

EXHIBIT 396



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National, State, and Local Area Vaccination Coverage Among Children Aged 19–35 Months — United States, 2011**Weekly****September 7, 2012 / 61(35);689-696**

High vaccination coverage in children by age 2 years has resulted in historically low levels of most vaccine-preventable diseases in the United States (1), but coverage must be maintained to reduce the burden of disease further and prevent a resurgence of these diseases, particularly in populations with lower vaccination coverage. This report describes national, state, and selected local area vaccination coverage by age 19–35 months for children born during January 2008–May 2010, based on 2011 National Immunization Survey (NIS) results. Vaccination coverage remained above the national *Healthy People 2020* target* of 90% for ≥1 dose measles, mumps, rubella vaccine (MMR) (91.6%), ≥3 doses of hepatitis B vaccine (HepB) (91.1%), ≥3 doses of poliovirus vaccine (93.9%), and ≥1 dose of varicella vaccine (90.8%). For the birth dose of HepB, coverage increased from 64.1% in 2010 to 68.6% in 2011; for the more recently recommended ≥2 doses of hepatitis A vaccine (HepA) and rotavirus vaccines, coverage increased from 49.7% to 52.2% and from 59.2% to 67.3%, respectively; and for the full series of *Haemophilus influenzae* type b vaccine (Hib), coverage increased from 66.8% to 80.4%, reflecting recovery from the Hib shortage that occurred during December 2007–September 2009 (2). The percentage of children who had not received any vaccinations remained at <1%. Children living below the poverty level had lower coverage than children living at or above poverty for ≥4 doses of diphtheria, tetanus toxoid, and acellular pertussis vaccine (DTaP) and ≥4 doses of pneumococcal conjugate vaccine (PCV) (by 6 percentage points each); the full Hib series (by 8 percentage points); and for rotavirus vaccination (by 10 percentage points). Continued partnerships among national, state, local, private, and public entities are needed to sustain current coverage levels and ensure that coverage for the more recently recommended vaccines continues to increase for all children.

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,† 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, surveys included landline and cellular telephone households.¶ During 2011, the response rate** was 61.7% for the landline telephone sample and 25.2% for the cellular telephone sample. Providers returned adequate vaccination records for 71.6% of children with completed household interviews, for a total of 19,534 children with provider-reported vaccination records included in this report: 17,309 from the landline sampling frame and 2,225 from the cellular telephone sampling frame. 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, and to test for significant interactions between race/ethnicity and 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.

From 2010 to 2011, national vaccination coverage increased from 66.8% to 80.4% for the full series of Hib, from 64.1% to 68.6% for the birth dose of HepB, from 49.7% to 52.2% for ≥2 doses of HepA, and from 59.2% to 67.3% for rotavirus vaccine (Table 1). For vaccines recommended before the inception of the NIS in 1994, coverage has remained stable since the mid-1990s,¶¶ with 2011 levels of 91.6% for ≥1 dose of MMR, 84.6% for ≥4 doses of DTaP, 91.1% for ≥3 doses of HepB, 90.8% for ≥1 dose of varicella vaccine, and 93.9% for ≥3 doses of poliovirus vaccine. Coverage with ≥4 doses of PCV was 84.4% in 2011, similar to coverage in 2010. As in 2009 and 2010, the seven-vaccine series (4:3:1:3:3:1:4)*** reported in 2011 excluded Hib because of the Hib shortage that occurred during December 2007–September 2009 (2). Coverage with the seven-vaccine series, excluding Hib, was 73.6% in 2011, similar to coverage in 2010. However, coverage with the seven-vaccine series (4:3:1:3*:3:1:4)††† that included the full series of Hib increased from 56.6% in 2010 to 68.5% in 2011 (Table 1).

Children living below the poverty level§§§ had lower coverage than children living at or above the poverty level for ≥3 doses of DTaP, ≥4 doses of DTaP, primary and full series of Hib, ≥4 doses of PCV, rotavirus vaccine, and the seven-vaccine series

(including and excluding Hib) (Table 2). Children living 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, varicella vaccine, ≥ 3 doses of PCV, or ≥ 2 doses of HepA.

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 complete 4:3:1:3*:3:1:4 series (Table 2). However, the association of race with coverage did not persist after adjustment for poverty status. American Indian/Alaska Native (AI/AN) children had lower coverage for ≥ 4 doses of DTaP and ≥ 4 doses of PCV compared with white children. These differences remained after adjustment for poverty status. Black children and AI/AN children had higher HepB birth dose coverage than white children, which remained significant after adjustment for poverty. In unadjusted analyses, Hispanic children had higher coverage than white children for the birth dose of HepB, varicella vaccine, and ≥ 2 doses of HepA. However, differences in coverage between Hispanic and white children varied by poverty status, with Hispanic children having higher coverage compared with white children only among those children living below the poverty level for ≥ 4 doses of DTaP (84.2% for Hispanic children compared with 78.6% for white children), the full series of Hib (80.7% compared with 71.7%), ≥ 4 doses of PCV (84.1% compared with 77.5%), ≥ 2 doses of HepA (57.8% compared with 45.0%), and rotavirus vaccine (66.1% compared with 57.4%). The observed difference in coverage between Hispanic and white children for varicella vaccine existed for children on both sides of the poverty line; the difference in coverage for the birth dose of HepB was no longer observed after adjustment for poverty status. Coverage was higher for Asian children compared with white children, independent of poverty status, for ≥ 3 doses of DTaP, ≥ 4 doses of DTaP, poliovirus vaccine, ≥ 3 doses of HepB, and varicella vaccine. Asian children had higher full Hib series coverage than white children only among children living below the poverty level (81.5% for Asian children compared with 71.7% for white children). All other observed differences in coverage between Hispanic and Asian children and white children did not persist after adjustment for poverty.

Vaccination coverage varied by state, with the largest variations for the birth dose of HepB and the more recently recommended vaccinations of HepA and rotavirus (Table 3). HepB birth dose coverage ranged from 23.1% in Vermont to 83.4% in Indiana and North Dakota, ≥ 2 doses of HepA coverage ranged from 29.3% in South Dakota to 69.2% in Nebraska, and rotavirus vaccine coverage ranged from 52.2% in Wyoming to 80.0% in Massachusetts. Although state-specific coverage was less variable for vaccines with longer-standing recommendations (e.g., MMR and DTaP), 15 states had coverage below the *Healthy People 2020* objective of 90% for MMR vaccine, and only two states (Nebraska and Hawaii) had coverage $\geq 90\%$ for ≥ 4 doses of DTaP.

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Editorial Note

The results of the 2011 NIS indicate that vaccination coverage among children aged 19–35 months remained stable or increased compared with 2010 for all recommended vaccines. Coverage continued to meet or exceed national *Healthy People 2020* objectives of 90% for MMR, HepB, poliovirus, and varicella vaccine. Coverage with the full series of Hib increased 13.6 percentage points compared with 2010. This increase likely reflects a recovery from the effect of the recommendation to defer the booster Hib dose during the Hib shortage that occurred during December 2007–June 2009 (2,3).

Coverage continued to increase for the more recently recommended vaccinations, including HepA and rotavirus, and the birth dose of HepB. PCV reached coverage levels comparable to those for DTaP, a vaccine that also requires 4 doses but with longer-standing recommendations. Although coverage did not yet reach the *Healthy People 2020* objectives for these vaccines, the reduction in disease already has been substantial. Incidence of hepatitis A in the United States has decreased an estimated 93% relative to the prevaccine era (1). Hospitalizations associated with rotavirus infection among infants and young children have decreased 66%–89% (4,5). Although coverage with ≥ 4 doses PCV is not yet at 90%, the incidence of invasive pneumococcal disease in children <5 years caused by the serotypes of *Streptococcus pneumoniae* contained in the heptavalent PCV had decreased by 99% by 2007 (6). Incidence of all invasive pneumococcal disease is expected to decrease even further since the introduction of the 13-valent PCV in 2010.

Coverage for many vaccines differs by poverty level. Although the Vaccines For Children program**** has been successful in eliminating differences in coverage between children living above and below the poverty level that once existed for vaccines such as MMR, polio, and HepB (7), coverage among children living below poverty still lags behind coverage of children living at or above poverty for newer vaccines and vaccines that require 4 doses to complete the series.

Few differences by racial/ethnic group were observed after adjustment for poverty status. Differences in coverage between white and black children could be explained by a higher prevalence of poverty among black children. AI/AN children had lower coverage compared with white children for many vaccines, which could not be explained by other, readily apparent factors such as poverty or the introduction of the cellular telephone sampling frame. Coverage among AI/AN children decreased from 81.8% in

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2010 to 72.7% in 2011 for ≥ 4 doses of DTaP, and from 85.3% to 75.3% for ≥ 4 doses of PCV. Because of a relatively small sample size for AI/AN children, differences could be attributable to random variation in the sample. Coverage among children in all other racial/ethnic groups was similar to or higher than coverage among white children for most vaccines.


Vaccination coverage continues to vary across states. Although coverage remains high nationally for many vaccines, clusters of unvaccinated children in geographically localized areas leave communities vulnerable to outbreaks of disease. Fifteen states have MMR coverage below 90%. The recent increases in measles outbreaks in the United States (8) underscore the importance of maintaining uniformly high coverage to protect from importation and transmission of disease.

The findings in this report are subject to at least four limitations. First, this was the first year that the NIS used a dual-frame sampling scheme that included landline and cellular telephone households. Estimates might not be comparable with those from previous years when surveys were conducted only via landline telephone. Although differences between national landline and dual-frame estimates for specific vaccines in the 2011 NIS were small, with absolute magnitude $<1\%$, larger variations were observed for state-specific coverage estimates. Comparisons of 2011 estimates with those of previous years at the state level should be interpreted with caution. Second, underestimates of vaccination coverage might have resulted from the exclusive use of provider-reported vaccination histories because completeness of these records is unknown, and estimates might have been biased upwards or downwards if coverage among children for whom provider records were not returned differed from coverage among children with adequate provider data. Third, bias resulting from nonresponse and exclusion of households without telephone service might persist after weighting adjustments. 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.

Most vaccine-preventable diseases have declined to historically low levels in the United States as a result of high vaccination coverage among preschool-aged children (1). Careful monitoring of coverage levels overall and in subpopulations (e.g., by race/ethnicity and by geographic area) is important to ensure that all children remain adequately protected. Many states can supplement NIS estimates with use of immunization information systems to track vaccination coverage at the community level. The results of the 2011 NIS indicate that coverage among young children has remained stable for vaccines with long-standing recommendations and continues to increase for more recently recommended vaccines. CDC encourages the use of evidence-based methods for improving and sustaining coverage, including components such as parent and provider reminders, reducing out-of-pocket costs, standing orders, home visits to vulnerable populations, vaccination requirements for child care centers, use of immunization information systems, and vaccination programs in child care centers and Special Supplemental Nutrition Program for Women, Infants, and Children (WIC) settings^{††††} (9). 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).

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* Additional information available at <http://healthypeople.gov/2020/topicsobjectives2020/objectiveslist.aspx?topicid=23> .

† The nine local areas separately sampled for the 2011 NIS 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) and two previously sampled areas (Dallas County, Texas, and El Paso County, Texas). Prince George's County, Maryland, was newly sampled in 2011. The territory of the U.S. Virgin Islands (including

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St. Croix, St. Thomas, St. John, and Water Island) was included in the July–September 2011 NIS sample. Data from the U.S. Virgin Islands are excluded from national coverage estimates.

§ 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/nispuf10_dug.pdf.

¶ A description of the dual-frame sampling methodology is available at <http://www.cdc.gov/vaccines/stats-surv/nis/dual-frame-sampling-08282012.htm>.

** 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/codeofstandards.cfm>. 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).

¶¶ Information on coverage with individual vaccines since the inception of NIS in 1994 through 2011 is available at http://wwwdev.cdc.gov/vaccines/stats-surv/nis/figures/2011_map.htm.

*** The 4:3:1:3:3:1:4 vaccine series includes ≥ 4 doses of DTaP/DT/DTP, ≥ 3 doses of poliovirus vaccine, ≥ 1 dose of measles-containing vaccine, ≥ 3 doses of Hib, ≥ 3 doses of HepB, ≥ 1 dose of varicella vaccine, and ≥ 4 doses of PCV.

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

§§§ Poverty status 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 2010 U.S. Census poverty thresholds, available at <http://www.census.gov/hhes/www/poverty.html>.

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

**** Additional information on the Vaccines for Children program is available at <http://www.cdc.gov/vaccines/programs/vfc/default.htm>.

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

What is already known on this topic?

Healthy People 2020 has set childhood vaccination targets of 90% for ≥ 1 dose measles, mumps, rubella vaccine (MMR), ≥ 3 doses of hepatitis B vaccine (HepB), ≥ 3 doses of poliovirus vaccine, ≥ 1 dose 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. For these and other vaccines, the National Immunization Survey estimates coverage among U.S. children aged 19–35 months.

What is added by this report?

Childhood vaccination coverage remains at or above national target levels for ≥ 1 dose of MMR (91.6%), ≥ 3 doses of HepB (91.1%), ≥ 3 doses of poliovirus vaccine (93.9%), and ≥ 1 dose of varicella vaccine (90.8%), and coverage with the more recently recommended vaccines continues to increase; however, coverage levels vary by state, and differences in coverage by poverty level

still exist.

What are the implications for public health practice?

Continued partnerships among national, state, local, private, and public entities are needed to sustain current coverage levels and ensure that coverage levels for the more recently recommended vaccines continue to increase to reduce the burden of vaccine-preventable diseases and prevent a resurgence of these diseases in the United States.

TABLE 1. Estimated vaccination coverage among children aged 19–35 months, by selected vaccines and dosages — National Immunization Survey, United States, 2007–2011*

Vaccine	2007		2008		2009		2010		2011	
	%	(95% CI)	%	(95% CI)	%	(95% CI)	%	(95% CI)	%	(95% CI)
DTaP										
≥3 doses	95.5	(±0.5)	96.2	(±0.5)	95.0	(±0.6)	95.0	(±0.6)	95.5	(±0.5)
≥4 doses	84.5	(±0.7)	84.6	(±1.0)	83.9	(±1.0)	84.4	(±1.0)	84.6	(±1.0)
Poliovirus										
MMR ≥1 doses	92.6	(±0.9)	93.6	(±0.6)	92.8	(±0.7)	93.3	(±0.7)	93.9	(±0.6)
Hib†										
≥3 doses	92.9	(±0.7)	90.9	(±0.7)	83.6	(±1.0)	90.4	(±0.9)	94.0	(±0.6)§
Primary series	NA		NA		92.1	(±0.8)	92.2	(±0.8)	94.2	(±0.6)§
Full series	NA		NA		54.8	(±1.4)	66.8	(±1.3)	80.4	(±1.1)§
HepB										
≥3 doses	92.7	(±0.7)	93.5	(±0.7)	92.4	(±0.7)	91.8	(±0.7)	91.1	(±0.7)
1 dose by 3 days (birth)¶	53.2	(±1.3)	55.3	(±1.3)	60.8	(±1.3)	64.1	(±1.3)	68.6	(±1.3)§
Varicella ≥1 doses	90.0	(±0.7)	90.7	(±0.7)	89.6	(±0.8)	90.4	(±0.8)	90.8	(±0.7)
PCV										
≥3 doses	90.0	(±1.0)	92.8	(±0.6)	92.6	(±0.7)	92.6	(±0.8)	93.6	(±0.6)§
≥4 doses	75.3	(±1.3)	80.1	(±1.1)	80.4	(±1.2)	83.3	(±1.0)	84.4	(±1.0)
HepA**										
≥1 dose	NA		70.5	(±1.1)	75.0	(±1.1)	78.3	(±1.1)	81.2	(±1.0)§
≥2 doses	NA		40.4	(±1.2)	46.6	(±1.4)	49.7	(±1.4)	52.2	(±1.4)§
Rotavirus††										
Combined series	NA		NA		43.9	(±1.4)	59.2	(±1.4)	67.3	(±1.3)§
4:3:1:3*:3:1§§	NA		NA		48.3	(±1.4)	59.2	(±1.3)	71.0	(±1.2)§
4:3:1:-:3:1¶¶	78.3	(±1.1)	78.7	(±1.1)	77.5	(±1.1)	77.8	(±1.1)	77.6	(±1.2)

4:3:1:3*:3:1:4***	NA	NA	44.3 (±1.4)	56.6 (±1.3)	68.5 (±1.3)§
4:3:1:-:3:1:4†††	67.0 (±1.3)	70.6 (±1.2)	70.5 (±1.2)	72.7 (±1.2)	73.6 (±1.2)
Children who received no vaccinations	0.6 (±0.1)	0.6 (±0.2)	0.6 (±0.1)	0.7 (±0.2)	0.8 (±0.2)

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

* For 2007, includes children born during January 2004–July 2006; for 2008, 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; and for 2011, children born during January 2008–May 2010.

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

§ Statistically significant increase in coverage compared with 2010 (p<0.05).

¶ HepB administered between birth and age 3 days.

** HepA coverage not available before 2008.

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

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

¶¶ Includes ≥4 doses of DTaP/DT/DTP, ≥3 doses of poliovirus vaccine, ≥1 doses of measles-containing vaccine, ≥3 doses of HepB, and ≥1 dose of varicella vaccine. Hib is excluded.

*** 4:3:1:3*:3:1:4 series, referred to as routine, includes ≥4 doses of DTaP/DT/DTP, ≥3 doses of poliovirus vaccine, ≥1 doses of measles-containing vaccine, 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.

††† Includes ≥4 doses of DTaP/DT/DTP, ≥3 doses of poliovirus vaccine, ≥1 doses of measles-containing vaccine, ≥3 doses of HepB, ≥1 dose of varicella vaccine, and ≥4 doses of PCV. Hib is excluded.

TABLE 2. Estimated vaccination coverage among children aged 19–35 months, by selected vaccines and dosages by race/ethnicity* and poverty level† — National Immunization Survey, United States, 2011§

Vaccine	Race/Ethnicity ¶						Poverty level									
	White		Black		Hispanic		American Indian/Alaska Native		Asian		Multiracial		Below		At or above	
	%	(95% CI)	%	(95% CI)	%	(95% CI)	%	(95% CI)	%	(95% CI)	%	(95% CI)	%	(95% CI)	%	(95% CI)
DTaP																
≥ 3 doses	95.5 (±0.7)	94.7 (±1.5)	95.6 (±1.0)	89.6 (±7.3)	97.9 (±1.3)**	95.3 (±2.7)	94.7 (±1.0)††	96.2 (±0.6)								
≥ 4 doses	85.0 (±1.3)	81.3 (±2.9)**	84.1 (±2.2)	72.7 (±9.5)**	92.0 (±2.5)**	87.1 (±3.7)	81.0 (±1.9)††	86.8 (±1.1)								
Poliovirus	93.9 (±0.8)	93.9 (±1.6)	93.8 (±1.4)	88.1 (±7.4)	96.5 (±1.7)**	93.5 (±3.0)	93.6 (±1.0)	94.2 (±0.7)								

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MMR ≥ 1 doses	91.1 (±0.9)	90.8 (±2.2)	92.4 (±1.8)	94.8 (±4.8)	93.9 (±2.8)	91.1 (±3.6)	91.3 (±1.3)	91.7 (±1.0)
Hib§§								
Primary series	94.2 (±0.8)	93.0 (±1.8)	94.5 (±1.2)	91.7 (±6.6)	94.6 (±2.3)	94.4 (±2.8)	92.9 (±1.1) ^{††}	95.4 (±0.6)
Full series	81.0 (±1.4)	74.6 (±3.3)**	81.6 (±2.2)	73.7 (±9.6)	83.5 (±4.7)	82.0 (±4.6)	75.5 (±2.1) ^{††}	83.4 (±1.2)
HepB								
≥ 3 doses	90.3 (±1.0)	92.1 (±1.8)	91.5 (±1.6)	92.6 (±6.5)	95.5 (±2.0)**	90.7 (±3.7)	91.8 (±1.2)	91.2 (±0.8)
1 dose by 3 days (birth) ^{¶¶}	66.0 (±1.6)	73.4 (±3.4)**	70.8 (±2.9)**	83.6 (±5.9)**	69.0 (±6.5)	65.2 (±6.0)	73.3 (±2.2) ^{††}	65.6 (±1.6)
Varicella ≥ 1 doses	89.6 (±1.0)	91.2 (±2.3)	92.0 (±1.5)**	90.1 (±7.2)	93.5 (±2.5)**	91.9 (±3.2)	90.2 (±1.4)	90.9 (±0.8)
PCV								
≥ 3 doses	93.4 (±0.8)	93.4 (±1.7)	94.3 (±1.2)	85.5 (±8.7)	92.5 (±2.9)	94.4 (±2.8)	93.4 (±1.1)	94.0 (±0.7)
≥ 4 doses	85.3 (±1.2)	81.3 (±2.8)**	84.6 (±2.1)	75.3 (±9.3)**	84.9 (±4.7)	84.0 (±4.2)	80.6 (±1.9) ^{††}	86.9 (±1.1)
HepA (≥ 2 doses)	50.0 (±1.6)	50.9 (±3.7)	56.3 (±3.2)**	NA	56.9 (±7.1)**	50.2 (±6.6)	50.7 (±2.5)	53.4 (±1.6)
Rotavirus***	68.3 (±1.6)	62.5 (±3.5)**	68.3 (±2.9)	57.7 (±9.5)	66.9 (±6.1)	67.8 (±5.7)	61.1 (±2.4) ^{††}	71.1 (±1.4)
Combined series								
4:3:1:3*:3:1:4 ^{†††}	68.8 (±1.6)	63.7 (±3.7)**	69.5 (±2.8)	65.9 (±9.5)	70.8 (±6.1)	70.9 (±5.5)	63.6 (±2.4) ^{††}	71.6 (±1.5)
4:3:1:-:3:1:4§§§	73.7 (±1.5)	70.7 (±3.4)	74.4 (±2.6)	69.5 (±9.5)	76.6 (±5.4)	74.5 (±5.1)	70.0 (±2.2) ^{††}	76.0 (±1.4)

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

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

† 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 2011 National Immunization Survey were born during January 2008–May 2010.

¶ Native Hawaiian or other Pacific Islanders were not included in the table because of small sample sizes.

** Statistically significant difference (p<0.05) in estimate compared with white, non-Hispanic children.

†† Statistically significant difference (p<0.05) in estimate compared with children living at or above the poverty level.

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

¶¶ HepB administered between birth and age 3 days.

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

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

§§§ Includes ≥ 4 doses of DTaP/DT/DTP, ≥ 3 doses of poliovirus vaccine, ≥ 1 doses of measles-containing vaccine, ≥ 3 doses of HepB, ≥ 1 dose of varicella vaccine, and ≥ 4 doses of PCV. Hib is excluded.

TABLE 3. Estimated vaccination coverage for vaccination series (modified)* and selected individual vaccines among children aged 19–35 months, by state and local area — National Immunization Survey, United States, 2011†

State/Area	MMR (≥ 1 doses)		DTaP (≥ 4 doses)		HepB (birth)§		HepA (≥ 2 doses)¶		Rotavirus** Vaccine series (modified)			
	%	(95% CI)	%	(95% CI)	%	(95% CI)	%	(95% CI)	%	(95% CI)		
U.S. National	91.6	(±0.8)	84.6	(±1.0)	68.6	(±1.3)††	52.2	(±1.4)††	67.3	(±1.3)††	73.6	(±1.2)
Alabama	94.0	(±2.9)	87.5	(±4.7)	75.3	(±5.8)	53.7	(±6.5)	75.5	(±5.7)††	73.3	(±5.9)
Alaska	90.8	(±3.9)	77.4	(±6.4)	63.9	(±7.1)	48.9	(±7.6)	55.6	(±7.5)	69.0	(±7.0)
Arizona	86.7	(±6.7)	86.0	(±6.0)	71.2	(±8.2)	51.2	(±9.1)	64.6	(±8.7)	65.1	(±8.8)
Arkansas	93.7	(±3.2)	84.5	(±5.5)	81.9	(±6.9)	33.2	(±7.2)	62.1	(±7.5)††	71.5	(±7.1)
California	91.0	(±3.7)	87.7	(±3.9)††	58.4	(±6.3)	59.6	(±6.4)	71.1	(±5.8)††	78.0	(±4.9)
Colorado	88.4	(±5.4)	81.0	(±7.7)	57.8	(±8.4)	46.8	(±8.5)	67.7	(±8.1)††	70.3	(±8.5)
Connecticut	95.0	(±2.6)	88.8	(±3.6)	71.1	(±5.6)††	53.9	(±6.8)	69.6	(±6.0)	79.0	(±5.0)
Delaware	90.6	(±5.1)	83.7	(±6.0)	68.4	(±6.7)	54.5	(±7.3)	72.5	(±6.9)§§	68.6	(±7.0)
District of Columbia	93.5	(±3.0)	87.4	(±4.6)	74.1	(±6.6)††	55.8	(±7.3)	62.1	(±7.0)	76.3	(±5.8)
Florida	90.8	(±4.1)	84.6	(±5.3)§§	52.7	(±6.9)	45.4	(±6.9)	59.5	(±6.7)	71.6	(±6.2)§§
Georgia	94.1	(±2.8)	87.5	(±4.4)	82.1	(±4.9)	65.3	(±6.5)	66.0	(±6.6)	79.5	(±5.6)
Hawaii	94.2	(±3.5)	90.6	(±4.1)	72.9	(±8.0)	51.9	(±8.3)	58.7	(±8.3)	78.5	(±6.9)
Idaho	89.5	(±4.8)	79.0	(±6.6)	70.2	(±7.5)	45.2	(±8.6)	62.0	(±8.2)††	66.9	(±7.7)
Illinois	90.8	(±3.3)	84.0	(±4.6)	69.4	(±5.2)	42.8	(±5.5)	64.1	(±5.5)	71.8	(±5.2)
City of Chicago	90.6	(±4.5)	87.7	(±5.1)	77.3	(±6.1)	50.9	(±7.7)	68.3	(±7.4)	74.1	(±6.5)
Rest of state	90.8	(±4.2)	82.7	(±6.0)	66.6	(±6.8)	40.0	(±6.9)	62.6	(±7.0)	71.1	(±6.7)
Indiana	90.6	(±3.9)	82.2	(±5.5)	83.4	(±4.6)	50.5	(±6.7)	63.9	(±6.7)	70.1	(±6.3)
Iowa	86.7	(±5.6)§§	85.7	(±5.5)	69.4	(±6.6)††	48.8	(±7.3)	69.9	(±7.0)	77.1	(±6.4)
Kansas	91.0	(±4.4)	87.6	(±5.1)	77.7	(±7.4)	60.8	(±8.2)††	63.6	(±8.2)	79.7	(±6.1)
Kentucky	91.4	(±4.9)	87.2	(±5.6)	83.3	(±6.3)	48.5	(±8.6)	66.0	(±7.7)	80.6	(±6.5)††

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Louisiana	92.6 (±3.6)	84.2 (±5.1)	76.7 (±6.0) ^{††}	55.5 (±7.0)	68.9 (±6.9) ^{††}	76.5 (±6.0)
Maine	90.3 (±4.0)	88.9 (±4.5)	68.8 (±6.2)	40.5 (±6.7) ^{††}	59.4 (±6.7) ^{††}	76.6 (±5.6)
Maryland	95.2 (±2.6)	89.5 (±3.8)	75.1 (±5.5)	55.5 (±6.1)	66.0 (±6.0) ^{††}	78.0 (±5.4) ^{††}
Prince George's County	94.6 (±3.3)	87.5 (±5.3)	81.9 (±5.6)	50.0 (±7.3)	68.5 (±7.0)	76.9 (±6.3)
Rest of state	95.3 (±3.0)	89.9 (±4.5)	73.8 (±6.4)	56.6 (±7.1)	65.5 (±7.0)	78.2 (±6.3)
Massachusetts	93.1 (±4.8)	88.4 (±6.2)	70.0 (±7.3)	55.5 (±7.9)	80.0 (±6.4) ^{††}	76.9 (±7.3)
Michigan	87.6 (±6.2)	81.7 (±6.7) ^{§§}	79.7 (±6.7)	53.5 (±7.8)	63.7 (±7.6)	71.8 (±7.4) ^{§§}
Minnesota	96.0 (±3.4)	86.7 (±6.1)	56.8 (±8.0)	52.6 (±8.0)	72.0 (±8.0)	74.9 (±6.9)
Mississippi	89.6 (±4.9)	80.8 (±6.4)	76.1 (±6.8)	42.6 (±7.8)	69.3 (±7.8) ^{††}	71.3 (±7.3)
Missouri	88.2 (±4.0)	80.8 (±5.3)	72.9 (±5.8)	46.5 (±6.2)	62.7 (±6.2)	67.9 (±6.0)
Montana	87.8 (±5.2)	76.8 (±7.9)	81.1 (±5.9) ^{††}	43.9 (±9.1)	59.8 (±8.8)	66.8 (±8.6)
Nebraska	95.3 (±3.5)	92.3 (±3.9)	77.5 (±6.1) ^{††}	69.2 (±7.3)	75.5 (±7.2)	82.6 (±5.6)
Nevada	90.5 (±4.6)	75.2 (±8.0)	65.2 (±8.8)	52.8 (±8.9)	56.6 (±9.0)	66.0 (±8.5)
New Hampshire	92.0 (±4.1)	84.6 (±5.8)	70.7 (±6.9)	54.6 (±7.7)	74.2 (±6.8)	72.6 (±7.1)
New Jersey	91.3 (±3.5)	86.7 (±4.1)	47.3 (±6.2) ^{††}	42.8 (±6.1)	56.3 (±6.2)	73.9 (±5.6) ^{††}
New Mexico	93.1 (±3.6)	86.7 (±4.7) ^{††}	64.0 (±7.6)	50.0 (±7.7)	72.9 (±6.6) ^{††}	75.6 (±6.0)
New York	91.0 (±2.8)	82.6 (±3.9)	53.7 (±5.1)	41.9 (±5.1)	60.7 (±5.1) ^{††}	65.1 (±5.1)
City of New York	91.5 (±3.6)	83.2 (±5.4)	46.3 (±7.4)	43.8 (±7.2)	60.5 (±7.2) ^{††}	66.6 (±7.0)
Rest of state	90.6 (±4.3)	82.0 (±5.5)	61.0 (±7.0)	40.0 (±7.2)	60.9 (±7.2)	63.7 (±7.5)

TABLE 3. (Continued) Estimated vaccination coverage for vaccination series (modified)* and selected individual vaccines among children aged 19–35 months, by state and local area — National Immunization Survey, United States, 2011[†]

State/Area	MMR (≥1 doses)		DTaP (≥4 doses)		HepB (birth) [§]		HepA (≥2 doses) [¶]		Rotavirus ^{**}		Vaccine series (modified)	
	%	(95% CI)	%	(95% CI)	%	(95% CI)	%	(95% CI)	%	(95% CI)	%	(95% CI)
North Carolina	92.3	(±5.1)	81.3	(±7.5)	75.0	(±6.7)	40.8	(±7.6)	70.5	(±7.6)	73.3	(±7.7)
North Dakota	95.8	(±3.0)	89.7	(±4.8)	83.4	(±6.6)	63.0	(±9.0)	74.9	(±8.4)	83.5	(±6.4)
Ohio	93.3	(±4.2)	85.2	(±7.3)	81.9	(±6.2)	44.7	(±8.2)	64.3	(±7.9)	76.4	(±8.3)
Oklahoma	94.0	(±3.3)	84.1	(±5.3)	70.9	(±6.8)	62.6	(±7.2)	57.6	(±7.4) ^{††}	72.7	(±6.4) ^{††}
Oregon	90.6	(±4.2)	76.6	(±7.8)	66.5	(±7.5)	56.6	(±8.0)	62.2	(±8.0)	65.2	(±8.1)
Pennsylvania	92.8	(±2.7)	85.8	(±3.8)	72.8	(±5.0)	59.2	(±5.3)	76.6	(±4.5) ^{††}	73.0	(±4.9)

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Philadelphia County	93.1 (±4.0)	85.4 (±5.6)	75.6 (±6.3)	61.7 (±7.1)	68.9 (±7.0)	70.3 (±7.0)
Rest of state	92.8 (±3.1)	85.9 (±4.5)	72.2 (±5.9)	58.8 (±6.2)	78.0 (±5.2) ^{††}	73.5 (±5.6)
Rhode Island	96.6 (±2.0)	84.5 (±5.4)	73.2 (±6.1)	49.3 (±6.9)	75.7 (±6.3)	76.7 (±5.8)
South Carolina	89.3 (±4.9)	79.5 (±6.1)	69.2 (±7.0)	42.6 (±7.5)	55.8 (±7.6)	69.8 (±7.0)
South Dakota	89.2 (±6.9)	75.8 (±9.7)	70.9 (±9.6)	29.3 (±7.9)	NA	NA
Tennessee	91.1 (±3.9)	81.9 (±5.8) ^{§§}	61.9 (±7.1)	55.7 (±7.2)	71.1 (±6.6)	73.3 (±6.4)
Texas	94.3 (±1.7)	82.7 (±3.7)	78.6 (±3.8) ^{††}	60.2 (±4.6)	72.3 (±3.8) ^{††}	74.9 (±3.9)
Bexar County	91.5 (±4.1)	77.0 (±6.3)	63.1 (±6.9)	55.2 (±7.1)	69.1 (±6.6)	69.4 (±6.8)
City of Houston	95.3 (±2.9)	87.2 (±4.7)	79.6 (±5.8) ^{††}	64.9 (±7.2)	65.6 (±8.0)	73.9 (±6.5)
Dallas County	90.8 (±4.3)	78.9 (±6.3)	82.9 (±4.8) ^{††}	55.2 (±7.4)	62.7 (±7.3)	71.3 (±6.7)
El Paso County	92.8 (±4.1)	79.1 (±6.6)	80.5 (±6.1)	53.8 (±7.7)	72.8 (±7.0)	69.0 (±7.2)
Rest of state	95.1 (±2.3)	83.1 (±5.3)	79.3 (±5.5)	60.9 (±6.6)	75.4 (±5.2) ^{††}	76.6 (±5.6)
Utah	88.8 (±4.6)	82.0 (±5.6)	74.2 (±6.8)	55.6 (±7.3)	68.1 (±6.8)	70.3 (±6.7)
Vermont	95.3 (±2.3)	88.2 (±4.7)	23.1 (±5.8)	44.4 (±7.1)	65.7 (±6.8) ^{††}	73.4 (±6.2)
Virginia	89.0 (±5.2)	84.4 (±6.0)	64.4 (±7.9)	52.3 (±7.9)	75.4 (±6.5)	72.2 (±6.9)
Washington	89.3 (±4.4)	85.5 (±5.3)	71.7 (±6.5)	51.4 (±7.4)	67.7 (±6.7) ^{††}	75.3 (±6.0)
West Virginia	85.8 (±4.3) ^{§§}	78.4 (±5.1)	60.7 (±6.1)	56.0 (±6.2)	60.2 (±6.2) ^{††}	67.0 (±5.9)
Wisconsin	94.9 (±2.7)	88.4 (±5.4)	74.5 (±6.6) ^{††}	48.5 (±7.7)	73.8 (±7.3)	79.2 (±6.5)
Wyoming	85.6 (±9.1)	75.5 (±9.5)	70.8 (±7.3)	45.3 (±8.9) ^{††}	52.2 (±9.2)	63.2 (±9.7)
U.S. Virgin Islands	73.6 (±5.2)	61.8 (±5.7)	78.6 (±4.7)	9.5 [±] (±3.4)	18.1 (±4.7)	46.3 (±5.8)

Abbreviations: CI = confidence interval; MMR = measles, mumps, and rubella vaccine; DTaP/DT/DTP = diphtheria, tetanus toxoids, and acellular pertussis vaccine (includes children who might have been vaccinated with diphtheria, tetanus toxoids, and pertussis vaccine [DTP] and diphtheria and tetanus toxoids vaccine [DT]); HepB = hepatitis B vaccine; HepA = hepatitis A vaccine; PCV = pneumococcal conjugate vaccine.

