument was designed. A definition of industry or commercial sponsorship was created (see Appendix A). Industry support for research and publication was determined by asking about

[1]The sampling procedures for the medical school portion of the study are described here. Procedures used to sample nursing school faculty will be described elsewhere.

[2]An additional screener was included in the questionnaire. Respondents were instructed not to fill it out if they had not published any research in the previous five years.

10 types of support from industry sponsors (Question 7, Appendix A). Overall support included these items, along with receipt of honoraria for serving as a consultant, on an advisory board, or giving a speech, with a separate item to identify those with chaired professorships funded entirely or in part from industry sources.

Instrument pretesting was accomplished in three phases. The first two used focus groups of University of Virginia (UVA) researchers. After debriefings to receive participant feedback, the survey was revised. The third phase involved a sample of 48 researchers, (not included in the final study survey population) drawn at random from the medical faculties of the national sample and offered a modest cash incentive for taking the revised pretest. Sixteen completed the telephone debriefing, and the questionnaire was revised a final time.

Respondents were asked to report their receipt of financial support in various forms from industry. They were also asked directly about industry sponsor pressures to favor the sponsor's interests. To alleviate concerns respondents may have about admitting to practices that compromise research integrity, two questions asked respondents whether they had "first-hand knowledge" of questionable practices within their working environment, rather than to report on their own behavior (see Appendix A). Other survey methodologists have used similar methods to encourage veracity about sensitive topics (California Environmental Protection Agency, 2002). This technique also obviates the risk if respondents' anonymity was breached. By limiting reports to *first-hand knowledge* and events at their own institution or within their own department/research unit, we sought to reduce reports based on suspicions or rumors about questionable practices in other departments or institutions, which would lead to overreporting of questionable practices.

Some questions applied to all respondents, whether or not they were involved in units with industry-sponsored research. Others were asked only of a subset of respondents who reported that people in their current department or research unit received financial support from industry-connected sponsors. These questions were, by design, answered by a smaller number of respondents.

Survey Administration

Questionnaires were sent to a sample of 1,548 clinical researchers, of whom we estimated that 1,156 were qualified for the study.[3] To maximize response rates, surveys were mailed by the UVA Center for Survey Research (CSR), following the principles and specific techniques developed by Dillman (Dillman, 2000). The study protocol was approved by the UVA Social and Behavioral Sciences Institutional Review Board.

A prenotice letter was sent to those selected to participate in the survey, followed by a questionnaire and cover letter. Anonymity was afforded to respondents by the use of a separate post-card returned by the respondent to acknowledge response. This allowed for tracking nonrespondents without identifiers on the questionnaires. A second survey was sent to nonresponders; final contact was made by telephone, asking for a response. CSR did not complete questionnaires by phone but mailed/faxed another copy of the questionnaire to any respondents who misplaced theirs.

[3]The overall sample also included about 500 nursing school researchers; results for the nurse subsample will be reported elsewhere. The estimated eligible respondents exclude those expressly disqualified, the unreachable (those for whom notice was received that the address was faulty), and the estimated number of disqualified and unreachable among the "open status" cases. The latter estimate was reached by first calculating the percentages of nonqualified and unreachable cases among those for which return mail was received, and then applying that percentage to those cases remaining in "open status." We follow the conventional assumption that the percentage of ineligibles among cases whose eligibility is unknown is the same as it is among those whose eligibility is determined.

Results

The overall response rate for the medical and nursing school sample (calculated by American Association for Public Opinion Research [AAPOR] Standard Rate RR4) (AAPOR, 2008), was 703/1479 (48%), of whom 528 were medical school researchers. Completed questionnaires were received from respondents in at least 102 medical school departments, representing every institution in the sample. Table 1 gives the demographics of the sample, excluding any who left a demographic question unanswered. Respondents were predominantly male, experienced, senior-ranked researchers with significant authorship activity. Responses were received from all 33 institutions included in the study.

Types of Industry Support

Sixty-six percent of respondents indicated that they have received some form of industry support (Table 2). Sixty-two percent reported receiving research and publication support (Table 3). Notably, 13% of respondents held an endowed chair, of which 14% were funded by industry. Overall, males (77%) and respondents with 11 years or more research experience (79%) were significantly more likely to receive overall support than were females (23%), and respondents with 5 years or less research experience (6%). Similarly, respondents who have worked 11 years or more at their institutions (60%) or had 11 years or more experience in clinical practice (45%) were significantly more likely to receive industry support. In addition, industry support occurred more frequently among investigators who held higher academic ranks and published more frequently. Full professors (51%) and respondents with 11 or more publications in the last two years (28%) were significantly more likely to receive overall industry support than were associate professors (25%), assistant professors (23%), or respondents with one or no publications during the last two years (5%). The same patterns apply when looking specifically at research and publication support (Table 3).

Respondents reported various types of financial arrangements with industry within the last five years. Seven percent (7%) owned an equity interest in a company that supported their research, generally a company doing pharmaceutical research. Of these respondents, half (50%) owned an equity interest in the $100,000–$500,000 range.

More than half of the respondents (57%) did not answer the question requesting the proportion of their salary covered by industry during 2003–2004. Of those answering this question, 68% said no part of their salary was covered by industry, with the remaining 32% indicating that some portion of their salary was paid for by industry. In addition, 50% of those responding indicated that some portion of staff salaries were covered by industry, and 56% responded that industry paid for supplies and/or equipment used in their research.

Importance of Industry Support

Overall, respondents indicated that industry support was important to their research and publications (Table 4). Of items with at least 25% of respondents receiving support, the following were most important: research grants or contracts (91% judging these to be extremely important, very important, or somewhat important), support for staff or study coordinators (79%), biomaterials (78%), and support for students or fellows (74%). Although smaller in number, industry support was extremely or very important in the areas of patents and new product/company development.

Disclosure to Human Subjects

Respondents who had received one or more forms of research and publication support from industry were asked a screening question to identify those whose research projects in the last five years involved human subjects. This subset of 139 medical researchers was then asked

about institutional disclosure requirements (mandated disclosure to human subjects) for financial arrangements with industry. They were asked if disclosure of each element was required at their institution, and—if not required—how often they make the disclosure in their own studies. Table 5 presents these results. Interestingly, many institutions do not require disclosure of investigator financial relationships with industry to research subjects. In institutions without such requirements, the data reveal considerable variability in researcher disclosure practices.

Industry Support and Research Integrity

Requests by Industry Sponsors—The questionnaire gave different treatment to questionable action by sponsors as opposed to questionable action by researchers themselves. With regard to sponsor requests or pressures, we directly asked respondents who reported having industry support for their research and publication: "Has an industry-connected sponsor ever asked you to do any of the following?" With respect to researchers acceding to improper requests (for example, actually suppressing unfavorable results), we protected our respondents by asking only for "first-hand knowledge" of such events.

Table 6 shows the results for industry requests, based on the reports of the 231 respondents who receive industry support for their research and publication and answered this series of questions. [4] Only 4% reported that a sponsor had ever asked them to withhold research results from publication, but 13% said they had been asked to delay publication of research results. Nearly 8% have been asked by a sponsor to present research results in a way that favors the sponsor's drug or product. About 7% have been asked by an industry sponsor to keep the research results secret. Far more common (and of lesser concern) were reports of being asked to give the sponsor prepublication review (61%) and being asked to acknowledge the sponsor in the publication (62%).

To investigate whether receipt of these requests was associated with the importance of industry support for the respondent's research, we constructed an index of industry support by summing together responses to the ten items listed in Question 7 (Appendix A). The construction of the index, which has a reliability (Cronbach's alpha) of .88, is detailed in Appendix B. As seen in Table 7, the importance of industry support to a respondent's research and publication has a significant relationship with the frequency of many sponsor requests. Considering only those who scored high on the index of support, meaning that they received several forms of industry support that they rated as "very important" or "extremely important," we found that 28% had been asked either to withhold results, delay publication, present results more favorably, or keep the project secret. The frequency of receiving one of these requests is significantly related to higher scores on the support index.

All Respondents' First-Hand Knowledge of Questionable Practices—All respondents were asked about their first-hand knowledge[5] of research practices associated with industry-sponsored research at their institution. Table 7 shows responses related to knowledge of compromises in research integrity because of a request or pressure from an industry sponsor. When all respondents are considered, fairly small percentages reported any compromise.

[4]Some respondents who answered "yes" to one or more of the research and publication support items in the Question 7 series skipped the long series of follow-up questions that applied to them. While 275 answered "yes" to one or more of the Question 7 items, only 231 answered the follow-ups. Most of those who skipped the follow-ups had reported little or no support that they considered important in the Question 7 series.

[5]*First hand* is defined as: from the original source or personal experience; direct. Compact Oxford English Dictionary. Available at http://www.askoxford.com.

However, when responses were categorized according to the importance of industry support, using the support index, statistically significant increases were seen in the reports of these compromises as the importance of industry support increased (Table 7). For those researchers who assigned the greatest importance to their industry support, the rates of first-hand knowledge were: 25% for delaying publication, 17% for presenting results to favor the sponsor, and 11% for suppression of publication because of pressure from the sponsor.

All respondents were asked whether there are people in their "department or work unit" currently receiving support from industry sources (question 22, Appendix A); 59% said "yes." Those who said "yes" were more likely to have first-hand knowledge of delaying publication (16% with knowledge compared to 9% without); to know of results presented to favor the sponsor (7% compared to 3%); and, to know of cases in which results were suppressed (6% compared to 2%). Each of these contrasts is statistically significant.

Respondents from Departments with Industry-Sponsored Research—A second set of questions asking for first-hand knowledge was directed only to the subset of respondents reporting (in question 22) that others in their department or research unit receive financial support from industry-connected sponsors (n = 173; see Table 8). Fifteen respondents out of 173 (9%) reported first-hand knowledge that the well-being of research participants at their institution was compromised because of industry support of researchers in their department. In 40% of these instances (six cases), the well-being of participants was either seriously or significantly compromised.

Other compromises were noted as well: 28% reported that the publication of research results had been compromised; 25% reported that the interpretation of research data at their institution had been compromised; and, 35% reported that research initiatives had been compromised because individuals in their department or research unit were supported by industry. Twenty percent believed that scientific advancement in their area of research had been compromised by industry support.

Consistent with our other findings, the more important industry support is to respondents' research and publication, the more likely it is that they have first-hand knowledge of these compromises to research. The pattern of increased reporting with increased importance of industry support to the researcher is evident to some extent for all five types of compromise, and is statistically significant for four of the five items.

Discussion

What new information does this study provide? It represents the first recent attempt to gather data from the leading research institutions on financial arrangements between medical school investigators and industry that explores not only what types of financial relationships exist and with whom but also shows association between industry support and first-hand knowledge of questionable integrity practices. We purposely sampled major research-intensive institutions, assuming that these institutions would yield the greatest number of active researchers receiving industry support.

An important new finding is the report of 9% of respondents with industry-funded colleagues that had first-hand knowledge of compromises to the well-being of research subjects at their institution because researchers in their department/research unit received industry sponsorship. One way to view this finding is that only a small subset of these participants (n = 15) reported this, with 9 respondents noting that the compromise was minor. However, the concern is not that compromising the well-being of human research participants happens frequently but that

it happens at all. There should be zero tolerance for compromising the well-being of human research participants in any study, regardless of the source of the study's support.

Further, the finding that significant numbers of respondents in units with industry support have noted compromises to research initiatives (35%), publication (28%), interpretation of data (25%), and overall scientific advancement (20%) is of concern.

This concern is compounded when you take into account our results showing that most respondents who received industry support indicated that industry financing of research through grants and contracts is important to their research/publications. This is particularly troubling in light of the finding that the more important the support of industry to respondents, the greater the pressure seen from sponsors and the greater the respondents' first-hand knowledge of compromises to research integrity. Researchers responding to this survey with more and important industry support are significantly more likely to report receiving requests to withhold research results, delay publication, present results in ways that favor the sponsor's product, or keep the project and results secret. Furthermore, the level of first-hand knowledge of such compromises is significantly greater among those for whom industry support is most important. This pattern of results can be understood in terms of Emerson's (Emerson, 1962) classic observation about power relations in a dyad: the power of A over B is the inverse of B's dependence on A for key resources. If an investigator rates industry support as very important, it may indicate a degree of dependence on such support that empowers the sponsor to make improper requests of the investigator.

Our data demonstrate that senior-level investigators who responded to the survey receive a wide variety of industry-sponsored support which is important for their careers, and that industry support of research and researchers is pervasive in the clinical and research departments of top U.S. research institutions.

Indeed, two-thirds (66%) of our sample reported receiving support from industry-connected sources. Full professors and those with large numbers of publications were significantly more likely to receive industry support than were their more junior colleagues. A recent study of practicing physicians (Campbell, Russell et al., 2007) also reported the prevalence of industry sponsorship. Examining a wider variety of support in more categories, our data show higher levels of industry support among our respondents, presumably due to our sampling method.

The data presented here now bring into national focus the quandary that industry sponsorship of research presents. Various financial relationships with industry are both prevalent and considered important by investigators with regard to the conduct of their research. This is not surprising given that industry is the primary financier of clinical research. Clearly, research grants, consulting, and honoraria are the primary means by which industry pays investigators (Tereskerz, 2007). In this study, ownership interests in sponsoring companies occur infrequently. However, when such an equity interest exists, it appears to be substantial. This type of financial entanglement has been implicated in some of the more notorious anecdotal cases of research abuse (Tereskerz, 2007).

That these patterns are seen among those most deeply immersed in industry supported research, and that these individuals are also the most senior and prolific members of their departments, is a disturbing finding. Our data thus lend credence to concerns being raised in the literature (Tereskerz, 2007; Bero and Rennie, 1996; Kjaergard and Als-Nielsen, 2002; Stelfox et al., 1998, Davidson, 1986; Friedberg et al., 1999; and Bekelman et al., 2003).

Our data indicate that researchers' financial arrangements with industry are not always fully disclosed to research subjects. In addition, research institutions do not universally require disclosure of researcher's equity interests in the sponsoring company, joint commercial

ventures with the sponsor, other financial payments, and funding of key personnel and equipment. In situations where such disclosures are not required by the institution, our respondents varied in their disclosure practices.

Taken together, these findings of nondisclosure of industry connections, compromises to research results, publications and scientific advancement, and compromises to human subject well-being provide evidence to suggest that efforts to educate investigators about their moral obligations have not fully succeeded. Even if one were to argue that these compromises are minor, they demonstrate a lack of respect for those who volunteer in good faith as research participants and a lack of attention to scientific objectivity and integrity. Industry sponsors and the scientific community need to review the adequacy of their efforts in light of these findings.

Because industry-supported respondents were significantly more likely to be the most senior and prolific researchers, their leadership and potential influence over the cultures of individual research units are considerable. Our data raise the possibility of research cultures in which abuses of research integrity are known but are not openly discussed or addressed. Recent findings of reluctance on the part of U.S. physicians to report incompetence or serious mistakes of peers (Campbell, Russell et al., 2007) lend credence to these concerns.

Study Limitations

The study's primary limitation is the response rate. Lower response rates are expected when the questions involve sensitive topics. In fact, this study's response rate compares favorably to a recent study reporting national survey results on research misconduct which had a 31% response rate (Pryor et al., 2007). In addition, others have noted increasing difficulty in obtaining physicians' responses to surveys and have reported response rates similar to those reported here (Campbell, Russell et al., 2007). It is well recognized among survey methodologists that physician response rates tend to be lower than those of other individuals (Campbell, Regan et al., 2007; Cummings et al., 2001; and VanGeest et al., 2007). Rates are even lower when no monetary incentive is used to encourage respondents to reply, as was the case in this study (Kaspryzk et al., 2001). We determined that it was inappropriate to use such an incentive in a study that had financial conflict of interest as a focus.

This issue and our purposive sampling approach mean that we cannot generalize from this sample to the U.S. medical school population. Additional research with larger samples is needed and likely will require incentives to increase the percentage of respondents.

By asking for first-hand knowledge of compromises to research integrity due to industry sponsorship, we chose to accept some risk that participants would respond from incomplete knowledge or low opinion of colleagues rather than based on their direct experience. Certainly our strict guarantees of anonymity were designed to mitigate this possibility, but we cannot assess whether responses were skewed based on these factors. Given the proportionally large number of respondents at selected institutions, there is a possibility that one incident was noted by multiple participants. To minimize this possibility, one of the two first-hand knowledge questions asked specifically about "people in your department or research unit" who were supported by industry-connected sponsors. To address the potential concern that a single case at one institution may be over represented, we examined the record of questionnaire returns by institution and department, based on those whose affiliation was known because they returned a separate postcard (N = 410) confirming participation. We cannot directly verify how many departments reported any specific practice. However, the broad pattern of response achieved across 102 departments from every institution sampled makes it unlikely that respondents' reports of questionable practices represent only one or two departments or institutions. In addition, we measured first-hand knowledge rather than specific incidents. While obtaining the latter information would be difficult, even with assurance of anonymity,

further study of the number of incidents and actual harms resulting from compromises to research integrity is needed.

Nonresponse bias might affect the survey results in either a positive or negative direction, or not at all, depending on whether or not response tendencies correlate with the variables measured in the survey. Since the survey deals with sensitive topics (industry sponsorship and research integrity) and asks specifically about prohibited or stigmatized practices, the most likely pattern of nonresponse would be that those with the most industry support and those with greatest knowledge of questionable practices would be less likely to return their questionnaires. Such a pattern would lead to underreporting of the questionable practices. A less likely scenario, but one of potentially greater concern for this study, would be the possibility that questionable practices are overreported. This would occur if those who knew of question-able practices (by their colleagues) were eager to report them and were more likely to respond to the survey than those who knew of no such practices.

Given our guarantees of anonymity to participants, no information is available on nonresponders that would allow direct test of these possibilities. However, we compared the data for early and late responders, as it is probable that late responders have more in common with nonresponders than do those who responded immediately to the survey request. This analysis compares the characteristics and responses of the 350 respondents who returned the questionnaire received in the first packet to the 159 who responded to the second packet or telephone reminder. Early and late responders did not differ significantly in their seniority, as measured by their years involved in research, years in clinical practice, years at institution, or number of publications. While 60% of the first-packet responders had received industry support, 69% of the second-packet responders had received such support, a statistically significant difference ($p = .05$) suggestive of modest underreporting of industry support. Of the three questionable practices reported in Table 7, two did not differ significantly: delay of publication and suppression of research results from sponsor pressure. However, later responders were more likely to report first-hand knowledge of results having been presented to favor the sponsor (10% of late responders as compared with 5% of early responders, $p = .045$). This result again suggests selective underreporting rather than overreporting in the survey results.

There was no difference between early and late responders in the percentage who had departmental colleagues receiving industry support. For the questions posed to this group reported in Table 8, there were no significant differences between early and late respondents in the percentages reporting any of the five questionable practices. These indirect comparisons of response bias demonstrate that early and late responders do not differ very much, and when they did differ, it was in the direction of underreporting. While indirect, this analysis lends support to the survey's findings.

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References

American Association for Public Opinion Research (AAPOR). Lenexa, KS: AAPOR; 2008 [Accessed March 18, 2009]. Standard Definitions: Final Dispositions of Case Codes and Outcome Rates for Surveys. Available at www.aapor.org/standarddefinitions.

Bekelman YL, Yan L, Gross CP. Scope and impact of financial coi's in biomedical research. JAMA 2003;289:454–465. [PubMed: 12533125]

Bero LA, Rennie D. Influences on the quality of published drug studies. Int J Technol Assess Health Care 1996;12:209–937. [PubMed: 8707496]

Blumenthal D, Campbell DG, Causion N, Seashore LK. Participation of life-science faculty in research relationships with industry. New Engl J Med 1996;335:1734–1739. [PubMed: 8929266]

Bodenheimer T. Uneasy alliance—Clinical investigators and the pharmaceutical industry. New Engl J Med 2000;342:1539–1544. [PubMed: 10816196]

Boyd E, Bero LA. Assessing faculty financial relationships with industry: A Case Study. JAMA 2000;284:2209–2214. [PubMed: 11056592]

California Environmental Protection Agency. Integrated Waste Management Board. Outreach Research —Survey and focus groups. DIYers and Used Oil Disposal. Initial results and recommendations. 2002 Jan.

Campbell EG, Regan S, Gruen RL, Ferris TG, Sowmya RR, Cleary PD, Blumenthal D. Professionalism in medicine: Results of a national survey of physicians. Annals of Internal Medicine 2007;147(11): 795–802. [PubMed: 18056665]

Campbell EG, Russell LG, Mountford J, Miller LG, Cleary PD, Blumenthal D. A national survey of physician-industry relationships. New Engl J Med 2007;356:1742–1750. [PubMed: 17460228]

Chaudhry S, Schroter S, Smith R, Morris J. Does declaration of competing interests affect readers' perceptions? A randomized trial. BMJ 2002;325:1391–1392. [PubMed: 12480854]

Cummings SM, Savitz LA, Konrad TR. Reported response rates to mailed physician questionnaires. Health Services Research 2001;35:1347–1355. [PubMed: 11221823]

Davidson RA. Source of funding and outcome of clinical trials. J Gen Int Med 1986;1:155–158.

Dillman, D. The Tailored Design Method. Vol. 2nd Edition. Hoboken, NJ: John Wiley; 2000. Mail and Internet Surveys.

Emerson RM. Power-dependence relations. American Sociological Review 1962;27(1):31–41.42 CFR Pt. 50 Subpart F

Friedberg M, Saffran B, Stinson TJ, Nelson W, Bennett CL. Evaluation of conflict of interest in economic analyses of new drugs used in oncology. JAMA 1999;282:1453–1457. [PubMed: 10535436]

Kaplan S, Brownlee S. Dying for a cure: Why cancer patients often turn to risk experimental treatments —and wind up paying with their lives. U.S. News & World Report 1999 Oct.;11:34. [PubMed: 10621514]

Kaspryzk D, Lawrence JS, Phillips WR. The effect of variations in mode of delivery and monetary incentive on physicians' responses to mailed survey assessing standard practice patterns. Evaluation & the Health Professions 2001;24:3–17.

Kim SYH, Millard RW, Nisbet P, Cox C, Caine ED. Potential research participants' views regarding researcher and institutional financial conflicts of interest. Journal of Medical Ethics 2004;30:73–79. [PubMed: 14872080]

Kjaergard LL, Als-Nielsen B. Association between competing interests and authors' conclusions: Epidemiological study of randomized clinical trials. BMJ 2002;325:249. [PubMed: 12153921]

Maatz CT. University physician-research conflicts of interest: The inadequacy of current controls and proposed reform. High Tech. L. J 1993;7:137–188.

National Institutes of Health. Conference on Human Subject Protection and Financial Coi's Transcript. 2000 Aug 16. Available at http://ohrp.osophs.dhhs.gov/coiconflictofinterest8-15.htm.

Peterson's Guide to Graduate Programs in the Biological and Agricultural Sciences. Vol. 28th ed.. Princeton, N.J: Peterson's Guides; 1997.

Pryor ER, Habermann B, Broome ME. Scientific misconduct from the perspective of research coordinators: A national survey. J Med Ethics 2007;33:365–369. [PubMed: 17526690]

Public Health Service. Draft Interim Guidance. Financial Relationships in Clinical Research: Issues for Institutions, Clinical Investigators, and IRBs to Consider When Dealing with Issues of Financial Interests and Human Subject Protection. 2001 Jan 10. Available at http://ohrp.osophs.dhhs.gov/nhrpac/mtg12-00/finguid.htm.

Reed CR, Camargo CA. Recent trends and controversies in industry-sponsored clinical trials. Acad Emerg Med 1999;6:833–839. [PubMed: 10463557]

Rochon PA, Berger PB, Gordon M. The evolution of clinical trials: Inclusion and representation. CMAJ 1998;159:1373–1374. [PubMed: 9861206]

Schroter S, Morris J, Chaudhry S, Smith R, Barratt H. Does the type of competing interest statement affect readers' perceptions of the credibility of research? BMJ 2004;328:742–743. [PubMed: 14980983]

Stelfox HT, Chua G, O'Rourke K, Detsky AS. Conflict of interest in the debate over calcium-channel antagonists. N Engl J Med 1998;338:101–106. [PubMed: 9420342]

Tereskerz, PM. Riding the Green Wave. Financial Coi's in Industry Sponsored Clinical Research: A Law and Policy Analysis. Hagerstown, MD: University Publishing Group; 2007.

Tereskerz PM, Moreno J. Ten steps to developing a national agenda to address financial coi's in industry sponsored clinical research. Account in Res 2005;12:1–17. [PubMed: 16021788]

VanGeest JB, Johnson TP, Welch V. Methodologies for improving response rates in surveys of physicians. Eval & Health Prof 2007;30:303–321.

Appendix A: Selected Survey Questions

Definition of Industry-Connected Support

We are interested in learning more about the support that university medical researchers receive from *industry-connected sources*. These sources include commercial and industrial firms that make or market drugs, medical devices, or other medical products. Also included are private foundations that are closely linked or associated with any such firm. We distinguish these industry-connected sources from other sources of funding, such as federal grants and contracts, funding from state and local government, quasi-governmental or public organizations, health-oriented nonprofits, or any other entity not closely linked to the medical industry itself.

> Definition: *Industry-connected sources* of research funding are for-profit firms that make or market medical products (including drugs and devices), and any private foundations or nonprofit organizations closely linked to them.

Wording of Specific Questions

Note: Questions 7 and 8 were used to define those with and without industry support and to construct the index of industry support. Question 17 is used in Table 6. Question 21 is used in Table 7. Question 23 is used in Table 8. Question 22 is used in the analysis.

7. We list ten types of support that researchers may receive from industry connected sources. How important was each of the following received *from industry-connected sources* in support of your research or publication?

If you have not received a particular type of support from an industry-connected source in the past five years, please indicate this by circling the number 8 in the last column.

Industry-connected support		Extremely important	Very mportant	Somewhat important	Not at all important	Not received in past 5 years
a.	Research contract or grant	1	2	3	4	8
b.	Equipment	1	2	3	4	8
c.	Biomaterials (reagents, clones, antibodies, tissues, cell lines, etc.)	1	2	3	4	8

Industry-connected support		Extremely important	Very mportant	Somewhat important	Not at all important	Not received in past 5 years
d.	Discretionary funds or gifts to your institution	1	2	3	4	8
e.	Support for students or fellows	1	2	3	4	8
f.	Trips to professional meetings	1	2	3	4	8
g.	Honoraria	1	2	3	4	8
h.	Gifts (worth more than $100) made to you as an individual	1	2	3	4	8
i.	Support for staff or study coordinators	1	2	3	4	8
j.	Funds for publication costs	1	2	3	4	8

Please summarize your responses above by answering this question:

8. In the past five years . . .

1. I have **NOT** received any research and publication support from industry-connected sources → SKIP TO PAGE 9

2. I **HAVE** received such support → GO TO THE NEXT PAGE

If you answered "Not Received" to all ten items in Question 7 above, then you have not had any *industry-sponsored* research in the past five years and you should SKIP TO QUESTION 20 ON PAGE 9. If you were able to rate any item in Question 7, please continue to Question 9 on the next page.

Direct Questions for Respondents with Industry Support

17. Has an industry-connected sponsor ever asked you to do any of the following?		No	Yes
a.	Withhold research results from publication	**N**	**Y**
b.	Delay publication of research results	**N**	**Y**
c.	Present results in a way which reflects more favorably on the sponsor's drug or product	**N**	**Y**
d.	Acknowledge the sponsor in the publication	**N**	**Y**
e.	Grant the sponsor prepublication review of any resulting manuscripts	**N**	**Y**

17. Has an industry-connected sponsor ever asked you to do any of the following?		No	Yes
f.	Keep the research project and results secret	N	Y
g.	Convey all resulting patents to the sponsor	N	Y
h.	Participate in research that involves proprietary information	N	Y

First-Hand Knowledge Questions for All Respondents

The following questions refer to any research conducted at your current institution, whether or not you were involved in the research.

21.	Do you have first-hand knowledge of any research conducted at your institution where any of the following occurred because of a request or pressure from an industry-connected sponsor?	No	Yes
a.	Research results were suppressed or withheld from publication	N	Y
b.	Publication of research results was delayed	N	Y
c.	Results were presented in a way that reflects more favorably on the sponsor's drug or product	N	Y

22. Are there other people in your current department or research unit who receive financial support from industry-connected sponsors?

1 No → **Go on to Question 25**
2 Yes
8 *Don't know (go on to Question 25)*

23. Based on your first-hand knowledge, to what extent have any of the following ever been compromised because people in your department or research unit were supported by industry-connected sponsors?

		Seriously	Significantly	Only in minor ways	No compromise occurred	Don't know
a.	Research initiatives	1	2	3	8	9
b.	Interpretation of data	1	2	3	8	9
c.	Publication of results	1	2	3	8	9
d.	The well-being of research subjects	1	2	3	8	9
e.	Scientific advancement in your area of research	1	2	3	8	9

Appendix B: The Index of Industry Support

Question 7 lists ten sources of industry support for research and publication. Respondents rated each item on a 1 to 4 scale, with 1 indicating “extremely important” and 4 indicating “not at all important.” They could also indicate if they had not received this form of support in the past five years. To create the support index, these responses were first recoded so that a 0 indicated no such support, a 1 indicated that the support was “not at all important,” and so on up to a 4 to indicate extreme importance. A reliability check on the items when so recoded yielded a Cronbach’s alpha score of .884, indicated strong inter-item correlations. Accordingly, the items were summed to yield an index that could range from 0 to 40. In this survey, actual scores on the index ranged from 0 to 36, with a median score of 3 and mean score of 5. For analysis purposes, this index was grouped into four categories: respondents with “no support,” as shown by a score of 0 (39% of the sample); those with “little support,” shown by a score of 1 to 4 (21%); those with “some support,” shown by a score of 5–12 (21%); and those with “important support,” with scores of 13 or more on the index (19%). In Table 6, the first two categories are grouped together and labeled as “unimportant support,” since the questions reported in that table were not supposed to be answered by those who had no support.

TABLE 1

Respondents' Demographic Characteristics

Label	Category	Overall	
		n	%
Gender (A42)	Male	360	71.1
	Female	146	28.9
Years involved in research (A37)	0–5	39	7.6
	6–10	94	18.3
	11+	382	74.2
Years involved in clinical practice (A38)	0–5	271	54.2
	6–10	43	8.6
	11+	186	37.2
Years worked at institution (A39)	0–5	124	23.9
	6–10	108	20.8
	11+	286	55.2
Number of publications in last 2 years (A40)	0–1	35	6.8
	2–3	123	24.0
	4–5	117	22.9
	6–10	123	24.0
	11+	114	22.3
Academic rank (A41)	Full Professor	231	44.7
	Associate Professor	121	23.4
	Assistant Professor	144	27.9
	Other	21	4.1

TABLE 2

Overall Support by Demographic Variables

Label	Category	Overall		*P* value	Industry support		No support		N
		n	%		n	%	n	%	
Gender (A42)	Male	360	71.1	.001	261	77.2	99	58.9	506
	Female	146	28.9		77	22.8	69	41.1	
Years involved in research (A37)	0–5	39	7.6	.001	22	6.4	17	9.9	515
	6–10	94	18.3		50	14.5	44	25.7	
	11+	382	74.2		272	79.1	110	64.3	
Years involved in clinical practice (A38)	0–5	271	54.2	<.001	157	47.1	114	68.3	500
	6–10	43	8.6		27	8.1	16	9.6	
	11+	186	37.2		149	44.7	37	22.2	
Years at worked at institution (A39)	0–5	124	23.9	.011	71	20.5	53	30.8	518
	6–10	108	20.8		69	19.9	39	22.7	
	11+	286	55.2		206	59.5	80	46.5	
Number of publications in last 2 years (A40)	0–1	35	6.8	<.001	18	5.2	17	10.1	512
	2–3	123	24.0		75	21.9	48	28.4	
	4–5	117	22.9		72	21.0	45	26.6	
	6–10	123	24.0		82	23.9	41	24.3	
	11+	114	22.3		96	28.0	18	10.7	
Academic rank (A41)	Full Professor	231	44.7	<001	176	50.9	55	32.2	517
	Associate Professor	121	23.4		87	25.1	34	19.9	
	Assistant Professor	144	27.9		79	22.8	65	38.0	
	Other	21	4.1		4	1.2	17	9.9	

TABLE 3

Research and Publication Support by Demographic Variables

Label	Category	Overall		*p* value	Industry support for Res&Pub		No support		n
		n	%		n	%	n	%	
Gender (A42)	Male	348	71.5	<.001	235	78.3	113	60.4	487
	Female	139	28.5		65	21.7	74	39.6	
Years involved in research (A37)	0–5	34	6.9	<.001	20	6.6	14	7.3	496
	6–10	92	18.5		40	13.2	52	27.1	
	11+	370	74.6		244	80.3	126	65.6	
Years involved in clinical practice (A38)	0–5	262	54.2	<.001	139	47.0	123	65.8	483
	6–10	40	8.3		24	8.1	16	8.6	
	11+	181	37.5		133	44.9	48	25.7	
Years worked at institution (A39)	0–5	120	24.0	.024	62	20.3	58	30.1	499
	6–10	102	20.4		61	19.9	41	21.2	
	11+	277	55.5		183	59.8	94	48.7	
Number of publications in last 2 years (A40)	0–1	34	6.9	<.001	15	5.0	19	10.0	493
	2–3	118	23.9		58	19.1	60	31.6	
	4–5	108	21.9		66	21.8	42	22.1	
	6–10	119	24.1		75	24.8	44	23.2	
	11+	114	23.1		89	29.4	25	13.2	
Academic rank (A41)	Full Professor	226	45.4	<.001	161	52.6	65	33.9	498
	Associate Professor	117	23.5		70	22.9	47	24.5	
	Assistant Professor	137	27.5		72	23.5	65	33.9	
	Other	18	3.6		3	1.0	15	7.8	

TABLE 4

Outcomes of Research over Past Five Years and Importance of Industry Support to Research and Outcomes

Label		Received support (%)			Importance (%)				
		Yes	No	n	Extremely important	Very important	Somewhat important	not at all important	n
a.	Research contract or grant	40.8	59.2	502	29.3	30.7	30.7	9.3	205
b.	Equipment	24.7	75.3	498	15.4	25.2	27.6	31.7	123
c.	Biomaterials (reagents, clones, antibodies, tissues, cell lines, etc.)	32.6	67.4	500	20.9	23.3	33.7	22.1	163
d.	Discretionary funds or gifts to your institution	25.0	75.0	500	10.4	14.4	38.4	36.8	125
e.	Support for students or fellows	25.9	74.1	498	14.7	25.6	34.1	25.6	129
f.	Trips to professional meetings	27.1	72.9	499	5.9	17.8	42.2	34.1	135
g.	Honoraria	38.5	61.5	499	2.1	8.3	24.5	65.1	192
h.	Gifts (worth more than $100) made to you as an individual	16.0	84.0	499	2.5	6.3	15.0	76.3	80
i.	Support for staff or study coordinators	26.5	73.5	502	24.1	28.6	26.3	21.1	133
j.	Funds for publication costs	21.0	79.0	501	3.8	16.2	37.1	42.9	105
k.	Patent applications	18.6	81.4	221	25.0	45.0	15.0	15.0	40
l.	Patents, trademarks, or license fees	12.3	87.7	220	30.8	34.6	26.9	7.7	26
m.	Development of a new product that is currently on the market or is market development	19.6	80.4	219	45.2	35.7	14.3	4.8	42
n.	Development of a new company or commercial enterprise	5.0	95.0	219	30.0	30.0	30.0	10.0	10
o.	Trade secrets	9.2	90.8	218	15.8	47.4	26.3	10.5	19
p.	Royalty agreements	8.6	91.4	220	27.8	16.7	33.3	22.2	18
q.	Consulting arrangements	31.7	68.3	221	15.9	23.2	37.7	23.2	69
r.	Discussion of employment with the sponsor	4.6	95.4	218	.0	33.3	22.2	44.4	9
s.	Joint commercial venture	1.8	98.2	219	.0	.0	.0	100.0	3

TABLE 5

Rate of Disclosure of Financial Relationships with Industry to Human Research Subjects

Label		Required (%)			If no, Disclosure (%)				
		Yes	No	n	Always	Sometimes	Never	Not applicable	n
In industry-sponsored research, does your institution require you to disclose:									
a.	equity interest in the sponsoring company?	69.8	30.2	139	29.4	8.8	14.7	47.1	34
b.	that key personnel have served as consultant or board member?	63.8	36.2	138	28.9	15.6	17.8	37.8	45
c.	if key personnel are paid as industry speaker?	54.5	45.5	134	22.6	14.5	24.2	38.7	62
d.	if salary for key personnel is paid for by industry sponsor?	57.8	42.2	135	28.6	14.3	24.5	32.7	49
e.	if equipment is donated by industry sponsor?	48.8	51.2	127	10.8	3.1	15.4	70.8	65
f.	if personnel received monetary gifts or honoraria from industry sponsor?	55.7	44.3	131	21.6	7.8	11.8	58.8	51
g.	if industry sponsor paid travel of personnel?	41.3	58.7	126	11.6	5.8	36.2	46.4	32
h.	royalty agreement with industry sponsor?	60.4	39.6	134	18.6	2.3	9.3	69.8	30
j.	if personnel have joint commercial venture with industry sponsor?	60.3	39.7	136	20.0	.0	11.1	68.9	31

TABLE 6

Respondents with Industry Support: Receipt of Requests from Industry Sponsors*

Industry sponsor requested	All respondents with industry support	Respondents with unimportant industry support	Respondents with some industry support	Respondents with important industry support	*p*-value of chi-square test
Withhold research results from publication	9/231 (4%)	2/66 (3%)	2/81 (3%)	4/80 (5%)	.662
Delay publication of research results	30/230 (13%)	7/66 (11%)	9/80 (11%)	14/80 (18%)	.380
Present results in a way which reflects more favorably on the sponsor's drug or product	18/231 (8%)	3/66 (5%)	2/81 (3%)	12/80 (15%)	.006
Keep the research project and results secret	15/230 (7%)	2/66 (3%)	4/81 (5%)	8/79 (10%)	.177
(One or more of the above four requests)	44/231 (19%)	9/66 (14%)	11/81 (14%)	22/80 (28%)	.036
Acknowledge the sponsor in the publication	143/231 (62%)	27/66 (41%)	58/81 (72%)	56/80 (70%)	.000
Grant the sponsor prepublication review of manuscripts	140/231 (61%)	29/66 (44%)	48/81 (59%)	61/80 (76%)	.000
Convey all resulting patents to the sponsor	34/225 (15%)	8/66 (12%)	12/80 (15%)	14/75 (19%)	.557
Participate in research that involves proprietary information	91/229 (40%)	14/66 (21%)	30/81 (37%)	46/78 (59%)	.000

*Denominators vary because some questions were relevant to or only answered by a subset of respondents, or there were missing data.

TABLE 7

All Respondents: Industry Support and Knowledge of Compromising Research integrity*

First-hand knowledge	All respondents	Respondents with no industry support	Respondents with unimportant industry support	Respondents with some industry support	Respondents with important industry support	*P*-value of chi-square test
Results were presented to favor sponsor's product because of pressure from sponsor	31/499 (6%)	6/194 (3%)	3/106 (3%)	6/106 (6%)	16/93 (17%)	.000
Publication of research results was delayed because of pressure from sponsor	64/500 (13%)	18/194 (9%)	10/106 (9%)	13/106 (12%)	23/94 (25%)	.002
Research results were suppressed because of pressure from sponsor	21/500 (4%)	5/194 (3%)	5/106 (5%)	1/106 (1%)	10/94 (11%)	.003

* Denominators vary because some questions were relevant to or only answered by a subset of respondents, or there were missing data.

TABLE 8

Industry Support and Compromising Research Integrity: Respondents with Individuals in their Department or Research unit who Receive Industry Support*

First-hand knowledge	All respondents with others in unit who get industry support	Respondents with no industry support	Respondents with unimportant industry support	Respondents with some industry support	Respondents with important industry support	*P*-value of chi-square test
Well-being of research participant compromised	15/173 (9%)	2/36 (6%)	2/27 (7%)	2/50 (4%)	9/60 (15%)	.179
Publication of results compromised	47/168 (28%)	9/35 (26%)	4/26 (15.4%)	8/47 (17%)	26/60 (43%)	.008
Interpretation of research data compromised	41/162 (25%)	7/33 (21%)	4/27 (15%)	8/46 (17%)	22/56 (39%)	.027
Research initiatives compromised because individuals were supported by industry	56/167 (35%)	10/34 (29%)	5/28 (18%)	9/46 (20%)	32/59 (54%)	.000
Scientific advancement compromised by industry support	35/172 (20%)	5/40 (13%)	5/26 (19%)	6/47 (13%)	19/59 (32%)	.040

* Denominators vary because some questions were relevant to or only answered by a subset of respondents, or there were missing data.

EXHIBIT 309

Editorial

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Preserving Intellectual Freedom in Clinical Medicine

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An eminent clinician of the past century, John A. Ryle, summarized the social responsibilities of the physician as follows: 'The life and work of the physician proceed under the direction of three main influences: the scientific, the humane, and the ethical. Whereas other men of science have, until now, found it possible to pursue their intellectual tasks without reference to human need and without regard for ethical considerations other than those immediately connected with the pursuit of the truth and respect for colleagues, the medical man has carried a far heavier and more complex burden of responsibility. He has had and has now in ever-increasing measure – and in the addition to the consideration which he owes to himself and his dependants – a special duty to his patients, to the community, to his colleagues, and to his science or calling' [1, p. 101].

These are values which Robert G. Petersdorf echoed 4 decades later, in 1989: 'We can no longer tolerate the dishonesty, cheating, fraud, and conflict of interest that have invaded science and medicine. By choosing these professions we have assumed a trust that is predicated upon integrity. We must not deviate from it' [2, p. 123].

Halstead R. Holman, in a paper published in Hospital Practice in 1976 [3], which anticipated some of the developments in health care over the following 4 decades, observed that 'the medical establishment is not primarily engaged in the disinterested pursuit of knowledge into medical practice; rather in significant part it is engaged in special interest advocacy, pursuing and preserving social power. The concept of excellence is a component of the ideological justification of that role' [3, p. 11]. Holman identified a decline in intellectual freedom as a major source of the 'excellence deception', which perpetuates prevailing practices, deflects criticism and insulates the profession from alternative views and social relations that would illuminate and improve health care. There are indeed increasing threats to the preservation of intellectual freedom in clinical medicine.

The Many Faces of Censorship

There have been growing concerns about the independence of academic medicine [4–7]. Corporate interests may result in self-selected academic oligarchies (special interest groups) that influence clinical and scientific information [5]. Members of special interest groups are not simply the easily recognizable prodigal experts who move from one meeting to another to illustrate the wonderful properties of the drugs to be launched, who have their slides prepared and checked by the companies, who sign ghostwritten papers and are promptly substituted if they do not have impact on prescriptions [8]. They are also the gatekeepers of corporate interest in scientific informa-

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tion. They act as editors, reviewers and consultants to medical journals, scientific meetings and nonprofit research organizations, with the task of systematically preventing dissemination of data that may be in conflict with the special interest they represent [5].

By carefully selecting the literature in a biased direction and offering a manipulated interpretation of clinical trials (including those supported by public sources) they become 'the role models whose views are to be taken seriously' [9]. The drug industry may thus take control of scientific societies, clinical practice guidelines and reporting investigations in meetings and journals. Independent investigators, who feel the moral obligation to tell the truth, may object to the manipulation of evidence operated by these special interest groups, who retaliate: excluding them from symposia, removing them from academic appointments and preventing access to sources of research funding [10]. Isolation is the ultimate outcome. For a pharmaceutical company delaying or minimizing knowledge of a side effect of a medication has cash value. Similarly, not publishing negative studies may shift the balance of subsequent meta-analyses. A recent paper [11] provides a good illustration as to how selected publication of antidepressant trials affects their apparent efficacy. Thirty-seven of the 74 FDA-registered studies that were associated with positive outcomes were published and 1 was not, whereas only 3 of the 36 negative studies were published [11]. Physicians who are not familiar with the scientific method may rely on meta-analyses for choosing their therapeutic tools [12]. Censorship may thus be the result of direct prevention of publication and dissemination of findings by the pharmaceutical company itself (displaying its power as an advertiser in medical journals, a supporter of meetings and the owner of the data) or by special interest groups (the trusted opinion leaders).

Yet, there are more subtle forms of censorship. One has to do with setting a financial threshold for publishing research findings. In recent years, there has been a progressive demand for the free availability of resources on the internet and for centralizing medical information. Public access to medical journals means that the authors will have to pay at least part of the expenses. Publications loaded with conflicts of interest would not really have any problem; however, this will be a major difficulty for young and unsupported investigators. These investigators, because of their inquisitive nature that may lead to new discoveries, are the lifeblood of science [10]. The issue is thus not open access to self-selected information, but the discrimination of independent sources within information overload [13].

Another subtle form of censorship is by counteracting undesirable published information with massive doses of propaganda. Noam Chomsky has been instrumental in disclosing the link between propaganda and media control [14]. Filtering information (selective perception), engineering opinions, using the public relations industry and marginalizing dissident cultures are the well-known modalities of action. The presentation of the literature on long-term treatment with antidepressant drugs exemplifies this strategy [15].

Yet, it is deliberate self-censorship that may yield the most dangerous effects. As suggested by a recent survey of journalists [16], it is common and eliminates the need for editorial cuts and modifications. The typical example is the intervention of an established investigator in a drug-sponsored symposium. He or she refrains from making promotional statements, leaving the dirty job to someone else in the symposium. However, he or she does not comment on unsubstantiated and commercial statements from other speakers in the panel.

Obviously, financial interests are not the only source of censorship in clinical medicine, and may be substituted or supplemented by cultural, political and ideological issues.

If medical knowledge is the cumulative experience of human history, 'a legacy from those who have gone before to those who live today' and 'a social possession' [3, p. 21], then the suppression of memory (i.e. reliance on the most recent papers) and ignorance of the historical intellectual debate may be other more subtle forms of censorship. Noam Chomsky, in an essay on the intellectual climate during the Cold War [17], reminds us of how the neglect of the history of the disciplines was instrumental to preventing a critical attitude toward the establishment. If we do not know where we came from, we have a very poor idea of where we are going to.

Preserving Intellectual Freedom

Viewing censorship simply in terms of power from special interest groups would be too simplistic. The submission process of scientific publications (with methodological requirements, peer reviews, journals' priorities and space) may also be perceived as a form of censorship. Would uncensored exchange of scientific results solve the problem? Not quite [13]. The challenge is to preserve pluralism, critical thinking and intellectual freedom in a setting more and more characterized by conformism, political appropriateness and the cult of mediocrity [18].

One way to address the problem has recently been suggested [5, 19], and has to do with the value that is represented by investigators who opted for not having any substantial conflicts of interest (i.e. being an employee of a private firm; being a regular consultant or in the board of directors of a firm; being a stockholder of a firm related to the field of research; owning a patent directly related to the published work) [5]. These criteria, which are based on work by Krimsky et al. [20], involve the concept of continuity of a relationship with a private firm. Occasional consultancies, grants for performing investigations, or receiving honoraria or refunds on specific occasions would not be a source of substantial conflict of interest [5]. We are often told that virtually all clinical investigators should have some ties with the industry, even though this is not true (and the characteristics of these relationships may vary a great deal) [21]. Researchers without substantial conflicts of interest, however, need support, which includes priority for obtaining grants from public agencies supported by taxpayers' money and priorities, for key positions in scientific societies and journal editorships. Clinical practice guidelines should be reserved to these investigators. Otherwise, the scientific community would soon drain itself of a reservoir of truly independent experts who can be called to advise government policy makers on the safety and efficacy of treatments, on the hazards of chemicals and on the safety of technology [20]. Taxpayers and members of professional societies deserve scientific leadership by those researchers who opt to be devoid of substantial conflicts of interest, and may counteract the feudal lords of medicine [10] and the artificial boundaries that the game of power has built in the medical system. The recent questioning of the American Psychiatric Association's financial management [22] underscores the need for major changes in leadership and handling the issue of conflict of interest.

The Journal's Mission

In line with the task that was set in the early nineties [23], this journal has tried to foster innovative and unconventional thinking at the interface between medical and behavioral sciences. Chomsky subdivides intellectuals into 2 categories: 'the "technocratic and policy-oriented intellectuals" – responsible, sober, constructive – and the "value-oriented intellectuals", a sinister grouping who pose a threat to democracy as they devote themselves to the derogation of leadership, the challenging of authority, and the unmasking of established institutions' [24, p. 214].

This journal seems to attract more and more 'value-oriented' scientists. As much as it can be judged by a crude and rough estimate such as the impact factor, its content does not pass unnoticed. The journal's 2007 Journal Citation Reports impact factor is 5.02, which places the journal as number 9 in the psychiatry ranking and number 4 (but actually the top journal among those that publish original investigations) in the psychology ranking. We have tried not to forget what the histories of our disciplines teach, with tributes to outstanding clinical scientists [25–28].

We will also try to be open to different and dissenting views, in the spirit Thomas Jefferson so aptly summarized: 'If [the] book be false in its facts, disprove them; if false in its reasoning, refute it. But, for God's sake, let us freely hear both sides, if we choose.'

Appendix

The following experts have supplemented the editorial board by reviewing the manuscripts submitted to Psychotherapy and Psychosomatics during 2008, and are gratefully acknowledged. We would like to thank also Carlotta Belaise, who has taken care of press releases. Both external referees and editorial board members have disclosed potential conflicts of interest. The Editor-in-Chief has no conflict of interest to declare for 2008.

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References

1 Ryle JA: Changing Disciplines: Lectures on the History, Method and Motives of Social Pathology. London, Oxford University Press, 1948.
2 Petersdorf RG: A matter of integrity. Acad Med 1989;64:119–123.
3 Holman HR: The 'excellence' deception in medicine. Hosp Pract 1976;11:11–21.
4 Lexchin J, Light DW: Commercial influence and the content of medical journals. BMJ 2006;332:1444–1447.
5 Fava GA: Financial conflicts of interest in psychiatry. World Psychiatry 2007;6:19–24.
6 Healy D: Irrational healers. Psychother Psychosom 2008;77:198–200.
7 Nierenberg AA, Smoller JW, Eidelman P, Wu YP, Tilley CA: Critical thinking about adverse drug effects: lessons from the psychology of risk and medical decision-making for clinical psychopharmacology. Psychother Psychosom 2008;77:201–208.
8 Moynihan R: Key opinion leaders: independent experts or drug representatives in disguise? BMJ 2008;336:1402–1403.
9 Iheanacho I: Paying for the view. BMJ 2008; 336:160.
10 Borgstein J, Watine J: Feudal lords of science and medicine. West J Med 2001;175:139–140.
11 Turner EH, Matthews AM, Linardatos E, Tell RA, Rosenthal R: Selective publication of antidepressant trials and its influence on apparent efficacy. N Engl J Med 2008;358: 252–260.
12 Feinstein AR: Meta-analysis: statistical alchemy for the 21st century. J Clin Epidemiol 1995;48:71–79.
13 Fava GA, Guidi J: Information overload, the patient and the clinician. Psychother Psychosom 2007;76:1–3.
14 Chomsky N: Media Control: The Spectacular Achievements of Propaganda. New York, Seven Stories, 1997.
15 Fava GA: Long-term treatment with antidepressant drugs: the spectacular achievements of propaganda. Psychother Psychosom 2002;71:127–132.
16 Lee FLF, Chan JM: Professionalism, political orientation, and perceived self-censorship. Issue Studies 2008;44:205–238.

17 Chomsky N: The cold war and the university; in Chomsky N, Katznelson I, Lewontin RC, Montgomery D, Nader L, Ohmann R, Siever R, Wallerstein I, Zinn H: The Cold War & the University. New York, New Press, 1997, pp 171–194.
18 Fava GA: The cult of mediocrity. Psychother Psychosom 2005;74:1–2.
19 Fava GA: Should the drug industry use key opinion leaders? No. BMJ 2008;336:1045.
20 Krimsky S, Rothenberg LS, Stott P, Kyle G: Scientific journals and their authors' financial interests: a pilot study. Psychother Psychosom 1998;67:194–201.
21 Campbell EG, Gruen RL, Mountford J, Miller LG, Cleary PD, Blumenthal D: A national survey of physician-industry relationships. N Engl J Med 2007;356:1742–1750.
22 Carey B, Harris G: Psychiatric group faces scrutiny over drug industry ties. New York Times, July 12, 2008.
23 Fava GA: The journal's task. Psychother Psychosom 1992;57:1–2.
24 Chomsky N: Interventions. San Francisco, City Lights Books, 2007.
25 Nierenberg AA, Sonino N: From clinical observations to clinimetrics: a tribute to Alvan R. Feinstein, MD. Psychother Psychosom 2004;73:131–133.
26 Bech P: The full story of lithium: a tribute to Mogens Schou (1918–2005). Psychother Psychosom 2006;75:265–269.
27 De Figuereido JM: Demoralization and psychotherapy: a tribute to Jerome D. Frank, MD, PhD (1909–2005). Psychother Psychosom 2007;76:129–133.
28 Fava GA, Rafanelli C, Tossani E, Grandi S: Agoraphobia is a disease: a tribute to Sir Martin Roth. Psychother Psychosom 2008;77:133–138.

EXHIBIT 310

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Essay

Medical Journals Are an Extension of the Marketing Arm of Pharmaceutical Companies

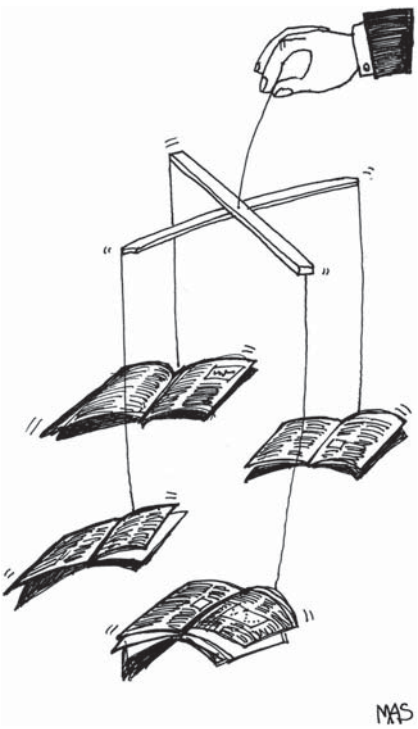
Richard Smith

"Journals have devolved into information laundering operations for the pharmaceutical industry", wrote Richard Horton, editor of the *Lancet*, in March 2004 [1]. In the same year, Marcia Angell, former editor of the *New England Journal of Medicine*, lambasted the industry for becoming "primarily a marketing machine" and co-opting "every institution that might stand in its way" [2]. Medical journals were conspicuously absent from her list of co-opted institutions, but she and Horton are not the only editors who have become increasingly queasy about the power and influence of the industry. Jerry Kassirer, another former editor of the *New England Journal of Medicine*, argues that the industry has deflected the moral compasses of many physicians [3], and the editors of *PLoS Medicine* have declared that they will not become "part of the cycle of dependency…between journals and the pharmaceutical industry" [4]. Something is clearly up.

The Problem: Less to Do with Advertising, More to Do with Sponsored Trials

The most conspicuous example of medical journals' dependence on the pharmaceutical industry is the substantial income from advertising, but this is, I suggest, the least corrupting form of dependence. The advertisements may often be misleading [5,6] and the profits worth millions, but the advertisements are there for all to see and criticise. Doctors may not be as uninfluenced by the advertisements as they would like to believe, but in every sphere, the public is used to discounting the claims of advertisers.

The much bigger problem lies with the original studies, particularly the clinical trials, published by journals. Far from discounting these, readers see randomised controlled trials as one of the highest forms of evidence. A large trial published in a major journal has the journal's stamp of approval (unlike the advertising), will be distributed around the world, and may well receive global media coverage, particularly if promoted simultaneously by press releases from both the journal and the expensive public-relations firm hired by the pharmaceutical company that sponsored the trial. For a drug company, a favourable trial is worth thousands of pages of advertising, which is why a company will sometimes spend upwards of a million dollars on reprints of the trial for worldwide distribution. The doctors receiving the reprints may not read them, but they will be impressed by the name of the journal from which they come. The quality of the journal will bless the quality of the drug.



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(Illustration: Margaret Shear, Public Library of Science)

Fortunately from the point of view of the companies funding these trials—but unfortunately for the credibility of the journals who publish them—these trials rarely produce results that are unfavourable to the companies' products [7,8]. Paula Rochon and others examined in 1994 all the trials funded by manufacturers of nonsteroidal anti-inflammatory drugs for arthritis that they could find [7]. They found 56 trials, and not one of the published trials presented results that were unfavourable to the company that sponsored the trial. Every trial showed the company's drug to be as good as or better than the comparison treatment.

By 2003 it was possible to do a systematic review of 30 studies comparing the outcomes of studies funded by the pharmaceutical industry with those of studies funded from other sources [8]. Some 16 of the studies looked at clinical trials or meta-analyses, and 13 had outcomes favourable to the sponsoring companies. Overall, studies funded by a company were four times more likely to have results favourable to the company than studies funded from other sources. In the case of the five studies that looked at economic evaluations,

The Essay section contains opinion pieces on topics of broad interest to a general medical audience.

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Competing Interests: RS was an editor for the *BMJ* for 25 years. For the last 13 of those years, he was the editor and chief executive of the BMJ Publishing Group, responsible for the profits of not only the *BMJ* but of the whole group, which published some 25 other journals. He stepped down in July 2004. He is now a member of the board of the Public Library of Science, a position for which he is not paid.

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the results were favourable to the sponsoring company in every case.

The evidence is strong that companies are getting the results they want, and this is especially worrisome because between two-thirds and three-quarters of the trials published in the major journals—*Annals of Internal Medicine*, *JAMA*, *Lancet*, and *New England Journal of Medicine*—are funded by the industry [9]. For the *BMJ*, it's only one-third—partly, perhaps, because the journal has less influence than the others in North America, which is responsible for half of all the revenue of drug companies, and partly because the journal publishes more cluster-randomised trials (which are usually not drug trials) [9].

Why Do Pharmaceutical Companies Get the Results They Want?

Why are pharmaceutical companies getting the results they want? Why are the peer-review systems of journals not noticing what seem to be biased results? The systematic review of 2003 looked at the technical quality of the studies funded by the industry and found that it was as good—and often better—than that of studies funded by others [8]. This is not surprising as the companies have huge resources and are very familiar with conducting trials to the highest standards.

The companies seem to get the results they want not by fiddling the results, which would be far too crude and possibly detectable by peer review, but rather by asking the "right" questions—and there are many ways to do this [10]. Some of the methods for achieving favourable results are listed in the Sidebar, but there are many ways to hugely increase the chance of producing favourable results, and there are many hired guns who will think up new ways and stay one jump ahead of peer reviewers.

Then, various publishing strategies are available to ensure maximum exposure of positive results. Companies have resorted to trying to suppress negative studies [11,12], but this is a crude strategy—and one that should rarely be necessary if the company is asking the "right" questions. A much better strategy is to publish positive results more than once, often in supplements to journals, which are highly profitable to the publishers and shown to be of dubious quality [13,14]. Companies will usually conduct multicentre trials, and there is huge scope for publishing different results from different centres at different times in different journals. It's also possible to combine the results from different centres in multiple combinations.

These strategies have been exposed in the cases of risperidone [15] and odansetron [16], but it's a huge amount of work to discover how many trials are truly independent and how many are simply the same results being published more than once. And usually it's impossible to tell from the published studies: it's necessary to go back to the authors and get data on individual patients.

Peer Review Doesn't Solve the Problem

Journal editors are becoming increasingly aware of how they are being manipulated and are fighting back [17,18], but I must confess that it took me almost a quarter of a century editing for the *BMJ* to wake up to what was happening. Editors work by considering the studies submitted to them. They ask the authors to send them any related studies, but editors have no other mechanism to know what other unpublished studies exist. It's hard even to know about related studies that are published, and it may be impossible to tell that studies are describing results from some of the same patients. Editors may thus be peer reviewing one piece of a gigantic and clever marketing jigsaw—and the piece they have is likely to be of high technical quality. It will probably pass peer review, a process that research has anyway shown to be an ineffective lottery prone to bias and abuse [19].

Furthermore, the editors are likely to favour randomised trials. Many journals publish few such trials and would like to publish more: they are, as I've said, a superior form of evidence. The trials are also likely to be clinically interesting. Other reasons for publishing are less worthy. Publishers know that pharmaceutical companies will often purchase thousands of dollars' worth of reprints, and the profit margin on reprints is likely to be 70%. Editors, too, know that publishing such studies is highly profitable, and editors are increasingly responsible for the budgets of their journals and for producing a profit for the owners. Many owners—including academic societies—depend on profits from their journals. An editor may thus face a frighteningly stark conflict of interest: publish a trial that will bring US$100 000 of profit or meet the end-of-year budget by firing an editor.

Examples of Methods for Pharmaceutical Companies to Get the Results They Want from Clinical Trials

- Conduct a trial of your drug against a treatment known to be inferior.
- Trial your drugs against too low a dose of a competitor drug.
- Conduct a trial of your drug against too high a dose of a competitor drug (making your drug seem less toxic).
- Conduct trials that are too small to show differences from competitor drugs.
- Use multiple endpoints in the trial and select for publication those that give favourable results.
- Do multicentre trials and select for publication results from centres that are favourable.
- Conduct subgroup analyses and select for publication those that are favourable.
- Present results that are most likely to impress—for example, reduction in relative rather than absolute risk.

Journals Should Critique Trials, Not Publish Them

How might we prevent journals from being an extension of the marketing arm of pharmaceutical companies in publishing trials that favour their products? Editors can review protocols, insist on trials being registered, demand that the role of sponsors be made transparent, and decline to publish trials unless researchers control the decision to publish [17,18]. I doubt, however, that these steps will make much difference. Something more fundamental is needed.

Firstly, we need more public funding of trials, particularly of large head-to-head trials of all the treatments available for treating a condition. Secondly, journals should perhaps stop publishing trials. Instead, the protocols and results should be made available on regulated Web sites. Only such a radical step, I think, will stop journals from being beholden to

companies. Instead of publishing trials, journals could concentrate on critically describing them. ■

This article is based on a talk that Richard Smith gave at the Medical Society of London in October 2004 when receiving the HealthWatch Award for 2004. The speech is reported in the January 2005 HealthWatch newsletter [20]. The article overlaps to a small extent with an article published in the BMJ *[21].*

References

1. Horton R (2004) The dawn of McScience. New York Rev Books 51(4): 7–9.
2. Angell M (2005) The truth about drug companies: How they deceive us and what to do about it. New York: Random House. 336 p.
3. Kassirer JP (2004) On the take: How medicine's complicity with big business can endanger your health. New York: Oxford University Press. 251 p.
4. Barbour V, Butcher J, Cohen B, Yamey G (2004) Prescription for a healthy journal. PLoS Med 1: e22. DOI: 10.1371/journal.pmed.0010022
5. Wilkes MS, Doblin BH, Shapiro MF (1992) Pharmaceutical advertisements in leading medical journals: Experts' assessments. Ann Intern Med 116: 912–919.
6. Villanueva P, Peiro S, Librero J, Pereiro I (2003) Accuracy of pharmaceutical advertisements in medical journals. Lancet 361: 27–32.
7. Rochon PA, Gurwitz JH, Simms RW, Fortin PR, Felson DT, et al. (1994) A study of manufacturer-supported trials of nonsteroidal anti-inflammatory drugs in the treatment of arthritis. Arch Intern Med 154: 157–163.
8. Lexchin J, Bero LA, Djulbegovic B, Clark O (2003) Pharmaceutical industry sponsorship and research outcome and quality. BMJ 326: 1167–1170.
9. Egger M, Bartlett C, Juni P (2001) Are randomised controlled trials in the BMJ different? BMJ 323: 1253.
10. Sackett DL, Oxman AD (2003) HARLOT plc: An amalgamation of the world's two oldest professions. BMJ 327: 1442–1445.
11. Thompson J, Baird P, Downie J (2001) The Olivieri report. The complete text of the independent inquiry commissioned by the Canadian Association of University Teachers. Toronto: Lorimer. 584 p.
12. Rennie D (1997) Thyroid storm. JAMA 277: 1238–1243.
13. Rochon PA, Gurwitz JH, Cheung M, Hayes JA, Chalmers TC (1994) Evaluating the quality of articles published in journal supplements compared with the quality of those published in the parent journal. JAMA 272: 108–113.
14. Cho MK, Bero LA (1996) The quality of drug studies published in symposium proceedings. Ann Intern Med 124: 485–489.
15. Huston P, Moher D (1996) Redundancy, disaggregation, and the integrity of medical research. Lancet 347: 1024–1026.
16. Tramèr MR, Reynolds DJM, Moore RA, McQuay HJ (1997) Impact of covert duplicate publication on meta-analysis: A case study. BMJ 315: 635–640.
17. Davidoff F, DeAngelis CD, Drazen JM, Hoey J, Hojgaard L, et al. (2001) Sponsorship, authorship, and accountability. Lancet 358: 854–856.
18. De Angelis C, Drazen JM, Frizelle FA, Haug C, Hoey J, et al. (2004) Clinical trial registration: A statement from the International Committee of Medical Journal Editors. Lancet 364: 911–912.
19. Godlee F, Jefferson T (2003) Peer review in health sciences, 2nd ed. London: BMJ Publishing Group. 367 p.
20. Garrow J (2005 January) HealthWatch Award winner. HealthWatch 56: 4–5.
21. Smith R (2003) Medical journals and pharmaceutical companies: Uneasy bedfellows. BMJ 326: 1202–1205.

EXHIBIT 311

Relationship Between Conflicts of Interest and Research Results

Lee S. Friedman, BA, Elihu D. Richter, MD, MPH

CONTEXT: **To date, research regarding the influence of conflicts of interest on the presentation of findings by researchers has been limited.**

OBJECTIVE: **To evaluate the sources of funding for published manuscripts, and association between reported findings and conflicts of interest.**

METHODS: **Data from both print and electronic issues of The New England Journal of Medicine (NEJM) and The Journal of the American Medical Association (JAMA) were analyzed for sources of funding, areas of investigation, conflict of interest (COI), and presentation of results. We reviewed all original manuscripts published during the year 2001 within NEJM (*N* = 193) and JAMA (*N* = 205). We use 3 definitions for COI in this paper: a broadly defined criterion, the criterion used by The International Council of Medical Journal Editors (ICMJE), and a criterion defined by the authors.**

RESULTS: **Depending on the COI criteria used, 16.6% to 32.6% of manuscripts had 1 or more author with COI. Based on ICMJE criterion, 38.7% of studies investigating drug treatments had authors with COI. We observed a strong association between those studies whose authors had COI and reported positive findings (*P* < .001). When controlling for sample size, study design, and country of primary authors, we observed a strong association between positive results and COI (ICMJE definition) among all treatment studies (adjusted odds ratio [OR], 2.35; 95% confidence interval [CI], 1.08 to 5.09) and drug studies alone (OR, 2.64; 95% CI, 1.09 to 6.39).**

CONCLUSION: **COI is widespread among the authors of published manuscripts and these authors are more likely to present positive findings.**

KEY WORDS: **conflict of interest; publication bias; biomedical ethics; funding; research.**
J GEN INTERN MED 2004; 19:51–56.

The influence of commercial interests on the principal players in the peer review process—researchers, reviewers, and editors—is an important and sensitive issue facing biomedical research. There is a need to comprehensively evaluate the degree of influence, direct and indirect, of private corporations on researchers.

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Studies have found the presence[1–4] and absence[5] of an association between funding from pharmaceutical companies and presentation of positive findings. However, none are readily available which have addressed this association among research funded by all health care industry manufacturers or within the broader framework of a conflicts of interest (COI) definition, which includes not only direct funding in the form of grants but also other types of personal financial associations and interests such as consultancy, employment, stock ownership, patent licensing, and honoraria. In addition, our review of the literature shows no study to date which has addressed the likelihood of publishing negative findings among authors with COI, which answers an entirely different question.

In this study we evaluate the sources of funding for published manuscripts. We also examine whether the reported relationship between positive findings and financial associations are sustained when using a COI definition and including nonpharmaceutical manufacturers in our analysis. Furthermore, we investigate the likelihood of publishing negative findings given COI.

METHODS

We selected the top 2 general medical journals based on their year 2000 impact factor as ranked by ISI Journal Citation Reports.[6] Data from both the print and electronic 2001 issues of The New England Journal of Medicine (NEJM) and The Journal of the American Medical Association (JAMA)[7,8] were analyzed for trends in sources of funding, areas of investigation, COI, and presentation of results. All monetary descriptions are in U.S. dollars.

In NEJM, we analyze only manuscripts defined by the journal as "Original Reports." In JAMA, we analyze 190 "Original Contribution" articles, and an additional 15 in the following subsection headings: 3 "Caring for critically ill patients," 3 "Clinical cardiology," 2 "Clinical evaluation," 4 "Clinical investigation," 2 "Preliminary communications," and 1 "Toward optimal laboratory use." Editorials, reviews, commentaries, case reports, and brief reports from both journals were excluded.

We use author descriptions to classify study design, number of subjects per study, and funding source. In cases where author/s did not define study design, we use the definitions in Abramson for categorization.[9]

Both journals request authors to disclose financial relationships with companies whose product they review in the manuscript. Sponsor and type of financial support were in most cases disclosed by authors. The authors of 33 studies from both journals combined did not disclose financial relationships. All 33 studies were categorized as studies without financial associations. Seven studies in

which the authors only provide the name of a financial sponsor, but not a description of the financial support, were categorized as "grant/funding."

We were unable to find broad consensus for any single definition of COI. We therefore use 3 definitions for COI in this paper: 1) a broadly defined criterion, 2) the criterion used by The International Council of Medical Journal Editors (ICMJE), and 3) a criterion defined by the authors.

The broadly defined COI criterion is defined as all financial relationships with companies whose products the researchers are evaluating in the manuscript, except for studies only supported by free drugs and equipment.

Second, we use the COI criterion set forth by the ICMJE.[10] This "narrowly defined" criterion refers to those financial relationships specifically cited as the most severe examples of conflict of interest that include consultancy, employment, stock ownership, patent licensing, and honoraria. This criterion excludes financial relationships based on grants, both general and specific funding, awards, fellowships, free drugs or equipment, and authors serving as speakers or on an advisory board.

Third, we use an internal definition of COI. Neither of the above criteria address the commercial components of the studies. A study must meet each of the following 4 criteria: 1a) one or more authors have financial associations with a private corporation in the form of grants, unspecified funding, consultancy, employment, stock ownership, or honoraria; and/or b) have a personal financial interest in the study because of a patent license in which an author is eligible to receive royalties or from personal investments. Free drugs and equipment, awards, fellowships, and serving on advisory boards or as speakers do not constitute COI in this definition; 2) drug/treatment/product reviewed by the author/s is manufactured by the funding corporation, or is in the same retail class[11] as a drug manufactured by a sponsoring competitor; 3) product(s) reviewed by author(s) must have current or near future commercial potential (i.e., sold for profit); and 4) presentation of main findings support commercial product, negate competitor's product, advocate cost benefit, and/or show product has a potential commercial value (demand, size, and growth).

To assess the association between COI and reported study findings, we classified the presentation of the results as follows: positive, mixed, negative, or other.

Positive results include studies that show a statistically significant ($P < .05$) clinical benefit from a treatment or absence of suspected side effects ($P > .05$), achieve statistically valid equivalence comparable to commonly used therapies, or support their product by observing side effects in a competitive product or insignificant association with intended outcome from use of competitor's product ($P > .05$; $N = 4$ studies for latter). Mixed results include studies noting both clinical benefits from a treatment and presence of significant adverse effects (both $P < .05$). Negative results include studies that report the absence of clinical benefits ($P > .05$) and/or evidence for numerous adverse effects ($P < .05$). "Other" category includes studies that are observational or cross-sectional emphasizing frequency and distribution rather than comparison between groups; trends in medical services and product usage; drug discontinuation protocol; or studies whose significance is yet unclear because it is a preliminary or pilot study.

Statistical Methods

We use SAS for Windows (version 8.0; SAS Institute, Inc., Cary, NC) for the statistical analysis. We use χ^2 tests for analysis of categorical variables. We fit a multiple logistic regression model including potential predictors to estimate adjusted odds ratios (OR) for reported positive/negative results and COI. We use both ICMJE and author-defined criteria for COI when fitting our model. Adjusted odds ratios for all treatment-related studies and drug-related studies, respectively, were calculated. The model included the following variables: sample size, study design, and country of origin of primary authors. To evaluate the association between positive results and COI, the categories used in Table 3 were aggregated (mixed, negative, and other). The same procedure was conducted to evaluate the association between negative results and COI (positive, mixed, and other were aggregated). A two-sided P value less than .05 was considered statistically significant.

RESULTS

Table 1 shows the general characteristics of original manuscripts published in NEJM and JAMA during 2001.

In 2001, NEJM and JAMA, respectively, published 193 and 205 original manuscripts. A total of 72.6% of the original manuscripts in NEJM were clinical trials or cohort studies compared to the 57.6% in JAMA. JAMA contained a larger number of cross-sectional and evaluation/validation studies (difference, 15%; 95% confidence interval (CI), 3%, 27%).

Large samples were frequently used in the manuscripts of both journals. Fifty-five percent of the manuscripts in JAMA had sample sizes ≥ 1,000.