* Includes ≥4 doses DTaP/DT/DTP, ≥3 doses of poliovirus vaccine, ≥1 dose of any measles-containing vaccine, ≥3 doses of HepB, ≥1 dose of varicella vaccine, and ≥4 doses of PCV; *Haemophilus influenzae* type B vaccine is excluded.

† Children in the 2011 National Immunization Survey were born during January 2008–May 2010.

§ 1 or more doses of HepB administered between birth and age 3 days.

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

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

†† Statistically significant increase in coverage compared with 2010 (p<0.05).

§§ Statistically significant decrease in coverage compared with 2010 (p<0.05).

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EXHIBIT 397

CURRENT TRENDS
IMMUNIZATION SURVEY - 1970

The 1970 United States Immunization Survey was conducted in September by the Bureau of the Census in cooperation with the Center for Disease Control (1). Information was obtained on the measles, poliomyelitis, and diphtheria-tetanus-pertussis (DTP) immunization status of specified age groups. The data were collected by the Bureau through a supplemental questionnaire attached to their monthly Current Population Survey which regularly obtains information from 37,500 randomly selected households in the United States.

The trends for the immunization levels of preschool children (1-4 years of age) against measles, polio, and DTP are shown in Figures 2-4 and Tables 3-5. While DTP immunization levels remained relatively constant in 1970, those for polio and measles declined. Polio immunization levels have been decreasing steadily since 1964. Those for measles, which had been increasing since licensure of the vaccine in 1963, declined sharply in 1970.

As one part of the national survey, information was obtained regarding the immunization status of preschool children in central city poverty areas (population \geq 250,000). These data indicate a significantly lower immunity level in preschool children in the poverty areas than in the nation as a whole (Table 6).

(Reported by the Field Services Branch, Epidemiology Program, and the Immunization Branch, State and Community Services Division, CDC.)

Figure 3
POLIO IMMUNIZATION, 1-4 YEAR AGE GROUP
UNITED STATES, 1959-1970

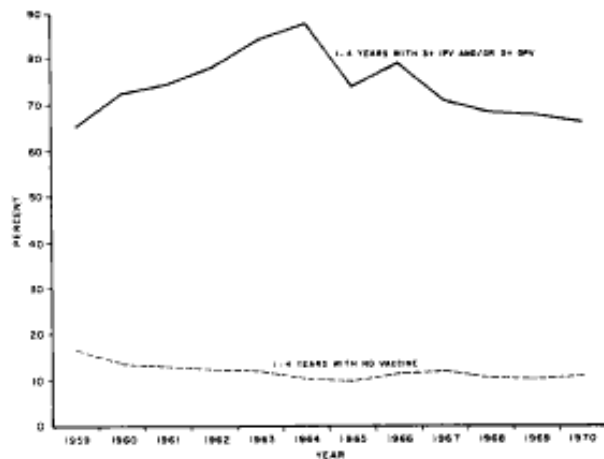


Figure 2
HISTORY OF MEASLES VACCINE, HISTORY OF MEASLES
INFECTION, AND HISTORY OF MEASLES VACCINE AND/OR
INFECTION, 1-4 YEAR AGE GROUP,
UNITED STATES, 1964-1970

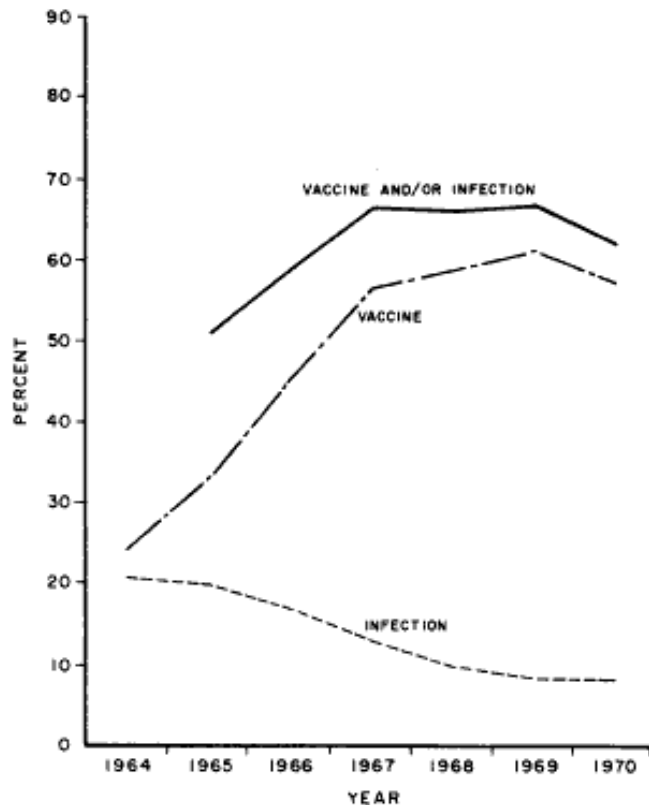


Table 3
PERCENT OF POPULATION, 1-4 YEARS OF AGE,
WITH MEASLES VACCINE, MEASLES INFECTION,
MEASLES VACCINE AND/OR INFECTION
UNITED STATES, 1964-1970

	1964	1965	1966	1967	1968	1969	1970
Vaccine	24.0	33.2	45.5	56.4	58.8	61.4	57.2
Infection	20.5	19.7	16.7	12.8	9.7	8.3	8.1
Vaccine and/or Infection	-	51.0	59.0	66.2	66.0	66.9	62.3

Table 4
PERCENT OF POPULATION, 1-4 YEARS OF AGE,
RECEIVING SPECIFIED DOSES OF POLIO VACCINE
UNITED STATES, 1959-1970

	1959	1960	1961	1962	1963	1964	1965	1966	1967	1968	1969	1970
3+ OPV and/or 3+ IPV	65.0	72.2	74.3	78.4	84.1	87.6	73.9	78.9	70.9	68.3	67.7	65.9
No Doses	16.2	13.4	12.9	12.3	11.9	10.2	9.9	11.3	11.7	10.5	10.2	10.8

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Table 5
PERCENT OF POPULATION, 1-4 YEARS OF AGE, RECEIVING SPECIFIED DOSES OF DIPHThERIA-TETANUS-PERTUSSIS VACCINE UNITED STATES, 1962-1970

	1962	1963	1964	1965	1966	1967	1968	1969	1970
3+ Doses	67.8	72.9	76.0	73.9	74.5	77.9	76.5	77.4	76.1
No Doses	14.1	12.7	11.4	10.9	10.8	9.3	8.6	7.2	7.0

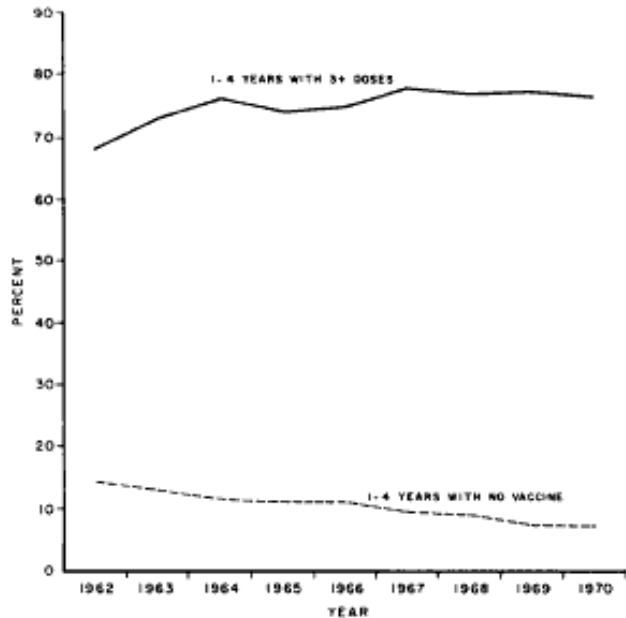
Table 6
PERCENT OF POPULATION, 1-4 YEARS OF AGE, IN POVERTY AREAS WITHIN CENTRAL CITIES ≥250,000 RECEIVING SPECIFIED VACCINES UNITED STATES, 1969-1970

VACCINE	1969	1970
Measles	46.1	41.1
Polio (3+OPV and/or 3+IPV)	55.1	50.9
DTP (3+ doses)	65.1	55.8

Editorial Note

These declining levels of immunization against poliomyelitis, measles, and diphtheria-tetanus-pertussis represent national averages. There are undoubtedly pockets of susceptible persons with even lower immunization levels. The recent rise in measles incidence in the United States is an indication of this declining immunity. There is also a threat of epidemic

Figure 4
DIPHThERIA-TETANUS-PERTUSSIS IMMUNIZATIONS, 1-4 YEAR AGE GROUP UNITED STATES, 1962-1970



poliomyelitis to the central city areas unless vigorous vaccination efforts are carried out.

Reference

1. Center for Disease Control: United States Immunization Survey - 1970, in press

EPIDEMIOLOGIC NOTES AND REPORTS
MEASLES - Alabama

Between Nov. 27 and Dec. 31, 1970, 37 cases of measles (rubeola) occurred in an elementary school (enrollment, 707 students) in a suburb of Birmingham, Alabama. The cases occurred in three waves, with peaks 12 days apart (Figure 5).

Twenty-five of the 37 children had previously received live, attenuated measles-virus vaccine. Fifteen, however, had been inoculated before the age of 1, and 14 of these had also received measles immune globulin at the time of vaccination.

(Continued on page 116)

Figure 5
MEASLES CASES, BY DATE OF ONSET, JEFFERSON COUNTY, ALABAMA, NOV. 25, 1970-JAN. 2, 1971

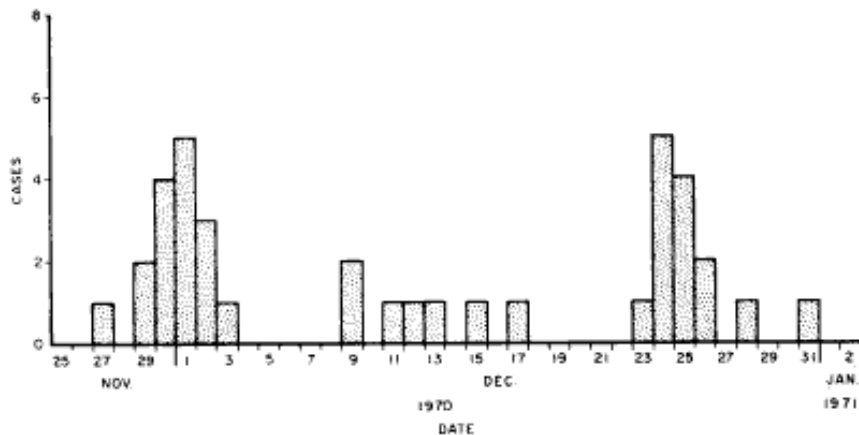


EXHIBIT 398



DEFINITIONS OF INFECTION SEVERITY

Life-threatening/Fatal:

1. Septic shock
2. Any infection clearly linked to death within 2 weeks
3. Life-threatening/fatal infections include:
 - Any proven/probable pulmonary or disseminated mold infection
 - CMV pneumonitis (CXR infiltrate + recovery of virus in BAL specimen or lung biopsy evidence)
 - Disseminated CMV
 - Respiratory virus pneumonitis Influenza/RSV/Parainfluenza virus of lung (CXR infiltrate + recovery)
 - Disseminated aspergillus
 - HHV-6 in central nervous system (CNS)
 - Toxoplasma in brain or CNS
 - PCP in lung

Severe:

1. Deep tissue (invasive) infection requiring IV or oral antibiotics used to treat infection
2. Any infection requiring hospitalization, if outpatient at onset
3. Any infection leading to need for oxygen, pressors or fluids to support BP, or intubation
4. Severe infections include:
 - Any proven or probable sinus (limited) mold infection
 - Pulmonary nodules that decrease in size after a minimum 4 week course of antifungal medications active against Aspergillus
 - Any Bacteremia, catheter-related bloodstream infection (excluding Coagulase negative staphylococcus and Diphtheroids which are MODERATE infections)
 - Any infection that requires adjunctive surgical intervention
 - Any Pneumonia not requiring ventilatory support (see life-threatening/fatal category for specific viral pneumonias)
 - Upper airway (limited) respiratory viruses (firm diagnosis)
 - CMV antigenemia or PCR positivity treated with an 8 week course of antiviral therapy
 - Hemorrhagic cystitis due to BK virus
 - Pseudomembranous colitis due to *C. difficile*
 - Typhlitis
 - Osteomyelitis
 - Meningitis
 - Disseminated or complicated zoster (i.e., ophthalmic)

BMT CTN Data Coordinating Center

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DEFINITIONS OF INFECTION SEVERITY

Page 2 of 2

Moderate:

1. IV or Oral antibiotics used to treat infection with complete resolution within 14 days
2. No need for hospitalization specifically to treat infection
3. If already hospitalized, no need for supplemental oxygen, pressors or fluids to support BP, or intubation
4. Moderate infections include:
 - Many gram positive Bacteremias (Coagulase negative staphylococcus, Corynebacterium, Propionibacterium acnes)
 - Any catheter site infection
 - Urinary tract infection
 - Soft tissue infection/infected wound (not extensive, not necrotizing)
 - Localized/dermatomal zoster
 - Oral HSV
 - Esophagitis due to HSV or candida
 - Sinusitis, bacterial
 - Infectious diarrhea, including uncomplicated C. difficile

Disseminated Infections:

1. Two or more non-contiguous sites with the SAME organism
2. A disseminated infection can occur at any level of severity

Recurrence Intervals to Determine Whether an Infection is the Same or New:

1. CMV, HSV: 2 months (≤ 60 days)
2. VZV, HZV: 2 weeks (≤ 14 days)
3. Bacterial, non-C. difficile: 1 week (≤ 7 days)
4. Bacterial, C. difficile: 1 month (≤ 30 days)
5. Yeast: 2 weeks (≤ 14 days)
6. Molds: 3 months (≤ 90 days)
7. Helicobacter: 1 year (≤ 365 days)
8. Adenovirus, Enterovirus, Influenza, RSV, Parainfluenza, Rhinovirus: 2 weeks (≤ 14 days)
9. Polyomavirus: 2 months (≤ 60 days)

For infections coded as “Disseminated,” any previous infection with the same organism but different site within the recurrence interval for that organism will be counted as part of the disseminated infection.

The Following Should NOT be Reported as an Infection:

1. Fever of undetermined origin
2. Upper respiratory infections, presumed viral
3. Potential infections where antibiotics were given but no infectious etiology identified
4. Stool candida

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EXHIBIT 399



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Provisional COVID-19 Death Counts by Sex, Age, and Week NCHS

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Visualize ▾

Export

API



Deaths involving coronavirus disease 2019 (COVID-19) reported to NCHS by sex and age group and week ending date.

Updated July 1, 2020

Data Provided by National Center for Health Statistics

About this Dataset

Mute Dataset

Updated
July 1, 2020

Data Last Updated July 1, 2020	Metadata Last Updated July 1, 2020
-----------------------------------	---------------------------------------

Date Created
May 15, 2020

Views 43K	Downloads 6,128
---------------------	---------------------------

Data Provided by National Center for Health Statistics	Dataset Owner NCHS
---	-----------------------

[Contact Dataset Owner](#)

Common Core

Contact Name	National Center for Health Statistics
Contact Email	cdcinfo@cdc.gov
Bureau Code	009:20
Program Code	009:020

Footnotes

Number of deaths reported in this table are the total number of deaths received and coded as of the date of analysis, and do not represent all deaths that occurred in that period. Data during this period are incomplete because of the lag in time between when the death occurred and when the death certificate is completed, submitted to NCHS and processed for reporting purposes. This delay can range from 1 week to 8 weeks or more.

Topics

Category	NCHS
Tags	nchs , coronavirus , covid-19 , sex , age group , week , united states

[Show More](#)

What's in this Dataset?

Rows	Columns
726	8

Columns in this Dataset

Column Name	Description	Type

Data as of	Date of analysis	Date & Time	📅	▼
State	Jurisdiction of occurrence	Plain Text	T	▼
MMWR Week	MMWR week number	Number	#	▼
Week ending Date	Week ending date	Date & Time	📅	▼
Sex	Sex	Plain Text	T	▼
Age Group	Age group	Plain Text	T	▼
Total Deaths	Deaths from all causes of death	Number	#	▼
				Show All (8)

Table Preview

View Data

Create Visualization

Data a...	State	MMW...	Week ...	Sex	Age G...	Total ...	COVID...
07/01/2020	United Sta...	5	02/01/2020	Female	Under 1 ye...	185	0
07/01/2020	United Sta...	5	02/01/2020	Female	1-4 years	28	0
07/01/2020	United Sta...	5	02/01/2020	Female	5-14 years	48	0
07/01/2020	United Sta...	5	02/01/2020	Female	15-24 years	146	0
07/01/2020	United Sta...	5	02/01/2020	Female	25-34 years	328	0
07/01/2020	United Sta...	5	02/01/2020	Female	35-44 years	593	0
07/01/2020	United Sta...	5	02/01/2020	Female	45-54 years	1,287	0
07/01/2020	United Sta...	5	02/01/2020	Female	55-64 years	2,957	0
07/01/2020	United Sta...	5	02/01/2020	Female	65-74 years	4,905	0
07/01/2020	United Sta...	5	02/01/2020	Female	75-84 years	6,730	0
07/01/2020	United Sta...	5	02/01/2020	Female	85 years a...	11,128	0
07/01/2020	United Sta...	6	02/08/2020	Female	Under 1 ye...	193	0
07/01/2020	United Sta...	6	02/08/2020	Female	1-4 years	35	0
07/01/2020	United Sta...	6	02/08/2020	Female	5-14 years	43	0

< Previous Next >

Showing Rows 1 to 14 out of 726

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EXHIBIT 400

Underlying Cause of Death, 1999-2018 Results

Census Region	Deaths	Population	Crude Rate Per 100,000
Census Region 1: Northeast (CENS-R1)	2,804	610,408	459.4
Census Region 2: Midwest (CENS-R2)	5,020	801,327	626.5
Census Region 3: South (CENS-R3)	9,424	1,494,786	630.5
Census Region 4: West (CENS-R4)	4,219	941,687	448.0
Total	21,467	3,848,208	557.8

Notes:

Caveats: Deaths of persons with Age "Not Stated" are included in "All" counts and rates, but are not distributed among age groups, so are not included in age-specific counts, age-specific rates or in any age-adjusted rates. [More information.](#) ([/wonder/help/ucd.html#Not Stated](#))

The population figures for year 2018 are bridged-race estimates of the July 1 resident population, from the Vintage 2018 postcensal series released by NCHS on June 25, 2019. The population figures for year 2017 are bridged-race estimates of the July 1 resident population, from the Vintage 2017 postcensal series released by NCHS on June 27, 2018. The population figures for year 2016 are bridged-race estimates of the July 1 resident population, from the Vintage 2016 postcensal series released by NCHS on June 26, 2017. The population figures for year 2015 are bridged-race estimates of the July 1 resident population, from the Vintage 2015 postcensal series released by NCHS on June 28, 2016. The population figures for year 2014 are bridged-race estimates of the July 1 resident population, from the Vintage 2014 postcensal series released by NCHS on June 30, 2015. The population figures for year 2013 are bridged-race estimates of the July 1 resident population, from the Vintage 2013 postcensal series released by NCHS on June 26, 2014. The population figures for year 2012 are bridged-race estimates of the July 1 resident population, from the Vintage 2012 postcensal series released by NCHS on June 13, 2013. The population figures for year 2011 are bridged-race estimates of the July 1 resident population, from the Vintage 2011 postcensal series released by NCHS on July 18, 2012. Population figures for 2010 are April 1 Census counts. The population figures for years 2001 - 2009 are bridged-race estimates of the July 1 resident population, from the revised intercensal county-level 2000 - 2009 series released by NCHS on October 26, 2012. Population figures for 2000 are April 1 Census counts. Population figures for 1999 are from the 1990-1999 intercensal series of July 1 estimates. Population figures for the infant age groups are the number of live births.

Note: Rates and population figures for years 2001 - 2009 differ slightly from previously published reports, due to use of the population estimates which were available at the time of release.

The population figures used in the calculation of death rates for the age group 'under 1 year' are the estimates of the resident population that is under one year of age. [More information.](#) ([/wonder/help/ucd.html#Age Group](#))

Help: See [Underlying Cause of Death, 1999-2018 Documentation](#) ([/wonder/help/ucd.html](#)) for more information.

Query Date: Jul 9, 2020 8:09:15 PM

Suggested Citation:

Centers for Disease Control and Prevention, National Center for Health Statistics. Underlying Cause of Death 1999-2018 on CDC WONDER Online Database, released in 2020. Data are from the Multiple Cause of Death Files, 1999-2018, as compiled from data provided by the 57 vital statistics jurisdictions through the Vital Statistics Cooperative Program. Accessed at <http://wonder.cdc.gov/ucd-icd10.html> on Jul 9, 2020 8:09:15 PM

Query Criteria:

Ten-Year Age Groups: < 1 year

Year/Month: 2018

Group By: Census Region

Show Totals: True

Show Zero Values: False

Show Suppressed: False

Calculate Rates Per: 100,000

Rate Options: Default intercensal populations for years 2001-2009 (except Infant Age Groups)

Content source: [CDC WONDER](#)

EXHIBIT 401

Underlying Cause of Death, 1999-2018 Results

Census Region	Deaths	Population	Crude Rate Per 100,000
Census Region 1: Northeast (CENS-R1)	130	610,408	21.3
Census Region 2: Midwest (CENS-R2)	510	801,327	63.6
Census Region 3: South (CENS-R3)	672	1,494,786	45.0
Census Region 4: West (CENS-R4)	254	941,687	27.0
Total	1,566	3,848,208	40.7

Notes:

Caveats: Deaths of persons with Age "Not Stated" are included in "All" counts and rates, but are not distributed among age groups, so are not included in age-specific counts, age-specific rates or in any age-adjusted rates. [More information.](#) ([/wonder/help/ucd.html#Not Stated](#))

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Note: Rates and population figures for years 2001 - 2009 differ slightly from previously published reports, due to use of the population estimates which were available at the time of release.

The population figures used in the calculation of death rates for the age group 'under 1 year' are the estimates of the resident population that is under one year of age. [More information.](#) ([/wonder/help/ucd.html#Age Group](#))

Help: See [Underlying Cause of Death, 1999-2018 Documentation](#) ([/wonder/help/ucd.html](#)) for more information.

Query Date: Jul 9, 2020 8:14:01 PM

Suggested Citation:

Centers for Disease Control and Prevention, National Center for Health Statistics. Underlying Cause of Death 1999-2018 on CDC WONDER Online Database, released in 2020. Data are from the Multiple Cause of Death Files, 1999-2018, as compiled from data provided by the 57 vital statistics jurisdictions through the Vital Statistics Cooperative Program. Accessed at <http://wonder.cdc.gov/ucd-icd10.html> on Jul 9, 2020 8:14:01 PM

Query Criteria:

ICD-10 Codes: V01-Y89 (External causes of morbidity and mortality)
Ten-Year Age Groups: < 1 year
Year/Month: 2018
Group By: Census Region
Show Totals: True
Show Zero Values: False
Show Suppressed: False
Calculate Rates Per: 100,000
Rate Options: Default intercensal populations for years 2001-2009 (except Infant Age Groups)

Content source: [CDC WONDER](#)

EXHIBIT 402

Effects of the COVID-19 Pandemic on Routine Pediatric Vaccine Ordering and Administration — United States, 2020

Jeanne M. Santoli, MD¹; Megan C. Lindley, MPH¹; Malini B. DeSilva, MD²; Elyse O. Kharbanda, MD²; Matthew F. Daley, MD³; Lisa Galloway¹; Julianne Gee, MPH⁴; Mick Glover⁵; Ben Herring⁶; Yoonjae Kang, MPH¹; Paul Lucas, MS¹; Cameron Noblit, MPH¹; Jeanne Tropper, MPH, MS, MBA¹; Tara Vogt, PhD¹; Eric Weintraub, MPH⁴

On May 8, 2020, this report was posted as an MMWR Early Release on the MMWR website (<https://www.cdc.gov/mmwr>).

On March 13, 2020, the president of the United States declared a national emergency in response to the coronavirus disease 2019 (COVID-19) pandemic (1). With reports of laboratory-confirmed cases in all 50 states by that time (2), disruptions were anticipated in the U.S. health care system's ability to continue providing routine preventive and other nonemergency care. In addition, many states and localities issued shelter-in-place or stay-at-home orders to reduce the spread of COVID-19, limiting movement outside the home to essential activities (3). On March 24, CDC posted guidance emphasizing the importance of routine well child care and immunization, particularly for children aged ≤ 24 months, when many childhood vaccines are recommended.*

Two data sources were examined to assess the impact of the pandemic on pediatric vaccination in the United States: Vaccines for Children Program (VFC) provider order data from CDC's Vaccine Tracking System and Vaccine Safety Datalink (VSD) vaccine administration data. Vaccination coverage is the traditional metric used to assess vaccine usage; however, provider orders and doses administered represent two immediately available proxy measures.

VFC is a national program that provides federally purchased vaccines to approximately 50% of U.S. children aged 0–18 years.[†] Cumulative doses of VFC-funded vaccines ordered by health care providers at weekly intervals during two periods (January 7, 2019–April 21, 2019 [period 1] and January 6, 2020–April 19, 2020 [period 2]) were tallied, and differences in cumulative weekly vaccine doses ordered between period 2 and period 1 were calculated for all noninfluenza vaccines[§] that the Advisory Committee on Immunization Practices (ACIP) recommends for children and, as an example,

for measles-containing-vaccines.[¶] VSD is a collaborative project between CDC's Immunization Safety Office and eight U.S. health care organizations serving publicly and privately insured patients.** Aggregate counts of measles-containing vaccine doses administered each week at VSD sites during period 2 were compared between two pediatric age groups: children aged ≤ 24 months and those aged >24 months through 18 years.

Vaccine Tracking System data indicate a notable decrease in orders for VFC-funded, ACIP-recommended noninfluenza childhood vaccines and for measles-containing vaccines during period 2 compared with period 1 (Figure). The decline began the week after the national emergency declaration; similar declines in orders for other vaccines were also observed. VSD data show a corresponding decline in measles-containing vaccine administrations beginning the week of March 16, 2020. The decrease was less prominent among children aged ≤ 24 months than among older children (Figure). The subsequent increase in vaccine administrations observed in late March was more prominent in younger than older children.

The substantial reduction in VFC-funded pediatric vaccine ordering after the COVID-19 emergency declaration is consistent with changes in vaccine administration among children in the VSD population receiving care through eight large U.S. health care organizations. The smaller decline in measles-containing vaccine administration among children aged ≤ 24 months suggests that system-level strategies to prioritize well child care and immunization for this age group are being implemented. Increases in vaccine administration to children aged ≤ 24 months beginning in late March might reflect early success of strategies implemented by VSD health care organizations to promote childhood vaccinations in the context of the pandemic, including outreach to patients overdue for vaccinations and changing office workflows to minimize contact between patients (4). Assessment of state and local

* <https://www.cdc.gov/coronavirus/2019-ncov/hcp/pediatric-hcp.html>.

[†] Children aged ≤ 18 years are eligible if they are Medicaid-eligible, uninsured, American Indian/Alaska Native, or underinsured and vaccinated at federally qualified health centers, rural health clinics, or provider sites with an approved deputization agreement with the state public health department. <https://www.cdc.gov/vaccines/programs/vfc/index.html>.

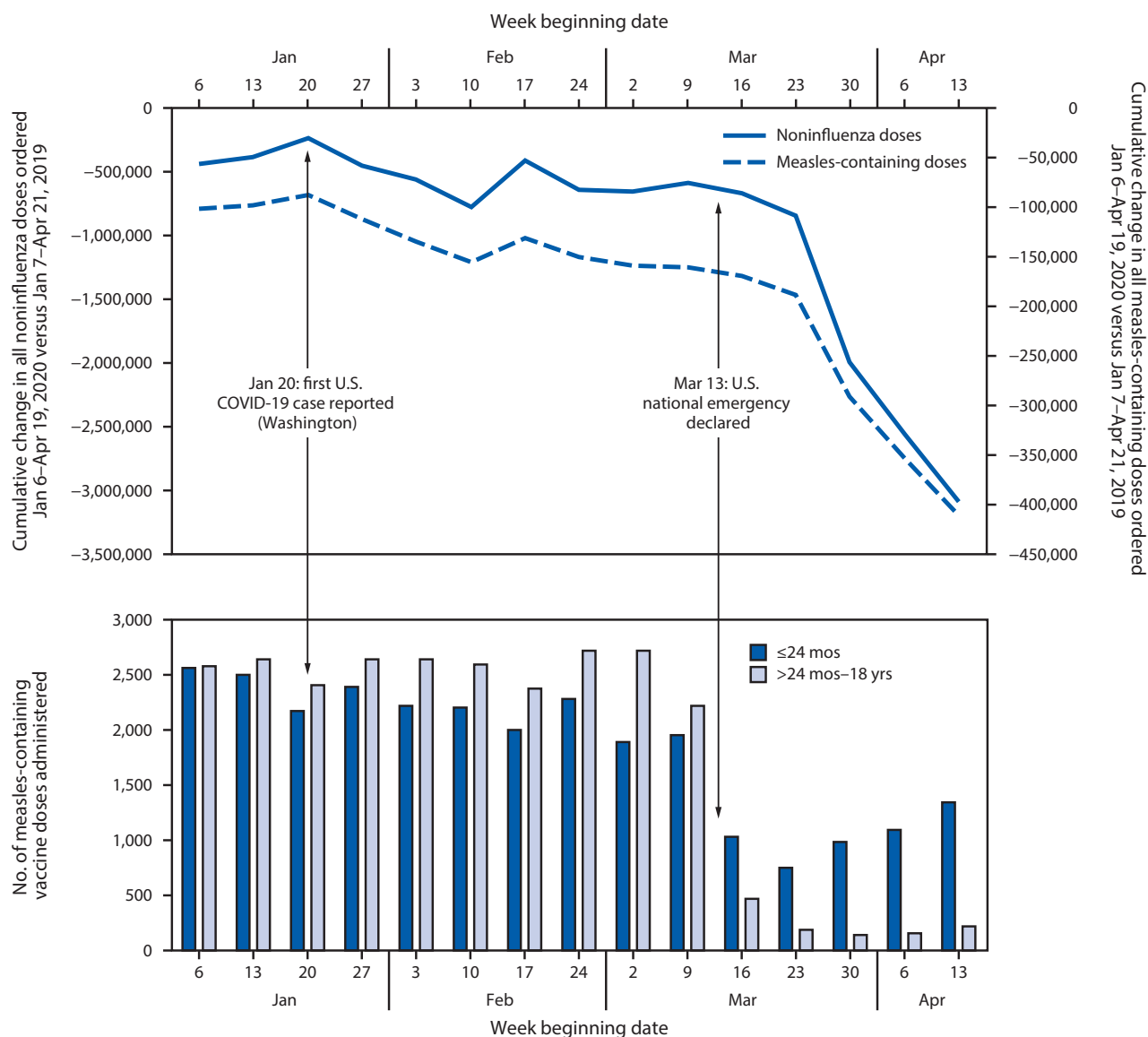
[§] <https://www.cdc.gov/vaccines/schedules/hcp/imz/child-adolescent.html>.

[¶] In the United States, two measles-containing vaccines are licensed for routine use in children: measles-mumps-rubella (MMR) vaccine and a combination MMR and varicella vaccine (MMRV). The Advisory Committee on Immunization Practices recommends that U.S. children receive a 2-dose series of measles-containing vaccines at ages 12–15 months and 4–6 years.

** <https://www.cdc.gov/vaccinesafety/ensuringsafety/monitoring/vsd/>.

Morbidity and Mortality Weekly Report

FIGURE. Weekly changes in Vaccines for Children Program (VFC) provider orders* and Vaccine Safety Datalink (VSD) doses administered† for routine pediatric vaccines — United States, January 6–April 19, 2020



* VFC data represent the difference in cumulative doses of VFC-funded noninfluenza and measles-containing vaccines ordered by health care providers at weekly intervals between Jan 7–Apr 21, 2019, and Jan 6–Apr 19, 2020.
 † VSD data depict weekly measles-containing vaccine doses administered by age group (age ≤24 mos and >24 mos–18 yrs).

vaccination coverage is needed to quantify the impact among U.S. children of all ages and prioritize areas for intervention. The ongoing COVID-19 pandemic is a reminder of the importance of vaccination. The identified declines in routine pediatric vaccine ordering and doses administered might indicate that U.S. children and their communities face increased risks for outbreaks of vaccine-preventable diseases. Parental concerns about potentially exposing their children to

COVID-19 during well child visits might contribute to the declines observed (5). To the extent that this is the case, reminding parents of the vital need to protect their children against serious vaccine-preventable diseases, even as the COVID-19 pandemic continues, is critical. As social distancing requirements are relaxed, children who are not protected by vaccines will be more vulnerable to diseases such as measles. In response, continued coordinated efforts between health care providers

Morbidity and Mortality Weekly Report

and public health officials at the local, state, and federal levels will be necessary to achieve rapid catch-up vaccination.

Acknowledgments

Vaccine Safety Datalink; Leslie Kuckler, Jingyi Zhu, HealthPartners Institute, Minneapolis, Minnesota.

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All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. No potential conflicts of interest were disclosed.

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EXHIBIT 403

Stanley A. Plotkin, Section Editor

Deaths Reported to the Vaccine Adverse Event Reporting System, United States, 1997–2013

Pedro L. Moro, Jorge Arana, Maria Cano, Paige Lewis, and Tom T. Shimabukuro

Immunization Safety Office, Centers for Disease Control and Prevention, Atlanta, Georgia

Background. Vaccines are among the safest medical products in use today. Hundreds of millions of vaccinations are administered in the United States each year. Serious adverse reactions are uncommon. However, temporally associated deaths can occur following vaccination. Our aim was to characterize main causes of death among reports submitted to the US Vaccine Adverse Event Reporting System (VAERS), a spontaneous vaccine safety surveillance system.

Methods. We searched VAERS for US reports of death after any vaccination from 1 July 1997 through 31 December 2013. Available medical records, autopsy reports, and death certificates were reviewed to identify cause of death.

Results. VAERS received 2149 death reports, most ($n = 1469$ [68.4%]) in children. Median age was 0.5 years (range, 0–100 years); males accounted for 1226 (57%) reports. The total annual number of death reports generally decreased during the latter part of the study period. Most common causes of death among 1244 child reports with available death certificates/autopsy reports included sudden infant death syndrome ($n = 544$ [44%]), asphyxia ($n = 74$ [6.0%]), septicemia ($n = 61$ [4.9%]), and pneumonia ($n = 57$ [4.6%]). Among 526 adult reports, most common causes of death included diseases of the circulatory ($n = 247$ [46.9%]) and respiratory systems ($n = 77$ [14.6%]), certain infections and parasitic diseases ($n = 62$ [11.8%]), and malignant neoplasms ($n = 20$ [3.8%]). For child death reports, 79.4% received >1 vaccine on the same day. Inactivated influenza vaccine given alone was most commonly associated with death reports in adults (51.4%).

Conclusions. No concerning pattern was noted among death reports submitted to VAERS during 1997–2013. The main causes of death were consistent with the most common causes of death in the US population.

Keywords. death; vaccines; epidemiology; surveillance; vaccine safety.

When a death occurs shortly following vaccination, it is important to assess whether it was related to vaccination. In 2009–2010, a close temporal association between receipt of the pandemic influenza A(H1N1) vaccine (pH1N1) and 107 deaths (among 15 million doses of vaccine distributed in Japan) resulted in concern about a possible causal relationship, despite a lack of compelling epidemiologic or clinical evidence [1, 2].

Deaths following vaccination have had a negative impact on vaccination programs [3, 4], particularly in low- and middle-income countries implementing large-scale infant vaccination programs [5], even when investigations do not find evidence of a causal relationship.