A total of 81.9% ($N = 158/193$) of original manuscripts in NEJM and 87.8% ($N = 180/205$) in JAMA received funding from government and/or private corporations. Private corporations alone funded 38.3% and 34.6% of the research articles in NEJM and JAMA, respectively. The 5 companies most frequently reported as study sponsors were GlaxoSmithKline, Aventis, Merck, Pfizer, and Hoffman-LaRoche.

Original manuscripts published in JAMA covered a broader scope of investigations than those published in NEJM, which primarily focused on risk assessment and treatment (85% of total; $P < .001$). A total of 16.6% of the original manuscripts in JAMA discussed health care issues of providers, physicians, and patients, whereas no original manuscripts in this area of investigation were published by NEJM.

Table 1. Descriptive Data for Original Manuscripts Published in 2001 in The New England Journal of Medicine and The Journal of the American Medical Association

	NEJM	JAMA
Circulation (paid subscriptions only)*	193,785	249,532
Impact factor	29.5	15.4
Number of Original Manuscripts published in 2001	193	205
Study Design		
Prevalence/cross-sectional, % (*n*)	2.6 (5)	15.1 (31)
Case-control, % (*n*)	16.1 (31)	4.9 (10)
Cohort, % (*n*)	24.4 (47)	32.7 (67)
Clinical trial, % (*n*)	48.2 (93)	24.9 (51)
Evaluation/validation, % (*n*)	3.1 (6)	16.6 (34)
Other,† % (*n*)	5.7 (11)	5.9 (12)
Mean number of subjects per study‡,§ (range)	8763 (2 to 679,942)	47,266 (2 to 1,900,000)
With ≤ 100 subjects, %	26.4	12.0
With ≥ 1,000 subjects, %	31.6	54.9
Funding Source§, (*n*)		
Government	117	146
Corporate/pharmaceutical	74	72
Not-for-profit	52	61
None reported	20	13
Area of Investigation		
Health care—providers, physicians, and patients, % (*n*)	0 (0)	16.6 (34)
Health promotion and primary prevention, % (*n*)	1.6 (3)	6.3 (13)
Risk assessment, % (*n*)	25.4 (49)	30.2 (62)
Screening (diagnostic and prognostic), % (*n*)	9.9 (19)	10.7 (22)
Treatment (primary through tertiary), % (*n*)	59.6 (115)	27.3 (56)
Other, % (*n*)	3.6 (7)	8.8 (18)

* *Source: Circulation, BPA International Journal Circulation Audit, June 2001; Impact factor (cites in 2000 to articles published divided by number of articles published in 2000), ISI Journal Citation Report, 2000.*
† *Study design, Other—includes case studies, cost analysis, and cost benefit studies, program reviews, meta-analysis, ecological, gene linkage, and heredity studies.*
‡ *Only human subjects included; 5 studies from NEJM and 8 from JAMA were excluded.*
§ *We report all sources of funding listed by authors; most research articles included multiple sources of funding.*
Reject null hypothesis that distribution by category between NEJM and JAMA is not different; P < .001.
NEJM, New England Journal of Medicine; JAMA, Journal of the American Medical Association.

Conflict of Interest

Table 2 notes the number of original manuscripts in which 1 or more authors reported financial associations with private corporations or had personal financial interests in the study product (patents, stock).

Based on our internally defined conflict of interest criterion, the authors of 27.5% of the original manuscripts in NEJM had potential COI compared to 20.0% in JAMA. When using the ICMJE criterion (including only consultancy, employment, stock ownership, patent licensing, and honoraria), the authors of 22.3% of the original manuscripts in NEJM had potential COI compared to 16.6% of the manuscripts in JAMA (Table 2).

Table 3 shows the distribution of study outcomes for manuscripts with and without COI. There exists a strong association between those studies whose authors had a COI and reported positive findings ($P < .001$). Based on the ICMJE criterion, we observed that 38.7% (46 out of 119) of studies investigating drug treatments had authors with COI compared to 20.0% (11 out of 55) of studies investigating nonpharmaceutical therapies.

Based on the ICMJE criterion, when controlling for sample size, study design, and country of primary authors, we observed a strong association between positive results and COI among all treatment studies (adjusted odds ratio [OR], 2.35; 95% CI, 1.08 to 5.09) and drug studies alone (adjusted OR, 2.64; 95% CI, 1.09 to 6.39). Using the author-defined COI criterion, we observed a strong association between positive results and COI among all treatment studies (adjusted OR, 4.07; 95% CI, 1.90 to 8.72) and drug studies alone (adjusted OR, 7.32; 95% CI, 2.87 to 18.71).

However, the strength of the association increased when comparing reported negative results and COI (ICMJE definition) for all treatment studies (adjusted OR, 0.107; 95% CI, 0.02 to 0.49) and drug studies only (adjusted OR, 0.05; 95% CI, 0.01 to 0.43). Based on our internal definition of COI, the relationship between reported negative results and COI for all treatment studies was OR = 0.03 (adjusted; 95% CI, 0.004 to 0.251) and for drug studies only was OR = 0.02 (adjusted; 95% CI, 0.001 to 0.189). The odds are extremely small that negative results would be published by authors with COI.

Table 2. Number of Original Manuscripts in Which One or More Authors Had Reported Corporate Financial Relationships and Conflict of Interest, The New England Journal of Medicine and The Journal of the American Medical Association (2001)

	NEJM		JAMA	
	Articles (*N*)	% of Total (*N*, 193)	Articles (*N*)	% of Total (*N* = 205)
Type of financial interest or association as reported by authors	76	39.4	76	37.1
Grant/funding	56	29.0	71	34.6
Consultant	25	13.0	22	10.7
Employee	16	8.3	10	4.9
Patent licensed to author	4	2.1	5	2.4
Honoraria	6	3.1	15	7.3
Stock ownership	7	3.6	9	4.4
Served as speakers	4	2.1	13	6.3
Awards/fellowships	2	1.0	4	2.0
Advisory board	2	1.0	7	3.4
Free drugs/gifts	11	5.7	17	8.3
Articles in Which One or More Authors Had a Conflict of Interest				
Broadly defined criterion*	63	32.6	53	25.9
ICMJE criterion†	43	22.3	34	16.6
Author-defined criterion‡	53	27.5	41	20.0

* *Broadly defined conflict of interest (COI) criteria: all financial relationships with companies whose products the researchers are evaluating in the manuscript, except for studies only supported by free drugs and equipment.*

† *The International Council of Medical Journal Editors (ICMJE) COI criteria: financial relationships specifically cited as the most severe examples of conflict of interest which include: consultancy, employment, stock ownership, patent licensing, and honoraria. These criteria exclude financial relationships based on grants, general/unspecified funding, awards, fellowships, free drugs/equipment, and authors serving as speakers or on the advisory board.*

‡ *Author-defined criteria: 1a) One or more authors have financial associations with a private corporation in the form of grants, unspecified funding, consultancy, employment, stock ownership, or honoraria, and/or b) has a personal financial interest in the study because of a patent license in which an author is eligible to receive royalties or from personal business ventures. Free drugs and equipment, awards, fellowships, and serving on advisory boards or as speakers do not constitute COI in this definition. 2) Drug/treatment/product reviewed by the author/s is manufactured by the funding corporation, or is in the same retail class[11] as a drug manufactured by a sponsoring competitor. 3) Product/s reviewed by author/s must have current or near future commercial potential (i.e., sold for profit). 4) Findings support commercial product, negate competitor's product, advocate cost benefit, and/or show product has a potential commercial value (demand, size, and growth). NEJM, New England Journal of Medicine; JAMA, Journal of the American Medical Association.*

DISCUSSION

Conflicts of Interest

Private corporations funded approximately 1 out of every 3 original manuscripts published in the largest 2 general medicine journals in the United States. Depending on the COI criterion, prevalence of COI by 1 or more authors varies between 19.4% and 29.2% of all original manuscripts published in both journals combined.

When in 1999 NEJM reported 19 drug review articles with apparent COI, they hoped to reduce the number the following year.[12] NEJM editors have contended that past failures to contain conflict of interest have been the result of "poor communication and coordination" among its editorial staff.[12] Recent easing of NEJM's COI rules for editorial and review articles may reflect the growing difficulty in finding articles from authors without ties to private industry.

NEJM cites the view[13] that conflict of interest is a condition, not a behavior, in which the circumstances and not the outcome determine the presence of COI. Our data suggest that the condition is pervasive. Furthermore, based on the ICMJE criterion, authors with COI were 10 to 20 times less likely to present negative findings than those without COI. The relationship was strongest among studies investigating drug treatments.

Based on a review of the literature, our study is the first to report an association between financial associations and reported findings using COI criterion. Past studies have focused on direct funding, which neglects other important forms of personal financial associations and interests which are addressed in a COI criterion such as consultancy, employment, stock ownership, patent licensing, and honoraria. In addition, our study shows that the relationship between funding and reported findings persists when including nonpharmaceutical companies in the analysis. While past studies have focused on positive findings, this study also addresses the likelihood of publishing negative findings among authors with COI.

We attempt to integrate commercial aspects of the product evaluated in our COI criterion. Because one of the criteria is that the main findings support the study product, our definition for COI should isolate only studies with positive or mixed findings. In the one case in which the findings were negative, the primary conclusion of the authors from both the abstract and discussion state that the negative effects of the study drug may be the result of

Table 3. Reported Study Outcomes Among Original Manuscripts by Conflict of Interest Criteria, and Study Focus The New England Journal of Medicine and The Journal of the American Medical Association (2001)

	All	Positive *n* (%),*	Mixed *n* (%),†	Negative *n* (%),‡	Other *n* (%),§	*P* Value″
Author-Defined Criterion¶						
Drug treatment studies with COI	60	51 (85.0)	7 (1.7)	1 (1.7)	1 (1.7)	
Drug treatment studies without COI	59	24 (40.7)	9 (15.3)	21 (35.6)	5 (8.5)	< .001
All treatment studies with COI	73	61 (83.6)	10 (13.7)	1 (1.4)	1 (1.4)	
All treatment studies without COI	101	53 (52.5)	14 (13.9)	28 (27.7)	6 (5.9)	< .001
ICMJE Criterion#						
Drug treatment studies with COI	46	36 (78.3)	9 (19.6)	1 (2.2)	0 (0.0)	
Drug treatment studies without COI	73	39 (53.4)	7 (9.6)	21 (28.8)	6 (8.2)	< .001
All treatment studies with COI	57	45 (78.9)	10 (17.5)	2 (3.5)	0 (0.0)	
All treatment studies without COI	117	69 (59.0)	14 (12.0)	27 (23.1)	7 (6.0)	< .01

* *Positive results: include studies that show a clinical benefit from a treatment or no/absence of suspected side effects, or support their product by observing problems in competitive product.*

† *Mixed results: include studies noting both clinical benefits from a treatment and presence of significant side effects.*

‡ *Negative results: include studies that do not show a clinical benefit and/or numerous side effects and/or serious side effects.*

§ *Other results: include studies that are observational or cross-sectional emphasizing frequency and distribution rather than comparison between groups; trends in medical service and product usage; drug discontinuation protocol; and studies whose significance is yet unclear because it is preliminary or pilot study.*

″ *P value derived from the* χ^2 *test for contingency tables* $x^2 = SUM[(Obs - Exp)^2/(Exp)]$.

¶ *The International Council of Medical Journal Editors (ICMJE) COI criteria: financial relationships specifically cited as the most severe examples of conflict of interest which include: consultancy, employment, stock ownership, patent licensing, and honoraria. These criteria exclude financial relationships based on grants, general/unspecified funding, awards, fellowships, free drugs/equipment, and authors serving as speakers or on the advisory board.*

Author-defined criteria: 1a) One or more authors have financial associations with a private corporation in the form of grants, unspecified funding, consultancy, employment, stock ownership, or honoraria, and/or b) has a personal financial interest in the study because of a patent license in which an author is eligible to receive royalties or from personal business ventures. Free drugs and equipment, awards, fellowships, and serving on advisory boards or as speakers do not constitute COI in this definition. 2) Drug/treatment/product reviewed by the author/s is manufactured by the funding corporation, or is in the same retail class as a drug manufactured by a sponsoring competitor. 3) Product/s reviewed by author/s must have current or near future commercial potential (i.e., sold for profit). 4) Findings support commercial product, negate competitor's product, advocate cost benefit, and/or show product has a potential commercial value (demand, size, and growth).

an operational bias. We felt that the manner in which the findings were presented to a degree support the product. Despite the bias that may arise from the use of our criterion, the direction of the results based on our definition are replicated when using the ICMJE definition.

Because of the limitations of our data, we are unable to determine the reasons for the observed association between COI and reported findings. One could surmise that drug companies are selective and only want to invest in treatments proven to produce positive results and that early clinical trials filter out the most promising treatments, which could explain the small number of studies funded by private corporations presenting negative findings. But we find 21 studies without corporate funding reporting negative findings regarding on-the-market drugs compared to only 1 study funded directly or indirectly by corporations (Table 3). Furthermore, the concern that Phase I clinical trials will bias results toward positive findings may not be valid. Because Phase I trials focus on the drug's pharmacokinetics and maximum tolerated dose in a small sample of healthy individuals, it is unlikely that subclinical and rare side effects would be revealed at this phase of investigation, particularly side effects more likely to develop in sick individuals.

The question arises as to whether an investigator with a conflict of interest may be more inclined to present findings in order to gain favor with the sponsor or achieve any other extraneous objective—e.g., to "spin." The issue of spinning findings goes beyond the lower likelihood to criticize the safety or efficacy of a treatment[1,14] or the withholding of data on adverse reactions.[15]

It appears that some companies selectively sponsor projects in which their drug is not evaluated but the findings are likely to support their commercial interests. We noted 5 studies in which the researchers focus on the shortcomings of a competitor's product or observe side effects resulting from the use of a widely prescribed therapy which can be treated by the sponsor's product. None of these studies mention the sponsor's drug in the analysis. Most COI policies fail to address these types of studies. These studies may be a good example of exploiting market pressures as a means of doing quality control on drugs, even though the motivations for funding such studies probably reflect commercial interests rather than therapeutic concerns.

The observation that negative findings are less commonly reported among studies funded by private corporations raises troublesome ethical questions. Researchers appear to be failing to promote both the benefits and negative side effects of commercial products they review or simply failing to submit negative studies for publication because they are viewed as uninteresting.[16] On the other

hand, editors are not proactively examining the possibility of bias from author relationships with private corporations.[17]

Furthermore, there is no system to effectively regulate and oversee researchers and journals. The current federal financial disclosure regulations do not require institutions to comprehensively collect, review, and disclose information on all significant financial interests in research irrespective of the source.[18]

At the academic level, it is unclear whether COI review committees,[18] as proposed by the Association of American Medical Colleges, would be effective in managing COI since they lack the ability to mandate the formation of review bodies and enforcement of disciplinary measures. In addition, the independence of academic bodies themselves is questionable considering academic faculties in the United States receive approximately $1.5 billion annually in research money from private industry.[19] This is a possible explanation for academe's strong resistance to external government regulation of their funding.[20]

Further research is required which clearly defines the parameters of COI (criterion, prevalence, strength of bias). In addition, greater detail is necessary about the types of remuneration received by authors in order to evaluate whether $10,000 is an appropriate federally defined cutoff for mandatory disclosure of significant financial relationships related to sponsored research and should consider other nonfinancial types of gratuity currently ignored.

CONCLUSION

Private health care companies heavily invest in "independent" researchers. Those researchers with COI are more likely to present positive findings. Pharmaceutical companies spent approximately $23 billion on clinical research in 2001 as compared with $18 billion from the National Institute of Health.[21] Physicians often begin receiving pharmaceutical gifts and remuneration as early as the first year of medical school.[22] These investments establish long-term relationships with the "middle-man" (i.e., clinical researchers) in order to have access to study populations[23] and capitalize upon the notion of consensual validity these "objective" independent researchers have among consumers.

Though remuneration does not necessarily result in unethical behavior, it can be a strong catalyst for it.[18] The need for independent researchers has long been understood, yet a large proportion of research continues to be conducted by those with COI. Today's system of oversight appears to be ineffective in monitoring COI among researchers. External regulation of data integrity and financial associations should be discussed as an avenue to monitor COI.

REFERENCES

1. Rochon PA, Gurwitz JH, Simms RW, et al. A study of manufacturer-supported trials of nonsteroidal anti-inflammatory drugs in the treatment of arthritis. Arch Intern Med. 1994;154:157–63.
2. Davidson RA. Source of funding and outcome of clinical trials. J Gen Intern Med. 1986;1:155–8.
3. Yaphe J, Edman R, Knishkowy B, Herman J. The association between funding by commercial interests and study outcome in randomized controlled drug trials. Fam Pract. 2001;18:565–8.
4. Friedberg M, Saffran B, Stinson TJ, Nelson W, Bennet CL. Evaluation of conflict of interest in economic analyses of new drugs in oncology. JAMA. 1999;282:1453–7.
5. Clifford TJ, Barrowman NJ, Moher D. Funding source, trial outcome and reporting quality: are they related? Results of a pilot study. BMC Health Serv Res. 2002;2:18.
6. ISI Journal Citation Report 2000. Available at: http://www.isinet.com/isi/. Accessed February 5, 2002.
7. N Engl J Med. 2001:344–345:1–1978 and 1–1882.
8. J Am Med Assoc. 2001;285–286:1–3129 and 1–3119.
9. Abramson JH. Survey Methods in Community Medicine, 4th edn. Churchill Livingstone;1990:ch. 2.
10. International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals. Updated October 2001.
11. Drug Monitor, IMS Health Global Services. 2002. Available at: http://www.imshealth.com. Accessed July 17, 2002.
12. Holden C. NEJM admits breaking its own tough rules. Science. 2000;287:1573.
13. Thompson DF. Understanding financial conflicts of interest. NEJM. 1993;329:573–6.
14. Stelfox HT, Chua G, O'Rourke K, Detsky A. Conflict of interest in the debate over calcium-channel antagonists. NEJM. 1998;338:101–6.
15. Kahn JO, Cherng DW, Mayer K, Murray H, Lagakos S. Evaluation of HIV-1 Immunogen, an immunologic modifier, administered to patients infected with HIV having 300–549, $X10^6$/L CD4 counts: a randomized controlled trial. JAMA 2000;284:2193–202.
16. Dickersin K, Min Y, Meinert CL. Factors influencing publication of research results. JAMA. 1992;267:374–8.
17. Schulman K, Sulmasy DP, Roney D. Ethics, economics and the publication policies of major medical journals. JAMA. 1994;272:154–6.
18. Task Force on Financial Conflicts of Interest in Clinical Research. Protecting Subjects, Preserving Trust, Promoting Progress—Policy and Guidelines for the Oversight of Individual Financial Interests in Human Subjects Research. Association of American Medical Colleges; 2001.
19. Boyd EA, Bero LA. Assessing faculty financial relationships with industry. JAMA. 2000;284:2209–14.
20. Korn D. Conflicts of interest in biomedical research. JAMA. 2000;285:2234–6.
21. Temptation to fudge scientific findings. The Virginian-Pilot and The Ledger-Star, Norfolk, Va. November 12, 2000.
22. Deangelis CD. Conflict of interest and the public trust. JAMA. 2000;284:2237–8.
23. Friedman Ross L. Correspondence to editor in reply to "Is Academic Medicine for Sale?" NEJM. 2000;342:508.

EXHIBIT 312

CAPITOL ALERT

Capitol Alert

Drug companies donated millions to California lawmakers before vaccine debate

By Jim Miller

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JUNE 18, 2015 03:27 PM , UPDATED MAY 28, 2019 07:32 PM

Hundreds of parents and their children protested against a mandatory vaccine bill at the Capitol on May 15, 2015. BY ALEXEI KOSEFF

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A subplot to the vociferous debate over the student vaccination bill moving through California's Capitol is opponents' allegations that the effort reflects the influence of the pharmaceutical industry.

Critics of Senate Bill 277, which would eliminate the personal belief and religious exemptions for schoolchildren, accuse the measure's supporters in the Legislature of

doing the bidding of donors who make vaccines and other pharmaceuticals.

The bill's proponents and drug companies dismiss the charge. The companies' lobbyist filings for the first quarter of this year as well as legislative committee reports show no connection between the pharmaceutical industry and SB 277.

"We aren't pushing this bill behind the scenes," said Priscilla VanderVeer, the senior director for communications for the Pharmaceutical Research and Manufacturers of America, known as PhRMA, the industry's main trade group. The group has no taken no position on SB 277, although the group has long backed vaccinations as sound public health policy, she said.

Other legislation has a more direct bearing on the industry, and it is an active political player. Pharmaceutical companies and their trade groups gave more than $2 million to current members of the Legislature in 2013-2014, about 2 percent of the total raised, records show. Nine of the top 20 recipients are either legislative leaders or serve on either the Assembly or Senate health committees. Receiving more than $95,000, the top recipient of industry campaign cash is Sen. Richard Pan, a Sacramento Democrat and doctor who is carrying the vaccine bill.

In addition, the industry donated more than $500,000 to outside campaign spending groups that helped elect some current members last year.

Leading pharmaceutical companies also spent nearly $3 million more during the 2013-2014 legislative session lobbying the Legislature, the governor, the state pharmacists' board and other agencies, according to state filings.

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Top drug maker donors

State records show that pharmaceutical companies and trade groups donated more than $2 million to current lawmakers in 2013-2014.

Pharmaceutical company or group	**Campaign donations to current state legislators**	**Direct lobbying payments**
Johnson & Johnson Inc.	$86,300	$583,926
GlaxoSmithKline	$32,250	$561,479
Eli Lilly & Company	$193,100	$280,863
Gilead Sciences Inc.	$77,600	$196,732
Biocom PAC	$30,000	$223,224
Sanofi	$48,000	$172,500
Abbott Laboratories	$173,600	$42,500
Astellas Pharma US Inc.	$47,900	$161,440
AstraZeneca Pharmaceuticals LLP	$157,300	$49,583
Merck & Co. Inc.	$91,600	$108,204
California Pharmacists Association	$53,389	$134,176
Pharmaceutical Research & Manufacturers Assn.	$137,950	$45,455
Eisai Inc.	$92,000	$88,000

Bristol-Myers Squibb Company	$32,300	$144,101
Pfizer	$150,600	$21,250
AbbVie	$138,425	$25,530
Amgen	$105,600	$45,455
Allergan USA Inc.	$120,100	$22,757
Takeda Pharmaceuticals USA Inc.	$40,000	$83,348
Pharmacy Professionals of California	$32,000	$0

Top drug maker recipients

Lawmaker	**Party/District**	**Amount**
Sen. Richard Pan*	D-Sacramento	$95,150
Assembly Speaker Toni Atkins	D-San Diego	$90,250
Sen. Ed Hernandez*	D-Azusa	$67,750
Sen. Holly Mitchell*	D-Los Angeles	$60,107
Assemblyman Brian Maienschein*	R-San Diego	$59,879
Senate President Pro Tem Kevin de León	D-Los Angeles	$56,648
Sen. Isadore Hall	D-Compton	$52,400
Sen. Jerry Hill	D-San Mateo	$50,209
Assemblyman Henry Perea	D-Fresno	$49,550

Assemblywoman Shirley Weber	D-San Diego	$47,000
Assemblyman Mike Gatto	D-Los Angeles	$46,491
Assemblywoman Susan A. Bonilla*	D-Concord	$45,600
Sen. Andy Vidak	R-Hanford	$42,800
Assemblyman Tom Daly	D-Anaheim	$40,300
Assemblyman Kevin Mullin	D-South San Francisco	$38,400
Assemblyman Adam Gray	D-Merced	$37,000
Assemblyman Rob Bonta*	D-Alameda	$36,750
Assemblyman Anthony Rendon	D-Lakewood	$36,200
Assemblyman Jimmy Gomez*	D-Los Angeles	$33,850
Assemblyman Richard Gordon	D-Menlo Park	$33,100

*Member of the Assembly or Senate health committees

Source: Bee analysis of secretary of state campaign finance and lobbying reports

RELATED STORIES FROM SACRAMENTO BEE

EXHIBIT 313

Fiscal Year 2017

Budget in Brief

Strengthening Health and Opportunity for All Americans

U.S. Department of Health & Human Services

HHS.GOV

Centers for Disease Control and Prevention

dollars in millions	2015 /1	2016	2017	2017 +/- 2016
Immunization and Respiratory Disease	798	798	748	-50
Prevention and Public Health Fund (non-add)	*210*	*324*	*336*	*+12*
Balances from P.L. 111-32 Pandemic Flu (non-add)	*15*	*15*	--	*-15*
Vaccines For Children	3,851	4,161	4,387	+226
HIV/AIDS, Viral Hepatitis, STIs and TB Prevention	1,118	1,122	1,128	+5
Emerging and Zoonotic Infectious Diseases	405	580	629	+50
Prevention and Public Health Fund (non-add)	*52*	*52*	*52*	--
Chronic Disease Prevention and Health Promotion	1,199	1,177	1,117	-60
Prevention and Public Health Fund (non-add)	*452*	*339*	*437*	*+98*
Birth Defects, Developmental Disabilities, Disability and Health	132	136	136	--
Prevention and Public Health Fund (non-add)	--	--	*68*	*+68*
Environmental Health	179	182	182	--
Prevention and Public Health Fund (non-add)	*13*	*17*	*14*	*-3*
Injury Prevention and Control	170	236	299	+63
Mental Health Mandatory Funding (non-add)	--	--	30	+30
Public Health Scientific Services	481	492	501	+9
Prevention and Public Health Fund (non-add)	--	--	*36*	*+36*
Occupational Safety & Health	335	339	286	-54
PHS Evaluation Funds (non-add)	--	--	*72*	*+72*
World Trade Center Health Program /2	261	300	335	+36
Energy Employee Occupational Illness Compensation Program	50	55	55	--
Global Health	446	427	442	+15
Public Health Preparedness and Response	1,353	1,405	1,402	-3
Buildings and Facilities	10	10	31	+21
CDC-Wide Activities and Program Support	274	274	114	-160
Prevention and Public Health Fund (non-add)	*160*	*160*	--	*-160*
Agency for Toxic Substances and Disease Registry (ATSDR)	75	75	75	--
ATSDR ACA Mandatory Funds /3	*19*	--	--	--
CORD MACRA Mandatory Funds /4	--	10	--	--
User Fees	2	2	2	--
Subtotal, Program Level	**11,158**	**11,781**	**11,868**	**+87**

Centers for Disease Control and Prevention

dollars in millions	2015	2016	2017	2017 +/- 2016
CDC Budget Totals – Less Funds from Other Sources				
Vaccines for Children	-3,851	-4,161	-4,387	-226
Energy Employee Occupational Injury Compensation Program	-50	-55	-55	--
Mental Health Mandatory Funding	--	--	-30	-30
World Trade Center Health Program /2	-261	-300	-335	-36
ATSDR ACA Mandatory Funds /3	19	--	--	--
PHS Evaluation Funds	--	--	-72	+72
CORD MACRA Mandatory Funds /4	--	-10	--	--
Prevention and Public Health Fund	-887	-892	-944	-52
User Fees	-2	-2	-2	--
Balances from P.L. 111-32 Pandemic Flu	-15	-15	--	+15
Total, Discretionary Budget Authority	**6,073**	**6,345**	**6,042**	**-303**
Full-Time Equivalents	11,129	11,151	11,151	--

1/ In addition, the FY 2015 appropriation (P.L. 113-235) provided $1.8 billion in emergency resources for Ebola response and preparedness activities.
2/ Federal share resources. This number does not reflect estimated carryover from FY 2016 that is available under reauthorization. Total WTCHP obligations in FY 2017 will be determined upon final review of the FY 2017 spend plan.
3/ Funds are available through FY 2020.
4/ Funds are available through FY 2017.

The Center for Disease Control and Prevention works 24/7 to protect America from health, safety and security threats, both foreign and domestic. Whether diseases start at home or abroad, are chronic or acute, curable or preventable, human error or deliberate attack, CDC fights disease and protects Americans.

The Centers for Disease Control and Prevention (CDC) is the nation's health protection agency, working to protect Americans from health and safety threats, both foreign and domestic. In addition, CDC's mission promotes quality of life and prevention of leading causes of disease, injury, disability, and death. These objectives are supported by programs that provide Americans with the essential health information and tools they need to make informed decisions, and protect and advance their health. CDC's highly trained staff provides critical national leadership that works around the world to save lives through proven prevention strategies, disease detection, and response to public health emergencies.

CDC scientists collect and analyze health data, determining how health threats affect specific populations. This has resulted in effective interventions that protect people from scores of public health threats each year. In the past two years, CDC has conducted more than 750 field investigations in 49 states, five United States territories, and in at least 35 different countries. This reach is vital to ensure CDC can determine the cause of illness and probability of additional exposure in order to facilitate proper communication and response.

The FY 2017 Budget request for CDC and the Agency for Toxic Substances and Disease Registry (ATSDR) is $11.9 billion, an increase of $87 million relative to FY 2016. This total includes $944 million from the Prevention and Public Health Fund (Prevention Fund). The Budget request advances CDC's core mission work by prioritizing efforts to combat antibiotic-resistant bacteria; address the outbreak of opioids misuse, abuse, and overdose; support the improvement of

health outcomes for American Indians and Alaskan Natives; support global health protection; and advance laboratory safety and quality. In addition, the Budget includes targeted reductions based on the increased availability of preventive services as a result of the Affordable Care Act.

IMMUNIZATION AND RESPIRATORY DISEASES

The mission of CDC's National Center for Immunization and Respiratory Diseases is to prevent disease, disability, and death through immunization and by control of respiratory and related diseases. In execution of this mission, CDC focuses on the specific needs of all populations at risk of vaccine-preventable diseases, from children to older adults.

CDC's vaccination efforts are supported by the discretionary Immunization program, and the mandatory Vaccines for Children program. These programs together help improve access to immunization services to uninsured or underinsured individuals in the United States.

The FY 2017 Budget includes $748 million for the discretionary programs supported within CDC's National Center for Immunization and Respiratory Diseases, a decrease of $50 million below FY 2016. The reduction reflects increased insurance coverage for immunization services through expansion of public and private health insurance included in the Affordable Care Act. This funding will continue to support the key activities necessary to achieve national immunization goals, sustain high vaccination coverage rates, and ultimately prevent death and disability from vaccine-preventable diseases. This funding will also continue to support influenza planning and response activities, focusing on: increased demand with healthcare providers for influenza vaccination each season through investments in health communication with providers and the general public; targeted outreach to high-risk populations; and partnerships with pharmacists as a means to extend the reach of influenza vaccinations. A study published in March 2015 indicated that seasonal influenza vaccine prevented more than 40,000 flu-associated deaths in the United States between 2005 and 2014.

HIV/AIDS, VIRAL HEPATITIS, SEXUALLY TRANSMITTED INFECTIONS AND TUBERCULOSIS PREVENTION

The Budget includes $1.1 billion for domestic HIV/AIDS, viral hepatitis, sexually transmitted infections, and tuberculosis prevention, an increase of $5 million over FY 2016. CDC will continue to align activities with *The National HIV/AIDS Strategy: Updated to 2020* through promotion of effective, scalable, and sustainable prevention strategies for individuals living with HIV, in addition to populations at the highest risk for HIV.

The Budget includes $20 million in additional funding for a new demonstration to support increased access to Pre-Exposure Prophylaxis (PrEP) for high-risk populations. PrEP has been shown to reduce the risk of HIV infection by greater than 90 percent when taken as prescribed. The demonstration proposed in the Budget will support expanded access to PrEP, building on pilot efforts to increase use of PrEP for unprotected high-risk individuals, potentially preventing a substantial number of new infections. This demonstration project will allow health departments to use up to 30 percent of these available funds to pay for PrEP medications as the payor of last resort.

The Budget includes a $5 million increase to stop transmission of the virus and prevent viral hepatitis-related illness, disability, and death. CDC's activities support effective vaccination and testing strategies, in addition to detection efforts to identify and treat outbreaks. These activities are critical given the rising infections and mortality associated with the estimated 3 million Americans living with hepatitis C. These efforts and others, align with the priorities outlined in the *HHS Action Plan for the Prevention, Care, and Treatment of Viral Hepatitis.*

To further improve efficiency and impact of prevention efforts, CDC initiated epidemic and economic modeling projects, which were developed in collaboration with University-based researchers. These projects inform planning and implementation of interventions targeting HIV, viral hepatitis, sexually transmitted infections, tuberculosis, and school health. These models will continue to provide critical information on the potential costs, benefits, and return on investment of specific intervention strategies that can have population-level impact.

EMERGING AND ZOONOTIC INFECTIOUS DISEASES

The Budget includes $629 million to support CDC's National Center for Emerging and Zoonotic Infectious Diseases, an increase of $50 million over FY 2016. This funding facilitates work to reduce illness and death associated with emerging and zoonotic infectious diseases and to protect against the intentional and unintentional spread of infectious diseases. CDC addresses not only rare, deadly diseases like anthrax and Ebola, but also foodborne diseases, mosquito-borne diseases such as Zika and Chikungunya, water safety issues, healthcare-associated infections, migration and quarantine issues, and the identification and control of diseases transmitted by animals and insects. CDC is staffed by some of the world's top disease detectives -- highly-trained doctors and scientists who investigate and respond to disease and other public health threats. CDC's disease experts contributed to the fight against smallpox, which resulted in eradication, in addition to the discovery of Legionnaire's disease, and work to stop the recent Ebola outbreak in West Africa.

The Budget includes $200 million, an increase of $40 million, to support CDC's Antibiotic Resistance Initiative, along with core antibiotic resistance investments of $18 million, for a total CDC investment in FY 2017 of $218 million to implement the *National Action Plan for Combating Antibiotic-Resistant Bacteria*. The Budget supports implementation of CDC's surveillance, prevention, and stewardship activities outlined in the *National Action Plan* to continue pushing forward to reach the ambitious prevention goals.

PUBLIC HEALTH SCIENTIFIC SERVICES

As a pioneer in collecting and using health data, CDC tracks the health of populations and provides timely data used to respond to urgent health issues. This vital information forms the basis of policymaking, biomedical and health services research, lab safety, and improved access to healthcare for everyone. In addition, CDC advises and supports safe, state-of-the-art laboratories across the United States, as a key line of defense against health threats.

The FY 2017 Budget includes $501 million to support these activities, a $9 million increase above FY 2016. CDC has significant impact through the development of multistate testing methods, data systems that collaborate together, and advanced management methods for domestic disease-detecting laboratories. CDC has also developed Epi INFO™, a software network that helps to rapidly identify diseases outbreaks, used by public health professionals in more than 35 countries.

PROGRAM HIGHLIGHT

Combating Antibiotic-Resistant Bacteria

Antibiotics and similar antimicrobial agents have been used for the last 70 years to treat patients who have infectious diseases. Since the 1940s, these drugs have greatly reduced illness and death. However, these drugs have been used so widely for so long that the infectious organisms the antibiotics are designed to kill have adapted to them, making the drugs less effective.

Each year in the United States, at least two million people become infected with bacteria that are resistant to antibiotics and at least 23,000 die each year as a direct result of these infections. More and more bacteria are becoming resistant to the antibiotics currently in use, which is why aggressive action is needed to prevent new resistance from developing and halt the existing resistance from spreading.

The Budget includes $200 million, an increase of $40 million, to support CDC's Antibiotic Resistance Initiative, along with core antibiotic resistance investments of $18 million, for a total CDC investment in FY 2017 of $218 million to implement the CARB Strategy. This funding will serve to implement the *National Action Plan for Combating Antibiotic-Resistant Bacteria* through activities to reduce the emergence and spread of antibiotic-resistant pathogens, protect patients and communities. CDC predicts that the implementation of measures aimed to prevent infections and improve prescribing practices could save up to 37,000 lives from drug-resistant infections over five years.

The FY 2017 Budget includes an increase of $5 million to continue support for CDC's implementation of laboratory safety recommendations, for a total of $38 million across CDC. This funding will enable CDC to maintain its ability to respond to outbreaks, determine unexplained illnesses, support state and local diagnostics, improve pathogen identification of emerging and re-emerging diseases and maintain the world's most advanced, state-of-the-art infectious disease and environmental public health laboratories.

CHRONIC DISEASE PREVENTION AND HEALTH PROMOTION

Chronic diseases are the leading cause of poor health, disability, and death in the United States. More than half of all adults have at least one chronic disease and seven of ten deaths each year are caused by chronic diseases. The medical costs associated with chronic diseases, including mental health and substance abuse, account for 86 percent of the nation's total health care costs, estimated at $2.9 trillion annually. While chronic diseases affect all populations, incidence and prevalence is not evenly distributed. Disease rates vary based on race, ethnicity, education, and income level, with the most disadvantaged Americans most often suffering the highest burden of diseases.

The FY 2017 Budget includes $1.1 billion for chronic disease prevention and health promotion activities, $60 million below FY 2016. This funding will provide critical support to combating the most significant chronic disease issues facing Americans, including tobacco use, heart disease, stroke, diabetes, and cancer.

The FY 2017 Budget includes $30 million for the Racial and Ethnic Approaches to Community Health, which will award a new cooperative agreement incorporating best practices from prior community grant programs, resulting in a stronger, more robust program. Approaches will focus on improving poor nutrition, lack of physical activity, tobacco use, and limited access to clinical and community services by increasing access to healthier environments and quality preventive services. This program will also translate and disseminate grantees' best practices that have demonstrated cost savings and improvement across health outcomes, magnifying the program's impact.

The Budget proposes targeted reductions for direct cancer screening services, due to increased coverage through the Affordable Care Act. In FY 2017 and beyond, CDC's programs will continue to realize cost savings through the benefits provided by Affordable Care Act.

BIRTH DEFECTS AND DEVELOPMENTAL DISABILITIES

CDC's National Center on Birth Defects and Developmental Disabilities focuses on protecting people who are especially vulnerable to health risks – babies, children, people with blood disorders, and people with disabilities. The FY 2017 Budget includes $136 million to support this center's activities, the same as FY 2016.

Birth defects affect one in 33 babies and are a leading cause of infant mortality in the United States. More than 5,500 infants die each year because of birth defects, which is twice as many as from sudden infant death syndrome. In addition, babies who survive and live with birth defects are at increased risk for developing many lifelong physical, cognitive, and social challenges.

PROGRAM HIGHLIGHT

Good Health and Wellness in Indian Country

American Indians and Alaskan Natives bear a disproportionate burden of death, disease, disability, and injury compared to other racial and ethnic groups in the United States. For example, this population has a higher prevalence of obesity – nearly 10 percent more – than their white counterparts.

There has also been increasing concern over the persistently high rates of suicide, particularly amongst the youth in this population. In 2013, the age-adjusted suicide rate for American Indians and Alaskan Natives was 18.3 per 100,000, compared to 13.8 for the overall population. These and other health issues are driven by higher rates of poverty, unemployment, and low educational achievement, which are linked to key risk behaviors, such as alcohol and tobacco use.

The FY 2017 Budget includes $15 million in additional funding for CDC to expand its existing Comprehensive Approach to Good Health and Wellness in Indian Country grant program. Through the current program, CDC works collaboratively with Tribes, tribal organizations, and Tribal Epidemiology Centers to prevent heart disease, diabetes, stroke, and associated risk factors, such as commercial tobacco. With the additional funding, CDC will build upon its existing program to more comprehensively address these chronic conditions, in addition to expanding to address other pressing health issues facing this population, including suicide, prescription drug overdose, and alcohol-related motor vehicle injuries.

CDC works to identify causes of birth defects, find opportunities to prevent them, and improve the health of those living with birth defects. This is accomplished through CDC's implementation of three distinct activities – surveillance or disease tracking, research to identify causes, and prevention research and programs. These key activities allow CDC to rapidly translate

scientific findings into appropriate public health interventions to aid in prevention.

Developmental disabilities, including autism spectrum disorder and cerebral palsy, are impairments in physical, learning, language, or behavioral areas. CDC works to uncover the risk factors for autism and other developmental disabilities to inform prevention programs. The key to successful interventions are CDC's efforts to detect existing developmental delays and intervene early. CDC will continue to support competitive autism awards to states and universities to enhance surveillance and research for autism and other developmental disabilities, monitor prevalence and contributing risk factors, and better inform policies and programs for prevention and services. This tracking and research infrastructure is key to better understanding autism and other developmental disabilities.

The Budget will continue to support activities that improve the health outcomes for individuals with blood disorders, including hemophilia, venous thromboembolism, thalassemia, and sickle cell disease. CDC works to capitalize on opportunities to improve the quality of life for individuals with blood disorders by reducing healthcare costs, improving healthcare utilization, maximizing the impact of proven prevention strategies, and ensuring the safety of America's blood supply.

ENVIRONMENTAL HEALTH

The World Health Organization estimates that 13 percent of the overall disease burden in the United States is due to environmental factors. Specific threats posed by the environment include contamination of drinking water, dangerous retail food practices, rising sea levels, extreme heat and drought, infectious disease, and radiation emergencies.

CDC's National Center for Environmental Health works to prevent illness, disability, and death from interactions between people and the environment. Specifically, this includes supporting research to investigate the effects of the environment on health, monitoring and evaluating environmentally-related health problems through surveillance, and collaborating with international and domestic partners to prepare for and respond to natural, technologic, humanitarian, and terrorism-related environmental emergencies.

This mission will continue to be supported by the FY 2017 Budget, which includes $182 million for these activities, the same as FY 2016. This funding includes $10 million to support a new hearing loss prevention, awareness, and education program that targets young to older adults, low to moderate hearing loss, and social stigma.

PROGRAM HIGHLIGHT

Prescription Drug Overdose

More people died from drug overdoses in the United States in 2014 than during any previous year on record. From 2000 to 2014 nearly half a million people in the United States died from drug overdoses. In 2014, there were approximately one and a half times more drug overdose deaths in the United States than deaths from motor vehicle crashes.

Overdose deaths are only part of the problem – for each death involving prescription opioids, hundreds of people abuse or misuse these drugs. Emergency department visits for prescription painkiller abuse or misuse have doubled in the past few years to nearly half a million. Prescription opioid-related overdoses cost an estimated $20 billion in medical and work-loss costs each year. Stemming this epidemic is essential to CDC's goal of preventing the leading cause of disease, disability, and death.

CDC plays an important role in understanding and addressing the causes of the epidemic and has found that higher prescribing of opioid pain relievers is associated with more overdose deaths. In FY 2017, the Budget includes $80 million for CDC's efforts to address prescription opioids, which is $10 million over FY 2016.

CDC applies its scientific expertise to help curb the epidemic in three ways: improving data quality and surveillance to monitor and respond to the epidemic; supporting states in their efforts to implement effective solutions and interventions; and equipping healthcare providers with the data and tools needed to improve the safety of their patients. The increase in FY 2017 will specifically support the comprehensive translation and dissemination of CDC's Prescription Drug Overdose guidelines for chronic pain outside end-of-life care. This step is critical to ensure increased uptake in the use of the guidelines amongst providers.

INJURY PREVENTION AND CONTROL

In the United States, violence and injuries cost more than $671 billion a year in medical costs and lost productivity. Almost 193,000 individuals in the United

States die from violence and injuries each year: nearly one person every three seconds. In the first half of life, more Americans die from violence and injuries – such as motor vehicle crashes, falls, or homicides – than from any other cause.

CDC's National Center for Injury Control and Prevention is the nation's leading authority on injury and violence, researching prevention techniques and applying solutions to real-world issues, keeping Americans safe, healthy, and productive. The FY 2017 Budget includes $299 million in budget authority for injury prevention and control activities, an increase of $63 million above FY 2016.

In addition to this amount, $30 million is included in the Budget to support a new suicide prevention program through a partnership with CDC's Injury Control Research Centers, state health departments, and in collaboration with the Substance Abuse and Mental Health Services Administration. This program will focus interventions on reducing key risk factors by increasing referral and treatment for suicide behavior, including substance abuse and mental illness, and addressing access to lethal means by individuals at greatest risk of harming themselves and others.

Injury prevention touches upon a variety of issues, including motor vehicle injury, prescription opioid overdose, child abuse and neglect, older adult falls, sexual violence, youth sports concussions, rape prevention, and gun violence. CDC's work has proven that prevention can save lives. For instance, seat belts have reportedly saved an estimated 63,000 lives between 2008 and 2012. Furthermore, school-based programs for violence prevention have been shown to cut violent behavior 29 percent among high school students.

One of CDC's high priorities in the FY 2017 Budget is support to address prescription drug and illicit opioid overdose and prevention. Drug overdose deaths have skyrocketed in the past decade, largely because of prescription opioids. The FY 2017 Budget includes $86 million in funding to support these efforts, which is an increase of $10 million over FY 2016. This funding aligns with the Department-wide opioid initiative. CDC's efforts will advance the initiative's first priority: to improve opioid prescribing practices and reduce opioid use disorders and overdose.

In 2010, an estimated 2.5 million emergency department visits, hospitalizations, or deaths were associated with a traumatic brain injury in the United States. In FY 2017, CDC will continue its work addressing this problem through surveillance, the identification of effective interventions, and work towards the implementation of strategies to prevent and address these injuries, including concussions. CDC will also continue existing collaborative activities with the Administration for Community Living and other partners to address traumatic brain injuries and prevention associated with older adult falls.

OCCUPATIONAL SAFETY AND HEALTH

CDC's National Institute for Occupational Safety and Health works to protect the nation's 157 million workers through research and applied science, addressing the injuries and illnesses that cost the United States $250 billion annually. This work specifically includes: research aimed to reduce work-related illness and injury; promotion of safe and healthy workplaces through interventions, recommendations, and capacity building; and enhancement of international workplace safety and health through global collaborations. This component of CDC works closely with the United States' Department of Labor Occupational Safety and Health Administration and Mine Safety and Health Administration Research to maximize efforts to protect American workers and miners. The FY 2017 Budget includes $286 million to support these programs, a decrease of $54 million below FY 2016. Reductions reflect the elimination of funding for the Agriculture, Forestry, and Fishing program and the Education and Research Centers, given the relation to CDC's mission and the ability to achieve a national impact in a limited-resource environment.

In addition, the Budget includes $335 million in mandatory funding supported by the World Trade Center Health Program, and $55 million in mandatory funding for the Energy Employees Occupational Illness Compensation Program Act. The World Trade Center Health Program has been extended through FY 2090 under the James Zadroga 9/11 Health and Compensation Reauthorization Act. CDC will continue to provide medical monitoring and treatment for eligible responders and survivors of the terrorist attacks that affected New York City, the Pentagon, and Shanksville, Pennsylvania on September 11, 2001.

PUBLIC HEALTH PREPAREDNESS AND RESPONSE

Health security depends on the ability of our nation to prevent, protect against, mitigate, respond to, and recover from public health threats. CDC's Office of Public Health Preparedness and Response is committed to strengthening the nation's health security by saving lives and protecting against public health threats, whether at home or abroad, natural or man-made. Specifically, CDC supports state, local, tribal, and territorial partners by providing funding, building capacity, offering technical assistance, and championing their critical role in protecting the public health.

The FY 2017 Budget includes $1.4 billion for CDC's preparedness and response activities, which is $3 million below FY 2016.

PROGRAM HIGHLIGHT

Global Health Security Agenda

Launched February 13, 2014, the Global Health Security Agenda (GHSA) brings the United States and partners around the world together to protect populations from pandemic threats, economic loss, instability, and loss of life. CDC is a key implementer of the GHSA because of its technical expertise, existing country platforms, and strong government-to-government relationships.

In the FY 2017 Budget, CDC's global health and other infectious disease funding supports the goals of the GHSA and includes a targeted $5 million increase to support the Phase Two countries. This level is necessary to maintain foundational support needed to continue to prevent, detect, and respond to infectious disease threats and to address on-going epidemics. Epidemic threats to national security arise at unpredictable intervals and from unexpected sources. Because these threats do not recognize national borders, the health of people overseas directly affects America's safety and prosperity, with far-reaching implications for economic security, trade, the stability of foreign governments, and the well-being of United States citizens at home. If we are to save lives and protect U.S. health security, CDC must accelerate efforts to build the systems and workforce needed to better respond to a range of disease threats.

Within CDC's preparedness activities, the Public Health Emergency Preparedness program advances public health system capability development and strengthens public health emergency management and response programs within state, local, and territorial public health agencies, enabling them to respond to public health threats and build resilient communities. To provide ongoing support to these agreements, the Budget includes $660 million, a decrease of $8 million below FY 2016, which reflects elimination of the Advanced Practice Centers. CDC will continue to support research and training for public health preparedness through the public health preparedness and response agenda. The Public Health Emergency Preparedness program closely aligns with and complements ASPR's Hospital Preparedness Program.

Within this funding, CDC will provide increased support to the improvement of informatics and health information technology, focusing largely on electronic death registration, the National Syndrome Surveillance Program, and disease surveillance enhancements.

The Budget includes $575 million for the Strategic National Stockpile, the same as FY 2016. This funding will provide ongoing support to CDC's management, delivery, storage, and replenishment costs to the medical countermeasures included in the stockpile. At this level, CDC will provide for ongoing replenishments, supporting the nation's level of preparedness for a variety of threats.

Within CDC's preparedness activities, the Budget includes an increase of $5 million for the Select Agent Program. In collaboration with the United States Department of Agriculture, this program is responsible for the regulation, possession, use, and transfer of potentially dangerous biological agents and toxins in the United States. The increase for the Federal Select Agent Program will allow for improved training of inspectors, increased frequency and number of inspections, and increased assistance to registered entities to prevent accidental or intentional release of select agents. Additionally, this program supports CDC's laboratory safety and quality initiative through its work in laboratories handling dangerous pathogens and toxins.

GLOBAL HEALTH

The most effective and least expensive way to protect Americans from diseases and other health threats that begin overseas is to stop them before they spread to our shores. CDC detects and controls disease outbreaks at the source, saving lives and reducing healthcare costs. In addition, fighting diseases like HIV/AIDS, malaria, and tuberculosis help reduce poverty and strengthen stability in developing countries.

CDC engages internationally with 1,700 staff in over 60 countries to protect the health of the American people and save lives worldwide. With scientists and health experts embedded in countries around the globe, CDC works with partners to adapt scientific evidence into policies and public health actions, strengthening public health capacity and improving health outcomes in partner countries.

The FY 2017 Budget includes $449 million for CDC global health activities, which is an increase of $15 million above FY 2016. This funding will continue supporting key global health activities including global HIV/AIDs, global tuberculosis, measles and other vaccine-preventable diseases, parasitic diseases and malaria, and ongoing global health protection. This funding level also includes an increase of $5 million to expand efforts supporting polio eradication. In addition, this funding supports efforts to expand global health protection worldwide, and implement the goals of the Global Health Security Agenda, to accelerate progress towards a world safe and secure from infectious disease threats and to promote global health security as an international security priority.

BUILDINGS AND FACILITIES

The FY 2017 Budget includes an increase of $21 million, for a total of $31 million, for CDC's facility repair and improvements. With a significant number of CDC's facilities in a mature phase of the facility life cycle, a rigorous, preventive maintenance program is paramount to ensure facility functionality and preparedness for continued service. Investments in FY 2017 will directly support CDC's ability to support its mission to improve public health.

AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY (ATSDR)

ATSDR serves the public by using the best science, taking responsible public health actions, and providing trusted health information to prevent harmful exposures and diseases related to toxic substances. Specific functions include public health assessments of waste sites, health consultations concerning specific hazardous substances, health surveillance and registries, response to emergency releases of hazardous substances, applied research in support of public health assessments, information development and dissemination, and education and training concerning hazardous substances.

The FY 2017 Budget includes $75 million for ATSDR, which is the same as FY 2016. This funding level will maintain ATSDR's scientific and programmatic capabilities necessary to safeguard human health.

National Institutes of Health

dollars in millions	2015 /1	2016	2017	2017 +/- 2016
Institutes/Centers				
National Cancer Institute	4,953	5,214	5,894	+680
National Heart, Lung and Blood Institute	2,996	3,114	3,114	—
National Institute of Dental and Craniofacial Research	398	413	413	—
National Inst. of Diabetes & Digestive & Kidney Diseases	1,899	1,966	1,966	—
National Institute of Neurological Disorders and Stroke	1,605	1,695	1,695	—
National Institute of Allergy and Infectious Diseases	4,418	4,716	4,716	—
National Institute of General Medical Sciences	2,372	2,512	2,512	—
Eunice K. Shriver Natl. Inst. of Child Health & Human Development	1,287	1,338	1,338	—
National Eye Institute	677	708	708	—
National Institute of Environmental Health Sciences: Labor/HHS Appropriation	667	694	694	—
National Institute of Environmental Health Sciences: Interior Appropriation	77	77	77	—
National Institute on Aging	1,198	1,598	1,598	—
Natl. Inst. of Arthritis & Musculoskeletal & Skin Diseases	522	542	542	—
Natl. Inst. on Deafness and Communication Disorders	405	423	423	—
National Institute of Mental Health	1,434	1,519	1,519	—
National Institute on Drug Abuse	1,016	1,051	1,051	—
National Institute on Alcohol Abuse and Alcoholism	447	467	467	—
National Institute of Nursing Research	141	146	146	—
National Human Genome Research Institute	499	513	513	—
Natl. Institute of Biomedical Imaging and Bioengineering	327	344	344	—
Natl. Institute on Minority Health and Health Disparities	271	281	281	—
Natl. Center for Complementary and Integrative Health	124	130	130	—
National Center for Advancing Translational Sciences	633	685	685	—
Fogarty International Center	68	70	70	—
National Library of Medicine	337	396	396	—
Office of the Director	1,414	1,571	1,716	+145
Buildings and Facilities	129	129	129	—
Total, Program Level	**30,311**	**32,311**	**33,136**	**+825**

dollars in millions	2015	2016	2017	2017 +/- 2016
Less Funds from Other Sources				
PHS Evaluation Funds	-715	-780	-847	-67
Type 1 Diabetes Research (NIDDK) /2	-150	-150	-150	—
Additional Mandatory Funds	—	—	-1,825	-1,825
Total, Discretionary Budget Authority	**29,446**	**31,381**	**30,314**	**-1,067**
Appropriations				
Labor/HHS Appropriation	29,370	31,304	30,237	-1,067
Interior Appropriation	77	77	77	—
Full-Time Equivalents	17,823	18,000	18,000	—

1/ In addition, the FY 2015 appropriation (P.L. 113-235) provided $239 million of emergency resources for Ebola response and preparedness research activities.
2/ These mandatory funds were appropriated in P.L. 114-10, the Medicare Access and CHIP Reauthorization Act of 2015, and P.L. 113-93, the Protecting Access to Medicare Act of 2014.

The mission of the National Institutes of Health is to seek fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to enhance health, lengthen life, and reduce illness and disability.

The National Institutes of Health (NIH) is the nation's medical research agency and leads the world in supporting innovative multidisciplinary biomedical and behavioral research. NIH investments across its 27 Institutes and Centers in basic research support translating scientific discovery into tangible improvements in our health care system. To date, 148 NIH supported researchers have been sole or shared winners of the Nobel Prize.

The FY 2017 Budget includes $33.1 billion, an increase of $825 million over FY 2016, for NIH to accelerate groundbreaking research on cancer, precision medicine, and the human brain, and to maintain the significant investments enacted in FY 2016. The Budget supports the Administration's priority to continue a strong focus in biomedical research that will increase the nation's knowledge base, cultivate a world-class scientific workforce, provide opportunity for new discovery, and promote longer and healthier lives.

In FY 2017, NIH estimates it will support a total of 36,440 research project grants, an increase of 600 above FY 2016, including a total of 9,946 new and competing grants. Of the total, approximately 81 percent of NIH resources will support the research community external to NIH which includes over 30,000 individuals at more than 2,500 organizations comprised of universities, medical schools, research facilities, and hospitals. The remaining 19 percent of resources will be invested within the agency to support clinical and basic research, as well as training to ensure that knowledge among NIH physician and scientists is leading the world.

NIH FY 2017 STRATEGIC RESEARCH PRIORITIES

In late 2015, NIH released an agency-wide research strategic plan for FY 2016 through FY 2020. This plan establishes the research framework for the next five years and describes how NIH will work with public and private sector partners to promote scientific innovation while also continuing to serve as wise stewards of resources to optimize investments for biomedical research. NIH will use this strategic plan to harmonize decisions across the agency while maintaining the visions of individual Institutes, Centers, and program offices. The NIH strategy focuses on four independent objectives:

1. Advance Opportunities in Biomedical Research;
2. Foster Innovation by Setting NIH Priorities;
3. Enhance Scientific Stewardship; and,
4. Excel as a Federal Science Agency by Managing for Results.

In FY 2017, NIH will use this strategic vision to focus on the priorities of generating basic science findings, translating these basic discoveries into improvements in personal and public health, the enhanced use of

comprehensive data sets and technology, and recruiting a diverse, creative, and talented workforce upon which the robust research enterprise depends.

The Foundation for Discoveries: Basic Research

Approximately 52 percent of the NIH research budget is devoted to basic biomedical and behavioral research. Genomics and proteomics have provided insights into how the basic components of life function. Advances in stem cells, imaging, and other technologies have transformed our understanding of how life works.

Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative: In FY 2017, NIH plans to spend $195 million, an increase of $45 million above FY 2016, to continue to address fundamental neuroscience questions and advance understanding of the human brain. In order to accomplish the ambitious goals of this Initiative, NIH will increase its investment to support groundbreaking neuroscience research, neuroimaging, and training initiatives, as well as potential projects to collaborate with industry to test and develop devices for mapping and tuning brain circuitry. Measuring activity at the scale of neural networks in living organisms has the potential to decode sensory experience, memory, emotion, and thought. Furthermore, developing these technologies may help reveal the mechanisms that underlie the pathology in various brain disorders and provide new therapeutic avenues to treat, cure, and prevent neurological and psychiatric conditions.

Translating Discovery into Health

NIH is committed to rapidly turning observations in the laboratory into effective interventions that improve the health of individuals. These new interventions include diagnostics, therapeutics, medical procedures, behavioral changes, and disease prevention strategies.

Antimicrobial Resistance: NIH estimates it will spend $413 million in FY 2017, the same as FY 2016, to respond comprehensively to the growing public health threat of antibiotic resistant bacteria. With antibiotic-resistant infections claiming the lives of 23,000 Americans each year, NIH is continuing to invest in research to support of the Administration's National Strategy to Combat Antibiotic Resistant Bacteria. These funds will accelerate the development of new therapeutics, vaccines, and first-in-class drugs to more effectively treat these "superbugs." To identify the root causes of this problem, NIH conducts basic research on how antimicrobial resistance emerges, spreads, and evolves. NIH is also intensifying studies on rapid diagnostics to help ensure that dangerous strains are quickly identified and appropriately treated; developing a national database of genome sequence data of all reported human antimicrobial-resistant infections; and creating a rapid response clinical trial network to test new antibiotics on individuals infected with resistant strains. NIH-funded researchers recently made a major breakthrough in the fight against antimicrobial resistance by using a new screening technology to discover a new, highly effective antibiotic identified from ordinary topsoil. This promising development is just one piece of NIH's ongoing efforts to fight antibiotic resistance.

Alzheimer's Disease: NIH will spend $910 million on Alzheimer's research in FY 2017, the same as FY 2016. The Budget continues to invest in aggressive efforts to understand and make progress in treating and preventing this disease. Research supported by NIH and other organizations has greatly expanded knowledge and understanding of brain function, risk factors, treatment, and prevention. NIH-supported imaging studies have provided dramatic insights into the disease's causes and progression, and the need to

NEW INITIATIVE

Vice President's Cancer Moonshot

As a part of the cancer "moonshot" announced by the President in the State of the Union Address, the Budget provides an increase of $755 million to accelerate progress in preventing, diagnosing, and treating cancer. The Budget's multi-year cancer initiative, with support beginning in FY 2016 within NIH, provides additional resources to NIH and the Food and Drug Administration in FY 2017, to improve health and outcomes for patients through investments in research and infrastructure, and brings together researchers across sectors and scientific disciplines. Within the $755 million total, the Budget allocates $680 million for NIH and $75 million for FDA.

Given new insights into the causes of cancer and its diagnosis and treatment, this initiative is poised to increase resources to make the most promising breakthroughs available to patients across America. Targeted investments will advance research on new approaches to preventing and treating cancer, such immunotherapy, enhanced early detection technologies, developing vaccines to prevent cancers caused by viruses, genomic analysis of tumor cells, and identifying common treatment opportunities for rare pediatric cancers through better collect and analysis of tumor specimens. This effort will drive progress toward a national effort to make dramatic progress in fight against cancer.

initiate clinical trials at the earliest stages of disease has become increasingly clear. While much more remains to be discovered, recent research has led to more than 90 drugs in clinical trials for Alzheimer's disease with many more in the pipeline awaiting regulatory approval to enter human testing. In addition, the Accelerating Medicines Partnership, a NIH-led public-private partnership to transform and accelerate drug development, recently launched a new Alzheimer's Big Data portal to catalyze new analyses and pharmaceutical discovery projects. These investments will contribute to meeting the goal to prevent and effectively treat Alzheimer's disease by 2025, in support of the National Plan to Address Alzheimer's Disease.

Cancer: In FY 2017, NIH plans to spend $6.3 billion on cancer research and treatment development, an increase of $680 million above FY 2016. NIH has been at the forefront of many exciting advancements such as transitioning the treatment of cancer from a one-size-fits-all approach to one in which treatments are based on the molecular characteristics of each patient's disease. Additionally, National Cancer Institute researchers have identified several types of gastrointestinal cancers that have tumor-specific mutations that can be recognized by the immune system, potentially offering a new therapeutic opportunity for patients with these tumors.

Building upon these recent developments, NIH plans to expand investments through an initiative to support the Vice President's Cancer Moonshot. In FY 2017, the Budget provides $680 million to NIH for this initiative in order to galvanize the nation's efforts to combat cancer. NIH will pursue new cancer vaccine technology, investigate novel diagnostic tests that detect tumors through simple blood tests, and expand access to clinical trial data in an effort to reduce the number of people who develop cancer and improve outcomes for those who do. These funds will also be used to invest in the Vice President's Exceptional Opportunities in Cancer Research Fund, ensuring that resources are available to pursue investigations, at academic sites or public-private partnerships, worthy of potential breakthrough status.

Strengthen and Sustain a Diverse and Talented Biomedical Research Workforce

The biomedical research workforce is the backbone is scientific discovery. Supporting a diverse, creative, innovative, and productive group of young scientists is key to sustaining the nation's biomedical research enterprise and achieving improved health for the American people. To fully support and sustain the best scientists in the biomedical workforce, NIH will expand ways to revitalize physician-scientist training, continue to encourage early stage investigators, further enhance workforce diversity, and support more person-centered grants that focus on an investigator's entire research program and their history of success rather than a specific project. In FY 2017, NIH will continue to emphasize several High-Risk, High Reward research programs to allow scientists more freedom to innovate and explore new lines of inquiry.

In order to continue to attract the brightest minds to biomedical research, NIH is committed to enhancing the diversity of its funded workforce. NIH will also continue to implement a series of steps to expand its effort to recruit and advance the careers of people traditionally underrepresented in the biomedical and behavioral research workforce. The Enhancing the Diversity of the NIH-funded Workforce initiative will make training awards focused on learning how to attract and retain students from diverse backgrounds into biomedical research, increase access to high-quality research mentorship, and develop and disseminate best practices for training and mentorship. The Budget includes an estimated total of $849 million to support 16,421 research scientist trainees through the Ruth L. Kirschstein National Research Service Awards program. To maintain stipends' purchasing power, NIH proposes a two percent stipend increase for predoctoral and postdoctoral recipients in FY 2017.

Advancing HIV/AIDS Research

In August 2015, NIH announced a strategic approach to investing resources for HIV/AIDS research by focusing on a set of new high priority areas:

- Reduce the incidence of HIV/AIDS, including by the development of safe and effective vaccines;
- Develop the next generation of HIV therapies with improved safety and ease of use;
- Improve our capability to prevent and treat HIV-associated comorbidities and co-infections; and,
- Support cross cutting areas of basic research, health disparities, and training.

These priorities, which were presented during a meeting of the Advisory Committee to the NIH Director, were identified by conducting a review of the agency-wide HIV/AIDS portfolio. The strategic focus areas will ensure that research funded is aligned with new HIV/AIDS research opportunities.

In FY 2017, NIH estimates it will maintain the level of support for research on HIV/AIDS from FY 2016 at $3.0 billion. Activities under this new framework will

EXHIBIT 314

ORIGINAL CONTRIBUTION

Contradicted and Initially Stronger Effects in Highly Cited Clinical Research

John P. A. Ioannidis, MD

Context Controversy and uncertainty ensue when the results of clinical research on the effectiveness of interventions are subsequently contradicted. Controversies are most prominent when high-impact research is involved.

Objectives To understand how frequently highly cited studies are contradicted or find effects that are stronger than in other similar studies and to discern whether specific characteristics are associated with such refutation over time.

Design All original clinical research studies published in 3 major general clinical journals or high-impact-factor specialty journals in 1990-2003 and cited more than 1000 times in the literature were examined.

Main Outcome Measure The results of highly cited articles were compared against subsequent studies of comparable or larger sample size and similar or better controlled designs. The same analysis was also performed comparatively for matched studies that were not so highly cited.

Results Of 49 highly cited original clinical research studies, 45 claimed that the intervention was effective. Of these, 7 (16%) were contradicted by subsequent studies, 7 others (16%) had found effects that were stronger than those of subsequent studies, 20 (44%) were replicated, and 11 (24%) remained largely unchallenged. Five of 6 highly-cited nonrandomized studies had been contradicted or had found stronger effects vs 9 of 39 randomized controlled trials ($P=.008$). Among randomized trials, studies with contradicted or stronger effects were smaller ($P=.009$) than replicated or unchallenged studies although there was no statistically significant difference in their early or overall citation impact. Matched control studies did not have a significantly different share of refuted results than highly cited studies, but they included more studies with "negative" results.

Conclusions Contradiction and initially stronger effects are not unusual in highly cited research of clinical interventions and their outcomes. The extent to which high citations may provoke contradictions and vice versa needs more study. Controversies are most common with highly cited nonrandomized studies, but even the most highly cited randomized trials may be challenged and refuted over time, especially small ones.

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CLINICAL RESEARCH ON IMPORTANT questions about the efficacy of medical interventions is sometimes followed by subsequent studies that either reach opposite conclusions or suggest that the original claims were too strong. Such disagreements may upset clinical practice and acquire publicity in both scientific circles and in the lay press. Several empirical investigations have tried to address whether specific types of studies are more likely to be contradicted and to explain observed controversies. For example, evidence exists that small studies may sometimes be refuted by larger ones.[1,2]

Similarly, there is some evidence on disagreements between epidemiological studies and randomized trials.[3-5] Prior investigations have focused on a variety of studies without any particular attention to their relative importance and scientific impact. Yet, most research publications have little impact while a small minority receives most attention and dominates scientific thinking and clinical practice. Impact is difficult to measure in all its dimensions. However, the number of citations received by a publication is a surrogate of the attention it has received in the scientific literature and its influence on scientific debate and progress. Citations are readily and objectively counted in established databases.[6] High citation count does not necessarily mean that these studies are accepted; citations may sometimes be critical of an article. Nevertheless, citation count is a measure of how much a study has occupied the thinking of other scientists and has drawn attention—for good or bad.

It is important to evaluate the replication of clinical research studies that have the highest citation impact. How frequently are such studies eventually contradicted by other research or are found to have too strong results compared with subsequent evidence? Is this more common for specific types of studies? Answering these questions would be useful for interpreting the results of influential clinical research.

METHODS

Eligible Original Studies

Eligible original studies for this analysis included all publications that had received more than 1000 Institute for Scientific Information (ISI)–indexed[6]

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citations; had been published between 1990 and 2003 in the 3 general medical journals with the current highest impact factor (*New England Journal of Medicine, JAMA, Lancet*) or in medical specialty journals with impact factor exceeding 7.0 (according to the Journal Citation Reports 2003) that are likely to publish clinical research (including in decreasing impact factor, the *Journal of the National Cancer Institute*, *Gastroenterology*, *Annals of Internal Medicine*, *Circulation*, *Journal of Clinical Oncology*, *Archives of General Psychiatry*, *Blood, Hepatology*, *American Journal of Respiratory and Critical Care Medicine*, *Diabetes*, *Brain*, *Annals of Neurology*, *Journal of the American College of Cardiology*, *Diabetes Care*, *Journal of the American Society of Nephrology*, *Arthritis and Rheumatism*, and the *American Journal of Psychiatry*); addressed the efficacy of therapeutic or preventive interventions; and pertained to primary data (excluding reviews and meta-analyses).

Citation counts for articles published between January 1, 1990, and December 31, 2003, in these journals were downloaded from ISI. Citation counts are censored on August 20, 2004. All articles with more than 1000 citations were screened further. Studies with group authorship may be cited in various ways; therefore, I summed up citations cataloged under different entries for the same article (using the first author name, group abbreviations, and anonymous entries).[7] The total citation count does not capture the few citations for which wrong name, journal, volume, or page might have been cited. Since citations depend on the time interval since publication, a separate citation count was limited to the first 3 years after the publication year.

Other Clinical Research on the Same Questions

For each eligible original study, a search was performed to identify whether there had been any other concurrently or subsequently published clinical research addressing the same question. Other research was considered eligible, only if the sample size was close to or larger than that of the highly cited original study or if it used a theoretically better controlled design. Thus, for highly cited randomized trials, I perused all randomized trials having at least 30% of the sample size of the eligible highly cited original study. Whenever available, quantitative meta-analyses of trials were used as summaries of trial results. Whenever several pertinent meta-analyses were available, the one including the largest number of studies was preferred. For highly cited nonrandomized studies, subsequently published pertinent randomized trials and meta-analyses thereof were eligible regardless of sample size; nonrandomized evidence was also considered, if randomized trials were not available.

Concurrently or subsequently published evidence was identified in PubMed using searches that combined terms pertaining to the tested interventions, disease and outcome, and terms pertinent to the search of randomized trials and meta-analyses. Searches followed the Cochrane algorithms for finding meta-analyses and randomized trials.[8]

Data Extraction and Classification of Studies

For each eligible original study, I recorded the study name, intervention, disease and outcomes of interest, study design, sample size, main conclusions, and citation counts. For the articles presenting or summarizing other relevant research, I recorded the study design, total sample size, and the findings as compared with those of the original highly cited study.

Highly cited studies were classified as negative (when they claimed the tested experimental intervention was ineffective, harmful, or no better from the control intervention), unchallenged (when no other clinical research of eligible design and sample size was available to validate the claimed efficacy), contradicted, initially stronger effects, or replicated effects. The classification of studies in these categories was based on the final interpretation of the results by the authors in the "Abstract" and "Discussion" sections of their original publications. Highly cited articles were classified according to whether their authors suggested that an intervention was overall effective or ineffective. When both benefits and harms or caveats were presented, I focused on the net conclusion of whether the experimental intervention merits consideration for use in clinical practice. Subsequent research was classified in the same manner. Contradiction was declared when the original highly cited study claimed the intervention to be effective, while subsequent research showed it to be ineffective. When both original and subsequent research claimed the intervention was effective, studies were compared further regarding the effect size for the major clinical outcome, the durability of the treatment effect, and the generalizability and applicability to various settings. Initially stronger effects were defined when the relative risk reduction for the main outcome in the subsequent research was half or less compared with what had been proposed by the original highly cited study (regardless of whether confidence intervals might overlap or not), or when the subsequent research showed that the originally proposed benefit was of short duration or its applicability and generalizability was limited. Classification of the studies independently by another investigator yielded a highly similar profile (weighted Cohen $\kappa = 0.92$).

Correlates of Contradicted or Initially Stronger Effects

Among original highly cited studies with efficacy claims, analyses examined whether those with contradicted or initially stronger effects differed from the replicated and unchallenged ones in study design, publication year, sample size, type of disease (heart disease vs other), journal of publication, citation count, early citation count, and average citations per year after publication. Comparisons used the Mann-Whitney *U* test for continuous variables and Fisher exact test for binary variables.

Comparison of Highly Cited Articles Against Less Cited Articles

To evaluate whether highly cited studies differ from other studies that are not so highly cited in their findings and potential for contradiction, a control group of articles pertaining to the assessment of interventions was also assembled. Control-group articles were 1:1 matched for journal, year of publication, and design (randomized vs nonrandomized) against each of the highly cited articles. Control articles were selected by screening chronologically the contents of the pertinent journals for each pertinent year starting July 1 (to ensure approximately similar follow-up for citations with the highly cited articles against which they were matched). Other research was searched and the control articles were categorized in a similar fashion as described for the highly cited articles above. Differences between highly cited and control articles were examined with conditional logistic regression to account for matching.

Analyses

Analyses were performed in SPSS version 12.0 (SPSS Inc, Chicago, Ill) and StatXact (Cytel Corp, Boston, Mass). *P* values are 2-tailed, and $P<.05$ was considered statistically significant.

RESULTS

Eligible Studies

One hundred fifteeen articles published between 1990 and 2003 had received more than 1000 citations (major general clinical journals, n=91; specialty journals, n=24). Of those, 66 were excluded (nonsystematic reviews or editorials, n=20; meta-analyses, n=7; case-control studies of risk factors, n=12; prevalence or incidence studies, n=8; cohort studies of risk factors, n=3; recommendations, n=3; prognostic models, n=4; time-trend analysis, n=1; case series, n=1; presentations of interviews, instruments, or assays n=3, classification criteria n=4). The remaining 49 articles were eligible (TABLE 1)[9-57] of which 47 had appeared in major general medical journals. They included 43 randomized trials, 4 prospective cohorts, and 2 case series. In recent years (1998 through 2003), the 3 general journals have published an almost equal number of highly cited articles (*New England Journal of Medicine*, n=4; *JAMA*, n=3; *Lancet*, n=3). A smaller proportion of highly cited articles published in specialty journals than those published in general journals were eligible for the analysis (2/24 vs 47/91, $P<.001$), because highly cited articles in specialized journals were mostly nonsystematic reviews or editorials (10/24); classification criteria (4/24); or descriptions of standardized interviews, instruments, and assays (3/24). Many diverse disciplines were represented, but the most common topic was heart disease (n=27).

Four eligible highly cited studies showed no efficacy for the tested interventions. They contradicted prior claims for potential efficacy of vitamin E, beta carotene, and retinol for lung cancer and/or coronary artery disease; and showed an increased risk of coronary artery disease with hormone therapy in postmenopausal women (TABLE 2).

Of the 45 eligible highly cited studies with efficacy claims (Table 2), 7 (16%) were contradicted by subsequent research, and another 7 (16%) were found to have initially stronger effects. In all these 14 cases (BOX 1), subsequent studies were either larger or better controlled (randomized vs a nonrandomized original study). The findings of 20 highly cited articles (44%) were replicated (also with a larger sample size in subsequent research compared with the original highly cited study) and 11 (24%) had remained largely unchallenged.[58-78]

Comparison of Contradicted or Initially Stronger vs Replicated or Unchallenged Findings

Five of 6 highly cited nonrandomized studies had been contradicted or had initially stronger effects while this was seen in only 9 of 39 highly cited randomized trials ($P=.008$). TABLE 3 shows that trials with contradicted or initially stronger effects had significantly smaller sample sizes and tended to be older than those with replicated or unchallenged findings. There were no significant differences on the type of disease. The proportion of contradicted or initially stronger effects did not differ significantly across journals ($P=.60$). There was also no significant difference in the number of citations received in the first 3 years between these 2 groups or in the overall number of citations over time although the citations per year tended to be nonsignificantly fewer in trials with contradicted or initially stronger effects.

Comparison of Highly Cited Articles Against Less-Cited Control Articles

Of the 49 articles in the control group[79-127] (with median of 157 citations, range 38-815, until 2004), the findings of 2 articles[91,119] were contradicted[128,129] and 8 studies* had initially stronger effects[130-137] (BOX 2); 20 articles† contained "positive" findings that were replicated,[68,138-155] 8 studies‡ remained unchallenged, and 11 studies§ did not have any "positive" results; in 7 articles with some "positive" finding,[79,87,91,98,108,112,120] there were also other interventions evaluated that had "negative" results although this mixture of "positive" and "negative" results had not been observed in any of the highly cited articles. The control articles had a larger number of "negative" findings compared with the highly cited articles (matched odds ratio [OR], 8; 95% confidence interval [CI], 1.8-34; $P=.006$ for any "negative" finding; and matched OR, 3.3; 95% CI, 0.92-12.0, $P=.07$ for exclusively "negative" findings). The highly cited articles did not have a smaller proportion of contradicted or initially stronger effects than the control articles if anything

*References 82, 90, 92, 95, 96, 109, 110, 117.
†References 79-81, 83, 86-89, 101, 103, 104, 106, 108, 111, 112, 118, 123, 125-127.
‡References 93, 97, 98, 102, 107, 114, 115, 120.
§References 84, 85, 94, 99, 100, 105, 113, 114, 119, 120, 122.

Table 1. Eligible Highly Cited Studies

Study	Type of Intervention and Disease	Design	Sample Size	No. of Citations	
				All	3-Year
ACTG019,[9] 1990	Zidovudine in asymptomatic HIV-1 infection	RCT	1338	1179	549
Brown et al,[10] 1990	Lipid lowering to decrease coronary lesions and CAD	RCT	146	1312	394
Moertel et al,[11] 1990	Levamisole and fluorouracil for colon cancer	RCT	246	1050	259
V-HeFT II,[12] 1991	Enalapril vs hydralazine + isosorbide for CHF	RCT	804	1469	386
Nurses' Health Study,[13] 1991	Postmenopausal hormonal therapy for CAD prevention	Cohort	48 470	1355	230
NASCET,[14] 1991	Carotid endarterectomy in high-grade stenosis	RCT	659	2434	347
HA-1A Sepsis,[15] 1991	Monoclonal antibody to endotoxin for gram-negative sepsis	RCT	200	1028	435
SOLVD,[16] 1991	Enalapril in patients with LV dysfunction	RCT	2569	2798	1113
SAVE,[17] 1992	Captopril for patients after MI	RCT	2231	2803	632
PAMI,[18] 1993	Angioplasty vs tPA thrombolysis in acute MI	RCT	395	1642	868
Captopril Collaborative,[19] 1993	Captopril for slowing disease progression in diabetic nephropathy	RCT	409	2090	388
Health Professionals,[20] 1993	Vitamin E for CAD prevention in men	Cohort	39 910	1281	409
Nurses' Health Study,[21] 1993	Vitamin E for CAD prevention in women	Cohort	87 245	1131	409
Rossaint et al,[22] 1993	Nitric oxide inhalation for acute respiratory distress syndrome	Case series	9	1025	399
DCCT,[23] 1993	Intensive management to reduce type 1 diabetes complications	RCT	1441	6005	1260
EPIC,[24] 1994	7E3 in high-risk angioplasty	RCT	2099	1467	203
ACTG076,[25] 1994	Zidovudine to reduce perinatal HIV-1 transmission	RCT	477	1449	461
STRESS,[26] 1994	Stent vs balloon angioplasty in CAD	RCT	410	2153	543
BENESTENT,[27] 1994	Stent vs balloon angioplasty in single-vessel CAD	RCT	520	2295	633
ABC,[28] 1994	Vitamin E and beta carotene for lung cancer	RCT	29 133	1872	542
NINDS rt-PA,[29] 1995	rt-PA in acute stroke	RCT	624	1939	485
WOSCOPS,[30] 1995	Pravastatin in hypercholesterolemia	RCT	6595	3163	901
CARE,[31] 1996	Pravastatin after MI with average cholesterol	RCT	4195	2795	908
US Carvedilol,[32] 1996	Carvedilol for CHF	RCT	1094	1544	543
BERET,[33] 1996	Beta carotene/retinol for preventing lung cancer/CAD	RCT	18 314	1044	439
Physicians' Health,[34] 1997	Aspirin to prevent MI in men with various C-reactive protein levels	RCT	1086	1597	539
ACTG320,[35] 1997	Triple therapy with indinavir vs 2 nucleosides in HIV-1 infection	RCT	1156	1293	728
EPILOG,[36] 1997	Abciximab glycoprotein IIb/IIIa blockade in PCI	RCT	2792	1066	596
HIT,[37] 1998	Interferon alfa-2b + ribavirin vs interferon alone for chronic hepatitis C	RCT	912	1319	612
LIPID,[38] 1998	Pravastatin for secondary CAD prevention	RCT	9014	1641	750
RALES,[39] 1999	Spironolactone in severe CHF	RCT	1663	1085	635
HOPE,[40] 2000	Ramipril to prevent CAD in high-risk patients without LV dysfunction/CHF	RCT	9297	1777	1323
SHEP,[41] 1991	Treatment of systolic hypertension in elderly adults	RCT	4736	1872	397
PEPI,[42] 1995	Postmenopausal estrogen/progestin for CAD risk factors	RCT	875	1300	320
ACAS,[43] 1995	Endarterectomy in asymptomatic stenosis >60%	RCT	1662	1427	416
HERS,[44] 1998	Estrogen/progestin for secondary CAD prevention	RCT	2763	2050	987
AFCAPS/TexCAPS,[45] 1998	Lovastatin for primary CAD prevention with average cholesterol	RCT	6605	1559	731
WHI,[46] 2002	Estrogen/progestin for CAD prevention	RCT	16 608	1468	2000*
MRC Vitamin,[47] 1991	Folate to prevent neural tube defects	RCT	1817	1096	378
Zutphen Elderly,[48] 1993	Flavonoids for CAD prevention	Cohort	805	1233	151
4S,[49] 1994	Simvastatin in hypercholesterolemia with previous CAD	RCT	4444	4614	990
CAPRIE,[50] 1996	Clopidogrel vs aspirin in patients at risk of ischemic events	RCT	19 185	1139	280
CHAOS,[51] 1996	Vitamin E to prevent MI and death in patients with CAD	RCT	2002	1004	425
HOT,[52] 1998	Intensive blood-pressure lowering/low-dose aspirin in hypertension	RCT	18 790	1539	799
IHIT,[53] 1998	Interferon alfa-2b + ribavirin vs interferon alone for chronic hepatitis C	RCT	832	1004	486
UKPDS 34,[54] 1998	Intensive management of type 2 diabetes with insulin or sulphonylureas	RCT	3867	2748	1238
CIBIS-II,[55] 1999	Bisoprolol for CHF	RCT	2647	1064	653
Castaigne et al,[56] 1990	All-trans retinoic acid for acute promyelocytic leukemia	Case series	22	1030	270
NSABP P-1,[57] 1998	Tamoxifen for breast cancer prevention	RCT	13 388	1470	745

Abbreviations: ABC, Alpha-Tocopherol, Beta Carotene Cancer Prevention; ACAS, Asymptomatic Carotid Atherosclerosis Study; ACTG, AIDS Clinical Trials Group; AFCAPS/TexCAPS, Air Force/Texas Coronary Atherosclerosis Prevention Study; BENESTENT, Belgian Netherlands Stent; BERET, Beta Carotene and Retinol Efficacy Trial; CAD, coronary artery disease; CAPRIE, Clopidogrel vs Aspirin in Patients at Risk of Ischemic Events; CARE, Cholesterol and Recurrent Events; CHAOS, Cambridge Heart Antioxidant Study; CHF, congestive heart failure; CIBIS-II, Cardiac Insufficiency Bisoprolol Study II; DCCT, Diabetes Control and Complications Trial; EPIC, Evaluation of 7E3 for the Prevention of Ischemic Complications; EPILOG, Evaluation in PTCA to Improve Long-Term Outcome with Abciximab Glycoprotein IIb/IIIa Blockade; HA-1H, human IgM monoclonal antibody; HERS, Heart and Estrogen/progestin Replacement Study; HIT, Hepatitis Interventional Therapy; HIV-1, human immunodeficiency virus type 1; HOPE, Heart Outcomes Prevention Evaluation; HOT, Hypertension Optimal Treatment; IHIT, International Hepatitis Interventional Therapy; LIPID, Long-Term Intervention with Pravastatin in Ischaemic Disease; LV, left ventricular; MI, myocardial infarction; MRC, Medical Research Council; NASCET, North American Symptomatic Carotid Endarterectomy Trial; NINDS rt-PA, National Institute of Neurological Disorders and Stroke recombinant tissue-Plasminogen Activator; NSABP P-1, National Surgical Adjuvant Breast and Bowel Project P-1; PAMI, Primary Angioplasty in Myocardial Infarction; PCI, percutaneous coronary intervention; PEPI, Postmenopausal Estrogen/Progestin Interventions; RALES, Randomized Aldactone Evaluation Study; RCT, randomized controlled trial; SAVE, Survival And Ventricular Enlargement; SHEP, Systolic Hypertension in the Elderly Program; SOLVD, Studies of Left Ventricular dysfunction; STRESS, Stent Restenosis Study; UKPDS 34, UK Prospective Diabetes Study 34; V-HeFT II, Vasodilator-Heart Failure Trial II; WHI, Women's Health Initiative; WOSCOPS, West of Scotland Coronary Prevention Study; 4S, Scandinavian Simvastatin Survival Study.

*Projected.

Table 2. Other Research and Current State of Knowledge

Highly Cited Study	Other Research	No. of Participants*	Comment on Current State of Knowledge
Contradicted studies			
Nurses' Health Study[13]	RCT[46]	16 608	Estrogen/progestin do not protect from but increase CAD risk in postmenopausal women
HA-1A Sepsis[15]	RCT[62]	2199	Contrary to initial findings, HA-1A did not improve survival in gram-negative sepsis
Health Professionals[20]	RCT[66]	6996	Contrary to initial findings, vitamin E supplementation does not reduce CAD in men
Nurses' Health[21]	RCT[66]	2545	Contrary to initial findings, vitamin E supplementation does not reduce CAD in women
Rossaint et al,[22] (nitric oxide)	MA RCT[67]	535	Despite initial claims of better oxygenation, nitric oxide does not improve survival in respiratory distress syndrome
PEPI[42]	RCT[46]	16 608	Estrogen/progestin do not protect from but increase CAD risk in postmenopausal women
CHAOS[51]	RCT[66]	9541	Contrary to initial findings, vitamin E does not prevent coronary events
Initially stronger effects			
ACTG019[9]	MA RCT[58]	5566	The early benefit of zidovudine against HIV-1 disease progression decreases over time
PAMI[18]	MA RCT[65]	2593	Superiority of angioplasty over tPA thrombolysis may be less prominent than originally proposed and pertinent mostly to specialized centers
STRESS[26]	MA RCT[69]	9918	Stents reduce restenosis and need for revascularization compared with simple angioplasty, but the effect may be inflated by lack of blinding and is probably modest
BENESTENT[27]	MA RCT[69]	9918	Stents reduce restenosis and need for revascularization compared with simple angioplasty, but the effect may be inflated by lack of blinding and is probably modest
NINDS rt-PA[29]	MA RCT[70]	2775	rt-PA may improve outcomes in acute ischemic stroke, but benefit is limited and seen only when treatment is given very early
ACAS[43]	MA RCT[75]	2440	Carotid endarterectomy has a small absolute benefit in asymptomatic stenosis >60%
Zutphen Elderly[48]	MA cohorts[76]	105 000	Flavonoids reduce the risk of CAD modestly
Replicated studies			
Brown et al,[10] (lipid lowering)	MA RCT[59]	148 321	Cholesterol and LDL lowering achieves significant risk reductions in CAD
Moertel et al,[11] (levamisole/5-FU)	MA RCT[60]	3302	Fluorouracil adjuvant therapy improves survival in colon cancer
NASCET[14]	MA RCT[61]	6092	Carotid endarterectomy is effective in symptomatic patients with 70%-99% stenosis
SOLVD[16]	MA RCT[63]	7105	ACE inhibition reduces mortality and hospitalizations in patients with CHF
SAVE[17]	MA RCT[64]	105 337	ACE inhibition reduces mortality after MI
EPIC[24]	MA RCT[68]	20 137	Glycoprotein IIB/IIIA antagonists reduce cardiovascular events in percutaneous revascularization
WOSCOPS[30]	MA RCT[59]	148 321	Statins achieve significant risk reductions in CAD
CARE[31]	MA RCT[59]	148 321	Statins achieve significant risk reductions in CAD
US Carvedilol[32]	MA RCT[71]	10 135	β-Blockers decrease mortality in patients with CHF
ACTG320[35]	MA RCT[72]	4686	Protease-inhibitor–based triple therapy improves survival compared with double nucleosides in HIV-1 infection
EPILOG[36]	MA RCT[68]	20 137	Glycoprotein IIB/IIIA antagonists reduce cardiovascular events in percutaneous revascularization
HIT[37]	MA RCT[73]	6585	Interferon alfa-2b + ribavirin has better outcomes than interferon alone in chronic hepatitis C
LIPID[38]	MA RCT[59]	148 321	Statins achieve significant risk reductions in CAD
SHEP[41]	MA RCT[74]	15 693	Treatment of isolated hypertension in elderly patients reduces the risk of stroke
AFCAPS/TexCAPS[45]	MA RCT[59]	148 321	Cholesterol and LDL lowering achieves significant risk reductions in CAD
4S[49]	MA RCT[59]	148 321	Statins achieve significant risk reductions in CAD
IHIT[53]	MA RCT[73]	6585	Interferon alfa-2b plus ribavirin has better outcomes than interferon alone in chronic hepatitis C
CIBIS-II[55]	MA RCT[71]	10 135	β-Blockers decrease mortality in patients with CHF
All-trans-retinoid acid[56]	RCT[77]	346	All-trans retinoic acid is effective for acute promyelocytic leukemia
NSABP P-1[57]	MA RCT[78]	28 406	Tamoxifen is effective for the prevention of breast cancer
Unchallenged studies			
V-HeFT II,[12]			ACE inhibition is superior to vasodilators for CHF
Captopril Collaborative[19]			ACE inhibition slows renal disease progression in diabetes with macroproteinuria (benefit subsequently extended to microproteinuria and patients without diabetes)
DCCT[23]			Intensive insulin management of type 1 diabetes reduces microvascular complications (subsequent research has addressed increasingly intensive management)
ACTG076[25]			Zidovudine reduces the risk of perinatal HIV-1 transmission (subsequent research has addressed shorter and more convenient regimens)
Physicians' Health[34]			Aspirin prevents MI especially in men with high levels of C-reactive protein
MRC Vitamin[47]			Folate supplementation significantly reduces the risk of neural tube defects (subsequent research has addressed various doses and modes of administration of folate)
RALES[39]			Spironolactone reduces morbidity and mortality in CHF (no other similar trial)
HOPE[40]			Ramipril prevents CAD events in high-risk patients without left ventricular dysfunction (no other similar trial)
CAPRIE[50]			Clopidogrel seems superior to aspirin in preventing stroke and MI in patients at risk of ischemic stroke (subsequent research has addressed the combination of clopidogrel and aspirin)
HOT[52]			Intensive blood pressure lowering decreases the risk of cardiovascular events (2 much smaller trials have shown similar effects of intensive blood pressure lowering in patients with diabetes)
UKPDS 34[54]			Intensive management of type 2 diabetes reduces the risk of microvascular complications
Negative studies			
ABC[28]			Neither α-tocopherol nor beta carotene prevents lung cancer
BERET[33]			Neither beta carotene nor retinol prevent lung cancer or CAD
HERS[44]			Estrogen/progestin are ineffective for secondary CAD prevention in postmenopausal women
WHI[46]			Estrogen/progestin do not protect from but increase CAD risk in postmenopausal women

Abbreviations: The abbreviations of the highly cited studies correspond to the popular names listed in Table 1. ACE, angiotensin-converting enzyme; CAD, coronary artery disease; CHF, congestive heart failure; HA-1A, human IgM monoclonal antibody; HIV-1, human immunodeficiency virus type 1; LDL, low-density lipoprotein; MA, meta-analysis; RCT, randomized controlled trial; rt-PA, recombinant tissue-type plasminogen activator; tPA, tissue plasminogen activator.
*For meta-analyses, the number of participants refers to the total sample size of all studies (large and small ones) and includes the sample size of the original highly cited study.

Box 1. Contradicted and Initially Stronger Effects in Highly Cited Studies

Contradicted Findings

The Nurses' Health Study,[13] a prospective cohort, found a 44% relative risk reduction in coronary artery disease events in women receiving hormone therapy. A small randomized trial[42] found major beneficial effects of this intervention on surrogate markers of coronary artery disease (lipoprotein and fibrinogen levels) claiming that this should translate to a major clinical benefit. Although the latter trial was not refuted at the level of surrogate outcomes, inferences for the anticipated effects on clinical outcomes were contradicted. The Women's Health Initiative,[46] a large randomized trial, found that estrogen and progestin significantly increased the relative risk of coronary events by 29% among postmenopausal women, and refuting results were also seen in another large randomized trial, the Heart and Estrogen/progestin Replacement Study (HERS).[44]

Two large prospective cohort studies, the Health Professionals Follow-Up study[20] and the Nurses' Health Study,[21] found that vitamin E was significantly associated with a decreased risk of coronary artery disease and a trial of 2002 patients also suggested a 47% relative risk reduction for cardiovascular deaths or nonfatal myocardial infarction with vitamin E.[51] However, an even larger randomized trial[66] subsequently showed absolutely no beneficial effect for vitamin E on coronary artery disease (relative risk 1.05 for cardiovascular deaths and 1.02 for myocardial infarction).

A small randomized trial (n=200) suggested that the human IgM monoclonal antibody to endotoxin could almost halve mortality due to gram-negative sepsis.[15] A subsequent randomized trial of more than 10-fold larger sample size[62] found a nonsignificant 11% relative risk increase for mortality.

Finally, a small series of 9 patients[22] proposed that nitric oxide inhalation is very effective in patients with respiratory distress syndrome by improving oxygenation. However 5 randomized trials involving 535 patients[67] failed to show any clinical benefit.

Initially Stronger Effects

The early results of a trial on zidovudine monotherapy in asymptomatic patients with human immunodeficiency virus infection[9] showed a significant 60% relative risk reduction against disease progression in the first year. The short-term benefit was not exaggerated. Yet this effect was short-lived and the benefit was lost after 18 months both in the same trial and also as shown in a subsequent meta-analysis.[58]

A randomized trial of 395 patients[18] showed that immediate angioplasty was superior to thrombolysis with tissue plasminogen activator in acute myocardial infarction, achieving a 58% relative risk reduction for death or reinfarction. However, a subsequent meta-analysis with more than 2500 patients[65] suggested that the benefit is probably much smaller (relative risk reduction 30%) and the largest and most recent trial that involved both specialized and nonspecialized centers had not shown any sizeable benefit of angioplasty (nonsignificant 20% risk reduction for death and nonsignificant 33% risk reduction for reinfarction).

Two randomized trials of 410 and 520 patients, respectively,[26,27] showed that stents were superior to balloon angioplasty for management of coronary artery disease with 31% and 42% relative risk reductions, respectively, in the need for revascularization. Current evidence, as summarized by a meta-analysis of almost 10 000 patients, suggests that the benefit is probably much smaller that originally thought (approximately 10% relative risk reduction), and unblinding may have led to an increased effect on repeat angioplasty in these trials.[69]

Another trial suggested a prime role for tissue plasminogen activator in acute ischemic stroke.[29] However, subsequent evidence has narrowed indications and the intervention is considered effective mostly when given very early after symptom onset.[70]

Carotid endarterectomy was initially reported to achieve a 5.9% absolute risk reduction for stroke or death, projected at 5 years,[43] in patients with asymptomatic stenosis of the carotid artery exceeding 60%. A meta-analysis of several trials suggested a more modest benefit with 2% absolute risk reduction at 3.1 years.[75]

Finally, a cohort study of 805 people found a 68% adjusted relative risk reduction for coronary artery disease with flavonoids[48] while a meta-analysis of prospective cohorts with total sample size exceeding 100 000 suggests only a 20% relative risk reduction in the top vs bottom third of flavonoid uptake.[76]

there was a trend for more contradicted or initially stronger effects in the highly cited articles (matched OR, 1.6; 95% CI, 0.6-4.0; $P=.35$; matched OR, 6.0; 95% CI, 0.7-50; $P=.10$ when limited to contradicted findings).

COMMENT

Original highly cited articles about medical interventions are published almost exclusively in 3 general medical journals. Actually, there has been an approximate equal share of very highly cited articles among these 3 journals since 1998 as impact factor differences have diminished among these 3 journals. Articles in specialty journals that reach such high numbers of citations are usually review articles or articles describing tools useful to specific diseases rather than original data. Contradicted and potentially exaggerated findings are not uncommon in the most visible and most influential original clinical research: 16% of the top-cited clinical research articles on postulated effective medical interventions that have been published within the last 15 years have been contradicted by subsequent clinical studies and another 16% have been found to have initially stronger effects than subsequent research. Contradiction or initially stronger effects have been encountered in 5 of 6 cases for which nonrandomized designs were used, but even randomized trials have not escaped controversy. More

Table 3. Comparison of Characteristics and Citation Counts of Randomized Trials With Contradicted or Initially Stronger Effects vs Those With Replicated or Unchallenged Findings

Characteristic	Contradicted or Initially Stronger Effects (n = 9)	Replicated or Unchallenged (n = 30)	*P* Value
Published in 1990-1995	8	15	.06
Heart disease topic	4	13	1.00
Sample size, median (IQR)	624 (403-1500)	2165 (892-5201)	.009
All citations received, median (IQR)	1427 (1104-2046)	1542 (1255-2513)	.43
Citations in 3 y, median (IQR)	485 (421-591)	622 (393-825)	.32
Citations per year, median (IQR)	149 (105-215)	214 (146-263)	.07

Abbreviations: IQR, interquartile range.

than a third of the top-cited randomized trials published from 1990 through 1995 have already been affected, while for more recent trials, the time frame is still early and more may be contradicted in the future. Sample size seems to be important, with smaller sample sizes in trials that have met controversy vs those that have not.

The classification of studies in this analysis involves many judgments pertaining to the complexity of studying a given research question with somewhat different populations, interventions, durations, and outcomes. However, these studies are widely known for their inferences and this is also proven by the high interrater agreement. Nevertheless, it should also be acknowledged that although the classification was performed in duplicate, the searches were performed by only 1 investigator. It is unavoidable that some other investigators may feel differently about the categorization of specific studies, especially for topics that may also have heavy debates surrounding them. However, this is unlikely to change the aggregate picture about refutation rates.

The examination of contradictions and refutations offers a fascinating look at the process of science. Four of the highly cited articles examined herein were refuting investigations with "negative" results. However, in a sense, even the other highly cited articles with "positive" results refuted prior knowledge and practice by introducing new concepts and proposing new interventions. We should acknowledge that there is no proof that the subsequent studies and meta-analyses were necessarily correct. A perfect gold standard is not possible in clinical research, so we can only interpret results of studies relative to other studies. Whenever new research fails to replicate early claims for efficacy or suggests that efficacy is more limited than previously thought, it is not necessary that the original studies were totally wrong and the newer ones are correct simply because they are larger or better controlled. Alternative explanations for these discrepancies may include differences in disease spectrum, eligibility criteria, or the use of concomitant interventions.[156] Different studies on the same question are typically not replicas of each other. In fact discrepancies may be interesting on their own because they require careful scrutiny of the data and reappraisal of our beliefs. Thus, it is probably not surprising that the citation rate of these refuted studies did not seem to be much affected. Nevertheless, the controversy generates considerable uncertainty for clinical practice and none of the contradicted interventions is currently recommended by practice guidelines.

The mere fact that a study is highly cited suggests that there is a strong active interest in the questions addressed from a clinical or research perspective. This may increase the chances that other, larger trials may eventually be conducted. However, for most clinical questions of interest, no large trials are ever conducted and evidence is based only on small trials or nonrandomized studies.[157] Small trials or meta-analyses thereof may often be refuted subsequently by large trials[1,2] when such large trials are performed. Small studies using surrogate markers may also sometimes lead to erroneous clinical inferences.[158] There were only 2 studies with typical surrogate markers among the highly cited studies examined herein, but both were subsequently contradicted in their clinical extrapolations about the efficacy of nitric oxide[22] and hormone therapy.[42] In the case of initially stronger effects, the differences in the effect sizes could often be within the range of what would be expected based on chance variability. This reinforces the notion that results from clinical studies, especially early ones, should be interpreted using not only the point estimates but also the uncertainty surrounding them. However, besides differences in effect sizes, most initially stronger effects pertained also to issues of durability, generalizability, or applicability of the proposed effects, as discussed above. Thus, clinicians should be aware that these important aspects may not be fully settled when an important treatment breakthrough is announced.

A third of the most-cited clinical research seems to have replication problems, and this seems to be as large, if not larger, than the vast majority of other, less-cited clinical research. The current analysis found that matched studies that were not so highly cited had a greater proportion of "negative" findings and similar or smaller proportions of contradicted results as the highly cited ones. Publication bias[159,160] and time-lag bias[161,162] favoring the rapid and prominent publication of "positive" findings may underlie some of the observed phenomena. Highly cited articles are already a selected sample with underrepresentation of "negative" findings compared with the average article on interventions published in major journals. It is possible that high-profile journals may tend to publish occasionally very striking findings and that this may lead to some difficulty in replicating some of these findings.[163] Poynard et al[164] evaluated the conclusions of hepatology-related articles published between 1945 and 1999 and found that, overall, 60% of these conclusions were

Box 2. Contradicted and Initially Stronger Effects in Control Studies

Contradicted Findings

In a prospective cohort,[91] vitamin A was inversely related to breast cancer (relative risk in the highest quintile, 0.84; 95% confidence interval [CI], 0.71-0.98) and vitamin A supplementation was associated with a reduced risk ($P=.03$) in women at the lowest quintile group; in a randomized trial[128] exploring further the retinoid-breast cancer hypothesis, fenretinide treatment of women with breast cancer for 5 years had no effect on the incidence of second breast malignancies.

A trial (n=51) showed that cladribine significantly improved the clinical scores of patients with chronic progressive multiple sclerosis.[119] In a larger trial of 159 patients, no significant treatment effects were found for cladribine in terms of changes in clinical scores.[129]

Initially Stronger Effects

A trial (n=28) of aerosolized ribavirin in infants receiving mechanical ventilation for severe respiratory syncytial virus infection[82] showed significant decreases in mechanical ventilation (4.9 vs 9.9 days) and hospital stay (13.3 vs 15.0 days). A meta-analysis of 3 trials (n=104) showed a decrease of only 1.8 days in the duration of mechanical ventilation and a nonsignificant decrease of 1.9 days in duration of hospitalization.[130]

A trial (n=406) of intermittent diazepam administered during fever to prevent recurrence of febrile seizures[90] showed a significant 44% relative risk reduction in seizures. The effect was smaller in other trials and the overall risk reduction was no longer formally significant[131]; moreover, the safety profile of diazepam was deemed unfavorable to recommend routine preventive use.

A case-control and cohort study evaluation[92] showed that the increased risk of sudden infant death syndrome among infants who sleep prone is increased by use of natural-fiber mattresses, swaddling, and heating in bedrooms. Several observational studies have been done since, and they have provided inconsistent results on these interventions, in particular, they disagree on the possible role of overheating.[132]

A trial of 54 children[95] showed that the steroid budenoside significantly reduced the croup score by 2 points at 4 hours, and significantly decreased readmissions by 86%. A meta-analysis (n=3736)[133] showed a significant improvement in the Westley score at 6 hours (1.2 points), and 12 hours (1.9 points), but not at 24 hours. Fewer return visits and/or (re)admissions occurred in patients treated with glucocorticoids, but the relative risk reduction was only 50% (95% CI, 24%-64%).

A trial (n=55) showed that misprostol was as effective as dinoprostone for termination of second-trimester pregnancy and was associated with fewer adverse effects than dinoprostone.[96] A subsequent trial[134] showed equal efficacy, but a higher rate of adverse effects with misoprostol (74%) than with dinoprostone (47%).

A trial (n=50) comparing botulinum toxin vs glyceryl trinitrate for chronic anal fissure concluded that both are effective alternatives to surgery but botulinum toxin is the more effective nonsurgical treatment (1 failure vs 9 failures with nitroglycerin).[109] In a meta-analysis[135] of 31 trials, botulinum toxin compared with placebo showed no significant efficacy (relative risk of failure, 0.75; 95% CI, 0.32-1.77), and was also no better than glyceryl trinitrate (relative risk of failure, 0.48; 95% CI, 0.21-1.10); surgery was more effective than medical therapy in curing fissure (relative risk of failure, 0.12; 95% CI, 0.07-0.22).

A trial of acetylcysteine (n=83) showed that it was highly effective in preventing contrast nephropathy (90% relative risk reduction).[110] There have been many more trials and many meta-analyses on this topic. The latest meta-analysis[136] shows a nonsignificant 27% relative risk reduction with acetylcysteine.

A trial of 129 stunted Jamaican children found that both nutritional supplementation and psychosocial stimulation improved the mental development of stunted children; children who got both interventions had additive benefits and achieved scores close to those of nonstunted children.[117] With long-term follow-up, however, it was found that the benefits were small and the 2 interventions no longer had additive effects.[137]

considered to be true in 2000 and that there was no difference between randomized and nonrandomized studies or high- vs low-quality studies. Allowing for somewhat different definitions, the higher rates of refutation and the generally worse performance of nonrandomized studies in the present analysis may stem from the fact that I focused on a selected sample of the most noticed and influential clinical research. For such highly cited studies, the turnaround of "truth" may be faster; in particular nonrandomized studies may be more likely to be probed and challenged than nonrandomized studies published in the general literature.

Finally, a certain proportion of highly cited trials may remain unchallenged. Sometimes the evidence from the original study may seem so overwhelming that further similar studies are deemed unethical to perform. The original study may be widely considered as a milestone for clinical practice and may provide the gold standard for testing new interventions. However, sometimes other, validating research may be in the works. Clinical research is time-consuming and challenging results may take several years to generate and publish. Therefore evidence from recent trials, no mater how impressive, should be interpreted with caution, when only one trial is available. It is important to know whether other similar or larger trials are still ongoing or being planned. Therefore, transparent and thorough trial registration is of paramount im-

portance[165] in order to limit premature claims for efficacy.

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REFERENCES

1. LeLorier J, Gregoire G, Benhaddad A, Lapierre J, Derderian F. Discrepancies between meta-analyses and subsequent large randomized, controlled trials. *N Engl J Med*. 1997;337:536-542.
2. Cappelleri JC, Ioannidis JP, Schmid CH, et al. Large trials vs meta-analysis of smaller trials: how do their results compare? *JAMA*. 1996;276:1332-1338.
3. Benson K, Hartz AJ. A comparison of observational studies and randomized, controlled trials. *N Engl J Med*. 2000;342:1878-1886.
4. Concato J, Shah N, Horwitz RI. Randomized, controlled trials, observational studies, and the hierarchy of research designs. *N Engl J Med*. 2000;342:1887-1892.
5. Ioannidis JP, Haidich AB, Pappa M, et al. Comparison of evidence of treatment effects in randomized and nonrandomized studies. *JAMA*. 2001;286:821-830.
6. Institute for Scientific Information. Web of Knowledge. Available at http://www.thompson.isi.com. Accessed August 20, 2004.
7. Dickersin K, Scherer R, Suci ES, Gil-Montero M. Problems with indexing and citation of articles with group authorship. *JAMA*. 2002;287:2772-2774.
8. *Cochrane Reviewer's Handbook*. Available at: http://www.cochrane.org/resources/handbook.
9. Volberding PA, Lagakos SW, Koch MA, et al; the AIDS Clinical Trials Group of the National Institute of Allergy and Infectious Diseases. Zidovudine in asymptomatic human immunodeficiency virus infection: a controlled trial in persons with fewer than 500 CD4-positive cells per cubic millimeter. *N Engl J Med*. 1990;322:941-949.
10. Brown G, Albers JJ, Fisher LD, et al. Regression of coronary artery disease as a result of intensive lipid-lowering therapy in men with high levels of apolipoprotein B. *N Engl J Med*. 1990;323:1289-1298.
11. Moertel CG, Fleming TR, Macdonald JS, et al. Levamisole and fluorouracil for adjuvant therapy of resected colon carcinoma. *N Engl J Med*. 1990;322:352-358.
12. Cohn JN, Johnson G, Ziesche S, et al. A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. *N Engl J Med*. 1991;325:303-310.
13. Stampfer MJ, Colditz GA, Willett WC, et al. Postmenopausal estrogen therapy and cardiovascular disease: ten-year follow-up from the Nurses' Health Study. *N Engl J Med*. 1991;325:756-762.
14. North American Symptomatic Carotid Endarterectomy Trial Collaborators. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. *N Engl J Med*. 1991;325:445-453.
15. Ziegler EJ, Fisher CJ Jr, Sprung CL, et al; the HA-1A Sepsis Study Group. Treatment of gram-negative bacteremia and septic shock with HA-1A human monoclonal antibody against endotoxin: a randomized, double-blind, placebo-controlled trial. *N Engl J Med*. 1991;324:429-436.
16. The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med*. 1991;325:293-302.
17. Pfeffer MA, Braunwald E, Moye LA, et al; the SAVE Investigators. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction: results of the survival and ventricular enlargement trial. *N Engl J Med*. 1992;327:669-677.
18. Grines CL, Browne KF, Marco J, et al; the Primary Angioplasty in Myocardial Infarction Study Group. A comparison of immediate angioplasty with thrombolytic therapy for acute myocardial infarction. *N Engl J Med*. 1993;328:673-679.
19. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD; the Collaborative Study Group. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. *N Engl J Med*. 1993;329:1456-1462.
20. Rimm EB, Stampfer MJ, Ascherio A, Giovannucci E, Colditz GA, Willett WC. Vitamin E consumption and the risk of coronary heart disease in men. *N Engl J Med*. 1993;328:1450-1456.
21. Stampfer MJ, Hennekens CH, Manson JE, Colditz GA, Rosner B, Willett WC. Vitamin E consumption and the risk of coronary disease in women. *N Engl J Med*. 1993;328:1444-1449.
22. Rossaint R, Falke KJ, Lopez F, Slama K, Pison U, Zapol WM. Inhaled nitric oxide for the adult respiratory distress syndrome. *N Engl J Med*. 1993;328:399-405.
23. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med*. 1993;329:977-986.
24. The EPIC Investigation. Use of a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor in high-risk coronary angioplasty. *N Engl J Med*. 1994;330:956-961.
25. Connor EM, Sperling RS, Gelber R, et al; Pediatric AIDS Clinical Trials Group Protocol 076 Study Group. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. *N Engl J Med*. 1994;331:1173-1180.
26. Fischman DL, Leon MB, Baim DS, et al; Stent Restenosis Study Investigators. A randomized comparison of coronary-stent placement and balloon angioplasty in the treatment of coronary artery disease. *N Engl J Med*. 1994;331:496-501.
27. Serruys PW, de Jaegere P, Kiemeneij F, et al; BENESTENT Study Group. A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease. *N Engl J Med*. 1994;331:489-495.
28. The Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group. The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. *N Engl J Med*. 1994;330:1029-1035.
29. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med*. 1995;333:1581-1587.
30. Shepherd J, Cobbe SM, Ford I, et al; West of Scotland Coronary Prevention Study Group. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *N Engl J Med*. 1995;333:1301-1307.
31. Sacks FM, Pfeffer MA, Moye LA, et al; Cholesterol and Recurrent Events Trial Investigators. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *N Engl J Med*. 1996;335:1001-1009.
32. Packer M, Bristow MR, Cohn JN, et al; US Carvedilol Heart Failure Study Group. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. *N Engl J Med*. 1996;334:1349-1355.
33. Omenn GS, Goodman GE, Thornquist MD, et al. Effects of a combination of beta carotene and vitamin A on lung cancer and cardiovascular disease. *N Engl J Med*. 1996;334:1150-1155.
34. Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. *N Engl J Med*. 1997;336:973-979.
35. Hammer SM, Squires KE, Hughes MD, et al; AIDS Clinical Trials Group 320 Study Team. A controlled trial of two nucleoside analogues plus indinavir in persons with human immunodeficiency virus infection and CD4 cell counts of 200 per cubic millimeter or less. *N Engl J Med*. 1997;337:725-733.
36. The EPILOG Investigators. Platelet glycoprotein IIb/IIIa receptor blockade and low-dose heparin during percutaneous coronary revascularization. *N Engl J Med*. 1997;336:1689-1696.
37. McHutchison JG, Gordon SC, Schiff ER, et al; Hepatitis Interventional Therapy Group. Interferon alfa-2b alone or in combination with ribavirin as initial treatment for chronic hepatitis C. *N Engl J Med*. 1998;339:1485-1492.
38. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med*. 1998;339:1349-1357.
39. Pitt B, Zannad F, Remme WJ, et al; Randomized Aldactone Evaluation Study Investigators. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *N Engl J Med*. 1999;341:709-717.
40. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G; the Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med*. 2000;342:145-153.
41. SHEP Cooperative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension: final results of the Systolic Hypertension in the Elderly Program (SHEP). *JAMA*. 1991;265:3255-3264.
42. The Writing Group for the PEPI Trial. Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women. *JAMA*. 1995;273:199-208.
43. Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. Endarterectomy for asymptomatic carotid artery stenosis. *JAMA*. 1995;273:1421-1428.
44. Hulley S, Grady D, Bush T, et al; Heart and Estrogen/progestin Replacement Study (HERS) Research Group. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. *JAMA*. 1998;280:605-613.
45. Downs JR, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. *JAMA*. 1998;279:1615-1622.
46. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA*. 2002;288:321-333.
47. MRC Vitamin Study Research Group. Prevention of neural tube defects: results of the Medical Research Council Vitamin Study. *Lancet*. 1991;338:131-137.
48. Hertog MG, Feskens EJ, Hollman PC, Katan MB, Kromhout D. Dietary antioxidant flavonoids and risk of coronary heart disease: the Zutphen Elderly Study. *Lancet*. 1993;342:1007-1011.
49. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet*. 1994;344:1383-1389.
50. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel vs aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet*. 1996;348:1329-1339.
51. Stephens NG, Parsons A, Schofield PM, Kelly F, Cheeseman K, Mitchinson MJ. Randomised controlled trial of vitamin E in patients with coronary disease: Cambridge Heart Antioxidant Study (CHAOS). *Lancet*. 1996;347:781-786.

52. Hansson L, Zanchetti A, Carruthers SG, et al; HOT Study Group. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. *Lancet*. 1998;351:1755-1762.
53. Poynard T, Marcellin P, Lee SS, et al; International Hepatitis Interventional Therapy Group (IHIT). Randomised trial of interferon alpha-2b plus ribavirin for 48 weeks or for 24 weeks vs interferon alpha-2b plus placebo for 48 weeks for treatment of chronic infection with hepatitis C virus. *Lancet*. 1998;352:1426-1432.
54. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet*. 1998;352:854-865.
55. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. *Lancet*. 1999;353:9-13.
56. Castaigne S, Cjomienne C, Daniel MT, et al. All-trans-retinoic acid as a differentiation therapy for acute promyelocytic leukemia, 1: clinical results. *Blood*. 1990;76:1704-1709.
57. Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. *J Natl Cancer Inst*. 1998;90:1371-1388.
58. Ioannidis JP, Cappelleri JC, Lau J, et al. Early or deferred zidovudine therapy in HIV-infected patients without an AIDS-defining illness. *Ann Intern Med*. 1995;122:856-866.
59. Law MR, Wald NJ, Rudnicka AR. Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis. *BMJ*. 2003;326:1423.
60. Gill S, Loprinzi CL, Sargent DJ, et al. Pooled analysis of fluorouracil-based adjuvant therapy for stage II and III colon cancer: who benefits and by how much? *J Clin Oncol*. 2004;22:1797-1806.
61. Rothwell PM, Eliasziw M, Gutnikov SA, et al. Analysis of pooled data from the randomised controlled trials of endarterectomy for symptomatic carotid stenosis. *Lancet*. 2003;361:107-116.
62. McCloskey RV, Straube RC, Sanders C, Smith SM, Smith CR; CHESS Trial Study Group. Treatment of septic shock with human monoclonal antibody HA-1A: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med*. 1994;121:1-5.
63. Garg R, Yusuf S; Collaborative Group on ACE Inhibitor Trials. Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure. *JAMA*. 1995;273:1450-1456.
64. Rodrigues EJ, Eisenberg MJ, Pilote L. Effects of early and late administration of angiotensin-converting enzyme inhibitors on mortality after myocardial infarction. *Am J Med*. 2003;115:473-479.
65. Cucherat M, Bonnefoy E, Tremeau G. Primary angioplasty vs intravenous thrombolysis for acute myocardial infarction. *Cochrane Database Syst Rev*. 2003;3:CD001560.
66. Yusuf S, Dagenais G, Pogue J, Bosch J, Sleight P; The Heart Outcomes Prevention Evaluation Study Investigators. Vitamin E supplementation and cardiovascular events in high-risk patients. *N Engl J Med*. 2000;342:154-160.
67. Sokol J, Jacobs SE, Bohn D. Inhaled nitric oxide for acute hypoxemic respiratory failure in children and adults. *Cochrane Database Syst Rev*. 2003;1:CD002787.
68. Karvouni E, Katritsis DG, Ioannidis JP. Intravenous glycoprotein IIb/IIIa receptor antagonists reduce mortality after percutaneous coronary interventions. *J Am Coll Cardiol*. 2003;41:26-32.
69. Brophy JM, Belisle P, Joseph L. Evidence for use of coronary stents: a hierarchical bayesian meta-analysis. *Ann Intern Med*. 2003;138:777-786.
70. Hacke W, Donnan G, Fieschi C, et al. Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA stroke trials. *Lancet*. 2004;363:768-774.
71. Brophy JM, Joseph L, Rouleau JL. Beta-blockers in congestive heart failure: a Bayesian meta-analysis. *Ann Intern Med*. 2001;134:550-560.
72. Yazdanpanah Y, Sissoko D, Egger M, Mouton Y, Zwahlen M, Chene G. Clinical efficacy of antiretroviral combination therapy based on protease inhibitors or non-nucleoside analogue reverse transcriptase inhibitors: indirect comparison of controlled trials. *BMJ*. 2004;328:249.
73. Kjaergard LL, Krogsgaard K, Gluud C. Interferon alfa with or without ribavirin for chronic hepatitis C: systematic review of randomised trials. *BMJ*. 2001;323:1151-1155.
74. Staessen JA, Gasowski J, Wang JG, et al. Risks of untreated and treated isolated systolic hypertension in the elderly: meta-analysis of outcome trials. *Lancet*. 2000;355:865-872.
75. Benavente O, Moher D, Pham B. Carotid endarterectomy for asymptomatic carotid stenosis: a meta-analysis. *BMJ*. 1998;317:1477-1480.
76. Huxley RR, Neil HA. The relation between dietary flavonol intake and coronary heart disease mortality: a meta-analysis of prospective cohort studies. *Eur J Clin Nutr*. 2003;57:904-908.
77. Tallman MS, Andersen JW, Schiffer CA, et al. All-trans-retinoic acid in acute promyelocytic leukemia. *N Engl J Med*. 1997;337:1021-1028.
78. Cuzick J, Powles T, Veronesi U, et al. Overview of the main outcomes in breast-cancer prevention trials. *Lancet*. 2003;361:296-300.
79. Watts NB, Harris ST, Genant HK, et al. Intermittent cyclical etidronate treatment of postmenopausal osteoporosis. *N Engl J Med*. 1990;323:73-79.
80. Smith P, Arnesen H, Holme I. The effect of warfarin on mortality and reinfarction after myocardial infarction. *N Engl J Med*. 1990;323:147-152.
81. Hussey GD, Klein M. A randomized, controlled trial of vitamin A in children with severe measles. *N Engl J Med*. 1990;323:160-164.
82. Smith DW, Frankel LR, Mathers LH, Tang AT, Ariagno RL, Prober CG. A controlled trial of aerosolized ribavirin in infants receiving mechanical ventilation for severe respiratory syncytial virus infection. *N Engl J Med*. 1991;325:24-29.
83. The National Institute of Child Health and Human Developments Intravenous Immunoglobulin Study Group. Intravenous immune globulin for the prevention of bacterial infections in children with symptomatic human immunodeficiency virus infection. *N Engl J Med*. 1991;325:73-80.
84. Green DM, Zevon MA, Lowrie G, Seigelstein N, Hall B. Congenital anomalies in children of patients who received chemotherapy for cancer in childhood and adolescence. *N Engl J Med*. 1991;325:141-146.
85. Bradley JD, Brandt KD, Katz BP, Kalasinski LA, Ryan SI. Comparison of an antiinflammatory dose of ibuprofen, an analgesic dose of ibuprofen, and acetaminophen in the treatment of patients with osteoarthritis of the knee. *N Engl J Med*. 1991;325:87-91.
86. Crawford J, Ozer H, Stoller R, et al. Reduction by granulocyte colony-stimulating factor of fever and neutropenia induced by chemotherapy in patients with small-cell lung cancer. *N Engl J Med*. 1991;325:164-170.
87. Maggioni AP, Franzosi MG, Santoro E, White H, Van de Werf F, Tognoni G; Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico II (GISSI-2) and The International Study Group. The risk of stroke in patients with acute myocardial infarction after thrombolytic and antithrombotic treatment. *N Engl J Med*. 1992;327:1-6.
88. Packer M, Gheorghiade M, Young JB, et al; RADIANCE Study. Withdrawal of digoxin from patients with chronic heart failure treated with angiotensin-converting enzyme inhibitors. *N Engl J Med*. 1993;329:1-7.
89. Jenkins DJ, Wolever TM, Rao AV, et al. Effect on blood lipids of very high intakes of fiber in diets low in saturated fat and cholesterol. *N Engl J Med*. 1993;329:21-26.
90. Rosman NP, Colton T, Labazzo J, et al. A controlled trial of diazepam administered during febrile illnesses to prevent recurrence of febrile seizures. *N Engl J Med*. 1993;329:79-84.
91. Hunter DJ, Manson JE, Colditz GA, et al. A prospective study of the intake of vitamins C, E, and A and the risk of breast cancer. *N Engl J Med*. 1993;329:234-240.
92. Ponsonby AL, Dwyer T, Gibbons LE, Cochrane JA, Wang YG. Factors potentiating the risk of sudden infant death syndrome associated with the prone position. *N Engl J Med*. 1993;329:377-382.
93. Winterkorn JM, Kupersmith MJ, Wirtschafter JD, Forman S. Treatment of vasospastic amaurosis fugax with calcium-channel blockers. *N Engl J Med*. 1993;329:396-398.
94. Greenberg ER, Baron JA, Tosteson TD, et al; Polyp Prevention Study Group. A clinical trial of antioxidant vitamins to prevent colorectal adenoma. *N Engl J Med*. 1994;331:141-147.
95. Klassen TP, Feldman ME, Watters LK, Sutcliffe T, Rowe PC. Nebulized budesonide for children with mild-to-moderate croup. *N Engl J Med*. 1994;331:285-289.
96. Jain JK, Mishell DR Jr. A comparison of intravaginal misoprostol with prostaglandin E2 for termination of second-trimester pregnancy. *N Engl J Med*. 1994;331:290-293.
97. Loprinzi CL, Michalak JC, Quella SK, et al. Megestrol acetate for the prevention of hot flashes. *N Engl J Med*. 1994;331:347-352.
98. O'Connell MJ, Martenson JA, Wieand HS, et al. Improving adjuvant therapy for rectal cancer by combining protracted-infusion fluorouracil with radiation therapy after curative surgery. *N Engl J Med*. 1994;331:502-507.
99. Suarez FL, Savaiano DA, Levitt MD. A comparison of symptoms after the consumption of milk or lactose-hydrolyzed milk by people with self-reported severe lactose intolerance. *N Engl J Med*. 1995;333:1-4.
100. Singh SN, Fletcher RD, Fisher SG, et al; Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure. Amiodarone in patients with congestive heart failure and asymptomatic ventricular arrhythmia. *N Engl J Med*. 1995;333:77-82.
101. Bhasin S, Storer TW, Berman N, et al. The effects of supraphysiologic doses of testosterone on muscle size and strength in normal men. *N Engl J Med*. 1996;335:1-7.
102. Stegeman CA, Tervaert JW, de Jong PE, Kallenberg CG; Dutch Co-Trimoxazole Wegener Study Group. Trimethoprim-sulfamethoxazole (co-trimoxazole) for the prevention of relapses of Wegener's granulomatosis. *N Engl J Med*. 1996;335:16-20.
103. van Hensbroek MB, Onyiorah E, Jaffar S, et al. A trial of artemether or quinine in children with cerebral malaria. *N Engl J Med*. 1996;335:69-75.
104. van der Horst CM, Saag MS, Cloud GA, et al; National Institute of Allergy and Infectious Diseases Mycoses Study Group and AIDS Clinical Trials Group. Treatment of cryptococcal meningitis associated with the acquired immunodeficiency syndrome. *N Engl J Med*. 1997;337:15-21.
105. Levine RJ, Hauth JC, Curet LB, et al. Trial of calcium to prevent preeclampsia. *N Engl J Med*. 1997;337:69-76.
106. Musch DC, Martin DF, Gordon JF, Davis MD, Kuppermann BD; the Ganciclovir Implant Study Group. Treatment of cytomegalovirus retinitis with a sustained-release ganciclovir implant. *N Engl J Med*. 1997;337:83-90.
107. Adams RJ, McKie VC, Hsu L, et al. Prevention of a first stroke by transfusions in children with sickle cell anemia and abnormal results on transcranial Doppler ultrasonography. *N Engl J Med*. 1998;339:5-11.
108. Stefanick ML, Mackey S, Sheehan M, Ellsworth N, Haskell WL, Wood PD. Effects of diet and exercise in men and postmenopausal women with low levels of

HDL cholesterol and high levels of LDL cholesterol. *N Engl J Med*. 1998;339:12-20.
109. Brisinda G, Maria G, Bentivoglio AR, Cassetta E, Gui D, Albanese A. A comparison of injections of botulinum toxin and topical nitroglycerin ointment for the treatment of chronic anal fissure. *N Engl J Med*. 1999; 341:65-69.
110. Tepel M, van der Giet M, Schwarzfeld C, Laufer U, Liermann D, Zidek W. Prevention of radiographic-contrast-agent-induced reductions in renal function by acetylcysteine. *N Engl J Med*. 2000;343:180-184.
111. Levine AM, Wernz JC, Kaplan L, et al. Low-dose chemotherapy with central nervous system prophylaxis and zidovudine maintenance in AIDS-related lymphoma: a prospective multi-institutional trial. *JAMA*. 1991;266:84-88.
112. Freeman EW, Rickels K, Sondheimer SJ, Polansky M. A double-blind trial of oral progesterone, alprazolam, and placebo in treatment of severe premenstrual syndrome. *JAMA*. 1995;274:51-57.
113. Williams-Russo P, Sharrock NE, Mattis S, Szatrowski TP, Charlson ME. Cognitive effects after epidural vs general anesthesia in older adults: a randomized trial. *JAMA*. 1995;274:44-50.
114. Meduri GU, Headley AS, Golden E, et al. Effect of prolonged methylprednisolone therapy in unresolving acute respiratory distress syndrome: a randomized controlled trial. *JAMA*. 1998;280:159-165.
115. Gulick RM, Mellors JW, Havlir D, et al. Simultaneous vs sequential initiation of therapy with indinavir, zidovudine, and lamivudine for HIV-1 infection: 100-week follow-up. *JAMA*. 1998;280:35-41.
116. Grady D, Herrington D, Bittner V, et al. Cardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/progestin Replacement Study follow-up (HERS II). *JAMA*. 2002;288: 49-57.
117. Grantham-McGregor SM, Powell CA, Walker SP, Himes JH. Nutritional supplementation, psychosocial stimulation, and mental development of stunted children: the Jamaican Study. *Lancet*. 1991;338:1-5.
118. Ghana VAST Study Team. Vitamin A supplementation in northern Ghana: effects on clinic attendances, hospital admissions, and child mortality. *Lancet*. 1993;342:7-12.
119. Sipe JC, Romine JS, Koziol JA, McMillan R, Zyroff J, Beutler E. Cladribine in treatment of chronic progressive multiple sclerosis. *Lancet*. 1994;344:9-13.
120. Karonga Prevention Trial Group. Randomised controlled trial of single BCG, repeated BCG, or combined BCG and killed *Mycobacterium leprae* vaccine for prevention of leprosy and tuberculosis in Malawi. *Lancet*. 1996;348:17-24.
121. Waldo AL, Camm AJ, deRuyter H, et al; the SWORD Investigators. Effect of d-sotalol on mortality in patients with left ventricular dysfunction after recent and remote myocardial infarction. *Lancet*. 1996;348:7-12.
122. Veronesi U, Maisonneuve P, Costa A, et al; Italian Tamoxifen Prevention Study. Prevention of breast cancer with tamoxifen: preliminary findings from the Italian randomised trial among hysterectomised women. *Lancet*. 1998;352:93-97.
123. The EPISTENT Investigators. Randomised placebo-controlled and balloon-angioplasty-controlled trial to assess safety of coronary stenting with use of platelet glycoprotein-IIb/IIIa blockade. *Lancet*. 1998;352:87-92.
124. CLIP Group (Cancer of the Liver Italian Programme). Tamoxifen in treatment of hepatocellular carcinoma: a randomised controlled trial. *Lancet*. 1998;352:17-20.
125. Torp-Pedersen C, Kober L; TRACE Study Group. Effect of ACE inhibitor trandolapril on life expectancy of patients with reduced left-ventricular function after acute myocardial infarction. *Lancet*. 1999;354:9-12.
126. Negrin RS, Haeuber DH, Nagler A, et al. Maintenance treatment of patients with myelodysplastic syndromes using recombinant human granulocyte colony-stimulating factor. *Blood*. 1990;76:36-43.
127. Budman DR, Berry DA, Cirrincione CT, et al; the Cancer and Leukemia Group B. Dose and dose intensity as determinants of outcome in the adjuvant treatment of breast cancer. *J Natl Cancer Inst*. 1998;90:1205-1211.
128. Veronesi U, De Palo G, Marubini E, et al. Randomized trial of fenretinide to prevent second breast malignancy in women with early breast cancer. *J Natl Cancer Inst*. 1999;91:1847-1856.
129. Rice GP, Filippi M, Comi G; Cladribine MRI Study Group. Cladribine and progressive MS: clinical and MRI outcomes of a multicenter controlled trial. *Neurology*. 2000;54:1145-1155.
130. Ventre K, Randolph A. Ribavirin for respiratory syncytial virus infection of the lower respiratory tract in infants and young children. *Cochrane Database Syst Rev*. 2004;4:CD000181.
131. Rantala H, Tarkka R, Uhari M. A meta-analytic review of the preventive treatment of recurrences of febrile seizures. *J Pediatr*. 1997;131:922-925.
132. Creery D, Mikrogianakis A. Sudden infant death syndrome. *Clin Evid*. 2003;10:457-467.
133. Russell K, Wiebe N, Saenz A, et al. Glucocorticoids for croup. *Cochrane Database Syst Rev*. 2004;1: CD001955.
134. Makhlouf AM, Al-Hussaini TK, Habib DM, Makarem MH. Second-trimester pregnancy termination: comparison of three different methods. *J Obstet Gynaecol*. 2003;23:407-411.
135. Nelson R. A systematic review of medical therapy for anal fissure. *Dis Colon Rectum*. 2004;47:422-431.
136. Nallamothu BK, Shojania KG, Saint S, et al. Is acetylcysteine effective in preventing contrast-related nephropathy? a meta-analysis. *Am J Med*. 2004;117:938-947.
137. Grantham-McGregor SM, Walker SP, Chang SM, Powell CA. Effects of early childhood supplementation with and without stimulation on later development in stunted Jamaican children. *Am J Clin Nutr*. 1997; 66:247-253.
138. Adachi JD, Roux C, Pitt PI, et al. A pooled data analysis on the use of intermittent cyclical etidronate therapy for the prevention and treatment of corticosteroid induced bone loss. *J Rheumatol*. 2000;27:2424-2431.
139. Anand SS, Yusuf S. Oral anticoagulant therapy in patients with coronary artery disease: a meta-analysis. *JAMA*. 1999;282:2058-2067.
140. Fawzi WW, Chalmers TC, Herrera MG, Mosteller F. Vitamin A supplementation and child mortality: a meta-analysis. *JAMA*. 1993;269:898-903.
141. Spector SA, Gelber RD, McGrath N, et al; Pediatric AIDS Clinical Trials Group. A controlled trial of intravenous immune globulin for the prevention of serious bacterial infections in children receiving zidovudine for advanced human immunodeficiency virus infection. *N Engl J Med*. 1994;331:1181-1187.
142. Lyman GH, Kuderer NM, Djulbegovic B. Prophylactic granulocyte colony-stimulating factor in patients receiving dose-intensive cancer chemotherapy: a meta-analysis. *Am J Med*. 2002;112:406-411.
143. Dundar Y, Hill R, Dickson R, Walley T. Comparative efficacy of thrombolytics in acute myocardial infarction: a systematic review. *QJM*. 2003;96:103-113.
144. Hood WB Jr, Dans AL, Guyatt GH, Jaeschke R, McMurray JJ. Digitalis for treatment of congestive heart failure in patients in sinus rhythm. *Cochrane Database Syst Rev*. 2004;2:CD002901.
145. Anderson JW, Randles KM, Kendall CW, Jenkins DJ. Carbohydrate and fiber recommendations for individuals with diabetes: a quantitative assessment and meta-analysis of the evidence. *J Am Coll Nutr*. 2004;23: 5-17.
146. Giorgi A, Weatherby RP, Murphy PW. Muscular strength, body composition and health responses to the use of testosterone enanthate: a double blind study. *J Sci Med Sport*. 1999;2:341-355.
147. Artemether-Quinine Meta-analysis Study Group. A meta-analysis using individual patient data of trials comparing artemether with quinine in the treatment of severe falciparum malaria. *Trans R Soc Trop Med Hyg*. 2001;95:637-650.
148. Saag MS, Cloud GA, Graybill JR, et al; National Institute of Allergy and Infectious Diseases Mycoses Study Group. A comparison of itraconazole vs fluconazole as maintenance therapy for AIDS-associated cryptococcal meningitis. *Clin Infect Dis*. 1999;28:291-296.
149. Martin DF, Kuppermann BD, Wolitz RA, Palestine AG, Li H, Robinson CA; Roche Ganciclovir Study Group. Oral ganciclovir for patients with cytomegalovirus retinitis treated with a ganciclovir implant. *N Engl J Med*. 1999;340:1063-1070.
150. Nieman DC, Brock DW, Butterworth D, Utter AC, Nieman CC. Reducing diet and/or exercise training decreases the lipid and lipoprotein risk factors of moderately obese women. *J Am Coll Nutr*. 2002;21:344-350.
151. Kaplan LD, Straus DJ, Testa MA, et al; National Institute of Allergy and Infectious Diseases AIDS Clinical Trials Group. Low-dose compared with standard-dose m-BACOD chemotherapy for non-Hodgkin's lymphoma associated with human immunodeficiency virus infection. *N Engl J Med*. 1997;336:1641-1648.
152. Diegoli MS, da Fonseca AM, Diegoli CA, Pinotti JA. A double-blind trial of four medications to treat severe premenstrual syndrome. *Int J Gynaecol Obstet*. 1998;62:63-67.
153. Flather MD, Yusuf S, Kober L, et al; ACE-Inhibitor Myocardial Infarction Collaborative Group. Long-term ACE-inhibitor therapy in patients with heart failure or left-ventricular dysfunction: a systematic overview of data from individual patients. *Lancet*. 2000;355: 1575-1581.
154. Ossenkoppele GJ, van der Holt B, Verhoef GE, et al; Dutch-Belgian Hemato-Oncology Cooperative Group. A randomized study of granulocyte colony-stimulating factor applied during and after chemotherapy in patients with poor risk myelodysplastic syndromes: a report from the HOVON Cooperative Group. *Leukemia*. 1999;13:1207-1213.
155. Citron ML, Berry DA, Cirrincione C, et al. Randomized trial of dose-dense vs conventionally scheduled and sequential vs concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: first report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741. *J Clin Oncol*. 2003;21:1431-1439.
156. Lau J, Ioannidis JP, Schmid CH. Summing up evidence: one answer is not enough. *Lancet*. 1998;351: 123-127.
157. Ioannidis JP, Cappelleri JC, Lau J. Issues in comparisons between meta-analyses and large trials. *JAMA*. 1998;279:1089-1093.
158. Fleming TR, DeMets DL. Surrogate end points in clinical trials: are we being misled? *Ann Intern Med*. 1996;125:605-613.
159. Dickersin K, Min YI. Publication bias: the problem that won't go away. *Ann N Y Acad Sci*. 1993;703: 135-146.
160. Easterbrook PJ, Berlin JA, Gopalan R, Matthews DR. Publication bias in clinical research. *Lancet*. 1991; 337:867-872.
161. Stern JM, Simes RJ. Publication bias: evidence of delayed publication in a cohort study of clinical research projects. *BMJ*. 1997;315:640-645.
162. Ioannidis JP. Effect of the statistical significance of results on the time to completion and publication of randomized efficacy trials. *JAMA*. 1998;279:281-286.
163. Wheatley K, Clayton D. Be skeptical about unexpected large treatment effects: the case of an MRC AML12 randomization. *Control Clin Trials*. 2003;24:66-70.
164. Poynard T, Munteanu M, Ratziu V, et al. Truth survival in clinical research: an evidence-based requiem? *Ann Intern Med*. 2002;136:888-895.
165. DeAngelis C, Drazen JM, Frizelle FA, et al. Clinical trial registration: a statement from the International Committee of Medical Journal Editors. *N Engl J Med*. 2004;351:1250-1251.

EXHIBIT 315

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ORIGINAL PAPER

On the Suppression of Vaccination Dissent

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Abstract Dissenters from the dominant views about vaccination sometimes are subject to adverse actions, including abusive comment, threats, formal complaints, censorship, and deregistration, a phenomenon that can be called suppression of dissent. Three types of cases are examined: scientists and physicians; a high-profile researcher; and a citizen campaigner. Comparing the methods used in these different types of cases provides a preliminary framework for understanding the dynamics of suppression in terms of vulnerabilities.

Keywords Vaccination · Dissent · Reputation · Free speech · Controversy

Introduction

Vaccination has long been a contentious topic (Colgrove 2006; Johnston 2004). The orthodox position, adopted by most physicians and government health departments, is that vaccination is vital in reducing illness and death from infectious disease (Andre et al. 2008; Offit and Bell 2003). Health authorities specify a recommended schedule of vaccinations for babies and children. As new vaccines are developed and tested, they are added to the schedule to reduce morbidity and death from additional diseases. The orthodox position is that adverse reactions to vaccines are rare, and insignificant compared to the benefits.

In the face of this dominant position, a number of physicians, scientists, and citizens argue that vaccination has significant shortcomings. They question the scale of the benefits, noting how death rates from infectious diseases declined dramatically before the introduction of mass vaccination. They maintain that the

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adverse effects of vaccination have been underestimated (Habakus and Holland 2011; Halvorsen 2007).

The vaccination debate is not just a disagreement about evidence concerning benefits and risks: values are involved too. For infectious disease to spread, there need to be susceptible individuals. Mass vaccination, according to proponents, reduces the likelihood of spread, because most people are immune. The result is what is called "herd immunity," causing an additional decline in disease even beyond vaccine-induced individual immunity. Because of this collective benefit, including the protection of those unable to be immunized, proponents see widespread vaccination as a moral imperative.

Critics, on the other hand, support parental choice in vaccination decisions. They oppose penalties for not vaccinating, such as requirements that children be fully vaccinated in order to attend school.

The vaccination debate can be incredibly emotional on both sides. Partly this seems to be because children's health is involved: parents react to their children becoming ill from infectious disease or suffering reactions to vaccines. The clash between collective benefits (herd immunity) and freedom of choice adds to the mix. Because vaccination is a signifier for the benefits of modern medicine, some proponents see any questioning of vaccination as a rejection of enlightened thinking.

When physicians and health authorities support vaccination based on careful assessments of benefits and risks, they may dismiss citizen critics as ill-informed. Because nearly all experts endorse vaccination, there may seem to be no rational basis for opposition. In this context, any physician or scientist who questions vaccination is a potential threat to the public perception that credentialed experts unanimously endorse vaccination. This sets the stage for suppression of dissent.

Suppression of dissent is action taken against dissenting individuals, or the research supporting their positions, that goes beyond fair debate. Methods of suppressing individuals include spreading of rumors, vilification, harassment, reprimands, demotions, deregistration, and dismissal (Martin 1999a). Methods of suppressing research data include censorship, denial of funding, and denial of access to research materials (Martin 1999b). There is an overlap between these modes of suppression. For example, a scientist's grant applications might be rejected, thereby denying opportunities for research.

Debate is a normal and desirable feature of the scientific enterprise. Suppression is different from debate in that individuals, and their capacity to do research and engage in debate, are targeted. Suppression is important because it skews research agendas and public discussions.

The focus here is on suppression of vaccination critics. In principle, it is possible for vaccination supporters to be suppressed, though in practice this is unlikely because critics do not have any significant capacity to impose sanctions.

It is worth mentioning that the existence of suppression of dissent does not necessarily mean dissenters are correct, nor that researchers deserve funding merely for dissenting. However, even if dissenters are completely wrong, suppressing them can be damaging in several ways (Sunstein 2003). It sets up a pattern of unfair behavior that can hinder open discussion of issues even within the dominant

viewpoint. It discourages supporters from thinking for themselves about the evidence and arguments, because they encounter contrary views less frequently. Critics can keep advocates honest and alert, with their arguments well formulated. Finally, suppression can aid the cause of critics by making them feel unfairly treated: some observers may wonder why proponents cannot rely on the arguments. When the struggle is open and honest, the outcome will seem more legitimate.

My own involvement in the vaccination debate is primarily as a defender of fair and open debate on contentious issues, given my long-term interest in dissent (Martin 1981; Martin et al. 1986). Personally, I do not hold strong views about vaccination.

The next section provides additional background about suppression of dissent, including triggers, methods, patterns, and tests. The following sections outline several cases, falling into three main types: scientists and physicians; a high-profile researcher; and a citizen campaigner. Following this is a comparison of the suppression methods used in the three types of cases. The conclusion spells out the implications of suppression for the vaccination issue.

Suppression of Dissent

Dissent is a disagreement with or challenge to standard views. Historically, the most familiar type is political dissent, especially any questioning of an authoritarian government. Struggles for political freedom have included, as a central feature, struggles for free speech, most famously articulated in the first amendment to the US Constitution.

Free speech remains contested even in countries where it is rhetorically supported and legally protected, with many examples of attacks on those who speak out (Boykoff 2006; Curry 1988; Ewing and Gearty 1990; Goldstein 1978; Hamilton and Maddison 2007; Jones 2001; Soley 2002). In many countries, especially those with repressive governments, criticism of the government remains a subversive activity, sometimes met with harsh measures.

Political speech is only one type of dissent. Others include challenges to corporations, professions, churches, and indeed any group with the capacity to influence opinions and exact reprisals.

A major gap in free speech protection is speech within organizations. Employees are seldom granted the same protections as citizens (Barry 2007; Ewing 1977; Kassing 2011). Whistleblowers, who are often employees, are often met with reprisals (Alford 2001; Glazer and Glazer 1989; Miceli et al. 2008).

Dissent in science can be understood within this wider context. In principle, scientists can speak out, challenging orthodoxy or powerholders. Indeed, within science, being able to question and challenge ideas is widely seen as essential for scientific advance. When governments impose a view about a scientific matter, as in the case of Lysenkoism in the former Soviet Union (Joravsky 1970), this is seen as an outrageous denial of scientific freedom.

In practice, scientific dissent remains risky (Deyo et al. 1997; Martin 1999a, b; Moran 1998; Sommer 2001). A typical scenario goes like this. A scientist does

research, or speaks out, in a way that threatens a powerful group and, as a result, comes under attack. The form of the attack depends on the circumstances, in particular on the scientist's vulnerabilities and on the resources available to attackers. The scientist's reputation can be harmed by the spreading of rumors, open denunciations, and formal proceedings with attached stigma. The scientist's opportunity to express views can be hindered by direct censorship (such as refusing permission to give talks or make public comments) and by rejecting articles. The scientist's opportunity to do research can be hindered by refusing access to data or research facilities, and by rejecting research grant applications. Finally, a scientist's livelihood can be threatened by dismissal.

The four areas of reputation, speech, research, and employment often interact. For example, a formal investigation into a scientist's alleged misdemeanors serves to harm the scientist's reputation and, by requiring large amounts of time and effort to defend, limits the scientist's opportunity to do research.

It is reasonable to ask, how can anyone know whether suppression of dissent is involved? After all, many of the actions involved, such as rejecting articles, rejecting grant applications, and dismissal, can be taken for quite legitimate reasons. The rumors might well be true, and public denunciations warranted. A scientist subject to such adverse actions might just be a poor researcher or, even worse, a cheat.

To determine whether actions are taken for legitimate reasons or can be characterized as suppression of dissent, there is ultimately no substitute for a detailed analysis of claims and actions. This can be a major undertaking, because many cases involve incredible detail, with claims and counter-claims and a complex set of circumstances (e.g., Delborne 2008). However, there are a few convenient tests that can be used to make a preliminary judgment (Martin 2013). In the following, for convenience I refer to a scientist; the same sorts of processes apply to physicians and others with specialist training and credentials.

First is the timing of actions. If a scientist speaks out and shortly afterwards is subject to adverse actions, this increases the chance that the adverse actions were reprisals. Reprisals against whistleblowers often display this timing correlation.

Second is the question of who receives criticism and complaints. When criticisms are made directly to a scientist, this usually can be understood as part of a process of dialogue and debate. When complaints are initially made to a scientist's boss, a government agency, or professional association, this often indicates an attempt to suppress dissent, aside from those situations in which mandatory reporting procedures are applicable.

Third is the double standard test. The scientist who is the target of adverse actions can be compared to other scientists who are not, in terms of publications, reputation, rank, seniority, and prior work evaluations. If the targeted scientist is equal to or superior to others in terms of performance, this raises suspicion that suppression is involved.

Fourth is the relationship to vested interests. If the scientist's research or public statements are threatening to a government, powerful corporation, profession or dominant orthodoxy, this is a plausible reason for suppression to occur.

Fifth is a pattern of similar adverse actions. In some fields, there are many examples of critics who experienced adverse actions. For example, quite a number of scientists who are critics of nuclear power, pesticides, and fluoridation have been targets of attack (Martin 1999a).

When several of these criteria are satisfied, this is a strong indication that suppression could be involved. Consider a scientist who speaks out critically about an issue and threatens a group with vested interests. Shortly afterwards, the scientist is denounced for poor work, whereas colleagues of lesser standing are left untouched. This combination of events provides strong prima facie evidence that suppression is involved.

Note that the analysis of suppression is largely independent of an assessment of the scientific validity of the claims made. The index of suppression is whether norms of fair treatment are followed, including for assessing publications, allowing free speech and allowing investigation of unfashionable topics. It is quite possible for a researcher to be completely wrong scientifically and yet be suppressed; likewise, it is quite possible for a researcher to be vindicated scientifically and yet to have been the recipient of favoritism in violation of norms of fairness. A classic case is the response to the astronomical and geological theories of Immanuel Velikovsky when first publicized in the 1950s: mainstream scientists, in rejecting Velikovsky's ideas, violated norms of fair play, for example in condemning Velikovsky by appealing to their own authority as scientists rather than examining the evidence, and by seeking to censor publication (de Grazia 1966). Nearly all scientists believe Velikovsky was wrong, but aspects of his treatment can still be classified as suppression.