In a review of reports of death following vaccination submitted to the Vaccine Adverse Event Reporting System (VAERS) from the early 1990s, the Institute of Medicine concluded that most were coincidental, not causally associated [6]. A separate review of 1266 death reports to VAERS from 1990 to 1997 found that almost half were attributable to sudden infant death syndrome (SIDS), which decreased in frequency following recommendations in the early 1990s to change infant sleep environment (ie, sleep on back or side) [7]. As new vaccines are added to the childhood vaccination schedule and use of existing vaccines expands, such as

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DOI: 10.1093/cid/civ423

the universal recommendation in 2010 for influenza vaccination for all persons aged ≥ 6 months [8, 9], it is important to continue to monitor death reports to VAERS. We reviewed reports of death after vaccination reported to VAERS from 1997 through 2013.

METHODS

Vaccine Adverse Events Reporting System

VAERS is a US national vaccine safety surveillance system, co-administered by the Centers for Disease Control and Prevention (CDC) and the US Food and Drug Administration, that receives spontaneous reports of adverse events following vaccination [10]. VAERS accepts reports from vaccine manufacturers, healthcare providers, vaccine recipients, and others. The VAERS report form collects information on age, sex, vaccines administered, the AE experienced, and health history. Signs and symptoms of adverse events are coded by trained personnel using the Medical Dictionary for Regulatory Activities (MedDRA), a clinically validated, internationally standardized terminology [11]. Each VAERS report may be assigned 1 or more MedDRA preferred terms. A report is considered serious based on the Code of Federal Regulations definition if 1 or more of the following is reported: death, life-threatening illness, hospitalization or prolongation of existing hospitalization, or permanent disability [12]. For nonmanufacturer serious reports, medical records are routinely requested and made available to VAERS personnel. For death reports, efforts are made to obtain autopsy reports and death certificates that contain information on the cause of death.

We analyzed VAERS death reports received by 1 June 2014 for individuals vaccinated with any vaccine from 1 July 1997 through 31 December 2013. Non-US and duplicate death reports were excluded. Hearsay reports (secondhand reports) with no vaccination date recorded were also excluded.

Clinical Review of Death Reports

CDC physicians reviewed the VAERS reports, available autopsy findings, death certificates, and medical records to assess causes of death. Cause of death was classified into major *International Classification of Diseases, Tenth Revision (ICD-10)* diagnostic categories, which have been described previously [13]. We did not attempt to assess death reports for causal relationships with vaccination, although we did review specific causes of death where causal relationships between vaccination and death have been established or a plausible theoretical risk exists; these included anaphylaxis, intussusception, Guillain-Barré syndrome (GBS), yellow fever vaccine-associated viscerotropic disease, smallpox complications leading to death, and syncope after vaccination leading to head trauma and subsequent death [14].

We calculated descriptive statistics for sex, age groups, onset interval (time from vaccination to death), year of vaccination,

cause of death, and vaccines administered. Calculations were performed using SAS software, version 9.2 (SAS Institute, Cary, North Carolina). Because VAERS is a routine surveillance program that does not meet the definition of research, it is not subject to institutional review board review and informed consent requirements.

RESULTS

We identified 2149 death reports in VAERS (Table 1). Most reports involved children aged 0–17 years and males. Autopsy reports and/or death certificates were available for 1770 (82.4%) reports. The median onset interval, the period from vaccination to death, was 3 days (range, 0–2442 days) for all ages, 2 days (range, 0–1478 days) for infants (<1 year of age), 5 days (range, 0–2442 days) for children 1–17 years, and 3 days (range, 0–2011 days) for adults (≥ 18 years). Among the 1469 reports in children aged 0–17 years, 1166 (79.4%) received >1 vaccine on the day of vaccination; among infants ($n = 1165$), 1004 (86.2%) received >1 vaccine. Among the 666 reports for adults aged ≥ 18 years, 92 (13.8%) received >1 vaccine on the day of vaccination.

Table 1. Death Reports in the Vaccine Adverse Event Reporting System Among Persons Vaccinated 1 July 1997–31 December 2013

Characteristic	No. (%)
Total reports	2149
Child reports (0–17 y)	1469 (68.4)
Adult reports (≥ 18 y)	666 (30.9)
Unknown age	14 (0.7)
Age, mo, median (range)	6 (0–1204)
Age group, y ^a	
<1	1165 (54.2)
1–4	197 (9.2)
5–9	30 (1.4)
10–17	77 (3.6)
18–45	139 (6.5)
46–64	152 (7.1)
≥ 65	375 (17.5)
Male sex ^b	1226 (57.0)
Onset, d, median (range), all reports ^c	3 (0–2442)
Onset, d, median (range), infants (<1 y)	2 (0–1478)
Type of reporter ^d (n = 2090)	
Vaccine provider	982 (47.1)
Other	672 (32.2)
Manufacturer	288 (13.8)
Parent/patient	144 (6.9)
With autopsy report and/or death certificate	1770 (82.4)

^a Age unknown for 14 reports.

^b Sex unknown for 21 reports.

^c Onset unknown for 170 reports.

^d Type of reporter unknown for 63 reports.

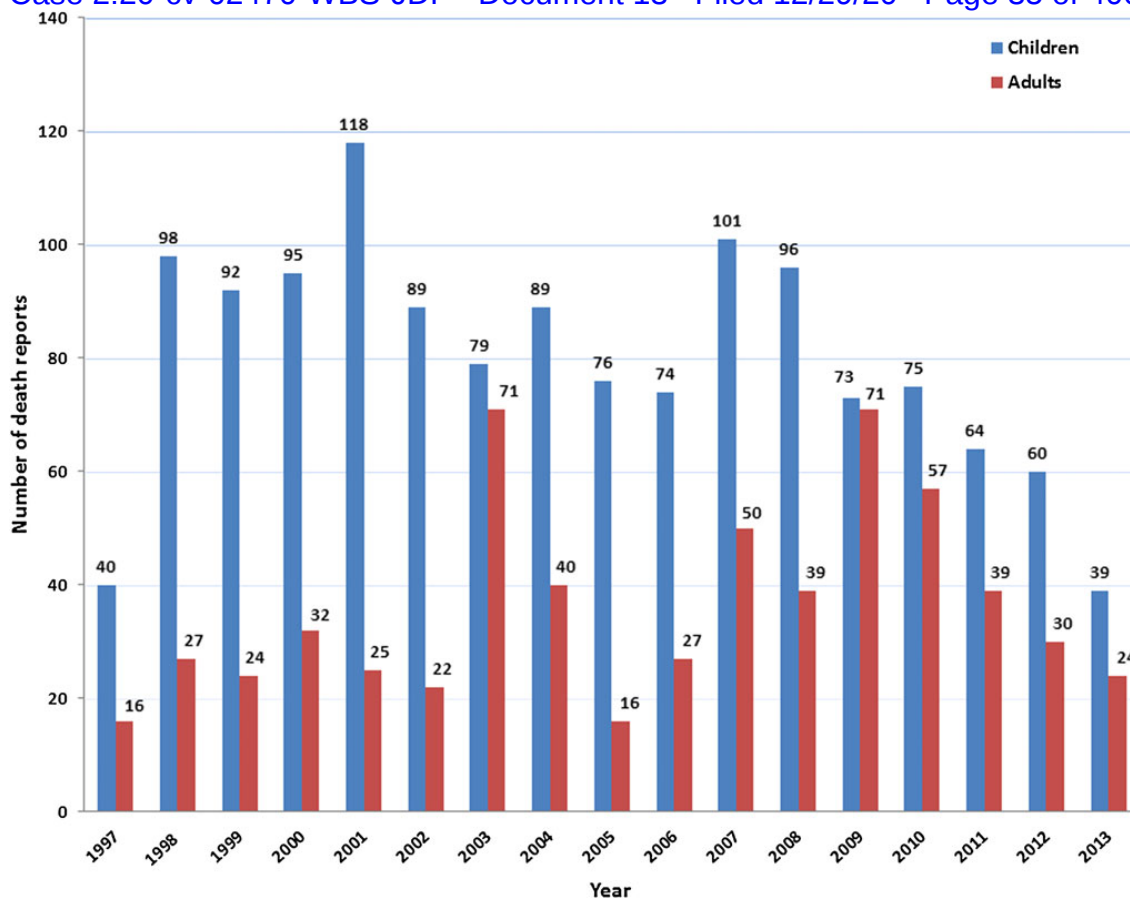


Figure 1. Trends in death reports in children (0–17 years old) and adults (≥ 18 years old) in the Vaccine Adverse Event Reporting System, 1 July 1997–31 December 2013.

The number of death reports in children exceeded those in adults in all years, and in both groups the number of reports has decreased in recent years (Figure 1).

Reports of Children

Causes of Death

Among reports of death in children with autopsy findings and/or death certificates available for review, the most common causes of death by *ICD-10* major group (Table 2) included SIDS and diseases of the respiratory system, with pneumonia as the most common cause of death in the respiratory category. “Injury, poisoning and certain other consequences of external causes” were noted in 96 reports, with asphyxiation being the most common cause of death in this category. Septicemia or sepsis was the fourth most common cause of death. In 146 of 1244 (11.7%) reports, the autopsy report or death certificate stated the cause of death was undetermined. SIDS reports progressively decreased in frequency from a peak in 1998 ($n = 50$) to a nadir in 2011 ($n = 21$). Most SIDS cases were among infants 2–4 months of age ($n = 398$ [66%]) and mostly among males

($n = 375$ [62.2%]) (Table 3). SIDS reports were most common among children who had received DTaP-HepB-IPV (diphtheria and tetanus toxoids and acellular pertussis adsorbed, hepatitis B, and inactivated poliovirus vaccine) plus *Haemophilus influenzae* type b (Hib) plus 7- or 13-valent pneumococcal conjugate vaccine (PCV7 or PCV13) (11.6%) followed by HepB vaccine given alone (9%).

Vaccines Administered

The most common vaccines and vaccine combinations associated with child death reports for all years combined are listed in Table 4. For child death reports, 79.4% received >1 vaccine on the same day. The most common vaccines in children were DTaP-HepB-IPV + Hib + PCV7 or PCV13 ($n = 127$ [8.7%]) followed by HepB vaccine given alone ($n = 115$ [7.8%]).

Among children aged 0–17 years, DTaP vaccine was most common among death reports from 1998 through 2002 (Figure 2). From 2003 through 2009, PCV7 became the predominant vaccine seen in death reports, and in 2011 and 2012, PCV13 was the predominant vaccine. PCV7 was licensed and recommended

Table 2. Most Common Causes of Death Among Reports in Persons Aged 0–17 Years (n = 1244) in the Vaccine Adverse Event Reporting System, 1 July 1997–31 December 2013

ICD-10 Major Group	No.(%)
Symptoms, signs, and abnormal clinical and laboratory findings, not elsewhere classified	703 (56.5)
Sudden infant death syndrome	544
Undetermined	146
Diseases of the respiratory system	98 (7.9)
Pneumonia	57
Injury, poisoning, and certain other consequences of external causes	96 (7.7)
Asphyxiation	74
Certain infections and parasitic diseases	80 (6.4)
Septicemia, sepsis	61
Diseases of the nervous system	73 (5.9)
Meningitis	18
Seizures	18
Diseases of the circulatory system	69 (5.5)
Other forms of heart disease	54
Congenital malformations, deformations, chromosomal abnormalities	39 (3.1)
Diseases of the digestive system	25 (2.0)
External causes of morbidity	16 (1.3)
Assault	11
Other causes of death	45 (3.6)

Abbreviation: ICD-10, *International Classification of Diseases, Tenth Revision*.

for use in 2000, and the first reports of death following PCV7 vaccination were reported that year (n = 20). The rotavirus pentavalent vaccine (RV5) was licensed for use in 2006, and the first reports of death following RV5 occurred that year.

Reports of Adults

Causes of Death

Among reports of death in adults with autopsy or death certificate findings (Table 5), the most common causes of death included diseases of the circulatory system, diseases of the respiratory system, and certain infections and parasitic diseases; the most common causes of death in each of these categories included ischemic heart disease, pneumonia, and septicemia or sepsis, respectively. In 16 of 526 (3%) reports, the cause of death was undetermined.

Vaccines Administered

Among adult reports, the most commonly associated vaccines (Table 4) included IIV3 (n = 342 [51.4%]), herpes zoster (shingles) vaccine (n = 41 [6.2%]), 23-valent pneumococcal polysaccharide vaccine (n = 39 [5.9%]), and 2009 pH1N1 inactivated monovalent vaccine (n = 37 [5.6%]), all of which were given alone. Of reports of death among adults, trivalent inactivated

Table 3. Characteristics of Sudden Infant Death Syndrome Reports in the Vaccine Adverse Event Reporting System, 1997–2013

Characteristic	No. (%)
SIDS reports	603 (28.1)
Male sex ^a	375 (62.2)
Onset, d, median (range)	3 (0–121)
Age, mo, median (range)	2 (0–37)
Type of reporter ^b (n = 581)	
Provider	340 (58.5)
Other	171 (29.4)
Parent/patient	37 (6.4)
Manufacturer	33 (5.7)
Age group, mo (n = 603)	
<12	582 (96.5)
12–48	20 (3.3)
Unknown	1 (0.2)
No. of SIDS reports with autopsy reports and/or death certificate	544 (90.2)
Top 4 vaccines given individually or simultaneously	
DTaP-HepB-IPV + Hib + PCV7 or PCV13	70 (11.6)
HepB	54 (8.9)
DTaP + Hib-HepB + IPV + PCV7 or PCV13	52 (8.6)
DTaP + Hep B + Hib + IPV	47 (7.8)
DTaP + Hib + IPV + PCV7 or PCV13	42 (6.9)

Total death reports = 2149.

Abbreviations: DTaP, diphtheria, tetanus, and acellular pertussis vaccine; DTaP-IPV-Hib, combination diphtheria, tetanus, and acellular pertussis, inactivated poliovirus, and *Haemophilus influenzae* type b conjugate vaccine; HepB, hepatitis B vaccine; Hib, *Haemophilus influenzae* type b conjugate vaccine; Hib-HepB, combination *Haemophilus influenzae* type b conjugate and hepatitis B vaccine; IPV, inactivated poliovirus vaccine; PCV7, 7-valent pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; SIDS, sudden infant death syndrome.

^a Sex unknown in 2 reports.

^b Type of reporter unknown for 22 reports.

influenza vaccine (IIV3) was the most commonly received vaccine for all years, with the exception of 2009 when the 2009 pH1N1 monovalent inactivated vaccine was the most commonly received vaccine and IIV3 was the second most common.

Prespecified Conditions as a Cause of Death

Anaphylaxis was identified as the cause of death in 6 reports; 5 after IIV3 vaccine. The onset interval for all 5 reports was <24 hours. In one report, the patient received IIV3 and ceftriaxone concomitantly. Intussusception was the stated cause of death in 6 reports; all involved administration of several vaccines simultaneously; in 5 reports patients received a rotavirus vaccine. The median onset interval was 5 days (range, 4–16 days) for these 5 reports. Two reports had an onset interval >6 days.

GBS was reported as the cause of death or a contributor to the death, or listed as a diagnosis, in 23 reports; vaccines administered

Table 4. Five Most Common Vaccines and Vaccine Combinations (Simultaneous Administration) for Child and Adult Death Reports in the Vaccine Adverse Event Reporting System, 1 July 1997–31 December 2013

Type of Report	No. (%)
Child reports (n = 1469)	
DTaP-HepB-IPV + Hib + PCV7 or PCV13	127 (8.7)
HepB	115 (7.8)
DTaP + Hib-HepB + IPV + PCV7 or PCV13	102 (7.0)
DTaP-HepB-IPV + Hib + PCV7 or PCV13 + RV5	84 (5.7)
DTaP + Hep B + Hib + IPV	77 (5.2)
Adult reports (n = 666)	
IIV3	342 (51.4)
Herpes zoster	41 (6.2)
PPSV23	39 (5.9)
Influenza A(H1N1) (pandemic) inactivated	37 (5.6)
IIV3 + PPSV23	15 (2.3)

Abbreviations: DTaP, diphtheria and tetanus toxoids and acellular pertussis vaccine adsorbed; DTaP-HepB-IPV, diphtheria and tetanus toxoids and acellular pertussis adsorbed, hepatitis B, and inactivated poliovirus vaccine; HepB, hepatitis B vaccine; Hib, *Haemophilus influenzae* type b conjugate vaccine; Hib-HepB, *Haemophilus influenzae* type b conjugate and hepatitis B vaccine; IIV3, trivalent inactivated influenza vaccine; IPV, inactivated poliovirus vaccine; PCV7, 7-valent pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine; RV5, rotavirus vaccine (pentavalent).

included only IIV3 in 20 reports and three reports where IIV3 was given in combination with pneumococcal vaccine, 2009 pH1N1 inactivated monovalent vaccine, or HepB/varicella zoster vaccine. The median onset interval for these 23 reports was 12 days (range, 2–44 days). In 19 of 23 reports, the GBS was verified as cause of death by review of medical records. There was one report of syncope after vaccination leading to head trauma and resulting in death; details about this case have been reported previously [15]. Two reports involved deaths resulting from possible complications of smallpox vaccine. One report involved a 26-year-old male active-duty soldier who died suddenly after smallpox and IIV3 vaccination. The cause of death was eosinophilic myocarditis (hypersensitivity myocarditis) compatible with postvaccinial myocarditis. A second death report involved a 18-year-old male active-duty soldier who received anthrax, smallpox, and typhoid fever vaccines and died 2 weeks later. The cause of death was “complications from smallpox vaccination.” Autopsy findings included myocarditis with dilated cardiopathy and pulmonary edema. Yellow fever vaccine viscerotropic disease was the stated cause of death in one report involving a 22-year-old woman who received yellow fever vaccine 7 days before death.

DISCUSSION

This comprehensive review of death reports to VAERS for the period 1 July 1997 through 31 December 2013 indicates that

the most common causes of death in VAERS were consistent with the leading causes of death in the US population (Table 6) [13]. The 2149 deaths described in this study were reported to VAERS during a period of time when approximately 2 billion doses of vaccine were distributed for use in the United States. This translates to roughly 1 reported death per 1 million doses of vaccine distributed. Because the majority of death reports were in children, the most common causes of death were in this age group. SIDS was the leading cause of death (28.1%) among all reports and accounted for 51.7% of death reports in infants, which is consistent with infant mortality data that place SIDS as the third leading cause of death in the United States among infants, after congenital malformations, deformations, and chromosomal abnormalities; and disorders related to short gestation and low birthweight [13,16]. The male predominance of death reports in our study is driven by SIDS reports in which males accounted for 62%. This is consistent with studies that found males to be at higher risk of SIDS [17]. SIDS occurs rarely during the first month of life and peaks between 2–3 months of age [17]. Because SIDS peaks at a time when children are receiving many recommended vaccinations, it would not be unexpected to observe a coincidental close temporal relationship between vaccination and SIDS [18]. SIDS deaths in the United States have been declining since the early 1990s for a variety of factors that include recommended changes in sleeping position and environment, clarification of the case definition, and diagnostic coding shifts [19–22]. This downward trend in SIDS reports has also been observed in SIDS reports submitted to VAERS since the early 1990s [7] and has continued during the years of this review from 1997 through 2013. There is considerable evidence that vaccination is not causally associated with SIDS [18, 22, 23], including an Institute of Medicine (IOM) review in 2003 that rejected a causal association between the whole cell pertussis-containing vaccine (which is no longer in use in the United States) and SIDS and between exposure to multiple simultaneous vaccines and SIDS [21].

Other leading causes of death among VAERS reports included diseases of the circulatory system and diseases of the respiratory system. Diseases of the circulatory system, the most common causes of death among VAERS death reports in adults, are the leading causes of death in the US population. Some other leading causes of death among VAERS reports included pneumonia and septicemia/sepsis, both of which rank among the top 11 leading causes of death in the US population [13].

In different age groups, the most common vaccines temporally associated with deaths tended to be those typically recommended and given at the particular age (Table 4). Thus, for child reports, the most common vaccines were combination vaccines given simultaneously with other vaccines (ie, DTaP-HepB-IPV, Hib, PCV7 or PCV13). An exception was the first dose of HepB vaccine, generally given during the first month

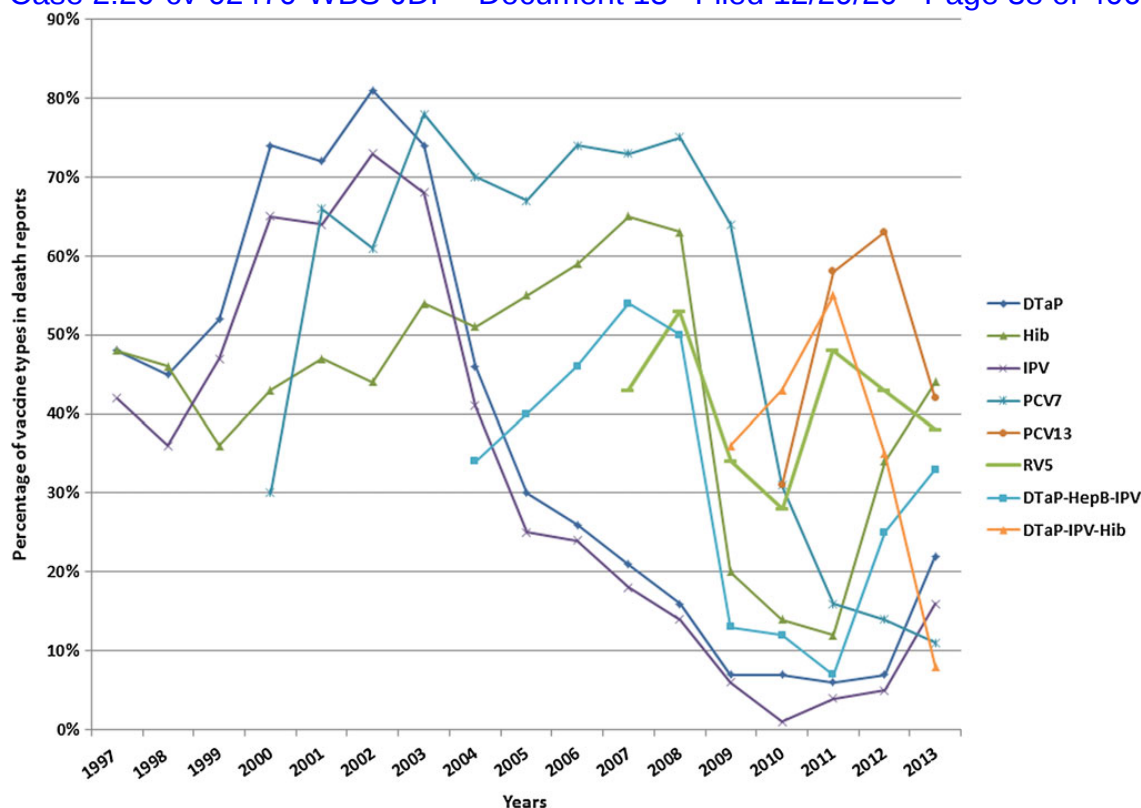


Figure 2. Trends in death reports by vaccine type in children aged 0–17 years, Vaccine Adverse Event Reporting System, 1 July 1997–31 December 2013. Only the most common vaccines associated with death reports are shown. Vaccines shown may be given alone or with other vaccines and may be single or combined antigen vaccines, so percentages of death reports in any given year may exceed 100%. Abbreviations: DTaP, diphtheria, tetanus, and acellular pertussis vaccine; DTaP-HepB-IPV, combination diphtheria, tetanus, and acellular pertussis, hepatitis B, and inactivated poliovirus vaccine; DTaP-IPV-Hib, combination diphtheria, tetanus, and acellular pertussis, inactivated poliovirus and *Haemophilus influenzae* type b conjugate vaccine; HepB, hepatitis B vaccine; Hib, *Haemophilus influenzae* type b conjugate vaccine; IPV, inactivated poliovirus vaccine; PCV7, 7-valent pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; RV5, rotavirus vaccine (pentavalent).

of life. HepB vaccine was the second most common vaccine associated with death reports. A previous study investigated neonatal death reports submitted to VAERS after HepB vaccine during 1991 through 1998 and did not find any safety pattern of concern [24], and a population-based study did not find a significant difference in the proportion of HepB-vaccinated (31%) and -unvaccinated (35%) neonates dying of unexpected causes [25].

We noted that death reports appear to follow the Weber effect [26], a tendency for new medical products or products perceived to be new to have higher reporting rates for adverse events initially, which then decline despite steadily increasing prescribing rates. For example, the peak in number of death reports during 2001 appears to coincide with an increase in PCV7 use following its licensure and recommendation for use in 2000. RV5 was licensed and recommended in 2006, and the peak in the number of death reports after RV5 occurred in 2008. DTaP-HepB-IPV was first licensed and recommended in 2002 and the first death reports in VAERS were observed in 2003 with the

highest number of reports in 2007, which was followed by a decline in subsequent years.

VAERS strengths include its broad national scope and timeliness, and its use for detecting signals of potential vaccine safety problems that may be further studied in other epidemiologic studies. However, any finding in VAERS needs to be interpreted with caution given the inherent limitations of passive surveillance systems, such as over- or underreporting, biased reporting, and inconsistency in quality and completeness of reports [10]. VAERS generally cannot assess if a vaccine caused an adverse event. VAERS does not collect data on the number of individuals vaccinated; therefore, with no denominator data, it is not possible to calculate rates of adverse events. Likewise, VAERS does not collect data on the total number of vaccinated individuals who died; therefore, it is not possible to calculate death rates following vaccination.

Because a large number of vaccines are given to young children (often simultaneously) at scheduled well-child visits, especially during the first year of life, deaths occurring in close

Table 5. Most Common Causes of Death Among Reports in Persons Aged ≥18 Years (n = 526) in the Vaccine Adverse Event Reporting System, 1 July 1997–31 December 2013

ICD-10 Major Group	No. (%)
Diseases of the circulatory system ^a	247 (46.9)
Ischemic heart disease	119
Other forms of heart disease	74
Cerebrovascular diseases	15
Hypertensive diseases	16
Diseases of the respiratory system	77 (14.6)
Pneumonia	34
Chronic lower respiratory diseases	20
Other diseases of the respiratory system	13
Certain infections and parasitic diseases	62 (11.8)
Septicemia, sepsis	48
Diseases of the nervous system	43 (8.2)
Malignant neoplasms	20 (3.8)
Injury, poisoning, and certain other consequences of external causes	20 (3.8)
Other causes of death	57 (10.8)

Abbreviation: ICD-10, *International Classification of Diseases, Tenth Revision*.

^a Pulmonary heart disease and diseases of pulmonary circulation (n = 12), diseases of arteries, arterioles, and capillaries (n = 7), diseases of veins, lymphatic vessels, and lymph nodes, not elsewhere classified (n = 3).

temporal association following vaccination are likely to occur by chance alone. It is important for immunization programs to be aware of background rates of adverse events, including mortality rates in the population, to develop risk communication strategies to help communities understand deaths following vaccination, which can be disruptive to vaccination programs [27]. For example, Hib vaccine has been introduced progressively into some Asian countries' immunization programs as a component of a combination pentavalent vaccine replacing diphtheria-whole-cell pertussis (DTwP) or DTwP-HepB. During introduction of these vaccines into Sri Lanka, India, and Vietnam in 2008–2010, deaths were reported among a small number of vaccine recipients, prompting authorities to suspend the use of these vaccines [5]. More recently, 4 deaths among elderly individuals who received the IIV3 vaccine in Italy prompted the Italian Medicines Agency to temporarily suspend the use of that vaccine in that country [28]. Investigations into the causes of death in all these examples found that the vaccines were not implicated. Other examples of how deaths following vaccinations can be disruptive to immunization programs and public health have been discussed in the scientific literature [27].

Few epidemiologic studies have investigated the occurrence of deaths following vaccination or assessed mortality rates in vaccinated and unvaccinated populations. A previous review of death reports in VAERS during 1990–1997 [7] did not identify any pattern of concern. The findings in our review are consistent with

Table 6. Age-Adjusted Mortality Rates for the 15 Leading Causes of Death in the United States, 2010^a

Cause of Death	Age-Adjusted Death Rate (per 100 000 US Standard Population)
All causes	747.0
1. Diseases of heart (heart disease)	179.1
2. Malignant neoplasms (cancer)	172.8
3. Chronic lower respiratory diseases	42.2
4. Cerebrovascular diseases (stroke)	39.1
5. Accidents (unintentional injuries)	38.0
6. Alzheimer's disease	25.1
7. Diabetes mellitus (diabetes)	20.8
8. Nephritis, nephrotic syndrome, and nephrosis (kidney disease)	15.3
9. Influenza and pneumonia	15.1
10. Intentional self-harm (suicide)	12.1
11. Septicemia	10.6
12. Chronic liver disease and cirrhosis	9.4
13. Essential hypertension and hypertensive renal disease (hypertension)	8.0
14. Parkinson's disease	6.8
15. Pneumonitis due to solids and liquids	5.1

Source: Murphy et al [16].

previous findings, especially related to SIDS reports. A study using electronic health record databases in the Vaccine Safety Datalink (VSD) between 2005 and 2008 estimated the mortality rate among vaccinated individuals and also assessed major causes of death [29]. The age-adjusted death rate within 60 days of vaccination was 442.5 deaths per 100 000 person-years, which is lower than the US death rate during 2008 reported by the National Center for Health Statistics of 758.3 per 100 000 population [29]. The authors attributed the lower death rate in the VSD vaccinated population to a “healthy vaccinee effect,” meaning that people are more likely to receive a vaccine when they are relatively healthy and free of disease. The leading causes of death in the VSD vaccinated population were similar to those reported by the National Center for Health Statistics for the general US population.

In our VAERS review, we did not detect any concerning patterns that would suggest causal relationships between vaccination and deaths. With rare exceptions (eg, anaphylaxis), the evidence from multiple VAERS reviews in combination with findings from IOM reviews and a VSD study using electronic health record databases do not suggest a causal relationship or increased risk of death following vaccination. Continuous monitoring and assessment of death reports in VAERS is warranted to ensure public confidence in the immunization program. Risk assessment and communication strategies should be in place to rapidly respond to reports of deaths following vaccination.

Notes

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Disclaimer. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention or the US Food and Drug Administration.

Potential conflicts of interest. All authors: No potential conflicts of interest.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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EXHIBIT 404



Tetanus

About Tetanus

Tetanus is different from other vaccine-preventable diseases because it does not spread from person to person. The bacteria are usually found in soil, dust, and manure and enter the body through breaks in the skin — usually cuts or puncture wounds caused by contaminated objects.

Today, tetanus is uncommon in the United States, with an average of about 30 reported cases each year. Nearly all cases of tetanus are among people who did not get all the recommended tetanus vaccinations. This includes people who have never received a tetanus vaccine and adults who don't stay up to date on their 10-year booster shots.



Causes and Transmission

Explains how tetanus spreads...



Symptoms and Complications

Lists symptoms of tetanus...



Diagnosis and Treatment

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Prevention

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EXHIBIT 405

Diphtheria Immunization

Effect Upon Carriers and the Control of Outbreaks

Louis W. Miller, MD; J. Justin Older, MD; James Drake; and Sherwood Zimmerman, Austin, Tex

A diphtheria epidemic in a small central Texas community centered in the elementary school. Epidemiological investigation at the school included throat cultures and immunization histories of 306 of the 310 students and staff. Of these, 104 (34%) had culture-proven diphtheria infections; 15 were symptomatic cases and 89 were carriers. There was no statistical difference in the risk of diphtheria infection among those with full, lapsed, inadequate, or no previous diphtheria immunizations. However, the risk of symptomatic diphtheria was 30 times as great for those with none, and 11.5 times as great for those with inadequate immunizations as for those fully immunized. Diphtheria toxoid helps prevent symptomatic disease but does not prevent the carrier state nor stop the spread of infection. Identifying, isolating, and treating carriers are very important aspects in the control of diphtheria outbreaks.

With the increase in the number of cases of diphtheria in the

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From the Epidemiology Program Center for Disease Control, Atlanta (Drs. Miller, Older, Drake, and Zimmerman); the Communicable Disease Services, Texas State Department of Health, Austin (Drs. Miller, Older, Drake, and Zimmerman); and the Department of Preventive Medicine, University of Maryland School of Medicine, Baltimore (Dr. Miller).

Reprint requests to Epidemiology Program, Center for Disease Control, Atlanta 30333.

Status	Definition
Full	Primary series (three or more injections), or a primary series plus a booster, completed within ten years.
Lapsed	Primary series, or a primary series plus booster, completed more than ten years ago.
Inadequate	Uncompleted primary series (less than three injections) at any time.
None	No diphtheria toxoid ever received.

* Adapted from the Center for Disease Control.⁶

United States during the past few years, the effect of immunization on the control of outbreaks has become an important question. In the Austin, Tex, diphtheria epidemic of 1967-1969¹ cases continued to occur despite the administration of 155,200 doses of diphtheria toxoid and the concomitant rise in immunization levels of school age children from 68% to 89%. Data from the Austin outbreak suggested that a large reservoir of carriers was important in the continued transmission of *Corynebacterium diphtheriae*. Other diphtheria outbreaks have shown that epidemics occur in populations with high immunization levels.²⁻⁴ A diphtheria outbreak in an elementary school in Elgin, Tex, in the spring of 1970 provided an op-

portunity to study the effects of immunization on carriers and on the control of an epidemic situation.

Materials and Methods

When it became obvious in the Elgin diphtheria epidemic (Older JJ et al, unpublished data) that cases were clustered in the elementary school, a special throat culture and immunization survey was begun there. Throat cultures were obtained from and immunization status was determined for 306 of 310 students and staff. Throat swabs were taken on three separate occasions from each person: April 7, April 17, and May 4. These were streaked on Loeffler blood serum or Pai medium and incubated overnight. Cystine tellurite blood agar and Tinsdale medium were used for isolation, Elek-King agar diffusion plates were used for toxigenicity determination.

Immunization status information was

obtained by personal interview and review of available school and medical records. The status of each person classified as "adequate," "lapsed," "inadequate," and "none," according to the definitions of the Center for Disease Control⁵ (Table 1).

Any person with a sore throat or other symptoms compatible with diphtheria and a positive culture for *C diphtheriae* organisms was classified as a "case." A person without symptoms but who had a positive throat culture for *C diphtheriae* organisms was classified as a "carrier." The term "infection" applied to anyone with a positive culture regardless of his clinical state and, therefore, included both cases and carriers.

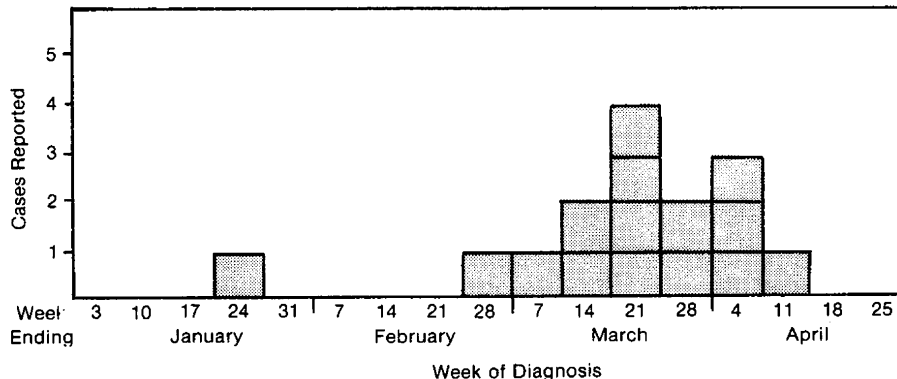
Results

When diphtheria was first diagnosed in the elementary school, 67% of the children and staff were already fully immunized, and 97% had had at least one dose of diphtheria toxoid. The first case in the elementary school population was diagnosed in late February 1970, and by April 8, 15 cases had occurred (Figure).

Throat cultures were done on 306 children and staff; toxigenic *C diphtheriae*, gravis type, was isolated from 104 (34%). Fifteen of these (14%) were cases, and 89 (86%) were carriers. There was no statistical difference in the risk of diphtheria infection among those with full, lapsed, inadequate, or no previous diphtheria immunization (Table 2). However, the risk of becoming a case was 30 times as great for those with no immunization and 11.5 times as great for those with inadequate immunizations as for those with full diphtheria immunization (Table 3). Among the 104 infected with *C diphtheriae*, the risk of being symptomatic was 13.3 times as great for those inadequately immunized and 37.0 times as great for those with no previous immunizations as for those who were fully immunized (Table 4).