The consequences of suppression can be severe: harm to reputation, hindrance of research, and even destruction of a career. Although the individual who is targeted suffers the most, the wider impact can be greater. Suppression of dissent can send a powerful signal to other scientists that it is risky to do research or speak out on certain topics. This chilling effect on research and speech can lead to entire research areas being neglected or distorted. Suppression thus operates as a tool in struggles over research agendas.

Suppression Cases

Here, several cases are described that seem to fit the criteria for suppression of dissent. The accounts here are brief and intended only to introduce material relevant to the possibility of suppression being involved, not to provide comprehensive treatments. Further information about the cases, from different perspectives, can be found in the references cited, and additional references cited in them. The accounts here do not address the validity of the dissent; rather, they invoke the tests, outlined in the previous section, for making a preliminary judgment.

First are two cases, involving a researcher and a physician, that are typical of suppression cases in other fields. Next is a high-profile case involving a researcher. The final case involves a citizen critic of vaccination.

A Researcher and a Physician

From 1995 to 2002, Gary Goldman served as the research/epidemiology analyst on a project studying chickenpox funded by the Centers for Disease Control and Prevention (CDC). The project was run in cooperation with the Los Angeles County Department of Health Services (LACDHS). Goldman discovered an increase in shingles among *un*vaccinated children and adults and hypothesized that this was associated with the universal varicella (chickenpox) vaccination program, with the idea that prior to widespread vaccinations, most people through interpersonal interactions were repeatedly exposed to varicella, thereby preventing shingles. Apparently because the co-principal investigators on the project wanted to protect the varicella vaccination program, Goldman's collaboration with a CDC modeler was terminated and Goldman was instructed not to continue his investigations into the incidence of shingles.

When Goldman sent copies of papers to his superiors, he received no feedback for months, even years; in contrast, their own paper, not challenging vaccination orthodoxy, was reviewed within a day. Goldman was formally required to have all his e-mails pre-screened by his superiors. He asked to interview ten shingles patients to gain extra information; his request was not answered. He resigned in 2002, feeling he did not have proper support to undertake objective research.

After Goldman independently submitted papers to peer-reviewed journals and contacted the CDC about appropriate co-authorship credits, he received a letter from the Los Angeles County Legal Department to "cease and desist" publication in a medical journal. This letter was initiated by Dr Laurene Mascola, head of the Acute Communicable Disease Control Unit of LACDHS. Goldman's lawyer said this order had no legal merit and that if it was pursued, he would file a legal action under state and federal false claims acts. The LA County Legal Department did not follow up with any action. Goldman's opponents also contacted editors to try to prevent or postpone publication of his papers (Goldman and King 2013; Orrin 2010). Goldman's claims about varicella have been challenged in print (Myers 2013) but not his claims about his treatment.

Jayne Donegan, a British general practitioner, was initially supportive of vaccination. Years into her practice, she had doubts and undertook a comprehensive study drawing on the medical literature. She later agreed to testify on behalf of two mothers who opposed vaccinating their children: the children's absent fathers had gone to court to mandate vaccinations. The General Medical Council, hearing comments about the case in the mass media, accused Donegan of professional misconduct. More than two years later, in 2006, the GMC produced its charges that Donegan had misrepresented the scientific evidence she had quoted in the court case (Dyer 2006). The GMC lost the case and Donegan was completely exonerated (Dyer 2007; GMC 2007). However, the bringing of charges stigmatized her, and the necessity to prepare lengthy rebuttals to the GMC's chosen experts took an enormous amount of time and effort. Donegan was only able to afford to contest the GMC's charges because of Medical Indemnity Insurance, which covered the more than £100,000 cost of legal fees, but not the considerable costs of accommodation and lost income. In the conclusion of Donegan's account of the experience, she

states, "Pleased as I am with the successful conclusion of my hearing, it has taken an inevitable and heavy toll on my children, our family and my professional life" (Donegan 2008).

A High-Profile Researcher

Andrew Wakefield was a gastroenterologist at Royal Free Hospital in Britain. He was lead author in a study of 12 children who developed gastrointestinal symptoms linked to regressive autism. The paper, published in 1998 in the prestigious medical journal *The Lancet,* was a case review study: it presented evidence suggestive of a new disease syndrome, with a possible but unproven link to the MMR (measles, mumps and rubella) triple vaccine (Wakefield et al. 1998).

On publication, and with the approval of the hospital administration, Wakefield took part in a press conference. Wakefield suggested it might be safer for the measles vaccine to be taken separately—he did not argue against vaccination—and many parents opted for single vaccines. Six months later, the British government withdrew the availability of single measles, mumps and rubella vaccines on the National Health Service, and vaccination rates declined.

The *Lancet* study became a major media event, with the possible link between MMR and autism turned into a giant scare. Much of the blame for the decline in vaccination rates was attributed to Wakefield; Goldacre (2009: 290–331) instead blames the media.

Journalist Brian Deer (2004) made allegations about Wakefield, leading to a lengthy case before the General Medical Council (GMC), which found Wakefield guilty of dishonesty and abuse of children who were subjects in the research, and stripped him of his license to practice medicine (GMC 2010). *The Lancet* then retracted the paper as flawed, a rare event in scientific publishing. Wakefield left the country and started a new career in the US. Later, Deer (2011) made new allegations against Wakefield. John Walker-Smith, a co-author with Wakefield of the paper in *The Lancet,* who was found guilty by the GMC along with Wakefield, was later cleared in a court action.

Critics of Wakefield say the sanctions taken against him and his work were justified by the seriousness of his transgressions. Wakefield (2010) contests the claims made by Deer, the General Medical Council, and others. The issues in the Wakefield saga have been analyzed at great length, and it is impossible to do justice to all the arguments in a short account. The modest aim here is determine whether the treatment of Wakefield fits into the category of suppression of dissent. The key criterion used here is the double standard test: have others guilty of transgressions similar to those alleged of Wakefield been treated in a similar way?

There is evidence of extensive bias in biomedical research, including undeclared conflicts of interest, withholding evidence, manipulating statistics, using bioactive placebos, ghostwriting, and much else (Abraham 1995; Angell 2005; Braithwaite 1984; Goldacre 2012; Kassirer 2005; Krimsky 2003; Smyth et al. 2010; Stamatakis et al. 2013). These serious violations of research ethics seldom result in any penalties for the violators, much less the sort of banner treatment suffered by Wakefield. Plagiarism by students, for example, is treated as a serious violation;

ghostwriting is a form of plagiarism, but is seldom penalized: "… to the best of my knowledge, no academic anywhere in the world has ever been punished for putting their name on a ghostwritten academic paper" (Goldacre 2012: 298).

Thus, even if Wakefield is guilty as charged, his treatment might be considered excessive by the norms in the field. If he is not guilty, as he argues (Wakefield 2010), then his treatment is even more obviously excessive. The key difference between Wakefield and others in the field is that the others are working for or funded by pharmaceutical companies and/or not challenging biomedical orthodoxy.

Some critics of Wakefield refer to the further claims by Brian Deer (2011) of fraud in clinical practice. There is a double standard here in the level of scrutiny to which Wakefield has been subjected. Few other scientists have had their research put through such an intense interrogation. Given the prevalence of bias and poor-quality research in biomedicine, it is quite possible that others subject to the same level of scrutiny would come up wanting.

Unlike most of his peers, Wakefield has been subject to a degradation ceremony, a ritualistic denunciation casting him out of the company of honest researchers (Thérèse and Martin 2010). By degrading Wakefield's reputation, vaccination is symbolically vindicated and the credibility of any criticism undermined. Supporters of vaccination have repeatedly used the example of Wakefield to suggest that criticism of vaccination is misguided (e.g., Grant 2011: 105–124; Offit 2010). The logic of using Wakefield's ignominy as an argument in defense of vaccination is not replicated in the case of a single biomedical scientist who supports standard views. Considering that bias and conflict of interest are endemic to pharmaceutical-company-sponsored research, it is striking that no supporter of orthodoxy concludes that this discredits support for pharmaceutical drugs generally. (Some critics draw this conclusion.)

Wakefield's extended degradation ceremony has served as a warning to others not to follow in his footsteps. In contrast, no pharmaceutical company scientist has been subject to an equivalent investigation and denunciation. There seems to be relatively little career risk in accepting corporate funding and participating in biased research, undeclared conflicts of interest, or ghostwriting. The public signal then is to avoid challenging orthodoxy.

This assessment of the Wakefield saga has had a limited objective: to determine whether he has been dealt with in the same way as other scientists with similar records but who have not challenged orthodox views on vaccination. If the case presented by Wakefield and his supporters (CryShame 2014; Wakefield 2010; Walker 2012) is accepted, then suppression of dissent definitely has been involved. If, on the other hand, the case presented by Wakefield's critics (Deer 2011; GMC 2010) is accepted, it is not feasible to make an informed assessment about suppression on present evidence: because the scrutiny of Wakefield has few comparators, it is not possible to do a simple double-standard comparison.

This assessment does not address the question of whether Wakefield's research was valid or whether he violated medical ethics by not declaring a conflict of interest, much less whether his views about the measles vaccine are valid. Wakefield may have been suppressed, or he may have been treated fairly in light of his

transgressions, but it is difficult to say for sure given that none of his orthodox peers have had their work investigated to the same level.

A Citizen Campaigner

Meryl Dorey is an Australian campaigner critical of government vaccination policy. After her son suffered adverse reactions to vaccines, in 1994 she set up a citizens' group, the Australian Vaccination Network (AVN), which presented the negative aspects of vaccination and argued for parental choice in vaccination choices for their children. The AVN is similar to other vaccine-critical groups in various countries (Hobson-West 2007).

Although Dorey lacks any training or credentials relevant to the vaccination issue, through years of personal study she became a formidable commentator and debater. This was significant in the Australian context, because there has been only one Australian scientist or physician—namely, scientist Dr Viera Scheibner—who has been an outspoken critic of vaccination (Scheibner 1993). Dorey, through her strenuous efforts, became the highest profile figure able to muster facts and figures critical of vaccination.

In 2009, a group called Stop the Australian Vaccination Network (SAVN) was set up with the stated aim of shutting down the AVN. SAVN's main presence was a Facebook page with thousands of friends. Those linked to SAVN—called here SAVNers—included some physicians, nurses, and other professionals, but there were no apparent links to professional organizations, such as the Australian Medical Association.

SAVNers and others used various techniques to attack the AVN. Dorey was singled out as a key target (AVN 2014; Martin 2011, 2012a; SAVN 2014).

- SAVN made unsupported claims that the AVN believed in a global conspiracy to implant mind-control chips via vaccination.
- SAVNers made abusive comments about Dorey and vaccine critics, and created derogatory images.
- SAVNers made dozens of complaints about the AVN to government agencies, serving as a form of harassment on those occasions when the AVN had to respond.
- When Dorey was scheduled to give a talk, SAVNers wrote to the venues criticizing her and seeking to prevent her speaking.
- After Dorey was interviewed or reported in the media, SAVNers complained to the media companies, seeking to discourage them from giving her any visibility.
- When Dorey commented on blogs of other vaccine-critical groups, SAVNers joined the blogs and disrupted the conversations through hostile comments about Dorey and the beliefs of the bloggers.
- Another group, Vaccine Information and Awareness Society, posted a "Hall of Shame" with names and addresses of critics of vaccination and of individuals and businesses who had advertised in the AVN's magazine *Living Wisdom,* opening them to harassment.

- Anonymous individuals sent pornographic images to Dorey and others in the AVN.
- Anonymous individuals made threatening calls to Dorey's phone. Two such calls were recorded and traced to the home of a founder of SAVN.

Discussion

Each of the individuals discussed here was critical, to some degree, of vaccination orthodoxy, and each was subject to adverse actions. The question, in each case, is whether the adverse actions were linked to their dissent on vaccination.

Their antagonists, in every instance, justified their actions by the shortcomings of the individual. What is distinctive is they never use the double standard test: in no case have the vaccine critic's performance and behavior been carefully compared to others who are pro-vaccination. Adverse actions are always justified on a case-by-case basis, with the standards essentially created for the occasion.

The analysis here is preliminary. Each of these cases could be investigated in more detail, and other cases examined. However, even with this limited data set, it seems plausible to conclude that a key factor in the actions taken against these individuals was their criticism of vaccination. Additional support for this conclusion comes from the pattern in this area.

The best counter-evidence to this conclusion would be a set of examples in which individuals supportive of vaccination suffered reprisals. Many more cases would be needed to provide convincing counter-evidence, given that there are many more supporters than critics of vaccination, especially among scientists and physicians.

One argument for the actions against critics is that it is not credible to criticize vaccination. Sometimes the label "anti-vaccination" is used, though seldom defined. For supporters of the orthodoxy, it seems that anyone who criticizes the orthodoxy in any way is labeled "anti-vaccination," though many of the critics have concerns only about some vaccines or about vaccination schedules. Sometimes the label "anti-science" is applied to critics, implying that there can be no legitimate scientific concerns about vaccination.

Although the number of cases is small, they can be used to illustrate the different sorts of vulnerabilities of individuals in different situations. It is useful to consider the four key areas of reputations, speech, research opportunities, and employment.

Reputation

In all cases, the individual's credibility was a key target for attack. Credibility can be damaged in several ways. The most direct is through derogatory comments, for example through abusive blogs or hostile media stories. However, probably more important is the reputation damage caused by official actions, such as deregistration hearings and adverse findings, such as *The Lancet*'s retraction of Wakefield's paper and the public warning about the Australian Vaccination Network issued by the Health Care Complaints Commission (HCCC). Official bodies are seen by many in

the public as being fair-minded, namely as dispensing justice, even when they are running an agenda, so when they take action it can be highly damaging to reputations. This is true even when the actions are later exposed as invalid, as was the HCCC's legal authority to issue a warning about the AVN. The impact of official actions is augmented by the efforts of pro-vaccination campaigners, who repeatedly highlight the official actions, and by journalists, who treat the statements of official bodies as newsworthy.

Speech

Communication opportunities include publication of scientific articles, papers given at scientific conferences, interviews in the mass media, and public talks. Different forums offer differing levels of credibility and different sorts of audiences. Attempts were made to prevent Goldman from submitting scientific papers and having them published. This sort of censorship was aimed at limiting his access to a highly credible forum, namely the scientific literature. In contrast, a citizen campaigner like Dorey seeks primarily to address wider audiences. Attempts were made to block her access to speaking venues and to news media.

Research Opportunities

For scientists, doing research may require laboratory facilities, access to research subjects, and funding to hire staff and pay for materials. Withdrawing or preventing research opportunities is a means for suppressing dissent. For example, Goldman was not given permission to interview parents about shingles, thereby blocking his capacity to deepen his studies. Research opportunities are less relevant to those not undertaking research, such as physicians and citizen campaigners.

Employment

Having a job provides income and sometimes may offer professional opportunities and enhance one's reputation. The threat of losing one's job or even one's career can be enough to discourage dissent. Scientists and physicians alike are vulnerable to threats to their employment. Deregistration can serve to bar a physician from their career, at least without making a huge upheaval. Donegan was threatened with deregistration; Wakefield was deregistered and left Britain to continue his career. In contrast, some citizen campaigners, such as Dorey, are less dependent on career employment. They may need to a job for purposes of income, but are not tied to a particular profession: they can obtain a job in an area unrelated to their dissent.

Conclusion

The cases described here provide evidence for a pattern—not a conspiracy—of suppression of vaccination dissent. A more comprehensive analysis would look at a larger number of cases and do a more systematic comparison between dissenters and

non-dissenters. However, even the limited number of cases treated here is enough to suggest that suppression of dissent occurs and to give some preliminary indications of methods used in different circumstances.

It is predictable that attacks on dissent will target the specific vulnerabilities of individual dissenters. Four main areas of potential vulnerability are apparent from the case studies: reputation, speech, research opportunities, and employment. Researchers can be targeted in all four areas, whereas physicians and citizen campaigners do not need to do research. Citizen campaigners are especially difficult to suppress, as suggested by the scale and diversity of the attack on Meryl Dorey and the Australian Vaccination Network.

Researchers are especially significant because of their status as scientists. In an area where health departments, prestigious scientists and physicians all support a position, even a few dissenting scientists can make a huge difference to public perceptions: they change the issue from apparent unanimity into one involving credible debate. This is why, in such circumstances, suppression of dissent is so important. If dissenters can be silenced or discredited, then it seems as if all experts agree. All that remain are citizen activists.

In an arena where citizens are the main critics of orthodoxy, a slightly different process can occur. Citizen campaigners who develop a profile remain a threat to orthodoxy, though not so potent as dissident scientists and physicians. Dorey developed considerable knowledge and skills, and few supporters of vaccination were willing to debate her. By silencing and discrediting her and her organization, visible dissent would be greatly reduced.

The consequences of suppressing dissent can be quite significant. Most obviously, the careers of those targeted can be disrupted or destroyed. Probably more important is the chilling effect: when others see what happens to dissenters, many will become less likely to do anything that risks triggering the same sort of reaction. Most of Wakefield's collaborators signed a retraction of an interpretation of their findings, something unlikely without the storm of protest against the paper. Because of the abuse experienced by Dorey, other members of the committee of the AVN preferred that their identity not be known so they would not be subject to similar treatment.

When researchers are reluctant to undertake studies in particular fields, and governments and corporations do not want to fund studies, the result can be a gap in knowledge: particular topics are understudied, even though resources are available to study them and some people would like them investigated. Such gaps in research due to the influence of vested interests are called "undone science" (Frickel et al. 2010; Hess 2006, 2009). The primary cause of undone science is the unwillingness of funding organizations to support research in the area, because the findings might be unwelcome. Suppression of dissent operates as a supplementary mechanism to prevent and discourage researchers from studying these topics.

Suppression of dissent, through its chilling effect, can skew public debates, by discouraging participation. In Australia, critics of vaccination have become aware that if they become visible, they are potentially subject to denigration and complaints. Because of the level of personal abuse by pro-vaccinationists, many of those who might take a middle-of-the-road perspective, perhaps being slightly

critical of some aspects of vaccine policy, are discouraged from expressing their views. The result is a highly polarized public discourse that is not conducive to the sort of careful deliberation desirable for addressing complex issues.

According to the highest ideals of science, ideas should be judged on their merits, and addressed through mustering evidence and logic. Suppression of dissent is a violation of these ideals. Challenging suppression is part of the struggle to push science towards its own stated principles.

References

Abraham, J. (1995). *Science, politics and the pharmaceutical industry: Controversy and bias in drug regulation*. London: UCL Press.

Alford, C. F. (2001). *Whistleblowers: Broken lives and organizational failure*. Ithaca, NY: Cornell University Press.

Andre, F. E., Booy, R., Bock, H. L., et al. (2008). Vaccination greatly reduces disease, disability, death and inequity worldwide. *Journal of the World Health Organization, 86*(2), 140–146.

Angell, M. (2005). *The truth about the drug companies: How they deceive us and what to do about it*. New York: Random House.

AVN (2014). Australian Vaccination Network Inc. http://avn.org.au/. Accessed 1 February 2014.

Barry, B. (2007). *Speechless: The erosion of free expression in the American Workplace*. San Francisco: Berrett-Koehler.

Boykoff, J. (2006). *The suppression of dissent: How the state and mass media squelch US American social movements*. New York: Routledge.

Braithwaite, J. (1984). *Corporate crime in the pharmaceutical industry*. London: Routledge & Kegan Paul.

Colgrove, J. (2006). *State of immunity: The politics of vaccination in twentieth-century America*. Berkeley, CA: University of California Press.

CryShame (2014). GMC hearings. http://www.cryshame.org/. Accessed 1 February 2014.

Curry, R. O. (Ed.). (1988). *Freedom at risk: Secrecy, censorship, and repression in the 1980s*. Philadelphia: Temple University Press.

De Grazia, A. (1966). *The Velikovsky Affair*. London: Sidgwick & Jackson.

Deer, B. (2004). Revealed: MMR research scandal. *Sunday Times,* 22 February.

Deer, B. (2011). Piltdown medicine: the missing link between MMR and autism. *BMJ Blogs,* 6 January.

Delborne, J. A. (2008). Transgenes and transgressions: Scientific dissent as heterogeneous practice. *Social Studies of Science, 38*(4), 509–541.

Deyo, R. A., Psaty, B. M., Simon, G., Wagner, E. H., & Omenn, G. S. (1997). The messenger under attack—Intimidation of researchers by special-interest groups. *New England Journal of Medicine, 336*, 1176–1180.

Donegan, J. (2008). Dr Jayne Donegan: GMC. http://www.jayne-donegan.co.uk/gmc. Accessed 1 February 2014.

Dyer, C. (2006). Doctor who used "junk science" in court faces GMC hearing. *The Guardian,* 2 October.

Dyer, O. (2007). GMC clears GP accused of giving court "junk science" on MMR vaccine. *BMJ, 335*, 416–417.

Ewing, D. W. (1977). *Freedom inside the organization: Bringing civil liberties to the workplace*. New York: Dutton.

Ewing, K. D., & Gearty, C. A. (1990). *Freedom under Thatcher: Civil liberties in Modern Britain*. Oxford: Clarendon Press.

Frickel, S., Gibbon, S., Howard, J., Kempner, J., Ottinger, G., & Hess, D. (2010). Undone science: Charting social movement and civil society challenges to research agenda setting. *Science, Technology and Human Values, 35*(4), 444–473.

Glazer, M. P., & Glazer, P. M. (1989). *The Whistleblowers: Exposing corruption in government and industry*. New York: Basic Books.

GMC (2007). General Medical Council Fitness to Practise Panel, 7 to 24 August (Dr Jayne Lavinia Mary Donegan).
GMC (2010). General Medical Council Fitness to Practise Panel, 28 January (Dr Andrew Jeremy Wakefield; Professor John Angus Walker-Smith; Professor Simon Harry Murch).
Goldacre, B. (2009). *Bad science*. London: Fourth Estate.
Goldacre, B. (2012). *Bad pharma: How drug companies mislead doctors and harm patients*. London: Fourth Estate.
Goldman, G. S., & King, P. G. (2013). Review of the United States universal varicella vaccination program: Herpes zoster incidence rates, cost-effectiveness, and vaccine efficacy based primarily on the Antelope Valley Varicella Active Surveillance Project data. *Vaccine, 31*, 1680–1694.
Goldstein, R. J. (1978). *Political repression in Modern America from 1870 to the Present*. Cambridge, MA: Schenkman.
Grant, J. (2011). *Denying science: Conspiracy theories, media distortions, and the war against reality*. Amherst, NY: Prometheus Books.
Habakus, L. K., & Holland, M. (Eds.). (2011). *Vaccine epidemic*. New York: Skyhorse.
Halvorsen, R. (2007). *The truth about vaccines*. London: Gibson Square.
Hamilton, C., & Maddison, S. (Eds.). (2007). *Silencing dissent: How the Australian government is controlling public opinion and stifling debate*. Sydney: Allen & Unwin.
Hess, D. (2006). *Alternative pathways in science and industry: Activism, innovation, and the environment in an era of globalization*. Cambridge, MA: MIT Press.
Hess, D. (2009). The potentials and limitations of civil society research: Getting undone science done. *Sociological Inquiry, 79*, 306–327.
Hobson-West, P. (2007). "Trusting blindly can be the biggest risk of all": Organised resistance to childhood vaccination in the UK. *Sociology of Health & Illness, 29*(2), 198–215.
Johnston, R. D. (2004). Contemporary anti-vaccination movements in historical perspective. In R. D. Johnston (Ed.), *The politics of healing: Histories of alternative medicine in twentieth-century North America* (pp. 259–286). New York: Routledge.
Jones, D. (Ed.). (2001). *Censorship: A world encyclopedia*. London: Fitzroy Dearborn.
Joravsky, D. (1970). *The Lysenko affair*. Cambridge, MA: Harvard University Press.
Kassing, J. W. (2011). *Dissent in organizations*. Cambridge: Polity.
Kassirer, J. P. (2005). *On the take: How medicine's complicity with big business can endanger your health*. Oxford: Oxford University Press.
Krimsky, S. (2003). *Science in the private interest: Has the lure of profits corrupted biomedical research?*. Lanham, MD: Rowman & Littlefield.
Martin, B. (1981). The scientific straightjacket: The power structure of science and the suppression of environmental scholarship. *Ecologist, 11*(1), 33–43.
Martin, B. (1999a). Suppression of dissent in science. *Research in Social Problems and Public Policy, 7*, 105–135.
Martin, B. (1999b). Suppressing research data: Methods, context, accountability, and responses. *Accountability in Research, 6*, 333–372.
Martin, B. (2011). Debating vaccination: Understanding the attack on the Australian Vaccination Network. *Living Wisdom, 8*, 14–40.
Martin, B. (2012a). Online onslaught: Internet-based methods for attacking and defending citizens' organisations. *First Monday: Peer-Reviewed Journal on the Internet,* 17(12). http://firstmonday.org/ojs/index.php/fm/article/view/4032/3379.
Martin, B. (2013). *Whistleblowing: A practical guide*. Sparsnäs: Irene Publishing.
Martin, B., Baker, C. M. A., Manwell, C., & Pugh, C. (Eds.). (1986). *Intellectual suppression: Australian case histories, analysis and responses*. Sydney: Angus & Robertson.
Miceli, M. P., Near, J. P., & Dworkin, T. M. (2008). *Whistle-blowing in organizations*. New York: Routledge.
Moran, G. (1998). *Silencing scientists and scholars in other fields: Power, paradigm controls, peer review, and scholarly communication*. Greenwich, CT: Ablex.
Myers, M. G. (2013). Vaccination to prevent varicella. *Vaccine, 31*, 1695.
Offit, P. A. (2010). *Autism's false prophets: Bad science, risky medicine, and the search for a cure*. New York: Columbia University Press.
Offit, P. A., & Bell, L. M. (2003). *Vaccines: What you should know* (3rd ed.). New York: Wiley.
Orrin, M. (ed. Goldman, G. S.) (2010). *The chickenpox vaccine: A new epidemic of disease and corruption.* Pearblossom, CA: Medical Veritas.

SAVN (2014). Stop the Australian Vaccination Network. https://www.facebook.com/stopavn. Accessed 1 February 2014.

Scheibner, V. (1993). *Vaccination: 100 years of orthodox research shows that vaccines represent a medical assault on the immune system*. Blackheath, NSW: Viera Scheibner.

Smyth, R. M. D., Kirkham, J. J., Jacoby, A., Altman, D. G., Gamble, C., & Williamson, P. R. (2010). Frequency and reasons for outcome reporting bias in clinical trials: Interviews with trialists. *BMJ,*. doi:10.1136/bmj.c7153.

Soley, L. (2002). *Censorship, Inc. The corporate threat to free speech in the United States*. New York: Monthly Review Press.

Sommer, T. J. (2001). Suppression of scientific research: *Bahramdipity* and *nulltiple* scientific discoveries. *Science and Engineering Ethics, 7*(1), 77–104.

Stamatakis, E., Weiler, R., & Ioannidis, J. P. A. (2013). Undue industry influences that distort healthcare research, strategy, expenditure and practice: A review. *European Journal of Clinical Investigation*. doi:10.1111/eci.12074.

Sunstein, C. R. (2003). *Why societies need dissent*. Cambridge, MA: Harvard University Press.

Thérèse, S., & Martin, B. (2010). Shame, scientist! Degradation rituals in science. *Prometheus, 28*(2), 97–110.

Wakefield, A. J. (2010). *Callous disregard: Autism and vaccines—The truth behind a tragedy*. New York: Skyhorse.

Wakefield, A. J., Murch, S. H., Anthony, A., et al. (1998). Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. *The Lancet, 351*, 637–641. (retracted).

Walker, M. (2012). Lots of law but little justice: the acquittal of Professor John Walker-Smith and the case of Dr Andrew Wakefield. http://www.anh-europe.org/news/lots-of-law-little-justice. Accessed 2 March 2013.

EXHIBIT 316

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Brief report

Greater freedom of speech on Web 2.0 correlates with dominance of views linking vaccines to autism

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ABSTRACT

Introduction: It is suspected that Web 2.0 web sites, with a lot of user-generated content, often support viewpoints that link autism to vaccines.
Methods: We assessed the prevalence of the views supporting a link between vaccines and autism online by comparing YouTube, Google and Wikipedia with PubMed. Freedom of speech is highest on YouTube and progressively decreases for the others.
Results: Support for a link between vaccines and autism is most prominent on YouTube, followed by Google search results. It is far lower on Wikipedia and PubMed. Anti-vaccine activists use scientific arguments, certified physicians and official-sounding titles to gain credibility, while also leaning on celebrity endorsement and personalized stories.
Conclusions: Online communities with greater freedom of speech lead to a dominance of anti-vaccine voices. Moderation of content by editors can offer balance between free expression and factual accuracy. Health communicators and medical institutions need to step up their activity on the Internet.

1. Introduction

Autism is a neurodevelopmental disorder characterized by impaired social interaction, communication, and repetitive or stereotyped behaviors [1] that appears to be increasing in prevalence [2,3]. Increasing public awareness has coincided with concern about autism being triggered by childhood vaccinations, particularly the MMR vaccine against Measles, Mumps and Rubella [4]. This was initiated by the publication of a study, which has since been retracted, in the journal The Lancet [5]. This has led to a decline in childhood vaccination rates and the resurgence of vaccine-preventable diseases [6].

The vaccine-autism controversy has been significantly enabled by the rise of the Internet. Fear of vaccine-induced illnesses, especially autism from the MMR vaccine, is the foremost concern expressed on anti-vaccine websites [7]. Anti-vaccine voices seem louder on Web 2.0 [8], but this has never been quantified. Web 2.0 refers to websites that feature a lot of user-generated content, even from non-credentialed sources [9]. Regarding the potential of Web 2.0 to improve health communication, one author stated that "the promise of open access in Web 2.0—freed of publishing barriers and multinational interests—is especially compelling", and noted the "opposing tensions of openness exemplified by Web 2.0 and the monolithic lack of openness in old forms of media" [9].

Although this increased openness is often beneficial to the purpose of health communication, we believe this has also diluted the voice of science in the public arena. In recent years, increasing attention has been devoted to the question of how to maintain a balance between facts and free speech on the Internet [10]. Therefore, we decided to obtain data on how the distribution of viewpoints on vaccines vis-à-vis autism varied on different Internet platforms. Primarily, we were interested in how viewpoints varied with the degree of "freedom of speech" offered. Secondarily, we assessed what techniques were employed to convince the public against the academic consensus. We compared viewpoints on YouTube, Google and Wikipedia, which are sources for the general public allowing significant user participation, with PubMed, which is primarily a resource for scientists and physicians.

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2. Materials and methods

2.1. Definitions of terms

We defined freedom of speech as being composed of two parameters:

(a) The ability of lay persons to add material to the website.
(b) The likelihood that this addition would be allowed to stay on the site, and be seen by future users.

The ability of lay persons to add material is constrained to various extents by individual websites. By "material", we refer to videos on YouTube, websites on Google search, edits and references on Wikipedia, and articles on PubMed. We did not include comments on YouTube videos or Google sites as part of our metric to define freedom of speech.

On YouTube, anyone can upload videos [11]. Similarly, any user of the Internet can make a website that gets indexed by Google's search algorithm. Wikipedia too allows lay users to make edits to most articles [12]. PubMed, however, allows only indexed scientific publications to be present in its search results [13].

When it comes to the likelihood that material added by lay persons would stay on the site to be seen by future users, the mechanisms employed by the site to index and display its contents are of crucial importance. The default setting on YouTube is to search by "relevance" which assesses the number of views, average view time, descriptions of the video, the title, and so on, but does not privilege institutional or scientific authority. This allows any user's addition to rise to the top of the search results, as long as a lot of people engage with it [14]. Google's search algorithm, on the other hand, promotes pages that have been linked to by several other pages, in the belief that these highly linked pages are likely to be important [15,16]. Institutional and mass media websites are often the beneficiaries of this bias toward highly interlinked pages. New additions and fringe viewpoints, although present, are often lower in the list of search results. Wikipedia has a requirement that those who make changes to articles provide references in support of their viewpoints [12]. It has editors who remove additions to articles that are not backed up by what the community determines to be reliable sources.

Therefore, for our purposes, freedom of speech varies in the following order – YouTube > Google > Wikipedia > PubMed.

2.2. Rationale for choice of targets

Although previous studies on vaccine information have assessed the material on anti-vaccine blogs and websites [7,17–19], there have not been any such studies specifically on the vaccine-autism topic. It is likely someone who is concerned about vaccination leading to autism would search for the terms "vaccines" and "autism" together, instead of something more generic like "vaccine". Indeed, one study in 2007 found that most videos on YouTube on the subject of "Vaccination" were pro-vaccine [17]. Also, YouTube, Google and Wikipedia, each of which receive more than 75 million unique visitors a month, play a large role in shaping public opinion, especially on science-related issues [20]. The differences in how content is generated on each of these websites made them good targets for our study.

2.3. Search protocols

2.3.1. YouTube

We searched YouTube between November 20 and 27, 2013, for the term "vaccines autism". We assessed the top 175 videos in the order returned by the search query using default search settings. We divided them into pro-vaccine (proclaiming vaccine safety, in keeping with current clinical guidelines) and anti-vaccine (arguing for a link between vaccines and autism, against the academic consensus). Other criteria we assessed were length, age in days, number of likes and dislikes, number of comments, presence of links to scientific articles, MD or DO speakers, celebrities and personalized stories, and whether the title was suggestive of a conspiracy to suppress such views.

2.3.2. Wikipedia

We searched Wikipedia on December 13, 2013, for the term "vaccines autism". Four relevant articles were found – "MMR vaccine controversy", "Vaccine controversies" (the subsection dealing with autism), "MMR vaccine" (the subsection dealing with autism) and "Controversies in autism" (the subsection dealing with vaccines). References on these Wikipedia articles were tallied as pro or anti-vaccine.

2.3.3. Google and PubMed

We assessed the top 100 results that resulted from a Google search for "vaccines autism" on February 20, 2014, and coded them as pro- or anti-vaccine based on their stance on whether vaccines caused autism. We also assessed whether these websites were part of "mainstream media" or not, which we defined as websites run by well-recognized TV channels, newspapers and magazines. On PubMed, we analyzed the top 100 abstracts returned by a search for "vaccines autism" on January 20, 2014. Articles which did not have the abstract or full text available online were excluded if the title was not indicative of their leanings.

2.3.4. Analysis

Analysis was performed using SPSS Version 21 (IBM) and Graphpad QuickCalcs (http://www.graphpad.com/quickcalcs/index.cfm). We compared the proportion of pro- and anti-vaccine views across the platforms using a Chi-square test. Descriptive statistics were performed on contents of the YouTube videos. Quantitative parameters with non-normal distributions were compared by Mann–Whitney U test, with median and interquartile range calculated. Fisher's exact test was used to compare proportions (since some cells had $n < 5$). Calculations were performed on data gathered by one author (AV). Cohen's kappa statistic for inter-observer reliability was calculated by comparing data gathered by author AV with data gathered by author NK. Kappa interpretation was performed per criteria laid out by Landis and Koch [21]. Kappa was calculated only for those questions where it was thought that decisions were subjective, in whole or in part.

3. Results

3.1. Distribution of pro- and anti-vaccine stances

On YouTube, of the top 175 videos, 39 (22.3%) were pro-vaccine, 130 (74.3%) were anti-vaccine, and 6 (3%) were ambivalent or neutral (Cohen's kappa = 0.804, 95% CI 0.702–0.906, $p < 0.0005$). Among the top 100 web results on Google search, 59 (59%) were pro-vaccine, 41 (41%) were anti-vaccine (Cohen's kappa = 0.817, 95% CI 0.703–0.931, $p < 0.0005$). On Wikipedia, 24 out of 150 references in "MMR vaccine controversy", 4 out of 42 in "Vaccine controversies", 1 out of 12 in "MMR vaccine", and 4 out of 25 in "Controversies in autism" were critical of vaccines. The overall proportion of anti-vaccine references was therefore 33/229 (14.4%), and the remaining were pro-vaccine (Cohen's kappa = 0.749, 95% CI 0.633–0.865, $p < 0.0005$). 17 of the top 100 results (17%) on PubMed Search for "vaccines autism" supported a link between vaccines and autism, whereas 82 (82%) did not, and one was a neutral overview

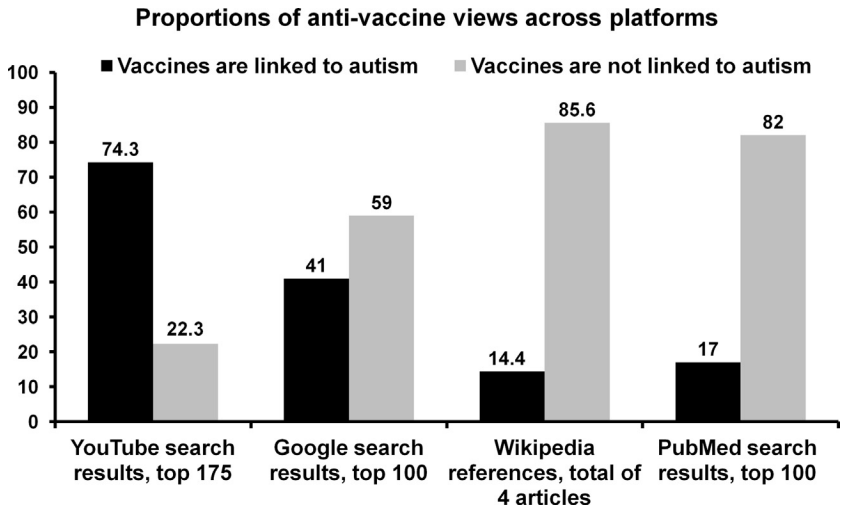

Fig. 1. Sources linking vaccines to autism represent a greater proportion of the discourse on those online platforms which offer greater freedom of speech.

(Cohen's kappa = 0.904, 95% CI 0.853–0.955, $p < 0.0005$). We found a significant difference in the distribution of pro- and anti-vaccine opinions on three user-generated websites (Chi-square = 157.13, $df = 2$, $p < 0.0001$) (Fig. 1).

3.2. Content analysis

Anti-vaccine videos on YouTube were significantly longer than pro-vaccine videos [median (interquartile range) = 6.5 (7) minutes for anti-vaccine videos vs 4 (7) minutes for pro-vaccine videos, $p = 0.006$], but no difference was noted between them in the days since upload [anti-vaccine 1085.5 (1163) vs pro-vaccine 1290 (1041)], number of views [anti-vaccine 3565.5 (10509.5) vs pro-vaccine 2342 (17961)], and in the number of likes [anti-vaccine 28 (79.5), pro-vaccine 17.5 (363.75)], dislikes [pro-vaccine 7 (17.75), anti-vaccine 4 (13)] and comments [anti-vaccine 19.5 (74.75) vs pro-vaccine 29 (364.75)] (Table 1). Since some videos disabled likes, dislikes and comments, the total number '*n*' was different for these measures. Significantly more pro-vaccine videos provided links to peer-reviewed scientific articles than anti-vaccine videos (15% vs 3%).

Speakers with an MD or DO degree were found in a higher percentage of anti-vaccine videos than pro-vaccine videos (36% vs 28%), although this did not reach statistical significance. 12 of 130 (9%) anti-vaccine videos made use of celebrities from Hollywood, primarily actors Jenny McCarthy, Jim Carrey and Rob Schneider, while no pro-vaccine videos did, but this did not quite reach statistical significance ($p = 0.07$) owing to the small numbers overall. Anti-vaccine videos had a significantly higher prevalence [13% (Cohen's kappa = 0.904, 95% CI 0.855–0.953, $p < 0.0005$), versus 0% in pro-vaccine videos] of personalized stories such as video montages of normal children apparently regressing into autism after vaccination, interviews of people who themselves claimed to have suffered following vaccination, and parents of affected children coming forward with their experiences.

More anti-vaccine videos (11%) than pro-vaccine videos (5%) had titles that suggested that there was a conspiracy to suppress their views, although this did not reach statistical significance (Fisher's exact test two-tailed $p = 0.365$). Cohen's kappa for this parameter was 0.714 (95% CI 0.538–0.890, $p < 0.0005$). Arguments found in the anti-vaccine videos included appeals to naturalism/holistic cures, arguing for the individual's right to refuse forcible vaccination by the government, and demands for greater spacing between vaccinations ("too many too soon").

On Google search results, of the twelve results on the first page, only three were anti-vaccine. Pages from the CDC, American Academy of Pediatrics and Wikipedia showed up on the first page of results. Nineteen of 59 pro-vaccine pages were from mainstream media sources, mostly stories from established newspapers or television news channels, as opposed to only 2 anti-vaccine pages. (Fisher's exact test two tailed $p = 0.0009$; Cohen's kappa for pro-vaccine sites = 0.625, 95% CI 0.407–0.843, Cohen's kappa for anti-vaccine sites = 0.539, 95% CI 0.094–0.984, $p < 0.0005$). Wikipedia's articles were broadly pro-vaccine, and in many cases a reference discussing anti-vaccine ideas was followed by refutations, or questions about its credibility.

4. Discussion

Postmodern medicine lays great emphasis upon decision-making authority shifting from the doctor to the patient, and the Internet is an important enabler of that transition [22]. In the Internet age, the credentials and hierarchies that formerly signified reliable sources of information no longer carry the weight they once did. Controversies have erupted around several topics such as anthropogenic global warming and vaccines causing autism, with views that oppose the mainstream academic consensus finding dense nuclei of support among the lay public.

In our study, greater freedom of speech (sites like YouTube and Google) correlated with anti-vaccine views. Videos linking vaccines to autism were significantly longer than pro-vaccine videos on YouTube. Anti-vaccine videos used celebrities, personal stories, anti-government and naturalist arguments to convince their viewers. On Google, anti-vaccine messages were mostly promoted by independent websites and blogs, such as infowars.com, though there were anti-vaccine webpages with titles like "National Vaccine Information Center" and "National Autism Association" that gave the impression of being governmental organizations. Mainstream media sources such as newspapers and television channels were overwhelmingly pro-vaccine. Wikipedia's strongly pro-vaccine stance can probably be attributed to this highly controversial topic attracting committed editors who strictly enforce the requirements for academic references.

Expert-moderated but user-generated arenas, similar to Wikis, may offer the best balance between openness and veracity. Mass media also seem resistant to the problems of Web 2.0 – reporters have broad freedom to write what they want, but they must pass editorial review. Google's search algorithm shows that privileging

Table 1
Characteristics of top 175 video results (search term "vaccines autism").

Parameter	Pro-vaccine (total $n = 39$)	Anti-vaccine (total $n = 130$)	Significance
Length, min	4 (7)	6.5 (7)	$p = 0.006$[a]
Time since upload, days	1290 (1041)	1085.5 (1163)	$p = 0.427$[a]
Total views	2342 (17,961)	3565.5 (10509.75)	$p = 0.381$[a]
Likes[c]	17.5 (363.75)	28 (79.5)	$p = 0.859$[a]
Dislikes[c]	7 (17.75)	4 (13)	$p = 0.495$[a]
Comments[d]	29 (364.75)	19.5 (74.75)	$p = 0.172$[a]
Videos with links to scientific articles	6 (15%)	4 (3%)	$p = 0.011$[b]
Videos with MD or DO speaker	11 (28%)	47 (36%)	$p = 0.443$[b]
Videos featuring celebrities	0	12 (9%)	$p = 0.070$[b]
Videos with personal stories	0	17 (13%)	$p = 0.013$[b]
Conspiracy theory in title	2 (5%)	15 (11%)	$p = 0.365$[b]

6 videos were not included as their stance was ambiguous.
[a] Mann–Whitney *U*-test; preceding columns show median (inter-quartile range in brackets).
[b] Fisher's exact test, two tailed; preceding columns show absolute number (% of total in brackets).
[c] $n = 36$ pro-vaccine and 121 anti-vaccine videos for likes and dislikes measures.
[d] $n = 38$ pro-vaccine and 130 anti-vaccine videos for comments measure.

highly networked "quality" sources more than fringe new additions can also increase the barriers to anti-scientific views gaining prominence, but it is not as effective as moderation by human editors. It is interesting to note that similar positions have been reached by several news organizations and blogs, where users are allowed to comment, but editors can remove comments which detract from the conversation [23]. This does have the effect of blocking out dissenting opinions – this may be desirable in scientific situations, but in politically charged situations can become restrictive, without allowing opinions to change under criticism and discussion.

5. Conclusion

Anti-vaccination viewpoints linking vaccines to autism are more prevalent in websites where lay users are allowed greater freedom of speech. Web 2.0 is highly interactive and prizes user-generated content, but in the absence of credentials and peer review, the public is as likely to be misinformed as to be correctly informed. Academic and governmental organizations can achieve greater penetration into popular consciousness through the use of websites such as YouTube. Our findings suggest that the tendency for alarmist voices to dominate in arenas with free speech can be modulated by editorial control.

References

[1] Diagnostic and statistical manual of mental disorders. Text revision. 4th ed. American Psychiatric Association; 2000.
[2] Taylor B, Jick H, Maclaughlin D. Prevalence and incidence rates of autism in the UK: time trend from 2004–2010 in children aged 8 years. BMJ Open 2013;3:e003219.
[3] Prevalence of autism spectrum disorder among children aged 8 years – autism and developmental disabilities monitoring network, 11 sites, United States, 2010. MMWR Surveill Summ 2014;63(Suppl. 2):1–21.
[4] Deer B. How the case against the MMR vaccine was fixed. BMJ 2011;342:c5347.
[5] Godlee F, Smith J, Marcovitch H. Wakefield's article linking MMR vaccine and autism was fraudulent. BMJ 2011;342:c7452.
[6] Cherry JD. Epidemic pertussis in 2012 – the resurgence of a vaccine-preventable disease. N Engl J Med 2012;367:785–7.
[7] Wolfe RM, Sharp LK, Lipsky MS. Content and design attributes of antivaccination web sites. JAMA 2002;287:3245–8.
[8] Betsch C, Brewer NT, Brocard P, Davies P, Gaissmaier W, Haase N, et al. Opportunities and challenges of Web 2.0 for vaccination decisions. Vaccine 2012;30:3727–33.
[9] Giustini D. How Web 2.0 is changing medicine. BMJ 2006;333:1283–4.
[10] Singer JB, Ashman I. Comment is free, but facts are sacred: user-generated content and ethical constructs at the guardian. J Mass Media Ethics 2009;24:3–21.
[11] Upload videos – YouTube help.
[12] Terms of use – Wikimedia Foundation. http://wikimediafoundation.org/wiki/Terms_of_Use
[13] Kejariwal D, Mahawar KK. Is your journal indexed in PubMed? Relevance of PubMed in biomedical scientific literature today; 2012.
[14] Robertson MR. Watch time: a guide to YouTube's most important ranking factor. Reelseo.com; 2014.
[15] Algorithms – Inside search – Google. https://www.google.com/insidesearch/howsearchworks/algorithms.html
[16] Facts about Google and competition. Web.archive.org.
[17] Keelan J, Pavri-Garcia V, Tomlinson G, Wilson K. YouTube as a source of information on immunization: a content analysis. JAMA 2007;298:2482–4.
[18] Bean SJ. Emerging and continuing trends in vaccine opposition website content. Vaccine 2011;29:1874–80.
[19] Kata A. A postmodern Pandora's box: anti-vaccination misinformation on the Internet. Vaccine 2010;28:1709–16.
[20] Brossard D. New media landscapes and the science information consumer. Proc Natl Acad Sci U S A 2013;110(Suppl.):14096–101.
[21] Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics 1977;33:159–74.
[22] Gray JM. Postmodern medicine. Lancet 1999;354:1550–3.
[23] Goodman E, Cherubini F, Waldhorn A. Online comment moderation: emerging best practices – WAN-IFRA. WPT-WEF Trends Rep 2013.

EXHIBIT 317

Centers for Disease Control and Prevention

Healthcare Providers / Professionals

Reminder Systems and Strategies for Increasing Childhood Vaccination Rates

The COVID-19 pandemic is changing rapidly and requires different strategies to maintain clinical preventive services, including immunization. Find up-to-date guidance on childhood, adult, and maternal vaccination and clinical practice.

An important component of an immunization provider practice is ensuring that the vaccines reach all individuals who need them. While attention to appropriate administration of vaccinations is essential, it cannot be assumed that these vaccinations are being given to every eligible person at the recommended age.

Specific concerns about U.S. immunization levels and areas for further study include the following:

- Childhood immunization rates are still suboptimal.
- Economic and racial disparities exist.

This page offers many resources and publications describing the need for increasing immunization levels and outlines strategies that providers can adopt to increase coverage in their own practice.

Specific strategies to increase **Adult vaccination rates** can be found on the Adult Vaccination Information for Healthcare and Public Health Professionals website

CDC Sources

- "Immunization Strategies": CDC's strategies that lead to high immunization levels in a practice – Chapter 3 in the "Pink Book"
  May 2015
  Explains the need for strategies to increase immunization rates, the AFIX approach (assessment, feedback, incentives, eXchange), and other essential strategies such as recordkeeping, recommendations and reinforcement, reminder and recall to patients and providers, reduction of missed opportunities and barriers to immunization.
- Immunization Information Systems
  Many recordkeeping tasks, as well as patient reminder/recall activities, can be greatly simplified by participation in a population-based immunization information system (IIS), also known as an immunization registry.
- Increasing Appropriate Vaccination: Client Reminder and Recall Systems
  CDC's The Community Guide May 2015
  Summary of the Task Force on Community Preventive Services' Recommendations and Findings covering reviews done between 2014 and 2016
- Recommendations of the ACIP: Programmatic Strategies to Increase Vaccination Rates — Assessment and Feedback of Provider-Based Vaccination Coverage Information (published 1996; historical document)

External Sources

- Checklist: Suggestions to Improve Your Immunization Services [2 pages] June 2008 Immunization Action Coalition
  For healthcare professionals to improve their efficiency in administering vaccines and increase their immunization rates.
- Population vs. Practice-Based Interventions to Increase Immunization Rates in Young Children June 2013
  Results of this study will provide data that will be relevant nationally in guiding future investment of resources to increase up-to-date rates in young children prior to school entry.
- Barriers and Strategies to Improving Influenza Vaccination among Health Care Personnel

Publications/Articles

Cost-effectiveness needs more research, regarding which strategies increase immunization levels with the least expenditure so these strategies can be prioritized.

Sustainable systems for vaccinating children, adolescents, and adults must be developed. High immunization rates cannot rest upon one-time or short-term efforts. Greater understanding of strategies to increase and sustain immunization levels is necessary in order to create lasting, effective immunization delivery systems.

Many strategies have been used to increase immunizations. Some, such as school entry laws, have effectively increased demand for vaccines, but the effectiveness of other strategies (e.g., advertising) is less well documented. Some proven strategies (e.g., reducing costs, linking immunization to Women Infants and Children (WIC) services, home visiting) are well suited to increasing rates among specific populations, such as persons with low access to immunization services.

A selection of the articles published on this topic are listed below. The first three are general reviews, and the remainder are stratified by strategy type.

General

- Increasing Adolescent Immunization Rates in Primary Care: Strategies Physicians Use and Would Consider Implementing . *Clin Pediatr*. 2013;52(8):710-20
- Increasing Immunization Coverage . *Pediatrics*. 2010;125:1295-1304
- IDSA's policy to strengthen adult and adolescent immunization coverage . Infectious Diseases Society of America (IDSA) *Clin Infect Dis*. 2007;44:1529-1531

Strategy Type Representative Articles

Home Visits

- Banach DB, Ornstein K, Factor SH, Soriano TA. Seasonal influenza vaccination among homebound elderly receiving home-based primary care in New York City . *J Community Health*. 2012;37(1):10-4.
- Szilagyi PG, Humiston SG, Gallivan S, Albertin C, Sandler M, Blumkin A. Effectiveness of a citywide patient immunization navigator program on improving adolescent immunizations and preventive care visit rates . *Arch Pediatr Adolesc Med*. 2011;165(6):547-53.

School requirements

- Bugenske E, Stokley S, Kennedy A, Dorell C. Middle school vaccination requirements and adolescent vaccination

coverage . *Pediatrics*. 2012;129(6):1056-63.

- Hadler JL, Yousey-Hindes K, Kudish K, Kennedy ED, Sacco V, Cartter ML. Impact of requiring influenza vaccination for children in licensed child care or preschool programs—Connecticut, 2012-13 influenza season. *MMWR*. 2014;63(10):224.

Client/family incentives

- Luthy KE, Thorpe A, Dymock LC, Connely S. Evaluation of an intervention program to increase immunization compliance among school children . *Journal of School Nursing*. 2011; 27(4):252-7.

Client reminder recall

- Kempe A1, Barrow J, Stokley S, Saville A, Glazner JE, Suh C, et al. Effectiveness and cost of immunization recall at school-based health centers . *Pediatrics*. 2012 Jun;129(6):e1446-52. doi: 10.1542/peds.2011-2921.
- Kharbanda EO1, Stockwell MS, Fox HW, Andres R, Lara M, Rickert VI. Text message reminders to promote human papillomavirus vaccination . *Vaccine*. 2011;29(14):2537-41. doi: 10.1016/j.vaccine.2011.01.065.
- Stockwell MS1, Kharbanda EO, Martinez RA, Vargas CY, Vawdrey DK, Camargo S. Effect of a text messaging intervention on influenza vaccination in an urban, low-income pediatric and adolescent population: a randomized controlled trial . *JAMA*. 2012;307(16):1702-8. doi: 10.1001/jama.2012.502.
- Szilagyi PG, Humiston SG, Gallivan S, Albertin C, Sandler M, Blumkin A. Effectiveness of a citywide patient immunization navigator program on improving adolescent immunizations and preventive care visit rates . *Archives of Pediatrics & Adolescent Medicine*. 2011;165(6):547-53.

Standing Orders

- Melinkovich P, Hammer A, Staudenmaier A, Berg M. Improving pediatric immunization rates in a safety-net delivery system . *Joint Commission Journal on Quality & Patient Safety*. 2007;33(4):205-10.

Provider reminders

- Patwardhan A, Kelleher K, Cunningham D, Spencer C. Improving the influenza vaccination rate in patients visiting pediatric rheumatology clinics using automatic best practice alert in electronic patient records . *Pediatric Rheumatology*. 2012;10(Suppl 1):A106.
- Fiks AG, Hunter KF, Localio AR, et al. Impact of electronic health record-based alerts on influenza vaccination for children with asthma . *Pediatrics*. 2009;124(1):159-69.

Provider feedback

- Brousseau N, Sauvageau C, Ouakki M, et al. Feasibility and impact of providing feedback to vaccinating medical clinics: evaluating a public health intervention . BMC Public Health. 2010;10(1):750.
- Brousseau N, Sauvageau C, Ouakki M, Audet D, Kiely M, Couture C, Pare A, Deceuninck G. Feasibility and impact of providing feedback to vaccinating medical clinics: evaluating a public health intervention . BMC Public Health 2010;10:750

Special Supplemental Nutrition Program for Women, Infants & Children (WIC) Settings

- Ghosh TS, Patnaik JL, Bennett A, Trefren L, Vogt RL. Assessment of missing immunizations and immunization-related

barriers among WIC populations at the local level . *Public Health Rep*. 2007;122(5):602-6.

Health Care System-Based Interventions Implemented in Combination

- Allison MA, Daley MF, Barrow J, et al. High influenza vaccination coverage in children with high-risk conditions during a vaccine shortage . *Archives of Pediatrics & Adolescent Medicine*. 2009;163(5):426-31.
- Hambidge SJ, Phibbs SL, Chandramouli V, Fairclough D, Steiner JF. A stepped intervention increases well-child care and immunization rates in a disadvantaged population . *Pediatrics*. 2009;124(2):455-64.
- Szilagyi PG, Humiston SG, Gallivan S, Albertin C, Sandler M, Blumkin A. Effectiveness of a citywide patient immunization navigator program on improving adolescent immunizations and preventive care visit rates . *Archives of Pediatrics & Adolescent Medicine*. 2011;165(6):547-53.

Community-Based Interventions Implemented in Combination

- Findley SE, Irigoyen M, Sanchez M, et al. Effectiveness of a community coalition for improving child vaccination rates in New York City . *American Journal of Public Health*. 2008;98(11):1959-62.
- Findley SE, Sanchez M, Mejia M, et al. Effective strategies for integrating immunization promotion into community programs . *Health Promotion Practice*. 2009;10(Suppl 2):128S-137S.
- Lemstra M, Rajakumar D, Thompson A, Moraros J. The effectiveness of telephone reminders and home visits to improve measles, mumps and rubella immunization coverage rates in children . *Paediatrics and Child Health*. 2011;16(1):e1-e5.

Reducing Client Out-of-Pocket Costs

- Carpenter LR, Lott J, Lawson BM, Hall S, Craig AS, Schaffner W et al. Mass distribution of free, intranasally administered influenza vaccine in a public school system . *Pediatrics* 2007;120(1):e172-8.
- Molinari NAM, Kolasa M, Messonnier ML, Schieber RA. Out-of-pocket costs of childhood immunizations: a comparison by type of insurance plan . *Pediatrics*. 2007;120(5):e1148. http://dx.doi.org/10.1542/peds.2006-3654.

Immunization Information Systems

- Adamkiewicz TV, Silk BJ, Howgate J, Baughman W, Strayhorn G, Sullivan K, et al. Effectiveness of the 7-valent pneumococcal conjugate vaccine in children with sickle cell disease in the first decade of life . *Pediatrics*. 2008;121(3):562-9.
- Allison MA, Daley MF, Barrow J, Crane LA, Beaty BL, Allred N, et al. High influenza vaccination coverage in children with high-risk conditions during a vaccine shortage . *Arch Pediatr Adolesc Med*. 2009;163(5):426-31.
- Feemster KA, Spain CV, Eberhart M, Pati S, Watson B. Identifying infants at increased risk for late initiation of immunizations: maternal and provider characteristics . *Public Health Rep*. 2009;124(1):42-53.
- Guh AY, Hadler JL. Use of the state immunization information system to assess rotavirus vaccine effectiveness in Connecticut, 2006-2008 . *Vaccine*. 2011;29(37):6155-8.
- Papadouka V, Metroka A, Zucker JR. Using an immunization information system to facilitate a vaccine recall in New York City, 2007 . *J Public Health Manag Pract* 2011;17(6):565-8.
- Saville AW, Albright K, Nowels C, Barnard J, Daley MF, Stokley S, et al. Getting under the hood: exploring issues that affect provider-based recall using an immunization information system . *Acad Pediatr*. 2011;11(1):44-9.

Schools and Organized Child Care Centers

- Guay M, Clouâtre AM, Blackburn M, et al. Effectiveness and cost comparison of two strategies for hepatitis B vaccination of schoolchildren . *Can J Public Health*. 2003;94(1):64-7.
- Effler PV, Chu C, He H, et al. Statewide school-located influenza vaccination program for children 5-13 years of age, Hawaii, USA. *Emerg Infect Dis*. 2010;16(2):244. http://dx.doi.org/10.3201/eid1602.091375.

Related Page

Vaccine Administration

Page last reviewed: July 18, 2018

EXHIBIT 318

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2018-2019 Maine School Immunization Assessment Report

State-mandated vaccination requirements for school entry protect children and communities against vaccine preventable diseases. Each school year, federally funded immunization programs collect and report kindergarten vaccination data to the Centers for Disease Control and Prevention (CDC). Federally funded immunization programs in all 50 states partner with their Department of Education (DOE) to assess vaccination coverage and exemption status of children enrolled in public and private kindergartens. In addition to kindergartens, the Maine Immunization Program (MIP) also collects coverage and exemption data for both seventh grade students and, beginning 2018-19, twelfth grade students. This information is collected through an annual immunization assessment survey of all State of Maine elementary, middle, and high schools.

Although each state mandate is different, Maine rules pursuant to 22 M.R.S. § 6359 requires any K-12 student enrolled in a designated public or private elementary, secondary, or special education facility which operates for children of school age to show proof of immunization with the following vaccines or documented immunity against the following vaccines:

- Diphtheria/Pertussis/Tetanus: Five doses of any DTP, DT or DTaP vaccine, a fifth dose is not needed if the fourth dose was administered on or after the fourth birthday. Beginning September 2017, one dose of Tdap is required for seventh grade entry;
- Measles/Mumps/Rubella: Two doses of MMR vaccine;
- Poliomyelitis: Four doses of OPV or IPV vaccine, a fourth dose is not needed if the third dose was given on or after the fourth birthday; and,
- Varicella: One dose of varicella (VAR) vaccine.
- Meningococcal Meningitis: Beginning September 2018, one dose of quadrivalent meningococcal meningitis vaccine (MenACWY) is required for seventh grade entry and two doses of MenACWY are required for twelfth grade entry.

A child who does not meet the immunization/immunity requirements above may be enrolled in school under the following circumstances:

- The parent provides the school with written assurance that the child will be immunized within ninety days of enrolling. This is a one-time provisional 90-day grace period.
- The parent (or child) presents to the school each year a physician's written statement that immunization against one of more of the diseases may be medically inadvisable (medical exemption in annual survey).
- The parent states in writing each year an opposition to immunization because of a sincere religious belief or for philosophical reasons (religious or philosophical exemption in survey).

The 2018-19 Maine Annual School Age Immunization Survey was conducted online from October to December 31, 2018 and aggregate results for kindergarten students were reported to the CDC in April 2019. The following tables (Tables 1-3) list the aggregate results gathered from the 2018-19 Maine Annual School Age Immunization Survey.

The annual immunization and exemption rates for each individual reporting school in Maine can be found on our website at: http://www.maine.gov/dhhs/mecdc/infectious-disease/immunization/publications/index.shtml

Table 1: 2018-19 MIP School Exemption and Immunization Rates, Kindergarten

2018-19 School Exemption and Immunization Rates By Individual Vaccine, Kindergarten							
Vaccine	Number of Students Surveyed	Number of Missing Records	Missing Records Rates	Total Exemptions (Medical, Religious & Philosophical)	Total Exemption Rates	Total Students Immune by Vaccine/Disease	Total Vaccination Rates
DTaP	12875	88	0.7%	616	4.8%	12171	94.5%
MMR	12875	124	1.0%	674	5.2%	12077	93.8%
Polio	12875	83	0.6%	623	4.8%	12169	94.5%
Varicella	12875	37	0.3%	493	3.8%	12345	95.9%

Table 2: 2018-19 MIP School Exemption and Immunization Rates, Seventh Grade

2018-19 School Exemption and Immunization Rates By Individual Vaccine, Seventh Grade							
Vaccine	Number of Students Surveyed	Number of Missing Records	Missing Records Rates	Total Exemptions (Medical, Religious & Philosophical)	Total Exemption Rates	Total Students Immune by Vaccine/Disease	Total Vaccination Rates
Tdap	13444	376	2.8%	502	3.7%	12566	93.5%
MenACWY	13444	503	3.7%	591	4.4%	12350	91.9%

Table 3: 2018-19 MIP School Exemption and Immunization Rates, Twelfth Grade

2018-19 School Exemption and Immunization Rates By Individual Vaccine, Twelfth Grade							
Vaccine	Number of Students Surveyed	Number of Missing Records	Missing Records Rates	Total Exemptions (Medical, Religious & Philosophical)	Total Exemption Rates	Total Students Immune by Vaccine/Disease	Total Vaccination Rates
MenACWY	13000	1329	10.2%	667	5.1%	11004	84.6%

School vaccination requirements provide an opportunity for children who are behind on early childhood vaccinations to be vaccinated by school entry. School vaccination assessments allow MIP to identify schools and communities where focused action could improve vaccination coverage to ensure that more children can benefit from the protection offered by vaccines. MIP and DOE will use this data to monitor incomplete vaccination records, coverage rates and exemptions and work with schools to ensure that all students receive all required Maine State school age vaccines.

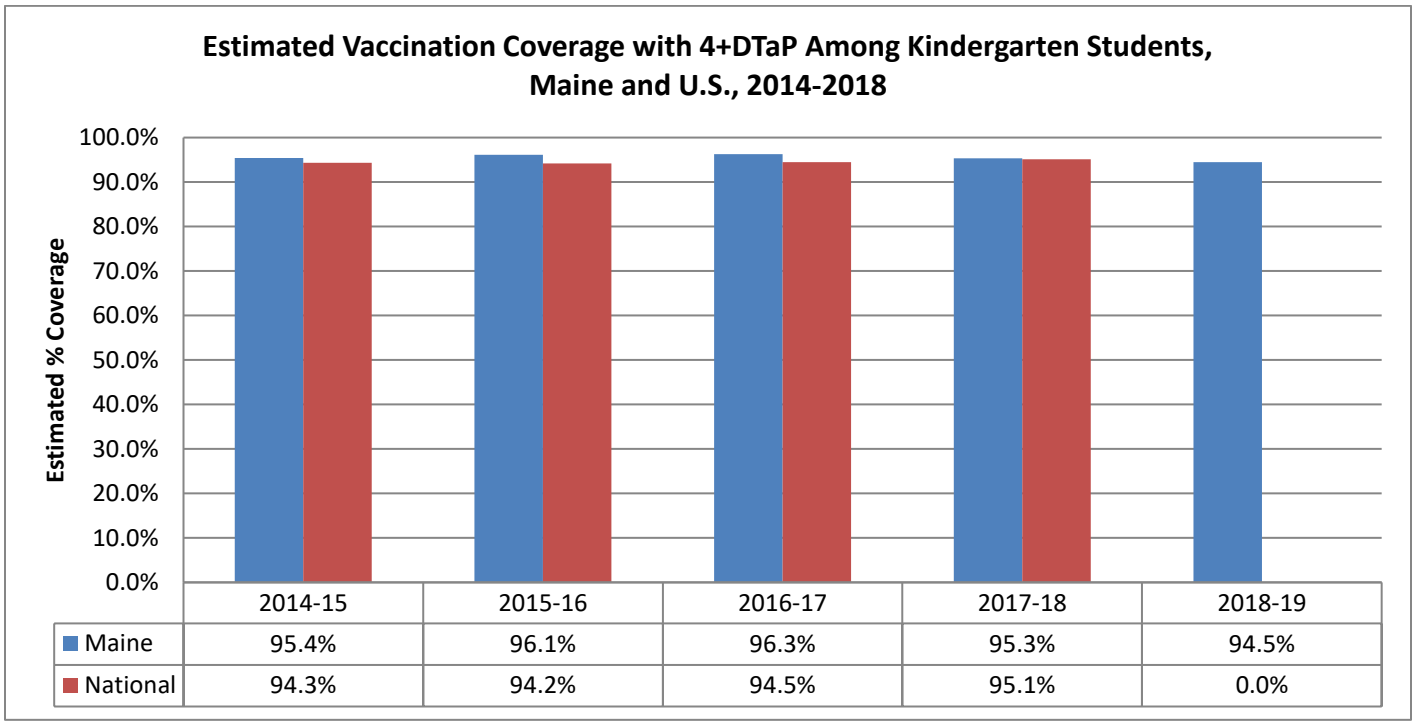
Vaccination is the most effective and efficient way to ensure that students and their family members, particularly those who are immunocompromised, are protected against these vaccine preventable diseases. This is perhaps one of the most important reasons why it would be advantageous for Maine State educational institutions to meet all requirements of the Immunization Requirements for School Children state law and to help reach the goal of the Maine Immunization Program to bring the State vaccine coverage rate average for each of these vaccines to 100%.

The Vaccination Coverage Among Children in Kindergarten – United States, 2018-19 School Year report data will be released in the fall of 2019. Historical reports were analyzed and graphical representations for each vaccine surveyed show trending comparisons for Maine and National U.S. immunization rates and exemption rates over the past 5 years (Figures 1-7). Please be aware that 2018-19 incudes Maine only at this time until National data is released in October 2019.

Additionally, graphical representations of immunization rates for Maine kindergarten students have been generated to show county specific rates compared to overall Maine state rates (Figures 8-11). Herd immunity (or community immunity) occurs when a high percentage of the community is immune to a disease (through vaccination and/or prior illness) making the spread of the disease from person to person unlikely. Herd immunity targets of 95% have been added to individual county vaccination rate graphs to represent which counties in Maine are susceptible to widespread disease.

As always, thank you for your commitment to keeping Maine's children free of vaccine preventable disease.

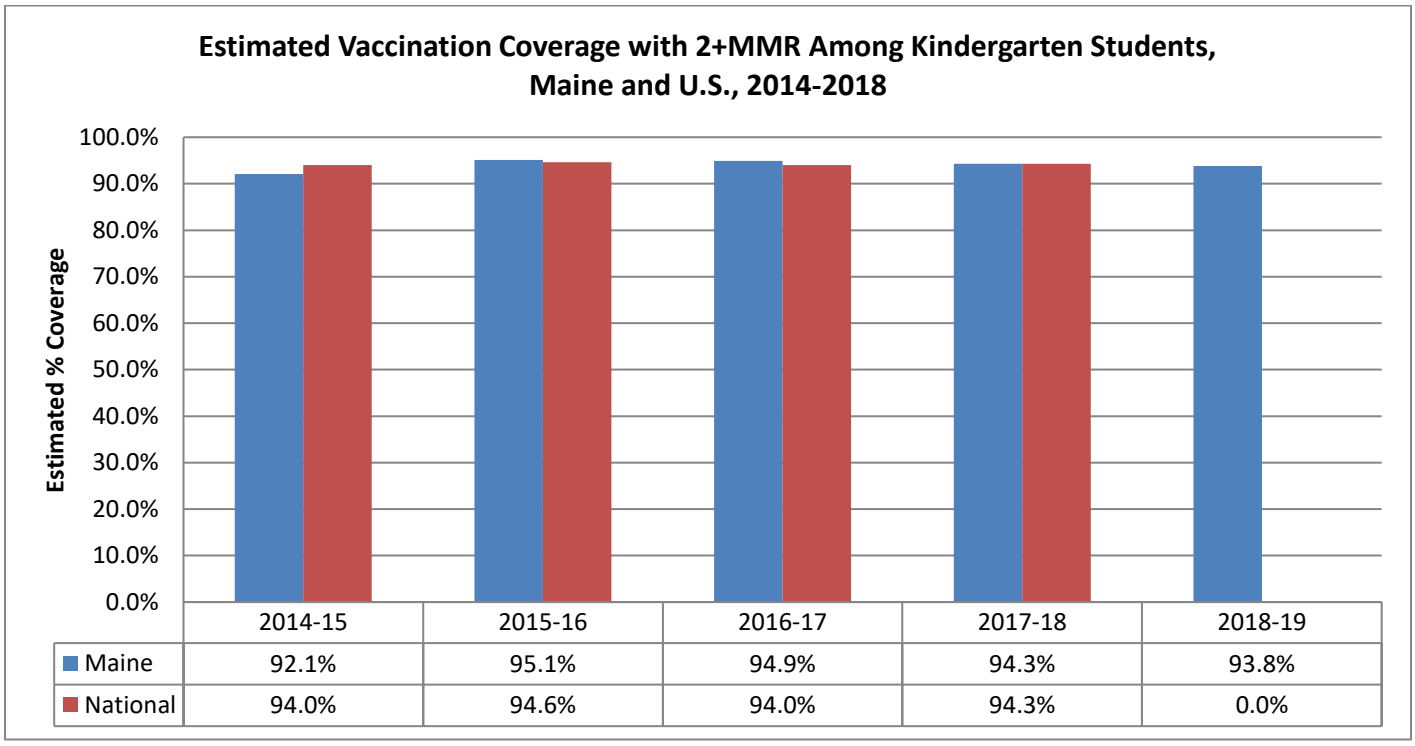
Figure 1: 4+DTaP Vaccine Coverage Estimate Among Kindergarten Students, Maine and U.S., 2014-2018



	2014-15	2015-16	2016-17	2017-18	2018-19
Maine	95.4%	96.1%	96.3%	95.3%	94.5%
National	94.3%	94.2%	94.5%	95.1%	0.0%

4+ DTaP ~ ≥4 doses of diphtheria and tetanus toxoids and acellular pertussis (DTaP) vaccine.
2018-19 National Kindergarten 4+DTaP rates unavailable until Fall 2019.

Figure 2: 2+MMR Vaccine Coverage Estimate Among Kindergarten Students, Maine and U.S., 2014-2018

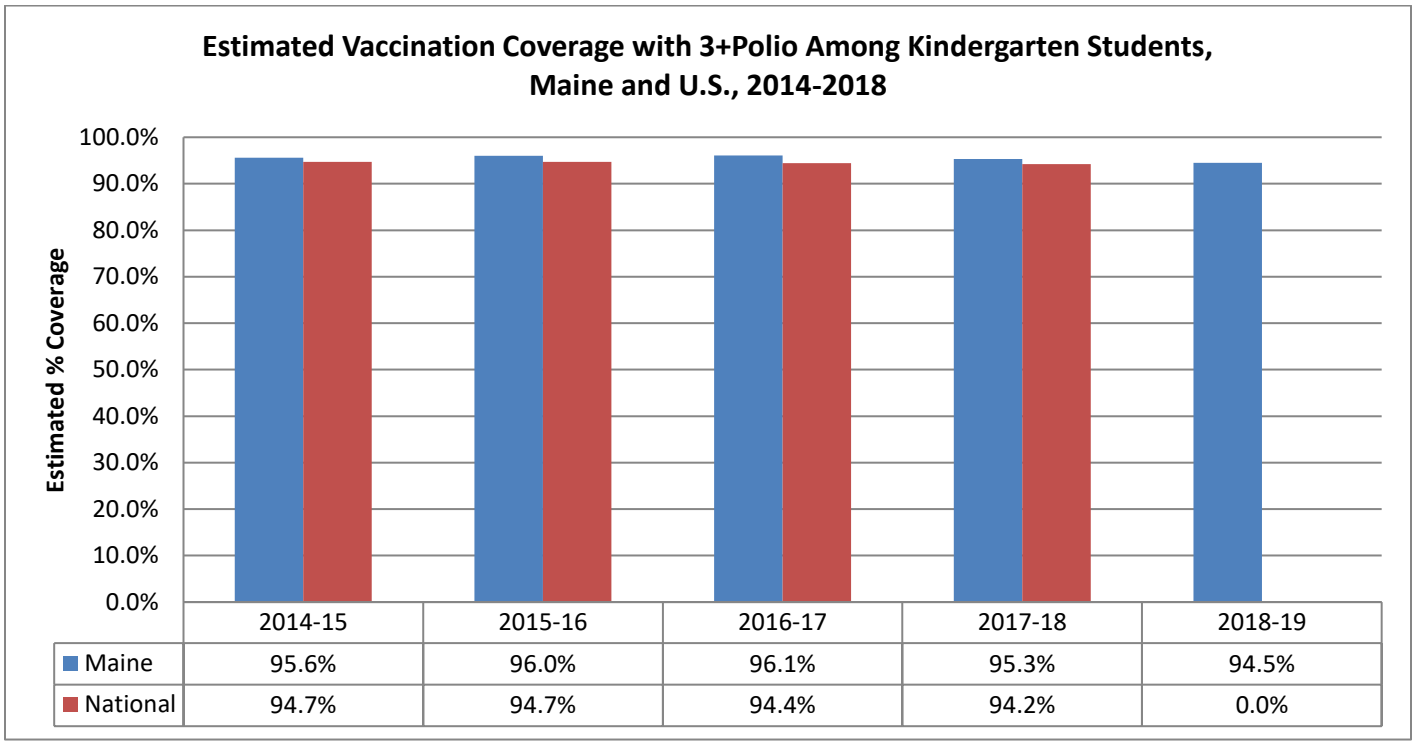


	2014-15	2015-16	2016-17	2017-18	2018-19
Maine	92.1%	95.1%	94.9%	94.3%	93.8%
National	94.0%	94.6%	94.0%	94.3%	0.0%

2+MMR~ ≥2 dose of measles-mumps-rubella (MMR) vaccine.
2018-19 National Kindergarten 2+MMR rates unavailable until Fall 2019.

Exhibit 318

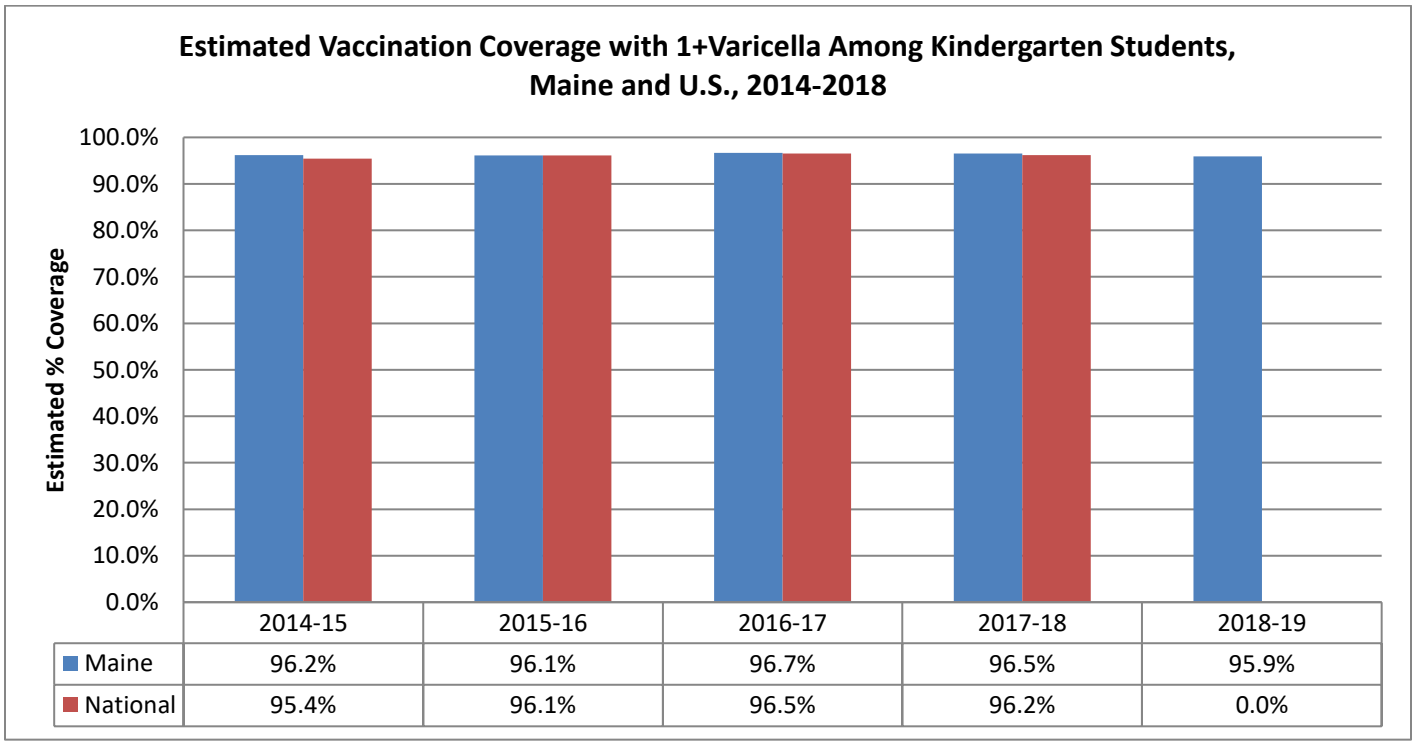
Figure 3: 3+Polio Vaccine Coverage Estimate Among Kindergarten Students, Maine and U.S., 2014-2018



	2014-15	2015-16	2016-17	2017-18	2018-19
Maine	95.6%	96.0%	96.1%	95.3%	94.5%
National	94.7%	94.7%	94.4%	94.2%	0.0%

3+ Polio ~ ≥3 doses of any poliovirus (Polio) vaccine.
2018-19 National Kindergarten 3+Polio rates unavailable until Fall 2019.

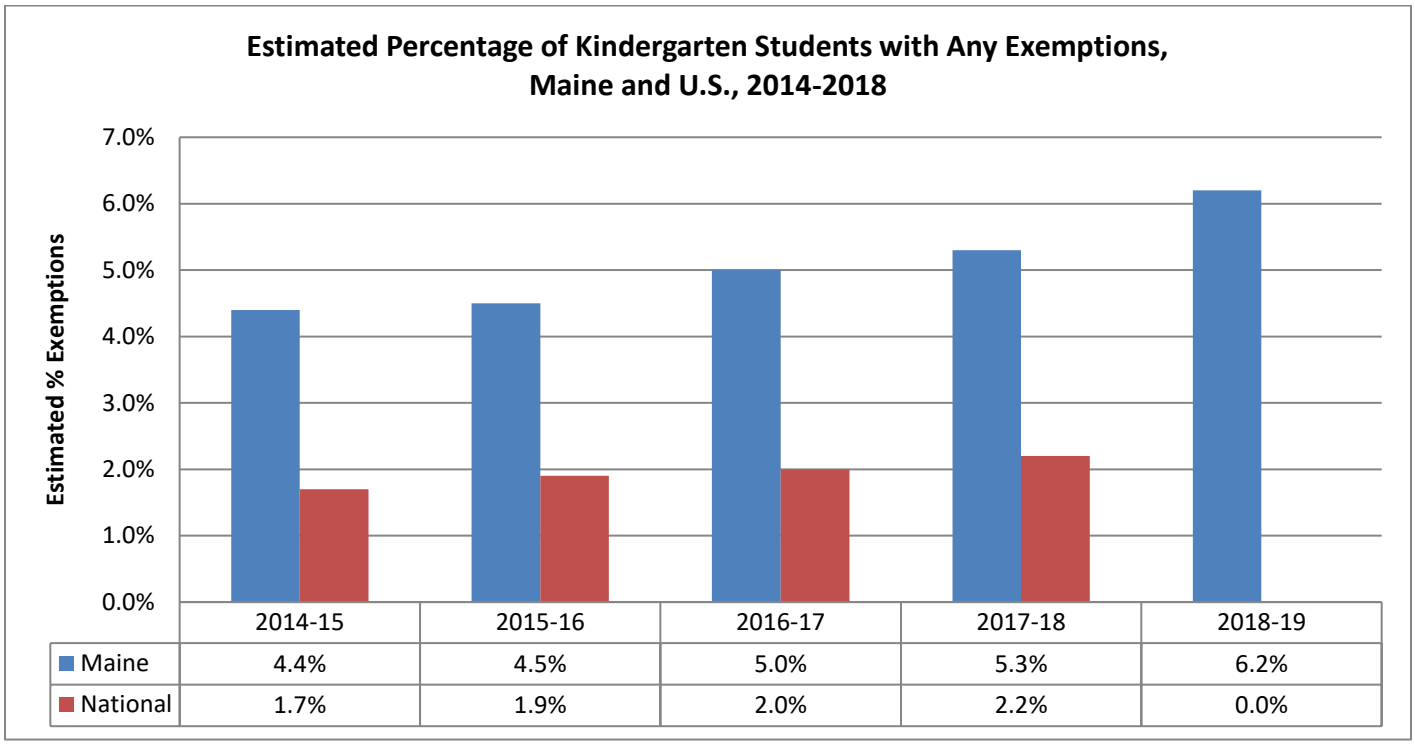
Figure 4: 1+VAR Vaccine Coverage Estimate Among Kindergarten Students, Maine and U.S., 2014-2018



	2014-15	2015-16	2016-17	2017-18	2018-19
Maine	96.2%	96.1%	96.7%	96.5%	95.9%
National	95.4%	96.1%	96.5%	96.2%	0.0%

1+Varicella ~ ≥ 1 dose of varicella (VAR) vaccine at or after child's first birthday, adjusted to include history of varicella disease
2018-19 National Kindergarten 1+Varicella rates unavailable until Fall 2019.

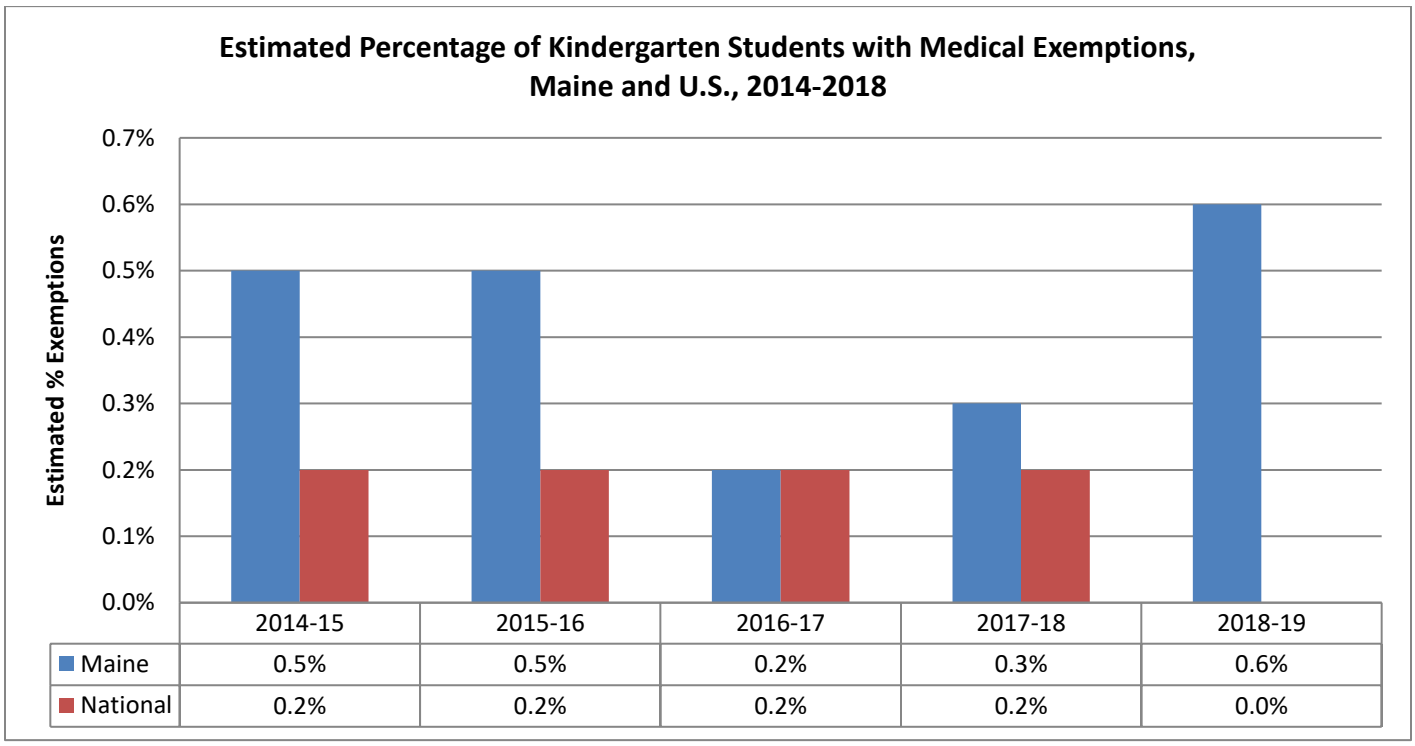
Figure 5: Any Exemptions Estimate Among Kindergarten Students, Maine and U.S., 2014-2018



	2014-15	2015-16	2016-17	2017-18	2018-19
Maine	4.4%	4.5%	5.0%	5.3%	6.2%
National	1.7%	1.9%	2.0%	2.2%	0.0%

Any Exemption ~ Includes medical, religious and philosophical exemptions for all school vaccines in Maine.
2018-19 National Kindergarten exemption rates unavailable until Fall 2019.

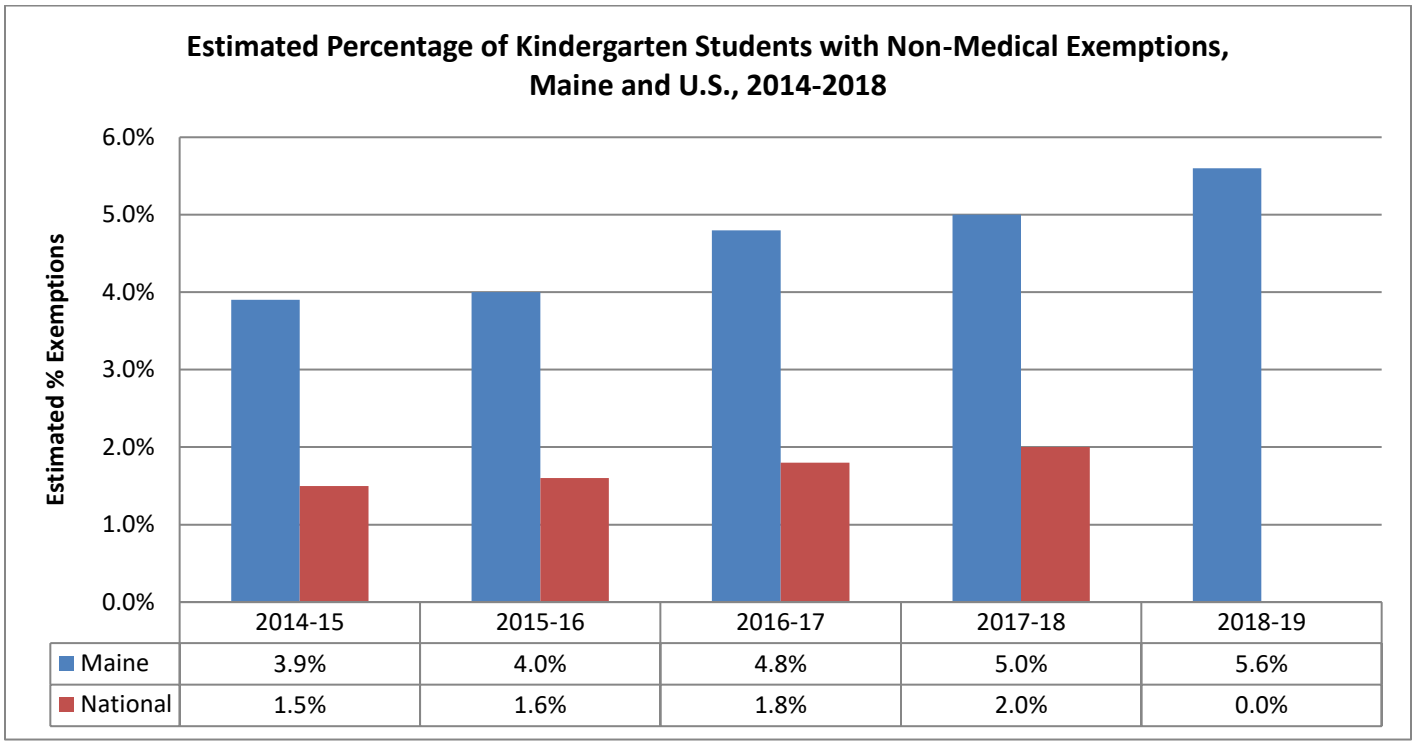
Figure 6: Medical Exemptions Estimate Among Kindergarten Students, Maine and U.S., 2014-2018



	2014-15	2015-16	2016-17	2017-18	2018-19
Maine	0.5%	0.5%	0.2%	0.3%	0.6%
National	0.2%	0.2%	0.2%	0.2%	0.0%

Medical Exemption ~ Includes medical exemptions only for all school vaccines in Maine. A medical note from physician is required annually.
2018-19 National Kindergarten exemption rates unavailable until Fall 2019.

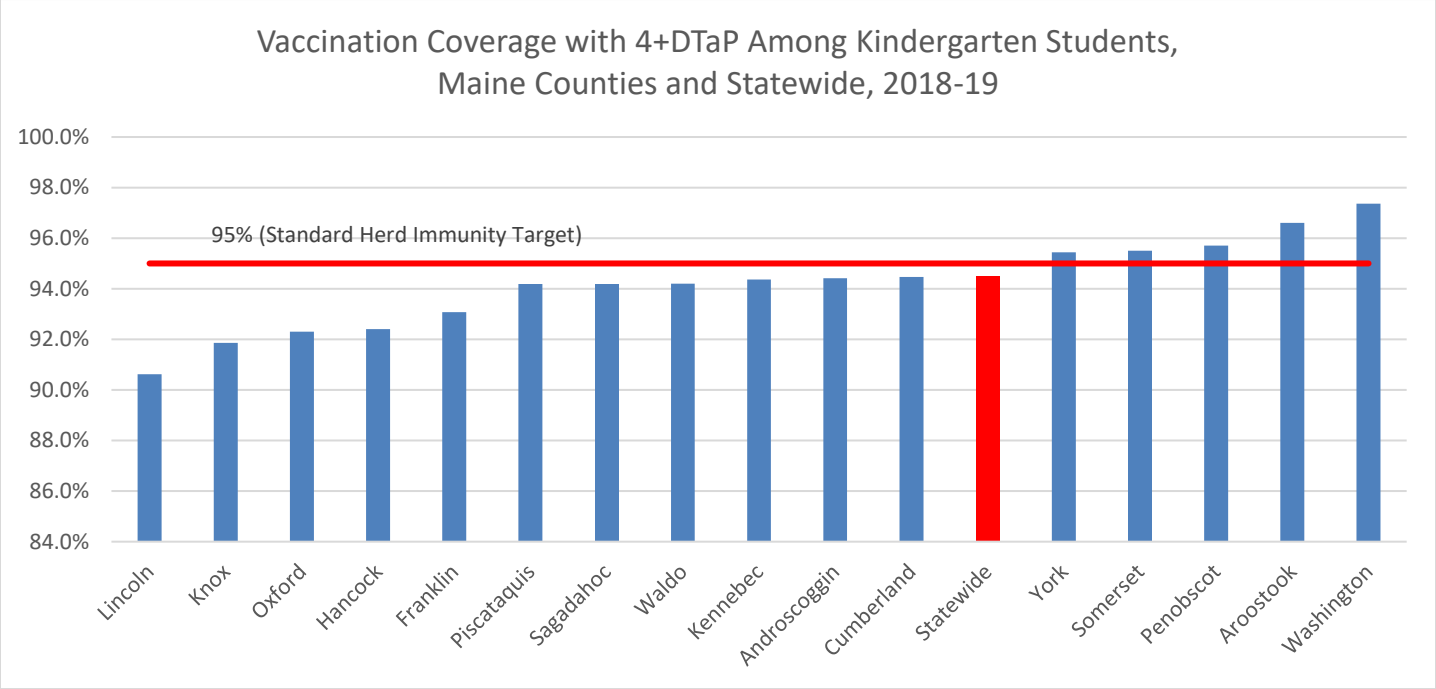
Figure 7: Non-Medical Exemptions Estimate Among Kindergarten Students, Maine and U.S., 2014-2018



	2014-15	2015-16	2016-17	2017-18	2018-19
Maine	3.9%	4.0%	4.8%	5.0%	5.6%
National	1.5%	1.6%	1.8%	2.0%	0.0%

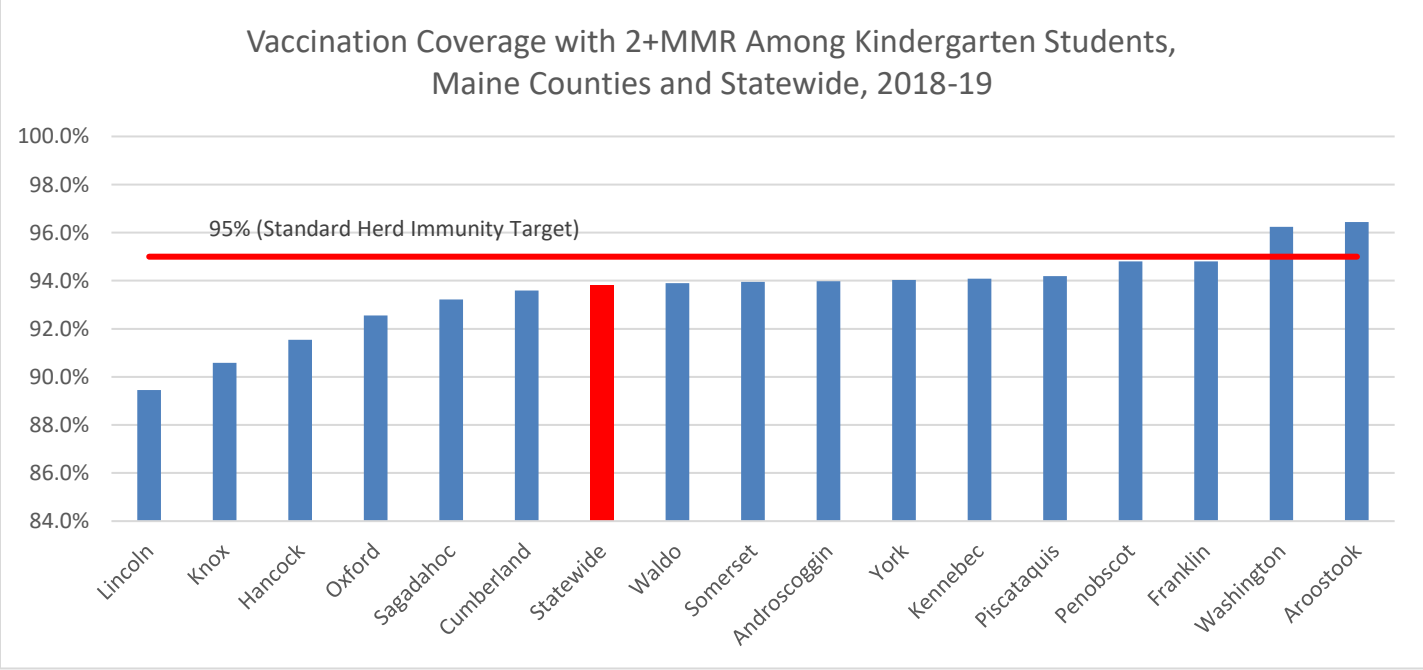
Non-Medical Exemption ~ Includes sincere religious belief and philosophical exemptions for all school vaccines in Maine. A parent/guardian signed note is required annually.
The National CDC Kindergarten Immunization Survey does not collect or publish individual religious or philosophical rates. They are combined as non-medical exemption rates.
2018-19 National Kindergarten non-medical exemption rates unavailable until Fall 2019.

Figure 8: 4+DTaP Vaccine Coverage Estimate Among Kindergarten Students, Maine Counties, 2018-19



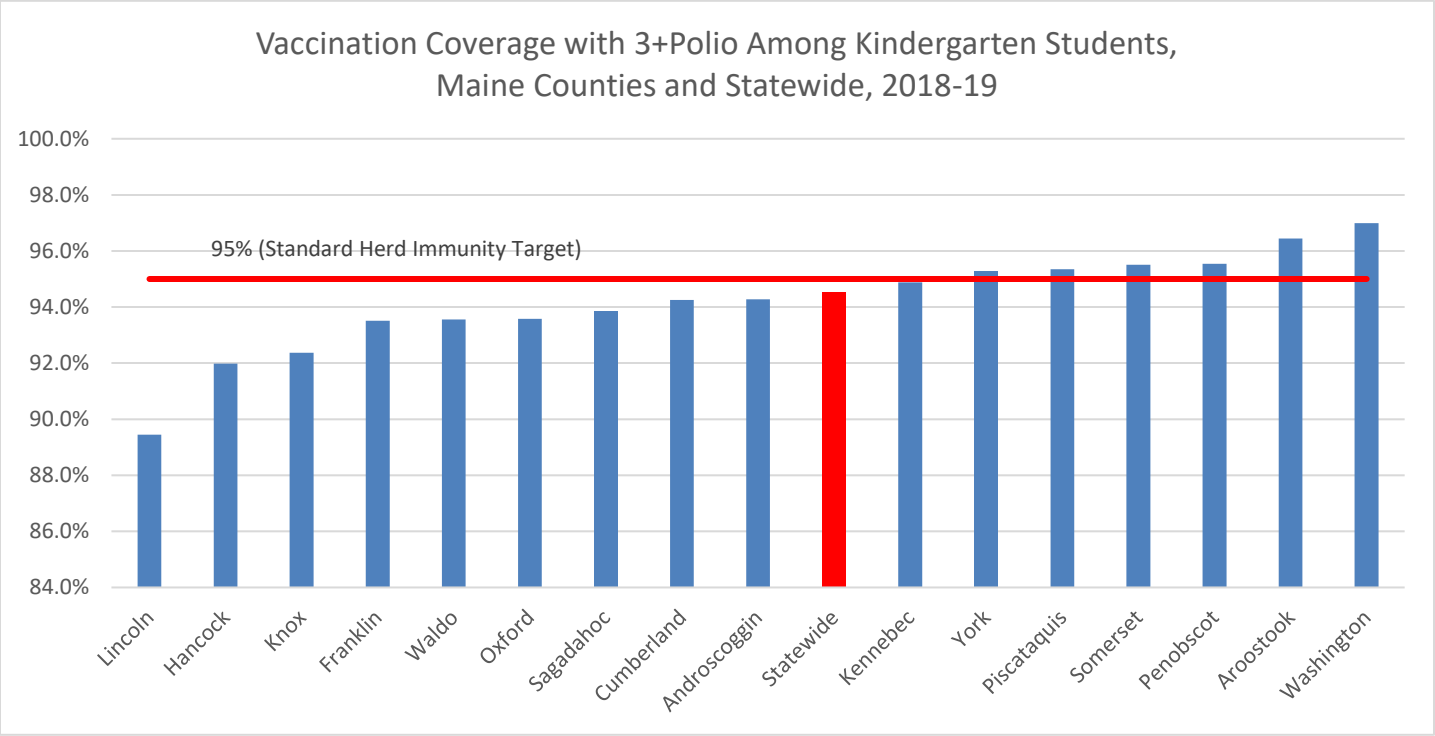
4+ DTaP ~ ≥4 doses of diphtheria and tetanus toxoids and acellular pertussis (DTaP) vaccine.

Figure 9: 2+MMR Vaccine Coverage Estimate Among Kindergarten Students, Maine Counties, 2018-19



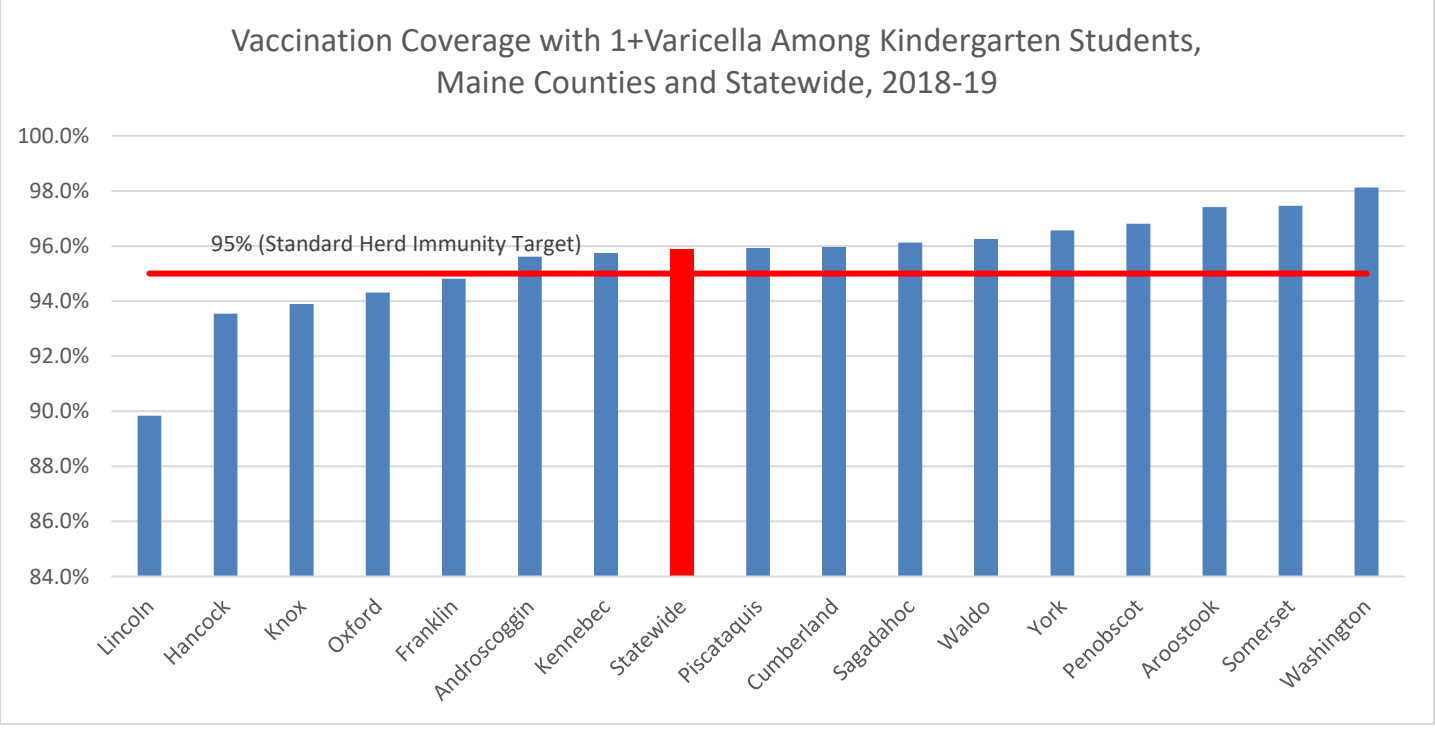
2+MMR~ ≥2 dose of measles-mumps-rubella (MMR) vaccine.

Figure 10: 3+Polio Vaccine Coverage Estimate Among Kindergarten Students, Maine Counties, 2018-19



3+ Polio ~ ≥3 doses of any poliovirus (Polio) vaccine.

Figure 11: 1+Varicella Vaccine Coverage Estimate Among Kindergarten Students, Maine Counties, 2018-19



1+Varicella ~ ≥ 1 dose of varicella (VAR) vaccine at or after child's first birthday, adjusted to include history of varicella disease

EXHIBIT 319

Influenza vaccination rates among Oregon health care workers fall short

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Director's Calendar (/oha/ERD/Pages/directors-calendar.aspx)

May 9, 2018

OHA report shows dialysis facility employees have highest flu immunization rates

PORTLAND, Ore.—Influenza vaccination rates among Oregon health care workers continue a steady rise, but they still fall short of national immunization goals, a new state report shows.

While health care worker flu vaccination rates have grown more than 40 percent between the 2011-2012 and 2016-2017 flu seasons, the 2016-2017 season's overall rate of 73 percent is just below the national Healthy People 2015 goal of a 75 percent flu vaccination rate. And it is far short of the Healthy People 2020 goal of 90 percent, according to the Oregon Health Care Worker Influenza Vaccination Annual Report: 2016-2017 Season. The report was published this week by the Acute and Communicable Disease Prevention Section at the Oregon Health Authority Public Health Division.

"Flu vaccination among health care workers is extremely important," said Rebecca Pierce, PhD, manager of the Healthcare-Associated Infections and Emerging Infections programs in the Acute and Communicable Disease Prevention Section. "These workers' care for vulnerable individuals, including patients who are at risk of serious illness and even death if exposed to the flu virus. Health care workers need to be our first line of defense—flu vaccination protects the safety of patients and our health care workforce."

The U.S. Department of Health and Human Services developed the Healthy People program with 10-year objectives for improving the health of all Americans.

Among health facility types, dialysis facilities in Oregon have the highest flu vaccination rates, beating the Healthy People 2015 goal and coming the closest to the Healthy People 2020 goal. Dialysis facilities' rate of 85 percent during the 2016-2017 flu season represents a slight drop from 89 percent the year before.

Hospitals also beat the national 2015 goal for worker immunizations against the flu, coming in at a rate of 79.5 percent during the 2016-2017 season, but still short of the 2020 goal. Since the 2011-2012 season, rates of flu immunizations among health care workers at hospitals has risen almost 35 percent.

Coming in below both the 2015 and 2020 national goals for health care worker vaccinations were ambulatory surgery centers and skilled nursing facilities. Ambulatory surgery centers had a rate of 72 percent during the 2016-2017 season, an increase of 41 percent from 2011-2012, while the rate at skilled nursing facilities was even lower: 57 percent during 2016-2017, representing only a 21 percent increase since 2011-2012. That rate also represented a 9.5 percent drop from the 2015-2016 season.

Pierce said publication of the report each year tracks progress toward the Healthy People 2020 goal and directs public health action, showing where additional support and education is needed.

To achieve 90 percent vaccination coverage, health care facilities can take some

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important steps. Among the recommendations included in the Oregon Health Care Worker Influenza Vaccination Annual Report are encouraging health care workers, including those not employed by the facility such as contractors and volunteers, to get vaccinated at the beginning of every influenza season. Facilities can host promotional activities, such as holding mass vaccination fairs, providing vaccines at no cost to employees, starting incentive programs, and documenting all employees' vaccination status and requiring staff members who forgo vaccination to turn in a form saying they decline to be vaccinated.

"We can do better," Pierce said. "While 90 percent vaccination rate is our goal for the next two years, a 100 percent vaccination rate is what we'd really like to see."

The report is available on the OHA website (/oha/PH/DiseasesConditions/CommunicableDisease/HAI/Pages/Reports-and-Data.aspx).

# # #

EXHIBIT 320

Need To Know

Body found floating in White Oak Bayou

Father, 4-year-old struck and killed on North Freeway

HISD officer's gun fires during struggle with road rage suspect

https://www.chron.com/news/nation-world/article/Mexico-bests-U-S-in-vaccinations-2097615.php

Mexico bests U.S. in vaccinations

Houston plagued by database, insurance gaps

EDWARD HEGSTROM, Copyright 2002 Houston Chronicle **Published 6:30 am CST, Sunday, December 22, 2002**

MONTERREY, Mexico -- If parents here are late getting their child inoculated, a public health nurse will come to their home, pull down the youngster's pants and give the vaccination right there in the living room.

If mom and dad are away at work, the nurse does not wait for them to come home and give permission. The shots are given anyway, and the paperwork is left with the baby sitter.

In Monterrey, like Houston an industrial city of more than a million with large pockets of underclass, the government divides its poor neighborhoods into sections of about four square blocks each, then puts a nurse in charge of supervising parents in each area to ensure all of the children are vaccinated on time.

It's a paternalistic approach almost impossible to imagine in the United States -- where privacy rights and other freedoms are highly valued and immunizations are increasingly feared -- but it has proved remarkably effective: Mexico has a 96 percent vaccination rate for children ages 1 to 4, compared with an immunization rate of 79 percent for 2-year-olds in the United States.

The disparity is even greater between Monterrey and Houston, which has one of the most stubbornly low vaccination rates in the United States. In Monterrey, 98 percent of the children ages 1 to 4 are fully immunized, a higher percentage than reached by any U.S. city. In Houston, barely 71 percent of 2-year-olds are caught up on their shots.

Mexico's immunization success is something Americans -- particularly Texans -- can cheer. Epidemics of preventable disease used to go back and forth between the two countries. That no longer happens, thanks mostly to the remarkable but unheralded improvements in Mexico and other countries in the region.

"One of the main reasons there is no longer measles in the United States is because we no longer have measles in Latin America and the Caribbean," said Dr. **Ciro de Quadros**, the recently retired director of immunizations for the **Pan American Health Organization**. Mexico, he said, has done a "remarkable" job of vaccinating its children in the past decade.

Conventional wisdom says it is harder to develop a public health system in a poor country. But Quadros notes that a wealthy country like the United States has problems of its own.

"In the United States, there are so many obstacles to vaccinations," said Quadros, a native of Brazil. "People have so many forms to fill out, and there are so many more lobbies -- anti-vaccine, anti-technology, anti-everything."

The differences in culture and outlook between Mexico and the United States make it difficult to compare the two systems of administering vaccinations. But there are similarities, particularly between two cities that share so much trade and human traffic.

Both Houston and Monterrey suffered from a terrible resurgence of measles more than a decade ago, and leaders in both places promised to respond by bolstering vaccine programs to ensure such an epidemic never happened again. The goal -- on both sides of the border -- was a 100 percent vaccination rate.

But while Monterrey and Mexico as a whole have come close to keeping that promise, the improvement in Houston's vaccination program has not been so great. Vaccinations are clearly up from the winter of 1988-89, when 10 children died from measles in Houston and organizers of the **Houston Livestock Show and Rodeo** distributed letters warning that participants may have been exposed to the disease and risked taking it to other parts of the country.

Public and private groups responded by forming a number of programs, such as mobile health clinics, which are designed to better reach the most needy areas of Houston. But Houston still has no coordinated vaccine registry, which officials say is necessary to reach the people effectively.

And the effectiveness of the patchwork services now offered by so many different organizations is hampered by a lack of any central vision for running an immunization program, critics say.

"There's no real local leadership on the immunization issue," said **Barbara Best**, with the **Children's Defense Fund**.

While no one predicts another measles resurgence, officials in Houston and the rest of Texas have already started to worry about a return of pertussis, also known as whooping cough.

Mexico, by contrast, has a sharply focused vision.

After the measles pandemic reached Mexico in 1990 and killed 5,899 babies, the Mexican government established a central authority to oversee the national vaccination campaign, known as the **National Immunization Program**.

Immunization campaigns are run three times a year, done with great fanfare. In addition, uniformed brigades of nurses keep careful watch over vaccination rates, neighborhood by neighborhood.

U.S. health officials who have seen the unsparing force of a Mexican immunization campaign tend to remember it with both awe and dread.

"In Mexico, they vaccinate anything that moves," says **Gloria Peña**, a health official in Laredo.

The public health nurses of Monterrey begin tracking babies before they are born.

The nurse in charge of immunizations in a particular neighborhood keeps a census of the area, including maps detailing where women of child-bearing age live and special notations for those who are pregnant.

Babies are given their first immunizations -- against polio and tuberculosis -- in the hospital right after birth. They also receive a government-issued National Vaccination Record, on which the vaccines they receive throughout their lives will be tallied. The vaccine record must be presented in order to enter school, to get passports or other identification papers and even to get some jobs and loans. Losing the record is not usually a problem, because the same information is recorded with the federal government and can be replaced.

Once home, the baby comes under the watchful eye of the same public health nurse who kept records on the mother. The nurse tracks the baby through grade school, recording changes in height, weight and -- of course -- vaccinations.

Most neighborhoods in Monterrey, a northern Mexico city of 3 million, have a public clinic that can be reached easily on foot or by bus, and mothers can bring their children in for free vaccines. In the public health center serving the working-class neighborhood known as *Colonia Independencia*, which sits on a hill west of downtown, about 60 percent of the mothers bring their children in for vaccines.

The job of reaching the other 40 percent rests in the hands of **Catalina Sanchez**, a government nurse with dyed red hair and a sympathetic smile that fades the moment her authority is questioned. Sanchez wears the easily identifiable green-and-white public health uniform, and she walks the neighborhood armed with her census book and an ice chest stocked with vaccines.

On a sunny afternoon earlier this month, the records indicated Sanchez needed to visit an 8-month-old baby named

Francisco Gonzalez, who was about a month overdue for a vaccination. The government census book listed the mother's name as Teresa.

"Are you Teresa?" she asked the woman who answered the door at the address where the baby lives.

No, it was a younger sister named Guadalupe, who was taking care of the baby during the day while the mother worked.

"The baby was due for his vaccinations November 11," Sanchez offered, with a slightly accusatory tone.

"He had a cold," the aunt replied.

After establishing that the baby no longer had a cold, the nurse invited herself into the living room, a dark, concrete-floored space crowded with four beds. The aunt held the baby while Sanchez prepared the dosages -- an oral polio vaccine and a five-part shot the Mexican government gives to infants as initial protection against diphtheria, pertussis, tetanus, hepatitis B and haemophilus influenza B.

The nurse then explained the normal side effects. She urged the aunt to seek help if the baby ran a fever, and she reminded her of the next round of shots the baby will need in March.

It's the personal attention and the careful records, Sanchez says, that ensure the neighborhood under her control stays vaccinated.

About 400 miles to the north, Dr. **Anu McDonald** also takes responsibility for vaccinating a population of mostly destitute, Spanish-speaking families. In fact, many of McDonald's patients are recent arrivals from Mexico.

But the similarities end there.

McDonald heads up Super Kids ("*Buenos Niños*"), a mobile clinic that makes a regular tour of the schools of southwest Houston's largely immigrant Gulfton area.

Though many of the patients are born here, most have no insurance. They grow up without regular checkups until reaching grade school, where administrators realize they are years behind in vaccines. The school nurse will then send a letter home urging the parents to take their child to Super Kids, which is funded and operated by **Texas Children's Hospital**.

"One hundred percent of the time they are in need of shots," McDonald said of her patients. "Ninety-five percent have no insurance."

The two problems are related. Most Houston parents get their kids immunized when someone from their pediatrician's office calls to remind them. But more than 150,000 Harris County children are not insured, one of the highest rates in the nation. Uninsured kids usually have no pediatrician, and no friendly reminder.

Before giving a shot, McDonald must interview the mother to see what shots the child has had.

Other cities in the United States now have centralized immunization registries, so that a doctor can type the name of the patient into a computer and get an instant report of the child's vaccination history. This ensures the child is never over-vaccinated.

McDonald has no such advantage.

Houston officials have worked for more than a decade to get an immunization registry for the city, but the program still has problems. Because the city has chosen not to bankroll the registry development, it relies heavily on private funding, and is officially run by Texas Children's Hospital, a major contributor. But new federal laws place severe restrictions on the sharing of information with registries run by private groups.

The state, meanwhile, established its own registry and managed to have it up and running before the city's. Harris County opted to use the state system. Because the city's program is private, the state cannot legally share information with it.

The city and Texas Children's are working to resolve this problem by turning official control of the registry over to a public entity, according to Brock Lamont, the head of immunizations for the city.

Meanwhile, a child vaccinated at a city clinic gets put into one registry, while a child vaccinated at a county clinic is entered into another. A child vaccinated at a clinic run by yet a third public entity, the Harris County Hospital District, is not put into any registry at all.

This obviously defeats the central purpose of a registry, which is to create a universal record system.

"What we have now are dueling databases," said one local official. "It's a mess."

Registries have another advantage. They can alert authorities when a child is overdue for a vaccination, so that a nurse can then call the parents and remind them.

But their very usefulness is what makes registries a particular concern to some parental groups. Parents who worry about the adverse side effects of vaccines see registries as an insidious effort by the government to gain more control.

"What they want is their hands on every kid's records," said Dawn Richardson, whose Austin-based group, Parents Requesting Open Vaccine Education, has successfully lobbied the state legislature to weaken registries. "They have a history of harassing parents for not following 100 percent of their schedule."

Without a registry, health officials have no way of ensuring a uniform distribution of vaccinations.

"Some kids are not immunized," said Binh Nguyen, who oversees Harris County's immunization program. "Others are over-immunized."

While the unvaccinated kids present by far the largest problem, some health workers tell horror stories of over-vaccinated children. After carefully interviewing one mother, the nurses at *Espiritu de Salud*, a mobile health clinic in the East End, concluded that her child had received 16 doses of the DPT vaccine, of which a child should normally have just five in a lifetime.

The mother would get the child vaccinated and then lose the record. When the school nurse asked for the record again, the mother took the child to get a new round of shots.

Health workers know to watch out for this problem, which is why a doctor like McDonald will make every effort to carefully interview the mother before vaccinating the kids.

McDonald works with a bilingual staff, and she is learning enough Spanish to communicate with the parents herself.

"Take this to the school nurse, mama," she will tell a mother. "*La enfermera*."

On a recent Tuesday, McDonald visited with families of children enrolled in Piney Point Elementary, in Gulfton.

One mother, Eva Orozco, showed up with her four children and produced the vaccination records for each, which she had carefully wrapped in a plastic bag. Though Orozco is Mexican herself, all of her children were born in Houston, making them citizens.

None carry health insurance, though McDonald offered to help get them enrolled.

Not all the parents arrive at Super Kids with such good records. Many of the kids come from Mexico, and they arrive with the standardized Mexican vaccination registry card -- stained, water-soaked or folded repeatedly to the point that it has split in four pieces and must be pieced back together to be read.

Some children are smuggled across the border, and they arrive with no records at all.

Local officials sometimes dream of sharing vaccination information with Mexico to eliminate duplication of shots, something one leader calls a "NAFTA for immunizations."

But there's little chance of that happening soon. For now, it is difficult enough just getting the city and county to share records.

EXHIBIT 321

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HEALTH AND SAFETY CODE - HSC

DIVISION 105. COMMUNICABLE DISEASE PREVENTION AND CONTROL [120100 - 122477] *(Division 105 added by Stats. 1995, Ch. 415, Sec. 7.)*

PART 2. IMMUNIZATIONS [120325 - 120480] *(Part 2 added by Stats. 1995, Ch. 415, Sec. 7.)*

CHAPTER 1. Educational and Child Care Facility Immunization Requirements [120325 - 120380] *(Chapter 1 added by Stats. 1995, Ch. 415, Sec. 7.)*

120325. In enacting this chapter, but excluding Section 120380, and in enacting Sections 120400, 120405, 120410, and 120415, it is the intent of the Legislature to provide:

(a) A means for the eventual achievement of total immunization of appropriate age groups against the following childhood diseases:

(1) Diphtheria.

(2) Hepatitis B.

(3) Haemophilus influenzae type b.

(4) Measles.

(5) Mumps.

(6) Pertussis (whooping cough).

(7) Poliomyelitis.

(8) Rubella.

(9) Tetanus.

(10) Varicella (chickenpox).

(11) Any other disease deemed appropriate by the department, taking into consideration the recommendations of the Advisory Committee on Immunization Practices of the United States Department of Health and Human Services, the American Academy of Pediatrics, and the American Academy of Family Physicians.

(b) That the persons required to be immunized be allowed to obtain immunizations from whatever medical source they so desire, subject only to the condition that the immunization be performed in accordance with the regulations of the department and that a record of the immunization is made in accordance with the regulations.

(c) Exemptions from immunization for medical reasons.

(d) For the keeping of adequate records of immunization so that health departments, schools, and other institutions, parents or guardians, and the persons immunized will be able to ascertain that a child is fully or only partially immunized, and so that appropriate public agencies will be able to ascertain the immunization needs of groups of children in schools or other institutions.

(e) Incentives to public health authorities to design innovative and creative programs that will promote and achieve full and timely immunization of children.

(Amended by Stats. 2015, Ch. 35, Sec. 1. (SB 277) Effective January 1, 2016.)

120330. The department, in consultation with the Department of Education, shall adopt and enforce all regulations necessary to carry out Chapter 1 (commencing with Section 120325, but excluding Section 120380) and to carry out Sections 120400, 120405, 120410, and 120415.

Exhibit 321

(Added by Stats. 1995, Ch. 415, Sec. 29. Effective January 1, 1996.)

120335. (a) As used in this chapter, "governing authority" means the governing board of each school district or the authority of each other private or public institution responsible for the operation and control of the institution or the principal or administrator of each school or institution.

(b) The governing authority shall not unconditionally admit any person as a pupil of any private or public elementary or secondary school, child care center, day nursery, nursery school, family day care home, or development center, unless, prior to his or her first admission to that institution, he or she has been fully immunized. The following are the diseases for which immunizations shall be documented:

(1) Diphtheria.

(2) Haemophilus influenzae type b.

(3) Measles.

(4) Mumps.

(5) Pertussis (whooping cough).

(6) Poliomyelitis.

(7) Rubella.

(8) Tetanus.

(9) Hepatitis B.

(10) Varicella (chickenpox).

(11) Any other disease deemed appropriate by the department, taking into consideration the recommendations of the Advisory Committee on Immunization Practices of the United States Department of Health and Human Services, the American Academy of Pediatrics, and the American Academy of Family Physicians.

(c) Notwithstanding subdivision (b), full immunization against hepatitis B shall not be a condition by which the governing authority shall admit or advance any pupil to the 7th grade level of any private or public elementary or secondary school.

(d) The governing authority shall not unconditionally admit or advance any pupil to the 7th grade level of any private or public elementary or secondary school unless the pupil has been fully immunized against pertussis, including all pertussis boosters appropriate for the pupil's age.

(e) The department may specify the immunizing agents that may be utilized and the manner in which immunizations are administered.

(f) This section does not apply to a pupil in a home-based private school or a pupil who is enrolled in an independent study program pursuant to Article 5.5 (commencing with Section 51745) of Chapter 5 of Part 28 of the Education Code and does not receive classroom-based instruction.

(g) (1) A pupil who, prior to January 1, 2016, submitted a letter or affidavit on file at a private or public elementary or secondary school, child day care center, day nursery, nursery school, family day care home, or development center stating beliefs opposed to immunization shall be allowed enrollment to any private or public elementary or secondary school, child day care center, day nursery, nursery school, family day care home, or development center within the state until the pupil enrolls in the next grade span.

(2) For purposes of this subdivision, "grade span" means each of the following:

(A) Birth to preschool.

(B) Kindergarten and grades 1 to 6, inclusive, including transitional kindergarten.

(C) Grades 7 to 12, inclusive.

(3) Except as provided in this subdivision, on and after July 1, 2016, the governing authority shall not unconditionally admit to any of those institutions specified in this subdivision for the first time, or admit or advance any pupil to 7th grade level, unless the pupil has been immunized for his or her age as required by this section.

(h) This section does not prohibit a pupil who qualifies for an individualized education program, pursuant to federal law and Section 56026 of the Education Code, from accessing any special education and related services required by his or her individualized education program.

(Amended by Stats. 2015, Ch. 35, Sec. 4. (SB 277) Effective January 1, 2016.)

120338. Notwithstanding Sections 120325 and 120335, any immunizations deemed appropriate by the department pursuant to paragraph (11) of subdivision (a) of Section 120325 or paragraph (11) of subdivision (b) of Section 120335, may be mandated before a pupil's first admission to any private or public elementary or secondary school, child care center, day nursery, nursery school, family day care home, or development center, only if exemptions are allowed for both medical reasons and personal beliefs.

(Added by Stats. 2015, Ch. 35, Sec. 3. (SB 277) Effective January 1, 2016.)

120340. A person who has not been fully immunized against one or more of the diseases listed in Section 120335 may be admitted by the governing authority on condition that within time periods designated by regulation of the department he or she presents evidence that he or she has been fully immunized against all of these diseases.

(Added by Stats. 1995, Ch. 415, Sec. 7. Effective January 1, 1996.)

120341. (a) The governing authority shall admit a foster child, as defined in subdivision (a) of Section 48853.5 of the Education Code, whose immunization records are not available or are missing.

(b) This section shall not alter the obligation of the governing authority to obtain a foster child's immunization records pursuant to Section 48853.5 of the Education Code or to ensure the immunization of a foster child pursuant to this chapter.

(Added by Stats. 2011, Ch. 463, Sec. 3. (AB 709) Effective January 1, 2012.)

120345. The immunizations required by Chapter 1 (commencing with Section 120325, but excluding Section 120380) and required by Sections 120400, 120405, 120410, and 120415 may be obtained from any private or public source desired if the immunization is administered and records are made in accordance with regulations of the department.

(Added by Stats. 1995, Ch. 415, Sec. 7. Effective January 1, 1996.)

120350. The county health officer of each county shall organize and maintain a program to make immunizations available to all persons required by Chapter 1 (commencing with Section 120325, but excluding Section 120380) and required by Sections 120400, 120405, 120410, and 120415 to be immunized. The county health officer shall also determine how the cost of the program is to be recovered. To the extent that the cost to the county is in excess of that sum recovered from persons immunized, the cost shall be paid by the county in the same manner as other expenses of the county are paid.

(Added by Stats. 1995, Ch. 415, Sec. 7. Effective January 1, 1996.)

120355. Any person or organization administering immunizations shall furnish each person immunized, or his or her parent or guardian, with a written record of immunization given in a form prescribed by the department.

(Added by Stats. 1995, Ch. 415, Sec. 7. Effective January 1, 1996.)

120360. The requirements of Chapter 1 (commencing with Section 120325, but excluding Section 120380) and of Sections 120400, 120405, 120410, and 120415 shall not apply to any person 18 years of age or older, or to any person seeking admission to a community college.

(Added by Stats. 1995, Ch. 415, Sec. 7. Effective January 1, 1996.)

120370. (a) (1) Prior to January 1, 2021, if the parent or guardian files with the governing authority a written statement by a licensed physician and surgeon to the effect that the physical condition of the child is such, or medical circumstances relating to the child are such, that immunization is not considered safe, indicating the specific nature and probable duration of the medical condition or circumstances, including, but not limited to, family medical history, for which the physician and surgeon does not recommend immunization, that child shall be exempt from the requirements of this chapter, except for Section 120380, and exempt from Sections 120400, 120405, 120410, and 120415 to the extent indicated by the physician and surgeon's statement.

(2) Commencing January 1, 2020, a child who has a medical exemption issued before January 1, 2020, shall be allowed continued enrollment to any public or private elementary or secondary school, child care center, day

nursery, nursery school, family day care home, or developmental center within the state until the child enrolls in the next grade span.

For purposes of this subdivision, "grade span" means each of the following:

(A) Birth to preschool, inclusive.

(B) Kindergarten and grades 1 to 6, inclusive, including transitional kindergarten.

(C) Grades 7 to 12, inclusive.

(3) Except as provided in this subdivision, on and after July 1, 2021, the governing authority shall not unconditionally admit or readmit to any of those institutions specified in this subdivision, or admit or advance any pupil to 7th grade level, unless the pupil has been immunized pursuant to Section 120335 or the parent or guardian files a medical exemption form that complies with Section 120372.

(b) If there is good cause to believe that a child has been exposed to a disease listed in subdivision (b) of Section 120335 and the child's documentary proof of immunization status does not show proof of immunization against that disease, that child may be temporarily excluded from the school or institution until the local health officer is satisfied that the child is no longer at risk of developing or transmitting the disease.

(Amended by Stats. 2019, Ch. 281, Sec. 1. (SB 714) Effective January 1, 2020.)

120372. (a) (1) By January 1, 2021, the department shall develop and make available for use by licensed physicians and surgeons an electronic, standardized, statewide medical exemption certification form that shall be transmitted directly to the department's California Immunization Registry (CAIR) established pursuant to Section 120440. Pursuant to Section 120375, the form shall be printed, signed, and submitted directly to the school or institution at which the child will attend, submitted directly to the governing authority of the school or institution, or submitted to that governing authority through the CAIR where applicable. Notwithstanding Section 120370, commencing January 1, 2021, the standardized form shall be the only documentation of a medical exemption that the governing authority may accept.

(2) At a minimum, the form shall require all of the following information:

(A) The name, California medical license number, business address, and telephone number of the physician and surgeon who issued the medical exemption, and of the primary care physician of the child, if different from the physician and surgeon who issued the medical exemption.

(B) The name of the child for whom the exemption is sought, the name and address of the child's parent or guardian, and the name and address of the child's school or other institution.

(C) A statement certifying that the physician and surgeon has conducted a physical examination and evaluation of the child consistent with the relevant standard of care and complied with all applicable requirements of this section.

(D) Whether the physician and surgeon who issued the medical exemption is the child's primary care physician. If the issuing physician and surgeon is not the child's primary care physician, the issuing physician and surgeon shall also provide an explanation as to why the issuing physician and not the primary care physician is filling out the medical exemption form.

(E) How long the physician and surgeon has been treating the child.

(F) A description of the medical basis for which the exemption for each individual immunization is sought. Each specific immunization shall be listed separately and space on the form shall be provided to allow for the inclusion of descriptive information for each immunization for which the exemption is sought.

(G) Whether the medical exemption is permanent or temporary, including the date upon which a temporary medical exemption will expire. A temporary exemption shall not exceed one year. All medical exemptions shall not extend beyond the grade span, as defined in Section 120370.

(H) An authorization for the department to contact the issuing physician and surgeon for purposes of this section and for the release of records related to the medical exemption to the department, the Medical Board of California, and the Osteopathic Medical Board of California.

(I) A certification by the issuing physician and surgeon that the statements and information contained in the form are true, accurate, and complete.

(3) An issuing physician and surgeon shall not charge for either of the following:

(A) Filling out a medical exemption form pursuant to this section.

(B) A physical examination related to the renewal of a temporary medical exemption.

(b) Commencing January 1, 2021, if a parent or guardian requests a licensed physician and surgeon to submit a medical exemption for the parent's or guardian's child, the physician and surgeon shall inform the parent or guardian of the requirements of this section. If the parent or guardian consents, the physician and surgeon shall examine the child and submit a completed medical exemption certification form to the department. A medical exemption certification form may be submitted to the department at any time.

(c) By January 1, 2021, the department shall create a standardized system to monitor immunization levels in schools and institutions as specified in Sections 120375 and 120440, and to monitor patterns of unusually high exemption form submissions by a particular physician and surgeon.

(d) (1) The department, at a minimum, shall annually review immunization reports from all schools and institutions in order to identify medical exemption forms submitted to the department and under this section that will be subject to paragraph (2).

(2) A clinically trained immunization department staff member, who is either a physician and surgeon or a registered nurse, shall review all medical exemptions from any of the following:

(A) Schools or institutions subject to Section 120375 with an overall immunization rate of less than 95 percent.

(B) Physicians and surgeons who have submitted five or more medical exemptions in a calendar year beginning January 1, 2020.

(C) Schools or institutions subject to Section 120375 that do not provide reports of vaccination rates to the department.

(3) (A) The department shall identify those medical exemption forms that do not meet applicable CDC, ACIP, or AAP criteria for appropriate medical exemptions. The department may contact the primary care physician and surgeon or issuing physician and surgeon to request additional information to support the medical exemption.

(B) Notwithstanding subparagraph (A), the department, based on the medical discretion of the clinically trained immunization staff member, may accept a medical exemption that is based on other contraindications or precautions, including consideration of family medical history, if the issuing physician and surgeon provides written documentation to support the medical exemption that is consistent with the relevant standard of care.

(C) A medical exemption that the reviewing immunization department staff member determines to be inappropriate or otherwise invalid under subparagraphs (A) and (B) shall also be reviewed by the State Public Health Officer or a physician and surgeon from the department's immunization program designated by the State Public Health Officer. Pursuant to this review, the State Public Health Officer or physician and surgeon designee may revoke the medical exemption.

(4) Medical exemptions issued prior to January 1, 2020, shall not be revoked unless the exemption was issued by a physician or surgeon that has been subject to disciplinary action by the Medical Board of California or the Osteopathic Medical Board of California.

(5) The department shall notify the parent or guardian, issuing physician and surgeon, the school or institution, and the local public health officer with jurisdiction over the school or institution of a denial or revocation under this subdivision.

(6) If a medical exemption is revoked pursuant to this subdivision, the child shall continue in attendance. However, within 30 calendar days of the revocation, the child shall commence the immunization schedule required for conditional admittance under Chapter 4 (commencing with Section 6000) of Division 1 of Title 17 of the California Code of Regulations in order to remain in attendance, unless an appeal is filed pursuant to Section 120372.05 within that 30-day time period, in which case the child shall continue in attendance and shall not be required to otherwise comply with immunization requirements unless and until the revocation is upheld on appeal.

(7) (A) If the department determines that a physician's and surgeon's practice is contributing to a public health risk in one or more communities, the department shall report the physician and surgeon to the Medical Board of California or the Osteopathic Medical Board of California, as appropriate. The department shall not accept a medical exemption form from the physician and surgeon until the physician and surgeon demonstrates to the department that the public health risk no longer exists, but in no event shall the physician and surgeon be barred from submitting these forms for less than two years.

(B) If there is a pending accusation against a physician and surgeon with the Medical Board of California or the Osteopathic Medical Board of California relating to immunization standards of care, the department shall not

accept a medical exemption form from the physician and surgeon unless and until the accusation is resolved in favor of the physician and surgeon.

(C) If a physician and surgeon licensed with the Medical Board of California or the Osteopathic Medical Board of California is on probation for action relating to immunization standards of care, the department and governing authority shall not accept a medical exemption form from the physician and surgeon unless and until the probation has been terminated.

(8) The department shall notify the Medical Board of California or the Osteopathic Medical Board of California, as appropriate, of any physician and surgeon who has five or more medical exemption forms in a calendar year that are revoked pursuant to this subdivision.

(9) Notwithstanding any other provision of this section, a clinically trained immunization program staff member who is a physician and surgeon or a registered nurse may review any exemption in the CAIR or other state database as necessary to protect public health.

(e) The department, the Medical Board of California, and the Osteopathic Medical Board of California shall enter into a memorandum of understanding or similar agreement to ensure compliance with the requirements of this section.

(f) In administering this section, the department and the independent expert review panel created pursuant to Section 120372.05 shall comply with all applicable state and federal privacy and confidentiality laws. The department may disclose information submitted in the medical exemption form in accordance with Section 120440, and may disclose information submitted pursuant to this chapter to the independent expert review panel for the purpose of evaluating appeals.

(g) The department shall establish the process and guidelines for review of medical exemptions pursuant to this section. The department shall communicate the process to providers and post this information on the department's website.

(h) If the department or the California Health and Human Services Agency determines that contracts are required to implement or administer this section, the department may award these contracts on a single-source or sole-source basis. The contracts are not subject to Part 2 (commencing with Section 10100) of Division 2 of the Public Contract Code, Article 4 (commencing with Section 19130) of Chapter 5 of Part 2 of Division 5 of Title 2 of the Government Code, or Sections 4800 to 5180, inclusive, of the State Administrative Manual as they relate to approval of information technology projects or approval of increases in the duration or costs of information technology projects.

(i) Notwithstanding the rulemaking provisions of the Administrative Procedure Act (Chapter 3.5 (commencing with Section 11340) of Part 1 of Division 3 of Title 2 of the Government Code), the department may implement and administer this section through provider bulletins, or similar instructions, without taking regulatory action.

(j) For purposes of administering this section, the department and the California Health and Human Services Agency appeals process shall be exempt from the rulemaking and administrative adjudication provisions in the Administrative Procedure Act Chapter 3.5 (commencing with Section 11340), and Chapter 4 (commencing with Section 11370), Chapter 4.5 (commencing with 11400), and Chapter 5 (commencing with Section 11500) of, Part 1 of Division 3 of Title 2 of the Government Code.

(Amended by Stats. 2019, Ch. 281, Sec. 2. (SB 714) Effective January 1, 2020.)

120372.05. (a) A medical exemption revoked pursuant to Section 120372 may be appealed by a parent or guardian to the Secretary of California Health and Human Services. Parents, guardians, or the physician who issued the medical exemption may provide necessary information for purposes of the appeal.

(b) The secretary shall establish an independent expert review panel, consisting of three licensed physicians and surgeons who have relevant knowledge, training, and experience relating to primary care or immunization to review appeals. The agency shall establish the process and guidelines for the appeals process pursuant to this section, including the process for the panel to contact the issuing physician and surgeon, parent, or guardian. The agency shall post this information on the agency's internet website. The agency shall also establish requirements, including conflict-of-interest standards, consistent with the purposes of this chapter, that a physician and surgeon shall meet in order to qualify to serve on the panel.

(c) The independent expert review panel shall evaluate appeals consistent with the federal Centers for Disease Control and Prevention, federal Advisory Committee on Immunization Practices, or American Academy of Pediatrics guidelines or the relevant standard of care, as applicable.

(d) The independent expert review panel shall submit its determination to the secretary. The secretary shall adopt the determination of the independent expert review panel and shall promptly issue a written decision to the child's parent or guardian. The decision shall not be subject to further administrative review.

(e) A child whose medical exemption revocation pursuant to subdivision (d) of Section 120372 is appealed under this section shall continue in attendance and shall not be required to commence the immunization required for conditional admittance under Chapter 4 (commencing with Section 6000) of Division 1 of Title 17 of the California Code of Regulations, provided that the appeal is filed within 30 calendar days of revocation of the medical exemption.

(f) For purposes for administering this section, the department and the California Health and Human Services Agency appeals process shall be exempt from the rulemaking and administrative adjudication provisions in the Administrative Procedure Act Chapter 3.5 (commencing with Section 11340), and Chapter 4 (commencing with Section 11370), Chapter 4.5 (commencing with 11400), and Chapter 5 (commencing with Section 11500) of, Part 1 of Division 3 of Title 2 of the Government Code.

(Amended by Stats. 2019, Ch. 281, Sec. 3. (SB 714) Effective January 1, 2020.)

120375. (a) The governing authority of each school or institution included in Section 120335 shall require documentary proof of each entrant's immunization status. The governing authority shall record the immunizations of each new entrant in the entrant's permanent enrollment and scholarship record on a form provided by the department. The immunization record of each new entrant admitted conditionally shall be reviewed periodically by the governing authority to ensure that within the time periods designated by regulation of the department the entrant has been fully immunized against all of the diseases listed in Section 120335, and immunizations received after entry shall be added to the pupil's immunization record.

(b) The governing authority of each school or institution included in Section 120335 shall prohibit from further attendance any pupil admitted conditionally who failed to obtain the required immunizations within the time limits allowed in the regulations of the department until that pupil has been fully immunized against all of the diseases listed in Section 120335, unless the pupil is exempted under Section 120370 or 120372.

(c) The governing authority shall file a written report, on at least an annual basis, on the immunization status of new entrants to the school or institution under their jurisdiction with the department and the local health department on forms prescribed by the department. As provided in paragraph (4) of subdivision (a) of Section 49076 of the Education Code, the local health department shall have access to the complete health information as it relates to immunization of each student in the schools or other institutions listed in Section 120335 in order to determine immunization deficiencies.

(d) The governing authority shall cooperate with the county health officer in carrying out programs for the immunization of persons applying for admission to any school or institution under its jurisdiction. The governing board of any school district may use funds, property, and personnel of the district for that purpose. The governing authority of any school or other institution may permit any licensed physician or any qualified registered nurse to administer immunizing agents to any person seeking admission to any school or institution under its jurisdiction.

(Amended by Stats. 2019, Ch. 278, Sec. 5. (SB 276) Effective January 1, 2020.)

120380. It is the intent of the Legislature that the administration of immunizing agents by registered nurses in school immunization programs under the direction of a supervising physician and surgeon as provided in Sections 49403 and 49426 of the Education Code shall be in accordance with accepted medical procedure. To implement this intent, the department may adopt written regulations specifying the procedures and circumstances under which a registered nurse, acting under the direction of a supervising physician and surgeon, may administer an immunizing agent pursuant to Sections 49403 and 49426 of the Education Code.

However, nothing in this section shall be construed to prevent any registered nurse from administering an immunizing agent in accordance with Sections 49403 and 49426 of the Education Code in the absence of written regulations as the department is authorized to adopt under this section.

(Amended by Stats. 1997, Ch. 97, Sec. 6. Effective July 21, 1997.)

EXHIBIT 322

Effective July 1, 2019

California Code of Regulations
Title 17, Division 1, Chapter 4

Subchapter 8. Immunization Against Poliomyelitis, Diphtheria, Pertussis, Tetanus, Measles, Mumps, Rubella, Haemophilus Influenzae Type B (Hib), Hepatitis B, and Varicella

Article 1. General

§ 6000. Definitions and Abbreviations.

(a) "Admission" means a pupil's first attendance in a school or pre-kindergarten facility or re-entry after withdrawing from a previous enrollment.

(1) "Unconditional admission" is admission based upon documented receipt of all required immunizations for the pupil's age or grade, in accordance with section 6025, except for those immunizations:

(A) permanently exempted for medical reasons in accordance with section 6051, or
(B) exempted for personal beliefs in accordance with Health and Safety Code section 120335.

(2) "Conditional admission" is provisional admission for a pupil who has received some but not all required immunizations and is not due for any vaccine dose at the time of admission in accordance with sections 6035 and 6050.

(b) "Governing authority" is defined in section 120335 of the Health and Safety Code.

(c) The following are abbreviations for immunizations:

(1) "DTaP" means diphtheria toxoid, tetanus toxoid, and acellular pertussis vaccine.
(2) "DTP" means diphtheria toxoid, tetanus toxoid, and pertussis vaccine.
(3) "Tdap" means tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine.
(4) "Td" means tetanus toxoid and reduced diphtheria toxoid vaccine.
(5) "Hep B" means hepatitis B vaccine.
(6) "Hib" means *Haemophilus influenzae*, type b vaccine.
(7) "IPV" means inactivated polio vaccine.
(8) "OPV" means oral polio vaccine.
(9) "MMR" means measles, mumps, and rubella vaccine.
(10) "MMRV" means measles, mumps, rubella, and varicella vaccine.

(d) "Kindergarten" means a school program or class prior to first grade, including a transitional kindergarten program.

(e) "K-12" means kindergarten through twelfth grade.

(f) "Licensed physician" means either of the following:

(1) An individual who holds a "physician's and surgeon's certificate" issued by the Medical Board of California to practice medicine in California pursuant to Chapter 5 (commencing with Section 2000) of Division 2 of the Business and Professions Code, or
(2) An individual who holds an "osteopathic physician's and surgeon's certificate" issued by the Osteopathic Medical Board of California to practice medicine in California pursuant to Chapter 5 (commencing with Section 2000) of Division 2 of the Business and Professions Code.

(g) "Parent or guardian" means, for a

(1) Minor: the adult(s) legally responsible for the pupil's care and custody, or
(2) Emancipated minor: the pupil.

(h) "Pre-kindergarten facility" means any private or public child care center, day nursery, nursery school, family day care home, pre-school, or development center for young children.

(i) "Pupil" means a person admitted to or seeking admission to any school or pre-kindergarten facility.

(j) "Pupil's record" means, for:

(1) Pre-kindergarten, any information relative to an individual pupil gathered within or without the pre-kindergarten facility and maintained within the pre-kindergarten facility, regardless of the physical form in which it is maintained, or
(2) K-12, a record as defined in section 430 of Title 5 of the California Code of Regulations.

(k) "School" means any private or public kindergarten, elementary, or secondary school.

(l) "The Department" means the California Department of Public Health.

(m) For purposes of this Article, "vaccine" means an immunization administered in the United States of America or other countries that is recommended by the federal Advisory Committee on Immunization Practices for the prevention of the respective diseases identified in section 120335 of the Health and Safety Code.

Article 2. *Requirements for Admission and Continued Attendance*

§ 6025. Unconditional Admission.

(a) A school or pre-kindergarten facility shall unconditionally admit or allow continued attendance to any pupil age 18 months or older whose parent or guardian has provided documentation of any of the following for each immunization required for the pupil's age or grade, as defined in Table A or B of this section:

(1) Receipt of immunization in accordance with sections 6065 and 6070 regardless of exemptions to other required vaccines.
(2) A permanent medical exemption in accordance with section 6051.
(3) A personal beliefs exemption in accordance with Health and Safety Code section 120335.

(b) Pupils admitted unconditionally at a younger age or earlier grade will be required to provide documentary proof of required immunizations at the time of any additional requirements at a later age or grade, as indicated in Table B of this section.

(c) Table A, "California Immunization Requirements for Pre-Kindergarten," and Table B, "California Immunization Requirements for Grades K-12," set forth, according to age or grade, the required immunizations and number of doses for admission to and attendance at a school or pre-kindergarten facility.