Comment

The importance of carriers in the spread of diphtheria was well documented by Doull and Lara⁶ in the



Diphtheria cases in Elgin, Tex, elementary school, spring 1970.

Table 2.—Immunization and Culture Status of Students and Staff, Elgin, Tex, Elementary School, Spring 1970

Immunization Status	Culture Status			Diphtheria Infection Attack Rate (per 100)
	Positive	Negative	Total	
Full	73	132	205	35.6
Lapsed	0	4	4	0
Inadequate	28	59	87	32.4
None	3	7	10	30.0
Total	104	202	306	34.0

Table 3.—Immunization Status of Diphtheria Cases, Elgin, Tex, Elementary School, Spring 1970

Immunization Status	Cases	No. at Risk	Diphtheria Case Attack Rate (per 100)
Full	2	205	1.0
Lapsed	0	4	0
Inadequate	10	87	11.5
None	3	10	30.0
Total	15	306	4.9

Table 4.—Risk of Symptoms and Immunization Status of Students and Staff With Positive Diphtheria Cultures, Elgin, Tex, Elementary School, Spring 1970

Immunization	Symptomatic Cases	Asymptomatic Carriers	Total Infected	Symptom Attack Rate (per 100 Positive Cultures)	Relative Risk
Full	2	71	73	2.7	...
Inadequate	10	18	28	35.8	13.3
None	3	0	3	100.0	37.0
Total	15	89	104	14.4	...

early 1920s. In very thorough investigations, only about 20% of diagnosed diphtheria cases could be traced to another suspected case, and the remaining 80% of the cases were attributed to asymptomatic carriers in the population. Recent epidemics in Austin¹ and Elgin,² Tex, provided ample evidence that carriers continue to play a very important role in the transmission of diphtheria.

When diphtheria toxoid became available, it was generally believed that it induced immunity that protected individuals from symptomatic illness but not from asymptomatic infection. This was based on the observation that immunity is related to the neutralization of toxin elaborated by *C diphtheriae* and not interference with diphtheria infection.

In 1936, Frost et al³ alluded to a paucity of observations on record concerning antitoxic immunity and the carrier state. Nonetheless, he stated that the limited data suggested that there is little, if any, difference between those individuals with and those without antitoxic immunity in their risk of becoming infected.

More recently, Tasman and Lansberg⁴ put forth the hypothesis that toxoid use reduces the number of carriers. This is based on surveys that

showed a steady decline in the prevalence of carriers. Since toxoid immunization does prevent cases and since cases are more contagious than carriers,⁵ the decline in carriers could be due to the decrease in contagious cases rather than to the direct effects of immunization.

The findings in Elgin corroborate the assumptions of Frost et al³ and show that there is no difference in the risk of diphtheria acquisition among those with full, lapsed, inadequate, and no immunizations. However, they also demonstrate the value of immunization in reducing the risk of disease and show that the protection against symptomatic illness afforded those infected with *C diphtheriae* is directly related to their immunization status.

Some authors⁶ have estimated that if 70% or 80% of the population were adequately immunized against diphtheria, spread of diphtheria would be prevented. However, diphtheria outbreaks have been described in populations with as much as 94% of the people being previously immunized.²⁻⁴ These outbreaks, the known importance of carriers in the spread of diphtheria, and the demonstrated failure of toxoid to prevent the carrier state lead us to conclude that the

concept of herd immunity is not applicable in the prevention of diphtheria. A high level of community immunization will not stop the transmission of diphtheria, but it will limit the number of contagious cases. At the first appearance of a diphtheria case, control activities should be directed toward identifying, isolating, and treating carriers, as well as toward immunizing persons with less than full immunization status. This dual approach will reduce or eliminate the spread of infection by reducing the number of carriers, and it will reduce the number of cases by improving the immunization status of exposed individuals.

Roy Morris, MD, Elgin city health officer, treated the majority of cases and arranged for treatment of carriers; Milton Saxon, Elgin school superintendent, and Eva C. Danklefs, Elgin school nurse helped arrange culture surveys; M.S. Dickerson, MD, coordinated federal, state, and local assistance and support; Will Callihan assisted in culture surveys, interviews, and immunization of patients; Jesse V. Irons, ScD, and Carl D. Heather, DVM, coordinated state laboratory assistance; H.D. Bredthauer and Lucie M. Hickman, Texas State Department of Health, processed bacteriological specimens; and Wallis Jones, PhD, Susan Bickham, Geraldine Wiggins, and Jane McLaughlin, Laboratory Division, Center for Disease Control, Atlanta, processed specimens and performed all typing of *C diphtheriae* organisms. All isolates from the initial throat cultures were typed by the Bacteria Immunology Unit, Center for Disease Control.

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FDA study helps provide an understanding of rising rates of whooping cough and response to vaccination

A new study is helping to provide a better understanding of vaccines for whooping cough, the common name for the disease pertussis. Based on an animal model, the study conducted by the U.S. Food and Drug Administration (FDA) and published November 25, 2013, in [The Proceedings of the National Academy of Sciences](#), shows that acellular pertussis vaccines licensed by the FDA are effective in preventing the disease among those vaccinated, but suggests that they may not prevent infection from the bacteria that causes whooping cough in those vaccinated or its spread to other people, including those who may not be vaccinated.

Whooping cough rates in the United States have been increasing since the 1980s and reached a 50-year high in 2012. Whooping cough is a contagious respiratory disease caused by *Bordetella pertussis* bacteria. Initial symptoms include runny nose, sneezing, and a mild cough, which may seem like a typical cold. Usually, the cough slowly becomes more severe, and eventually the patient may experience bouts of rapid, violent coughing followed by the “whooping” sound that gives the disease its common name, when trying to take a breath. Whooping cough can cause serious and sometimes life-threatening complications, permanent disability, and even death, especially in infants and young children.

There are two types of pertussis vaccines, whole-cell and acellular. Whole-cell pertussis vaccines contain a whole-cell preparation, which means they contain killed, but complete, *B. pertussis* bacteria. The acellular pertussis vaccine is more purified and uses only selected portions of the pertussis bacteria to stimulate an immune response in an individual. In response to concerns about the side effects of the whole cell pertussis vaccine, acellular vaccines were developed and replaced the use of whole-cell pertussis vaccines in the U.S. and other countries in the 1990s; however, whole-cell pertussis vaccines are still used in many other countries.

“This study is critically important to understanding some of the reasons for the rising rates of pertussis and informing potential strategies to address this public health concern,” said Karen Midthun, M.D., director of the FDA’s Center for Biologics Evaluation and Research, where the study was conducted. “This research is a valuable contribution and brings us one step closer to understanding the problem. We are optimistic that more research on pertussis will lead to the identification of new and improved methods for

preventing the disease.”

While the reasons for the increase in cases of whooping cough are not fully understood, multiple factors are likely involved, including diminished immunity from childhood pertussis vaccines, improved diagnostic testing, and increased reporting. With its own funds plus support from the National Institutes of Health (NIH), the FDA conducted the study to explore the possibility that acellular pertussis vaccines, while protecting against disease, might not prevent infection.

“There were 48,000 cases reported last year despite high rates of vaccination,” said Anthony S. Fauci, M.D., director of the NIH’s National Institute of Allergy and Infectious Diseases. “This resurgence suggests a need for research into the causes behind the increase in infections and improved ways to prevent the disease from spreading.”

The FDA conducted the study in baboons, an animal model that closely reproduces the way whooping cough affects people. The scientists vaccinated two groups of baboons – one group with a whole-cell pertussis vaccine and the other group with an acellular pertussis vaccine currently used in the U. S. The animals were vaccinated at ages two, four, and six months, simulating the infant immunization schedule. The results of the FDA study found that both types of vaccines generated robust antibody responses in the animals, and none of the vaccinated animals developed outward signs of pertussis disease after being exposed to *B. pertussis*. However, there were differences in other aspects of the immune response. Animals that received an acellular pertussis vaccine had the bacteria in their airways for up to six weeks and were able to spread the infection to unvaccinated animals. In contrast, animals that received whole-cell vaccine cleared the bacteria within three weeks.

This research suggests that although individuals immunized with an acellular pertussis vaccine may be protected from disease, they may still become infected with the bacteria without always getting sick and are able to spread infection to others, including young infants who are susceptible to pertussis disease.

For more information:

- [FDA: Vaccines](#)
- [National Institute of Allergy and Infectious Diseases](#)

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EXHIBIT 407

Acellular pertussis vaccines protect against disease but fail to prevent infection and transmission in a nonhuman primate model

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Edited by Rino Rappuoli, Novartis Vaccines and Diagnostics Srl, Siena, Italy, and approved October 22, 2013 (received for review August 5, 2013)

Pertussis is a highly contagious respiratory illness caused by the bacterial pathogen *Bordetella pertussis*. Pertussis rates in the United States have been rising and reached a 50-y high of 42,000 cases in 2012. Although pertussis resurgence is not completely understood, we hypothesize that current acellular pertussis (aP) vaccines fail to prevent colonization and transmission. To test our hypothesis, infant baboons were vaccinated at 2, 4, and 6 mo of age with aP or whole-cell pertussis (wP) vaccines and challenged with *B. pertussis* at 7 mo. Infection was followed by quantifying colonization in nasopharyngeal washes and monitoring leukocytosis and symptoms. Baboons vaccinated with aP were protected from severe pertussis-associated symptoms but not from colonization, did not clear the infection faster than naïve animals, and readily transmitted *B. pertussis* to unvaccinated contacts. Vaccination with wP induced a more rapid clearance compared with naïve and aP-vaccinated animals. By comparison, previously infected animals were not colonized upon secondary infection. Although all vaccinated and previously infected animals had robust serum antibody responses, we found key differences in T-cell immunity. Previously infected animals and wP-vaccinated animals possess strong *B. pertussis*-specific T helper 17 (Th17) memory and Th1 memory, whereas aP vaccination induced a Th1/Th2 response instead. The observation that aP, which induces an immune response mismatched to that induced by natural infection, fails to prevent colonization or transmission provides a plausible explanation for the resurgence of pertussis and suggests that optimal control of pertussis will require the development of improved vaccines.

therapeutic for established disease, and the highly contagious nature of pertussis. Although a variety of small-animal models have been used to study pertussis, none of them adequately reproduce the human disease (16). To address this gap, we recently developed a nonhuman primate model of pertussis using baboons (*Papio anubis*) and found the disease is very similar to severe clinical pertussis. Upon challenge, baboons experience 2 wk of heavy respiratory colonization and leukocytosis peaking between 30,000–80,000 cells/mL, similar to the range in pertussis-infected infants (1, 17). In addition, baboons experience a paroxysmal cough illness characterized by repeated fits of 5–10 coughs. The coughing fits last on average >2 wk in the baboon, although this is less than some severely infected children, where the cough can last up to 12 wk (1, 17). We also characterized airborne transmission of *B. pertussis* from infected to naïve animals, which is the route of transmission postulated to occur between humans (18). Because this is the only model of pertussis to reproduce the cough illness and transmission of the human disease, we believe it provides the unique opportunity to test our hypothesis that aP vaccines fail to prevent *B. pertussis* colonization, thus enabling transmission among vaccinated individuals.

Using this model we have confirmed that, as in humans, aP vaccines provide excellent protection against severe disease in baboons. However, aP vaccines do not prevent colonization following direct challenge or infection by transmission. In addition, aP-vaccinated animals are capable of transmitting disease to naïve contacts. By comparison, wP-vaccinated animals cleared infection significantly more quickly than aP-vaccinated or naïve

whooping cough | T-cell memory | animal models | adaptive immunity | IL-17

Pertussis is a highly contagious, acute respiratory illness caused by the bacterial pathogen *Bordetella pertussis* (1, 2). Infection results in a wide spectrum of clinical manifestations ranging from mild respiratory symptoms to a severe cough illness accompanied by marked leukocytosis and the hallmark inspiratory whoop and posttussive emesis (3). Because acellular pertussis vaccines replaced whole-cell vaccines in the 1990s, pertussis has reemerged at a startling rate in the United States despite nationwide vaccine coverage in excess of 95% (4). With a 50-y high of 42,000 reported cases in the United States in 2012, pertussis is the most common of the vaccine-preventable diseases (5). This resurgence is mirrored throughout the industrial world despite similar high rates of vaccination (6–9). Two common hypotheses for the resurgence have been proposed: *i*) current acellular pertussis vaccines (aP) vaccines are less effective than the whole-cell pertussis (wP) vaccines they replaced and *ii*) aP-induced immunity wanes more quickly than anticipated (10–13). However, pertussis resurgence is not completely understood (14, 15).

Hampering our ability to counteract this resurgence is the fact that pertussis pathogenesis and immunity to natural infection have not been well studied in humans because typical pertussis is sporadic given high rates of vaccination in developed countries. Human challenge studies have been proposed but never conducted due to a variety of logistical and ethical problems including the potential for severe disease, the lack of an effective

Significance

Pertussis has reemerged as an important public health concern since current acellular pertussis vaccines (aP) replaced older whole-cell vaccines (wP). In this study, we show nonhuman primates vaccinated with aP were protected from severe symptoms but not infection and readily transmitted *Bordetella pertussis* to contacts. Vaccination with wP and previous infection induced a more rapid clearance compared with naïve and aP-vaccinated animals. While all groups possessed robust antibody responses, key differences in T-cell memory suggest that aP vaccination induces a suboptimal immune response that is unable to prevent infection. These data provide a plausible explanation for pertussis resurgence and suggest that attaining herd immunity will require the development of improved vaccination strategies that prevent *B. pertussis* colonization and transmission.

Author contributions: J.M.W. and T.J.M. designed research; J.M.W., L.I.Z., and T.J.M. performed research; J.M.W. and T.J.M. analyzed data; and J.M.W. and T.J.M. wrote the paper.

The authors declare no conflict of interest.

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See Commentary on page 575.

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animals. We also found that aP vaccination induces T helper 2 (Th2) and T helper 1 (Th1) immune memory responses, whereas infection and—to a lesser extent—wP vaccination induce Th17 and Th1 memory. Our results suggest that in addition to the potential contribution of reduced efficacy and waning immunity of aP, the inability of aP to prevent colonization and transmission provides a plausible explanation for pertussis resurgence.

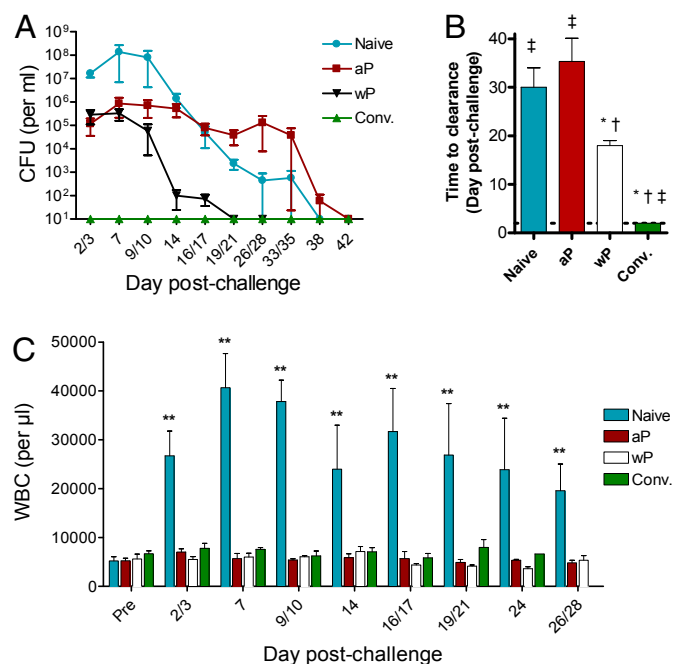
Results

Acellular Pertussis Vaccines Protect Against Disease but Fail to Prevent Infection. Several observational studies recently concluded that children primed with aP vaccine are at greater risk for pertussis diagnosis compared with wP-primed children (19–22). Although these data suggest aP vaccine is less effective than wP vaccine at preventing colonization, the rate of undiagnosed *B. pertussis* carriage in vaccinated individuals is unknown. To assess the ability of each vaccine to prevent colonization and clinical pertussis symptoms, baboons were vaccinated according to the US schedule at 2, 4, and 6 mo of age with human doses of combination diphtheria, tetanus, and pertussis vaccines containing aP or inactivated wP (Table 1 provides a list of the components of each vaccine). At 7 mo of age, vaccinated, naïve, and previously infected (convalescent) animals were challenged with D420, a *B. pertussis* clinical isolate that causes severe infection in humans and baboons (17). Naïve animals were heavily colonized with peak levels between 10^7 – 10^8 cfu/mL in nasopharyngeal washes (Fig. 1A). After 2 wk, colonization gradually decreased, and the infection cleared after 30 d. Consistent with our previous finding, none of the convalescent animals were colonized (17). Compared with naïve animals, aP-vaccinated animals had slightly reduced colonization for the first 10 d but remained consistently colonized before clearing after 35 d. In wP-vaccinated animals the initial colonization was similar to aP-vaccinated animals but the infection cleared after 18 d, significantly faster than naïve and aP-vaccinated animals (Fig. 1B).

To assess the efficacy of the vaccines in preventing the symptoms of severe pertussis, peripheral blood was drawn serially, and complete blood counts were performed to monitor leukocytosis, a significant marker of morbidity in pertussis-infected infants (23). Compared with preinfection levels, naïve animals had a significant increase in circulating white blood cells at each time point, peaking at over 40,000 cells per μ L, an eightfold increase over preinfection levels (Fig. 1C). In contrast to the colonization data, aP vaccination, wP vaccination, and convalescence all prevented leukocytosis (Fig. 1C). In addition, wP-vaccinated, aP-vaccinated, and convalescent animals did not cough and showed no reduction of activity, loss of appetite, or other outward signs of disease.

Acellular Vaccines Fail to Prevent Infection Following Natural Transmission.

To assess the ability of vaccination to prevent pertussis infection by transmission, two aP-vaccinated animals and one unvaccinated animal were cohoused with a directly challenged, unvaccinated animal. Similar to our previous findings (18), all animals became colonized 7–10 d after cohousing with the infected animal (Fig. 2). The peak levels and kinetics of colonization were indistinguishable between the naïve and aP-vaccinated animals.



IU, international units; Lf, limit of flocculation units.

Fig. 1. The effect of vaccination or convalescence on colonization and leukocytosis. Naïve animals, aP-vaccinated animals, wP-vaccinated animals, and previously infected [convalescent conv.] animals were directly challenged with *B. pertussis* ($n = 3$ –4 per group). (A) Colonization was monitored by quantifying *B. pertussis* cfu per mL in biweekly nasopharyngeal washes with a limit of detection of 10 cfu per mL. For each animal the time to clearance is defined as the first day that no *B. pertussis* cfu were recovered from nasopharyngeal washes. (B) The mean time to clearance is shown for each group ($n = 3$ per group). Because no *B. pertussis* organisms were recovered from the conv. animals, the mean time to clearance was defined as the first day of sampling (day 2, indicated by the dashed line). * $P < 0.05$ vs. Naive, † $P < 0.05$ vs. aP, ‡ $P < 0.05$ vs. wP. (C) The mean circulating white blood cell counts before and after challenge are shown for each group of animals ($n = 3$ –4 per group). ** $P < 0.01$ vs. preinfection from same group.

Acellular-Vaccinated Animals Are Capable of Transmitting *B. pertussis* to Naïve Contacts.

Because aP fails to prevent colonization we hypothesized that aP-vaccinated animals can transmit *B. pertussis* infection to contacts. To test this hypothesis, two aP-vaccinated animals were challenged with *B. pertussis* and placed in separate cages. After 24 h, a naïve animal was added to each cage, and all animals were followed for colonization. Both of the naïve animals were infected by transmission from their aP-vaccinated cage mates (Fig. 3).

Vaccination and Previous Infection Induce Robust Antibody Responses.

Sera collected before vaccination or primary infection and again at 1 wk before challenge were analyzed for IgG antibodies against heat-killed *B. pertussis* and the vaccine antigens

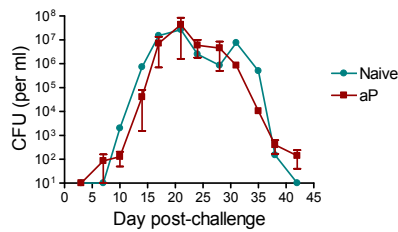


Fig. 2. aP does not protect against colonization following natural transmission. A naïve animal was directly challenged. After 24 h, a naïve animal and two aP-vaccinated animals were placed in the same cage as the directly challenged animal and followed for colonization as in Fig. 1.

pertussis toxin (PT), filamentous hemagglutinin (FHA), pertactin (PRN), and fimbriae types 2 and 3 (FIM). We show that wP, aP, and natural infection induce high-antibody titers to all antigens, and the aP group generally possessed equivalent or greater pre-challenge titers, suggesting that the differences in colonization between the groups do not correlate with levels of circulating antipertussis antibodies (Fig. 4). Following challenge, the titers for vaccinated animals were essentially unchanged, whereas boosting was observed for some antigens in convalescent animals (Fig. S1).

T-Cell Memory Response Elicited by Acellular Pertussis Vaccination Is Mismatched Compared with Natural Infection. Although a large number of clinical studies have characterized the antibody response to pertussis infection and vaccination, key deficiencies remain in our understanding of pertussis-induced helper T-cell immune responses in humans and primates. Importantly, no clinical studies have investigated whether the primary series of pertussis vaccines induce Th17 memory, a recently identified T cell that specializes in controlling extracellular bacterial infections at mucosal surfaces through stimulating neutrophil recruitment (24). To assess *B. pertussis*-specific T-cell memory responses in naïve, aP-vaccinated, wP-vaccinated, and convalescent animals, peripheral blood mononucleated cells (PBMCs) were collected 1 wk before infection. Total PBMC were incubated either with medium alone or with heat-killed *B. pertussis* as an ex vivo simulation of the memory responses recalled during the ensuing challenge. Following an overnight incubation, non-adherent PBMC, including T cells, were collected and separated using magnetic beads into the following fractions: CD4⁻, CD4⁺, CD95⁻CD4⁺, or left unseparated (total nonadherent cells). Memory helper T cells in primates are characterized by surface expression of CD4 and CD95 (25, 26). After further culture of all fractions, the supernatants were analyzed for secretion of IL-17, IFN- γ , and IL-5; cytokines that are characteristic of Th17, Th1, and Th2 cells, respectively. Very low background cytokine secretion was observed from nonstimulated cells isolated from naïve, vaccinated, or convalescent animals or from stimulated cells from naïve animals (Figs. S2 and S3). When stimulated with heat-killed *B. pertussis*, both total nonadherent cells and CD4⁺ cells from convalescent animals secreted high levels of IL-17, some IFN- γ , and no IL-5. When the CD95⁺ memory cells were depleted, the CD95⁻CD4⁺ cells did not secrete IL-17 or IFN- γ , consistent with induction of *B. pertussis*-specific Th17 and Th1 memory cells (Fig. 5). Stimulated total nonadherent cells and CD4⁺ cells from aP-vaccinated animals secreted significant IFN- γ , but the response was weaker than convalescent cells ($P = 0.01$), and there was no significant increase in IL-17 secretion. However, there was a significant IL-5 response, consistent with skewing toward Th2 and Th1 memory (Fig. 5). Total nonadherent cells and CD4⁺ cells from wP-vaccinated animals secreted similar IFN- γ compared with aP cells, but no IL-5. IL-17 secretion was between levels for naïve and convalescent cells, suggesting that T-cell memory induced by wP vaccination is similar to natural infection, but the Th17 and Th1 memory responses were weaker.

Discussion

The introduction of whole-cell vaccines consisting of inactivated *Bordetella pertussis* organisms in the United States in the 1940s caused a precipitous decrease in pertussis incidence (27). However, over the past 30 y, pertussis has resurged in the United States. The resurgence began during the wP vaccine era, but the pace has quickened since aP vaccines were recommended for all primary and booster doses (11). This correlation has led many to hypothesize that aP vaccines are less effective on a population scale than the wP vaccines they replaced (10, 12, 13). Consistent with this notion, several recent observational studies concluded that children primed with aP vaccine had a twofold to fivefold greater risk of pertussis diagnosis compared with wP-primed children (19–22). Our results in nonhuman primates add to these findings by showing that animals vaccinated with wP cleared infection by a direct challenge twice as fast as animals vaccinated with aP. However, neither vaccine was able to prevent colonization as well as immunity from a previous infection.

Another hypothesis as to why pertussis is reemerging is that the duration of immunity in aP-vaccinated children is shorter than anticipated. Although some first-generation acellular vaccines had poor immunity and efficacy, double-blinded clinical trials and field-efficacy studies for the US-licensed acellular vaccines estimated the short-term efficacy to be excellent: ~85% after three doses and 98% after five doses (28–30). However, recent cohort and case-control studies concluded that 5 y following the fifth aP dose, children are fourfold to 15-fold more likely to acquire pertussis compared with within the first year, consistent with waning aP immunity (30–33).

We hypothesized an additional explanation for pertussis resurgence is that aP-vaccinated individuals can act as asymptomatic or mildly symptomatic carriers and contribute significantly to transmission in the population. Observational studies suggest that asymptomatic pertussis can occur in vaccinated children and adults based on PCR or serological data (34, 35). However, during the aP vaccine trials, participants were not screened for *B. pertussis* infection unless they presented with pertussis-like symptoms and at least 7–21 d cough (12). Therefore, no experimental data exist on whether vaccination prevents *B. pertussis* colonization or transmission in humans. In the present study we show that aP-vaccinated primates were heavily infected following direct challenge, and the time to clearance was not different compared with naïve animals. Similarly, there was no difference in the kinetics or peak level of colonization between aP-vaccinated and naïve animals that were infected by natural transmission. Importantly, we also show in two experiments that aP-vaccinated animals transmitted *B. pertussis* to naïve cage mates. Together these data form the key finding of this study: aP vaccines do not prevent infection or

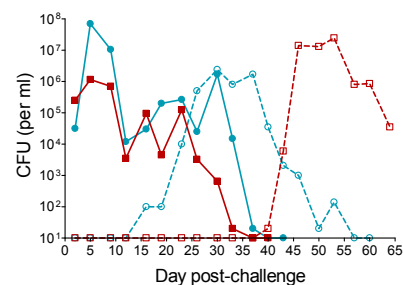


Fig. 3. Infected aP vaccinees can transmit pertussis to naïve contacts. Two animals vaccinated with aP were housed in separate cages, and each was directly challenged. Twenty four hours after challenge, an unchallenged naïve animal was placed in each cage. All animals were followed for colonization as in Fig. 1. One cage pairing is shown with turquoise lines with circles, and the other is shown with maroon lines with squares. Solid lines with closed symbols indicate the aP-vaccinated, directly challenged animals, and open symbols with dashed lines are used for the unchallenged, naïve contacts.

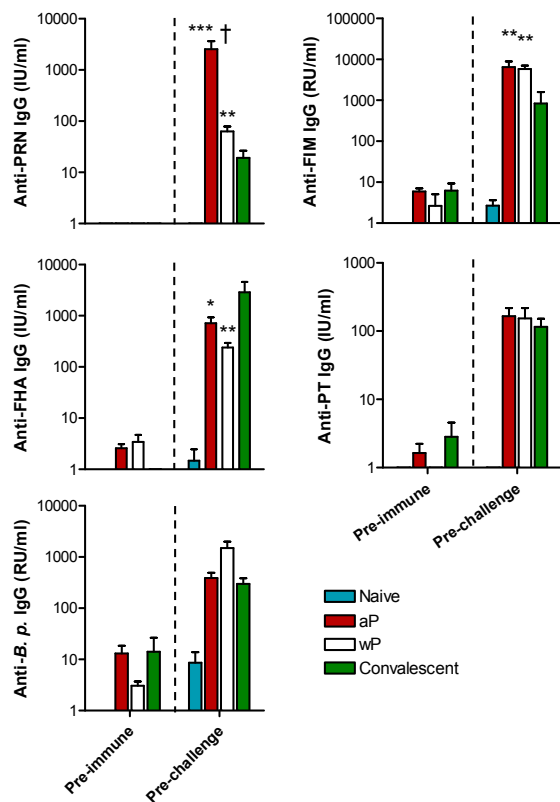


Fig. 4. Vaccination and previous infection induce robust serum antibody responses. Antibody responses to the four vaccine antigens—PRN, FIM, FHA, and PT—and to heat-killed *B. pertussis* (*B. p.*) were measured by ELISA. Preimmune sera were collected from vaccinated animals before immunization and from conv. animals before initial infection ($n = 3-4$ per group). Because Infanrix does not contain FIM, four Daptacel-vaccinated animals were included in the anti-FIM ELISA. Prechallenge sera were collected from all animals 1 wk before challenge. International Units (IU) or relative units (RU) in each sample were determined by comparing the responses to the WHO international standard pertussis antiserum on each plate. *** $P < 0.001$, ** $P < 0.01$, * $P < 0.05$ vs. Convalescent. † $P < 0.001$ vs. wP.

transmission of *Bordetella pertussis* even 1 mo after completing the primary vaccination series.

We show that wP, aP, and natural infection all induce high-antibody titers. The prechallenge titers in aP-vaccinated animals were generally equivalent or higher than those observed in convalescent and wP-vaccinated animals, suggesting that aP is immunogenic in baboons and that the inability to prevent infection was not due to low-antibody titers. Compared with the large number of clinical studies that have characterized the antibody response to pertussis infection and vaccination, very few have investigated pertussis-induced helper T-cell immune responses in humans. Taken as a whole, these limited data suggest that aP vaccination induces Th2 or mixed Th2/Th1 responses, whereas wP vaccination and natural infection induce a Th1 response (13). However, none of these studies tested for Th17 memory, a recently identified T cell that specializes in controlling extracellular bacterial infections at mucosal surfaces (24). Our data show that natural infection induced robust Th17 and Th1 immunity. Animals vaccinated with wP, which cleared infection faster than naive and aP-vaccinated animals, showed similar but weaker T-cell responses. wP vaccination is generally believed to induce strong Th1 responses, but what we observed here was relatively weak. This observation might be explained by heterogeneity in the manufacturing of different wP vaccines. Future studies will compare the immune response induced by wP vaccines produced by three different manufacturers. In comparison with natural infection and wP, aP-induced immunity was mismatched,

showing a Th2 response with a weaker Th1 response and no significant Th17 response.

Together, the cytokine and T-cell immunological data observed in baboons are generally consistent with those observed in mice (13). We previously showed that pertussis infection in baboons induces a mucosal immune response characterized by production of IL-17 and a variety of chemokines and cytokines associated with IL-17 signaling, including IL-6 and IL-8. This primary immune response correlated with long-lived Th17 and Th1 memory responses that lasted >2 y (36). Mice infected with *B. pertussis* also express mucosal IL-17, IL-6, and IL-8 homologs and induce Th17 and Th1 memory (37–40). Mice vaccinated with wP also develop Th17 and Th1 memory that results in partial protective immunity, similar to what we observed in the baboon model (41, 42). A recent report by Ross et al. (42) concluded that an aP containing PT, FHA, and PRN induces Th1, Th2, and Th17 immune responses in C57BL/6 mice (42). However, a previous study from the same group found Th1 and Th2 but no

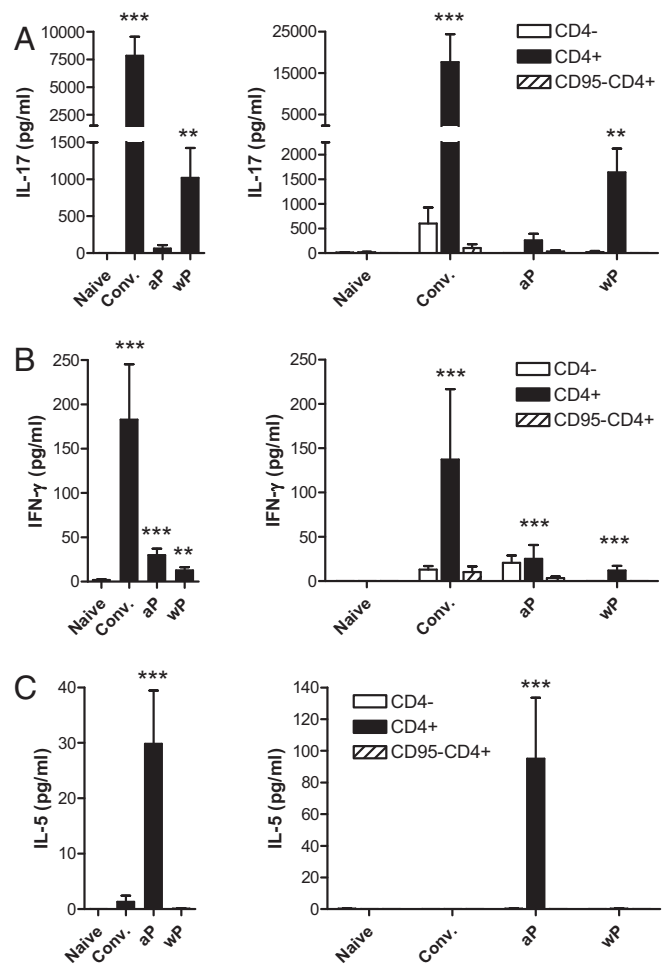


Fig. 5. Helper T-cell responses induced by vaccination and infection. PBMC collected from naive, aP-vaccinated, wP-vaccinated, and conv. animals 1 wk before infection were incubated overnight with either medium alone or medium containing heat-killed *B. pertussis* ($n = 3-4$ per group). For each growth condition, nonadherent cells were collected and either left unseparated (total nonadherent cells) or separated using anti-CD4 and anti-CD95 magnetic particles. Total nonadherent, CD4-, CD4+, and CD95-CD4+ cells were then cultured under the same conditions as before (with medium alone or stimulated with heat-killed *B. pertussis*). After 36 h, supernatants were collected and analyzed for IL-17 (A), IFN- γ (B), and IL-5 (C). Cytokine secretion in response to *B. pertussis* stimulation is presented for total nonadherent cells (Left) and separated cells (Right). *** $P < 0.001$, ** $P < 0.01$, * $P < 0.05$ vs. same fraction from naive animals.

significant Th17 responses in C3H/HeJ and C3H/HeN mouse strains vaccinated with an aP containing PT and FHA (41). Nevertheless, data from two clinical studies recently showed negligible Th17 recall responses (~ 10 pg/mL) in PBMC isolated from aP-vaccinated 4-y-old children before and after booster, suggesting aP does not induce Th17 memory in humans (43, 44).

Taken as a whole, the data presented in this study suggest that antibodies induced by aP vaccination are sufficient for preventing severe pertussis symptoms but do not mitigate colonization. Inhibition of leukocytosis likely occurs through antibody-mediated neutralization of PT, a toxin which interferes with leukocyte extravasation by blocking chemokine receptor signaling (1). The mechanism by which aP prevents coughing despite heavy bacterial colonization is not known but deserves further attention. On the other hand, induction of Th17/Th1 memory responses correlated with the ability to clear infection: convalescent and wP-vaccinated animals possessed strong Th17 responses and Th1 responses and cleared infection more quickly than aP-vaccinated animals which lacked Th17 responses but possessed Th1/Th2 memory. Although we have not definitively shown that Th17 cells are required for *B. pertussis* clearance, this correlation is consistent with the role these cells play in fighting extracellular bacterial infections at mucosal surfaces by inducing neutrophil chemotaxis. The current studies were not designed to look at immune cell recruitment to the respiratory tract, but additional experiments are underway to determine the role of neutrophils in the immune response to pertussis infection and vaccination in baboons. We are also investigating other possible mechanisms that could prevent mucosal colonization; for example, a possible role for IgA and IgD which are secreted in primate lower and upper respiratory tracts, respectively (45, 46).