TABLE A: CALIFORNIA IMMUNIZATION REQUIREMENTS FOR PRE-KINDERGARTEN[1]

AGE WHEN ADMITTED	TOTAL NUMBER OF DOSES REQUIRED OF EACH IMMUNIZATION[2,3]				
2 through 3 months	1 Polio	1 DTaP	1 Hep B	1 Hib	
4 through 5 months	2 Polio	2 DTaP	2 Hep B	2 Hib	
6 through 14 months	2 Polio	3 DTaP	2 Hep B	2 Hib	
15 through 17 months	3 Polio	3 DTaP	2 Hep B		1 Varicella
	On or after the 1st birthday:			1 Hib[4]	1 MMR
18 months through 5 years	3 Polio	4 DTaP	3 Hep B		1 Varicella
	On or after the 1st birthday:			1 Hib[4]	1 MMR

[1] A pupil's parent or guardian must provide documentation of a pupil's proof of immunization to the governing authority no more than 30 days after a pupil becomes subject to any additional requirement(s) based on age, as indicated in Table A.
[2] Combination vaccines (e.g., MMRV) meet the requirements for individual component vaccines. Doses of DTP count towards the DTaP requirement.
[3] Any vaccine administered four or fewer days prior to the minimum required age is valid.
[4] One Hib dose must be given on or after the first birthday regardless of previous doses. Required only for children who have not reached the age of five years.

TABLE B: CALIFORNIA IMMUNIZATION REQUIREMENTS FOR GRADES K-12

GRADE	NUMBER OF DOSES REQUIRED OF EACH IMMUNIZATION[1, 2, 3]				
K-12 Admission	4 Polio[4]	5 DTaP[5]	3 Hep B[6]	2 MMR[7]	2 Varicella
(7th-12th)[8]	1 Tdap				
7th Grade Advancement[9,10]	2 Varicella[10]	1 Tdap[8]			

[1] Requirements for K-12 admission also apply to transfer pupils.
[2] Combination vaccines (e.g., MMRV) meet the requirements for individual component vaccines. Doses of DTP count towards the DTaP requirement.
[3] Any vaccine administered four or fewer days prior to the minimum required age is valid.
[4] Three doses of polio vaccine meet the requirement if one dose was given on or after the fourth birthday.
[5] Four doses of DTaP meet the requirement if at least one dose was given on or after the fourth birthday. Three doses meet the requirement if at least one dose of Tdap, DTaP, or DTP vaccine was given on or after the 7th birthday. One or two doses of Td vaccine given on or after the seventh birthday count towards the requirement.
[6] For seventh grade admission, refer to Health and Safety Code section 120335, subdivision (c).
[7] Two doses of measles, two doses of mumps, and one dose of rubella vaccine meet the requirement, separately or combined. Only doses administered on or after the first birthday meet the requirement.
[8] For 7th-12th graders, at least one dose of pertussis-containing vaccine is required on or after the seventh birthday.
[9] For children in ungraded schools, pupils 12 years and older are subject to the seventh grade advancement requirements.
[10] The varicella requirement for seventh grade advancement expires after June 30, 2025.

§ 6035. Conditional Admission.

(a) Any pupil seeking admission to a school or pre-kindergarten facility who lacks documentation of having received all the required vaccine doses for the pupil's age or grade as specified in Table A or B of section 6025, and has not obtained an exemption in accordance with section 6051 and Health and Safety Code sections 120335 and 120370, may be admitted conditionally if:

(1) The pupil has commenced receiving doses of all vaccines required for the pupil's age or grade in accordance with Table C or D of this section and is not currently due for any doses at the time of admission. The governing authority shall notify the pupil's parent or guardian of the date(s) by which the pupil must complete all remaining doses in accordance with Table C or D of this section; or

(2) The pupil is younger than 18 months and has received all immunizations required for the pupil's age but will require additional vaccine doses at an older age. The governing authority shall notify the pupil's parent or guardian of the date by which the pupil must complete all the remaining doses as they become due in accordance with Table A of section 6025; or

(3) The pupil's parent or guardian has obtained a temporary medical exemption from some or all required immunization(s) in accordance with section 6050. The governing authority shall notify the pupil's parent or guardian of the date by which the parent or guardian must provide documentation of receipt of the immunization(s) included in the temporary medical exemption.

(b) The governing authority shall review records of any pupil admitted conditionally to a school at least every 30 days from the date of admission, inform the parent or guardian of the remaining required vaccine doses until all required immunizations are received or an exemption is filed, and update the immunization information in the pupil's record.

(c) Continued attendance after conditional admission is contingent upon documentation of receipt of the remaining required immunizations in accordance with this section and sections 6025 and 6065.

(d) (1) For a pupil transferring into a school in California from another school in the United States at kindergarten through 12th grade whose immunization record, as specified in section 6065 or 6070, has not been received by the new school at the time of admission, the governing authority of the school may admit the pupil for up to 30 school days. If the governing authority admits the pupil for up to 30 school days and the pupil's immunization record has not been received at the end of this period, the governing authority shall exclude the pupil from further attendance until the parent or guardian provides documentation of compliance with the immunization requirements specified in this section and sections 6025 and 6040(a). Documentation of compliance from the parent or guardian must be provided as specified in sections 6050, 6051, and 6065, as applicable.

(2) Notwithstanding paragraph (1) of this subdivision, a pupil transferring into a school in California from another school in the United States on the first day of seventh grade, who has not provided documentation that the pertussis requirement has been met to the new school by the time of admission, shall not be admitted by the governing authority.

(e) Table C, "Conditional Admission Immunization Schedule for Pre-Kindergarten," and Table D, "Conditional Admission Immunization Schedule for Grades K-12," set forth the vaccine and time interval between doses required for conditional admission and attendance in a school or pre-kindergarten facility.

TABLE C: CONDITIONAL ADMISSION SCHEDULE FOR PRE-KINDERGARTEN

Before admission a child must obtain the first dose of each required vaccine and any subsequent doses that are due because the period of time allowed before exclusion has elapsed.

DOSE	Earliest Dose May be Given	Exclude if not Given by
Polio #2	4 weeks after 1st dose	8 weeks after 1st dose
Polio #3	4 weeks after 2nd dose	12 months after 2nd dose
DTaP #2, #3	4 weeks after previous dose	8 weeks after previous dose
DTaP #4	6 months after 3rd dose	12 months after 3rd dose
Hib #2	4 weeks after 1st dose	8 weeks after 1st dose
Hep B #2	4 weeks after 1st dose	8 weeks after 1st dose
Hep B #3	8 weeks after 2nd dose	12 months after 2nd dose and at least 4 months after 1st dose

TABLE D: CONDITIONAL ADMISSION SCHEDULE FOR GRADES K-12

Before admission a child must obtain the first dose of each required vaccine and any subsequent doses that are due because the period of time allowed before exclusion has elapsed.

DOSE	EARLIEST DOSE MAY BE GIVEN	EXCLUDE IF NOT GIVEN BY
Polio #2	4 weeks after 1st dose	8 weeks after 1st dose
Polio #3	4 weeks after 2nd dose	12 months after 2nd dose
Polio #4 [1]	6 months after 3rd dose	12 months after 3rd dose
DTaP #2	4 weeks after 1st dose	8 weeks after 1st dose
DTaP #3 [2]	4 weeks after 2nd dose	8 weeks after 2nd dose
DTaP #4	6 months after 3rd dose	12 months after 3rd dose
DTaP #5	6 months after 4th dose	12 months after 4th dose
Hep B #2	4 weeks after 1st dose	8 weeks after 1st dose
Hep B #3	8 weeks after 2nd dose	12 months after 2nd dose and at least 4 months after 1st dose
MMR #2	4 weeks after 1st dose	4 months after 1st dose
Varicella #2	*Age less than 13 years:* 3 months after 1st dose	4 months after 1st dose
	Age 13 years and older: 4 weeks after 1st dose	8 weeks after 1st dose

[1] Three doses of polio vaccine meet the requirement if one dose was given on or after the fourth birthday.

[2] If DTaP #3 is the final required dose, DTaP #3 should be given at least six months after DTaP #2, and pupils should be excluded if not given by 12 months after second dose. Three doses meet the requirement if at least one dose of Tdap, DTaP, or DTP vaccine was given on or after the seventh birthday. One or two doses of Td vaccine given on or after the seventh birthday count towards the requirement.

§ 6040. Requirements for Continued Attendance of Pupils Already Admitted.

(a) If a pupil attending a school or pre-kindergarten facility who was previously believed to be in compliance is subsequently discovered to not be in compliance with either the unconditional admission requirements specified in section 6025 or the conditional admission requirements specified in section 6035:

(1) The governing authority shall notify the parent or guardian of the time period within which the doses must be received. This time period may be no more than 10 school days after notification.

(2) The pupil shall continue in attendance only if the parent or guardian provides documentation that the immunization requirements have been met within the time period designated by the governing authority.

(b) The parent or guardian shall submit documentation that seventh grade immunization requirements have been met to the governing authority prior to first 7th grade attendance.

§ 6045. Special Immunization Schedules.

The Department may approve alternative immunization schedules when warranted by substantial medical or other conditions, such as an outbreak, epidemic, or vaccine shortage. The Department may post alternative schedules on the Department website and by other methods as needed.

§ 6050. Conditional Admission with Temporary Medical Exemption.

(a) A pupil with a temporary medical exemption from a required immunization shall be admitted conditionally if all other immunization requirements are met as specified in section 6025 or section 6035. The governing authority shall grant a temporary medical exemption from required immunization(s) if it receives a signed, written statement by a licensed physician stating:

(1) The specific nature of the physical condition or medical circumstance for which the licensed physician does not recommend immunization;
(2) The probable duration of the physical condition or medical circumstance;
(3) Each specific required immunization from which the pupil is exempt; and
(4) The date that the medical exemption expires for each respective immunization.

(b) To continue in attendance, at the termination of the temporary exemption, all immunization requirements shall be met pursuant to section 6025 or section 6035.

(c) Notwithstanding subdivision (a)(4), a temporary medical exemption shall not exceed twelve calendar months from the date of the licensed physician's written statement.

(d) The fact of the temporary medical exemption for specific immunization(s) and expiration date for the exemption(s) shall be recorded in the pupil's record.

(e) A pupil with a temporary medical exemption may be subject to exclusion pursuant to section 6060.

§ 6051. Unconditional Admission with Permanent Medical Exemption.

(a) A pupil with a permanent medical exemption from a required immunization shall be admitted unconditionally if all other required immunizations as specified in section 6025 have been documented as received. The governing authority shall grant a permanent medical exemption from required immunization(s) if it receives a signed, written statement by a licensed physician stating:

(1) The specific nature of the physical condition or medical circumstance for which the licensed physician does not recommend immunization;
(2) That the physical condition or medical circumstance is permanent; and
(3) Each specific required immunization from which the pupil is permanently exempt.

(b) The fact of the permanent medical exemption for specific immunization(s) shall be recorded in the pupil's record in accordance with section 6070.

(c) A pupil with a permanent medical exemption may be subject to exclusion pursuant to section 6060.

Article 3. Exclusion

§ 6055. Exclusion.

The governing authority shall exclude any pupil who does not meet the requirements for admission or continued attendance as specified in Article 2 of this subchapter and Health and Safety Code section 120335.

§ 6060. Pupil Not Completely Immunized for Age or Grade and Exposed to Communicable Disease.

(a) The governing authority shall maintain a list of all pupils not completely immunized for age or grade, including pupils with exemptions or who are admitted conditionally. The list shall include the immunizations not yet received for each pupil.

(b) Whenever the governing authority has good cause to believe that a pupil who is not completely immunized against a particular communicable disease may have been exposed to that disease, the governing authority shall immediately inform the local health officer. The local health officer shall determine whether the pupil is at risk of developing or transmitting the disease and, if so, may require the exclusion of the pupil from that school or pre-kindergarten facility until the completion of the incubation period or, if infection is suspected or occurs, until completion of the period in which the disease is communicable.

Article 4. *Records as Evidence of Immunization*

§ 6065. Documentary Proof.

(a) The person or organization administering the immunization shall give the person immunized or his or her parent or guardian an immunization record which shall contain the following information:

(1) Name of the person.
(2) Birthdate.
(3) Type of vaccine(s) administered.
(4) Month, day, and year of each immunization.
(5) Name of the physician or agency administering the vaccine(s).

(b) The governing authority of the school or pre-kindergarten facility shall review the pupil's immunization record and document the immunization information specified in section 6070.

(c) When the pupil's immunization record is not available, the pupil shall not be admitted, conditionally or otherwise, until the pupil has commenced receiving doses of all required vaccines in accordance with section 6035.

§ 6070. Recording of Immunization Information by California Schools and Pre-Kindergarten Facilities.

(a) Pre-kindergarten facility and school personnel must record information for each pupil regarding all doses of required immunizations and the status of all requirements, as defined in Article 2 of this subchapter, using an immunization record that is provided by the parent or guardian that complies with the documentary proof requirements of section 6065, from a prior school, or in an immunization registry or information system governed by Health and Safety Code section 120440. The governing authority of each school and pre-kindergarten facility shall maintain this information for each pupil in the pupil's record.

(b) The immunization information shall include the following elements:

(1) Pupil Name (Last, First, Middle).
(2) Statewide Student Identifier (SSID) (if assigned).
(3) Name of Parent/Guardian (Last, First).
(4) Birthdate (month, day, and year).
(5) Sex.
(6) Ethnicity (Hispanic/Latino, Non-Hispanic/Non-Latino).
(7) Race (African-American/Black, American Indian/Alaska Native, Asian, Native Hawaiian/Other Pacific Islander, White, Other).

(8) As specified in Table A or B of section 6025 for age or grade, the date (month, day, and year) each of the following required vaccine doses were given:

(A) IPV/OPV (Polio).
(B) DTaP/DTP (Diphtheria, Tetanus and [acellular] Pertussis).
(C) MMR (Measles, Mumps, and Rubella).
(D) Hib (Haemophilus influenzae type b; required for pre-kindergarten only).
(E) Hep B (Hepatitis B).
(F) VAR/VZV (Varicella or Chickenpox).
(G) Tdap (Tetanus, reduced Diphtheria and [acellular] Pertussis; required for 7th grade advancement and 7th-12th grade admission).

(9) Permanent medical exemption (indicate for each vaccine as applicable).

(10) Status of requirements at admission to pre-kindergarten:

(A) Name of staff who reviewed the pupil's immunization record.
(B) (If applicable) Pupil is currently up-to-date but more doses are due as specified in Tables A and C of sections 6025 and 6035, respectively.
i. Follow-up date (month, day and year).
(C) (If applicable) Pupil has Temporary Medical Exemption as specified in section 6050.
i. Follow-up date (month, day and year).
(D) The date (month, day and year) pupil met requirements for admission as specified in section 6025.

(11) Status of requirements at admission to K-12:

(A) Name of staff who reviewed the pupil's immunization record.
(B) (If applicable) Pupil is currently up-to-date but more doses are due as specified in Tables B and D of sections 6025 and 6035, respectively.
i. Follow-up date (month, day and year).
(C) (If applicable) Pupil has Temporary Medical Exemption as specified in section 6050.
i. Follow-up date (month, day and year).
(D) The date (month, day and year) pupil met requirements for admission as specified in section 6025.

(12) Status of requirements at admission or advancement to 7th grade:

(A) Name of staff who reviewed the pupil's immunization record.
(B) (If applicable) Pupil is currently up-to-date but more doses are due as specified in Tables B and D of sections 6025 and 6035, respectively.
i. Follow-up date (month, day and year).
(C) (If applicable) Pupil has Temporary Medical Exemption as specified in section 6050.
i. Follow-up date (month, day and year).

(D) The date (month, day and year) pupil meets requirements for admission as specified in section 6025.

(c) Pursuant to subdivision (c) of section 120375 of the Health and Safety Code, the local health department shall have access to the health information as it relates to immunization of each pupil.

§ 6075. Reporting.

(a) The governing authority of each school or pre-kindergarten facility shall file annual immunization status reports with the Department, as specified in this section. Procedures and instructions for completing and filing the reports are posted on the Department website at www.cdph.ca.gov, or are available from the California Department of Public Health, Immunization Branch, 850 Marina Bay Parkway, Building P, 2nd floor, Richmond, CA, 94804.

(b) All immunization reports shall contain the following information:

(1) Facility number (nine-digit number assigned by Department of Social Services) or County-District School (CDS) Code.
(2) County.
(3) Facility or school name.
(4) Physical address (street address, city, zip).
(5) Mailing address (street address, city, zip).
(6) Phone number.
(7) Facility type (public, private, Head Start) or school type (public, private).
(8) Staff member completing form (name, email, phone number).
(9) Designated contact (name, email, phone number).
(10) Date of submission (month, day, year).

(c) Pre-kindergarten Facility Annual Immunization Reports must include the elements listed in subdivision (b) and the following information:

(1) Number of pupils admitted for each age group:
(A) Under two years old.
(B) Two years and older.

(2) If applicable, reason no pupils age 2-5 years old are admitted:
(A) No pupils age 2-5 years old this year.
(B) No pupils age 2-5 years old ever.
(C) Facility closed.

(3) Status of immunization requirements for admission for each category:
  (A) Number of pupils with all required immunizations.
  (B) Number of pupils conditionally admitted including temporary medical exemptions who do not meet the requirement for:
    i. Polio.
    ii. DTP/DTaP.
    iii. MMR.
    iv. Hib.
    v. Hepatitis B.
    vi. Varicella.
  (C) Number of pupils with a personal beliefs exemption (filed before January 1, 2016).
  (D) Number of pupils with a personal beliefs exemption (filed before January 1, 2016) for each required vaccine.
  (E) Number of pupils conditionally admitted with a temporary medical exemption.
  (F) Number of pupils with a permanent medical exemption.
  (G) Number of pupils with a permanent medical exemption from each required vaccine.
  (H) Number of pupils with no required immunizations.
  (I) Number of pupils admitted that do not meet criteria (A)-(H).

(d) Kindergarten Annual Immunization Reports must include the elements listed in subdivision (b) and the following information:
(1) Public school district.
(2) School subtype (traditional, home, online/e-learning).
(3) Number of pupils admitted to kindergarten.
(4) If applicable, reason no pupils are admitted to kindergarten:
  (A) No pupils in kindergarten this year.
  (B) No pupils in kindergarten ever.
  (C) Facility closed.

(5) Status of immunization requirements for admission to kindergarten for each category:
  (A) Number of pupils with all required immunizations.
  (B) Number of pupils conditionally admitted including temporary medical exemptions who do not meet the requirement for:
    i. Polio.
    ii. DTP/DTaP.
    iii. MMR.
    iv. Hepatitis B.
    v. Varicella.
  (C) Number of pupils conditionally admitted with a temporary medical exemption.
  (D) Number of pupils with a permanent medical exemption.

(E) Number of pupils with a permanent medical exemption from each required vaccine.
(F) Number of pupils with no required immunizations.
(G) Number of pupils admitted that do not meet criteria (A)-(F).

(e) Seventh Grade Annual Immunization Reports must include the elements listed in subdivision (b) and the following information:
(1) Public school district.
(2) School subtype (traditional, home, online/e-learning).
(3) Number of pupils attending seventh grade this year.
(4) If applicable, reason no pupils are attending seventh grade:
(A) No pupils in seventh grade this year.
(B) No pupils in seventh grade ever.
(C) Facility closed.
(5) Status of immunization requirements for attendance in seventh grade for each category:
(A) Number of pupils with all required immunizations.
(B) Number of pupils conditionally admitted who do not meet the requirement for:
i. Tdap.
ii. Varicella.
(C) Number of pupils conditionally admitted with a temporary medical exemption.
(D) Number of pupils with a permanent medical exemption.
(E) Number of pupils with a permanent medical exemption from each required vaccine.
(F) Number of pupils with no required immunizations.
(G) Number of pupils admitted that do not meet criteria (A)-(F).

(f) Additional immunization status reports may be requested by the Department to prevent or control vaccine-preventable disease and may include, but not be limited to, information in subsections (b) through (e).

EXHIBIT 323

Review > S D Med. 2013;Spec no:68-72.

Becoming a Vaccine Champion: Evidence-Based Interventions to Address the Challenges of Vaccination

Erick Temoka [1]

Affiliations

PMID: 23444594

Abstract

The incidence, prevalence, morbidity and mortality rates of vaccine-preventable diseases have decreased drastically since the advent of modern vaccination by Edward Jenner at the end of the 18th century. In recent years, however, a growing number of parents have been refusing or delaying vaccination for their children for socioeconomical, medical, religious and/or philosophical reasons. This has resulted in a loss of herd immunity that has caused a resurgence of many infectious diseases. This article describes evidence-based methods by which a pediatric clinic can become a vaccine champion by aiming at vaccination rates of 100 percent. This goal can be attained by a team effort that addresses the challenges of vaccination by using every visit as a chance to vaccinate, educate, address the fears and the concerns of the parents and provide articles and other written documentations on the benefits and side effects of vaccines. A standardized system that identifies and tracks patients who need vaccines is also essential to find those who are seldom brought to medical attention. A consistent and systematic use of these evidence-based methods by a dedicated staff is essential to attain vaccination rates close to 100 percent.

LinkOut - more resources

Medical

MedlinePlus Health Information

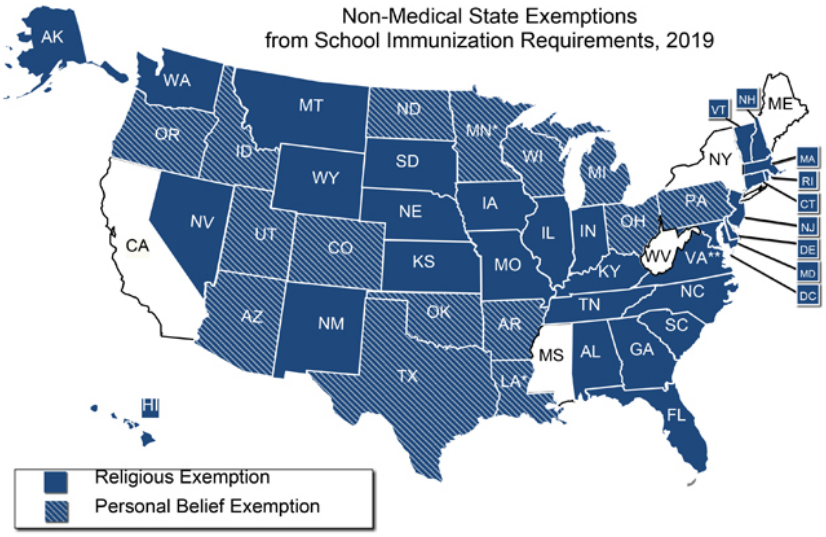
EXHIBIT 324

NCSL NATIONAL CONFERENCE OF STATE LEGISLATURES

States With Religious and Philosophical Exemptions From School Immunization Requirements

1/3/

All 50 states have legislation requiring specified vaccines for students. Although exemptions vary from state to state, all school immunization laws grant exemptions children for medical reasons. There are 45 states and Washington D.C. that grant religious exemptions for people who have religious objections to immunizations. Currently, 15 states allow philosophical exemptions for those who object to immunizations because of personal, moral or other beliefs.



Source: Adapted from the LexisNexis StateNet Database and the Immunization Action Coalition, May 2019.
* The existing statute in Minnesota and Louisiana does not explicitly recognize religion as a reason for claiming an exemption, however, as a practical matter, the nc medical exemption may encompass religious beliefs.

**In Virginia, parents can receive a personal exemption only for the HPV vaccine.

***Missouri's personal belief exemption does not apply to public schools, only child care facilities.

Enacted Legislation 2019

- Washington House Bill 1638 removes the personal belief exemption for the measles, mumps and rubella vaccine requirement for public schools, private schools day care centers.
- Maine House Bill 586 removes personal and religious belief exemptions for public school immunization requirements.
- New York Senate Bill 2994 removes the religious exemption for public school immunization requirements.

Enacted Legislation 2017

- Indiana House Bill 1069 adds meningitis to the required immunizations a student enrolling in a residential campus of an approved postsecondary educational

institution must be immunized against.

- Utah House Bill 308 requires the Department of Health to create an online education module regarding certain preventable diseases; amends the grounds for exemptions from required vaccines; requires the renewal of a student's vaccination exemption under certain conditions; create a new vaccination exemption for allows for the vaccination exemption form to be completed online in conjunction with the education module and discontinues the practice of allowing local health departments to vaccinate students and recover costs.

Enacted Legislation 2016

- Delaware House Bill 91 adds language around its existing religious exemption, explaining that in the event that the Division of Public Health declares that there is outbreak of a vaccine preventable disease, or if in the estimation of the Division of Public Health, an unvaccinated child has had, or is at risk of having an exposur a vaccine preventable disease, the child shall be temporarily excluded from attendance at the public school. It also gives the Division of Public Health the authorit review medical exemptions signed by a physician.
- Minnesota House Bill 2749 applied its statutes related public school immunization requirements and exemption criteria to its free voluntary prekindergarten program.

Enacted Legislation 2015

- With the passage of Senate Bill No. 277, California removed exemptions based on personal beliefs, which are defined in that state as also including religious objections.
- Connecticut HB 6949 requires an annual, notarized, statement from parents or guardians specifying religious objection to required vaccinations.
- Illinois SB1410, awaiting the governors' action in June 2015, would require each public school district to make exemption data available to the public. It also woul require parents or guardians who claim a religious exemption to detail their objections for specific immunizations, obtain a health care provider's signature, and submit an exemption certificate for each child before kindergarten, sixth and ninth grade. Local school authorities would determine if the exemption request constitutes valid religious objection, as philosophical exemption is not permitted in Illinois.
- South Dakota's new law requires a child's immunization records to be shared among health care providers, federal and state health agencies, child welfare agenc and schools, unless the patient or guardian signs a refusal. It requires providers to inform parents or guardians that they have the right to refuse disclosure of records.
- With passage of H. 98, Vermont became the first state to repeal its personal belief exemption. (The legislation does not change the existing exemption for parent who wish to opt out for religious reasons.) , Vermont H. 98 also requires schools and child care facilities to provide school immunization rates to parents.
- West Virginia Senate Bill No. 286, among other things, requires certification by a licensed physician for medical exemption requests. It also authorizes the commissioner of the Bureau for Public Health to appoint an immunization officer to make determinations about requests for exemptions.

School Vaccine Requirements and Exemptions

State	Statute	Religious Exemption	Philosophical Exemption
Alabama	Ala. Code § 16-30-3	Yes	No
Alaska	Ak. Stat. §14.30.125	Yes	No
Arizona	Ariz. Rev. Stat. Ann. § 15-872, 873	Yes	Yes
Arkansas	Ark. Code Ann. § 6-18-702	Yes	Yes
California	Cal. Health & Safety Code § 120325 et seq.	No	No
Colorado	Colo. Rev. Stat. § 25-4-902, 903	Yes	Yes
Connecticut	Conn. Gen. Stat. § 10-204a	Yes	No
Delaware	Del. Code Ann. tit. 14 § 131	Yes	No
Washington, DC	D.C. Code Ann. § 38-501, 506	Yes	No
Florida	Fla. Stat. Ann. § 1003.22	Yes	No
Georgia	Ga. Code Ann. § 20-2-771	Yes	No
Hawaii	Haw. Rev. Stat. § 302A-1154, 1156	Yes	No

Idaho	Idaho Code § 39-4801, 4802	Yes	Yes
Illinois	105 Ill. Comp. Stat. § 5/27-8.1	Yes	No
Indiana	Ind. Code Ann. § 21-40-5	Yes	No
Iowa	Iowa Code Ann. § 139A.8	Yes	No
Kansas	Kan. Stat. Ann. § 72-5209	Yes	No
Kentucky	Ky. Rev. Stat. Ann. § 214.034	Yes	No
Louisiana	La. Rev. Stat. Ann. § 17:170(A); 40:31.16	Yes	Yes
Maine	Me. Rev. Stat. Ann. tit. 20-A § 6355	Yes	Yes
Maryland	Md. Code Ann. Educ. § 7-403	Yes	No
Massachusetts	Mass. Gen Laws ch.76, § 15	Yes	No
Michigan	Mich. Comp. Laws Ann. § 333.9208, 9215	Yes	Yes
Minnesota	Minn. Stat. Ann. § 121A-15	Yes	Yes
Mississippi	Miss. Code Ann. § 41-23-37	No	No
Missouri	Mo. Rev. Stat. § 167.181, 210.003	Yes	Yes*
Montana	Mont. Code Ann. § 20-5-403, 405	Yes	No
Nebraska	Neb. Rev. Stat. Ann. § 79-217, 221	Yes	No
Nevada	Nev. Rev. Stat. § 392.435, 437, 439	Yes	No
New Hampshire	N.H. Rev. Stat. Ann. § 141-C:20-a, 20-c	Yes	No
New Jersey	N.J. Stat. Ann. § 26:1A-9, 9.1	Yes	No
New Mexico	N.M. Stat. Ann. § 24-5-1, 3	Yes	No
New York	N.Y. Pub. Health Law § 2164	Yes	No
North Carolina	N.C. Gen. Stat. § 130A-155, 156, 157	Yes	No
North Dakota	N.D. Cent. Code § 23-07-17.1	Yes	Yes
Ohio	Ohio Rev. Code Ann. § 3313.671	Yes	Yes
Oklahoma	Okla. Stat. Ann. tit. 70, § 1210.191, 192	Yes	Yes
Oregon	Or. Rev. Stat. § 433.267	Yes	Yes
Pennsylvania	28 Pa. Code § 23-83, 84	Yes	Yes
Rhode Island	R.I. Gen. Laws § 16-38-2	Yes	No
South Carolina	S.C. Code Ann. § 44-29-180	Yes	No
South Dakota	S.D. Codified Laws § 13-28-7.1	Yes	No
Tennessee	Tenn. Code Ann. § 49-6-5001	Yes	No
Texas	Tex. Edu Code Ann. § 38.001	Yes	Yes
Utah	Utah Code Ann. § 53A-11-301, 302	Yes	Yes
Vermont	Vt. Stat. Ann. tit. 18, § 1121, 1122	Yes	No
Virginia	Va. Code Ann. § 22.1-271.2, § 32.1-46	Yes	No
Washington	Wash. Rev. Code Ann. § 28A.210.080, 90	Yes	Yes
West Virginia	W. Va. Code § 16-3-4	No	No

Wisconsin	Wis. Stat. Ann. § 252.04	Yes	Yes
Wyoming	Wyo. Stat. Ann. § 21-4-309	Yes	No

Religious exemption indicates that there is a provision in the statute that allows parents to exempt their children from vaccination if it contradicts their sincere religious beliefs.

Philosophical exemption indicates that the statutory language does not restrict the exemption to purely religious or spiritual beliefs. For example, Maine allows restrictions based on "moral, philosophical or other personal beliefs," and Minnesota allows objections based on "conscientiously held beliefs of the parent or guardian."

Sources: Chart adapted from Immunization Action Coalition, "Exemptions Permitted for State Immunization Requirements," 2017; LexisNexis; StateNet 2017

Note: List may not be comprehensive, but is representative of state laws that exist. NCSL appreciates additions and corrections.

NCSL Resources: "Vaccination Policies: Requirements and Exemptions for Entering Schools," NCSL LegisBrief, December 2017

"Calling the Shots," State Legislatures Magazine Article, February 2015

EXHIBIT 325

PEDIATRICS COVID-19 COLLECTION
We are fast-tracking and publishing the latest research and articles related to COVID-19 for free. View the collection.

COVID-19 Guidance for Pediatricians. Find AAP resources here.

AAP News

Elimination of non-medical vaccine exemptions ranked top priority at Annual Leadership Forum

March 16, 2019

AAP leaders have called for elimination of non-medical* exemptions to vaccination to be the top priority for the year, ranking it first among the top 10 resolutions during the Annual Leadership Forum (ALF).

"Given the measles outbreaks, prioritizing the elimination of non-medical vaccine exemptions is a timely undertaking," said AAP President Kyle E. Yasuda, M.D., FAAP.

The resolution asks the Academy's Board of Directors to advocate for the "development of a toolkit that highlights successful chapter strategies for the purpose of helping chapters work with their state legislatures to eliminate/reduce non-medical* exemptions that have allowed immunization refusals."

Top 10 resolutions:

1. Eliminating Non-medical* Exemptions to Vaccinating Children
2. Family Separations at the Border: Safeguarding Children's Health
3. Limitation of Prior Authorization Requirements for Medications
4. Continuity of Medicaid Benefits When Recipients Move
5. Access to Evidence-Based Treatment for Children and Adolescents With Neurodevelopmental Disorders Beyond Autism
6. Affordable Insulin Access for all Children With Diabetes
7. Revising the AAP Bright Futures Guidelines on Gun Safety Anticipatory Guidance
8. Drowning Prevention Recommendation Statement and Education
9. Providing Guidance on School Response to E-cigarette Use by Students
10. Public Education About Intramuscular Vitamin K Administration at Birth

*The title and resolved were revised to include other kinds of exemptions.

The ALF brings together chapter, committee, council and section leaders from across the U.S. and Canada, drawing on their diverse perspectives and expertise to advise the AAP Board of Directors. The event also provides leadership education and promotes networking and understanding of AAP priorities.

Prior to the forum, AAP groups and members submitted resolutions for consideration, and members

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Elimination of non-medical vaccine exemptions ranked top priority at Annual Leadership Forum

were able to comment on them online.

Look to http://bit.ly/2JhLDXl and the May issue of *AAP News* for more on the top 10 resolutions and the 2019 ALF.

EXHIBIT 326

American Medical Association Journal of Ethics
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POLICY FORUM

Forced Sterilizations of HIV-Positive Women: A Global Ethics and Policy Failure

Stephanie Bi and Tobin Klusty

In an attempt to combat mother-to-child HIV transmission, there has been a preponderance of forced sterilizations of HIV-positive women in countries around the world, especially those with high HIV rates [1, 2]. "Forced sterilization" is a sterilization procedure, such as tubal ligation, performed without informed consent from the patient [3]. Forced sterilization violates the human right to autonomy and the principle of informed consent. Although the practice conflicts with their ethical duties, many physicians still forcibly sterilize HIV-positive women in an attempt to limit mother-to-child transmission of the virus [4-7]. This practice further marginalizes these women, who can already face discrimination due to the stigmas associated with womanhood and HIV [8]. South Africa, Namibia, and Chile all provide examples of the widespread use of and legal advocacy against this marginalizing practice [1, 2, 4, 9-17]. This is clearly a pressing ethical problem that reflects global discrimination against women with HIV. All nations must restrict forced sterilization by implementing and enforcing appropriate policy.

Forced Sterilization in South Africa, Namibia, and Chile

The country that has perhaps received the most attention for forced sterilization from the media and researchers is South Africa, due to the irony of its highly progressive laws concerning women's sexual and reproductive rights [9]. South Africa was the first country to grant the right to "health care, including reproductive health services" in its national constitution [10]. In addition, a 1998 South African law prohibited sterilization without informed consent [11]. Despite the promise of these progressive laws, enforcement is sorely lacking. For example, a South African study for the Her Rights Initiative interviewed 22 women who were sterilized and given no legal justice [4]. Eighteen of these women were coerced into signing consent waivers, which protected the medical staff from liability [4].

A neighboring country, Namibia, is facing the same problem [12], although, to some degree, Namibia has addressed the issue in its courts. In 2014, the Namibian Supreme Court upheld the High Court's ruling that medical personnel at public hospitals had sterilized three HIV-positive women without their consent [13]. The Court ruled that "individual autonomy and self-determination are the overriding principles towards which our jurisprudence should move in this area of the law" [13] and declared that "[t]hese

principles require that in deciding whether or not to undergo an elective procedure, the patient must have the final word" [14].

In Chile, forced sterilization of HIV-positive women is widespread, and legal advocacy has been less effective. A 2004 study showed that 12.9 percent of sterilized HIV-positive women had been sterilized without consent and 29 percent had consented under coercion [15]. In *F. S. v. Chile*, the advocacy groups Vivo Positivo and Center for Reproductive Rights sued on behalf of a 27-year-old HIV-positive woman who was sterilized during a cesarean section without her knowledge [15]. Following several years of unsuccessful litigation, the advocacy groups filed a complaint with the Inter-American Commission on Human Rights (IACHR) in 2009 [16]. Four years later, the commission announced it would hear the case—the first it has admitted related to HIV-positive women's sexual and reproductive rights [17]—which is still pending.

Forced Sterilization as a Violation of Medical Duty

Physicians performing forced sterilizations are violating not only internationally-recognized human rights, but also their duties as medical professionals. Autonomy, as recognized by Amnesty International, is the right to make "choices free from outside pressure or violence, whether mental or physical" [18]. According to the American Medical Association's (AMA) *Code of Ethics*, a "patient should make his or her own determination about treatment" [19]. Such determination includes a woman's decision regarding what happens to her body [18]. Her ability to do so is diminished, and thus her right to autonomy is lost, if she is coerced into accepting a medical procedure.

The World Medical Association's (WMA) International Code of Medical Ethics lists several duties that physicians are expected to uphold regardless of the geographic locations of their practices: to "respect a competent patient's right to accept or refuse treatment," "not allow [clinical] judgment to be influenced by…unfair discrimination," "respect the rights and preferences of patients," "act in the patient's best interest when providing medical care" and "owe his/her patients complete loyalty and all the scientific resources available to him/her" [20].

Forcing sterilization upon women diagnosed with HIV conflicts with all of these duties. Firstly, it is a violation of their right to autonomy and the doctrine of informed consent. Many HIV-positive women in South Africa, Namibia, and Chile are sterilized without their knowledge or are compelled to accept the procedure to receive food or necessary medical treatment [1, 2, 4]. Lindsey McLaughlin reports that women in South Africa were threatened with halting of life-sustaining antiretroviral medication if they did not sign a consent form for sterilization [21]. HIV-positive women often succumb to sterilization due to this kind of duress and coercion, as well as to fear of disappointing or inconveniencing health care professionals or lack of knowledge of their right to autonomy [4]. One South African survey participant explained, "Today, I would have said

no, I would have taken my own decision. But in those days we did not know much about our rights. One was simply told, and to say to a doctor, 'I do not want' was unheard of. You were just told to do this or else you had to leave the clinic or hospital" [22].

Furthermore, this procedure violates the medical ethics principle of beneficence, that treatments must benefit the patient. The main medical rationale for these sterilizations, that HIV-positive-women should be sterilized to reduce mother-to-child HIV transmission [5], is flawed. Sterilization is not necessary for this purpose; consistent antiretroviral treatment has been shown to reduce risk of mother-to-child HIV transmission to less than 2 percent in nonbreastfeeding populations [7]. These medications, developed in the 1990s, are available inexpensively even in countries without fully developed health care systems [23]. And if the justification for sterilization is not medical benefit but the public good, as can be the case [7], the duty of loyalty to the patient is violated.

Forced Sterilization and Intersectional Discrimination

Intersectional discrimination is defined as "the phenomenon of multiple and compounded forms of discrimination" [24]. According to Ronli Sifris, separate marginalized qualities may overlap and eventually compound the degree of discrimination a person faces [8].

In South Africa, for example, "being part of a group of people who are [already] structurally and systematically discriminated against increases one's chances of contracting HIV" [25]. Consequently, the prevalence of HIV is disproportionately high among already marginalized groups, such as women, members of sexual and racial minorities, those in poverty, and drug users, due to the lack of access to essential health care and social resources among these groups [25]. Specifically, the subordinate social status of South African women hinders their ability to "negotiate safer sex" or participate in the workforce, factors that may make a woman feel compelled to remain in a relationship with an HIV-positive partner and that heighten vulnerability to HIV [25]. After an HIV diagnosis, women are further stigmatized by the cultural assumption that they have engaged in deviant behavior [26]. As a result, South African women with HIV are viewed as irresponsible and promiscuous, leading to social isolation [27] and, in some cases, sterilization. In South African medical culture, an imbalanced physician-patient power dynamic disproportionately affects women [6]. Exemplifying this power imbalance, physicians judge women with HIV to be irresponsible and thus "unworthy" of having children, and sterilize them to prevent public harm [28].

Sterilization leads to even more cultural stigma due to the great emphasis in South African culture on marriage and motherhood for women [29]. Because a husband must pay a "lobola" (bride price), married women are expected to be fertile and experience pressure from their husbands to have children for financial reasons [30]. After

sterilization, women sometimes become social outcasts who are banned from family activities, weddings, and funerals [29]. To evade this extreme stigma, many sterilized women avoid telling their families and partners about their sterilization [31]. In this sense, HIV-positive status can be likened to having a history of mental illness or sexual assault: it constitutes a "concealable stigmatized identity," the strain of which can manifest as depression, anxiety, and/or self-reported illness symptoms [31]. Sterilization thus harms already marginalized HIV-positive women.

The use of forced sterilization is a widespread violation of internationally recognized human rights. As Lindsay McLaughlin has recommended, laws must be created or amended to prohibit sterilization without informed consent, and the punishments for violating these laws should be made more stringent [32]. She recommends that, in addition to fines and incarceration, the medical license of health care workers be suspended or revoked if they perform sterilization without informed consent [32]. The laws should be strictly enforced to provide a sufficient deterrent through such means as reducing barriers to women's accessing adequate legal representation, using a special court to address these cases in order to reduce the formality and intimidation of a traditional courtroom, requiring all-female adjudicators, and allowing anonymous testimony [33]. In addition, medical staff should be educated on the issue and trained to provide adequate information for the patient to give informed consent [32]. Lastly, she argues, women who have been forcefully sterilized should be granted reparations to mitigate social and psychological damage, perhaps in the form of not only monetary compensation, but also free trauma counseling and mental health care [34].

Conclusion

Forced sterilization of HIV-positive women is a global problem of great ethical importance. Sterilization without informed consent is a violation of women's right to autonomy, and sterilization to prevent transmission to children is medically unnecessary. To help achieve reproductive justice, there needs to be a global call to end forced sterilizations through well-implemented and enforced policy.

References

1. McLaughlin LC. The price of failure of informed consent law: coercive sterilizations of HIV-positive women in South Africa. *Law Inequal*. 2014;32:69-93.
2. Nair P. Litigating against the forced sterilization of HIV-positive women: recent developments in Chile and Namibia. *Harv Hum Rights J*. 2010;23:223-231.
3. Nair, 223.
4. Strode A, Mthembu S, Essack Z. "She made up a choice for me": 22 HIV-positive women's experiences of involuntary sterilization in two South African provinces. *Reprod Health Matters*. 2012;20(39)(suppl):61-69.
5. McLaughlin, 73.
6. McLaughlin, 76-77.

7. Sifris R. Involuntary sterilization of HIV-positive women: an example of intersectional discrimination. *Hum Rights Q*. 2015;37(2):464-491.
8. Sifris, 480-490.
9. McLaughlin, 71-72.
10. McLaughlin, 74-75.
11. Strode, Mthembu, Essack, 62.
12. Nair, 229.
13. Smith AD. Namibia court rules HIV-positive women sterilised without consent. *Guardian*. July 30, 2012. http://www.theguardian.com/global-development/2012/jul/30/namibia-hiv-women-sterilised-without-consent. Accessed August 3, 2015.
14. Chingore-Munazvo N. A win for victims of forced sterilization in Namibia. Open Society Foundations. December 17, 2014. https://www.opensocietyfoundations.org/voices/win-victims-forced-sterilization-namibia. Accessed August 12, 2015.
15. Nair, 227.
16. Nair, 228.
17. Nair, 228-229.
18. Amnesty International. Respect my rights, respect my dignity: module three – sexual and reproductive rights are human rights. January 1, 2015:53. https://www.amnesty.org/mwg-internal/de5fs23hu73ds/progress?id=G8ZHG94FGD&dl. Accessed August 5, 2015.
19. American Medical Association. Opinion 8.08 Informed consent. *Code of Medical Ethics*. http://www.ama-assn.org/ama/pub/physician-resources/medical-ethics/code-medical-ethics/opinion808.page. Accessed August 3, 2015.
20. World Medical Association. WMA International Code of Medical Ethics. Updated October 2006. http://www.wma.net/en/30publications/10policies/c8/index.html.pdf?print-media-type&footer-right=%5Bpage%5D/%5BtoPage. Accessed August 3, 2015.
21. McLaughlin, 70.
22. Strode, Mthembu, Essack, 64.
23. Nair, 224-225.
24. Sifris, 476-477.
25. Sifris, 481.
26. Sifris, 484.
27. Sifris, 481-484.
28. Sifris, 487.
29. McLaughlin, 75.
30. McLaughlin, 76.

31. Quinn DM, Chaudoir SR. Living with a concealable stigmatized identity: the impact of anticipated stigma, centrality, salience, and cultural stigma on psychological distress and health. *J Pers Soc Psychol*. 2009;97(4):634-651.
32. McLaughlin, 87-88.
33. McLaughlin, 90.
34. McLaughlin, 92-93.

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ISSN 2376-6980

EXHIBIT 327

The Washington Post
Democracy Dies in Darkness

Judge rules New York county can't ban unvaccinated children from schools, parks

By **Frances Stead Sellers**

April 6, 2019 at 10:44 a.m. PDT

Ten days after a New York county banned unvaccinated children from public places in an effort to stem the rise of measles cases, a state judge put the injunction on hold.

"Children are hereby permitted to return to their respective schools forthwith and otherwise to assemble in public places," Judge Rolf Thorsen wrote in his Friday decision.

The controversial ban, announced by a spokesman for Rockland County Executive Ed Day, was an effort to address an outbreak in Rockland County, where 167 confirmed cases of measles had been reported as of Friday.

Officials in the county declared a state of emergency, as Lindsey Bever reported in The Washington Post last week, announcing that the ban would remain in place for 30 days or until unvaccinated minors receive the MMR vaccine to protect them against measles, mumps and rubella. Unvaccinated minors, official said, would not be permitted in enclosed places like churches, schools and shopping centers.

"We must not allow this outbreak to continue," Day said at a news conference. "We will not sit idly by while children in our community are at risk."

Dorit Reiss, a professor at U.C. Hastings College of Law in San Francisco, said a ban by executive order was an unusual step, one that prompted outrage in the national anti-vaccine community.

But she saw it largely as a symbolic measure.

"It wasn't as aggressive as it could have been," Reiss said. "They weren't intending to do mass arrests."

Day said cases in which parents and guardians violated the ban would be referred to the district attorney's office. Violations would be considered misdemeanors, punishable by a $500 fine or up to six months in jail.

Thorsen made his ruling after some parents from a private Waldorf school filed a suit calling the action "arbitrary, capricious" and "an unprecedented 'declaration of a local emergency.' " The parents claimed that the county had acted beyond its legal authority. They said the declaration caused "children to be denied attendance at nursery programs and schools and has effectively prohibited their movement and denied them the right to congregate and assemble in public places."

Thorsen's decision, Reiss said, rested on the question of whether the outbreak was an emergency. With an outbreak of such a highly contagious virus, she said, "There is a reasonable argument that it is an emergency."

Measles can cause pneumonia, brain damage, hearing loss and even death, according to the Centers for Disease Control and Prevention. Between January 1 and late March, 387 cases of measles have been confirmed in 15 states across the country, from California to Kentucky to New Jersey — the second-greatest number of cases since measles was eliminated in the United States in 2000.

New York state has been particularly hard hit, with 259 confirmed cases in Brooklyn and Queens since October, many of them in the Orthodox Jewish community. According to the state's Department of Health and Mental Hygiene, the outbreak began after an unvaccinated child acquired measles on a visit to Israel, where there has also been an outbreak of the disease.

The measles outbreaks — and the increasingly aggressive public health response to them — have also prompted a spike in activity among anti-vaccine activists. Across the nation and around the world, a global movement that spreads misinformation about vaccines has helped drive down child immunizations, lowering the community immunity that is critical for protection against one of the world's most contagious diseases.

After Rockland County's ban, anti-vaccination activists likened the public health measures to the Nazi persecution of Jews that included forcing them to wear yellow stars.

Reiss suspects that it may not be worth it to local officials to fight Thorsen's ruling.

"It was a short ban," she said. "This might be the end of it."

Lena Sun contributed to this report.

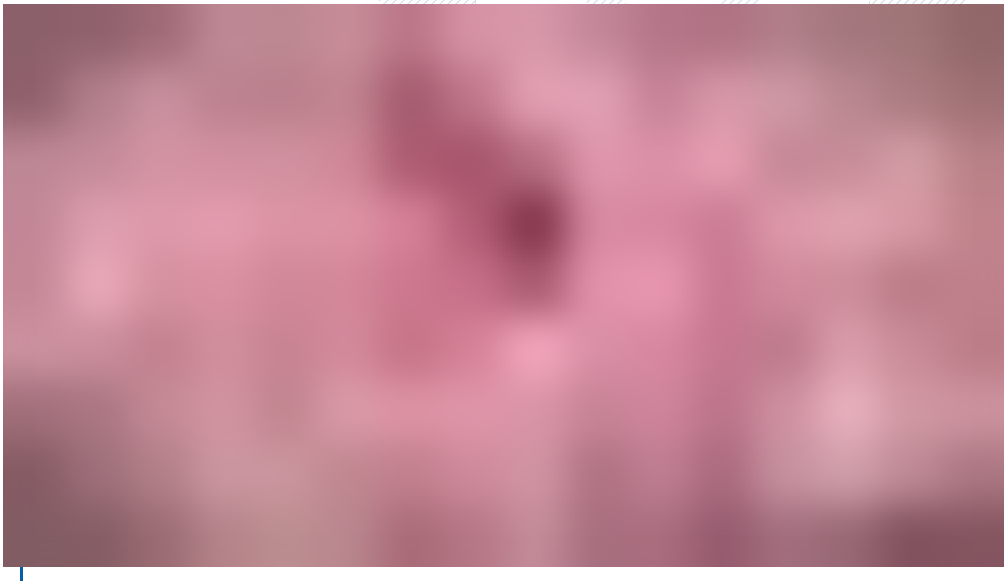
Frances Stead Sellers
Frances Stead Sellers is a senior writer at The Washington Post. Follow

EXHIBIT 328

LOCAL

Florida College isolating unvaccinated students amid measles scare

The school also canceled Parent Weekend and a lecture series.



Author: **Dale Greenstein (WTSP)**
Published: **1:02 PM EST January 28, 2020**
Updated: **1:02 PM EST January 28, 2020**

TEMPLE TERRACE, Fla — One case was all it took.

Florida College is not taking chances with the measles, after the health department confirmed one person on campus came down with the highly contagious virus.

The school in Temple Terrace announced on its website students who can't prove they've been vaccinated are being isolated in their dorms, and two upcoming events are being canceled.

Parent Weekend was scheduled for Jan. 30 – Feb. 1. That's not happening anymore.

Florida College Lectures was supposed to take place between Feb. 1 – 4. They're being pushed to next year.

The Tampa Bay Times reports meals are being brought to the isolated students four times a day, and a nurse is checking on them once a day. The college is making accommodations for the classes they're missing, according to the Times.

The Florida Health Department says measles symptoms include:

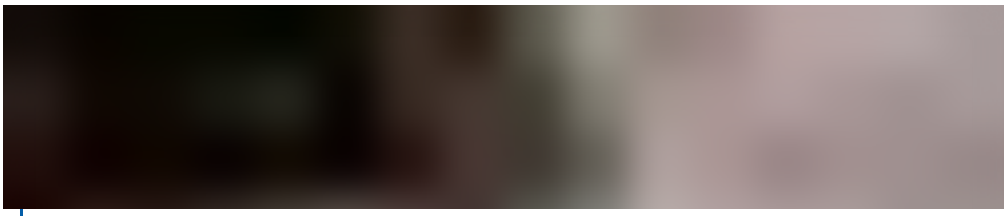
- High fever
- Cough
- Runny nose
- Red, watery eyes
- Face and neck rash that can spread

But those symptoms are just how it starts. Measles can lead to several serious health complications.

Some of them can prove deadly.

- Ear infections
- Diarrhea
- Pneumonia
- Encephalitis

Doctors say the best way to avoid measles is to get vaccinated. It's included in the MMR vaccine, which combats measles, mumps and rubella.



Credit: AP

FILE - This May 15, 2019 file photo shows a vial of a measles, mumps and rubella vaccine at a clinic in Vashon Island, Wash. On Thursday, May 30, 2019, U.S. health officials reported this year's U.S. measles epidemic surpassed a 25-year-old record, and experts say it's not clear when the wave of illnesses will stop. There were 971 cases so far this year, eclipsing the 963 measles illnesses reported for all of 1994. (AP Photo/Elaine Thompson, File)

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EXHIBIT 329

Print Close

Md. Judge to Parents: Vaccinate Kids or Go to Jail

By ,

Published January 13, 2015

Associated Press

Hundreds of grumbling parents facing a threat of jail lined up at a courthouse Saturday to either prove that their school-age kids already had their required vaccinations or see that the youngsters submitted to the needle.

The get-tough policy in the Washington suburbs of Prince George's County was one of the strongest efforts made by any U.S. school system to ensure its youngsters receive their required immunizations.

Two months into the school year, school officials realized that more than 2,000 students in the county still didn't have the vaccinations they were supposed to have before attending class.

So Circuit Court Judge C. Philip Nichols ordered parents in a letter to appear at the courthouse Saturday and either get their children vaccinated on the spot or risk up to 10 days in jail. They could also provide proof of vaccination or an explanation why their kids didn't have them.

By about 8:30 a.m., the line of parents stretched outside the courthouse in the county on the east side of Washington.

Many of them complained that their children already were properly immunized but the school system had misplaced the records. They said efforts to get the paperwork straightened out had been futile.

"It was very intimidating," Territa Wooden of Largo said of the letter. She said she presented the paperwork at the courthouse Saturday and resolved the matter.

"I could be home asleep. My son had his shots," said Veinell Dickens of Upper Marlboro, who also blamed errant paperwork.

Aloma Martin of Fort Washington brought her children, Delontay and Taron, in 10th and 6th grade, for their hepatitis shots. She said she had been trying to get the vaccinations for more than a month, since the school system sent a warning letter. She had an appointment for Monday, but came to the courthouse to be safe.

"It was very heavy handed," she said of the county's action. "From that letter, it sounded like they were going to start putting us in jail."

School officials deemed the court action a success. School system spokesman John White said the number of children lacking vaccinations dropped from 2,300 at the time the judge sent the letter to about 1,100 Friday. Hundreds more were expected to be in compliance after Saturday's session.

Officials said they did not know how many students got shots Saturday and how many merely had paperwork problems. It was also unclear how many claimed medical or religious exemptions to the requirement.

White said the school system, with about 132,000 students, has been trying for two years to get parents to comply with state law. That law allows children to skip vaccines if they have a medical or religious exemption.

Maryland, like all states, requires children to be immunized against several childhood illnesses including polio, mumps and measles. In recent years, it also has required that students up to high school age be vaccinated against hepatitis B and chicken pox.

Nichols said nobody actually came before him Saturday, but he was there if any parent asked to see him.

The judge noted the unhappy looks of some of the kids in line waiting for vaccinations.

"It's cute. It looks like their parents are dragging them to church," Nichols said.

Any children who still lack immunizations could be expelled. Their parents could then be brought up on truancy charges, which can result in a 10-day jail sentence for a first offense and 30 days for a second.

Prince George's State's Attorney Glenn Ivey couldn't say Saturday whether he would prosecute parents who fail to comply.

"We have to sit down with school and health services," he said. "We haven't ruled anything out. We need to figure out where we stand."

Several organizations opposed to mass vaccinations demonstrated outside the courthouse. While the medical consensus is that vaccines are safe and effective, some people blame immunizations for a rise in autism and other medical problems.

"People should have a choice" in getting their children immunized, said Charles Frohman, representing a physicians' group opposed to vaccines.

EXHIBIT 330

Parental Refusal of Childhood Vaccines and Medical Neglect Laws

Efthimios Parasidis, JD, MBioethics, and Douglas J. Opel, MD, MPH

Objectives. To examine the relation of vaccine refusal and medical neglect under child welfare laws.

Methods. We used the Westlaw legal database to search court opinions from 1905 to 2016 and identified cases in which vaccine refusal was the sole or a primary reason in a neglect proceeding. We also delineated if religious or philosophical exemptions from required school immunizations were available at the time of adjudication.

Results. Our search yielded 9 cases from 5 states. Most courts (7 of 9) considered vaccine refusal to constitute neglect. In the 4 cases decided in jurisdictions that permitted religious exemptions, courts either found that vaccine refusal did not constitute neglect or considered it neglect only in the absence of a sincere religious objection to vaccination.

Conclusions. Some states have a legal precedent for considering parental vaccine refusal as medical neglect, but this is based on a small number of cases. Each state should clarify whether, under its laws, vaccine refusal constitutes medical neglect. (*Am J Public Health.* 2017;107:68–71. doi:10.2105/AJPH.2016.303500)

Parental refusal of childhood vaccines is a contentious issue in pediatrics and public health. With increasing numbers of parents exempting their child from required school-entry vaccines[1] and few evidence-based interventions to address vaccine hesitancy,[2] pediatric providers are struggling with how to respond to parental vaccine refusal.[3] One strategy recently promoted is to treat vaccine refusal as neglect and report parents to child protective services (CPS) or another comparable agency.[4]

Although child welfare laws vary by state, the legal concept of medical neglect has a common denominator. New York's law is paradigmatic: a neglected child is one whose "condition has been impaired or is in imminent danger of becoming impaired" because the parent has failed "to exercise a minimum degree of care in supplying the child with adequate" health care.[5] Medical neglect is a subset of child neglect, which refers to parental acts of omission in the care of their child not exclusive to health care. Both child neglect and child abuse (parental acts of commission that result in harm to the child) constitute child maltreatment.

Pediatric providers (and other mandatory reporters) have an obligation to report suspected child abuse or neglect to CPS. CPS must determine whether a report requires an investigation and, if so, whether investigation findings meet the relevant legal standards. A finding of medical neglect can trigger court action that may result in the temporary or permanent loss of custody or parental decision-making authority.

Although the application of medical neglect to parental vaccine refusal has some salience—a child is exposed to some potential risk of harm by a parental act of omission—it is not clear whether it is salient to CPS or meets the legal threshold for neglect. For instance, some maintain that CPS screens out reports solely based on failure to vaccinate,[6] and Michigan has an explicit policy to this effect.[7] A few states codify that vaccine refusal regardless of reason,[8] or solely for sincere religious beliefs,[9] does not constitute medical neglect. Furthermore, even if vaccine refusal amounts to medical neglect, it is not clear that this finding requires state intervention. Ross and Aspinwall[10] contend that there should be a distinction between medical neglect and state intervention, arguing that vaccine refusal constitutes the former but does not warrant the latter. Chervenak et al.[4] argue that the purpose of reporting parents who refuse childhood vaccines to CPS for neglect is not to provoke "highly intrusive measures," such as loss of custody, but to "engage [CPS] in further efforts to persuade the parents."(p308) Simply invoking CPS, however, may undermine parents' views of providers as a trusted vaccine resource and important influence on their vaccine decision-making. Indeed, the American Academy of Pediatrics states that it "does not support the stringent application of medical neglect laws when children do not receive recommended immunizations."[11(p279)]

A key gap in our understanding of the applicability of medical neglect to vaccine refusal is an analysis of court opinions. This is especially important because most states do not define medical neglect in their statutes.[12] We quantified and categorized adjudicated neglect proceedings for vaccine refusal and describe their features and outcomes.

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Correspondence should be sent to Efthimios Parasidis, JD, MBioethics, Associate Professor of Law and Public Health, Moritz College of Law, The Ohio State University, 55 W 12th Ave, Columbus, OH 43210 (e-mail: parasidis.1@osu.edu). Reprints can be ordered at http://www.ajph.org by clicking the "Reprints" link.

This article was accepted September 23, 2016.

doi: 10.2105/AJPH.2016.303500

TABLE 1—Court Cases Involving Vaccine Refusal and Medical Neglect: Westlaw Legal Database, United States, 1905–2016

State and Case (Year)	Allegations of Neglect and Issue of Immunization	Availability of Nonmedical Exemptions at Time of Adjudication	Holding and Rationale
Arkansas[a]			
Cude v State, Supreme Court of Arkansas (1964)	Parents refused smallpox vaccine for religious reasons. School refused to allow child to attend because child was not vaccinated.	None	Child deemed neglected. State law requires immunization and attendance at an accredited school. Law does not allow for a religious exemption. Parental refusal to vaccinate, when it prevents child from attending school, constitutes neglect.
Mannis v State, Supreme Court of Arkansas (1966)	Parents refused smallpox vaccine for religious reasons. Child was enrolled in parochial school at their church, which did not require immunization.	None	Child deemed neglected. State law requires immunization and attendance at an accredited school (public or private). The parochial school is analogous to a private school. Parental refusal to vaccinate constitutes neglect.
District of Columbia[b,c]			
In re Ang.P., District of Columbia Court of Appeals (2013)	Mother heavily medicated because of severe back pain, had home health aide (7:00 AM to 5:00 PM, 7 d/wk); had difficulty meeting needs of her children, ages 5 and 13 y; often failed to get 5-year-old child to school on time; occasionally left children at home without adult supervision. Mother failed to keep 5-year-old up-to-date with immunizations. Failure to immunize was not based on any specified objection to vaccinations.	Religious exemptions	Child not deemed to be neglected. Issues are concerning, as a whole, but they are insufficient to support a finding of neglect. Court notes that the prosecutor did not cite 1 case, nor could the court find 1 case, in which a child was deemed neglected because of failure to keep immunizations up-to-date.
Pennsylvania[b]			
In re Marsh, Pennsylvania Superior Court (1940)	Public school refused to allow child to attend school because child had not received the smallpox vaccine. Parents refused smallpox vaccine, although the basis of the refusal is not explained in the court opinion.	None	Child deemed neglected. Failure to attend school constitutes neglect. Must vaccinate child so that he or she can attend public, private, or parochial school or provide "other adequate and systematic instruction" such as a home tutor.
New York[b]			
In re Whitmore, Domestic Relations Court (1944)	Child refused entry into public school because parents refused to vaccinate child for religious reasons.	None	Child deemed neglected.

Continued

TABLE 1—*Continued*

State and Case (Year)	Allegations of Neglect and Issue of Immunization	Availability of Nonmedical Exemptions at Time of Adjudication	Holding and Rationale
In re Elwell, Family Court, Dutchess County (1967)	Children barred entry to school because not immunized with polio vaccine. Parents claimed a religious exemption.	Religious exemptions	Children deemed neglected. Insufficient evidence that the parents' religion precluded vaccination; rather, refusal to vaccinate appeared to be based on "personal opinions." Religious exemption to vaccination does not apply. Failure to vaccinate, which precludes children from attending school, constitutes neglect.
In re Maria R., New York Family Court (1975)	Parents failed to vaccinate child. Parents claimed vaccination violates their religious beliefs.	Religious exemptions	Child not deemed to be neglected. Religious exemption to vaccination permitted because parents maintain sincere religious belief. Formal church membership is not required.
Matter of Christine M., Family Court, Kings County (1992)	Parents failed to vaccinate child with measles vaccine during a measles outbreak in New York City. Child admitted to hospital after she accidentally ingested rat poison, at which point doctors recommended that child be given measles vaccine. Father opposed vaccine on religious grounds.	Religious exemptions	Child deemed neglected. In the midst of confirmed outbreak or epidemic, failure to vaccinate constitutes neglect unless there is a sincere religious objection to vaccination. Court does not find father's religious objections to be sincere. Because outbreak subsided at the time of the court's decision, however, court declines to use its discretionary power to order inoculation. Child remains with parents.
West Virginia[d]			
Underwood v West Virginia Department of Health and Human Services et al, US District Court for the Southern District of West Virginia (2013)	The mother indicated that she did not keep her child's immunizations current because she had an outstanding bill with the pediatrician, and the office refused to see her child until the bill was paid. During a hearing before a state court judge, the mother admitted that failure to vaccinate constitutes medical neglect. The state used that admission as the sole basis for a charge of neglect. Mother now alleges that the state did not prove that failure to vaccinate constitutes medical neglect.	None	Child deemed neglected. The mother's admission is sufficient, and the state did not have to independently prove that failure to vaccinate constitutes medical neglect. The court did not evaluate whether failure to vaccinate constitutes medical neglect under West Virginia law.

[a]Arkansas now permits religious and philosophical exemptions.
[b]Currently, District of Columbia, Pennsylvania, and New York permit religious exemptions.
[c]Because the District of Columbia maintains its own judicial district and has its own legal code, we considered it a state for purposes of this analysis.
[d]Currently, West Virginia does not permit religious or philosophical exemptions.

METHODS

We searched the Westlaw legal database for the terms *immuniz**, *inoculat**, or *vaccin** and *abuse**, *neglect**, or *medical neglect* to identify state or federal court opinions from 1905 to 2016 where vaccine refusal was the sole or a primary reason for a neglect proceeding. We chose this time frame because 1905 was the year that the Supreme Court held in *Jacobson v Massachusetts* (197 U.S. 11 [1905]) that a state's police power includes the ability to issue vaccine mandates.

We defined *primary reason* to include any case (involving more than 1 alleged reason for child neglect or abuse) in which the court provided a legal analysis of vaccine refusal in the context of medical neglect. We also delineated if nonmedical (religious or philosophical) exemptions from required school immunizations were available at the time of adjudication.

RESULTS

Our search yielded 9 cases adjudicated in 5 states from 1940 to 2013 (Table 1). Of these, 5 cases were decided in states that, at the time, did not permit nonmedical exemptions. All 5 found that failure to vaccinate constituted neglect, but 1 case (West Virginia) was based solely on a parent's concession that vaccine refusal constituted neglect.

The 4 remaining cases were adjudicated in 2 jurisdictions (New York and the District of Columbia) that permitted religious exemptions. A 2013 District of Columbia court held that failure to vaccinate did not constitute neglect, regardless of whether the refusal was based on a sincere religious belief. In the 3 New York cases, parents opposed vaccination on religious grounds, and the sincerity of their beliefs was determinative. The courts did not find the parents' religious beliefs to be sincere in the 1967 and 1992 cases and, therefore, determined that the children were neglected; in the 1975 case, the court found the parents' beliefs sincere and the child not neglected. In addition, the 1992 case involved a parent's refusal of the measles vaccine during a measles epidemic. Although the court determined that this refusal constituted neglect, it ruled that it would not force vaccination because the epidemic had subsided at the time of adjudication.

DISCUSSION

In our analysis, we found that most courts (7 of 9) considered vaccine refusal to constitute neglect. However, a few caveats deserve mention. First, of the 7 cases in which vaccine refusal was considered neglect, 5 were adjudicated in jurisdictions at a time when nonmedical exemptions were not permitted. Today, nonmedical exemptions are allowed in all but 1 of the jurisdictions in our sample (West Virginia). Nationally, 47 states and the District of Columbia allow religious exemptions, and 18 also allow philosophical exemptions (California and Mississippi also do not allow nonmedical exemptions). Therefore, the 4 cases that were adjudicated in jurisdictions that allowed religious exemptions are perhaps more germane. The courts in these 4 cases either found that vaccine refusal did not constitute neglect or considered vaccine refusal to be neglect only in the absence of a sincere religious belief.

Second, only 1 of the cases was adjudicated in the last 20 years (District of Columbia, 2013). The reasons for this paucity amid a rise in vaccine hesitancy are unclear. Some states limit public access to court records or proceedings regarding child abuse or neglect, and additional vaccine refusal cases may be unpublished, unreported, or not captured by the Westlaw database or our searches. Pediatric providers (or other mandatory reporters) also may not report vaccine refusal to CPS because they do not—or do not think CPS will—consider it neglect. Similarly, CPS may not be investigating the reports. Although these factors are more likely to explain the situation in states that have explicitly indicated that vaccine refusal does not constitute neglect,[7–9] most states have not provided such guidance. Additional studies on the practices and rationales of pediatric providers, other mandatory reporters, and CPS caseworkers regarding this issue would be elucidatory.

PUBLIC HEALTH IMPLICATIONS

This study has several public health implications. First, because so few courts have addressed whether vaccine refusal constitutes medical neglect, invoking child welfare laws to improve compliance with vaccine recommendations deserves caution. Second, in the absence of a clear statutory mandate, state public health officials should issue guidance for providers and CPS as to whether vaccine refusal constitutes medical neglect. Finally, state lawmakers should debate whether vaccine refusal constitutes medical neglect and incorporate their conclusions into state statutes. AJPH

CONTRIBUTORS

Both authors contributed substantially to the conceptualization, design, and analysis of the study; made all final decisions regarding case categorization and case analysis; drafted and revised the article; and approved the final version. E. Parasidis and 5 research assistants conducted the searches.

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HUMAN PARTICIPANT PROTECTION

This project did not require institutional review board approval because the study did not involve human participants.

REFERENCES

1. Omer SB, Richards JL, Ward M, Bednarczyk RA. Vaccination policies and rates of exemption from immunization, 2005-2011. *N Engl J Med*. 2012;367:1170–1171.

2. Sadaf A, Richards JL, Glanz J, Salmon DA, Omer SB. A systematic review of interventions for reducing parental vaccine refusal and vaccine hesitancy. *Vaccine*. 2013;31:4293–4304.

3. Fierman AH. Voices from the field: controversies in vaccine mandates. *Curr Probl Pediatr Adolesc Health Care*. 2010;40(3):59.

4. Chervenak FA, McCullough LB, Brent RL. Professional responsibility and early childhood vaccination. *J Pediatr*. 2016;169:305–309.

5. New York Family Ct Act §1012(f).

6. DePasquale S. Childhood immunizations and the role of a county department of social services. *Juvenile Law Bull*. January 2015; No. 2015/01.

7. Michigan Department of Health & Human Services. Children's Protective Services. Mandated Reporters' Resource Guide. 2016. Available at: http://www.michigan.gov/documents/dhs/Pub-112_179456_7.pdf. Accessed October 4, 2016.

8. Oregon Administrative Rule 413-015-1000(3)(d)(B). The CPS Assessment Dispositions. 2016; Colorado Revised Statutes Annotated, §25-4-2403 §7 (2016).

9. Illinois Compiled Statutes Annotated. ch 750, Act 50/1, §1(Q), 2016.

10. Ross LF, Aspinwall TJ. Religious exemptions to the immunization statutes: balancing public health and religious freedom. *J Law Med Ethics*. 1997;25:202–209.

11. Religious objections to medical care. American Academy of Pediatrics Committee on Bioethics. *Pediatrics*. 1997;99(2):279–281.

12. State Child Welfare Policy Database. Medical neglect specifically defined in statute. 2010. Available at: http://www.childwelfarepolicy.org/maps/single?id=144. Accessed August 18, 2016.

EXHIBIT 331

The Washington Post
Democracy Dies in Darkness

Tech platforms must move against the anti-vaxxers now

By **Molly Roberts**

May 23, 2019 at 6:01 a.m. PDT

Vaccines don't kill, but insisting otherwise can. Facebook, Google and Twitter know that — which is why, as measles outbreaks send children to intensive-care units across the country, they have all decided to do something about it.

"Do something!" is exactly what people around the world have been saying to social media sites that, until recently, refused to accept responsibility for what happened on their platforms. That attitude is changing, but what "something" means is still up in the air. Do what, exactly, to whom? And will it help?

The most prominent platforms already ban hate speech and incitements to violence, at least in theory. They remain more reluctant, however, to remove or limit falsehoods. They're not the arbiters of truth, they say, and they have always looked to free speech as a lodestar. Policies differ from platform to platform. But firms should take aggressive action when there's a high likelihood of real-world harm.

It's not a perfect metric. Neither is anything else. Even amid the messiness, though, agitating against life-saving inoculations falls cleanly on the wrong side of the line. Health officials studying the resurgence of a disease that was supposed to have been eliminated in this country almost two decades ago have made it clear: The outbreak of misinformation online is facilitating literal outbreaks of disease.

Companies apparently agree — to a point. Platforms could remove all anti-vax material, but so far they won't, citing either squeamishness about policing belief or a desire not to stop parents from having conversations about so personal a decision. They could remove people, pages or groups that systematically promote anti-vax material, but they won't do that, either. That leaves seeking to limit the reach of false messages on their platforms without banning them altogether.

Facebook has announced it is down-ranking anti-vaxxer groups and pages in users' news feeds and in searches, as well as cutting them out entirely from recommendations and predictions and getting rid of their advertisements. Its sister company Instagram has blocked hashtags such as #vaccinescauseautism or #vaccineskill.

YouTube, which is owned by Google, has stopped anti-vaccination channels from running ads, and says hoaxes will appear less often in its "up next" module. When viewers do watch those videos, they'll also see "information panels" with corrective context. Twitter has created a tool that pulls up a handy link to a government website offering facts about vaccination for anyone who searches for the subject, and it won't auto-suggest terms that tend to lure people toward the inaccurate.

The remedies that focus on searches seek to fill what's known as a "data void" — a sort of digital black hole that sucks curious consumers into the realm of the factless. If you search "did the Holocaust happen," for example, you may be more likely to find sources that say it did not, because they're the ones bothering to weigh in on what everyone else feels is settled fact. Vaccines, similarly, are settled science.

But these approaches can fall short. Search "#vaccines" on Instagram, leaving the whole "cause autism" or "kill" thing out, and the first accounts to show up are conspiratorial, with names such as "vaccines_uncovered" and "vaccines_revealed." Believe it or not, they aren't dedicated to touting the benefits of polio shots. Results on Facebook land users in similarly treacherous territory: "The Truth About Vaccines Docu-Series," for example, is followed closely by "Tongue Ties, Autism, MTHFR, Vaccine, Leaky Gut — What's the connection?" None, really, but these pages will tell you otherwise.