The baboon model offers many advantages, chiefly the ability to investigate pertussis pathogenesis, transmission, and host immune responses to infection and vaccination in a primate species that is $>96\%$ genetically similar to humans (47). However, there are also several limitations associated with this model. There are far fewer animals available for research compared with smaller-animal models. In addition, there is a paucity of immunological reagents that are validated for baboons compared with mice and humans. Although antibodies against cell surface markers are generally cross-reactive, anti-cytokine antibodies tend to be much more species-specific. For this reason we have so far been unable to assess T-cell responses using intracellular cytokine staining and flow cytometry. This led us to develop the cell separation assay as an alternative method for phenotyping the memory T-cell responses induced by pertussis infection and vaccination (36). One limitation of our assay is that during the CD4⁺ cell purification, antigen-presenting cells such as macrophages and dendritic cells are removed after an overnight incubation. This likely explains the low IFN- γ secretion observed in all groups because antigen-presenting cells increase IFN- γ secretion by antigen-specific CD4⁺ T cells through a positive feedback loop (48). In line with this hypothesis, our previous data showed that restimulated whole PBMC from convalescent animals secreted much higher levels of IFN- γ . In addition, restimulation assays using human PBMC or murine splenocytes after infection or vaccination also show higher levels of secreted IFN- γ (42, 49). Together these observations suggest that although our assay is valuable for phenotyping T-cell memory, it likely underrepresents the magnitude of Th1 memory responses. We used heat-killed *B. pertussis* as an antigen for our restimulation assays because we believe this is the most relevant method for ex vivo simulation of T-cell memory recalled during infection. However, it is possible that this assay underdetects immune responses that would be observed had we used purified vaccine antigens. Another disadvantage of primate models is that it is not feasible to directly link an immune response to protection. Although protection from pertussis has been shown to be mediated by IFN- γ and, to a lesser extent, IL-17 signaling using knockout mouse strains lacking specific gene products (13),

the relative protection afforded by Th17 or Th1 responses in vaccinated or convalescent baboons or humans is not known.

Currently, a major focus of public health agencies is the prevention of pertussis infection in young infants who have not completed their primary aP series and have considerable morbidity and mortality to pertussis infection (1). One recommendation to reduce transmission of pertussis to infants is by “cocooning,” or vaccinating people who have contact with infants (11). Our data show that aP-vaccinated animals are infected and transmit pertussis to naïve contacts. Consistent with these findings, seroepidemiological studies have concluded that *B. pertussis* circulation is still high in countries with excellent aP uptake (27, 50), and a cross-sectional study showed that postpartum aP vaccination of mothers did not reduce pertussis illness in young infants (51). These data suggest that cocooning is unlikely to be an effective strategy to reduce the burden of pertussis in infants. However, it is important to note that our data in combination with human data show that vaccination with aP provides excellent protection from severe pertussis (52). Therefore, any short-term plan for addressing the resurgence of pertussis should include continued efforts to enhance aP immunization. However, to protect the most vulnerable members of the population and achieve optimal herd immunity, it will be necessary to develop a vaccination strategy that effectively blocks pertussis infection and transmission.

Materials and Methods

Ethics Statement. All animal procedures were performed in a facility accredited by the Association for Assessment and Accreditation of Laboratory Animal Care International in accordance with protocols approved by the Center for Biologics Evaluation and Research Animal Care and Use Committee and the principles outlined in the *Guide for the Care and Use of Laboratory Animals* by the Institute for Laboratory Animal Resources, National Research Council (53).

Bacterial Strains and Media. *B. pertussis* strain D420 was grown on Bordet–Gengou and Regan–Lowe plates prepared as described previously (17). Heat-killed *B. pertussis* was prepared by resuspending to an OD₆₀₀ of 0.90 (5×10^9 cfu/mL) in PBS and heating at 65 °C for 30 min.

Vaccination, Infection, and Evaluation of Baboons. Baboons obtained from the Oklahoma Baboon Research Resource at the University of Oklahoma Health Sciences Center were inoculated with human doses of aP or wP administered intramuscularly at 2, 4, and 6 mo of age. For studies using aP, equal numbers of animals were vaccinated with Daptacel (Sanofi Pasteur Ltd.) and Infanrix (GlaxoSmithKline). For wP, animals were vaccinated with Triple Antigen (Serum Institute of India Ltd.), which meets the World Health Organization (WHO) recommendations for potency. Naïve animals were age-matched but not vaccinated. Previously infected animals were clear of *B. pertussis* infection for 1 to 2 mo before reinfection. Direct challenge and transmission studies were performed as described previously (17, 18). The inoculum for each direct challenge was between 10^9 – 10^{10} cfu as determined by measurement of optical density and confirmed by serial dilution and plating to determine the number of cfu per mL of inoculum. Baboons were evaluated twice weekly as described previously for enumeration of circulating white blood cells and serum separation (17). Nasopharyngeal washes were diluted and plated on Regan–Lowe plates to quantify bacterial cell counts.

Isolation of PBMC and Cell Separation. Baboons were anesthetized, and PBMC were isolated from peripheral blood as described previously (36) and cryopreserved in RPMI-1640 medium supplemented with 10% (vol/vol) DMSO and 12.5% (wt/vol) BSA using Mr. Frosty containers (Nalgene). After thawing, cells were washed twice and nonadherent cells were collected as described previously. For each growth condition, cells were incubated overnight with either medium alone or medium containing heat-killed *B. pertussis* (50 bacteria:1 PBMC). Nonadherent cells were collected, and 2×10^6 cells were left unseparated (total nonadherent cells). Using the method previously described, 4×10^6 cells were separated using anti-CD4 magnetic particles, and another 4×10^6 cells were depleted of CD95⁺ cells and then separated with anti-CD4 magnetic particles (36). The following fractions were collected: Total nonadherent, CD4⁻, CD4⁺, and CD95⁻CD4⁺. After incubation with or without heat-killed *B. pertussis*, cells were pelleted and supernatants were collected for IL-17A quantitation by ELISA (Aniara) and quantitation of IFN- γ and IL-5 using the Milliplex MAP nonhuman primate kit according to the manufacturer’s instructions (Millipore). Data are presented as

the cytokine concentration secreted by *B. pertussis*-stimulated cells minus the basal concentration secreted by cells incubated with medium alone.

Detection of Serum Antibodies to Pertussis Antigens. Nunc Maxisorp 96-well plates were coated overnight with 0.2 µg/mL PT, 0.5 µg/mL FHA, 2 µg/mL PRN, or 0.2 µg/mL FIM (List Biologicals) as described previously (17, 54). For whole-bacteria ELISA, plates were coated overnight at 37 °C with heat-killed *B. pertussis* prepared as described above. Serum IgG for each antigen was measured as described previously (17). Each plate contained a standard curve from the WHO international standard pertussis antiserum (National Institute for Biological Standards and Control) used to assign international units for PT, FHA, and PRN and relative units for FIM and heat-killed *B. pertussis* by comparison with the linear portion of the standard curve. Because Infanrix does not contain FIM, only Daptacel-vaccinated animals were included in the anti-FIM ELISA.

Statistics. All data are reported as mean ± SEM. Statistical analyses were performed by ANOVA with post hoc *t* test using JMP (version 9) software (SAS Institute, Inc.). Antibody and cytokine data were normalized by log transformation before analysis.

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EXHIBIT 408

Pertactin-Negative *Bordetella pertussis* Strains: Evidence for a Possible Selective Advantage

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Background. A recent increase in *Bordetella pertussis* without the pertactin protein, an acellular vaccine immunogen, has been reported in the United States. Determining whether pertactin-deficient (PRN⁻) *B. pertussis* is evading vaccine-induced immunity or altering the severity of illness is needed.

Methods. We retrospectively assessed for associations between pertactin production and both clinical presentation and vaccine history. Cases with isolates collected between May 2011 and February 2013 from 8 states were included. We calculated unadjusted and adjusted odds ratios (ORs) using multivariable logistic regression analysis.

Results. Among 753 isolates, 640 (85%) were PRN⁻. The age distribution differed between cases caused by PRN⁻ *B. pertussis* and cases caused by *B. pertussis* producing pertactin (PRN⁺) ($P = .01$). The proportion reporting individual pertussis symptoms was similar between the 2 groups, except a higher proportion of PRN⁺ case-patients reported apnea ($P = .005$). Twenty-two case-patients were hospitalized; 6% in the PRN⁺ group compared to 3% in the PRN⁻ group ($P = .11$). Case-patients having received at least 1 pertussis vaccine dose had a higher odds of having PRN⁻ *B. pertussis* compared with unvaccinated case-patients (adjusted OR = 2.2; 95% confidence interval [CI], 1.3–4.0). When restricted to case-patients at least 1 year of age and those age-appropriately vaccinated, the adjusted OR increased to 2.7 (95% CI, 1.2–6.1).

Conclusions. The significant association between vaccination and isolate pertactin production suggests that the likelihood of having reported disease caused by PRN⁻ compared with PRN⁺ strains is greater in vaccinated persons. Additional studies are needed to assess whether vaccine effectiveness is diminished against PRN⁻ strains.

Keywords. *Bordetella pertussis*; pertactin; acellular vaccine; waning immunity; mutations.

In the United States, pertussis is currently the least well-controlled vaccine-preventable disease despite excellent vaccination coverage and 6 vaccine doses recommended between 2 months of age and adolescence. In 2012, several states reported epidemic levels of disease, with >48 000 cases reported nationwide, the highest number since 1955 [1]. Increased rates were seen across all ages, with the greatest increases reported in older

children and teens [2]. Waning immunity from acellular pertussis vaccines appears to be a significant factor leading to the increasing incidence [3–5]. Additionally, circulating *Bordetella pertussis* strains are undergoing genetic changes that may allow the organism to evade vaccine-induced immunity or be more virulent [6–10], which may be contributing to the increasing rates of pertussis. Notably, molecular analysis has identified a range of mutations resulting in *B. pertussis* not producing pertactin, a pertussis acellular vaccine immunogen thought to play a role in adherence to the upper respiratory epithelium [11–20]. All acellular pertussis vaccines currently used in the United States contain pertactin.

Bordetella pertussis isolates lacking pertactin production have been reported at low frequencies from Italy [19], France [20], Japan [13], and Finland [14] and at

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a high frequency from Australia [21]. A study of 1300 US surveillance and outbreak-related isolates from 1935 to 2012 documented a recent increase in pertactin-deficient (PRN⁻) *B. pertussis* isolates [18]. There have been no large studies in the United States assessing for differences in clinical presentation or case-patient vaccine receipt by whether or not *B. pertussis* is producing pertactin. Understanding the epidemiologic and clinical relevance of pertactin deficiency is necessary to fully elucidate the possible reasons for the current increase in pertussis in the United States.

MATERIALS AND METHODS

Isolates from 753 case-patients collected during May 2011 to February 2013 from 8 states were included in the analyses (Table 1). Six of the states participate as Enhanced Pertussis Surveillance/Emerging Infections Program Network sites (Colorado, Connecticut, Minnesota, New Mexico, New York, and Oregon) that routinely collect isolates on cases of all ages. The other 2 states, Washington and Vermont, experienced epidemic levels of pertussis during 2012 and had a large proportion of culture-confirmed cases and stored isolates available for molecular testing. The availability of isolates from each state was dependent on the routine pertussis diagnostic practices used by healthcare providers in the individual states; however, all available isolates from case-patients were sent to the Centers for Disease Control and Prevention for analysis.

Isolates were screened for an array of mutations that have been documented to cause pertactin deficiency by previously described polymerase chain reaction amplification and molecular sequencing methods [18]. Isolates not found to have a previously identified mutation by molecular methods were assessed for pertactin production by Western blots (previously described) [18] and/or enzyme-linked immunosorbent assay (ELISA). For the ELISA, microtiter plates were coated with *B. pertussis* cell preparations and incubated overnight at 37°C;

washed and incubated at 37°C for 1 hour each with 1:40 000 diluted sheep anti-PRN sera 97/558 (NIBSC, Hertfordshire, England) and then 1:2000 diluted peroxidase-labeled antisheep immunoglobulin G antibody (KPL, Gaithersburg, Maryland); and washed and incubated for 10 minutes with tetramethylbenzidine color substrate. Optical densities were read at 450 nm.

Routinely collected case-investigation data included demographics, pertussis symptoms, and vaccination history. Pertussis symptoms and vaccine histories were linked to isolates by unique identifiers. Case-patients aged <13 years of age were considered to be fully vaccinated if they received diphtheria and tetanus toxoids and acellular pertussis vaccine doses 1–3 by 1 year of age, dose 4 between ages 1 and 2 years, and dose 5 between ages 4 and 6 years. Those older than 13 years also needed to have received a dose of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis (Tdap) vaccine to be considered fully vaccinated. Only case-patients confirmed during case-investigation interviews as unvaccinated were classified as unvaccinated to distinguish them from those with missing dose information.

We calculated unadjusted odds ratios (ORs) as well as adjusted ORs using multivariable logistic regression analysis using SAS software, version 9.3. When modeling the association between pertactin production and vaccination receipt, we first compared all case-patients with at least 1 documented dose of pertussis vaccine to those documented to be unvaccinated. Second, vaccinated case-patients were restricted to those who were up-to-date according to schedule, and we only included vaccinated and unvaccinated case-patients at least 1 year of age to limit the population to those who were eligible to receive at least 3 doses of pertussis vaccine.

RESULTS

Overall, 85% (640/753) of isolates were PRN⁻. The proportion of PRN⁻ isolates ranged from 67% in Colorado to 100% in New Mexico; however, the number of isolates available for testing from each state varied widely (range, 4–255) (Table 1). Nine previously recognized mutations that result in pertactin deficiency were identified among the isolates, and 2 isolates with uncharacterized mutations were also found to be PRN⁻ by ELISA [18].

Table 2 provides a breakdown of case-patient demographic and clinical variables by *B. pertussis* pertactin production. Although the overall age distribution of case-patients with isolates was largely similar to the national age distribution of reported cases in 2012 (data not shown), we found a significant difference in the age distribution between the PRN⁻ and pertactin-producing (PRN⁺) groups (unadjusted $P = .01$). No significant differences were found between the 2 groups for sex or race. The proportion of case-patients reporting pertussis symptoms

Table 1. Number of *Bordetella pertussis* Isolates Collected Between May 2011 and February 2013

State Submitting Isolate	Pertactin Protein Deficient, No. (%)	Pertactin Protein Produced, No. (%)	Total
Colorado	6 (67)	3 (33)	9
Connecticut	13 (81)	3 (19)	16
Minnesota	83 (95)	4 (5)	87
New Mexico	4 (100)	0 (0)	4
New York	51 (94)	3 (6)	54
Oregon	68 (79)	18 (21)	86
Vermont	235 (92)	20 (8)	255
Washington	180 (74)	62 (26)	242
Total	640 (85)	113 (15)	753

Table 2. Case-Patient Demographic and Clinical Characteristics

Characteristic	Pertactin Protein Deficient, No. (%)	Pertactin Protein Produced, No. (%)	<i>P</i> Value*
Age group			
<6 mo	31 (5)	13 (12)	.01
6 mo–7 y	104 (17)	23 (21)	
7–11 y	152 (24)	22 (20)	
11–13 y	84 (13)	14 (13)	
13–18 y	172 (27)	17 (16)	
≥18 y	87 (14)	20 (18)	
Sex			
Male	308 (49)	47 (42)	.20
Female	322 (51)	67 (58)	
Race			
Black	13 (3)	2 (2)	.71
White	364 (91)	74 (89)	
Other	25 (6)	7 (8)	
Apnea			
Yes	126 (23)	37 (37)	.005
No	415 (77)	64 (63)	
Whoop			
Yes	170 (32)	34 (33)	.74
No	367 (68)	68 (67)	
Posttussive vomit			
Yes	239 (44)	46 (45)	.83
No	310 (56)	57 (55)	
Paroxysms			
Yes	487 (87)	92 (90)	.37
No	72 (13)	10 (10)	
Cyanosis			
Yes	10 (6)	7 (12)	.14
No	160 (94)	51 (88)	
Cough ≥2 wk			
Yes	462 (87)	86 (88)	.91
No	67 (13)	12 (12)	
Cough ≥3 wk			
Yes	182 (37)	33 (38)	.81
No	316 (63)	54 (62)	
Hospitalized			
Yes	16 (3)	6 (6)	.11
No	560 (97)	98 (94)	

* *P* value calculation did not include missing data.

was similar by PRN⁻ and PRN⁺, with the exception that a higher proportion of case-patients infected with PRN⁺ *B. pertussis* reported apnea (unadjusted *P* = .005; Table 2). The results for apnea remained significant after controlling for age group and state (*P* = .01). The proportion of case-patients reporting at least 2 or at least 3 weeks of cough did not differ by PRN⁻ and PRN⁺ status (Table 2). A total of 22 case-patients were hospitalized, with 6% in those with PRN⁺ *B. pertussis* compared to 3% in those with PRN⁻ *B. pertussis* (unadjusted *P* = .11).

Table 3. Case-Patient Counts by Vaccine Receipt

Vaccine Receipt	Pertactin Protein Deficient	Pertactin Protein Produced	Unadjusted OR (95% CI)	Adjusted OR (95% CI) ^a
Vaccinated: ≥1 dose	462	65	3.2 (1.9–5.3)	2.2 (1.3–4.0)
Unvaccinated	65	29	Referent	Referent
Vaccinated: Up-to-date, according to schedule and >1 y of age	248	26	3.7 (1.9–7.1)	2.7 (1.2–6.1)
Unvaccinated and >1 y of age	52	20	Referent	Referent

Abbreviations: CI, confidence interval; OR, odds ratio.

^a ORs adjusted for age group and submitting state.

Vaccinated case-patients receiving at least 1 dose had a significantly higher odds of having PRN⁻ *B. pertussis* compared with unvaccinated case-patients (unadjusted OR = 3.2; 95% confidence interval [CI], 1.9–5.3). When case-patients were restricted to those at least 1 year of age and vaccinated case-patients were further restricted to those according to schedule and fully up to date with pertussis vaccinations, the OR increased to 3.7 (95% CI, 1.9–7.1). When the analyses were adjusted for submitting state and age group, the ORs remained significant (Table 3).

DISCUSSION

Our finding of a 2- to 4-fold greater odds of having PRN⁻ *B. pertussis* when fully vaccinated according to schedule suggests that vaccinated persons have greater susceptibility to PRN⁻ strains compared with PRN⁺ strains. Waning of immunity in children and adolescents primed with pertussis acellular vaccines is believed to be one of the primary drivers behind the changing epidemiology in the United States. All birth cohorts born since 2000 in the United States have received exclusively acellular vaccines, including increasing numbers of preteens receiving a Tdap booster following acellular priming. As these cohorts age, they are experiencing higher rates of pertussis, and recent studies suggest that the lifelong risk of pertussis among children primed with acellular vaccines is greater than in those primed with whole-cell vaccines [22, 23]. Additionally, data from a nonhuman primate model indicate that acellular vaccines may not prevent infection, although they can prevent disease symptoms [24]. We hypothesize that the increasing population-level susceptibility to pertussis among children and adolescents primed with a limited number of acellular vaccine antigens may have contributed to increasing transmission

and allowed the rapid proliferation of PRN⁻ *B. pertussis* in the United States once those strains appeared. Furthermore, the multiple different mutations and mechanisms of pertactin non-production found in our sample, rather than clonal expansion of a single PRN⁻ strain, argues for a selective advantage to lacking the protein [18].

Pertactin was included in acellular vaccines due to its putative role in mediating adherence to the epithelium of the respiratory tract [25]. Acellular vaccines including pertactin generally had greater efficacy in licensure trials than those without [26–31], although the actual role of pertactin and antibodies directed against it remains unclear. Murine models provide evidence that pertactin may also play a functional role in resisting neutrophil-mediated clearance [32, 33], which could impact persistence of infection and, theoretically, transmission or severity of disease. Despite the 50-year record number of cases reported in 2012 and a high proportion caused by PRN⁻ *B. pertussis*, other than for apnea, we note no differences between clinical presentation of case-patients with PRN⁺ and PRN⁻ strains. Analysis from France similarly reported no major differences in assessed clinical outcomes in infants with PRN⁻ or PRN⁺ *B. pertussis* [15]. With no indication of diminished capacity to infect or alteration in clinical presentation of severity, the full ramifications of the appearance and rapid proliferation of pertactin deficiency are unclear. If pertactin plays an important role in infection and persistence, compensatory changes may have occurred; however, the corresponding genetic and proteomic changes that have filled this functional niche are unknown but warrant investigation. Absent substantial compensatory changes, renewed investigation into the role of anti-pertactin antibody in protection against pertussis is needed.

Although Enhanced Pertussis Surveillance sites provide high-quality data with minimal missing data, vaccination history collected through case investigations may still be incomplete. We expect some misclassification in vaccination receipt status. The misclassification is likely nondifferential between case-patients with PRN⁻ and PRN⁺ *B. pertussis*, meaning that the misclassification rates are likely similar between the groups and should bias the findings toward the null hypothesis of no association with vaccine receipt. Additionally, some case-patients included in our analysis could have received a 2-component acellular vaccine (discontinued in the United States in 2011) that does not include pertactin for all or some of the childhood doses. Because data on vaccine brand are often missing, we are unable to control for this in our results. The cases included in our analysis may not have represented the full spectrum of clinical presentation; milder cases may not have sought medical care, or clinicians may not have considered pertussis for atypical or mild illness.

Although our findings may be influenced by the predominant strains that are circulating in different geographic areas

and possibly by other factors such as age, we attempted to control for these potential differences in exposure by controlling for submitting state and age group in the multivariable models. Our findings remained significant when controlling for these factors. This suggests that our findings are not solely due to differences in the strains to which vaccinated and unvaccinated case-patients are exposed.

Although recently conducted effectiveness studies provide evidence that acellular vaccines continue to provide good protection against pertussis in the short term [3, 5, 34], additional studies are needed to further assess whether effectiveness or durability of protection of acellular vaccine is diminished against PRN⁻ strains. Ongoing surveillance for pertactin production in circulating *B. pertussis* is needed, as well as surveillance for other possible changes to the *B. pertussis* population including lack of expression of other immunogens included in acellular vaccines. Additional studies that bridge between the clinical and epidemiological findings and these novel molecular genomic and proteomic findings are necessary to continue to expand the evidence base for the development of more-effective vaccines against pertussis disease.

Notes

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EXHIBIT 409

Review

Systematic Review of Mucosal Immunity Induced by Oral and Inactivated Poliovirus Vaccines against Virus Shedding following Oral Poliovirus Challenge

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Abstract: Inactivated poliovirus vaccine (IPV) may be used in mass vaccination campaigns during the final stages of polio eradication. It is also likely to be adopted by many countries following the coordinated global cessation of vaccination with oral poliovirus vaccine (OPV) after eradication. The success of IPV in the control of poliomyelitis outbreaks will depend on the degree of nasopharyngeal and intestinal mucosal immunity induced against poliovirus infection. We performed a systematic review of studies published through May 2011 that recorded the prevalence of poliovirus shedding in stool samples or nasopharyngeal secretions collected 5–30 days after a “challenge” dose of OPV. Studies were combined in a meta-analysis of the odds of shedding among children vaccinated according to IPV, OPV, and combination schedules. We identified 31 studies of shedding in stool and four in nasopharyngeal samples that met the inclusion criteria. Individuals vaccinated with OPV were protected against infection and shedding of poliovirus in stool samples collected after challenge compared with unvaccinated individuals (summary odds ratio [OR] for shedding 0.13 [95% confidence interval [CI] 0.08–0.24]). In contrast, IPV provided no protection against shedding compared with unvaccinated individuals (summary OR 0.81 [95% CI 0.59–1.11]) or when given in addition to OPV, compared with individuals given OPV alone (summary OR 1.14 [95% CI 0.82–1.58]). There were insufficient studies of nasopharyngeal shedding to draw a conclusion. IPV does not induce sufficient intestinal mucosal immunity to reduce the prevalence of fecal poliovirus shedding after challenge, although there was some evidence that it can reduce the quantity of virus shed. The impact of IPV on poliovirus transmission in countries where fecal-oral spread is common is unknown but is likely to be limited compared with OPV.

Introduction

The development and licensing of inactivated poliovirus vaccine (IPV) in 1955 and subsequently of the live-attenuated oral poliovirus vaccine (OPV) in 1961 had an enormous impact on poliomyelitis in the Western world and raised the possibility of global eradication [1]. In 1988 the World Health Assembly adopted a resolution to eradicate poliomyelitis, which led to a successful global programme that has reduced the number of children paralysed by poliomyelitis from approximately 350,000 each year to 1,349 in 2010. Eradication of poliomyelitis through the use of these vaccines relies on herd immunity, whereby unimmunized children are less likely to become infected because neighboring children have been vaccinated. Eradication is achieved even if all children have not been successfully immunized

so long as the average number of secondary infections generated by each infected individual (the “reproduction number”) is less than 1.

Critically important to the herd immunity effect is the degree of mucosal immunity offered by vaccination against infection and shedding of poliovirus. The success to date of the Global Polio Eradication Initiative (GPEI) in eliminating wild-type poliovirus transmission from most of the world can largely be ascribed to mass vaccination campaigns with OPV. This vaccine was chosen not only because of the ease of administration, but also because of its superior ability to induce local intestinal mucosal immunity [2]. Immunization with live-attenuated vaccine mimics natural infection and results in the induction of a local secretory antibody (IgA) response that is associated with a reduction in shedding of poliovirus from the intestine [3,4]. In contrast, intramuscular injection of IPV induces serum antibodies but does not induce secretory IgA at the mucosal surfaces [3] and has a much more limited impact on the resistance of the intestine to infection [5]. However, IPV can induce gut-homing lymphocytes and an increase in the secretion of poliovirus-specific IgA among individuals who have been previously exposed to live-attenuated or wild-type poliovirus [6,7]. The impact of this immune boosting on resistance of the intestine to infection is unknown.

After the eradication of wild-type polioviruses, coordinated global cessation of the use of OPV is envisaged to prevent vaccine-associated paralytic poliomyelitis and the emergence of vaccine-derived polioviruses [8]. The majority of higher-income and some middle-income countries that previously used OPV and have been free of indigenous wild-type poliovirus transmission for several years have already switched to IPV in their routine immunization schedules for these same reasons. At the time of OPV cessation, many other countries are likely to want to use IPV for a period of

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time to protect their population against potential outbreaks of vaccine-derived or wild-type poliovirus. For this reason the GPEI has supported an aggressive programme of research towards developing an “affordable” IPV. This has included dose-reduction strategies based on the addition of adjuvants, intradermal administration, or reduced schedules; development of safer poliovirus “seed” strains to allow manufacture of IPV in lower-income countries; and engagement with vaccine manufacturers to determine market size and supply capacity [9–11]. There have also been calls for IPV use in areas with persistent wild-type poliovirus transmission where OPV immunogenicity and effectiveness are compromised [12]. In these settings a dose of IPV could, it is argued, boost intestinal IgA better than an additional dose of OPV.

The increasingly significant role of IPV highlights the need for a better understanding of the impact of this vaccine, alone and in combination with OPV, on nasopharyngeal and intestinal mucosal immunity. Studies will be especially important in settings with efficient fecal-oral transmission of poliovirus where herd-protection through the use of IPV has never been adequately demonstrated [13].

Mucosal immunity to poliovirus in an individual can be assessed by measuring vaccine poliovirus shedding after administration of a “challenge” dose of OPV. This is considered a reasonable surrogate for immunity to infection with wild-type polioviruses after natural exposure, although the relationship between protection of the individual and prevention of transmission in the population is not well defined.

A large number of poliovirus challenge studies of variable size, location, and design have been published over the last 50 years. Although a number of clinical trials that examine the impact of IPV on mucosal immunity in tropical settings are currently under way, review of published studies from a variety of settings will also be fundamental in providing the evidence base on which countries can make their decisions about the optimal vaccination strategy—in the final stages of eradication and after global cessation of OPV use. A number of review articles have examined some of the larger OPV challenge studies [2,14,15], but we are not aware of any attempt at a systematic review of the large and heterogeneous group of published studies.

Here we present a systematic review of challenge studies that examine poliovirus shedding in secretions in the nasopharynx and in stool samples collected from individuals 5–30 days after administration of OPV. We present a meta-analysis of the odds of shedding poliovirus among studies that compared two or more vaccination schedules using IPV, OPV, or a combination of these vaccines. The implications for poliovirus vaccination policy are discussed.

Results

Identified Studies

A total of 1,981 published articles were identified in the PubMed and Web of Knowledge databases using the search terms described in the Methods, and a further six studies were identified from literature cited in key references (Figure 1). Screening the title and abstracts of these articles resulted in 171 potentially relevant papers, which were read in full-text to identify 31 studies of poliovirus shedding in stool and four of shedding in the nasopharynx that met the inclusion criteria for the analysis (Tables S1 and S2). One publication included studies from three different countries, and these are included in the systematic review as separate studies [16].

Statistical Analysis

From the 31 studies of poliovirus shedding in stool, there were 22 studies that compared shedding after challenge with the same OPV among individuals with different vaccination histories (Table S1). Classification of these vaccination histories into unvaccinated, OPV-only, IPV-only, and combined schedules permitted comparison of OPV vaccinated with unvaccinated children (Figure 2), IPV vaccinated with unvaccinated children (Figure 3), OPV with IPV vaccinated children (Figure 4), and OPV vaccinated with combined OPV/IPV vaccinated children (Figure 5; combined schedules mainly involved simultaneous administration of IPV and OPV, see figure legend for details). Summary odds ratios (ORs) for these comparisons were calculated independently for each poliovirus serotype based on fixed ($n = 7$) or random ($n = 4$) effect models according to the significance of the χ^2 test for heterogeneity. Only one study compared serotype 2 poliovirus shedding in OPV-only and OPV/IPV vaccinated individuals, and so a summary OR was not calculated (Figure 5). There was no evidence for an association between individual study ORs and study size. In total, results from 18 studies were included in the meta-analyses that compared different vaccination histories.

Only four studies that met the inclusion criteria for the systematic review examined poliovirus shedding in the nasopharynx after administration of OPV (Table S2). Two of these studies compared IPV vaccinated with OPV vaccinated children and one compared IPV vaccinated with unvaccinated children. Very few samples were positive for poliovirus in these studies, and there was insufficient power to compare the prevalence of poliovirus in the nasopharynx of children with different vaccination histories.

Discussion

Systematic review and meta-analysis of published studies confirms the large protective effect of prior immunization with OPV on shedding of poliovirus in the intestine following administration of a challenge dose of OPV. The odds of vaccine poliovirus shedding was significantly reduced among children immunized solely with OPV compared with unvaccinated children (overall OR 0.13 [95% CI 0.08–0.24]). In contrast, IPV had no significant impact on the prevalence of challenge poliovirus shedding in stool samples, either on its own or when added to an OPV schedule (overall ORs 0.81 [0.59–1.11] and 1.14 [0.82–1.58], respectively). The superior impact of OPV on intestinal mucosal immunity is confirmed by the meta-analysis of studies that directly compared schedules that exclusively used OPV or IPV (overall OR for OPV compared with IPV immunized children was 0.15 [0.08–0.27]).

Although IPV does not significantly reduce the prevalence of poliovirus shedding in stool samples collected after challenge, it may reduce the duration and quantity of virus shed compared with unvaccinated children. Five studies that quantified poliovirus shedding found a 63%–91% (or an absolute 0.43–1.0 \log_{10}) reduction in the mean quantity of poliovirus shed in stool samples collected from IPV vaccinated compared with unvaccinated children [5,17–20] (Table S1). Three of these studies also examined the duration of shedding and two found a shorter period of shedding in IPV vaccinated children [17,19]. Using data from one of these studies [17], it has been noted that the combined reduction in both the quantity and duration of vaccine poliovirus shedding would reduce the total amount of poliovirus shed during the course of an infection by approximately 95% [15]. Because IPV is unable to induce a secretory IgA response in the intestine of naïve individuals, it has been suggested that secondary exposure to OPV shed by vaccinated children or to

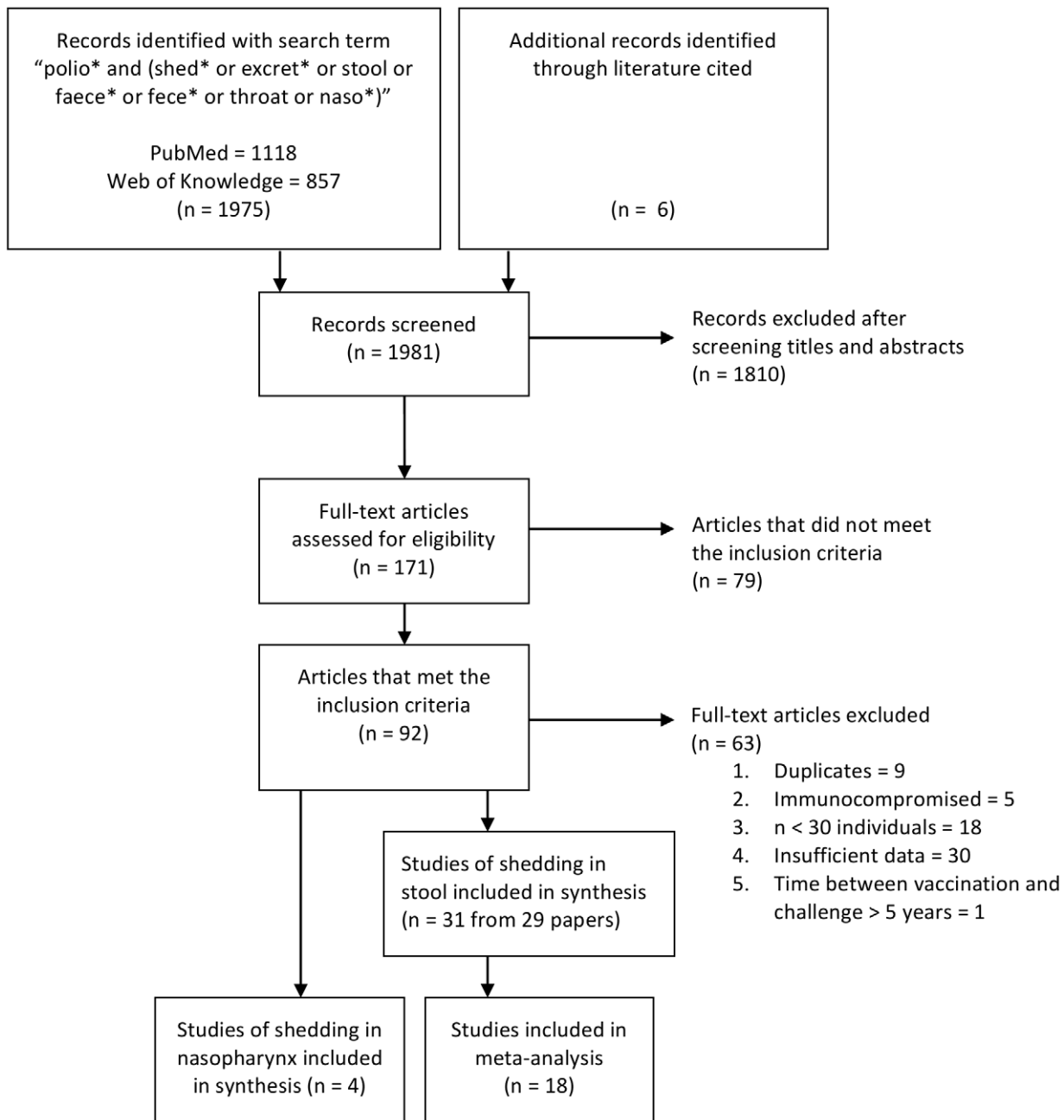


Figure 1. Flow diagram showing included studies according to PRISMA guidelines [46]. The number of published articles identified by the given search term for initial screening and the resulting studies identified and included in the systematic review and meta-analysis are shown. doi:10.1371/journal.ppat.1002599.g001

wild-type poliovirus in the environment may have primed the mucosal immune response of children in some of these earlier studies. The effect of IPV could therefore be at least partially explained by boosting of secretory IgA among mucosally primed individuals [7]. However, the low prevalence of non-challenge poliovirus serotypes in stool samples collected during these studies suggests that mucosal priming was limited, and in the more recent study the possibility of secondary exposure to poliovirus was deliberately excluded [18]. The impact of IPV in these studies is perhaps more likely to relate to local immunity induced by IPV through transudation of serum IgG rather than induction of a local secretory IgA response [7].

There were insufficient studies that examined the impact of IPV or OPV on poliovirus shedding in the nasopharynx after administration of OPV to draw any conclusions. Three studies of wild-type poliovirus shedding in the nasopharynx after natural exposure during epidemics in the United States in 1956–1960 found a lower prevalence of shedding among children who had a history of vaccination with IPV [21–24]. This reduction in shedding was not apparent when stool samples were examined. However, interpretation of these studies is limited by their small size and the potential for confounding by age and socioeconomic status between IPV immunization status and the degree of exposure to wild-type poliovirus.

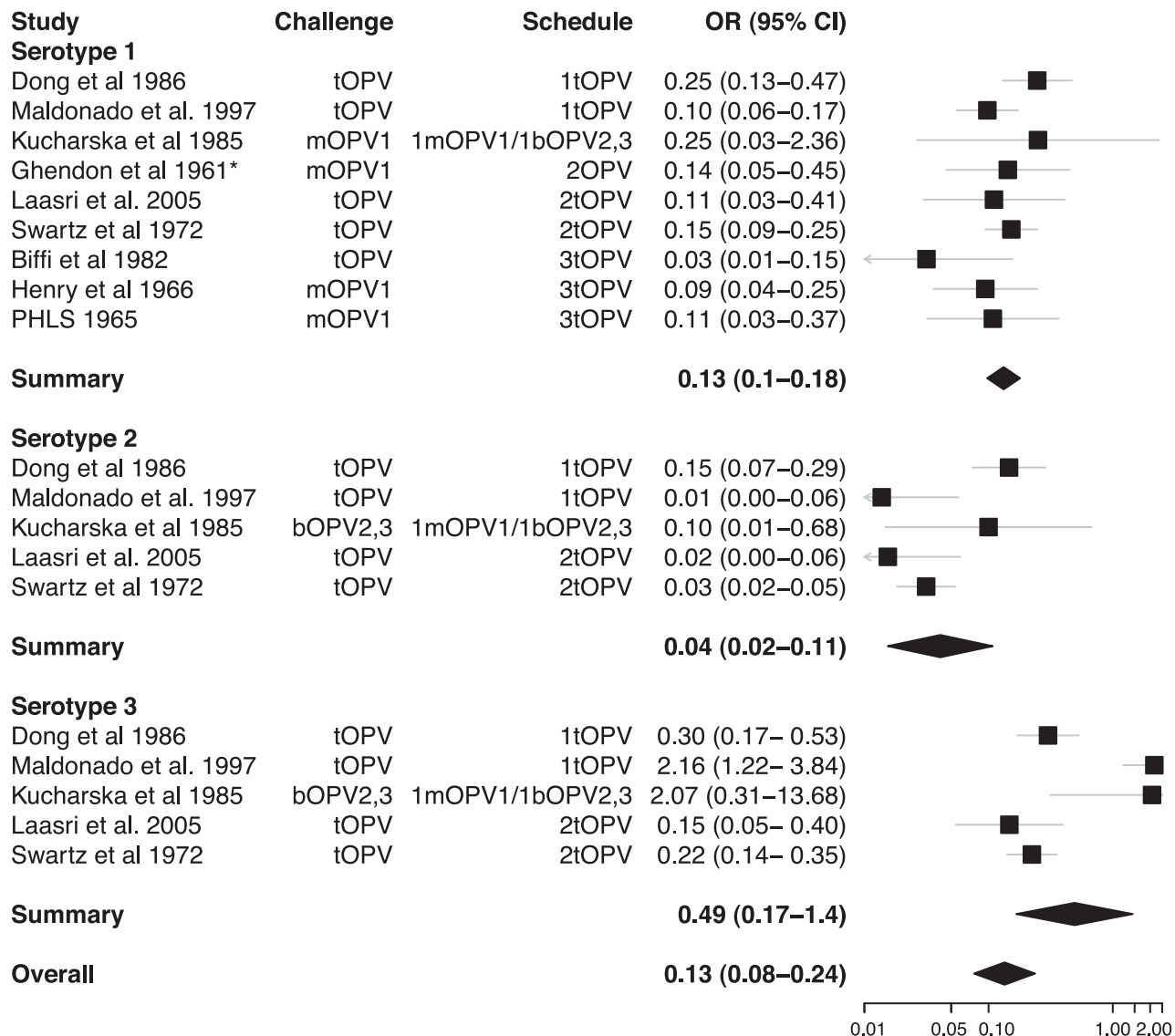


Figure 2. Relative odds of shedding vaccine poliovirus after challenge among individuals vaccinated with OPV compared with unvaccinated individuals. Odds ratios (ORs) and 95% confidence intervals for individual studies are indicated by the boxes and grey lines. The summary odds ratio for each serotype is given by a diamond with the 95% confidence interval (CI) indicated by its width. The χ^2 test for heterogeneity among studies was significant for serotypes 2 and 3 (p -values 0.33, <0.001, and 0.001 for serotypes 1, 2, and 3, respectively) and for the overall odds ratio (p -value<0.001). Details of the studies included are given in Table S1. *Ghendon et al. 1961 [17] compare vaccinated and unvaccinated children who were confirmed seropositive and seronegative, respectively. doi:10.1371/journal.ppat.1002599.g002

The relationship between reduced poliovirus shedding among vaccinated children observed in challenge studies and the impact of vaccination on wild-type or vaccine-derived poliovirus circulation is unknown and likely to vary significantly according to the characteristics of the population. Challenge with a high titer of attenuated vaccine (Sabin) poliovirus, which is homologous to the immunizing strain in the case of OPV vaccinees, is different than natural exposure to wild-type poliovirus, which has an estimated median infectious dose for humans of about 10 median tissue culture infectious doses (TCID₅₀) compared with about 10³ for Sabin polioviruses [25]. Furthermore, the relationship between the quantity of virus shed and the probability of onwards transmission is unknown and likely to depend on the importance of different routes of transmission and dissemination in the environment.

The impact of IPV on poliovirus circulation is expected to be more limited compared with OPV in areas with poor sanitation and efficient fecal-oral transmission because of the absence of any significant effect of this vaccine on the prevalence of poliovirus shedding in stool. However, there are no studies with adequate control populations that investigate the impact of IPV on wild-type poliovirus transmission in such areas [13]. Indeed, IPV has rarely been used in lower-income countries except as part of private practice. The recent switch to routine immunization with IPV in a pilot project in Yogyakarta in Indonesia and in a number of middle-income countries in South America may provide some information about the ability of IPV to prevent circulation of vaccine-derived polioviruses in areas with poor sanitation, given the continued use of OPV in neighboring areas or during national immunization days, respectively [26,27].

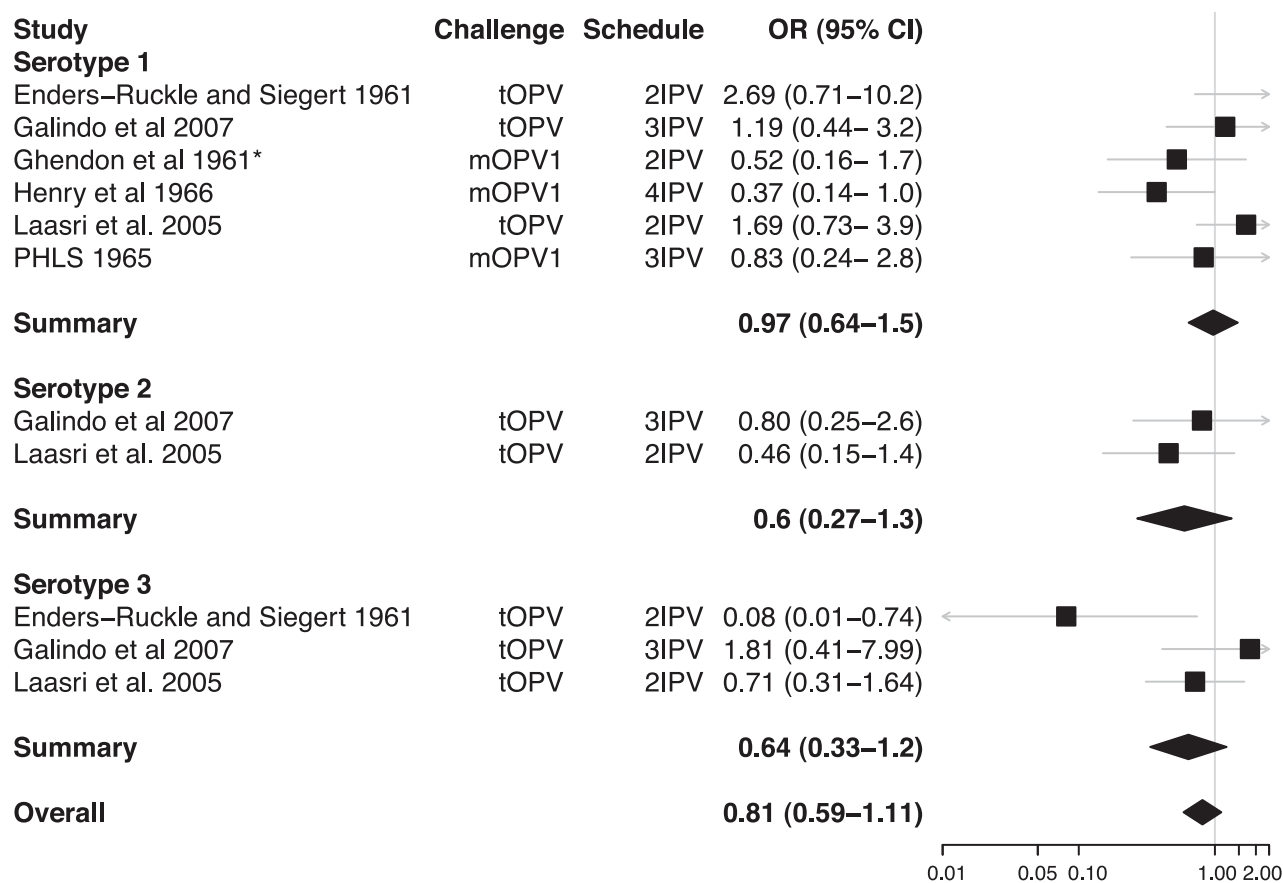


Figure 3. Relative odds of shedding vaccine poliovirus after challenge among individuals vaccinated with IPV compared with unvaccinated individuals. Labeling as for Figure 2. The χ^2 test for heterogeneity among studies was not significant for any serotype (p -values 0.11, 0.47, and 0.07) or for the overall odds ratio (p -value 0.10). *Ghendon et al. 1961 [17] compare vaccinated and unvaccinated children who were confirmed seropositive and seronegative, respectively. doi:10.1371/journal.ppat.1002599.g003

In northern European countries (France, Netherlands, Sweden, Finland, Iceland), IPV schedules have resulted in the eradication of wild-type polioviruses and protected against large outbreaks of paralytic disease for several decades [28]. The impact of IPV in these countries has been attributed to an effect of IPV on shedding in the nasopharynx in settings where oral-oral transmission is likely to predominate. Where importations of wild-type polioviruses to these countries have been documented, they have resulted in outbreaks ranging from a single case to over 100 cases of poliomyelitis [29–32]. These outbreaks have usually been restricted to unvaccinated communities, indicating the reduction in poliovirus transmission that results from vaccination with IPV. To date, no outbreaks have been reported from countries that have recently switched to exclusive use of IPV. However, there is some evidence from Israel that IPV-using communities are more at risk compared with OPV-using communities [33]. Furthermore, asymptomatic wild poliovirus shedding has been detected among IPV vaccinated children during outbreaks in these European countries, albeit at lower frequencies than in unvaccinated children [32,34]. IPV vaccinated children may therefore play a role in the circulation of imported wild poliovirus, and for this reason these outbreaks have usually been controlled through the reintroduction of OPV to induce adequate mucosal immunity to stop transmission.

In some of the comparisons of vaccination schedules, the meta-analysis identified significant heterogeneity in the OR from

different studies. Heterogeneity is likely to arise from a number of sources, including variable times for sample collection after challenge, different numbers and timing of vaccine doses prior to challenge, and variable laboratory procedures, as well as unmeasured factors such as the prevalence of enteric infections that may interfere with vaccine poliovirus shedding. Indeed, the prevalence of challenge poliovirus shedding was highly variable among studies, even for those that examined very similar vaccination schedules (Table S1). There were insufficient studies to permit a formal meta-regression model that included these variables. However, we did examine some of them by stratifying the meta-analysis and present the results together with the number of doses of vaccine received prior to challenge because of the association of this variable with the prevalence of shedding (Figures 2–5). For example, studies that compared poliovirus shedding among children who had received just a single dose of OPV with unvaccinated children typically found a limited impact on serotype 3 poliovirus, presumably because of the poor immunogenicity of a single dose of serotype 3 Sabin poliovirus, particularly in the trivalent formulation [35].

Despite over 50 years of vaccination with Salk's IPV, questions remain about the ability of this vaccine to prevent poliovirus circulation in remaining polio-endemic countries. In addition, basic immunology research is required to better understand the mucosal immune response to both IPV and OPV, and in particular the adaptive cellular and innate components [36,37].

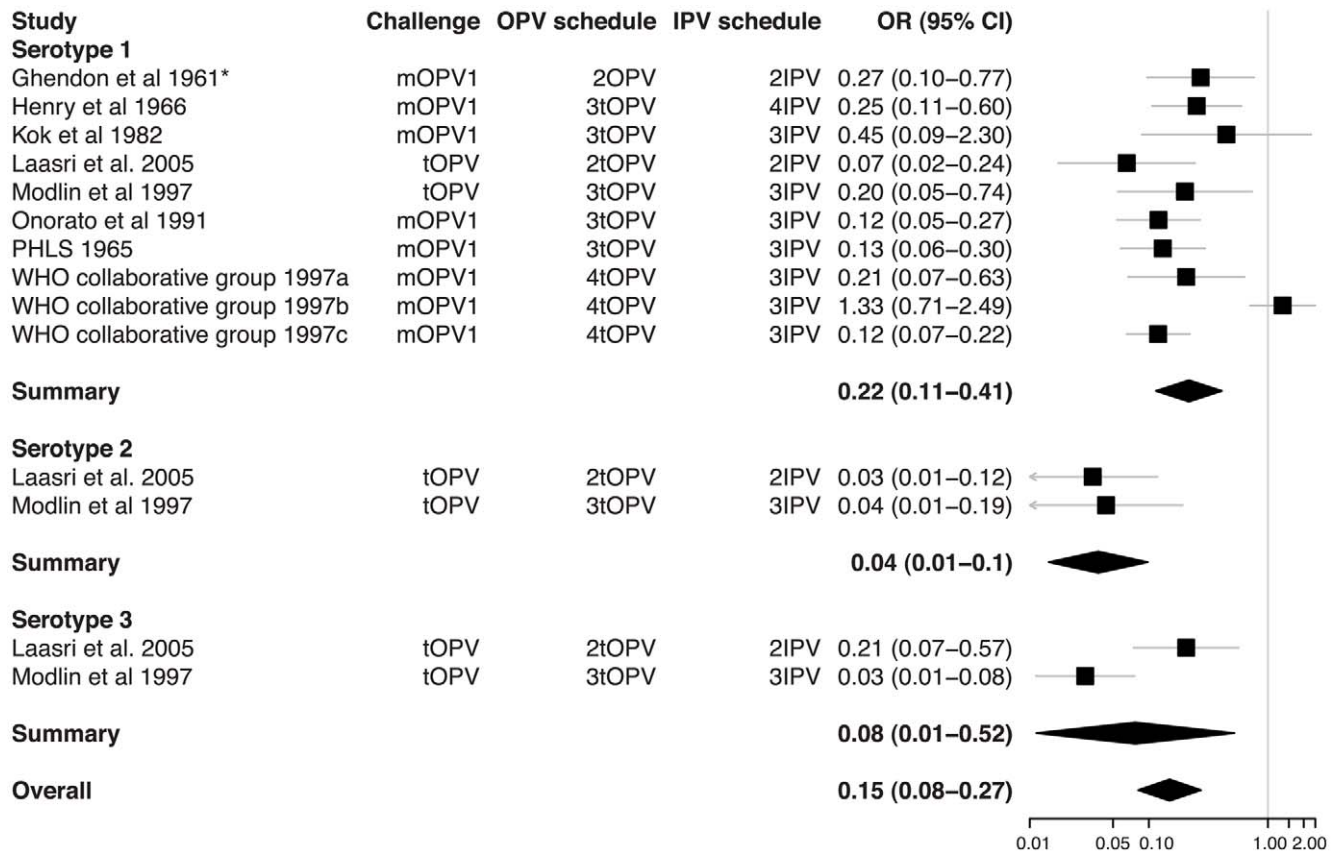


Figure 4. Relative odds of shedding vaccine poliovirus after challenge among individuals vaccinated with OPV compared with IPV. Labeling as for Figure 2. The χ^2 test for heterogeneity among studies was significant for serotypes 1 and 3 (p -values < 0.001, 0.79, and 0.01 for serotypes 1, 2, and 3, respectively) and for the overall odds ratio (p -value < 0.001). *Ghendon et al. 1961 [17] compare vaccinated and unvaccinated children who were confirmed seropositive and seronegative, respectively. doi:10.1371/journal.ppat.1002599.g004

Recent evidence from India for waning intestinal immunity to poliovirus within a year of vaccination with OPV [38] and identification of wild-type polioviruses in stool samples from OPV immunized children [39] has generated interest in the potential for IPV to boost intestinal immunity among these children. Studies of immune boosting following IPV or OPV are therefore currently under way to assess the possible role for IPV in combination with OPV to interrupt wild-type poliovirus transmission in endemic countries. After eradication of wild-type polioviruses and global cessation of vaccination with OPV, the role of IPV in lower-income countries has yet to be defined. Research towards an affordable IPV aims to provide the option to use this vaccine during routine immunization and could protect children from poliomyelitis in the event of an outbreak of wild-type or vaccine-derived poliovirus. It is unknown whether this vaccine would limit the spread of poliovirus, but it would potentially provide the protection needed before an outbreak response using OPV. Continued research and programmatic use of IPV will eventually provide evidence for the impact of IPV on poliovirus circulation in countries with fecal-oral transmission of infection. It is hoped that this evidence will emerge in the context of successful global eradication of poliomyelitis.

Materials and Methods

Identification and Review of Studies

A literature search was carried out in May 2011 using the PubMed (<http://www.ncbi.nlm.nih.gov>) and ISI Web of Knowl-

edge (<http://isiknowledge.com>) citation databases by searching title, abstract, and keywords with the search term “polio* and (shed* or excret* or stool or faece* or fece* or throat or naso*)”. The asterisk functions as a wildcard that permits partial word matching. We did not apply any language or publication restrictions except the restrictions of the databases themselves. Additionally, the bibliographies of key studies and reviews were examined to identify further relevant studies [2,14,40]. Publications in languages other than English that did not provide an English summary were translated by the authors or proficient speakers.

The titles and abstracts of articles identified by the initial search were screened and those that did not describe measures of poliovirus-specific immunity or shedding of vaccine poliovirus were removed. Full-text copies of the remaining articles were read using documents sourced from the original electronic journals or the holdings of the British Library. Data on the prevalence and quantity of vaccine poliovirus shed in nasopharyngeal or stool samples were extracted from those articles that met the inclusion criteria. These were: 1) study records the prevalence of vaccine poliovirus shedding in stool or nasopharyngeal samples collected after administration of a challenge dose of live-attenuated poliovirus; 2) samples collected 5–30 days after challenge (shedding of virus up to 4 days after challenge was excluded, because it has been suggested that this can be the result of transient passage of vaccine rather than infection of the mucosal surfaces [41]). Studies were excluded if they: 1) duplicated findings

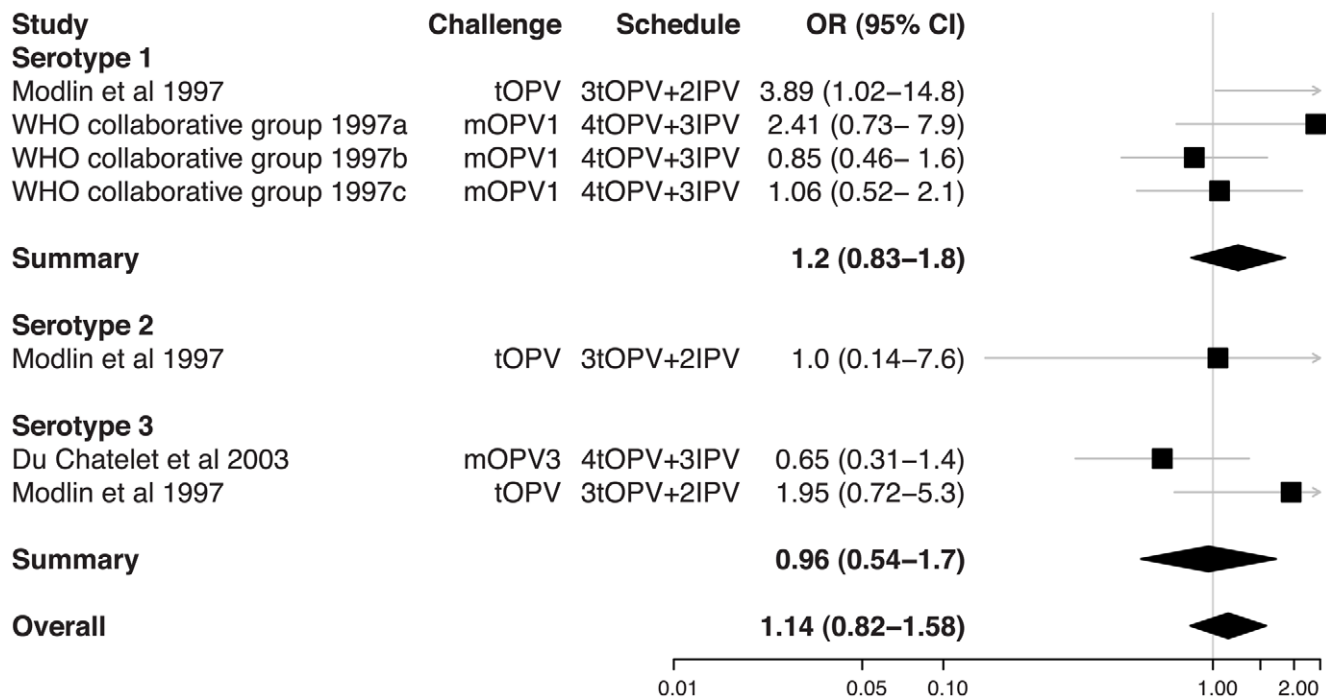


Figure 5. Relative odds of shedding vaccine poliovirus after challenge among individuals vaccinated with IPV in addition to OPV compared with individuals vaccinated with OPV only. Labeling as for Figure 2. The schedule indicates the number and type of OPV doses received by both groups and the number of doses of IPV that were added in the intervention group. In two studies, IPV was administered simultaneously with OPV at 6, 10, and 14 weeks (Modlin et al. 1997 [47] and du Chatelet et al. 2003 [48]), and in one study IPV was administered before and at the same time as OPV (schedule was IPV, IPV/OPV, OPV, OPV at 2, 4, 6, 15 months; WHO Collaborative Study Group on Oral and Inactivated Poliovirus Vaccines 1997 [49]). The χ^2 test for heterogeneity among studies for serotypes 1 and 3 was not significant for each serotype (p -values 0.13 and 0.08) or for the serotypes combined (p -value 0.14). doi:10.1371/journal.ppat.1002599.g005

reported earlier; 2) included immuno-compromised individuals; 3) included fewer than 30 individuals; 4) included insufficient information describing poliovirus serotype, vaccine schedules prior to challenge, or prevalence of shedding by individual rather than by sample; 5) challenged with OPV more than 5 years after vaccination. These criteria ensured consistent information was available for all studies, minimizing the risk of selective reporting of favorable results within a study.

Data that were extracted from studies meeting the inclusion criteria were the vaccine type and schedule prior to challenge, challenge vaccine type and dose, the nature of the sample, and the laboratory methods (cell culture-based versus direct detection using real-time PCR). The number of individuals who shed or did not shed vaccine poliovirus was recorded by serotype and time of sample collection. Where samples were collected at multiple time points, these data were recorded separately. Data on the quantity of vaccine poliovirus shed based on titration of samples or quantitative PCR were recorded where available. We also recorded the mean duration of shedding when given or estimated this from the data where possible by taking the mean of an exponential curve fit to the prevalence of shedding over time using a least-squares approach. Data were extracted independently by the two authors and compared for errors before producing a consolidated database. Where reported data were incomplete, an effort was made to contact the authors of the relevant studies.

Statistical Analysis

We included challenge studies that compared shedding of challenge poliovirus across two or more vaccination schedules in a meta-analysis. Where stool samples were available for more than

one time point, we used data from the sample taken closest to 7 days after challenge. For the purposes of the meta-analysis, schedules were grouped into four categories—unvaccinated, trivalent OPV only, IPV only, and combined schedules—and the relative odds of poliovirus shedding calculated in pairwise comparisons between these groups. There were insufficient studies of monovalent or bivalent OPV immunization schedules to warrant a separate category for these vaccines. We only compared combined schedules with OPV or IPV-only schedules where the combination schedule involved the administration of additional doses of IPV (we did not, for example, include studies that compared a schedule of six doses of trivalent OPV with a schedule of five doses of trivalent OPV and one dose of IPV, as examined in some studies, e.g., [42]). Evidence for heterogeneity among studies was assessed on the basis of the χ^2 statistic [43]. Summary ORs and 95% confidence intervals were calculated on a log scale assuming either fixed effects or normally distributed random effects among studies according to the results of the χ^2 test [44]. The association between the individual study ORs and study size was examined for evidence of potential publication bias. All analyses were implemented in the R programming language using the rmeta package [45].

Supporting Information

Checklist S1 PRISMA statement.
(DOC)

Table S1 Studies included in the systematic review that examined poliovirus shedding in stool samples taken after administration of OPV. Vaccination schedules are given

as the number of doses followed by the type of vaccine. tOPV = trivalent OPV, mOPV1 = serotype 1 monovalent OPV, mOPV3 = serotype 3 monovalent OPV, bOPV2,3 = bivalent OPV containing serotypes 2 and 3. - = not available. Mean duration of shedding was estimated from the fit of an exponential curve to the prevalence of shedding over time unless given directly in the paper.
(DOCX)

Table S2 Studies included in the systematic review that examined poliovirus shedding in nasopharyngeal secre-

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EXHIBIT 410

Influenza Vaccine Effectiveness in the Community and the Household

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(See the Editorial Commentary by Treanor and Szilagyi on pages 1370–2.)

Background. There is a recognized need to determine influenza vaccine effectiveness on an annual basis and a long history of studying respiratory illnesses in households.

Methods. We recruited 328 households with 1441 members, including 839 children, and followed them during the 2010–2011 influenza season. Specimens were collected from subjects with reported acute respiratory illnesses and tested by real-time reverse transcriptase polymerase chain reaction. Receipt of influenza vaccine was defined based on documented evidence of vaccination in medical records or an immunization registry. The effectiveness of 2010–2011 influenza vaccination in preventing laboratory-confirmed influenza was estimated using Cox proportional hazards models adjusted for age and presence of high-risk condition, and stratified by prior season (2009–2010) vaccination status.

Results. Influenza was identified in 78 (24%) households and 125 (9%) individuals; the infection risk was 8.5% in the vaccinated and 8.9% in the unvaccinated ($P = .83$). Adjusted vaccine effectiveness in preventing community-acquired influenza was 31% (95% confidence interval [CI], –7% to 55%). In vaccinated subjects with no evidence of prior season vaccination, significant protection (62% [95% CI, 17%–82%]) against community-acquired influenza was demonstrated. Substantially lower effectiveness was noted among subjects who were vaccinated in both the current and prior season. **There was no evidence that vaccination prevented household transmission once influenza was introduced; adults were at particular risk despite vaccination.**

Conclusions. Vaccine effectiveness estimates were lower than those demonstrated in other observational studies carried out during the same season. The unexpected findings of lower effectiveness with repeated vaccination and no protection given household exposure require further study.

Keywords. influenza; vaccine effectiveness; households with children.

Annual evaluation of influenza vaccine effectiveness, which may vary from year to year, is critical to inform the medical community, maintain public confidence in the vaccine, and determine the effect of virus drift on protection. Efficacy determinations with random assignment

to vaccine or placebo interventions are no longer ethically acceptable in the United States given the current recommendation for universal vaccination [1]. As a result, there has been increased emphasis on use of observational studies for determination of effectiveness.

Innovative observational approaches have been developed to estimate vaccine effectiveness with laboratory-confirmed outcomes, particularly in preventing medically attended acute respiratory infections (MAARI). Recent MAARI studies in Europe, Canada, and the United States have used an approach in which vaccine effectiveness is estimated by comparing vaccination coverage in persons who test positive for influenza with those who test negative [2–5]. These studies

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utilize a variation of the traditional case-control design and it is not yet clear whether they adequately account for the range of biases typically associated with such studies [6].

There has been a long tradition of using household cohorts to study incidence and transmission of respiratory illnesses of all severities [7]. Households are thought to play a major role in community spread of influenza and as such have been the focus of planning for community influenza control [8, 9]. Data from household studies carried out decades ago were vital more recently in developing models to determine national response to an influenza pandemic [8, 10]. During the recent pandemic, a limited number of studies of influenza transmission and vaccine effectiveness at the household level were carried out [11, 12].

We recruited and followed a cohort of 328 households during the 2010–2011 influenza season, and estimated vaccine effectiveness in preventing symptomatic laboratory-confirmed influenza whether medically attended or not. This study offered the unique opportunity to examine vaccine effectiveness in preventing community-acquired influenza and influenza acquired in persons with confirmed household exposure.

METHODS

Recruitment and Enrollment

The cohort of households was derived from persons who had selected a primary healthcare provider from within the University of Michigan Health System based in Ann Arbor. Eligible households (shared residence) were comprised of at least 4 members, at least 2 of whom were children aged <18 years. Households with appropriate composition and local residence were targeted for study enrollment by direct mail.

Interested households attended an enrollment visit at the research study site at the University of Michigan, School of Public Health (UM-SPH); adult household members provided written informed consent for participation for themselves and their children, and children aged 7–17 years provided their oral assent. Study eligibility was verified, and member demographic data recorded. Adult household members reported, for themselves and their children, whether or not influenza vaccine had been received for the current season. The study was approved by the institutional review board at the University of Michigan Medical School.

Influenza Surveillance

Surveillance was initiated in October 2010 and carried out through the end of local influenza circulation in April 2011. Households were instructed at enrollment and via weekly telephone or email reminders to report all acute respiratory illnesses defined by 2 or more of the following symptoms:

cough, fever or feverishness, nasal congestion, chills, headache, body aches, or sore throat [13]. This case definition was intended to facilitate collection of specimens from even mild illnesses. Subjects with eligible illnesses attended an illness visit (at the research study site) within 7 days of illness onset and had a throat swab (or nasal swab in children age <7 years) collected for influenza virus identification. Illnesses were followed for collection of data on illness characteristics, including whether or not the participant sought medical attention.

Collected specimens were tested for influenza identification by means of real-time reverse transcriptase polymerase chain reaction (RT-PCR) using the SuperScript III Platinum One-Step Quantitative RT-PCR system and an ABI 7500 RT-PCR system platform (Life Technologies). The primers and probes used were developed by the Influenza Division of the Centers for Disease Control and Prevention, and designed for universal detection of influenza A and B, and subtype identification of influenza A viruses. Laboratory tests were performed in the investigators' respiratory virus laboratory at UM-SPH.

Statistical Analyses

Households were characterized by size and composition, and subjects by demographics, health history, and vaccination status. Receipt of influenza vaccine was defined on the basis of documented evidence of vaccination in health system medical records or the Michigan Care Improvement immunization registry. Medical records were also reviewed to document the presence of health conditions considered high risk for complications of influenza [1]. Associations of subject characteristics with influenza vaccination status and influenza outcomes were examined and compared. Categorical data were analyzed using a χ^2 test.

Cox proportional hazards models were used to estimate the effectiveness of influenza vaccination at least 14 days prior to symptom onset in preventing laboratory-confirmed influenza. To adjust for correlation of exposures and outcomes among subjects in the same household, we computed robust variances for model parameter estimates using sandwich estimators [14]. Vaccine effectiveness was calculated as $100 \times (1 - \text{hazard ratio})$, and estimated in both unadjusted and adjusted models. Adjusted models included prespecified potential confounders (age and presence of a high-risk health condition); in preliminary analyses, no other confounders were identified. Stratified models examined the influence of prior season (2009–2010) vaccination status on effectiveness estimates based on evidence of effect modification demonstrated in preliminary analyses. Effect modification was noted for both prior seasonal (trivalent) and prior pandemic (monovalent) vaccination, but was statistically significant only for prior seasonal vaccination. Receipt of prior season vaccine(s) was based on documented evidence of vaccination in medical records.

Analyses estimated vaccine effectiveness in preventing community-acquired influenza (household index cases) and, separately, household-acquired influenza (secondary cases resulting from exposure to household index cases). A secondary (household-acquired) case was defined by transmission link to an index case if both cases were the same influenza type/subtype and illness onset in the secondary case occurred from 1 to 7 days after illness onset in the index case. Vaccine effectiveness in the community was estimated by comparing the hazard of laboratory-confirmed influenza among vaccinated and unvaccinated subjects; cases that were linked by transmission (household-acquired) were censored at the time of

illness onset. Vaccine effectiveness in the household was estimated by comparing the hazard of laboratory-confirmed influenza, among those vaccinated and unvaccinated subjects exposed to a household index case. Only the first influenza illness was considered for those individuals with multiple influenza outcomes in analysis of community-acquired influenza (3 outcomes excluded); similarly, only influenza outcomes resulting from the first introduction of influenza to a household were considered (4 outcomes excluded). Additional analyses estimated influenza type/subtype-specific vaccine effectiveness for community-acquired illnesses. All statistical analyses were conducted using SAS (release 9.2, SAS Institute) software. A *P* value <.05 was considered to indicate statistical significance.

Table 1. Characteristics of Participating Household Members by Documented Influenza Vaccine Receipt and Influenza Outcomes

Participant Characteristics	All Subjects ^a	Documented Influenza Vaccination ^{b,c}	Influenza Positive Cases ^d
Age category			
<9 y	468 (32.5)	323 (69.0)**	70 (15.0)**
9–17 y	371 (25.7)	225 (60.6)	23 (6.2)
18–49 y	544 (37.8)	280 (51.5)	31 (5.7)
50–72 y	58 (4.0)	38 (65.5)	1 (1.7)
Race categories			
White	1097 (76.1)	662 (60.3)	103 (9.4)
Asian	120 (8.3)	81 (67.5)	6 (5.0)
Black	83 (5.8)	40 (48.2)	5 (6.0)
Other/unknown	141 (9.8)	83 (58.9)	11 (7.8)
Sex			
Female	728 (50.5)	458 (62.9)*	57 (7.8)
Male	713 (49.5)	408 (57.2)	68 (9.5)
Documented high-risk health condition			
Any	162 (11.2)	122 (75.3)**	19 (11.7)
None	1279 (88.8)	744 (58.2)	106 (8.3)
Documented influenza vaccination^b			
Yes	866 (60.1)	...	74 (8.5)
No	575 (39.9)	...	51 (8.9)
Total	1441(100)	866 (60.1)	125 ^e (8.7)

Household Influenza Vaccine Effectiveness (HIVE) Study, Ann Arbor, Michigan (2010–2011 Influenza Season). Data are presented as No. (%).

^a Denominator for percentages presented in this column is all subjects (N = 1441).

^b At least 1 influenza vaccine given anytime during the 2010–2011 vaccination period as documented in the medical record or state registry.

^c Denominator for percentages presented in this column is all subjects (vaccinated and unvaccinated) in the given characteristic row.

^d Denominator for percentages presented in this column is all subjects (with and without influenza) in the given characteristic row.