You can't fill a data void with more emptiness, so approaches that don't also surface enough authoritative sources to replace the junk have a fatal flaw. Twitter's pop-ups help solve that half of the problem by linking to a government site, but the platform leaves alone the anti-vax content that appears right below. YouTube's model, which seems to prioritize mostly verified videos from channels such as the Mayo Clinic and the Centers for Disease Control and Prevention, does a better job.

Even if platforms try to push down trustworthy sources and prop up reliable ones, algorithms miss things. They're even more likely to miss when their targets dodge. The anti-vaccine community, which prefers the term "vaccine hesitant," is no stranger to language games. Shifting rhetoric to talk about "doubts" or the need for parents to "decide" for themselves can skirt automatic filters. Hoaxers can also avoid policies about what counts as a lie, leaving the humans who set the rules flummoxed over where they should draw their lines.

Maybe some combination of strategies, over time, will spare some children the misery of measles or tetanus or whooping cough. Or maybe platforms will eventually have to supplement all that reach-limiting with some speech-limiting, too, at least for the most dangerous actors, many of whom prey on vulnerable communities. Maybe the answer is more fundamental, and sites will have to alter the incentives, from engagement algorithms to likes to follower counts, that reward extremism and sensationalism. Maybe, and it's likely, they will have to do all these things at once.

The Internet didn't create vaccine denialism, just as it didn't create the other maladies platforms are now being asked to moderate away. It did, however, help the hoax go viral. The Web was meant to empower everyone, and now those who oversee it are trying to — have to — take some of that power away. Doing something isn't as easy as it sounds, but controlling this outbreak can at least offer lessons about how to handle the next one.

Read more:

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The Post's View: There is no excuse for the needless revival of measles outbreaks

Letter: I've had measles. You don't want it.

Molly Roberts
Molly Roberts writes about technology and society for The Post's Opinions section. Follow

EXHIBIT 332

Pinterest Restricts Vaccine Search Results to Curb Spread of Misinformation

By Christina Caron

Feb. 23, 2019

Pinterest, a digital platform popular with parents, took an unusual step to crack down on the proliferation of anti-vaccination propaganda: It purposefully hobbled its search box.

Type “vaccine” into its search bar and nothing pops up. “Vaccination” or “anti-vax”? Also nothing.

Pinterest, which allows people to save pictures on virtual pinboards, is often used to find recipes for picky toddlers, baby shower décor or fashion trends, but it has also become a platform for anti-vaccination activists who spread misinformation on social media.

It is an especially effective way to reach parents: 80 percent of mothers and 38 percent of fathers in the United States are on Pinterest, according to 2017 data from comScore. The company has more than 250 million monthly active users and is expected to go public this year.

Other platforms like Facebook and YouTube have also been infiltrated with misinformation about vaccines, and are taking steps to combat it. One of YouTube’s policies is to demonetize anti-vaccine videos.

But only Pinterest, as first reported by The Wall Street Journal, has chosen to banish results associated with certain vaccine-related searches, regardless of whether the results might have been reputable.

“Right now, blocking results in search is a temporary solution to prevent people from encountering harmful misinformation,” said Jamie Favazza, a spokeswoman. The company said it was working with experts to develop a more tailored long-term approach.

The changes, which were not publicly announced, started in September and October.

Opposition to vaccinations can be traced to the introduction of the first vaccine in the 18th century. Over time most people accepted vaccines, and diseases that could be prevented by them declined. They declined so much, in fact, that the success of vaccines may have muted the dangers associated with those diseases.

The World Health Organization identified “vaccine hesitancy” as one of this year’s 10 notable threats to global health.

“I think this is stunning,” said Dr. Gregory A. Poland, director of the Mayo Clinic’s Vaccine Research Group in Rochester, Minn. “It shows the magnitude of the problem.”

Despite clear evidence that vaccines are effective and safe, some people still choose not to get vaccinated or to vaccinate their children, which has contributed to a surge in measles cases worldwide. In the United States, there have been five measles outbreaks this year and at least 127 individual cases.

One or two in 1,000 children who contract this highly contagious disease will die. Last year, measles killed 72 adults and children in the European region, where measles has reached its highest levels in two decades. While measles deaths are rare in developed countries, the illness can have severe lasting consequences, such as vision loss.

There are several reasons for vaccine hesitancy: worries about side effects, cost, moral or religious objections, fears about a debunked link to autism and lack of knowledge about immunizations.

“We’re just seeing all sorts of misinformation flying around on social media,” said Arthur L. Caplan, head of the Division of Medical Ethics at the New York University School of Medicine, who has been writing about vaccine ethics and policy for 25 years.

“Fake news. Fake science,” he said on Friday. “Everybody’s an expert.”

Last week, Representative Adam B. Schiff of California, a Democrat and the chairman of the House Intelligence Committee, wrote a letter to Mark Zuckerberg, the chief executive of Facebook, asking what steps the company was taking to prevent anti-vaccine information from being recommended to users. He sent a similar letter to Sundar Pichai, the chief executive of Google, which owns YouTube.

YouTube said on Thursday that it started surfacing more authoritative content in late 2017 for people searching for vaccination-related topics, and that its algorithmic changes would become more accurate over time.

YouTube also said it does not permit anti-vaccine videos to show ads.

“We have strict policies that govern what videos we allow ads to appear on, and videos that promote anti-vaccination content are a violation of those policies,” a YouTube spokeswoman said on Friday. “We enforce these policies vigorously, and if we find a video that violates them we immediately take action and remove ads.”

An analysis by The Daily Beast of seven Facebook pages that promote anti-vaccine posts found that the pages had bought a combined 147 Facebook ads that had been viewed millions of times. Most of them targeted women over the age of 25, it reported.

“We’ve taken steps to reduce the distribution of health-related misinformation on Facebook, but we know we have more to do,” Andrea Vallone, a Facebook spokeswoman, said in a statement. “We’re currently working on additional changes that we’ll be announcing soon.”

The company said it was considering reducing or removing this type of content from recommendations and demoting it in search results.

Dr. Poland, an internist who has spent 35 years in the vaccine field, said he often encountered patients who relied on social media when researching health questions.

“I will explain to a patient in detail the answer to their question and they’ll look at me and say, ‘Yeah, but I saw on Facebook that …’” he said, his voice trailing off. “You just want to tear your hair out.”

Twitter said that it had no specific policy to stem the spread of misinformation about vaccines but that its real-time nature was a “powerful antidote.”

“We, as a company, should not be the arbiter of truth,” Katie Rosborough, a Twitter spokeswoman, said in a statement on Friday, adding that the company was working to surface the highest-quality and most relevant content first.

For all of these companies, containing the spread of misinformation, particularly about something as emotionally charged as vaccines, will be a lasting challenge as they balance fears about censorship with the need to promote useful content, experts said.

“It’s a mess that I don’t see easily solved,” Dr. Poland said.

EXHIBIT 333

Morbidity and Mortality Weekly Report

Vaccination Coverage by Age 24 Months Among Children Born in 2015 and 2016 — National Immunization Survey-Child, United States, 2016–2018

Holly A. Hill, MD, PhD[1]; James A. Singleton, PhD[1]; David Yankey, PhD[1]; Laurie D. Elam-Evans, PhD[1]; S. Cassandra Pingali, MPH, MS[1]; Yoonjae Kang, MPH[1]

The Advisory Committee on Immunization Practices (ACIP) recommends that children be vaccinated against 14 potentially serious illnesses during the first 24 months of life (*1*). CDC used data from the National Immunization Survey-Child (NIS-Child) to assess vaccination coverage with the recommended number of doses of each vaccine at the national, state, territorial, and selected local levels* among children born in 2015 and 2016. Coverage by age 24 months was at least 90% nationally for ≥3 doses of poliovirus vaccine, ≥1 dose of measles, mumps, and rubella vaccine (MMR), ≥3 doses of hepatitis B vaccine (HepB), and ≥1 dose of varicella vaccine, although MMR coverage was <90% in 20 states. Children were least likely to be up to date by age 24 months with ≥2 doses of influenza vaccine (56.6%). Only 1.3% of children born in 2015 and 2016 had received no vaccinations by the second birthday. Coverage was lower for uninsured children and for children insured by Medicaid than for those with private health insurance. Vaccination coverage can be increased by improving access to vaccine providers and eliminating missed opportunities to vaccinate children during health care visits. Increased use of local vaccination coverage data is needed to identify communities at higher risk for outbreaks of measles and other vaccine-preventable diseases.

The NIS-Child is a random-digit–dialed telephone survey† of parents or guardians of children aged 19–35 months. Respondents are asked to provide contact information for all providers who administered vaccines to their children. With parental consent, a survey is mailed to each identified provider, requesting the child's vaccination history. Multiple responses for an individual child are synthesized into a comprehensive vaccination history which is used to estimate vaccination coverage. To estimate coverage for the 25,059 children with adequate provider data§ born in 2015 and 2016, NIS-Child data from 2016–2018 were combined; for survey year 2018, the Council of American Survey Research Organizations' response rate was 24.6%, and 54.0% of children with household interviews had adequate provider data.¶ With this report, CDC has transitioned to reporting NIS-Child data by birth year rather than survey year. Vaccination coverage by age 24 months was estimated using Kaplan-Meier (time to event) analysis to account for children who were aged <24 months on the date vaccination status was assessed. Coverage with ≥2 doses of hepatitis A vaccine (HepA) was assessed at 35 months (the maximum age included in the survey), because the second dose of HepA can be administered as late as age 41 months under the current schedule. Previous NIS-Child weighting methods were modified to optimize estimation by birth year and to reflect the shift from a dual landline and cellular telephone sample frame to an exclusively cellular telephone sampling frame in 2018.** Differences in coverage estimates were evaluated using

* Estimates for states, selected local areas, and the territory of Guam are available online at https://www.cdc.gov/vaccines/imz-managers/coverage/childvaxview/data-reports/index.html. Certain local areas that receive federal Section 317 immunization funds are sampled separately and included in the NIS-Child sample every year (Chicago, Illinois; New York, New York; Philadelphia County, Pennsylvania; Bexar County, Texas; and Houston, Texas). Other local areas in Texas have been sampled in some survey years and not others, including El Paso County (survey years 2014–2017); Dallas County (survey years 2016 and 2017); Hildago County (survey years 2015 and 2018); Tarrant County (survey year 2018); and Travis County (survey year 2017). The NIS-Child was also conducted in Guam, Puerto Rico, and U.S. Virgin Islands; however, data collection in Puerto Rico and U.S. Virgin Islands was suspended during 2017 because of the severity of the hurricane season and did not occur at all in 2018, resulting in insufficient data for estimation of vaccination coverage by 24 months among children born during 2015–2016. National estimates in this report exclude all territories.

† NIS-Child used a landline-only sampling frame from 1995 through 2010. From 2011 through 2017, the survey was conducted using a dual-frame design, with both cellular and landline sampling frames included. In 2018, the NIS-Child returned to a single-frame design, with all interviews conducted by cellular telephone.

§ Children with at least one vaccination reported by a provider and those who had received no vaccinations were considered to have adequate provider data. "No vaccinations" indicates that the vaccination status is known because the parent indicated there were no vaccinations and the providers returned no immunization history forms or returned them indicating that no vaccinations had been given.

¶ The Council of American Survey Research Organizations (CASRO) household response rate is calculated as the product of the resolution rate (percentage of the total telephone numbers called that were classified as nonworking, nonresidential, or residential), screening completion rate (percentage of known households that were successfully screened for the presence of age-eligible children), and the interview completion rate (percentage of households with one or more age-eligible children that completed the household survey). The CASRO household response rate is equivalent to the American Association for Public Opinion Research type 3 response rate http://www.aapor.org/AAPOR_Main/media/publications/Standard-Definitions20169theditionfinal.pdf. For CASRO response rates and the proportions of children with household interviews that had adequate provider data for survey years 2013–2017, see: https://www.cdc.gov/vaccines/imz-managers/nis/downloads/NIS-PUF17-DUG.pdf, (Appendix G).

** https://www.cdc.gov/vaccines/imz-managers/coverage/childvaxview/pubs-presentations/NIS-child-vac-coverage-estimates-2014-2018.html.

t-tests on weighted data; p-values of <0.05 were considered statistically significant. Analyses were performed using SAS (version 9.4; SAS institute) and SUDAAN (version 11.0.1; Research Triangle Institute). No evidence for a change in survey accuracy from the 2017 to 2018 survey year was detected (https://www.cdc.gov/vaccines/imz-managers/coverage/childvaxview/pubs-presentations/NIS-child-vac-coverage-estimates-2014-2018-tables.html#supp-table-01) (*2*).

National Vaccination Coverage

Coverage by age 24 months was ≥90% for ≥3 doses of poliovirus vaccine (92.7%), ≥1 dose of MMR (90.4%), ≥3 doses of HepB (91.0%), and ≥1 dose of varicella vaccine (90.0%) (Table 1). Compared with estimates for children born in 2013 and 2014, coverage for children born during 2015–2016 increased for the HepB birth dose (3.2 percentage points), ≥1 dose of HepA (1.5 percentage points), and ≥2 doses of influenza vaccine (3.6 percentage points). Coverage with ≥2 HepA doses by age 35 months increased from 74.0% for children born during 2013–2014 to 76.6% for children born during 2015–2016. Children were least likely to be up to date by age 24 months with ≥2 doses of influenza vaccine (56.6%) and the combined 7-vaccine series[††] (68.5%).

Vaccination Coverage by Selected Characteristics and Geographic Location

For most of the vaccines assessed, uninsured children, and children with Medicaid or other nonprivate insurance, had lower coverage than did privately insured children (Table 2). Compared with privately insured children, coverage disparities were largest among uninsured children, ranging from 7.8 percentage points for the HepB birth dose to 33.8 percentage points for ≥2 doses of influenza vaccine. The proportion of children who received no vaccinations was higher among uninsured children (7.4%) than among those with private insurance (0.8%). Disparities were also observed for race/ethnicity (Supplementary Table 1, https://stacks.cdc.gov/view/cdc/81681), poverty level (Supplementary Table 2, https://stacks.cdc.gov/view/cdc/81682), and metropolitan statistical area[§§] (MSA) (Supplementary Table 2, https://stacks.cdc.gov/view/cdc/81682) but tended to be smaller than those seen with health insurance status. Coverage varied widely by state/local area for many vaccines (Supplementary Table 3, https://stacks.cdc.gov/view/cdc/81683). Coverage with ≥1 dose of MMR was <90% in 20 states; only six states had coverage of 94% or higher (Figure).

Summary

What is already known about this topic?

The Advisory Committee on Immunization Practices recommends that children be vaccinated against 14 potentially serious illnesses before age 24 months.

What is added by this report?

Among children born in 2015 and 2016, coverage was high and stable for most vaccines. There were sociodemographic disparities in coverage, especially by health insurance status. The proportion of completely unvaccinated children remained small.

What are the implications for public health practice?

Coverage can be improved with increased access to providers and health insurance, administration of all recommended vaccines during office visits, and more effective patient education about vaccine safety and efficacy. Actionable local level data are a priority for creating targeted interventions to prevent outbreaks of measles and other vaccine-preventable diseases.

Trends in Vaccination Coverage

Vaccination coverage was stable by single birth year from 2011 through 2016 (https://www.cdc.gov/vaccines/imz-managers/coverage/childvaxview/pubs-presentations/NIS-child-vac-coverage-estimates-2014-2018-tables.html#supp-figure-01), except for an increase in ≥2 doses of HepA by age 35 months from 71.1% (2011) to 76.6% (2016). The proportion of children that received no vaccinations by age 24 months increased slightly across birth years 2011 through 2016, with an estimated change per year of 0.09 percentage points (https://www.cdc.gov/vaccines/imz-managers/coverage/childvaxview/pubs-presentations/NIS-child-vac-coverage-estimates-2014-2018-tables.html#supp-figure-02). Only 1.3% of children born in 2015 and 2016 received no vaccinations (Table 1).

Discussion

Vaccination coverage by the second birthday among children born during 2015–2016 remained high, with small increases in coverage with hepatitis A and B and influenza vaccines; only 1.3% of children received no vaccinations. However, several opportunities for improvement were apparent. Coverage was lower for children without private health insurance, especially those with no insurance, as well as those living below the poverty level and in more rural areas. Vaccination coverage also varied by state, with 20 states having MMR coverage <90%.

[††] The combined 7-vaccine series (4:3:1:3*:3:1:4) includes ≥4 doses of diphtheria and tetanus toxoids and acellular pertussis vaccine; ≥3 doses of poliovirus vaccine; ≥1 dose of measles-containing vaccine; ≥3 or ≥4 doses (depending upon product type) of *Haemophilus influenzae* type b conjugate vaccine; ≥3 doses of hepatitis B vaccine; ≥1 dose of varicella vaccine; and ≥4 doses of pneumococcal conjugate vaccine.

[§§] MSA status was determined based on household reported city and county of residence and was grouped into three categories: MSA principal city, MSA nonprincipal city, and non-MSA. MSAs and principal cities were as defined by the U.S. Census Bureau (https://www.census.gov/programs-surveys/metro-micro.html). Non-MSA areas include urban populations not located within an MSA as well as completely rural areas.

TABLE 1. Estimated vaccination coverage by age 24 months* among children born during 2013–2016 for selected vaccines and doses — National Immunization Survey-Child, United States, 2014–2018

Vaccine/Dose	% (95% CI)		
	Birth years†		Difference
	2013–2014	2015–2016	(2013–2014) to (2015–2016)
DTaP§			
≥3 doses	93.6 (93.0 to 94.2)	93.8 (93.1 to 94.5)	0.2 (-0.7 to 1.1)
≥4 doses	80.6 (79.7 to 81.6)	80.3 (79.0 to 81.5)	-0.4 (-1.9 to 1.2)
Poliovirus (≥3 doses)	91.7 (91.0 to 92.4)	92.7 (92.0 to 93.4)	1.0 (0.0 to 2.0)
MMR (≥1 dose)¶	90.0 (89.3 to 90.7)	90.4 (89.5 to 91.2)	0.3 (-0.8 to 1.5)
Hib**			
Primary series	92.7 (92.1 to 93.3)	92.7 (91.8 to 93.5)	0.0 (-1.1 to 1.0)
Full series	80.2 (79.3 to 81.1)	79.6 (78.3 to 80.9)	-0.6 (-2.1 to 1.0)
HepB			
Birth dose††	71.8 (70.7 to 72.8)	75.0 (73.7 to 76.2)	3.2 (1.6 to 4.9)§§
≥3 doses	90.9 (90.2 to 91.6)	91.0 (90.2 to 91.9)	0.1 (-1.0 to 1.2)
Varicella (≥1 dose)¶	89.3 (88.6 to 90.1)	90.0 (89.1 to 90.9)	0.7 (-0.5 to 1.8)
PCV			
≥3 doses	91.9 (91.2 to 92.5)	92.0 (91.1 to 92.8)	0.1 (-1.0 to 1.2)
≥4 doses	81.5 (80.6 to 82.4)	81.0 (79.8 to 82.3)	-0.4 (-2.0 to 1.1)
HepA			
≥1 dose	83.2 (82.4 to 84.1)	84.7 (83.6 to 85.8)	1.5 (0.1 to 2.9)§§
≥2 doses (by 35 months)	74.0 (72.8 to 75.3)	76.6 (74.7 to 78.4)	2.6 (0.4 to 4.8)§§
Rotavirus (by 8 months)¶¶	72.4 (71.3 to 73.4)	73.6 (72.2 to 74.9)	1.2 (-0.5 to 2.9)
Influenza (≥2 doses)***	53.0 (51.9 to 54.1)	56.6 (55.2 to 58.0)	3.6 (1.8 to 5.4)§§
Combined 7-vaccine series†††	68.4 (67.3 to 69.5)	68.5 (67.1 to 69.9)	0.1 (-1.7 to 1.9)
No vaccinations	1.1 (1.0 to 1.3)	1.3 (1.1 to 1.5)	0.1 (-0.2 to 0.4)

Abbreviations: CI = confidence interval; DTaP = diphtheria, tetanus toxoids, and acellular pertussis vaccine; HepA = hepatitis A vaccine; HepB = hepatitis B vaccine; Hib = *Haemophilus influenzae* type b conjugate vaccine; MMR = measles, mumps, and rubella vaccine; PCV = pneumococcal conjugate vaccine.

* Includes vaccinations received by age 24 months (before the day the child turns 24 months), except for the HepB birth dose, rotavirus vaccination, and ≥2 HepA doses by 35 months. For all vaccines, except the HepB birth dose and rotavirus vaccination, the Kaplan-Meier method was used to estimate vaccination coverage to account for children whose vaccination history was ascertained before age 24 months (35 months for ≥2 HepA doses).

† Data for the 2013 birth year are from survey years 2014, 2015, and 2016; data for the 2014 birth year are from survey years 2015, 2016, and 2017; data for the 2015 birth year are from survey years 2016, 2017, and 2018; data for the 2016 birth year are considered preliminary and come from survey years 2017 and 2018 (data from survey year 2019 are not yet available).

§ Includes children who might have received diphtheria and tetanus toxoids vaccine or diphtheria, tetanus toxoids, and pertussis vaccine.

¶ Includes children who might have received measles, mumps, rubella, and varicella combination vaccine.

** Hib primary series: receipt of ≥2 or ≥3 doses, depending on product type received; full series: primary series and booster dose, which includes receipt of ≥3 or ≥4 doses, depending on product type received.

†† One dose HepB administered from birth through age 3 days.

§§ Statistically significantly different from 0 at p<0.05.

¶¶ Includes ≥2 doses of Rotarix monovalent rotavirus vaccine, or ≥3 doses of RotaTeq pentavalent rotavirus vaccine. The maximum age for the final rotavirus dose is 8 months, 0 days.

*** Doses must be at least 24 days apart (4 weeks with a 4-day grace period).

††† The combined 7-vaccine series (4:3:1:3*:3:1:4) includes ≥4 doses of DTaP, ≥3 doses of poliovirus vaccine, ≥1 dose of measles-containing vaccine, the full series of Hib (≥3 or ≥4 doses, depending on product type), ≥3 doses of HepB, ≥1 dose of varicella vaccine, and ≥4 doses of PCV.

Coverage with ≥2 doses of influenza vaccine was the lowest among all recommended childhood vaccines.

The importance of achieving and sustaining high vaccination coverage across all communities is illustrated by the 22 measles outbreaks occurring in the United States in 2019, with 1,249 measles cases identified during January 1–October 1, 2019 (*3*). Most cases have been among persons who were not vaccinated against measles. Pockets of low vaccination coverage, because of lack of access to vaccination services or to hesitancy resulting from the spread of inaccurate information about vaccines, increase the likelihood of a measles outbreak. Strategies are needed to increase access to vaccination services, identify communities at risk, and implement initiatives to counter inaccurate vaccine information (*4*).

Lower vaccination coverage among children who are uninsured, insured by Medicaid or other nonprivate insurance, living below the poverty level, and living in rural areas suggests challenges with access to affordable vaccinations or optimal vaccination services. Uninsured children are eligible for vaccine at no cost through the Vaccines for Children¶¶ program, but efforts to promote the program might not be reaching this population and therefore might need to be modified.

¶¶ https://www.cdc.gov/vaccines/programs/vfc/index.html.

TABLE 2. Estimated vaccination coverage by age 24 months* among children born during 2015–2016,† by selected vaccines and doses and health insurance status§ — National Immunization Survey-Child, United States, 2016–2018

Vaccine/Dose	Health insurance status, % (95% CI)			
	Private only (referent) (n = 12,702)	Any Medicaid (n = 9,442)	Other insurance (n = 2,141)	Uninsured (n = 774)
DTaP¶				
≥3 doses	96.9 (96.3–97.5)	91.8 (90.5–93.1)**	93.9 (92.2–95.3)**	80.6 (75.2–85.5)**
≥4 doses	87.1 (85.7–88.5)	75.8 (73.6–77.9)**	78.8 (75.4–82.0)**	59.8 (53.8–65.9)**
Poliovirus (≥3 doses)	96.1 (95.4–96.7)	90.7 (89.3–92.0)**	92.3 (90.4–94.0)**	79.3 (73.9–84.3)**
MMR (≥1 dose)††	93.7 (92.8–94.5)	88.6 (87.0–90.1)**	89.8 (87.6–91.8)**	73.2 (67.4–78.7)**
Hib§§				
Primary series	95.7 (94.5–96.8)	90.7 (89.3–92.1)**	93.7 (91.9–95.1)	78.4 (72.8–83.5)**
Full series	85.5 (83.7–87.1)	75.9 (73.8–78.0)**	79.1 (75.8–82.1)**	58.1 (52.1–64.2)**
HepB				
Birth dose¶¶	75.6 (73.9–77.2)	76.1 (74.0–78.1)	68.2 (64.3–71.9)**	67.8 (61.9–73.2)**
≥3 doses	93.0 (91.8–94.0)	90.0 (88.5–91.4)**	91.9 (89.9–93.6)	78.6 (73.3–83.5)**
Varicella (≥1 dose)††	93.2 (92.3–94.0)	88.6 (86.9–90.1)**	89.1 (86.8–91.2)**	70.3 (64.5–75.9)**
PCV				
≥3 doses	94.9 (93.5–96.0)	90.3 (88.9–91.7)**	92.0 (90.1–93.7)**	77.2 (71.7–82.4)**
≥4 doses	87.3 (85.6–88.8)	76.8 (74.7–78.9)**	80.9 (77.7–83.9)**	62.5 (56.7–68.3)**
HepA				
≥1 dose	87.5 (85.9–89.0)	83.7 (81.9–85.4)**	84.0 (81.2–86.6)**	65.5 (59.7–71.3)**
≥2 doses (by 35 months)	80.5 (77.9–83.1)	75.2 (72.2–78.0)**	76.8 (71.3–81.9)	48.2 (41.0–56.0)**
Rotavirus (by 8 months)***	83.5 (81.9–85.0)	65.9 (63.5–68.1)**	72.4 (68.5–76.0)**	59.8 (53.8–65.5)**
Influenza (≥2 doses)†††	68.5 (66.6–70.4)	48.2 (45.9–50.5)**	52.7 (48.6–56.9)**	34.7 (29.4–40.7)**
Combined 7-vaccine series§§§	75.4 (73.5–77.2)	64.3 (62.0–66.6)**	65.9 (62.1–69.6)**	46.7 (40.9–52.9)**
No vaccinations	0.8 (0.6–1.0)	1.2 (0.9–1.6)	1.8 (1.2–2.6)**	7.4 (4.7–10.7)**

Abbreviations: CI = confidence interval; DTaP = diphtheria, tetanus toxoids, and acellular pertussis vaccine; HepA = hepatitis A vaccine; HepB = hepatitis B vaccine; Hib = *Haemophilus influenzae* type b conjugate vaccine; MMR = measles, mumps, and rubella vaccine; PCV = pneumococcal conjugate vaccine.

* Includes vaccinations received by age 24 months (before the day the child turns 24 months), except for the HepB birth dose, rotavirus vaccination, and ≥2 HepA doses by 35 months. For all vaccines, except the HepB birth dose and rotavirus vaccination, the Kaplan-Meier method was used to estimate vaccination coverage to account for children whose vaccination history was ascertained before age 24 months (35 months for ≥2 HepA doses).

† Data for the 2015 birth year are from survey years 2016, 2017, and 2018; data for the 2016 birth year are considered preliminary and come from survey years 2017 and 2018 (data from survey year 2019 are not yet available).

§ Children's health insurance status was reported by parent or guardian. "Other insurance" includes the Children's Health Insurance Program, military insurance, coverage via the Indian Health Service, and any other type of health insurance not mentioned elsewhere.

¶ Includes children who might have received diphtheria and tetanus toxoids vaccine or diphtheria, tetanus toxoids, and pertussis vaccine.

** Statistically significant ($p<0.05$) difference compared with the referent group.

†† Includes children who might have received measles, mumps, rubella, and varicella combination vaccine.

§§ Hib primary series: receipt of ≥2 or ≥3 doses, depending on product type received; full series: primary series and booster dose, which includes receipt of ≥3 or ≥4 doses, depending on product type received.

¶¶ One dose HepB administered from birth through age 3 days.

*** Includes ≥2 doses of Rotarix monovalent rotavirus vaccine (RV1), or ≥3 doses of RotaTeq pentavalent rotavirus vaccine (RV5). The maximum age for the final rotavirus dose is 8 months, 0 days.

††† Doses must be at least 24 days apart (4 weeks with a 4-day grace period).

§§§ The combined 7-vaccine series (4:3:1:3*:3:1:4) includes ≥4 doses of DTaP, ≥3 doses of poliovirus vaccine, ≥1 dose of measles-containing vaccine, the full series of Hib (≥3 or ≥4 doses, depending on product type), ≥3 doses of HepB, ≥1 dose of varicella vaccine, and ≥4 doses of PCV.

Targeted programs to address logistical issues such as expanded office hours and transportation to vaccination appointments could facilitate access to vaccination services, regardless of the child's type of insurance. Providers need to use every patient encounter to screen for and offer vaccinations. An analysis of NIS-Child data for children born during 2005–2015 found that disparities in coverage with ≥4 doses of diphtheria, tetanus toxoids, and acellular pertussis vaccine (DTaP) for those with Medicaid compared with those with private health insurance could have been reduced by 42% had opportunities for receipt of the fourth DTaP dose not been missed during visits when other vaccinations were received (*5*).

The transition to reporting by birth year rather than by survey year more directly assesses recent changes in vaccination coverage and provides more interpretable estimates and more accurate comparisons to evaluate immunization information systems (*2*,*6*,*7*). With a standard age at assessment (e.g., 24 months), estimates by birth year might be slightly lower for some vaccines than were estimates by survey year, which on average, assessed vaccination by age 27.5 months. Trends in vaccination coverage by birth year and survey year are similar (*8*). Other changes include addition of assessment of ≥2 HepA doses by age 35 months to better reflect current

ACIP recommendations and the addition of vaccination with 2 doses of influenza vaccine by age 24 months.***

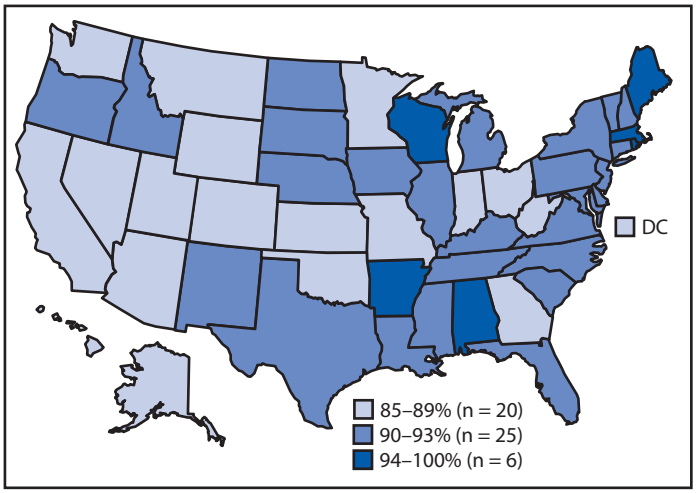
The findings in this report are subject to at least two limitations. First, as with previous NIS-Child estimates by survey year, vaccination coverage estimates by birth year might be biased because of an incomplete sample frame, nonresponse, and underascertainment of vaccination (*6*). No evidence for change in survey accuracy from 2017 to 2018 was detected. Second, starting in 2018, the NIS-Child sample was drawn only from cellular telephone numbers. Vaccination coverage trends should thus be viewed with caution, although the effect of dropping the landline sample is likely small.

Improvements in childhood vaccination coverage will require that parents and other caregivers have access to vaccination providers and believe in the safety and effectiveness of vaccines. Increased opportunity for vaccination can be facilitated through expanded access to health insurance, greater promotion of available vaccines through the Vaccines for Children program, and solutions to logistical challenges such as transportation, child care, and time off from work. Providers can improve vaccination coverage overall and reduce disparities by administering all recommended vaccines during office visits. Compelling and accessible educational materials, combined with effective techniques for providers to use when discussing vaccination, can be used to counter inaccurate claims and communicate the value of vaccines in protecting the health of children (*9*). In addition, actionable data at a local level are needed so that interventions can be targeted to areas at risk for outbreaks of measles and other vaccine-preventable diseases. More immunization information systems will contribute to this effort because they streamline their data collection processes and improve data quality (*10*).††† Given low survey response rates, CDC is working to better assess accuracy of NIS-Child vaccination coverage estimates, evaluate new survey approaches (e.g., switching to an address-based sample frame), and integrate data from immunization information systems and, potentially, other data sources (*7*).

*** This measure of influenza vaccination differs from other estimates from NIS-Flu (see https://www.cdc.gov/flu/fluvaxview/coverage-1718estimates-children.htm): it is based on provider-reported vaccinations instead of relying on parental report; and it reflects vaccinations that might have been received over two influenza seasons, while NIS-Flu estimates are for one season. Receipt of two influenza vaccinations by age 24 months is also a Healthcare Effectiveness Data and Information Set measure (https://www.ncqa.org/hedis/measures/childhood-immunization-status/); this measure can be used to identify commercial and Medicaid health plans within states with lower vaccination coverage.

††† General information about immunization information systems is available at https://www.cdc.gov/vaccines/programs/iis/about.html. Guidance on using immunization information systems to identify geographic areas of populations at risk for outbreaks of vaccine-preventable diseases is available at https://repository.immregistries.org/files/resources/5bae51a16a09c/identifying_immunization_pockets_of_need-_final2.pdf.

FIGURE. Estimated coverage with ≥1 dose of MMR by age 24 months among children born 2015–2016* — National Immunization Survey-Child, United States, 2016–2018



Abbreviations: DC = District of Columbia; MMR = measles, mumps, and rubella vaccine.

* Data for the 2015 birth year are from survey years 2016, 2017, and 2018; data for the 2016 birth year are considered preliminary and come from survey years 2017 and 2018 (data from survey year 2019 are not yet available).

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References

1. Robinson CL, Romero JR, Kempe A, Pellegrini C, Szilagyi P. Advisory Committee on Immunization Practices recommended immunization schedule for children and adolescents aged 18 years or younger—United States, 2018. MMWR Morb Mortal Wkly Rep 2018;67:156–7. https://doi.org/10.15585/mmwr.mm6705e2
2. CDC. Evaluating vaccination coverage trends with the National Immunization Survey-Child (NIS-Child), 2013–2017, United States, technical appendix. Atlanta, GA: US Department of Health and Human Services, CDC; 2018. https://www.cdc.gov/vaccines/imz-managers/coverage/childvaxview/pubs-presentations/NIS-vax-trends-2013-2017.html
3. Patel M, Lee AD, Clemmons NS, et al. National update on measles cases and outbreaks—United States, January 1–October 1, 2019. MMWR Morb Mortal Wkly Rep 2019;68:893–6.
4. Bocquier A, Ward J, Raude J, Peretti-Watel P, Verger P. Socioeconomic differences in childhood vaccination in developed countries: a systematic review of quantitative studies. Expert Rev Vaccines 2017;16:1107–18. https://doi.org/10.1080/14760584.2017.1381020

5. Zhao Z, Hill HA, Elam-Evans LD, Singleton JA. Disparities in potentially achievable vaccination coverage by selected socio-demographic factors among children in the United States. Presented at the 2019 Joint Statistical Meeting annual conference, Denver, CO; July 27–August 1, 2019.
6. Hill HA, Elam-Evans LD, Yankey D, Singleton JA, Kang Y. Vaccination coverage among children aged 19–35 months—United States, 2017. MMWR Morb Mortal Wkly Rep 2018;67:1123–8. https://doi.org/10.15585/mmwr.mm6740a4
7. Singleton JA. American Immunization Registry Association (AIRA) Snapshots. Evolving approaches for vaccination coverage assessment among young children. Washington, DC: American Immunization Registry Association; 2019;82:9–12. https://repository.immregistries.org/files/resources/5d126c84483b3/aira_snapshots_june_2019-0.pdf
8. Singleton JA, Hill HA, Yankey D, et al. Monitoring childhood vaccination coverage by annual birth cohort: a paradigm shift. Presented at the American Association for Public Opinion Research 74th annual conference, Toronto, Ontario, Canada; May 17, 2019.
9. Chung Y, Schamel J, Fisher A, Frew PM. Influences on immunization decision-making among US parents of young children. Matern Child Health J 2017;21:2178–87. https://doi.org/10.1007/s10995-017-2336-6
10. Murthy N, Rodgers L, Pabst L, Fiebelkorn AP, Ng T. Progress in childhood vaccination data in immunization information systems—United States, 2013–2016. MMWR Morb Mortal Wkly Rep 2017;66:1178–81. https://doi.org/10.15585/mmwr.mm6643a4

EXHIBIT 334

Virtual Mentor

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CLINICAL CASE

Treating Children Whose Parents Refuse to Have Them Vaccinated

Commentary by Kimberly Insel, MD, MPH

Dr. Feyn, a Denver pediatrician, mentions to his colleague Dr. Manning that parents' refusal of vaccines for their children has become more popular among parents in his patient panel in the last 5 years. "Most of these parents have similar reasons for choosing not to vaccinate their children. They cite alternative vaccination schedules, celebrity campaigns against vaccine side effects, even online forum discussions with other parents."

Dr. Manning responds, "The CDC has recommended schedules for vaccination, but I know you would like to respect the discretion of patients and parents of patients as much as possible. So what are you going to do?"

"In the past I have documented the vaccine refusal and moved on, but I'm considering changing my approach," Dr. Feyn responds. "As the number of unvaccinated children in my practice increases, I wonder if I am creating a risky environment for vaccine-preventable infections in my community. We recently witnessed an outbreak of pertussis nearby in Boulder because the percentage of immunized kids at a certain school was below threshold necessary for herd immunity.

"I'm thinking of insisting that my patients receive vaccinations according to the standard schedule, unless, of course, there is a specific health-related reason why an individual child should not be vaccinated. I am also considering not treating children in my practice unless they are vaccinated. What do you think of that?"

Commentary

Parental refusal of vaccination for children has led to an emergence of vaccine-preventable illness nationally. In the case of vaccination against measles, national trends of vaccine refusal have increased the number of measles cases. According the Centers for Disease Control and Prevention's (CDC) *Morbidity and Mortality Weekly Report (MMWR),* between January 1st and May 20th, 2011, 24 states reported 118 cases of measles [1]. This is the highest number of measles cases reported since 1996. Of these cases, 89 percent were unvaccinated persons.

Outbreak investigations over the past 4 years reveal increased numbers of cases related to intentional refusal of vaccination by parents. In an outbreak of measles in San Diego County in 2008, an association was found between cases and intentional avoidance of vaccination [2]. In this instance, one imported case of measles resulted

in 839 exposed persons. Both the index case and 75 percent of all related cases were in children whose parents had intentionally avoided vaccinating their children. Similarly, many of the 21 children affected by the largest measles outbreak in 2011 were unvaccinated because of parental concerns about the safety of the measles, mumps, and rubella (MMR) vaccine [3, 4].

Although the problem of inadequate vaccination is not an entirely new problem, the role of the physician in protecting vulnerable populations cannot be overemphasized. To understand whether it is ethical not to treat children whose parents refuse to vaccinate them, it may be beneficial to define the population of interest and strategies found to be effective in communicating with their parents.

Vulnerable Populations

Particularly vulnerable populations of children are those that cannot be immunized or develop an immune response. These children rely primarily on herd immunity, the vaccination of a critical mass of the population against life-threatening diseases. These populations include children under 12 months of age (too young for vaccination) and children who have chronic medical conditions that prevent them from being able to receive vaccinations. In 2011, 15 percent of cases of measles were in children too young for vaccination. Within the 165 deaths associated with measles cases between 1987 and 1992, 14-16 percent were in children who had pre-existing conditions that prevented them from being vaccinated [4]. Vulnerable groups of children are at particular risk when exposed to the children of parents who willingly choose not to vaccinate their children, not only because of their increased susceptibility but because that increased susceptibility can also lead to worse sequelae in those infected [5].

Other vulnerable populations include children who are not vaccinated for reasons other than medical indications. An analysis of the risk of measles within the population of children exempt from vaccination for nonmedical reasons showed that between 1985 and 1992 these children were 35 times as likely to contract measles as those without exception [6]. Requirements for vaccination of children in school have also waned. As more nonmedical exemptions from vaccination are accepted by schools, cases of vaccine-preventable illness rise [7-9]. Traditionally, it has been the role of public health authorities to protect the most vulnerable groups within a population. If vaccination refusal is leading to more cases of vaccine-preventable illness affecting vulnerable groups of children, it is imperative that we equip physicians and parents with tools to assist in protecting children at risk.

A History of Vaccination Requirements

Vaccination status improved nationwide after 1962 when the Vaccination Assistance Act was passed, providing ongoing financial support to state or local health departments. Initial goals set in 1977 by the Childhood Immunization Initiative were to achieve 90 percent immunization levels. These goals were superseded in 1980 when 50 states passed laws requiring immunizations for students entering schools. With improved vaccination rates nationally, vaccine-preventable deaths decreased.

Vaccine adverse events were recorded as early as 1972 and developed formally into the Vaccine Adverse Events Reporting System in 1986—a passive surveillance system receiving reports nationally from clinicians and the families of vaccine recipients [10].

Trends in Vaccine Refusal

Early surveys of vaccination refusal by the National Immunization Program demonstrated several reasons for vaccination refusal, the most prevalent of which were fear of vaccine safety and the perception that vaccines did not provide sufficient benefits to outweigh the risks [11-14]. Controversy over vaccine safety began to grow in 1980, after some allegations were made that the diphtheria/tetanus/pertussis (DTP) vaccine was a cause of infant deaths and other permanent injury. Following early doubts in vaccine safety, vaccine refusal focused on unsubstantiated claims that vaccines were associated with the onset of autism, attention deficit disorder, and other cognitive deficits affecting children.

Vaccine refusal is thus not a new problem. Cases of vaccine-preventable disease resulting from inadequate vaccination were identified in the 1980s and ’90s. At that time, vaccine-preventable illness predominantly affected unvaccinated preschool- and school-aged children [15, 16]. Between 1987 and 1992, it was estimated that there were 165 measles-associated deaths [4], accounting for an attack rate of 2.54-2.83 deaths per 1,000 reported cases in the United States. Deaths related to measles, a vaccine-preventable disease, were most commonly caused by measles-associated pneumonia or encephalitis. These deaths occurred out of a total of over 55,000 cases of measles in the United States during the same period [4].

The vaccination refusal that physicians see varies by community and specialty, but some surveys have found trends. One survey found that parents of unvaccinated children were more likely than parents of undervaccinated children (those who receive at least one vaccine) to be white, married, college-educated, and high-income earners and to have five or more children [17]. Another study found that the parents of unvaccinated children were more likely than the parents of vaccinated children to have the perceptions that their children were not as susceptible as other children to disease, that the diseases vaccines protected against did not have severe health consequences, and that vaccines were not efficacious in disease prevention [18]. For all parents refusing vaccination, the most common worry regarded vaccine safety.

The Physician’s Role

When there is poor vaccine acceptance, the role of the physician becomes crucial. The importance of physicians’ role in vaccine acceptance and vaccine-related education cannot be overemphasized. This was demonstrated in the case of a measles outbreak in San Diego. During this outbreak, inadequate vaccination against measles was associated with physicians’ assumptions that vaccination was contraindicated in sick children, clinicians’ choosing not to give multiple vaccinations in one visit, and private doctors’ referring children who lacked insurance to other clinicians [19].

Several studies have found that parents' preferred source of vaccination information is health care professionals [20, 21]. A survey of 21,420 households conducted by the National Center for Immunization and Respiratory Diseases in 2009 concluded that the most important source of help in decisions about vaccinating young children was the child's doctor or nurse. In the survey, 86.5 percent of respondents reported that they usually followed the clinician's advice, and 84 percent reported that they trusted it. A second study from the University of Michigan reiterated the importance of physician advice to parental decision making about vaccination. Of the 2,521 online survey responses, 76 percent of parents reported trusting a physician in regards to vaccine-safety information, and only 2 percent reported not trusting a physician at all [22].

In the context of these data, some strategies may be better than others in approaching parents who refuse vaccination. In light of evidence regarding physicians as trusted sources of information about vaccine safety, it would seem a bit premature to turn away patients whose parents refuse vaccination. Instead, it may be more beneficial to engage the parents of our patients. In this way, we can fulfill our role as patient educators, patient advocates, and public health practitioners. Important to an understanding of our role is a clear acknowledgement of the risk vaccine refusal presents to intentionally unvaccinated children and children who cannot be vaccinated due to age or medical condition. Considering the hundreds of unnecessary deaths and illnesses among children caused by vaccine-preventable illness every year in our country, it is our duty to do what we can to ward off preventable illness. In the case of vaccine refusal, this may take the form of a simple conversation with parents.

References

1. Centers for Disease Control and Prevention (CDC). Measles--United States, January--May 20, 2011. *MMWR Morb Mortal Wkly Rep*. 2011;60(20);666-668.
2. Sugerman DE, Barskey AE, Delea MG, et al. Measles outbreak in a highly vaccinated population, San Diego, 2008: role of the intentionally undervaccinated. *Pediatrics*. 2010;125(4):747-755.
3. Centers for Disease Control and Prevention (CDC). Measles outbreak--Hennepin County, Minnesota, February--March 2011. *MMWR Morb Mortal Wkly Rep*. 2011;60(13):421.
4. Gindler J, Tinker S, Markowitz L, et al. Acute measles mortality in the United States, 1987-2002. *J Infect Dis*. 2004;189(Suppl 1):S69-S77.
5. Poehling KA, Talbot TR, Griffin MR, et al. Invasive pneumococcal disease among infants before and after introduction of pneumococcal conjugate vaccine. *JAMA*. 2006;295:1668-1674.
6. Salmon DA, Haber M, Gangarosa EJ, Phillips L, Smith NJ, Chen RT. Health consequences of religious and philosophical exemptions from immunization laws: individual and societal risk of measles. *JAMA*. 1999;282:47-53.
7. Omer SB, Salmon DA, Orenstein WA, deHart MP, Halsey N. Vaccine refusal, mandatory immunization, and the risks of vaccine-preventable diseases. *N Engl J Med*. 2009;360(19):1981-1988.

8. Omer SB, Pan WK, Halsey NA, et al. Nonmedical exemptions to school immunization requirements: secular trends and association of state policies with pertussis incidence. *JAMA*. 2006;296(14):1757-1763.
9. Omer SB, Enger KS, Moulton LH, et al. Geographic clustering of nonmedical exemptions to school immunization requirements and associations with geographic clustering of pertussis. *Am J Epidemiol*. 2008;168(12):1389-1396.
10. Centers for Disease Control and Prevention (CDC). Vaccine-preventable diseases, immunizations, and MMWR--1961-2011. *MMWR Morb Mortal Wkly Rep.* 2011;60(04);49-57.
11. Smith PJ, Humiston SG, Marcuse EK, et al. Parental delay or refusal of vaccine doses, childhood vaccination coverage at 24 months of age and the Health Belief Model. *Public Health Rep*. 2011;126 Suppl 2:135-146.
12. Smith PJ, Kennedy, AM, Wooten, K. et al. Association between health care providers' influence on parents who have concerns about vaccine safety and vaccination coverage. *Pediatrics*. 2006;118;e1287.
13. Salmon DA, Moulton LH, Omer SB, Dehart MP, Stokley S, Halsey NA. Factors associated with refusal of childhood vaccines among parents of school-aged children: a case-control study. *Arch Pediatric Adolesc Med*. 2005;159:470-476.
14. National Vaccine Advisory Committee. The measles epidemic: the problems, barriers and recommendations. *JAMA*. 1991;266:1547-1552.
15. Markowitz LE, Preblud SR, Orenstein WA, et al. Patterns of transmission in measles outbreaks in the United States, 1985–1986. *N Engl J Med*. 1989;320:75-81.
16. Gindler JS, Atkinson WL, Markowitz LE, Hutchins SS. Epidemiology of measles in the United States in 1989 and 1990. *Pediatr Infect Dis J*. 1992;11:841–846.
17. Smith PJ, Chu SY, Barker LE. Children who have received no vaccines: who are they and where do they live? *Pediatrics*. 2004;114(1):187-195.
18. Salmon DA, Pan WK, Omer SB, et al. Vaccine knowledge and practices of primary care providers of exempt vs. vaccinated children. *Hum Vaccin*. 2008;4(4):286-291.
19. Centers for Disease Control and Prevention (CDC). Provider resources for vaccine conversations with parents. http://www.cdc.gov/vaccines/spec-grps/hcp/conversations.htm. Accessed December 18, 2011.
20. Kennedy A, Basket M, Sheedy K. Vaccine attitudes, concerns and information sources reported by parents of young children: results from 2009 HealthStyles Survey. *Pediatrics*. 2011;127 Suppl 1;S92.
21. Gellin BG, Mailbach EW, Marcuse EK. Do parents understand immunizations? A national telephone survey. *Pediatrics*. 2000;106(5):1097-1102.
22. Freed, GL. Clark SJ, Butchart AT, Singer DC, Davis MM. Sources and perceived credibility of vaccine-safety information for parents. *Pediatrics*. 2011;127 Suppl 1:S107.

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EXHIBIT 335

Education and debate

When placebo controlled trials are essential and equivalence trials are inadequate

Martin R Tramèr, D John M Reynolds, R Andrew Moore, Henry J McQuay

Arguments against the use of placebo groups in clinical trials have been based on opinion rather than evidence. Ethical issues have been raised,[1] but these are contentious.[2 3] Scientific requirements should not override ethical ones, but if placebo controls are not used, then active controlled trials (trials using other active drugs as controls) have to be able to determine the efficacy of an intervention and its likelihood of causing harm.

Summary points

- Many consider the use of placebos in clinical trials to be unethical, but can trials without placebo controls provide sensible and useful results?
- One problem is finding a gold standard comparator—for example, no gold standard comparator exists for the prophylactic antiemetic ondansetron
- Another problem is the underlying variation in likelihood of an event (wanted or unwanted); the incidence of postoperative nausea and vomiting, for example, can range from 1% to 80% within 6 hours and from 10% to 96% within 48 hours after surgery
- Ondansetron (pooled 4 mg and 8 mg data) seems better than metoclopramide 10 mg at preventing postoperative nausea and vomiting within 6 hours of surgery but not after 6 hours; comparisons with all the other antiemetics and data on adverse effects are inconclusive
- In clinical settings where no gold standard treatment exists and where event rates vary widely, trial designs without placebo controls are unlikely to yield sensible results
- The ethics of recruiting patients into trials that cannot yield sensible results is dubious
- Systematic reviews could provide ethics committees and trialists with the necessary information to question the ethics of a trial design

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Evidence from placebo controlled trials

We used the antiemetic ondansetron to explore the value of active controlled trials for two reasons. Firstly, the ethics of using placebo controls in ondansetron trials has been questioned repeatedly, both in oncology[4 5] and after surgery,[6] causing confusion for trialists[7] and ethics committees.[8] Secondly, we had good estimates of ondansetron's antiemetic efficacy and harm postoperatively from a systematic review.[9] That showed a dose-response and defined the optimal dose: 8 mg intravenously or 16 mg orally achieved a number needed to treat to prevent emesis of about 6 compared with placebo.[9] It also showed that 1 in 30 patients treated with ondansetron will have a headache or raised concentrations of liver enzymes—they would not have had these complications without the drug.[9] We compared these estimates of efficacy and harm with those from active controlled comparisons.

Active controlled trials—methods of quantitative systematic review

The methods used in systematic search, quality score, data extraction, and meta-analysis of active controlled ondansetron trials are described in detail elsewhere.[9] Efficacy data for ondansetron as a treatment of established postoperative nausea and vomiting[10] and trials without an active control arm[9] were not analysed. Propofol anaesthesia was not regarded as an antiemetic comparator.[11]

Evidence from active controlled trials

Multiple different comparators - lack of a gold standard

Evidence

Data on included and excluded trials (retrieved up to September 1996) are shown in figure 1. Thirty three randomised controlled trials with data from 4827 patients (1837 treated with ondansetron) were finally analysed.[12–44] The median size of ondansetron treatment groups was 33 (range 10-465) patients. The median quality score[45] of all reports was 2 (1-5).

Tables with relevant data extracted from the analysed reports are available on the internet (www.jr2.ox.ac.uk/Bandolier/painres/ondA/ondA.html).

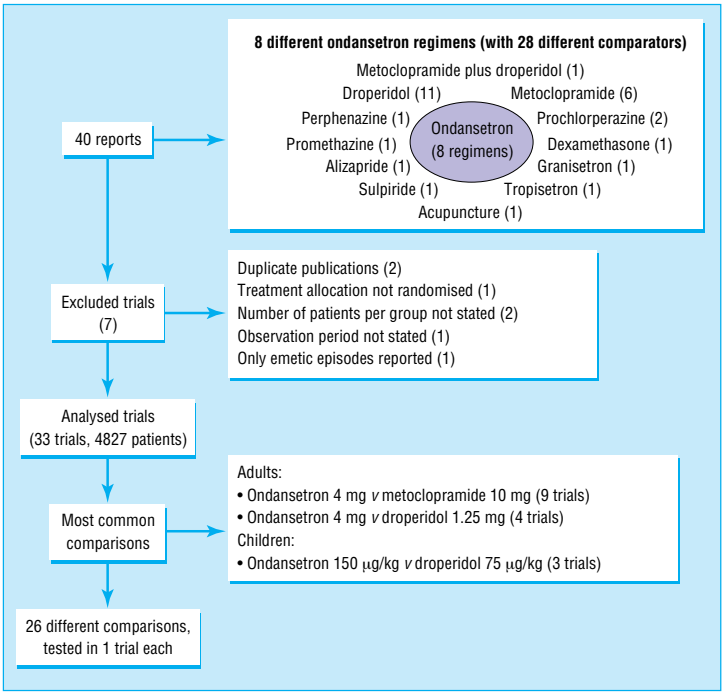

Fig 1 Data on included and excluded trials

Comment

Many different ondansetron regimens were compared with many different antiemetic controls. This shows uncertainty, both about which regimen of ondansetron is the best, and about which established antiemetic should be used as the gold standard active control. A gold standard is needed to establish the relative efficacy and harm of a new treatment, and that gold standard should be the most effective and the least harmful.[46] There is still no such standard for prevention of postoperative nausea and vomiting. Only a minority of these trials used the optimal intravenous dose of ondansetron—namely, 8 mg.[9] We do not know the most effective dose for any other antiemetic.

Underlying variation in likelihood of nausea and vomiting (control event rate)

Evidence

Nineteen trials included a placebo arm[14 16 18 20–24 27 28 31–35 38 41 43 44] and two trials included a "no treatment" arm.[15 30] The median number of patients in ondansetron groups in these trials was 32 (10 to 465). The median quality score was 2 (1 to 5). Graphically, the comparison of any dose of ondansetron with placebo in the trials that included a placebo arm suggested superiority of ondansetron (fig 2 (top)). Nausea or vomiting rates in placebo groups varied between 1% and 80% for outcomes up to six hours after surgery, and between 10% and 96% for outcomes up to 48 hours after.

Comment

The extraordinary variation in the incidence of nausea and vomiting that was shown in placebo controlled trials (10% to 96%) is a big problem. If some patients do not vomit then prophylactic antiemetic efficacy cannot be shown. If everybody vomits then prophylactic antiemetic efficacy will be exaggerated. The variation is not an artefact of trial design or measurements and it is not confined to antiemetics.[47] Reasons for this phenomenon are poorly understood.[48] It may be due partly to random variation in small trials.[49]

Equivalence

Evidence

Ondansetron was no better than placebo in 19 of the 52 possible comparisons with all outcomes.[14 18 20 23 24 27 30 32 33 35 44] The median number of patients in ondansetron groups in the 11 trials that failed to show a difference between ondansetron and placebo in at least one comparison was 30 (10 to 83).

Comment

Many of the trials showed no difference between ondansetron and its active control—that is, they showed equivalence. Failure to show a difference between two treatments, however, does not necessarily mean equivalence.[50] The only conclusions that can be drawn if both drugs show similar efficacy are: *(a)* both

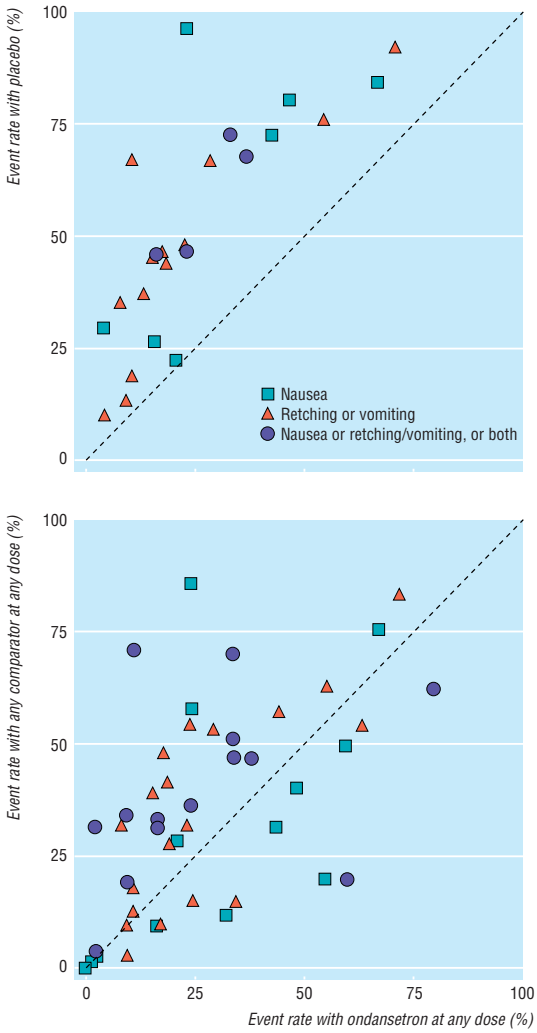

Fig 2 Event rate scattergrams showing cumulative event rates up to 48 hours after surgery from (top) placebo and "no treatment" controlled trials and (bottom) active controlled trials (dotted line represents equality)

Table 1 Meta-analysis of ondansetron (combined regimens) *v* droperidol (combined regimens) and metoclopramide (combined regimens) in adults and children, showing data on efficacy

Prevention of:	No of patients with event/total No receiving drug: Ondansetron	Comparator	Relative benefit (95% CI)	No needed to treat (95% CI)	References
Ondansetron 4-8 mg *v* droperidol 0.25-3.75 mg (adults)					
Early nausea	112/136	108/137	1.04 (0.93 to 1.16)	28 (7.8 to ∞)	12, 35, 40, 43
Early vomiting	218/251	210/255	1.05 (0.98 to 1.13)	22 (9.3 to ∞)	12, 32, 33, 35, 40, 43
Early any event	47/78	58/75	0.78 (0.63 to 0.97)	–5.9 (–3.2 to –38)	13, 21
Late nausea	117/169	109/162	0.98 (0.72 to 1.33)*	51 (8.3 to ∞)	13, 23-25, 33, 35
Late vomiting	150/242	132/241	1.05 (0.89 to 1.23)*	15 (6.5 to ∞)	13, 23-25, 32, 33, 35
Late any event	79/122	87/118	1.06 (0.84 to 1.36)*	–11 (–4.9 to ∞)	13, 23, 25, 39
Ondansetron 4-8 mg *v* metoclopramide 10 mg (adults)					
Early nausea	122/163	96/163	1.20 (0.91 to 1.57)*	6.3 (3.8 to 17)	12, 17, 30, 36, 37
Early vomiting	122/140	87/137	1.13 (0.94 to 1.36)*	5.6 (3.9 to 9.9)	12, 17, 30, 33, 36, 37
Early any event	48/83	40/82	1.19 (0.89 to 1.59)	11 (4.1 to ∞)	17, 21
Late nausea	248/592	199/585	1.23 (1.08 to 1.41)	12.7 (7.5 to 43)	15, 17, 30, 33, 41
Late vomiting	289/577	233/570	1.25 (0.96 to 1.63)*	10.9 (6.7 to 29)	17, 18, 30, 33, 41
Late any event	100/143	72/134	1.32 (0.96 to 1.80)*	6.2 (3.6 to 20)	15, 17, 28, 31
Ondansetron 5 mg/m^2, 100-150 μg/kg *v* droperidol 40-75 μg/kg (children)					
Early vomiting	230/265	170/248	1.25 (1.14 to 1.37)	5.7 (4.1 to 9.3)	16, 20, 22, 26, 42
Late vomiting	196/284	157/275	1.21 (1.07 to 1.37)	8.4 (5.0 to 25)	19, 20, 29, 34, 42
Ondansetron 5 mg/m^2, 150 μg/kg *v* metoclopramide 0.12-0.5 mg/kg (children)					
Early vomiting	98/111	67/109	1.34 (0.86 to 2.10)*	3.7 (2.6 to 6.3)	14, 22, 38
Late vomiting	36/50	23/50	1.57 (1.11 to 2.22)	3.9 (2.2 to 14)	29, 38

Early=0-6 hours after surgery; late=0-48 hours after. Vomiting includes retching. Any event=nausea or vomiting, or nausea and vomiting.
∞=absence of a significant difference between treatments.
*Random effects model (heterogeneity P>0.1); otherwise fixed effect model.
If point estimate for number needed to treat is positive, ondansetron is more efficacious than comparator.
If point estimate for number needed to treat is negative, comparator is more efficacious than ondansetron.

drugs are effective to a similar degree; *(b)* both drugs are equally ineffective; or *(c)* the trial design was inadequate—for example, too small—to show the real difference between the two treatments. In equivalence trials we need to know that both treatments were indeed effective in an A versus B comparison of two active drugs.[50] To meet this criterion we need to know the extent of the placebo response and that it does not vary. Otherwise a result seeming to show no difference between A and B could mean that both A and B were effective or that neither A nor B was effective. Only in trials with proved internal sensitivity (a positive dose-response or an active drug is better than a placebo) can we draw correct conclusions about equivalence. One trial produced a remarkable result—ondansetron seemed to be equivalent to placebo but significantly better than the active comparator.[14] Only because there was a placebo group was the obvious lack of internal sensitivity detectable.

Can we interpret these active comparisons?

Evidence of efficacy

The event rate scatter suggested little difference between any ondansetron regimen and any dose of any comparator (fig 2 (bottom)). With both ondansetron and comparators early event rates ranged from 0% to about 60% and late event rates from 0% to about 80%.

As in the original meta-analysis of placebo controlled ondansetron trials[9] we intended to combine clinically homogeneous efficacy data—namely, similar active drug and comparator, similar dose and route of administration, similar emetic events, and similar observation periods. We could not do this here for more than two trials at a time, except for the comparison of ondansetron 4 mg with metoclopramide 10 mg. We therefore combined data from different doses of ondansetron and compared these data with combined data from different doses of any given comparator, but only if the trials at least reported similar emetic events and similar observation periods. The same was done for adverse effects. Only one active group was considered in trials with different doses of ondansetron or comparators.[28 39 43] The major results of the meta-analysis—that is, comparisons between ondansetron and either droperidol or metoclopramide—are shown in tables 1 and 2.

Ondansetron was also compared with nine other antiemetics in one trial each. During the first six hours after surgery there was no difference between ondansetron 4 mg and perphenazine 5 mg,[21] promethazine 1 mg/kg,[30] or dexamethasone 8 mg.[27] Similarly, ondansetron 60 μg/kg was not different from prochlorperazine 0.1 mg/kg or 0.2 mg/kg.[44] In the first 48 hours after surgery, ondansetron 60 μg/kg was significantly better than intravenous prochlorperazine 0.1 mg/kg (number needed to treat 6 (95% confidence interval 3.3 to 39)) and intramuscular prochlorperazine 0.2 mg/kg

Table 2 Meta-analysis of ondansetron (combined regimens) and droperidol (combined regimens) in trials with a placebo arm showing data on harm

Adverse drug reactions	No of patients with adverse reaction/total No receiving drug	Relative risk (95% CI)	No needed to harm (95% CI)	References
Restlessness, agitation, or fear/anguish				
Droperidol 1.25-3.75 mg	14/169	2.31 (0.92 to 5.80)	21 (10 to ∞)	21, 32, 35
Placebo	6/170			
Headache				
Ondansetron 4-8 mg, 60 μg/kg	50/219	1.46 (0.98 to 2.16)	14.8 (7.0 to ∞)	18, 27, 32, 35, 44
Placebo	32/199			

∞=absence of a significant difference between treatments.

(number needed to treat 6.8 (3.5 to 114)) in preventing any emetic event,[44] and ondansetron 8 mg was significantly more efficacious than sulpiride 50 mg (number needed to treat 4 (2 to 328)) in preventing any emetic event.[39] During the same time period there was no difference between ondansetron 4 mg and promethazine 1 mg/kg,[30] dexamethasone 8 mg,[27] tropisetron 5 mg,[31] or granisetron 3 mg,[31] and ondansetron 8 mg was no better than alizapride 50 mg.[15]

Comment on efficacy

The scattergram suggests qualitatively that ondansetron was no better than droperidol, perphenazine, prochlorperazine, promethazine, alizapride, sulpiride, tropisetron, granisetron, or dexamethasone (fig 2 (bottom). Ondansetron seemed to be more effective than metoclopramide (table 1), but the clinical importance of any difference is doubtful. At least six adult patients would have to be treated with ondansetron 4 mg or 8 mg to prevent one patient who would have vomited or been nauseous had he or she received metoclopramide 10 mg from vomiting or being nauseous in the first six hours after surgery. Unlike ondansetron,[9] the optimal dose of metoclopramide is still not known; 10 mg may have been too low a dose. Before a sensible comparison between ondansetron and metoclopramide can be made, the optimal dose of metoclopramide needs to be established. This is true for all the other comparators. Ondansetron's antivomiting effect compared with droperidol or metoclopramide seemed to be more pronounced in children than in adults. Reasons for this are unknown. The effect on nausea was not reported in paediatric trials.

Evidence of adverse effects

Possible drug related adverse effects were reported in 19 trials, in 11 of them in dichotomous form. In three placebo controlled trials postoperative anxiety, restlessness, or agitation was described in patients treated with droperidol, and in six placebo controlled trials postoperative headache was reported in patients receiving ondansetron (table 2). No extrapyramidal symptoms were reported in any trial.

In trials without a placebo arm adverse effects described in relation to ondansetron were flush and urticaria in three patients[12 36] and nodal rhythm in three patients.[34] Ten patients (0.2% of all patients) were admitted or readmitted to hospital because of excessive or prolonged postoperative nausea and vomiting (five children had received droperidol 50 µg/kg or 75 µg/kg,[20 22 42] two children ondansetron 150 µg/kg,[42] and one adult metoclopramide 10 mg,[28] and in two adults the treatment was not specified[33]).

Comment on adverse effects

Only placebo controlled trials enabled us to draw meaningful conclusions on drug related harm. The widely held view that use of droperidol is limited by adverse reactions was not supported.

Discussion

Arguments against the use of placebos include the general one that placebos are unethical[51] and the specific one that, because ondansetron has proved more effective than placebo, we do not need further placebo controlled trials and what we need is to determine ondansetron's clinical role, through comparisons with existing antiemetics (active controlled trials).[6 52] These 33 active controlled ondansetron trials provided the opportunity to check whether these trials alone—that is, in the absence of any placebo controlled trials—would have been adequate to determine relative efficacy and likelihood of harm. They would not: three major shortcomings were discovered (fig 3).

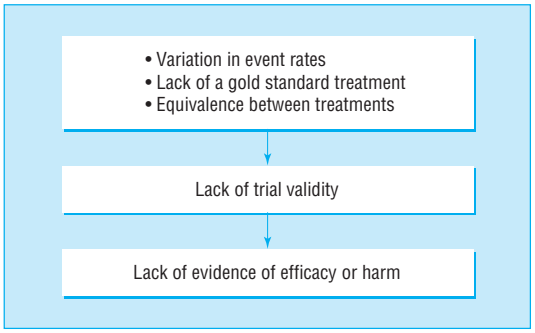

Fig 3 Potential shortcomings of active controlled trials

Why we need placebos

In this review 36% of all trials did not include a placebo (or a no treatment) group. We do not know if these trials provide valid data because we do not know the event rates without antiemetic prophylaxis in these study populations, and because they lack an index of internal sensitivity. Interpretation of these trials is, therefore, impossible. It is likely that the use of placebos would have avoided most of the drawbacks in these active controlled trials. Moreover, placebo controls would have enabled estimation of efficacy and likelihood of harm for a variety of regimens of the new antiemetic ondansetron, compared with a standard comparator, a placebo. Models for estimation of an intervention's relative efficacy without direct comparisons have been proposed.[47 53]

The problems of variation in control event rate (underlying variation in likelihood of an event) and lack of gold standard comparator justify the use of placebos as an index of a trial's validity. This is true in many therapeutic areas, not just in antiemetic trials. In a qualitative systematic review on the analgesic efficacy of intra-articular morphine, for example, only a minority of retrieved trials could be regarded as valid assays with proved internal sensitivity.[54]

Ethical argument against placebos

Why then, despite potential drawbacks, did 12 trials in this review not include a placebo arm? In some trials placebos were omitted on ethical grounds.[12] This is illogical because studies destined to produce unreliable results should themselves be considered unethical.[3 55] The use of placebos is one of the thorniest issues facing clinical researchers today.[56] It has been claimed that if an arm of a study is known to be less beneficial or more harmful than alternatives, investigators must protect patients from that additional known risk[4] and that assignment of patients to placebo treatment when an effective treatment already exists is therefore unethi-

cal.[1] Such general statements may be misinterpreted. This systematic review shows clearly that we do not know which treatment is most beneficial or least harmful in postoperative nausea and vomiting. Such systematic reviews could provide ethics committees with the necessary information to question the ethics of a trial design.[7 8 57]

Ethical acceptability of placebos

The important question then is whether the use of placebos in trials of postoperative nausea and vomiting is unethical. Use of a placebo would be unethical if it meant that life was endangered or symptoms were made intolerable.[3] These trials are designed to establish the number of patients who do not develop nausea or vomiting after surgery.[58] Antiemetic "rescue" treatment would be needed both for the patients who were denied active prophylaxis—that is, who received a placebo and who do vomit—and for the patients receiving active prophylaxis in whom that intervention failed. No evidence exists that treatment of established postoperative nausea and vomiting is less efficacious than prevention.[10] Although postoperative nausea and vomiting may induce serious complications,[59] it is most often a minor adverse effect of anaesthesia and surgery; it does not become chronic; and almost never kills. The use of placebos in trials investigating postoperative nausea and vomiting may therefore be justified. Informed consent and adequate rescue antiemetic treatment are of course necessary to ensure ethical legitimacy.

Conclusions

This set of trials does not support the general argument that we should eschew placebo controlled trials in favour of direct comparisons alone.[1 4–6 51 52] These trials failed to improve our understanding of the therapeutic role of prophylactic ondansetron in prevention of postoperative nausea and vomiting, and that failure was entirely predictable from their equivalence design. The ethical acceptability of placebos is likely to be dependent on the setting. In situations such as postoperative nausea and vomiting that lack a gold standard treatment and where the likelihood of an outcome is expected to vary widely, trial designs without placebo controls are unlikely to yield sensible results. We contend that the ethics of recruiting patients into trials that cannot yield sensible results is dubious.

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Competing interest: None.