^e One hundred thirty influenza cases were identified in 125 individuals. The characteristics of those individuals are presented here.

* χ^2 *P* < .05, comparing vaccinated and unvaccinated subjects or subjects with and without laboratory-confirmed influenza.

** χ^2 *P* < .001, comparing vaccinated and unvaccinated subjects or subjects with and without laboratory-confirmed influenza.

RESULTS

Characteristics of Households and Participants

Enrollment of households closed in October 2010 when the sample size goal was met; a total of 524 (12% of 4511 targeted households) expressed an interest in study participation, and 328 households with 1441 participants were enrolled. Household size ranged from 4 to 9 members (mean, 4.4 [SD, 0.7]). Based on enrollment criteria, all households had at least 2 participating children; 238 (73%) households had 1 or more young children (age <9 years).

Participant characteristics, including distributions of vaccination status and influenza outcomes, are presented in Table 1. Among the 1441 enrolled individuals, 58% were children aged <18 years, and 99% reported health insurance coverage. Race categories reflected the local community. Eleven percent of subjects had medical record documentation of health conditions placing them at increased risk of complications from influenza [1].

Overall, 866 (60%) participants had medical record or immunization registry documentation of influenza vaccine receipt for the 2010–2011 season. Sixty-eight (5%) additional subjects reported vaccine receipt that could not be documented; all provided information on type, date, and place of vaccine receipt. Documented vaccine coverage significantly varied by age category (*P* < .001); coverage was lowest among adults aged 18–49 years (52%). Among children aged <9 years, 323 (69%) had documented receipt of at least 1 dose of vaccine and 252 (54%) were considered fully vaccinated [1]. Female subjects were significantly more likely than male subjects to have documented vaccine receipt (*P* = .028); 75% of subjects with 1 or more high-risk health conditions were vaccinated compared with 58% of subjects without high-risk conditions (*P* < .001). Among vaccinated subjects, 758 (88%) had documented receipt of an inactivated vaccine, and 108 (12%) the live attenuated vaccine; children were the primary

recipients of the live attenuated vaccine (96% of doses administered).

Illness Surveillance and Influenza Outcomes

From October 2010 through April 2011, 624 (43%) individuals from 238 (73%) households reported 1028 acute respiratory illnesses and 983 (96%) specimens were collected. All specimens were tested for influenza by RT-PCR and 130 (13%) were determined to be positive; influenza circulated locally between early January and early April 2011. Among the influenza cases, 59 (45%) were identified as influenza type A (H3N2), 44 (34%) type B, 26 (20%) type A (pH1N1), and 1 (1%) type B/type A (pH1N1) coinfection. Based on national data, circulating influenza strains were considered antigenically matched to the vaccine strains (A/California/7/2009 [pH1N1], A/Perth/16/2009 [H3N2], and B/Brisbane/60/2008) for the 2010–2011 season [15]. Forty-two (32%) of the 130 influenza cases were identified as medically attended on the basis of medical record review; 38% of cases among children were medically attended compared with 16% among adults ($P = .020$). Vaccinated cases were slightly more likely than unvaccinated cases to be medically attended (34% vs 30%; $P = .67$).

Influenza was identified in 78 (24%) households and 125 (9%) individuals, including 5 individuals with 2 separate infections. Influenza infection risks significantly varied by age category and were highest among young children ($P < .001$). There were no significant differences in infection risk by sex or presence of high-risk health conditions. Fifty-nine percent of influenza cases had confirmed receipt of an influenza vaccine at least 14 days prior to illness. The influenza infection risk was 8.5% (74 of 866) in the vaccinated and 8.9% (51 of 575) in the unvaccinated ($P = .83$).

Influenza Vaccine Effectiveness

The effectiveness of influenza vaccination in preventing symptomatic laboratory-confirmed influenza was estimated separately for community-acquired and household-acquired outcomes. Thirty influenza cases were considered household-acquired based on exposure to 100 index or co-index community-acquired infections. Results from unadjusted, adjusted, and stratified models are presented in Table 2; models were adjusted for age in years and high-risk health status, and stratified by 2009–2010 seasonal influenza vaccination status. Estimates were calculated for all ages combined and separately by age category; young children were considered separately because of their specific vaccination recommendation [1], and older adults (aged ≥ 50 years) were included with younger adults because of their limited numbers.

Adjusted vaccine effectiveness in preventing community-acquired influenza was 31% (95% confidence interval [CI],

–7 to 55); point estimates were lowest in young children and modestly higher in adults. Stratified analyses indicated substantial differences in vaccine effectiveness based on whether or not seasonal influenza vaccine had been received the prior season (interaction term: $P = .014$). Among subjects with documented evidence of prior season vaccination, estimates of current season vaccine effectiveness were low overall and in each of the age groups examined. In contrast, for those subjects without evidence of prior season vaccine receipt, effectiveness estimates were higher for all age groups and statistically significant overall (62% [95% CI, 17%–82%]).

Results from analysis of vaccine effectiveness in preventing community-acquired influenza by type/subtype are also presented in Table 2. In adjusted analyses for all ages combined, effectiveness estimates were highest against influenza type B (48% [95% CI, –5% to 75%]), and lower for A (pH1N1) (26% [95% CI, –68% to 67%]) and A (H3N2) (10% [95% CI, –74% to 54%]). In analyses stratified by prior season vaccination status, estimates were substantially higher for those subjects without evidence of prior season vaccine receipt.

In models examining household-acquired influenza, there was no evidence that vaccination prevented household transmission once influenza was introduced (Table 2). Adults were at particular risk of infection despite vaccination. In fact, 9 of 11 (82%) adults with household-acquired influenza were vaccinated, compared with 11 of 19 (58%) children. No substantial differences in estimates of household vaccine effectiveness were demonstrated based on prior season vaccination status.

To aid interpretation of the observed differences in vaccine effectiveness based on 2009–2010 vaccination status, we examined influenza infection risks based on combinations of prior and current season vaccination status (Table 3). The lowest infection risks were seen among subjects vaccinated in the current but not the prior season. Infection risks were similar for subjects with documented seasonal vaccine receipt in both years and subjects without evidence of vaccine receipt in either year. The pattern of infection risks seen among young children varied from that seen in older children and adults. Specifically, the highest infection risks were seen in young children without evidence of vaccine receipt in either year. Similar patterns were demonstrated with stratification by prior season pandemic vaccine receipt; among those subjects vaccinated in the prior season, 65% had received both seasonal and pandemic vaccine.

DISCUSSION

In countries with established influenza vaccination programs, observational studies of vaccine effectiveness have become a standard way of routinely evaluating how well influenza vaccines protect population groups [2–5]. These studies utilize a

Table 2. Estimates of Vaccine Effectiveness in Preventing Community-Acquired and Household-Acquired Influenza

Analysis Set	Influenza Positive No./ Total No. (%)	Vaccine Effectiveness ^a (VE%) ^b			
		Unadjusted VE% (95% CI)	Adjusted 1 ^c VE% (95% CI)	Stratified by Prior (2009–2010) Seasonal Vaccine Receipt ^d	
				Prior Season: Vaccinated VE% (95% CI)	Prior Season: Nonvaccinated VE% (95% CI)
Community-acquired influenza^e					
All ages	97/1441 (6.7)	17 (–27 to 46)	31 (–7 to 55)	–45 (–226 to 35)	62 (17–82)
<9 y	55/468 (11.8)	30 (–27 to 61)	30 (–27 to 61)	–148 (–959 to 42)	53 (–19 to 81)
9–17 y	21/371 (5.7)	11 (–103 to 61)	33 (–62 to 72)	–6 (–291 to 71)	80 (–85 to 98)
≥18 y	21/602 (3.5)	44 (–37 to 77)	39 (–49 to 75)	17 (–328 to 84)	79 (–65 to 97)
Community-acquired influenza A/H3N2	42/1441 (2.9)	–1 (–93 to 48)	10 (–74 to 54)	–34 (–323 to 58)	37 (–84 to 78)
Community-acquired influenza A/H1N1	21/1441 (1.5)	6 (–121 to 60)	26 (–68 to 67)	–6 (–387 to 77)	70 (–131 to 96)
Community-acquired influenza B	37/1441 (2.6)	36 (–30 to 68)	48 (–5 to 75)	–166 (–1937 to 65)	61 (–2 to 92)
Household-acquired influenza^f					
All ages	26/267 (9.7)	–67 (–286 to 28)	–51 (–254 to 36)		
<9 y	14/84 (16.7)	10 (–167 to 70)	27 (–126 to 28)		
9–17 y	2/55 (3.6)	17 (–1196 to 95)	0 (–826 to 89)		
≥18 y	10/128 (8.5)	–260 (–1618 to 24)	–283 (–1733 to 20)		

Household Influenza Vaccine Effectiveness (HIVE) study, Ann Arbor Michigan, 2010–2011 influenza season.

Abbreviations: CI, confidence interval; VE, vaccine effectiveness.

^a Effectiveness of at least 1 dose of influenza vaccine ≥14 days before illness onset in preventing laboratory-confirmed influenza.

^b VE% = 100*(1 – hazard ratio).

^c Model adjusted for age in years and medical record documented high-risk health status (present/absent).

^d Model stratified by 2009–2010 seasonal vaccination status, and adjusted for age and high-risk health status.

^e One hundred cases of influenza were defined as community acquired, but 3 cases are excluded here because they occurred in a subject with a prior case of community-acquired influenza.

^f Thirty cases of influenza were defined as household-acquired, but 4 cases are excluded here because they occurred as a result of a second introduction of influenza (different type/subtype and/or >7 days from prior case) to a household.

sensitive and specific laboratory method to confirm illnesses as influenza, and require documentation of influenza vaccine receipt, thus reducing the risk of misclassifying key outcomes and exposures. However, data from all observational studies still require attention to reduce the possibility of bias and adjust for confounding, given self-selection for vaccination and, in most study designs, the influence of healthcare-seeking behavior.

This study was designed in part to complement current studies conducted in the healthcare setting, using an alternative approach to the case-control design. Defining a cohort of households with children, in advance of the influenza season and with follow-up through the season, offers several advantages. As demonstrated here, influenza illnesses of all severities can be studied, and vaccine effectiveness against both community-acquired illnesses and among household members with confirmed household exposures can be examined. In addition, household transmission risks can be determined and characterized [16, 17]. However, longer follow-up and availability of

household-level data are balanced with the limitation of reduced power, as the number of cases identified will be smaller compared with case-control studies that enroll participants when eligible illnesses occur.

Based on our sample size of >1400 subjects with 60% vaccine coverage, and a community infection risk of 6.7%, we had 80% power to estimate significant vaccine effectiveness as low as approximately 45%. Unfortunately, in unadjusted models and models adjusted for age and presence of high-risk health conditions, effectiveness estimates for prevention of community-acquired influenza of all severities were all <40% and not statistically different than zero. This unexpected finding was seen in a season with circulation of influenza strains that were considered matched to vaccine strains [15], and where evaluations of vaccine effectiveness using case-control designs indicated significant reductions of 52%–60% in medically attended influenza outcomes in vaccinated patients of all ages [2, 5].

In preliminary analyses, significant interaction of prior (2009–2010) seasonal vaccine receipt with current season

Table 3. Influenza Infection Risks Among Participants Based on Combinations of 2010–2011 Seasonal Vaccination Status With Prior Season (2009–2010) Seasonal and Pandemic Vaccination Status

	2010–2011 Vaccinated, N = 866 (60.1%)		2010–2011 Unvaccinated, N = 575 (39.9%)	
	Cases ^a /Total	% Positive	Cases ^a /Total	% Positive
2009–2010 seasonal, vaccinated ^b				
<9 y	35/255	13.7	3/39	7.7
≥9 y	27/370	7.3	5/78	6.4
All ages	62/625	9.9	8/117	6.8
2009–2010 seasonal, unvaccinated				
<9 y	8/68	11.8	24/106	22.6
≥9 y	4/173	2.3	19/352	5.4
All ages	12/241	5.0	43/458	9.4
2009–2010 pandemic, vaccinated ^c				
<9 y	34/239	14.2	2/34	5.9
≥9 y	23/282	8.2	8/57	14.0
All ages	57/521	10.9	10/91	11.0
2009–2010 pandemic, unvaccinated				
<9 y	9/84	10.7	25/111	22.5
≥9 y	8/261	3.1	16/373	4.3
All ages	17/345	4.9	41/484	8.5

Household Influenza Vaccine Effectiveness (HIVE) study, Ann Arbor Michigan, 2010–2011 influenza season.

^a One hundred thirty influenza cases were identified in 125 individuals. Only an individual's first case is considered here (n = 125).

^b Indicates receipt of 2009–2010 seasonal vaccine only or both 2009–2010 seasonal and pandemic vaccines.

^c Indicates receipt of 2009–2010 pandemic vaccine only or both 2009–2010 pandemic and seasonal vaccines.

vaccination was noted. Stratified models suggested substantial differences in vaccine effectiveness with unexpectedly low estimates demonstrated for those subjects who were vaccinated both years. In contrast, among those subjects without evidence of prior seasonal vaccine receipt, statistically significant vaccine effectiveness was demonstrated for all ages combined. In immunogenicity studies, attenuated immunologic responses with repeated vaccine receipt have been demonstrated [18–20]; responses may vary based on the degree of similarity between vaccine strains across years [21]. Corresponding reductions in vaccine effectiveness with repeated vaccinations have not been consistently demonstrated [22, 23]. In examining the modifying effect of prior vaccination on current season vaccine effectiveness in our observational study, it is difficult to separate the possible effects of immunologic response due to prior vaccination from associated (and unmeasured) factors for which repeated vaccination may be a surrogate.

We found no evidence of vaccine effectiveness in preventing within-household transmission once influenza was introduced.

Sample sizes in these analyses were small and we had very limited power to detect significant differences even if vaccine protection had been demonstrated. It is interesting to speculate that these estimates may reflect the intensity and duration of exposure once influenza is introduced to a confined environment. Excess risk for adult household members may have been a consequence of providing care for those with illness.

In addition to examining vaccine effectiveness based on documented vaccine receipt, we performed a sensitivity analysis with vaccination status defined by documented vaccine receipt or self-reported vaccination that could not be documented, and separately, defined by self-reported status only. Effectiveness estimates in the first analysis (documented or self-reported vaccine receipt) were similar (33% [95% CI, –4% to 58%]) to estimates requiring documented evidence (31% [95% CI, –7% to 55%]). Estimates in the second analysis (self-reported only) differed based on whether those with missing data were considered unvaccinated (20% [95% CI, –24% to 48%]) or excluded (35% [95% CI, –4% to 60%]). These findings do not affect our overall conclusions, but they do suggest some misclassification of vaccination status with our strategy for documentation. Confirmation of vaccination status is challenging given the many options for vaccine delivery, making sensitivity analyses that consider reported vaccination increasingly important.

Our vaccine effectiveness estimates for prevention of community-acquired influenza were lower than those demonstrated in other observational studies carried out in the same season [2, 5]. We also did not demonstrate reduced utilization of medical care among vaccinated cases; going forward, we plan to expand our assessment of illness severity. The findings suggesting lower effectiveness with prior vaccination and no protection with household exposure require further study. We will continue to evaluate vaccine effectiveness in the household setting in order to confirm or refute the current observations. With multiple years of data accumulated, further examination of the effects of prior vaccination and past influenza infection on effectiveness estimates can be conducted. In future study years we also plan to collect serologic specimens from household members to estimate preseason susceptibility to circulating influenza viruses; these efforts should assist in explaining observations.

Notes

Disclaimer. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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EXHIBIT 411



Cochrane Database of Systematic Reviews

Influenza vaccination for healthcare workers who care for people aged 60 or older living in long-term care institutions (Review)

Thomas RE, Jefferson T, Lasserson TJ

Thomas RE, Jefferson T, Lasserson TJ.
Influenza vaccination for healthcare workers who care for people aged 60 or older living in long-term care institutions.
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Influenza vaccination for healthcare workers who care for people aged 60 or older living in long-term care institutions (Review)

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WILEY



[Intervention Review]

Influenza vaccination for healthcare workers who care for people aged 60 or older living in long-term care institutions

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ABSTRACT

Background

A systematic review found that 3% of working adults who had received influenza vaccine and 5% of those who were unvaccinated had laboratory-proven influenza per season; in healthcare workers (HCWs) these percentages were 5% and 8% respectively. Healthcare workers may transmit influenza to patients.

Objectives

To identify all randomised controlled trials (RCTs) and non-RCTs assessing the effects of vaccinating healthcare workers on the incidence of laboratory-proven influenza, pneumonia, death from pneumonia and admission to hospital for respiratory illness in those aged 60 years or older resident in long-term care institutions (LTCIs).

Search methods

We searched CENTRAL (2015, Issue 9), MEDLINE (1966 to October week 3, 2015), EMBASE (1974 to October 2015) and Web of Science (2006 to October 2015), but Biological Abstracts only from 1969 to March 2013 and Science Citation Index-Expanded from 1974 to March 2013 due to lack of institutional access in 2015.

Selection criteria

Randomised controlled trials (RCTs) and non-RCTs of influenza vaccination of healthcare workers caring for individuals aged 60 years or older in LTCIs and the incidence of laboratory-proven influenza and its complications (lower respiratory tract infection, or hospitalisation or death due to lower respiratory tract infection) in individuals aged 60 years or older in LTCIs.

Data collection and analysis

Two authors independently extracted data and assessed risk of bias. Effects on dichotomous outcomes were measured as risk differences (RDs) with 95% confidence intervals (CIs). We assessed the quality of evidence with GRADE.

Main results

We identified four cluster-RCTs and one cohort study (n = 12,742) of influenza vaccination for HCWs caring for individuals ≥ 60 years in LTCIs. Four cluster RCTs (5896 residents) provided outcome data that addressed the objectives of our review. The studies were comparable in their study populations, intervention and outcome measures. The studies did not report adverse events. The principal sources of bias in the

Influenza vaccination for healthcare workers who care for people aged 60 or older living in long-term care institutions (Review)

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studies related to attrition, lack of blinding, contamination in the control groups and low rates of vaccination coverage in the intervention arms, leading us to downgrade the quality of evidence for all outcomes due to serious risk of bias.

Offering influenza vaccination to HCWs based in long term care homes may have little or no effect on the number of residents who develop laboratory-proven influenza compared with those living in care homes where no vaccination is offered (RD 0 (95% CI -0.03 to 0.03), two studies with samples taken from 752 participants; low quality evidence). HCW vaccination probably leads to a reduction in lower respiratory tract infection in residents from 6% to 4% (RD -0.02 (95% CI -0.04 to 0.01), one study of 3400 people; moderate quality evidence). HCW vaccination programmes may have little or no effect on the number of residents admitted to hospital for respiratory illness (RD 0 (95% CI -0.02 to 0.02, one study of 1059 people; low quality evidence). We decided not to combine data on deaths from lower respiratory tract infection (two studies of 4459 people) or all cause deaths (four studies of 8468 people). The direction and size of difference in risk varied between the studies. We are uncertain as to the effect of vaccination on these outcomes due to the very low quality of evidence. Adjusted analyses, which took into account the cluster design, did not differ substantively from the pooled analysis with unadjusted data.

Authors' conclusions

Our review findings have not identified conclusive evidence of benefit of HCW vaccination programmes on specific outcomes of laboratory-proven influenza, its complications (lower respiratory tract infection, hospitalisation or death due to lower respiratory tract illness), or all cause mortality in people over the age of 60 who live in care institutions. This review did not find information on co-interventions with healthcare worker vaccination: hand-washing, face masks, early detection of laboratory-proven influenza, quarantine, avoiding admissions, antivirals and asking healthcare workers with influenza or influenza-like illness (ILI) not to work. This review does not provide reasonable evidence to support the vaccination of healthcare workers to prevent influenza in those aged 60 years or older resident in LTCIs. High quality RCTs are required to avoid the risks of bias in methodology and conduct identified by this review and to test further these interventions in combination.

PLAIN LANGUAGE SUMMARY

Influenza vaccination for healthcare workers who care for people aged 60 or older living in long-term care institutions

Review question

We wanted to know if vaccinating healthcare workers against influenza reduces the risk of older individuals in long-term care institutions (LTCIs) acquiring influenza infections from healthcare workers.

Background

The signs and symptoms of influenza are similar to those of many other respiratory illnesses, therefore it is important in studies testing the effects of influenza vaccination to prove by laboratory tests, which are highly accurate, whether residents in LTCIs actually have influenza or another respiratory illness.

Study characteristics

Our evidence is current to October 2015. Overall five studies were included in our review but we used data from three trials with 5896 residents. In one trial the average age was 77 and 71% were female, in another this was 82 years and 70% were female, and in the last this was 86 years and 77% were female. One study was supported by the Greater Glasgow Health Board Care of the Elderly Unit, one by the Wellcome Trust and for one there was no statement.

Key results and quality of the evidence

The method of randomisation used was at low risk in two trials and unclear in one. In all three studies allocation concealment and blinding were unclear. In two studies data could not be included from everyone who was recruited and this put their results at a high risk of bias. All three studies reported outcomes completely. However, in all three trials there was performance bias due to incomplete influenza vaccination of healthcare workers in the intervention arms. No studies reported on adverse events.

Offering influenza vaccination to healthcare workers who care for those aged 60 or over in LTCIs may have little or no effect on laboratory-proven influenza (low quality evidence). HCW vaccination programmes probably have a small effect on lower respiratory tract infection (moderate quality evidence), but they may have little or no effect on admission to hospital (low quality evidence). It is unclear what effect vaccination programmes have on death due to lower respiratory tract illness (very low quality evidence) or all cause deaths (very low quality evidence).

This review did not find information on other interventions used in conjunction with vaccination of healthcare workers (for example, hand-washing, face masks, early detection of laboratory-proven influenza, quarantine, avoiding new admissions, prompt antiviral use, asking healthcare workers with an influenza-like illness not to work). High quality randomised controlled trials testing combinations of these interventions are needed.

EXHIBIT 412



Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

Viral Hepatitis

Hepatitis B Questions and Answers for the Public

Index of Questions

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Pregnant Women and their Newborns

+

- Are pregnant women tested for hepatitis B?
- If a pregnant woman has hepatitis B, is there a way to prevent her baby from getting hepatitis B?
- Why is the hepatitis B vaccine recommended for all babies?

Hepatitis B Overview

What is hepatitis?

Hepatitis means inflammation of the liver. When the liver is inflamed or damaged, its function can be affected. Heavy alcohol use, toxins, some medications, and certain medical conditions can all cause hepatitis. However, hepatitis is often caused by a virus. In the United States, the most common hepatitis viruses are hepatitis A virus, hepatitis B virus, and hepatitis C virus.

What is the difference between hepatitis A, hepatitis B, and hepatitis C?

[Hepatitis A](#), [Hepatitis B](#), and [Hepatitis C](#) are liver infections caused by three different viruses. Although each can cause similar symptoms, they are spread in different ways and can affect the liver differently. Hepatitis A is usually a short-term infection. Hepatitis B and hepatitis C can also begin as short-term infections but in some people, the virus remains in the body and causes chronic, or lifelong, infection. There are vaccines to prevent hepatitis A and hepatitis B; however, no vaccine is available for hepatitis C.

The page "[What is viral hepatitis?](#)" explains in detail the differences between hepatitis A, hepatitis B, and hepatitis C.

What is hepatitis B?

Hepatitis B is a liver infection caused by the hepatitis B virus. Some people with hepatitis B are sick for only a few weeks (known as "acute" infection), but for others, the disease progresses to a serious, lifelong illness known as chronic hepatitis B.

What is acute (short-term) hepatitis B?

Acute hepatitis B is a short-term illness that occurs within the first 6 months after someone is exposed to the hepatitis B virus. Some people with acute hepatitis B have no symptoms at all or only mild illness. For others, acute hepatitis B causes a more severe illness that requires hospitalization.

What is chronic (long-term) hepatitis B?

Some people, especially those who get infected in adulthood, are able to clear the virus from their bodies without treatment. For other people, acute hepatitis B leads to life-long infection known as chronic hepatitis B. Over time, chronic hepatitis B can cause serious health problems, including liver damage, cirrhosis, liver cancer, and even death.

Who is most likely to get chronic (long-term) hepatitis B?

Age plays a role in whether hepatitis B will become chronic. The younger a person is when infected with the hepatitis B virus, the greater the chance of developing chronic infection. About 9 in 10 infants who become infected go on to develop life-long, chronic infection. The risk goes down as a child gets older. About one in three children who get infected before age 6 will develop chronic hepatitis B. By contrast, almost all older children (those aged ≥ 6) and adults infected with the hepatitis B virus recover completely and do not develop chronic infection.

How common is hepatitis B in the United States?

In 2017, a total of 3,409 cases of acute (short-term) hepatitis B were reported to CDC. Since many people may not have symptoms or don't know they are infected, their illness is often not diagnosed so it can't be reported or counted. CDC estimates the actual number of acute hepatitis B cases was closer to 22,200 in 2017. Many more people (about 862,000) are estimated to be living with chronic, long-term hepatitis B.

How common is hepatitis B around the world?

An estimated 257 million people are living with hepatitis B worldwide.

Hepatitis B Transmission

How is hepatitis B spread?

Hepatitis B is spread when blood, semen, or other body fluid infected with the hepatitis B virus enters the body of someone who is not infected. People can become infected with the virus from:

- Birth (spread from an infected mother to her baby during birth)
- Sex with an infected partner
- Sharing needles, syringes, or drug preparation equipment
- Sharing items such as toothbrushes, razors, or medical equipment (like a glucose monitor) with an infected person
- Direct contact with the blood or open sores of an infected person
- Exposure to an infected person's blood through needlesticks or other sharp instruments

Hepatitis B is not spread through food or water, sharing eating utensils, breastfeeding, hugging, kissing, hand holding, coughing, or sneezing.

Can a person spread the hepatitis B virus and not know it?

Yes. Many people with hepatitis B don't know they are infected with the virus because they don't feel or look sick. However, they can still spread the virus to others.

Can the hepatitis B virus be spread through sex?

Yes. The hepatitis B virus can be found in the blood, semen, and other body fluids of an infected person. A person who has sex with an infected partner can become infected with the virus.

Can hepatitis B be spread through food?

Unlike hepatitis A, hepatitis B is not usually spread through food or water.

Who is at risk for hepatitis B?

Although anyone can get hepatitis B, these people are at greater risk:

- Infants born to infected mothers
- People who inject drugs or share needles, syringes, and other types of drug equipment
- Sex partners of people with hepatitis B
- Men who have sex with men
- People who live with someone who has hepatitis B
- Health-care and public-safety workers exposed to blood on the job
- Hemodialysis patients

Who should be tested for hepatitis B?

CDC recommends hepatitis B testing for:

- [People born in certain countries where hepatitis B is common](#)
- People born in the United States not vaccinated as infants whose [parents were born in countries with high rates of hepatitis B](#)
- Men who have sex with men
- People who inject drugs
- People with HIV
- Household and sexual contacts of people with hepatitis B
- People requiring immunosuppressive therapy
- People with end-stage renal disease (including hemodialysis patients)
- People with hepatitis C
- People with elevated ALT levels
- Pregnant women
- Infants born to HBV-infected mothers

What should I do if I think I have been exposed to the hepatitis B virus?

If you are concerned that you might have been exposed to the hepatitis B virus, call your health-care provider or your local health department immediately. Infection with the hepatitis B virus can be prevented if you get the hepatitis B vaccine and/or a shot called "HBIG" (hepatitis B immune globulin) as soon as possible after exposure to the virus, ideally within 24 hours.

What is hepatitis B immune globulin (HBIG)?

Hepatitis B immune globulin is a substance made from human blood samples that contain antibodies against the hepatitis B virus. It is given as a shot to people exposed to the hepatitis B virus to protect them from infection.

How long does the hepatitis B virus survive outside the body?

The hepatitis B virus can survive outside the body for at least 7 days. During that time, the virus is still capable of causing infection.

How should blood spills be cleaned from surfaces to make sure that hepatitis B virus is gone?

All blood spills (including those that have already dried) should be cleaned and disinfected with a mixture of bleach and water (1 part household bleach to 10 parts water). Gloves should always be worn when cleaning up any blood spills. Even dried blood can cause infection.

If I have been infected with the hepatitis B virus in the past, can I get it again?

No. If you have been infected with hepatitis B in the past, you can't get infected again. However, some people, especially those infected during early childhood, remain infected for life because they never cleared the virus from their bodies. These people are considered to have chronic infection and are at risk for developing severe liver disease.

Can I donate blood if I have hepatitis B?

The [American Red Cross](#) does not accept blood donations from anyone who has tested positive for hepatitis B or anyone experiencing symptoms of viral hepatitis.

Can I donate organs if I have hepatitis B?

According to the [U.S. Department of Health & Human Service's online information on organ donation and transplantation](#), few conditions would prevent someone from being an organ, eye, or tissue donor. Even with a history of hepatitis B, you may be able to donate your organs or tissues. The transplant team will determine what organs or tissue can be used based on a clinical evaluation, medical history, and other factors. CDC has recently published information about how to [assess solid organ donors and monitor transplant recipients for hepatitis B infection](#).

Prevention through Vaccination

Can hepatitis B be prevented?

Yes. The best way to prevent hepatitis B is by getting vaccinated. The hepatitis B vaccine is safe and effective. Completing the series of shots (2, 3, or 4 doses, depending on the manufacturer) is needed to be fully protected.

Who should get vaccinated against hepatitis B?

Hepatitis B vaccination is recommended for:

- All infants
- All children and adolescents younger than 19 years of age who have not been vaccinated
- People at risk for infection by sexual exposure
 - People whose sex partners have hepatitis B
 - Sexually active people who are not in a long-term, mutually monogamous relationship (for example, people with more than one sex partner in the past 6 months)
 - People seeking evaluation or treatment for a sexually transmitted infection
 - Men who have sex with men
- People at risk for infection by exposure to blood
 - People who inject drugs
 - People who live with someone who has hepatitis B
 - People who live or work in facilities for people with developmental disabilities

- Health-care and public-safety workers at risk for exposure to blood or blood-contaminated body fluids on the job
- People who receive hemodialysis
- People with diabetes who are 19–59 years of age (people with diabetes who are age 60 or older should ask their health care professional).
- International travelers to countries where hepatitis B is common
- People with hepatitis C virus infection
- People with chronic liver disease
- People with HIV infection
- People who are in jail or prison
- All other people seeking protection from hepatitis B virus infection

Is the hepatitis B vaccine recommended before international travel?

Only people visiting [countries where hepatitis B is common](#) should get the hepatitis B vaccine before travel.

Is the hepatitis B vaccine safe?

Yes. The hepatitis B vaccine is safe, and soreness at the injection site is the most common side effect. As with any medicine, there are very small risks that a serious problem could occur after getting the vaccine. The safety of vaccines is always being monitored. For more information, visit CDC's [vaccine safety](#) site.

Can I get hepatitis B from being vaccinated?

No. The hepatitis B vaccine does not contain any live virus and can't cause hepatitis B.

Is it harmful to have an extra dose of hepatitis B vaccine or to repeat the entire hepatitis B vaccine series?

No, getting extra doses of hepatitis B vaccine is not harmful.

What should be done if hepatitis B vaccine series was not completed?

If the hepatitis B vaccine series is interrupted, the next dose should be given as soon as possible. The first dose(s) does not need to be repeated.

Who should not receive the hepatitis B vaccine?

Anyone who has had a serious allergic reaction to a prior dose of hepatitis B vaccine, any part of the vaccine, or yeast should not get the hepatitis B vaccine.

What is a booster dose, and do I need one?

A "booster" dose is an extra dose of vaccine that can increase or extend the effectiveness of the vaccine. Most healthy people do not need a booster dose, but a blood test can be performed to check your immunity and decide if a booster dose of vaccine is necessary.

Is there a vaccine that will protect me from both hepatitis A and hepatitis B?

Yes, there is a combination vaccine approved for adults that protects people from both hepatitis A and hepatitis B. The combined hepatitis A and B vaccine is usually given as three separate doses over a 6-month period.

Can I get the hepatitis B vaccine at the same time as other vaccines?

Yes. Getting two different vaccines at the same time is not harmful.

Where can I get the hepatitis B vaccine?

Talk to your health-care provider or local health department about getting vaccinated. Some clinics offer free or low-cost hepatitis B vaccines.

Symptoms

Does acute (short-term) hepatitis B cause symptoms?

Sometimes. Most children younger than 5 and people with serious health problems (like having compromised immune systems) have no symptoms. Up to half of all older children, adolescents, and adults experience symptoms of acute hepatitis B.

What are the symptoms of acute (short-term) hepatitis B?

Symptoms of acute hepatitis B can include:

- Fever
- Fatigue
- Loss of appetite
- Nausea
- Vomiting
- Abdominal pain
- Dark urine
- Clay-colored bowel movements
- Joint pain
- Jaundice (yellow color in the skin or the eyes)

How soon after exposure to the hepatitis B virus will symptoms appear, and how long do they last?

If symptoms occur, they begin an average of 90 days (or 3 months) after exposure to the virus, but they can appear any time between 8 weeks and 5 months after exposure. They usually last several weeks, but some people can feel sick for as long as 6 months.

Can a person spread hepatitis B without having symptoms?

Yes. Many people with hepatitis B have no symptoms, but they can still spread the virus to others.

What are the symptoms of chronic (long-term) hepatitis B?

Most people with chronic hepatitis B do not have any symptoms, do not feel ill, and remain symptom free for decades. When and if symptoms do appear, they are similar to the symptoms of [acute infection](#), but can be a sign of advanced liver disease. About 1 in 4 people who become chronically infected during childhood and about 15% of those who

become chronically infected after childhood will eventually die from serious liver conditions, like cirrhosis (scarring of the liver) or liver cancer. Some people still do not have symptoms even after their liver becomes diseased, although certain blood tests for liver function might show some abnormalities.

How serious is chronic (long-term) hepatitis B?

Chronic hepatitis B can develop into a serious disease resulting in long-term health problems, including liver damage, liver failure, liver cancer, and even death. There were 1,649 deaths related to hepatitis B virus reported to CDC in 2018, but this is an underestimate.

Tests

How do I know if I have hepatitis B?

Talk to your health-care provider if you have risk factors for or think you might have hepatitis B. Since many people with hepatitis B do not have symptoms, blood tests are used to diagnose the infection. Several different hepatitis B tests are available. Depending on the test, they can determine whether you

- have chronic or acute hepatitis B;
- are immune to hepatitis B after vaccination; or
- were infected in the past, have cleared the virus from your body, and are protected from future infection.

Certain tests can even determine how likely it is that someone who is infected with hepatitis B will transmit it to others. Ask your health-care provider to explain what tests were ordered, when you can expect to get the results, and what those results mean.

What should I do after learning that I have hepatitis B?

If test results show that you are infected with the hepatitis B virus, you should consult a health-care provider that is experienced in caring for people with hepatitis B. This can be an internist or family medicine practitioner, or it may be someone who specializes in treating people with infectious, digestive, or liver diseases.

Treatment

How is acute (short-term) hepatitis B treated?

There is no medication available to treat acute hepatitis B. For people with mild symptoms, health-care providers usually recommend rest, adequate nutrition, and fluids. Those with more severe symptoms may need to be hospitalized.

How is chronic hepatitis B treated?

Several medications have been approved to treat people who have chronic hepatitis B, and new drugs are in development. However, not every person with chronic hepatitis B needs medication, and the drugs may cause side effects in some patients. People who start hepatitis B treatment may need to take medication indefinitely because these medications do not lead to a cure.

What can people with chronic hepatitis B do to take care of their liver?

People with chronic hepatitis B should be under the care of a health-care provider that is knowledgeable about this illness (like an internist or provider that specializes in treating people with infectious, digestive, or liver diseases) and is able to regularly monitor their liver function. People recently diagnosed with hepatitis B should

- get vaccinated against hepatitis A and tested for hepatitis C;
- avoid drinking alcohol;
- follow a healthy diet and stay physically active, especially patients who are overweight (i.e., those with body mass index [BMI] $\geq 25\text{kg/m}^2$) or obese (BMI $\geq 30\text{kg/m}^2$); and
- check with a health professional before taking any prescription pills, nutritional or herbal supplements, or over-the-counter medications, as these can potentially damage the liver.