1 Rothman KJ, Michels KB. The continuing unethical use of placebo controls. *N Engl J Med* 1994;331:394-8.
2 Gilbert EM, Packer EM. Letter to editor. *N Engl J Med* 1995;332:61.
3 Collier J. Confusion over use of placebos in clinical trials. *BMJ* 1995;311:821-2.
4 Citron ML. Placebos and principles: a trial of ondansetron. *Ann Intern Med* 1993;118:470-1.
5 Markman M. When regulatory requirements conflict with ethical study design: the case of oral ondansetron. *Cancer Invest* 1994;12:654-6.
6 Aspinall RL, Goodman NW. Denial of effective treatment and poor quality of clinical information in placebo controlled trials of ondansetron for postoperative nausea and vomiting: a review of published trials. *BMJ* 1995;311:844-6.
7 Stone PG, Blogg CE. National research ethics committee is needed. *BMJ* 1997;315:60-1.
8 Talbot D, Reynolds DJM. Local research ethics committees. *BMJ* 1997;315:1464.
9 Tramèr MR, Reynolds DJM, Moore RA, McQuay HJ. Efficacy, dose-response, and safety of ondansetron in prevention of postoperative nausea and vomiting: a quantitative systematic review of randomised placebo-controlled trials. *Anesthesiology* 1997;87:1277-89.
10 Tramèr MR, Moore RA, Reynolds DJM, McQuay HJ. A quantitative systematic review of ondansetron in treatment of established postoperative nausea and vomiting. *BMJ* 1997;314:1088-92.
11 Eriksson H, Korttila K. Recovery profile after desflurane with or without ondansetron compared with propofol in patients undergoing outpatient gynecological laparoscopy. *Anesth Analg* 1996;82:533-8.
12 Alon E, Himmelseher S. Ondansetron in the treatment of postoperative vomiting: a randomized, double-blind comparison with droperidol and metoclopramide. *Anesth Analg* 1992;75:561-5.
13 Alon E, Biro P, Lenzlinger PM, Atanassoff PG. Ondansetron als Prophylaxe für postoperative Übelkeit und Erbrechen. Eine prospektive, randomisierte Doppelblind-Vergleichsstudie mit Droperidol. *Anaesthesist* 1994;43:500-3.
14 Calamandrei M, Andreuccetti T, Crescioli M, Messeri A, Sarti A, Sestini G, et al. Effets de l'ondansétron et du métoclopramide sur les nausées et vomissements postopératoires après anesthésie péridurale chez l'enfant. *Cah Anesth* 1994;42:19-23.
15 Cantanna R, Morini M, Lopez T, Mariana A. Efficacia di un 5HT3 antagonista nella prevenzione del vomito postoperatorio. *Minerva Anestesiol* 1994;60(suppl 1):109-11.
16 Cetica P, Di Filippo A, Rizzo L, Benvenuti S, Novelli GP. Prevenzione della nausea e del vomito postoperatorio nella chirurgia strabologica in etá pediatrica. *Minerva Anestesiol* 1994;60(suppl 1):41-3.
17 Chen PP, Chui PT, Gin T. Comparison of ondansetron and metoclopramide for the prevention of post-operative nausea and vomiting after major gynaecological surgery. *Eur J Anaesth* 1996;13:485-91.
18 D'Ari M, Caccia A, Lo Sapio D, Verde A, Badolato A, Chiefari M. Ondansetron vs metoclopramide e placebo nella prevenzione della nausea e del vomito postoperatorio. *Minerva Anestesiol* 1994;60(suppl 1): 85-7.
19 Davis A, Krige S, Moyes D. A double-blind randomized prospective study comparing ondansetron with droperidol in the prevention of emesis following strabismus surgery. *Anaesth Intens Care* 1995;23:438-43.
20 Davis PJ, McGowan FX Jr, Landsman I, Maloney K, Hoffmann P. Effect of antiemetic therapy on recovery and hospital discharge time. A double-blind assessment of ondansetron, droperidol, and placebo in pediatric patients undergoing ambulatory surgery. *Anesthesiology* 1995;83:956-60.
21 Desilva PH, Darvish AH, McDonald SM, Cronin MK, Clark K. The efficacy of prophylactic ondansetron, droperidol, perphenazine, and metoclopramide in the prevention of nausea and vomiting after major gynecologic surgery. *Anesth Analg* 1995;81:139-43.
22 Furst SR, Rodarte A. Prophylactic antiemetic treatment with ondansetron in children undergoing tonsillectomy. *Anesthesiology* 1994;81:799-803.
23 Gan TJ, Collis R, Hetreed M. Double-blind comparison of ondansetron, droperidol and saline in the prevention of postoperative nausea and vomiting. *Br J Anaesth* 1994;72:544-7.
24 Giorgi L, Cavuta M, Novelli GP. Ondansetron nella prevenzione della nausea e vomito postoperatorio nella chirurgia dell'orecchio medio. *Minerva Anestesiol* 1994;60(suppl 1):73-5.
25 Grond S, Lynch J, Diefenbach C, Altrock K, Lehmann KA. Comparison of ondansetron and droperidol in the prevention of nausea and vomiting after inpatient minor gynecologic surgery. *Anesth Analg* 1995;81:603-7.
26 Litman RS, Wu CL, Lee A, Griswold JD, Voisine R, Marshall C. Prevention of emesis after strabismus repair in children: a prospective, double-blinded, randomized comparison of droperidol versus ondansetron. *J Clin Anesth* 1995;7:58-62.
27 Lopez-Olaondo L, Carrascosa F, Pueyo FJ, Monedero P, Busto N, Saez A. Combination of ondansetron and dexamethasone in the prophylaxis of postoperative nausea and vomiting. *Br J Anaesth* 1996;76:835-40.
28 Malins AF, Field JM, Nesling PM, Cooper GM. Nausea and vomiting after gynaecological laparoscopy: comparison of premedication with oral ondansetron, metoclopramide and placebo. *Br J Anaesth* 1994;72:231-3.
29 Maltepe F, Günerli A, Sagiroglu E, Kuvaki B, Mavioglu O. Çocuklarda postoperatif emezisin profilaksisinde dehidrobenzperidol metklopramid ve ondansetron'un karsilastirilmasi. *Türk Anest Rean Cem* 1996;24:180-3.
30 Modesti C, Rodola F, Caricato A. La profilassi dell'emesi post-operatoria in ortopedia e traumatologia: valutazione comparative di ondansetron, metoclopramide e prometazina. *Acta Anaesth Ital* 1995;46:73-8.
31 Naguib M, El Bakry AK, Khoshim MHB, Channa AB, El Gammal M, El Gammal K, et al. Prophylactic antiemetic therapy with ondansetron, tropisetron, granisetron and metoclopramide in patients undergoing laparoscopic cholecystectomy: A randomized, double-blind comparison with placebo. *Can J Anaesth* 1996;43:226-31.
32 Paech MJ, Pavy TJG, Evans SF. Single-dose prophylaxis for postoperative nausea and vomiting after major abdominal surgery: ondansetron versus droperidol. *Anaesth Intens Care* 1995;23:548-54.
33 Paxton LD, McKay AC, Mirakhur RK. Prevention of nausea and vomiting after day case gynaecological laparoscopy. A comparison of ondansetron, droperidol, metoclopramide and placebo. *Anaesthesia* 1995;50:403-6.
34 Paxton D, Taylor RH, Gallagher TM, Crean PM. Postoperative emesis following otoplasty in children. *Anaesthesia* 1995;50:1083-5.
35 Pueyo FJ, Carrascosa F, Lopez L, Iribarren MJ, Garcia Pedrajas F, Saez A. Combination of ondansetron and droperidol in the prophylaxis of postoperative nausea and vomiting. *Anesth Analg* 1996;83:117-22.
36 Raphael JH, Norton AC. Antiemetic efficacy of prophylactic ondansetron in laparoscopic surgery: randomized, double-blind comparison with metoclopramide. *Br J Anaesth* 1993;71:845-8.

37 Roccatagliata DC, Boutseros A, Fuccaro P, Mazzarello MR, Sburlati E. Ondansetron versus metoclopramide nella prevenzione del vomito post-operatorio nelle IVG. *Minerva Anestesiol* 1994;60(suppl 1):95-8.
38 Rose JB, Martin TM, Corddry DH, Zagnoev M, Kettrick RG. Ondansetron reduces the incidence and severity of poststrabismus vomiting in children. *Anesth Analg* 1994;79:486-9.
39 Rossi AK, Lamarca S, Scanni E, Corcione A, Grandis V, Mastronardi P. Valutazione comparative dell'ondansetron come antiemetico nella paziente ostetrica. *Minerva Anestesiol* 1994;60(suppl 1):99-101.
40 Rowe L, de Boer F, Crocker S. Nausea and vomiting following day case gynaecological surgery: a comparison of ondansetron with droperidol as prophylaxis. *J One-Day Surg* 1995;winter:9-10.
41 Rust M. Intravenöse Gabe von Ondansetron vs Metoclopramid zur Prophylaxe von postoperativer Übelkeit und Erbrechen. *Anaesthesist* 1995;44:288-90.
42 Splinter WM, Rhine EJ, Roberts DW, Baxter MRN, Gould HM, Hall LE, et al. Ondansetron is a better prophylactic antiemetic than droperidol for tonsillectomy in children. *Can J Anaesth* 1995;42:848-51.
43 Tang J, Watcha MF, White PF. A comparison of costs and efficacy of ondansetron and droperidol as prophylactic antiemetic therapy for elective outpatient gynecologic procedures. *Anesth Analg* 1996;83:304-13.
44 Van den Berg AA. Comparison of ondansetron and prochlorperazine for the prevention of nausea and vomiting after adenotonsillectomy. *Br J Anaesth* 1996;76:449-51.
45 Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJM, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996;17:1-12.
46 Eddy DM. Principles for making difficult decisions in difficult times. *JAMA* 1994;271:1792-8.
47 McQuay HJ, Tramèr M, Nye BA, Carroll D, Wiffen PJ, Moore RA. A systematic review of antidepressants in neuropathic pain. *Pain* 1996;68:217-27.
48 Ernst E, Resch KL. Concept of true and perceived placebo effects. *BMJ* 1995;311:551-3.
49 Moore RA, Gavaghan D, Tramèr MR, Collins S, McQuay HJ. Size is everything—large amounts of information are needed to overcome random effects in estimating direction and magnitude of treatment effects. *Pain* (in press).
50 Jones B, Jarvis P, Lewis JA, Ebbutt AF. Trials to assess equivalence: the importance of rigorous methods. *BMJ* 1996;313:36-9.
51 Rothman KJ. Placebo mania. *BMJ* 1996;313:3-4.
52 Lewis MA, Fishman DA. Ondansetron for postoperative nausea and vomiting: decisions in the absence of comparative trials. *Am J Hosp Pharm* 1994;51:524-5.
53 Tramèr M, Moore A, McQuay H. Meta-analytic comparison of prophylactic antiemetic efficacy for postoperative nausea and vomiting: propofol anaesthesia vs omitting nitrous oxide vs a total i.v. anaesthesia with propofol. *Br J Anaesth* 1997;78:256-259.
54 Kalso E, Tramèr MR, Carroll D, McQuay HJ, Moore RA. Pain relief from intra-articular morphine after knee surgery: a qualitative systematic review. *Pain* 1997;71:127-34.
55 McQuay H, Moore A. Placebos are essential when extent and variability of placebo response are unknown. *BMJ* 1996;313:1008.
56 Taubes G. Use of placebo controls in clinical trials disputed. *Science* 1995;267:25-6.
57 Savulescu J, Chalmers I, Blunt J. Are research ethics committees behaving unethically? Some suggestions for improving performance and accountability. *BMJ* 1996;313:1390-3.
58 Korttila K. The study of postoperative nausea and vomiting. *Br J Anaesth* 1992;69(suppl 1):20-3S.
59 Bremner WGM, Kumar CM. Delayed surgical emphysema, pneumomediastinum and bilateral pneumothoraces after postoperative vomiting. *Br J Anaesth* 1993;71:296-7.

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Action on clinical audit: progress report 2

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In the first progress report on "Action on clinical audit" I described how West Middlesex University Hospital NHS Trust is looking at the role of stakeholder ownership in clinical audit.[1] This second report follows the progress of the Essex Rivers Healthcare Trust and its use of open space technology for redesigning services for children with diabetes.

Summary points

- The Essex Rivers Healthcare Trust used the action on clinical audit project to look at local services for children with diabetes
- The local team collected information on where diabetic children lived and attended for care, and on admissions policy
- An open space technology workshop identified key elements of a service for diabetic children
- At a follow up workshop key tasks were proposed and volunteers sought to take responsibility for them

Setting the scene

Essex Rivers Healthcare Trust is a combined acute and community trust with a district general hospital in the city of Colchester and community hospitals in Clacton, Harwich, and Halstead. The trust has set up its own clinical effectiveness programme, and became interested in the action on clinical audit project partly as an offshoot of this. The feeling from some clinicians within the trust is that audit is struggling, and while many audit projects are conducted with worthwhile aims in mind, the end product is all too often "a report that ends up in a drawer."

What the trust hopes to achieve

The Essex Rivers' local action team—Charles Bodmer (consultant physician and specialist in diabetes), Anne Ferris (senior nurse in gynaecology and paediatrics), and Chris Howes (clinical audit officer)—has chosen to use the project to look at local paediatric services for patients with diabetes. Until now, the district's service has been provided by three general paediatricians in different locations, and all children with newly diagnosed diabetes have been admitted to hospital. The St Vincent's declaration, the 1989 international agreement about standards for diabetes care, however, suggests that paediatric services should be coordinated by a dedicated paediatric diabetes care team led by a paediatrician with an interest in diabetes. Furthermore, the declaration suggests that it is unnecessary to admit every newly diagnosed child to hospital.

"We already knew that the service needed changing," says Bodmer, "but until now there's been real inertia over finding out what everyone's up to." So instead of using audit to simply review the existing service by collecting "measurements," the team is using audit to bring all the relevant stakeholders together to investigate what they would ideally like to see happening. This includes what services they would like to see provided, in addition to defining outcomes

EXHIBIT 336

Source: https://www.statista.com/statistics/265102/revenues-in-the-global-vaccine-market/

Global vaccine market revenues 2014-2020

Published by Matej Mikulic, Aug 9, 2019

The global vaccine market is showing some escalating growth and it is expected that it will reach total revenues of nearly 60 billion U.S. dollars by 2020. That would be almost double the size the market had back in 2014. Driver of the growth is the increase of various infectious diseases like influenza, swine flu, hepatitis, tuberculosis, diphtheria, Ebola, and meningococcal and pneumococcal diseases. Leading manufacturers of vaccines are big pharma companies like GlaxoSmithKline, Merck & Co., and Pfizer.

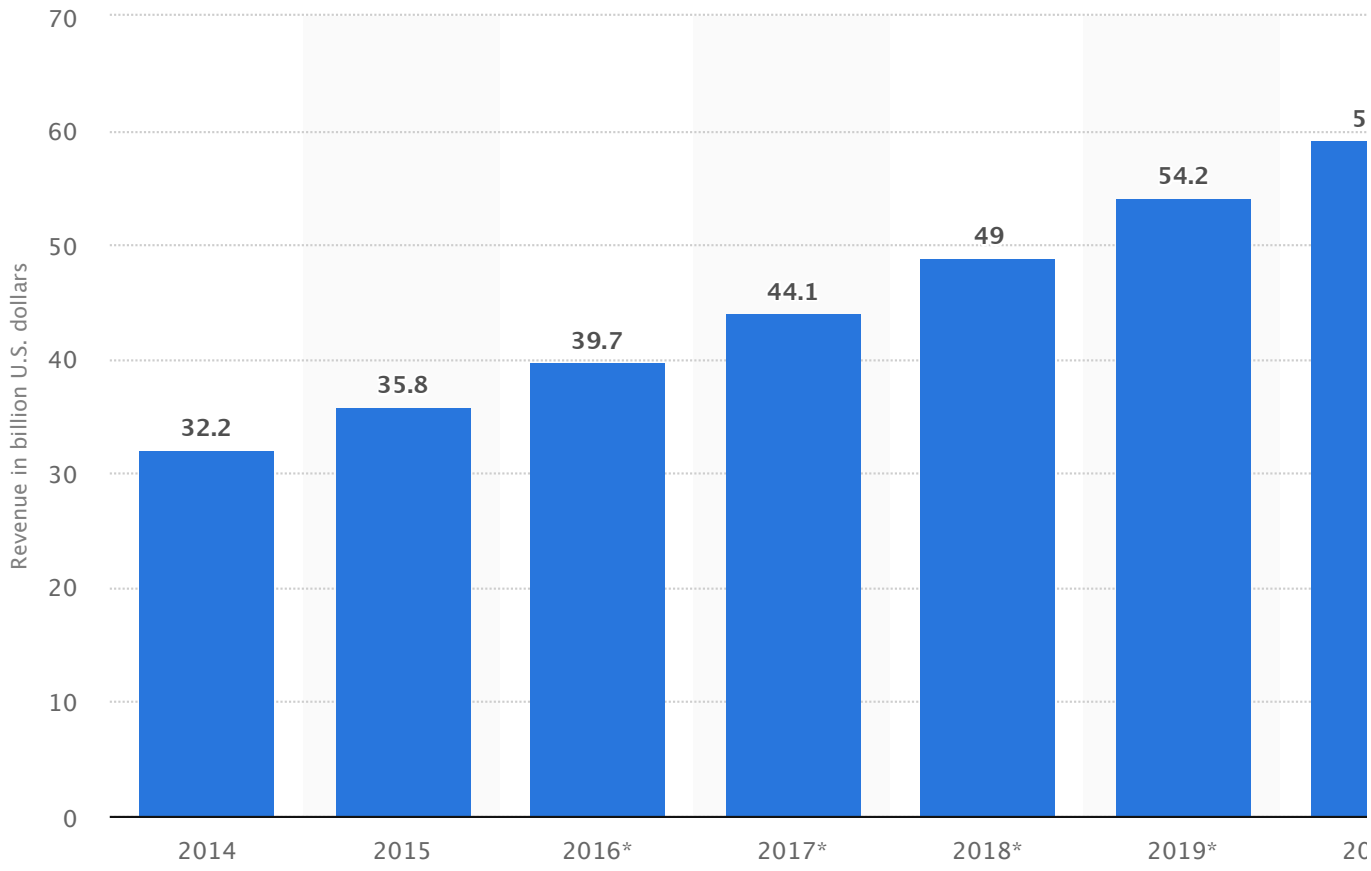
How vaccines work

The concept behind the functioning of vaccines - also known as immunizations - is relatively simple: inject a weakened form, or a fragment, of a disease to a person so the body learns to produce antibodies or to start other processes of immunity. As a result, the person's body is ready to fight the same infection next time. By this way, infectious diseases which once had high death rates like polio and smallpox have been nearly eradicated. Others like measles, mumps, and whooping cough, are mostly under control and larger epidemics have been successfully prevented. While some immunizations last lifelong, others have to be renewed to stay efficient. Despite the obvious success of immunizations and their huge role for public health, there are discussions about the safety and consequences of vaccines in the U.S. and many other countries.

The vaccine market

At this moment, Pfizer's Prevnar 13 is the world's leading vaccine product, generating around 5.7 billion U.S. dollars of revenue. Prevnar 13 is a vaccine for the prevention of invasive disease caused by 13 streptococcus pneumoniae strains and can be used in children and adults. The United States are the world's largest national market for vaccines, while North America is, accordingly, the largest regional market. The global vaccine market is largely dominated by vaccines which are administered intramuscularly. These vaccines make up over half of global revenues, while vaccines which are administered subcutaneously make up around one fifth of the market. Other common routes of administration are oral or intravenous.

Global vaccine market revenues from 2014 to 2020 (in billion U.S. dollars)*



Details: Worldwide; Zion Market Research; Statista estimates; 2016

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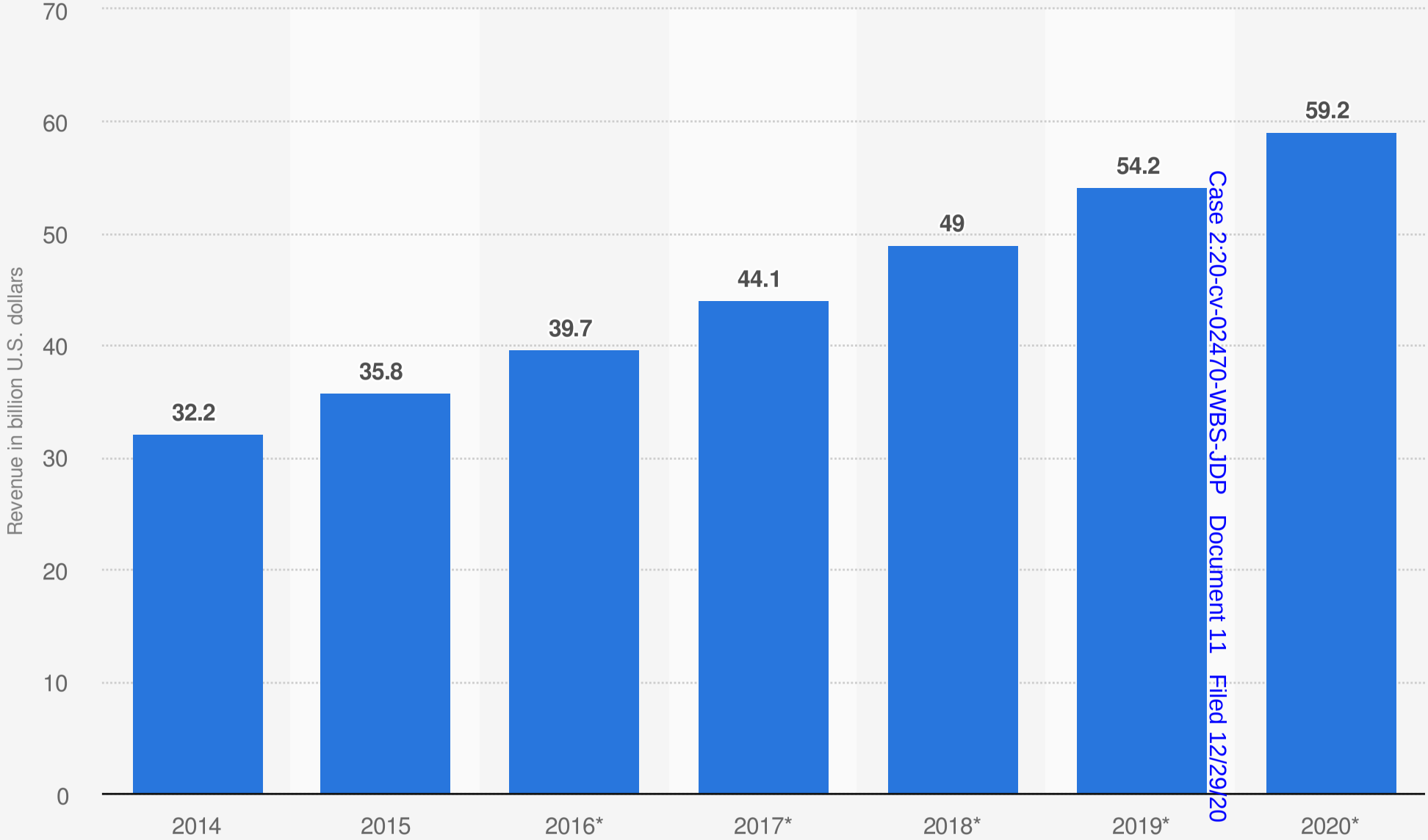
Sources
Zion Market Research; Statista estimates

Survey by
Zion Market Research; Statista estimates

Published by
Statista

Global vaccine market revenues from 2014 to 2020 (in billion U.S. dollars)*



Sources
Zion Market Research; Statista estimates
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Additional Information:
Worldwide; Zion Market Research; Statista estimates; 2016

EXHIBIT 337

Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

Vaccines for Children Program (VFC)

CDC Vaccine Price List

« Back to Vaccines For Children program
« Back to Immunization Managers Home page

Prices last reviewed/updated: June 1, 2020

Note 1: The CDC Vaccine Price Lists posted on this website provide current vaccine contract prices and list the private sector vaccine prices for general information. Contract prices are those for CDC vaccine contracts that are established for the purchase of vaccines by immunization programs that receive CDC immunization cooperative agreement funds (i.e., state health departments, certain large city immunization projects, and certain current and former U.S. territories). Private providers and private citizens cannot directly purchase vaccines through CDC contracts. Private sector prices are those reported by vaccine manufacturers annually to CDC. All questions regarding the private sector prices should be directed to the manufacturers.

Note 2: The CDC price list does not represent all possible routinely recommended vaccine presentations available to providers in the United States. The price list represents only those vaccine presentations available through CDC contracts.

- Vaccine Supply Information (for routine vaccines)
- Vaccine package insert information
  From this page, you can get to all of the vaccines licensed in the US. Each product page includes links to the prescribing information (package inserts).

As of 5-14-10, the CDC Vaccine Price List also shows the NDC code and contract number for each vaccine.

Archived Pages:

- Archived Prices list 2001-present

Pediatric/VFC Vaccine Price List

Vaccine	Brandname/ Tradename	NDC	Packaging	CDC Cost/ Dose	Private Sector Cost/ Dose	Contract End Date	Manufacturer	Contract Number
DTaP [1]	**Daptacel®**	**49281-0286-10**	10 pack – 1 dose vial	$18.546	$31.70	03/31/2021	Sanofi Pasteur	75D3012(
DTaP [1]	**Infanrix®**	**58160-0810-52**	10 pack – 1 dose syringe	$19.163	$24.71	03/31/2021	GlaxoSmithKline	75D3012(

DTaP-IPV [2]	**Quadracel™**	**49281-0562-10**	10 pack – 1 dose vial	$41.797	$54.63	03/31/2021	Sanofi Pasteur	75D3012(
DTaP-IPV [2]	**Kinrix®**	**58160-0812-11**	10 pack – 1 dose vial	$42.459	$52.14	03/31/2021	GlaxoSmithKline	75D3012(
		58160-0812-52	10 pack – 1 dose syringe	$42.459	$52.14			
DTaP-Hep B-IPV [4]	**Pediarix®**	**58160-0811-52**	10 pack – 1 dose syringe	$60.709	$79.15	03/31/2021	GlaxoSmithKline	75D3012(
DTaP-IP-HI [4]	**Pentacel®**	**49281-0510-05**	5 pack – 1 dose vial	$61.648	$99.83	03/31/2021	Sanofi Pasteur	75D3012(
e-IPV [5]	**IPOL®**	**49281-0860-10**	10 dose vial	$13.85	$35.17	03/31/2021	Sanofi Pasteur	75D3012(
Hepatitis A Pediatric [5]	**Vaqta®**	**00006-4095-02**	10 pack – 1 dose syringe	$20.61	$33.295	03/31/2021	Merck	75D3012(
Hepatitis A Pediatric [5]	**Havrix®**	**58160-0825-52**	10 pack – 1 dose syringe	$21.113	$32.89	03/31/2021	GlaxoSmithKline	75D3012(
Hepatitis A-Hepatitis B 18 only [3]	**Twinrix®**	**58160-0815-52**	10 pack – 1 dose syringe	$63.282	$104.00	03/31/2021	GlaxoSmithKline	75D3012(
Hepatitis B [5] Pediatric/Adolescent	**Engerix B®**	**58160-0820-52**	10 pack – 1 dose syringe	$15.38	$23.72	03/31/2021	GlaxoSmithKline	75D3012(
Hepatitis B [5] Pediatric/Adolescent	**Recombivax HB®**	**00006-4981-00**	10 pack – 1 dose vial	$12.53	$23.95	03/31/2021	Merck	75D3012(
Hib [5]	**PedvaxHIB®**	**00006-4897-00**	10 pack – 1 dose vial	$13.514	$26.233	03/31/2021	Merck	75D3012(
Hib [5]	**ActHIB®**	**49281-0545-03**	5 pack – 1 dose vial	$9.746	$17.14	03/31/2021	Sanofi Pasteur	75D3012(
Hib [5]	**Hiberix®**	**58160-0818-**	10 pack – 1 dose vial	$9.46	$10.85	03/31/2021	GlaxoSmithKline	75D3012(

		11						
HPV – Human Papillomavirus 9-valent [5]	**Gardasil®9**	**00006-4121-02**	10 pack – 1 dose syringe	$187.01	$227.931	03/31/2021	Merck	75D3012(
MENB – Meningococcal Group B [5]	**Trumenba®**	**00005-0100-10**	10 pack – 1 dose syringe	$114.36	$149.89	03/31/2021	Pfizer	75D3012(
MENB – Meningococcal Group B [5]	**Bexsero®**	**58160-0976-20**	10 pack – 1 dose syringe	$120.24	$170.75	03/31/2021	GlaxoSmithKline	75D3012(
Meningococcal Conjugate (Groups A, C, Y and W-135) [5]	**Menactra®**	**49281-0589-05**	5 pack – 1 dose vial	$96.232	$128.38	03/31/2021	Sanofi Pasteur	75D3012(
Meningococcal Conjugate (Groups A, C, Y and W-135) [5]	**Menveo®**	**58160-0955-09**	5 pack – 1 dose vial	$95.78	$130.75	03/31/2021	GlaxoSmithKline	75D3012(
Measles, Mumps and Rubella (MMR) [1]	**M-M-R®II**	**00006-4681-00**	10 pack – 1 dose vial	$21.708	$78.678	03/31/2021	Merck	75D3012(
MMR/Varicella [2]	**ProQuad®**	**00006-4171-00**	10 pack – 1 dose vial	$137.516	$224.937	03/31/2021	Merck	75D3012(
Pneumococcal 13-valent [5] (Pediatric)	**Prevnar 13™**	**00005-1971-02**	10 pack – 1 dose syringe	$143.82	$202.00	03/31/2021	Pfizer	75D3012(
Pneumococcal Polysaccharide (23 Valent)	**Pneumovax®23**	**00006-4837-03**	10 pack – 1 dose syringe	$59.12	$105.194	03/31/2021	Merck	75D3012(
Rotavirus, Live, Oral, Pentavalent [5]	**RotaTeq®**	**00006-4047-41**	10 pack – 1 dose tube	$71.88	$84.532	03/31/2021	Merck	75D3012(
		00006-4047-20	25 pack – 1 dose tube	$71.88	$84.531			
Rotavirus, Live, Oral, Oral [5]	**Rotarix®**	**58160-0854-52**	10 pack – 1 dose vial	$97.508	$120.95	03/31/2021	GlaxoSmithKline	75D3012(

Tetanus and Diphtheria Toxoids [3]	**Tenivac®**	**49281-0215-15**	10 pack – 1 dose syringe	$21.18	$34.80	03/31/2021	Sanofi Pasteur	75D3012(
		49281-0215-10	10 pack – 1 dose vial	$21.18	$34.80			
Tetanus and Diphtheria Toxoids [3]	**TDVAX™**	**13533-0131-01**	10 pack – 1 dose vial	$16.343	$25.876	03/31/2021	Grifols	75D3012(
Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis [1]	**Boostrix®**	**58160-0842-11**	10 pack – 1 dose vial	$33.14	$41.19	03/31/2021	GlaxoSmithKline	75D3012(
		58160-0842-52	10 pack – 1 dose syringe	$33.14	$41.19			
Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis [1]	**Adacel®**	**49281-0400-10**	10 pack – 1 dose vial	$32.634	$46.80	03/31/2021	Sanofi Pasteur	75D3012(
		49281-0400-20	5 pack – 1 dose syringe	$32.634	$46.80			
Varicella [5]	**Varivax®**	**00006-4827-00**	10 pack – 1 dose vial	$109.26	$135.725	03/31/2021	Merck	75D3012(

Adult Vaccine Price List

Vaccine	Brandname/ Tradename	NDC	Packaging	CDC Cost/ Dose	Private Sector Cost/ Dose	Contract End Date	Manufacturer	Contract Number
Hepatitis A Adult [5]	**Vaqta®**	**00006-4096-02**	10 pack – 1 dose syringe	$30.758	$69.580	6/30/2020	Merck	75D30119D0510
		00006-4841-41	10 pack – 1 dose vial	$30.758	$69.580			
Hepatitis A Adult [5]	**Havrix®**	**58160-0826-52**	10 pack – 1 dose syringe	$30.758	$69.56	6/30/2020	GlaxoSmithKline	75D30119D0510
Hepatitis A-	**Twinrix®**	**58160-**	10 pack – 1	$61.858	$104.00	6/30/2020	GlaxoSmithKline	75D30119D0510

Hepatitis B Adult [3]		**0815-52**	dose syringe					
Hepatitis B Adult [5]	**Heplisav-B™**	**43528-0003-05**	5 pack – 1 dose syringe	$69.75	$115.75	6/30/2020	Dynavax	75D30119D0510
Hepatitis B Adult [5]	**Engerix-B®**	**58160-0821-11**	10 pack – 1 dose vial	$29.733	$58.95	6/30/2020	GlaxoSmithKline	75D30119D0510
		58160-0821-52	10 pack – 1 dose syringe	$33.515	$58.95			
HPV-Human Papillomavirus 9 Valent [5]	**Gardasil®9**	**00006-4121-02**	10 pack – 1 dose syringe	$140.587	$227.931	6/30/2020	Merck	75D30119D0510
Measles, Mumps, & Rubella [1]	**M-M-R®II**	**00006-4681-00**	10 pack – 1 dose vial	$48.861	$78.678	6/30/2020	Merck	75D30119D0510
Meningococcal Conjugate (Groups A, C, Y and W-135) [5]	**Menveo®**	**58160-0955-09**	5 pack – 1 dose vial	$67.618	$130.75	6/30/2020	GlaxoSmithKline	75D30119D0510
Meningococcal Conjugate (Groups A, C, Y and W-135) [5]	**Menactra®**	**49281-0589-05**	5 pack – 1 dose vial	$75.066	$128.38	6/30/2020	Sanofi	75D30119D0510
MENB – Meningococcal Group B [5]	**Trumenba®**	**00005-0100-10**	10 pack – 1 dose syringe	$85.10	$149.89	6/30/2020	Pfizer	75D30119D0511
MENB – Meningococcal Group B [5]	**Bexsero®**	**58160-0976-20**	10 pack – 1 dose syringe	$103.938	$170.75	6/30/2020	GlaxoSmithKline	75D30119D0510
Pneumococcal 13-valent [5]	**Prevnar 13™**	**00005-1971-02**	10 pack – 1 dose syringe	$125.07	$202.00	6/30/2020	Pfizer	75D30119D0511
Pneumococcal Polysaccharide (23 Valent)	**Pneumovax®23**	**00006-4837-03**	10 pack – 1 dose syringe	$62.689	$105.194	6/30/2020	Merck	75D30119D0510
Tetanus and Diphtheria Toxoids [3]	**TDVAX™**	**13533-0131-01**	10 pack – 1 dose vial	$16.027	$25.876	6/30/2020	Grifols	75D30119D0510
Tetanus	**Adacel®**	**49281-**	10 pack – 1	$24.491	$46.80	6/30/2020	Sanofi	75D30119D0510

Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis [1]		**0400-10**	dose vial					
		49281-0400-20	5 pack – 1 dose syringe	$24.890	$46.80			
Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis [1]	**Boostrix®**	**58160-0842-11**	10 pack – 1 dose vial	$24.49	$41.19	6/30/2020	GlaxoSmithKline	75D30119D0510
		58160-0842-52	10 pack – 1 dose syringe	$25.10	$41.19			
Varicella [5]	**Varivax®**	**00006-4827-00**	10 pack – 1 dose vial	$82.039	$135.725	6/30/2020	Merck	75D30119D0510
Zoster Vaccine Recombinant, Adjuvanted	**Shingrix®**	**58160-0819-12**	1 pack – 1 dose vial	$101.510	$151.41	6/30/2020	GlaxoSmithKline	75D30119D0510
		58160-0823-11	10 pack – 1 dose vial	$102.316	$151.41			

Pediatric Influenza Vaccine Price List

Note: The table below reflects contracts for the 2020-2021 Pediatric Flu.

Vaccine	Brandname/ Tradename	NDC	Packaging	CDC Cost/ Dose	Private Sector Cost/ Dose	Contract End Date	Manufacturer	Contract Number
Influenza [5] (Age 6 months and older)	**Fluzone® Quadrivalent**	**49281-0633-15**	10 dose vial	$13.55	$16.939	2/28/2021	Sanofi Pasteur	75D30120D07115
Influenza [5] (Age 6 months and older)	**Fluzone® Quadrivalent**	**49281-0420-50**	10 pack – 1 dose syringe	$13.50	$18.144	2/28/2021	Sanofi Pasteur	75D30120D07115
		49281-0420-10	10 pack – 1 dose vial	$13.50	$18.144			
Influenza [5]	**Fluarix® Quadrivalent**	**58160-0885-**	10 pack- 1 dose syringe	$13.75	$17.30	2/28/2021	GlaxoSmithKline	75D30120D07111

(Age 6 months and older)		**52**						
Influenza [5] (Age 6 months and older)	**FluLaval Quadrivalent**	**19515-0816-52**	10 pack – 1 dose syringe	$13.75	$17.30	2/28/2021	GlaxoSmithKline	75D30120D07111
Influenza [5] (Age 4 years and older)	**Flucelvax® Quadrivalent**	**70461-0320-03**	10 pack – 1 dose syringe	$16.02	**$25.763**	2/28/2021	Seqirus USA, Inc	75D30120D07117
		70461-0420-10	10 dose vial	$15.15	**$24.419**			
Influenza [5] (Age 6 -35 months)	**Afluria® Quadrivalent**	**33332-0220-20**	10 pack – 1 dose syringe	$13.26	**$18.659**	2/28/2021	Seqirus USA, Inc	75D30120D07117
Influenza [5] (Age 36 months and older)	**Afluria® Quadrivalent**	**33332-0320-01**	10 pack – 1 dose syringe	$13.26	**$18.659**	2/28/2021	Seqirus USA, Inc	75D30120D07117
Influenza [5] (Age 6 months and older)	**Afluria® Quadrivalent**	**33332-0420-10**	10 dose vial	$12.45	**$17.257**	2/28/2021	Seqirus USA, Inc	75D30120D07117
Influenza [5] Live, Intranasal (Age 2-49 years)	**FluMist® Quadrivalent**	**66019-0307-10**	10 pack- 1 dose sprayer (Intranasal)	$18.88	$23.70	2/28/2021	AstraZeneca	75D30120D07113

Adult Influenza Vaccine Price List

Note: The table below reflects contracts for the 2020-2021 Adult Flu.

Vaccine	Brandname/ Tradename	NDC	Packaging	CDC Cost/ Dose	Private Sector Cost/ Dose	Contract End Date	Manufacturer	Contract Number
Influenza	**Fluzone®**	**49281-**	10 dose vial	$12.808	$16.939	2/28/2021	Sanofi Pasteur	75D30120D07114

[5] (Age 6 months and older)	**Quadrivalent**	**0633-15**						
Influenza [5] (Age 6 months and older)	**Fluzone® Quadrivalent**	**49281-0420-10**	10 pack – 1 dose vial	$13.705	$18.144	2/28/2021	Sanofi Pasteur	75D30120D07114
		49281-0420-50	10 pack – 1 dose syringe	$13.705	$18.144			
Influenza [5] (Age 6 months and older)	**Fluarix® Quadrivalent**	**58160-0885-52**	10 pack- 1 dose syringe	$12.45	$17.30	2/28/2021	GlaxoSmithKline	75D30120D07110
Influenza [5] (Age 6 months and older)	**FluLaval Quadrivalent**	**19515-0816-52**	10 pack- 1 dose syringe	$12.45	$17.30	2/28/2021	GlaxoSmithKline	75D30120D07110
Influenza [5] (Age 4 years and older)	**Flucelvax Quadrivalent**	**70461-0320-03**	10 pack – 1 dose syringe	$15.45	**$25.763**	2/28/2021	Seqirus USA, Inc	75D30120D07116
		70461-0420-10	10 dose vial	$14.44	**$24.419**			
Influenza [5] (Age 36 months and older)	**Afluria® Quadrivalent**	**33332-0320-01**	10 pack – 1 dose syringe	$12.48	**$18.659**	2/28/2021	Seqirus USA, Inc	75D30120D07116
Influenza [5] (Age 6 months and older)	**Afluria® Quadrivalent**	**33332-0420-10**	10 dose vial	$11.67	**$17.257**	2/28/2021	Seqirus USA, Inc	75D30120D07116
Influenza [5] Live, Intranasal (Age 2-49 years)	**FluMist® Quadrivalent**	**66019-0307-10**	10 pack- 1 dose sprayer (Intranasal)	$18.19	$23.70	2/28/2021	AstraZeneca	75D30120D07112

Footnotes

1. CDC Vaccine cost includes $2.25 per dose Federal Excise Tax
2. CDC Vaccine cost includes $3.00 per dose Federal Excise Tax
3. CDC Vaccine cost includes $1.50 per dose Federal Excise Tax
4. CDC Vaccine cost includes $3.75 per dose Federal Excise Tax
5. CDC Vaccine cost includes $0.75 per dose Federal Excise Tax

Page last reviewed: June 1, 2020
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EXHIBIT 338

Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

Vaccines & Immunizations

Immunization: The Basics

Definition of Terms

Let's start by defining several basic terms:

Immunity: Protection from an infectious disease. If you are immune to a disease, you can be exposed to it without becoming infected.

Vaccine: A product that stimulates a person's immune system to produce immunity to a specific disease, protecting the person from that disease. Vaccines are usually administered through needle injections, but can also be administered by mouth or sprayed into the nose.

Vaccination: The act of introducing a vaccine into the body to produce immunity to a specific disease.

Immunization: A process by which a person becomes protected against a disease through vaccination. This term is often used interchangeably with vaccination or inoculation.

Links to Basic Immunization Information

- Why immunize?
  Learn how getting vaccinated can protect your grandchildren, prevent epidemics, and eliminate diseases and their serious consequences.
- Brief overview of adult and childhood vaccine-preventable diseases and vaccines
  Read about the serious diseases that cause long-term illnesses, hospitalization, and even death, and which can be prevented by vaccines.
- 10 things a parent should know about immunizations
  Includes how many vaccine doses your child needs, the importance of keeping records, side effects, etc.
- How immunity works: types of immunity
  Learn the difference between the two basic types of immunity: active and passive.
- Common questions
  Find answers to common questions about immunization.
- What would happen if we stopped vaccinations?
  See how diseases that are rare today could once again become common—and deadly—if vaccination coverage does not continue at high levels.
- Life-cycle of an immunization program

See how a successful immunization program can lead to a temporary increase in disease. Follow the evolution of a disease, from a time when there was no vaccine untilit is eradicated.

Related Information and Materials

- The Parents' Guide to Childhood Immunizations
  68-page booklet introducing parents to all childhood diseases and the vaccines that can protect children from them
- The Vaccines for Children Program
  The Vaccines for Children (VFC) Program offers vaccines at no cost for eligible children through VFC-enrolled doctors. Find out if your child qualifies. Vaccinating on time means healthier children, families and communities.

Related Pages

Vaccines: The Basics

Making the Vaccine Decision

Ingredients of Vaccines

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EXHIBIT 339

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Herd immunity and herd effect: new insights and definitions

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"Words are not only vehicles to convey ideas but also their drivers."

Anon.

Abstract. The term herd immunity has been used by various authors to conform to different definitions. Earlier this situation had been identified but not corrected. We propose that it should have precise meaning for which purpose a new definition is offered: "the proportion of subjects with immunity in a given population". This definition dissociates herd immunity from the indirect protection observed in the unimmunised segment of a population in which a large proportion is immunised, for which the term 'herd effect' is proposed. It is defined as: "the reduction of infection or disease in the unimmunised segment as a result of immunising a proportion of the population". Herd immunity can be measured by testing a sample of the population for the presence of the chosen immune parameter. Herd effect can be measured by quantifying the decline in incidence in the unimmunised segment of a population in which an immunisation programme is instituted. Herd immunity applies to immunisation or infection, human to human transmitted or otherwise. On the other hand, herd effect applies to immunisation or other health interventions which reduce the probability of transmission, confined to infections transmitted human to human, directly or via vector. The induced herd immunity of a given vaccine exhibits geographic variation as it depends upon coverage and efficacy of the vaccine, both of which can vary geographically. Herd effect is determined by herd immunity as well as the force of transmission of the corresponding infection. Clear understanding of these phenomena and their relationships will help improve the design of effective and efficient immunisation programmes aimed at control, elimination or eradication of vaccine preventable infectious diseases.

Introduction

The term 'herd immunity' is increasingly frequently seen in recent literature on the epidemiology of infectious diseases and on their prevention and control by immunisation. This was found by Medline search (1992–1998) using the key words 'herd immunity' and 'herd effect'. While a large number of papers were found with the key word 'herd immunity', none was found with the key word 'herd effect'. A review of several papers has shown that 'herd immunity' is used by different authors for different ideas, such as a concept, a phenomenon or a measurable parameter. In this paper we offer new insights and suggest a new definition of the term 'herd immunity' and dissociate it from the indirect effect of immunisation of part of a population on the incidence of infection or disease in the unimmunised remainder, for which the term 'herd effect' is proposed and defined.

Definitions currently available for herd immunity

Three definitions of herd immunity given in recent text or reference books are quoted below. The emphasis of phrases is ours.

(1) "Herd immunity. The *resistance* of a group to attack by a disease because of the immunity of a large proportion of the members and the consequent lessening of the likelihood of an affected individual coming into contact with a susceptible individual" [1].

(2) "Herd immunity. It is not necessary to immunise every person in order to stop transmission of an infectious agent through a population. For those organisms dependent upon person-to-person transmission, there may be a definable *prevalence of immunity* in the population above which it becomes difficult for the organism to circulate and reach new susceptibles. This *prevalence* is called herd immunity" [2].

(3) "Herd immunity. It is well known that *not everyone in a population needs to be immunised to eliminate disease* – often referred to as herd immunity. This is because successful immunisation reduces the number of susceptibles in the population and this effectively reduces the efficiency with which the microbe is transmitted from one person to the other. This has the same effect on the incidence of infection as a reduction in the number of individuals in a population. The microbe cannot sustain itself and disease disappears at some level of vaccine

coverage that is less than 100%. On the other hand, coverage below that needed to prevent disease may have little impact on the total number of susceptibles – as has been predicted using mathematical models and verified, in the case of rubella, by observation. The implementation of immunisation programmes needs to be accompanied by case surveillance, in conjunction with analysis of appropriate serological samples both before and after the introduction of the vaccine. If such data are not carefully scrutinised, the consequence may be dire. For example, an immunisation programme may reduce the number of cases but at the same time may increase the average age at which the infection occurs. If the severity of disease increases with age of acquisition, as in rubella (the risk of an infected foetus in an infected woman) and polio (the risk of paralytic disease), an immunisation programme may be less useful than none at all'' [3].

The first definition considers herd immunity conceptually as the resistance to disease due to reduced risk of infection in a group of individuals as a result of a large proportion among them (but not all) being immune, not necessarily due only to immunisation [1]. The second definition clarifies that the term applies to the actual proportion of immunised individuals necessary to make it difficult for the organism to circulate and reach new susceptibles [2]. By this definition herd immunity is a threshold value of a measurable parameter (vaccination coverage) resulting in retardation of person-to-person transmission of an infection. Elimination of infection or disease is not required but only implied in this definition. How can we arrive at a definable level (proportion) of immunity when the end point is merely difficulty of transmission, which is not defined, hence not measurable? The third definition is closely similar to the first but it develops it further to a phenomenon providing the means to eliminate an infectious disease from a population when a proportion that is less than 100% is immunised [3]. Here the phenomenon has a measurable end point – that of the disappearance or elimination of disease in a group. In contrast to the second definition, here the actual input (immunisation coverage) necessary to achieve this measurable endpoint can be quantified. However it seems that the term herd immunity refers to the phenomenon of zero incidence in the unimmunised segment rather than the actual proportion immunised to achieve it [3]. The strict application of this definition requires the disappearance of disease due to immunisation coverage of less than 100% of susceptibles. This is a very rare event, exemplified by the global eradication of smallpox without immunising all susceptibles and the elimination of poliomyelitis due to wild polioviruses form North America when only some 65 to 70% immunisation coverage had been reached [4]. Interestingly, in the case of poliomyelitis, near 100% coverage of infants and additional annual repetitive vaccination of the same cohorts of susceptible children were necessary for 8–9 years to interrupt transmission in Brazil, showing that 'herd immunity' was not evident for the same vaccine against the same disease, but in a different region [5]. This clearly shows that herd immunity (by the third definition) is a function of not only immunisation but also the force of transmission of the pathogen. This definition is ambiguous about one aspect of the end point: is it zero disease or infection? The second definition clearly addresses infection while the first one focuses on infection and disease. Only the second definition clarifies that we are dealing with only person-to-person transmitted infectious diseases.

A new insight in the third definition is that in some cases it might be harmful to immunise a proportion and obtain only partial or incomplete 'herd immunity', since it might worsen the problem by delaying infection and not eliminating it, as in the case of maternal and foetal rubella [2]. This is an important point. A similar situation might arise in the cases of immunisation against hepatitis A and varicella also. Partial coverage of children may slow down virus circulation and delay infection in the unimmunised. Hepatitis A and varicella are more severe in adults than in children. Here a new phrase such as 'partial' or 'incomplete' herd immunity had to be introduced to overcome the problem caused by the very definition which demands disappearance of disease.

A review of several recent publications with the key word herd immunity showed that the term has most often been used to mean the concept of reduced transmission due to high immunisation level, in accordance with one or another of the three definitions given above. For example the 'concept of herd immunity' has been advocated as useful in designing immunisation programmes. [6, 7]. Herd immunity has been qualified as a 'key concept' in population based immunisation programmes [7]. The author of a landmark review of the history, theory and practical aspects of herd immunity chose not to prefer ''any single definition of herd immunity, rather accepting the varied uses of the term by different authors'' [8]. Recognising the consequent potential for confusion, the reviewer coined the phrase 'herd immunity threshold' to indicate the minimum prevalence of immune individuals necessary to interrupt transmission of infection [8]. Its major purpose was to distinguish between the desirable outcome of interruption of transmission from the potentially undesirable effect mentioned above. In general herd immunity is considered desirable by most authors, but there is incongruity in using the term 'immunity' to cover adverse outcomes also. In summary, the definitions are not clear, precise or complete; nor do they agree among themselves. A precise definition is necessary. We do not favour the status quo approach adopted by one reviewer [8].

The proposed new definition for herd immunity

The term herd immunity contains two words, herd (meaning a group or community) and immunity which has to be interpreted. Previously the term immunity did mean a state of protection but today it means a state in which the immune system of the body has reacted specifically to defined immunogen(s). It is an attribute of the individual, not a group. If so desired immunity can be tested for, as the presence of antibody, or as skin test or lymphocyte response to stimulation, against the chosen antigen. Putting the two terms together, it is proposed that herd immunity be now defined simply as the proportion of subjects with immunity in a given population. Under this definition herd immunity is quantifiable by testing a sample of the population for the presence of the selected immune parameter. It may be due to natural infection, or immunisation, or a combination of both. It is not dependent on the ease or difficulty of circulation of an infectious agent, nor its elimination. In certain cases, past infection (inducing long lasting immunity) and immunisation (inducing near 100% immunity which is long lasting) may be used as surrogates of immunity for quantifying herd immunity.

Indeed, some authors have actually used the term herd immunity to mean the proportion of subjects with immunity, in conformity with our new definition and clearly at variance with the definitions cited earlier [9–11]. They have obviously assumed that they were using the term correctly [9–11]. For example, in a survey of antibody prevalence by age to varicella-zoster virus, the prevalence was referred to as herd immunity [9]. In a study of measles outbreaks in two adjacent towns in Japan, the term 'herd immunity level' was used interchangeably with the sum of frequency of vaccination and of previous history of measles [10]. The authors presented it as the complement of 'susceptibility rate' [10]. In another study of antibody prevalence and hepatitis A outbreaks, the former was equated to herd immunity [11]. There are many more such publications in which the term herd immunity has been used in accordance with our new definition.

To recapture the spirit of the earlier but imprecise definitions, we can say that as herd immunity due to immunisation increases, at some point, which is short of 100% coverage, the circulation of the corresponding agent may cease. That point or value of herd immunity (called 'herd immunity threshold' by one author) cannot be the same for different diseases and for the same diseases it need not be the same in different communities [8]. An interesting question could be asked: can the consequence (short of elimination of infection) of increasing herd immunity by immunisation be measured? If it can be, then the fixation on the requirement of interruption of transmission can be eliminated. For this purpose a different term, namely 'herd effect' is introduced to denote the perturbation, if any, on the incidence of disease or infection in the unimmunised segment of a population, induced by the herd immunity of immunisation.

The proposed definition of herd effect

It is proposed that herd effect be defined as the alteration of the epidemiological frequency parameters (of infection or disease as the case may be) in the unimmunised segment of a population as a result of immunising a proportion of the population. The alteration is usually a decline of incidence of infection (hence lower incidence of disease). Therefore it may be simpler to define it as the reduction of infection or disease in the unimmunised segment as a result of immunising a proportion of the population. Lowered incidence of infection due to the herd effect of immunisation may, in some cases, be associated with increased incidence of disease consequent upon an upward shift in age of infection (example hepatitis A, maternal rubella syndrome in infants) or increased severity disease (such as adult varicella). However, in the age group immunised there will always be a reduction of incidence if there was herd effect. In most, if not all other cases, herd effect of high herd immunity induced by immunisation is beneficial in reducing the burden of disease; its extreme benefit is the interruption of transmission itself. In some earlier publications by one of us, the term herd effect had actually been used with this meaning [12, 13].

Earlier we had drawn attention to the contrast between North America where polioviruses were eliminated with routine immunisation coverage (with 3 doses of oral poliovaccine) of below 80% and South America where near 100% coverage with some 9–10 doses were required for the same effect [5]. According to the new definitions the herd immunity and the herd effect were different in these two regions. The reason for dissimilar herd immunity is the geographic difference in vaccine efficacy, necessitating a higher level of vaccine coverage in the region with lower vaccine efficacy to achieve a similar level of herd immunity. The large difference in the vaccine coverage and number of doses needed to eliminate polioviruses in South America in comparison to North America cannot be attributed to the lower herd immunity alone but to insufficient herd effect as well. The difference in herd effect for similar levels of herd immunity is due to difference in the force of transmission of wild polioviruses [12, 13]. In other words, when 100 children are given three doses, whereas in North America virtually 100% herd immunity is induced, in South America and in India only some 70% is induced, proving lower vaccine efficacy [12, 13]. Whereas the median age of poliomyelitis (in the pre-immunisation era) in North America was above 15 years, it was below 15 months in India, proving

higher force of transmission [12, 13]. The confounding of the assumed direct relationship between vaccine coverage and incidence of infection by these two phenomena (dissimilar herd immunity for similar vaccine coverage and dissimilar herd effect for similar herd immunity) confused many world experts on polio, who persisted with the three-dose dogma (until about 1990), mainly because of the lack of clear definition of the term herd immunity and the lack of understanding of the relationships between herd immunity, herd effect and transmission of polioviruses. As an aside, the enhanced potency inactivated poliovaccine does not show any geographic variation of vaccine efficacy. We have observed much better herd effect of the latter vaccine; this is additional evidence for our argument presented above [12, 13], In short, when herd immunity is redefined to mean the immunity prevalence in a population, the cessation of transmission due to immunisation can be seen as the herd effect of high herd immunity due to high immunisation coverage with a vaccine having high vaccine efficacy.

Since herd effect is not necessarily break in transmission, but the reduction in transmission, a lower coverage level would have a lower herd effect and a very high coverage level could result in high herd effect leading to zero incidence even in the unimmunised. While herd immunity is applicable to any infection irrespective of its transmission pathways and to immunity induced naturally (by infection) or artificially (by immunisation), herd effect applies only when infected persons participate in the transmission of an agent and when immunisation induces at least some protection against infection (and not merely against disease). Thus, immunisation against tetanus or rabies (even if given routinely) will have no herd effect. As BCG inoculation seems to protect only against progressive primary tuberculosis and not against secondary type pulmonary tuberculosis, it also has no herd effect.

The measurement of herd effect

To be useful in understanding and quantifying the effects of immunisation it is not sufficient to differentiate herd effect from herd immunity, but we should be able to measure them. It was pointed out earlier that herd immunity is measurable by testing a sample of the population for the required parameter of immunity. Under certain circumstances, herd effect can also be measured. One of the best studies in which it was measured is that of immunisation of children with pertussis toxoid decreasing the spread of pertussis within the family [14]. The investigators found that vaccination of children with the toxoid was followed by significant reduction in incidence of pertussis among siblings and parents. They did not use the term herd effect, but called it 'indirect protection'. Interestingly they measured this effect as: (Indirect protection) = $(1 - R)$, where R was the ratio of incidence rates in contacts (parents and siblings) of recipients of toxoid (immunised) and of placebo (unimmunised) [14]. This parallels the method of measurements of vaccine efficacy, (VE) = $(1 - R)$, where R is the ratio of the incidence rates in immunised and unimmunised. Therefore, for ease of use, we may use the term 'VE equivalent' for the measure of herd effect, since the method of measurement and the way it is expressed as the percent reduction in incidence are both very much like VE itself.

It now becomes obvious that herd effect confounds the measurements of VE, since the incidence in the unimmunised is altered by the introduction of immunisation in a group. Thus, the measurement of VE subsumes herd effect when it is estimated in 'field' (community) immunisation programme settings. An interesting corollary of this relationship between herd effect and VE is that in a community in which immunisation has already been introduced the true VE cannot be measured by comparing the incidences in the vaccinated and the unvaccinated; the measured VE will be an underestimate. In such situations either historical data on incidence prior to introducing vaccination or incidence in an unvaccinated but similar community must be used to obtain the true measure of VE, corrected for herd effect. If VE is measured in a clinical study, in which a limited number of children living in a large community are immunised, implying thereby that herd effect is minimum or none, then we may get a different value. If the immune response of immunised children is measured in the clinical setting, then we get only a surrogate for VE without exhibiting protection, and not confounded by herd effect. For these reasons, the term vaccine efficacy should be qualified as 'immunogenic VE,' 'clinical VE' and 'field level VE' as has already been suggested [12].

Relevance of herd effect and herd immunity in immunisation programmes

From the definitions of and relationships between herd effect and herd immunity stated above it is clear that neither is relevant for the vaccination of an occasional individual, but both are important elements in large scale or community wide immunisation programmes. Programme managers are advised to factor in these issues in planning an immunisation programme, or when introducing a new vaccine in an existing programme, and also to monitor herd immunity and herd effect in the community as part of planned assessment/evaluation. The relationship between the two will depend on the type of immunity in consideration, its realised value at a point in time and the rate at which it is realised. Immunising agents

which provide protection only against disease but not against infection may have no herd effect. Many vaccines protect well against disease but not so well against infection. Since infection without disease is silent, it would seem that the protection is against infection also. Partial protection against infection may result in lower extent of multiplication or shorter duration of potential transmissibility, thereby tending to reduce the risk of infection in others. The level of herd effect induced by a vaccine (providing at least some protection against infection) will depend on the level of herd immunity at a point in time, probably in a non-linear fashion and this would further be modified by the rate at which this level is achieved in relation to time. For example, we have shown that the herd effect achieved in 'pulse immunisation' is very much higher than that of routine immunisation programme, for the same level of herd immunity [12, 13, 15]. In our pioneering experiment, with 65% coverage with 3 doses of OPV given in pulse fashion, the transmission of poliovirus appeared to have ceased abruptly, in contrast to its continued circulation in spite of over 90% coverage in year round routine immunisation [15]. Even though this difference may be partly due to the short duration of gut immunity induced by OPV, the principle of excellent herd effect of pulse immunisation is still valid as has been shown with successful elimination of measles from a community by annual single day pulse immunisation of only children over one year [16].

Investigation, clear conceptualisation and application of these relationships will improve our ability to design effective and efficient immunisation programmes aimed at control, elimination or eradication of vaccine preventable infectious diseases in the transmission of which humans participate significantly.

Herd effect of interventions other than vaccination

It is worthwhile to realise that herd effect is the consequence of reducing transmission. Therefore other interventions which also reduce the transmission potential will have similar herd effect. To control lymphatic filariasis, mass treatment with Ivermectin or diethyl carbamazine is being used in many endemic areas. By reducing the parasitaemia in individuals and reducing the number of parasitaemic individuals, the drug causes a reduction in transmission to susceptibles even if they had not taken the drug. Mass application of the drug is akin to pulse application of a vaccine. If done well, filariasis could be eliminated by this approach since there is no extra-human source of infection. Even though 100% of population do not (and need not) receive treatment, the reduction of infection in the untreated segment is the herd effect of pulse therapy with the drug.

The public health approach to tuberculosis control is the early detection and antimicrobial treatment of pulmonary tuberculosis in the hope that further spread may be curtailed. This is another example of 'indirect protection' not due to immunity but due to decreased chance of spread, very much like in the case of reduced transmission due to immunisation. If increasing proportions of persons with pulmonary tuberculosis are diagnosed and treated early, the incidence of infection in the susceptible population should continue to decline; this may also be called herd effect. On the other hand, if multi-drug therapy of leprosy should have similar herd effect, we must be sure that transmission occurs from the infected persons directly (like tuberculosis) or via vector (like filariasis). The lack of conclusive evidence for such transmission is a lacuna in the strategy to control leprosy taking advantage of the assumed herd effect of multi-drug therapy. In the case of malaria, chemoprophylaxis in a large proportion of persons and/or the use of insecticide-impregnated bed nets may also have some herd effect. This is due to the fact that each prevented infection reduces further transmission and also because mosquitoes may not get access to infected persons sleeping in nets.

Thus herd effect may in general be defined as the change (reduction) in the incidence of infection or disease in the un-intervened segment of a susceptible population due to the intervention in the rest of the population, compared to the incidence in the absence of intervention in the entire population. However, we have focused on the herd effect of immunisation programmes in this paper and we recommend that the term be qualified by the nature of intervention when appropriate (as due to early diagnosis and treatment, mass treatment etc). In ordinary use, when not qualified, herd effect will be taken as due to herd immunity.

References

1. Saunders WB. Dorland's Illustrated Medical Dictionary. 28th Edn. Philadelphia: 1994; p 812.
2. Keusch GT, Bart KJ. Immunization and Vaccine Use. In: Fauci AS, Brawnwald E, Isselbacher KJ, et al. (eds), Harrison's Practice of Internal Medicine. 14th Edn, New York: McGraw Hill, 1998; pp 758–771.
3. Isaacs D, Moxon ER. Immunisation. In: Weatherall DJ, Ledingham JGG, Warrel DA (eds), Oxford Text Book of Medicine. 3rd Edn, Vol. 1. Oxford: Oxford University Press, 1996; p 315–321.
4. Nathanson N. Eradication of poliomyelitis in the United States. Rev Infect Dis 1982; 4: 940–945.
5. De Quadros CA, Andrus JK, Olive JM, Carrasco P. Strategies for poliomyelitis eradication in developing countries. Public Health Rev 1993/94; 21: 65–81.
6. Anderson RM. The concept of herd immunity and the design of community-based immunisation programmes. Vaccine 1992; 10: 928–935.
7. Anderson RM, Donnelly CA, Gupta S. Vaccine design, evaluation and community-based use for antigenically variable infectious agents. Lancet 1997; 350: 1466–1470.

8. Fine PEM. Herd Immunity: History, theory, practise. Epidemiol Rev 1993; 15: 265–302.
9. Ooi PL, Goh KT, Doraisingham S, Ling AE. Prevalence of varicella-zoster virus infection in Singapore. South East Asian J Trop Med Public Health 1992; 23: 22–25.
10. Ohga S, Okada K, Miyazaki C, Akazawa K, Ueda K. The measles outbreak in Chikuhau district, Fukuoka, Japan, 1990: Correlation between herd immunity level and outbreak size. Acta Paediatr Japan 1992; 4: 447–453.
11. Rooney PJ, Coyle PV. The role of herd immunity in an epidemic cycle of hepatitis A. J Infect 1992; 24: 327–331.
12. John TJ. Immunisation against polioviruses in developing countries. Rev Med Virology 1993; 3: 149–160.
13. John TJ. Can we eradicate poliomyelitis? In: Sachdev HPS, Choudhury P (eds), Frontiers in Paediatrics, New Delhi: Jaypee Brothers, 1996; p 76–90.
14. Trollfors B, Taranger J, Lagergard T, Sundh V, Bryla DA, Schneerson R, Robbins JB. Immunisation of children with pertussis toxoid decreases spread of pertussis within the family. Pediatr Infect Dis J 1998; 17: 196–199.
15. John TJ, Pandian R, Gadomski A, et al. Control of poliomyelitis by pulse immunisation in Vellore, India. Brit Med J 1983; 286: 31–32.
16. John TJ, Ray M, Steinhoff MC. Control of measles by annual pulse immunization. Amer J Dis Child 1984; 138: 299–300.

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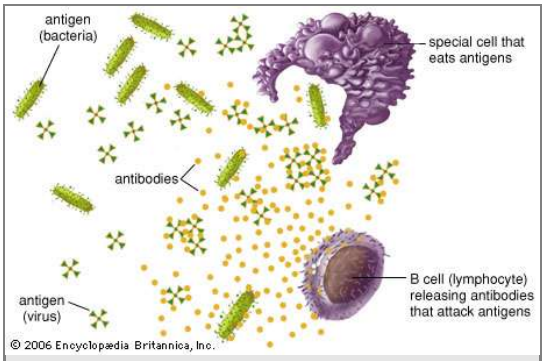
EXHIBIT 340

Antigen

Antigen, substance that is capable of stimulating an immune response, specifically activating lymphocytes, which are the body's infection-fighting white blood cells. In general, two main divisions of antigens are recognized: foreign antigens (or heteroantigens) and autoantigens (or self-antigens). Foreign antigens originate from outside the body. Examples include parts of or substances produced by viruses or microorganisms (such as bacteria and protozoa), as well as substances in snake venom, certain proteins in foods, and components of serum and red blood cells from other individuals. Autoantigens, on the other hand, originate within the body. Normally, the body is able to distinguish self from nonself, but in persons with autoimmune disorders, normal bodily substances provoke an immune response, leading to the generation of autoantibodies. An antigen that induces an immune response—i.e., stimulates the lymphocytes to produce antibody or to attack the antigen directly—is called an immunogen.



antigen; antibody; lymphocyte

Phagocytic cells destroy viral and bacterial antigens by eating them, while B cells produce antibodies that bind to and inactivate antigens.

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On the surface of antigens are regions, called antigenic determinants, that fit and bind to receptor molecules of complementary structure on the surface of the lymphocytes. The binding of the lymphocytes' receptors to the antigens' surface molecules stimulates the lymphocytes to multiply and to initiate an immune response—including the production of antibody, the activation of cytotoxic cells, or both—against the antigen. The amount of antibody formed in response to stimulation depends on the kind and amount of antigen involved, the route of entry to the body, and individual characteristics of the host.

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Appropriate Risk to Benefit Ratio (page 1 of 3)

Risk is defined as the probability of physical, psychological, social, or economic harm occurring as a result of participation in a research study. Both the probability and magnitude of possible harm in human research may vary from minimal to considerable.

The federal regulations define only "minimal risk."

Minimal risk exists where the probability and magnitude of harm or discomfort anticipated in the proposed research are not greater, in and of themselves, than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.
[45 CFR 46.102(i)]

Risk above this standard is more than minimal (moderate, maximal) and that imposes limitations on the conduct of the research and increases the requirements for monitoring. It also requires more stringent approval processes when studying children or otherwise vulnerable populations. Increased risk should be accompanied by the probability of appropriately increased benefits.

Benefit applies to the potential of the research treatment to ameliorate a condition or treat a disease. This can apply to an individual participant or to a population. In research as in clinical medicine, results cannot be guaranteed but, as a consequence of prior work, a benefit may appear to be a reasonable expectation. Since this is research, an advantage for the treatment groups cannot be presupposed. Since the risks have not been fully evaluated, a statement of individual benefit should be made most cautiously if at all. The investigator should always distinguish between research and treatment and never lure the patient into participating in hopes of remission or cure.

A main role of IRBs is to determine the risk versus benefit ratio for clinical studies. They must make sure that the physical risk is not disproportionate to the benefits. When the physical risk is minimal they must determine that psychological and social risks such as stigma are not important. It is not ethical to conduct a study in which an individual or a group is labeled so as to be stigmatized or to be made less employable or insurable.

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EXHIBIT 342

FAQs About Rare Diseases

What is a rare disease?

In the United States, a rare disease is defined as a condition that affects fewer than 200,000 people in the US. This definition was created by Congress in the Orphan Drug Act of 1983 (https://www.fda.gov/downloads/ForIndustry/DevelopingProductsforRareDiseasesConditions/HowtoapplyforOrphanProductDesignation/UCM517741.pdf). Rare diseases became known as orphan diseases because drug companies were not interested in adopting them to develop treatments. The Orphan Drug Act created financial incentives to encourage companies to develop new drugs for rare diseases. The rare disease definition was needed to establish which conditions would qualify for the new incentive programs.

Other countries have their own official definitions of a rare disease. In the European Union, a disease is defined as rare when it affects fewer than 1 in 2,000 people.

How many rare diseases are there?

There may be as many as 7,000 rare diseases. The total number of Americans living with a rare disease is estimated at between 25-30 million. This estimate has been used by the rare disease community for several decades to highlight that while individual diseases may be rare, the total number of people with a rare disease is large.

In the United States, only a few types of rare diseases are tracked when a person is diagnosed. These include certain infectious diseases, birth defects, and cancers. It also includes the diseases on state newborn screening tests. Because most rare diseases are not tracked, it is hard to determine the exact number of rare diseases or how many people are affected.

If you are looking for statistics on a specific disease, check to see if the disease is listed in Genetics Home Reference (http://ghr.nlm.nih.gov/), GeneReviews (http://www.ncbi.nlm.nih.gov/books/NBK1116/), or Medscape Reference (http://reference.medscape.com/). These resources usually include statistical information. To find medical journal articles with statistics, you can conduct a PubMed search (http://www.ncbi.nlm.nih.gov/pubmed) using the disease name and the word "prevalence" or "incidence."

What causes rare diseases?

There are many different causes of rare diseases. The majority are thought to be genetic, directly caused by changes in genes or chromosomes. In some cases, genetic changes that cause disease are passed from one generation to the next. In other cases, they occur randomly in a

person who is the first in a family to be diagnosed.

Many rare diseases, including infections, some rare cancers, and some autoimmune diseases, are not inherited. While researchers are learning more each year, the exact cause of many rare diseases is still unknown.

What is being done to develop treatments for rare diseases?

Researchers have made progress in learning how to diagnose, treat, and even prevent a variety of rare diseases. However, there is still much to do because most rare diseases have no treatments.

The National Institutes of Health (NIH) supports research to improve the health of people with rare diseases. Many of the 27 Institutes and Centers at the NIH fund medical research for rare diseases. One of these Centers, the National Center for Advancing Translational Sciences (NCATS), focuses on getting new cures and treatments to all patients more quickly. NCATS supports research through collaborative projects to study common themes and causes of related diseases. This approach aims to speed the development of treatments that will eventually serve both rare and common diseases.

The NCATS Office of Rare Diseases Research (ORDR) guides and coordinates NIH-wide activities involving research for rare diseases. Some of the NCATS programs for rare diseases include:

- Rare Diseases Clinical Research Network (https://ncats.nih.gov/rdcrn) (RDCRN)
- Therapeutics for Rare and Neglected Diseases (https://ncats.nih.gov/trnd) (TRND)
- Rare Diseases Registry Program (https://ncats.nih.gov/radar) (RaDaR)
- Genetic and Rare Diseases Information Center (https://ncats.nih.gov/gard) (GARD)

Efforts to improve and bring to market treatments for rare diseases are coordinated by the Food and Drug Administration (FDA). The Office of Orphan Products Development (http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/OfficeofScienceandHealthCoordination/ucm2018190.htm) (OOPD) provides incentives for drug companies to develop treatments for rare diseases. Between 1973 and 1983, fewer than 10 treatments for rare diseases were approved. Since 1983, the OOPD program has helped develop and bring to market more than 400 drugs and biologic products for rare diseases.

Which diseases are included on the GARD website?

GARD maintains a list of rare diseases and other terms to help people find reliable information. We use available data in the medical literature to determine if the condition meets the U.S. rare disease definition. Inclusion on this list does not serve as official recognition by the

NIH as a rare disease. The list is updated regularly, but it should not be used as a reference that a disease is rare. The prevalence of a rare disease usually is an estimate and may change over time.

Other types of diseases or terms on the GARD website include:

Genetic conditions that are not rare (Example: Down syndrome).

Common conditions when genetic factors increase risk to develop the condition (Example: celiac disease).

Conditions or terms for which we receive numerous questions with answers that are hard to find elsewhere (Example: diffuse idiopathic skeletal hyperostosis or DISH).

Last updated: 11/30/2017

EXHIBIT 343

Guidelines for Preparing Core Clinical-Safety Information on Drugs

Report of CIOMS Working Group III

Geneva

ACKNOWLEDGEMENTS

The Council for International Organizations of Medical Sciences is greatly indebted to the members of the Working Group on Guidelines for Preparing Core Clinical-Safety Information on Drugs, and the drug regulatory authorities and pharmaceutical companies they represented, for the efficient and expeditious way in which they brought this project to its successful conclusion. Special thanks are due to the co-chairs, Dr Win Castle and Dr Gottfried Kreutz, for their capable leadership and to Ms. Susan Roden, the secretary of the Group, who very effectively coordinated and collated the contributions of its individual members. We thank also Dr S. Gallagher for his assistance in the editing of the final report.

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d. Frequency of Adverse Drug Reactions

- *Whenever possible, an estimate of frequency should be provided, expressed in a standard category of frequency.*

It is always difficult to estimate incidence on the basis of spontaneous reports, owing to the uncertainty inherent in estimating the denominator and degree of under-reporting. However, the Working Group felt that, whenever possible, an estimate of frequency should be provided and in a standard form. The following standard categories of frequency are recommended:

*very common**	$\geq 1/10$ ($\geq 10\%$)
common (frequent)	$\geq 1/100$ and $< 1/10$ ($\geq 1\%$ and $< 10\%$)
uncommon (infrequent)	$\geq 1/1000$ and $< 1/100$ ($\geq 0.1\%$ and $< 1\%$)
rare	$\geq 1/10{,}000$ and $< 1/1000$ ($\geq 0.01\%$ and $< 0.1\%$)
*very rare**	$< 1/10{,}000$ ($< 0.01\%$)

* Optional categories.

Precise rates will inevitably be based on studies and limited to the more common reactions. For reactions that are fewer than "common," estimates of frequency will inevitably be based on spontaneous reports or on very large post-marketing studies or other special studies, and the numbers will be less precise; therefore, the source of the estimates (spontaneous or clinical) should be indicated. Stating the absolute numbers of cases reported may be misleading since they inevitably will become outdated.

e. Good Safety Information: Ten General Principles

As the Working Group discussed the sample case-histories and formulated its proposals, it developed ten general principles governing the overall content of CSI and the use of suitable language.

- *In general, statements that an adverse reaction does not occur or has not yet been reported should not be made.*
  When a side-effect is predictable pharmacologically or has been observed with other drugs in the same class, yet has not occurred despite extensive exposure in a susceptible population, it may be mentioned. In general, however, statements that an adverse reaction does not occur or has not yet been reported could be misleading and should be avoided. Often there has been inadequate exposure on which to base a decision.
- *As a general rule, clinical descriptions of specific cases should not be part of the CSI*
  Even though a single case-report of high quality may carry more weight than many of poorer quality, it is usually not appropriate to include in the CSI clinical descriptions of specific cases.
- *If the mechanism of the reaction is known it should be stated, but speculation about the mechanism should be avoided.*
  If the mechanism of a reaction is known, it should be described, as it could alert prescribers to identify other, related reactions. If unknown, speculation about a possible mechanism should be avoided. In addition, care should be taken not to use terms that imply that the pathophysiology is known unless it