Pregnant Women and their Newborns

Are pregnant women tested for hepatitis B?

Yes. When a pregnant woman comes in for prenatal care, she is given a series of routine blood tests, including one that checks for hepatitis B virus infection.

If a pregnant woman has hepatitis B, is there a way to prevent her baby from getting hepatitis B?

Yes. Almost all cases of hepatitis B can be prevented in babies born to infected mothers, but these newborns must receive the necessary shots at the recommended times. The combination of hepatitis B immune globulin (known as HBIG) and hepatitis B vaccine can be given to infants born to infected mothers within 12 hours of birth to protect them from infection. To best protect your baby, follow the advice from your baby's doctor.

Why is the hepatitis B vaccine recommended for all babies?

Nearly all newborns who become infected with the hepatitis B virus develop lifelong hepatitis B. This can eventually lead to serious health problems, including liver damage, liver cancer, and even death. Hepatitis B vaccination is recommended for all babies to protect them from this serious but preventable disease.

Page last reviewed: July 7, 2020

Content source: [Division of Viral Hepatitis, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention](#)

EXHIBIT 413



Explosive School-based Measles Outbreak

Intense Exposure May Have Resulted in High Risk, Even among Revaccinees

Mikko Paunio,¹ Heikki Peltola,² Martti Valle,³ Irja Davidkin,³ Martti Virtanen,⁴ and Olli P. Heinonen¹

Even high levels of measles vaccination coverage have not always prevented outbreaks of measles spread by airborne transmission. It has been suggested that a large inoculum might increase vaccine failure risk. Airborne transmission might occasionally entail a large measles inoculum. The epidemiologic relevance of measles among properly vaccinated persons (i.e., those vaccinated after 15 months of age and with live attenuated virus) is increased when they become contagious. The authors studied inoculum intensities as measured by proxy variables and the contagiousness of properly vaccinated persons who contracted measles among 51 measles patients infected in one school, at home, or elsewhere, utilizing preexisting records of measles cases and 214 healthy controls from an explosive school outbreak that occurred in a rural Finnish municipality in 1989. One "super-spreader" infected 22 others in one day, including eight once-vaccinated students and one twice-vaccinated student, probably during an assembly of 144 students in a poorly ventilated hallway with no sunlight. Those infected later at home had high measles risk, even if they were revaccinees. **When siblings shared a bedroom with a measles case, a 78 percent risk (seven out of nine children) was observed among vaccinees.** Vaccinees had approximately 2 days' shorter incubation time than unvaccinated persons. **Vaccinated and unvaccinated students were equally able to infect their siblings.** Total protection against measles might not be achievable, even among revaccinees, when children are confronted with intense exposure to measles virus. *Am J Epidemiol* 1998;148:1103–10.

communicable diseases; disease outbreaks; disease transmission; immunization; measles; measles vaccine; measles virus; vaccination

The extreme contagiousness of measles creates problems with its control, and ultimately its eradication (1). Outbreaks have occurred among highly vaccinated schoolchildren, especially after documented airborne transmission, even in groups with close to 100 percent vaccination coverage (2–5). Case reports from physicians' offices (6–9) also suggest that measles is transmissible by small droplet nuclei (<5 μm in diameter) that can remain unprecipitated from indoor air for several hours (10). The overall importance of the airborne transmission of measles is not fully un-

derstood (1, 5). Some clarification may be afforded by a theory (11) which postulates that a large measles inoculum can cause vaccine failure, since airborne transmission might occasionally entail a massive inoculum. Theoretical vaccination coverage calculations for herd immunity assume a person-to-person contact model and lifelong immunity after successful vaccination (12).

Vaccinees receiving their first measles vaccination after 15 months of age are considered properly immunized, as the mother's antibodies no longer interfere with the process. The epidemiologic relevance of vaccine failure increases if properly vaccinated persons become truly contagious and participate in the chain of transmission (13).

We examined whether differences in measles inoculum intensity affected measles risk among vaccinees and whether properly vaccinated measles patients became contagious during an explosive school outbreak in Honkajoki, a small rural Finnish municipality, in 1989.

MATERIALS AND METHODS

Vaccination

In Finland, children are vaccinated free of charge by public health nurses at child health care centers.

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Abbreviations: MMR vaccine, trivalent live attenuated measles-mumps-rubella vaccine (M-M-R® II or Virivac®); Mo vaccine, monovalent live attenuated measles vaccine (Rimevax®).

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Vaccination is voluntary. Each vaccination is registered on the individual's health card, which is kept at the health care center, and on a vaccination card kept at home. The health card, which also includes any history of measles, is transferred from the health center to the school nurse when the child begins school.

All children born between 1973 and 1981 should have received the monovalent live attenuated Schwarz strain (Mo) measles vaccine (Rimevax®; SmithKline Biologicals, Rixensart, Belgium). This program started in 1975, and children at least 14 months old were targeted. Preschool children born before 1973 also occasionally received Mo vaccine. Since 1982, the trivalent measles–mumps–rubella (MMR) vaccine (M-M-R® II (Merck and Company, Inc., West Point, Pennsylvania), distributed in Finland as Virivac® (SBL Vaccine AB, Stockholm, Sweden)) containing the More Attenuated Enders-Edmonston strain of measles virus has been used exclusively; it has been administered first at 14–18 months of age and again at 6 years according to a comprehensive national vaccination program (14, 15). Children born between 1975 and 1981 were covered by both the Mo and the MMR vaccination programs, receiving Mo vaccine at 14 months of age and, with rare exceptions, the first MMR vaccination at 2–5 years of age. After October 31, 1982, children older than 18 months of age were allowed to become vaccinated with MMR whenever they visited public health nurses. These children were to receive a third measles vaccination routinely at 6 years of age. The interval required between successive measles vaccinations was at least 6 months. No routine evaluation of vaccination coverage was done prior to the outbreak in Honkajoki.

Setting

Honkajoki is a small agricultural municipality in southwestern Finland with 2,398 inhabitants, 749 living in the central village.

Seven elementary schools (grades 1–6) are scattered around Honkajoki. In 1989, the town's lone high school had three junior classes (grades 7–9; *n* = 76) and three senior classes (grades 10–12; *n* = 68) occupying a single, poorly ventilated building. This building had been efficiently heat-insulated after the 1974 energy crisis, and ventilation was particularly poor in the hallway, which also had no sunlight penetration. Every school day began with a student assembly in the hallway (figure 1).

Vaccines were brought to Honkajoki from a refrigerator 16 miles (25 km) away approximately once or twice per month. They were transported via automobile by the public health nurse, who carried 5–10 doses per journey in her handbag. They were refrigerated after arrival in Honkajoki and were removed from the refrigerator only for vaccination. Against this background, it is possible that vaccines were exposed temporarily to heat exceeding 30°C for 15–30 minutes during local transportation.

The local outbreak of the present study was part of the last large outbreak season in Finland in 1988–1989, when 1,749 cases of measles were serologically confirmed (14). No cases of measles had been detected in Honkajoki since 1979 prior to February 4, 1989, when an 18-year-old male nonvaccinee at the high school developed symptoms. We could not base the dates of measles onset on the onset of rash, because the local nurse had asked each person who contracted measles the date on which he or she “came down with

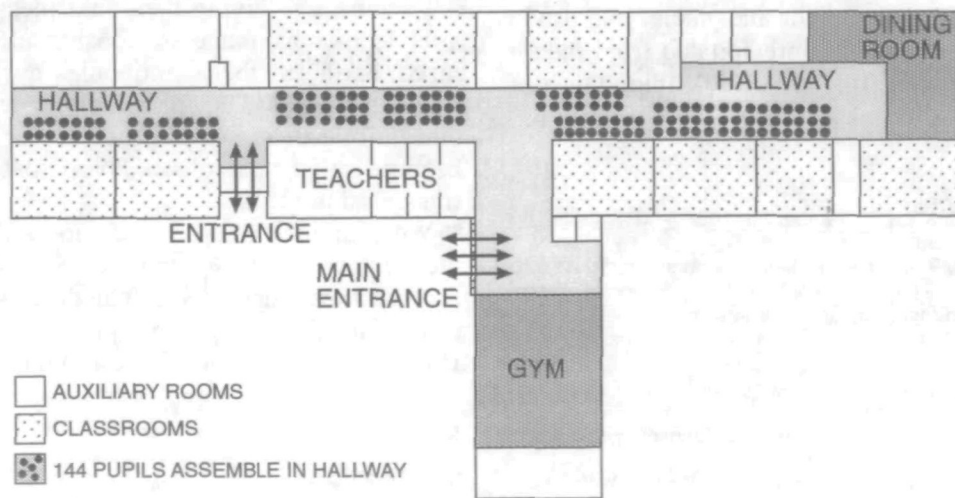


FIGURE 1. Floor plan of the high school affected by a 1989 measles outbreak, showing the location of morning student assembly in the hallway, Honkajoki, Finland.

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measles," which is a less precise definition (16, 17). The 18-year-old index case was unvaccinated because he did not belong to the birth cohorts included in the official vaccination programs, nor had he been exposed to live virus in the sparsely populated rural areas covered by the Mo vaccination program beginning in 1975. After the index case became ill, 21 13- to 15-year-old junior high school students and one senior high school student developed measles in one generation during days 8–14 of the epidemic (figure 2). In the first class (grade 10) of the senior high school, two measles cases, neither sharing a home with an index case, were identified on days 19 and 23. Two

vaccinated cases soon appeared in elementary schools during epidemic days 5 and 6. Secondary cases within families appeared an average of 10 days after those in the high school. All vaccinees who contracted measles had received their first vaccination after 15 months of age. Emergency vaccination with the MMR vaccine was targeted at senior high school students, both with ($n = 26$) and without ($n = 23$) a recorded measles history, who had previously received only Mo vaccine. On February 28, 20 students were vaccinated; on April 1–3, 13 students were vaccinated; and on April 10, 16 students were vaccinated. The outbreak was contained within 3 weeks.

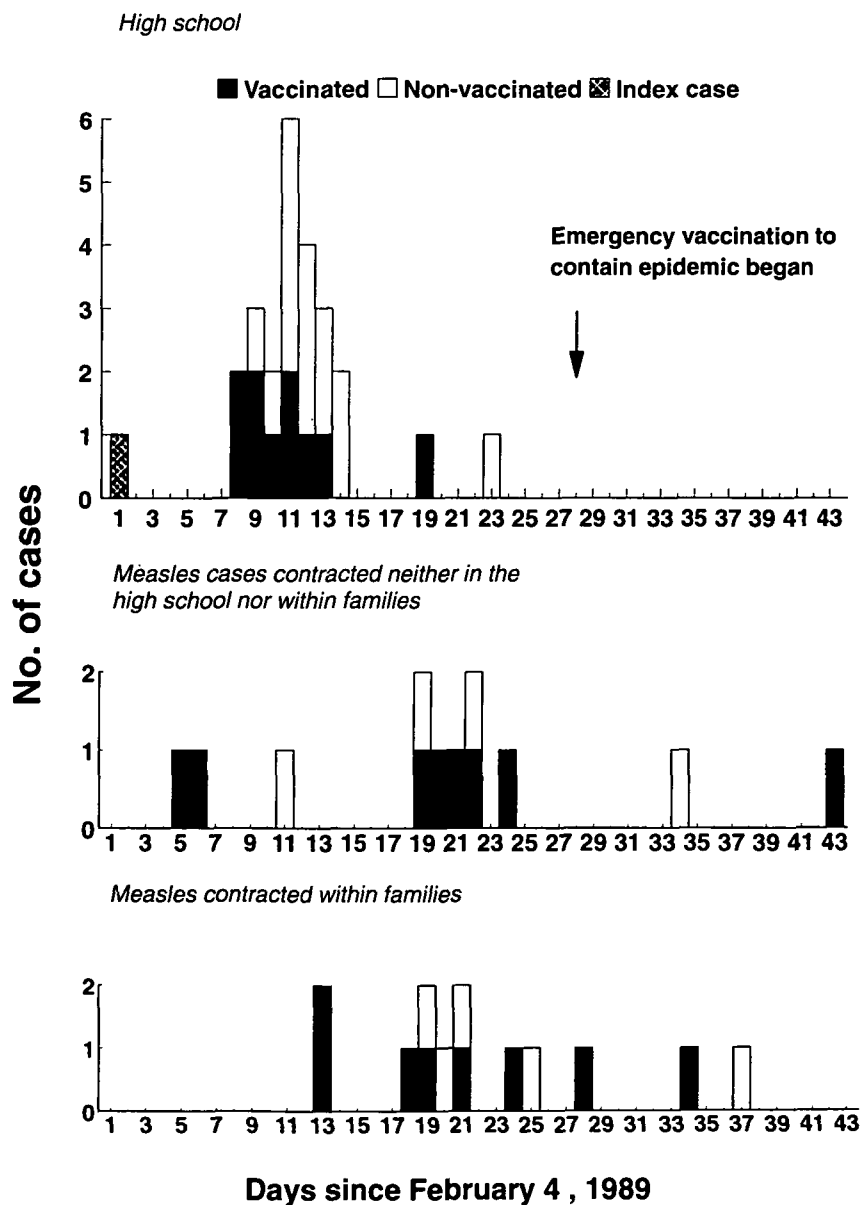


FIGURE 2. Course of the measles outbreak in Honkajoki, Finland, by setting, February 4–March 18, 1989.

Data on cases and controls

The diagnosis of measles was serologically confirmed in 34 (67 percent) of 51 patients, including the index case. The public health nurse collected data on age, sex, vaccination history, and the date of disease onset. The cases were divided into primary cases (infected outside the home) and secondary cases (infected at home by a sibling) according to modified (i.e., disease onset was not based on onset of rash) US Centers for Disease Control and Prevention criteria (16, 17). A case was deemed secondary when symptoms and signs commenced 7–18 days after the onset of symptoms in another case in the same household.

History of measles and measles vaccination was checked for both cases ($n = 25$) and healthy controls ($n = 119$) in the high school, and for the secondary cases ($n = 15$) and all healthy family members ($n = 23$) within the families of primary cases. Data were also collected from a systematic sample of healthy younger preschool children ($n = 36$) and from healthy children in seven elementary schools ($n = 36$)—six individuals from each annual birth cohort in the central health card register of Honkajoki, which includes all of the town's residents. All vaccination and measles data were abstracted from official health cards. The nurse also checked whether the bedroom of the primary case in the family was shared with one or more siblings. Bedroom data were incomplete.

Since the nurse was familiar with the detailed living conditions in most families, it was possible to separate the secondary cases occurring in the older, more air-permeable wooden houses from those occurring in the well-insulated, poorly ventilated newer homes. Homes built of brick after the 1974 energy crisis were virtually sealed against the movement of air because of the newer construction standards, and were considered airtight.

Statistical methods

The statistical significance of the difference in mean incubation times between vaccinated and unvaccinated individuals was assessed by *t* test.

Measles attack rates were calculated directly for the high school and for the homes of primary cases, as all contact information regarding these settings was available. For preschoolers and elementary school children, denominators for calculation of attack rates were estimated from the total number of children in each age group, multiplying this by the proportion of each measles and vaccination history category in the control series.

The vaccination status of the primary case in the family and the airtightness of the home and shared

bedroom were both considered factors potentially affecting the subsequent measles attack rate in the families. Relative risks and their 95 percent confidence intervals were calculated by the method of Greenland and Robins (18).

RESULTS

The 18-year-old high school student in Honkajoki (the index case) probably infected 22 students by airborne transmission during the course of one day (2); therefore, a single, unimodal wave was expected, with a characteristic normal distribution on a logarithmic time scale due to the point-source nature of the exposure (19). Instead, vaccinated individuals contracted the disease earlier, on average, than unvaccinated individuals, and two incubation period distributions seemed to be superimposed on the first bimodal wave of high school cases (figure 2). The period since exposure was constructed for the secondary cases in the families ($n = 15$) and for the 22 cases following the index case in the school.

Only 4 percent (5/135) of vaccinated elementary school students and 1 percent (2/165) of recently MMR-vaccinated preschool children with no measles history were attacked when not exposed within the family (table 1). Including within-family exposures as well, the corresponding attack rates were 12 percent (16/135) and 3 percent (5/165). Thirty-six percent (9/25) of the vaccinated junior high school students and 8 percent (1/13) of the vaccinated senior high school students with no history of measles were attacked (table 1). Unexpectedly, the attack rate among unvaccinated senior high school students who had no record of previous measles was only 6 percent (2/33).

Measles risk was high among within-family exposed subjects, regardless of the number of vaccinations (table 2), and the risk was particularly high when the primary case in the family shared a bedroom with one or more siblings (table 3). The air permeability of the home also seemed to play a role (table 3). In relatively new and airtight buildings, the vaccine failure rate was 48 percent (10/21). In contrast, no cases occurred in the older, more air-permeable houses. At least 69 percent (18/26) of vaccine failures occurred after intense indoor exposure, either in the local high school or at home.

In the attacked families, one 8-month-old baby contracted measles, while four babies (<1 year old) remained healthy. When infants younger than 1 year of age were omitted, a high (83 percent (5/6)) attack rate was observed among the unvaccinated siblings within families; only one 13-month-old toddler did not develop clinical measles (table 2).

Because time since vaccination or between two sub-

TABLE 1. Measles attack rates (%) in different population and vaccination groups, Honkajoki, Finland, 1989*

School attendance and age range	History of measles, with 0-2 previous vaccinations	No measles history			Total
		2 or 3 previous vaccinations	1 previous vaccination	No previous vaccination	
Preschool, 1-6 years	0 (0/0)†	0 (0/36)	2 (2/129)	0 (0/7)	1 (2/172)
Seven elementary schools, 7-12 years	3 (1‡/34)	5 (5/106)	0 (0/29)	60 (3/5)	5 (9/174)
Outbreak high school					
Junior classes, 13-15 years	0 (0/17)	25 (1/4)	38 (8/21)	38 (13/34)	29 (22/76)
Senior classes, 16-18 years	0 (0/22)	0 (0/3)	10 (1/10)	6 (2/33)	4 (3/68)
Total	1 (1/73)	4 (6/149)	6 (11/189)	23 (18/79)	7 (36/490)

* Cases infected at home were not included. All vaccinations were properly administered, i.e., after 15 months of age.

† Numbers in parentheses, no. of cases/total number of children.

‡ Serologically confirmed case, in the daughter of the local public health nurse. The patient and her mother suffered from presumably genetically determined hypo-gamma-globulinemia and/or low complement level. This child was close to death, and she recovered only after receiving passive immunization in the hospital. She was unvaccinated because of repeated infections.

sequent vaccinations or revaccinations did not alter measles risk, adjustments for these factors are not shown. Attack rates among once-vaccinated high school students who had been vaccinated <5 years, 5-9 years, and ≥10 years previously were 20 percent (1/5), 67 percent (2/3), and 25 percent (6/24), respectively.

TABLE 2. Measles attack rates (%) for cases infected at home by a primary case, according to measles history and vaccination history, Honkajoki, Finland, 1989

Measles history	Vaccination history*	Attack rate
Yes	Any	0 (0/4)†
No	2 or 3	40 (6/15)
No	1	31 (4/13)
No	0	83 (5/6‡)
Total		40 (15/38)

* All vaccinations were properly administered, i.e., after 15 months of age.

† Numbers in parentheses, no. of cases/total no. of children.

‡ One 13-month-old toddler remained without clinical measles.

TABLE 3. Sharing a bedroom and living in an airtight home with a primary case as risk factors for vaccine failure in a measles outbreak, Honkajoki, Finland, 1989

Risk factor	Vaccine* failure rate (%)	Relative risk	95% confidence interval
Shared bedroom			
No†	25 (3/12)‡	1.0	
Yes	78 (7/9)	3.1	1.1-8.8
Airtight home			
No†	0 (0/7)	NA§	NA
Yes	48 (10/21)	NA	NA

* All vaccinations were properly administered, i.e., after 15 months of age.

† Reference category.

‡ Numbers in parentheses, no. of cases/total no. of children.

§ NA, not assessed.

Vaccinated high school students had a 2 days' shorter mean incubation period than unvaccinated students ($p < 0.001$) (figure 2). Inclusion of measles cases contracted within families did not influence this disparity, although statistical significance was lost ($p < 0.1$) because of increased variance (figure 3).

Both properly vaccinated and unvaccinated primary patients were equally contagious within families: The attack rates among family members were 47 percent (9/19) and 43 percent (6/14), respectively.

DISCUSSION

The basis for modern measles eradication is reliance on some type (20) of two-dose vaccination schedule, which minimizes the primary vaccine failures remaining after the first dose. The outbreak described here is unusual for its high risk of measles among those who had received two or three doses of vaccine when they were exposed to measles virus in the local high school or in the home of an infected sibling. Possible explanations include 1) a poor cold chain and 2) the impact of a large measles inoculum by airborne transmission.

High vaccine failure rates have been associated with defective refrigerators (21, 22), and as there was some possibility of a cold chain disturbance in Honkajoki, it would be tempting to conclude that deficient primary serologic response was responsible for the observed high vaccine failure rate. The fact that time since vaccination did not explain vaccine failures may be taken to support this conventional interpretation. Cold boxes were not used in short local vaccine transportation, but no other weak point in the cold transport chain was detected. The small volume of vaccines carried during each local journey might have favored heat shocks, because the temperature of vaccines rises more readily when small numbers are transported.

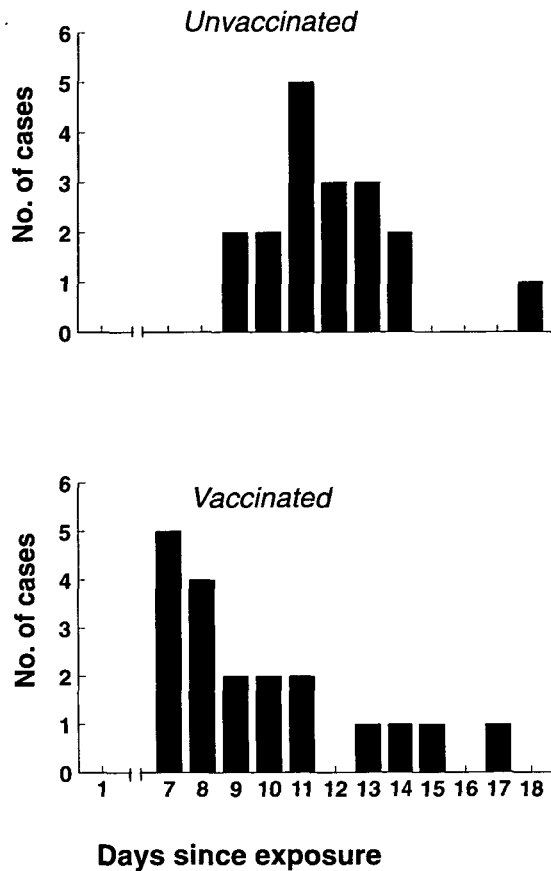


FIGURE 3. Measles incubation periods in unvaccinated and vaccinated individuals, Honkajoki, Finland, February 4–March 18, 1989.

On the other hand, certain facts reduce the likelihood of simple primary vaccine failures in this local outbreak. In ordinary settings, primary vaccine failure rates should be clearly below 10 percent (23). Revaccination effectively corrects primary vaccine failures (24). Even if we assume a high 25 percent primary failure rate in consecutive vaccinations of individuals, we would have expected failure rates of approximately 5 percent among revaccinees infected at home, instead of the observed 40 percent.

Measles did not spread markedly to preschool and elementary school children, although, according to the conventional explanation model, almost 80 percent of vaccinations could have been technically deficient, as seven out of nine failed when a sibling shared a bedroom with an index case. Furthermore, even if the division of vaccine failures into clearly either primary or secondary failure was accurate, an increased inoculum of measles would not have altered vaccine failure risk. Our findings seem to be congruent with a Danish theory (11) which postulates that a large measles inoculum resulting from within-family exposure increases vaccine failure risk. However, our vacci-

nated index cases were no less contagious than unvaccinated index cases, as was found in West Africa (11). Properly vaccinated children with measles have also been observed to become infectious in the United States (25).

In Honkajoki, the low attack rate among senior high school students probably results from unrecorded contact with wild measles virus during the 1970s, as these students were already 7–9 years of age by the time measles had disappeared from Honkajoki. Vaccinations are meticulously recorded in Finland, but the usual accuracy could not be achieved with measles, a disease previously regarded by mothers as trivial.

The reason why few ($n = 7$) unvaccinated preschoolers did not get measles when they were not exposed at home could be that they did not mingle with school-age children and/or that they were only casually in contact with older children other than their siblings. Most families with small children lived some distance from each other, which might also have protected the preschool-aged nonvaccinees.

A very similar explosive outbreak occurred in 1985 in a US (Illinois) high school, in which a common nonventilated hallway was also considered the crucial site of measles transmission (2). Almost 100 percent of the US students had been vaccinated, many even twice, but the revaccinated students were not better protected. The case students who had been exposed at school also appeared in one generation in that study, and it was unlikely that the index case had had close contact with all subsequent patients. The investigators concluded that measles was effectively spread by airborne transmission (2).

Other factors also may have accelerated the outbreak in Honkajoki: A complete lack of ultraviolet light in the hallway and low humidity during the winter months might have effectively prevented disinfection of indoor air (10, 26). Airborne transmission is uncommon in the literature, and its overall importance in measles outbreaks remains to be clarified (1–3, 5). In general, one has to be cautious when making generalizations from exceptional outbreaks (27), as they need something “unusual” in order to be triggered. In Honkajoki, it is probable that a hacking cough in an unfavorable environment with high contact density triggered an explosive outbreak, which normally would occur rarely. Considering that measles transmission now appears to be blocked in Finland (14, 15), it is unlikely that airborne transmission poses a major obstacle for national measles control when a two-dose vaccination program with high coverage is maintained. Nevertheless, important lessons can be learned from outbreaks such as this one.

The more rapid onset of disease among vaccinees

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compared with nonvaccinees could be explained by various mechanisms assuming an anamnestic response (28–33). The imprecise definition of measles onset used in this study should have made the difference between the incubation periods of vaccinees and nonvaccinees weaker, not created a difference. High and more rapid convalescent titers among vaccinees compared with nonvaccinees were observed in the late 1960s, which lends biologic credibility to our finding (33). To our knowledge, it has not been previously suggested that the incubation period among vaccinees may be shorter than that among nonvaccinees; therefore, this observation must be validated by additional studies. In the classic study of the Faroe Islands outbreak of 1846, rash appeared, on average, 14 days after inoculation (34). Interestingly, in the US high school, it took 12.5 days, on average (median, 12.0), for rash to appear in the vaccinees after the rash of the vigorously coughing index case appeared (2).

It is understandable that measles cases have been observed among fully vaccinated schoolchildren, since airborne transmission sometimes causes “astronomical” contact rates between the spreader and susceptible persons, and this mode of transmission effectively picks up the remaining few nonvaccinees and stochastic primary vaccine failures, who would enjoy herd immunity under conventional circumstances of person-to-person transmission. However, since airborne transmission might occasionally exceed the measles inoculum threshold, this could explain why even revaccinated individuals get measles. It would thus appear that the presence of airborne transmission is one reason why eradication of measles has been much more difficult than originally anticipated.

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EXHIBIT 414



Environmental factors potentially associated with mumps transmission in Yeshivas during a mumps outbreak among highly vaccinated students: Brooklyn, New York, 2009–2010

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Environmental factors potentially associated with mumps transmission in Yeshivas during a mumps outbreak among highly vaccinated students Brooklyn, New York, 2009–2010

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Keywords: mumps, mumps transmission, environmental risk factors, high MMR vaccine coverage, mumps outbreak

During 2009–2010, a large US mumps outbreak occurred affecting two-dose vaccinated 9th–12th grade Orthodox Jewish boys attending all-male yeshivas (private, traditional Jewish schools). Our objective was to understand mumps transmission dynamics in this well-vaccinated population. We surveyed 9th–12th grade male yeshivas in Brooklyn, NY with reported mumps case-students between 9/1/2009 and 3/30/2010. We assessed vaccination coverage, yeshiva environmental factors (duration of school day, density, mixing, duration of contact), and whether environmental factors were associated with increased mumps attack rates. Ten yeshivas comprising 1769 9th–12th grade students and 264 self-reported mumps cases were included. The average yeshiva attack rate was 14.5% (median: 13.5%, range: 1–31%), despite two-dose measles-mumps-rubella vaccine coverage between 90–100%. School duration was 9–15.5 h/day; students averaged 7 h face-to-face/day with 1–4 study partners. Average daily mean density was 6.6 students per 100 square feet. The number of hours spent face-to-face with a study partner and the number of partners per day showed significant positive associations ($p < 0.05$) with classroom mumps attack rates in univariate analysis, but these associations did not persist in multivariate analysis. This outbreak was characterized by environmental factors unique to the yeshiva setting (e.g., densely populated environment, prolonged face-to-face contact, mixing among infected students). However, these features were present in all included yeshivas, limiting our ability to discriminate differences. Nonetheless, mumps transmission requires close contact, and these environmental factors may have overwhelmed vaccine-mediated protection increasing the likelihood of vaccine failure among yeshiva students.

Introduction

Mumps is a viral infection characterized by parotitis and fever, and can result in orchitis, deafness, or meningoencephalitis.¹ In the pre-vaccine era, mumps outbreaks often occurred in congregate settings, including schools and military barracks.^{2–4} In 1977, the Advisory Committee on Immunization Practices (ACIP) recommended one mumps vaccine dose for routine childhood vaccination,⁵ and in 1989, recommended two doses of measles-mumps-rubella (MMR) vaccine for improved measles control.⁶ In the US, the first MMR dose is administered at ages 12–15 mo and the second dose at 4–6 y.⁷

Following the implementation of the one- and two-dose MMR vaccine programs, reported mumps cases declined to fewer than 500 annually in the US from 2000–2005.² However, in 2006, an outbreak of 6,584 cases occurred, primarily affecting two-dose vaccinated Midwest college students living in dormitories.⁸

In 2009, another outbreak began in New York at an Orthodox Jewish boys' camp that spread to affect 3,502 individuals in the Northeast.⁹ Brooklyn, New York was most affected with 1,737 (50%) of the total reported outbreak cases.

This outbreak primarily affected two-dose vaccinated adolescent males aged 13–18 y in the Orthodox Jewish community who attended yeshivas.⁹ Yeshivas are schools where Orthodox Jewish 9th–12th grade males intensively study religious texts. School days typically last ≥ 12 h. A unique yeshiva feature is *chevrusa* (study partner) style study: one-on-one interaction with a partner where students sit opposite each other at tables with other *chevrusa* pairs, usually in a large study hall termed a *beis midrash*.

Our objective was to understand mumps transmission dynamics in this well-vaccinated population. Although inclusion of heterogeneous, lightly-affected schools would have allowed us to elucidate differences explaining transmission, 97% of cases

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were in the Orthodox Jewish population⁹ and there were only two non-yeshivas with at least one male mumps case in the targeted grades (9th–12th), limiting the types of schools we could include. Thus, we examined school characteristics and potential environmental risk factors for mumps transmission in selected Brooklyn yeshivas.

Results

Inclusion. Of 93 schools with mumps cases reported to the New York City Department of Health and Mental Hygiene (NYCDOH), 57 did not meet the inclusion criteria (e.g., all-female, not high school level, outside Brooklyn, non-yeshiva) and 23 lacked contact information, leaving 13 (14%) yeshivas that met the inclusion criteria. Of the remaining 13, 11 (85%) completed the classroom survey where students were asked to self-report whether they had mumps-like illness, whether they saw a healthcare provider for mumps symptoms, and whether they stayed home from school for mumps. One yeshiva was subsequently excluded because the cases were not in grades 9–12. Two yeshivas did not respond to multiple attempted contacts. Thus, 10 yeshivas comprising 1769 9th–12th grade students and 264 self-reported mumps cases met the inclusion criteria, completed the classroom survey, and were assessed. Although cases were self-reported, 241 (91%) reported visiting a healthcare provider for their symptoms and 100% were either sent home or stayed home from school.

Vaccination coverage. In the 10 yeshivas, 9th–12th graders comprised 39 grades and 63 classes (4 yeshivas had multiple classes per grade). All 10 yeshivas had overall one- and two-dose MMR coverage rates between 97–100% and 90–100%, respectively (Table 1). Three (8%) grades had two-dose vaccination coverage rates < 90% (i.e., 82%, 87% and 89%), but all other grades had two-dose coverage rates ≥ 90% (average: 95%).

Yeshiva characteristics. Duration and mixing. On average, school lasted 12.7 h/day (range: 9–15.5 h) Monday through Thursday, with half days on Fridays, no class on Saturdays and shortened days on Sundays. School weeks averaged 63.0 h (range: 49–74.5 h). We obtained schedules from 9 (90%) yeshivas. On average, 9th–12th graders spent: 6.2, 3.7, 3.4 and 2.0 h/day in the classroom, respectively, where they predominantly faced forward; 3.0, 5.8, 6.6 and 7.9 h/day studying in the study hall (*beis midrash*), respectively, where they sat face-to-face with a study partner (*chevrusa*); 1.7 h/day facing forward during prayers in the beis midrash; and 1.2 h/day in the cafeteria.

On average, students spent 7 h/day face-to-face with their chevrusas (range: 1–11 h) and changed chevrusas 2.5 times/day (range: 1–4 times). Mixing occurred within classes (e.g., chevrusas were from the same class). Although all students gathered in the beis midrash, and multiple grades often ate in the cafeteria concurrently, students sat with their own class and mixing among grades rarely occurred.

Approximately 850 (48%) students in 4 yeshivas rode school buses daily. Three yeshivas reported that buses carried students from several grades concurrently; none carried students from multiple schools.

Density. Yeshivas had an average of 26.5 students per classroom. When all students gathered in the beis midrash for study hall and prayers, an average of 195 students were in the same room. Average room densities for the classroom, study hall, prayer time and cafeteria were: 5.8, 6.2, 7.1 and 8.4 students per 100 square feet, respectively. Average daily mean density was 6.6 students per 100 square feet.

Ventilation. Nine yeshivas provided ventilation data. Five (56%) used central heating, 9 (100%) had windows that could open and 8 (89%) had central air conditioning, of which 3 also used fans.

Prevention Measures. Seven (70%) yeshivas increased sanitization practices during the outbreak, 9 (90%) communicated with parents or students about mumps (e.g., letters, school announcements) and all yeshivas sent symptomatic students home. None of the yeshivas cancelled or postponed classes.

Attack rates. The average mumps attack rates in the yeshivas was 14.5% (median: 13.5%, range: 1–31%); 8 (80%) yeshivas had attack rates ≥ 10%. Tenth and twelfth grades had the highest mean attack rates at 18% each; ninth and eleventh grades had mean attack rates of 11% each. Class attack rates ranged from 0–42%. Class attack rates in Yeshiva A, which had the lowest yeshiva attack rate (1%), ranged from 0–13%, whereas class attack rates in Yeshiva J, which had the highest yeshiva attack rate (31%), ranged from 19–42%.

The class with the highest attack rate (42%) had 95% two-dose vaccination coverage. Eleven classes had 0 case-students, all in Yeshiva A; two-dose MMR vaccination coverage in these 11 classes was 96–100%.

Analysis. We included data from the 9 yeshivas for which we had scheduling information. When accounting for clustering, the number of hours spent face-to-face with a chevrusa and the number of chevrusas per day showed significant positive associations ($p < 0.05$) with classroom mumps attack rates in univariate analysis, but these associations did not persist in multivariate analysis (Table 2). The number of hours per school day and mean density were not significant in univariate analysis. The results were similar when we used continuous and categorical variables.

Discussion

The yeshiva setting was characterized by close contact: students averaged 7 h of face-to-face exposure to an average of 2.5 chevrusas per day. Close contact is essential for mumps transmission; mumps spreads through respiratory droplets or secretions.¹ To become infected, a person must be within three feet of an infected person or have direct contact with his or her secretions.^{10,11} Although in multivariate analysis we did not find a significant association between classroom mumps attack rates and face-to-face time or number of chevrusas/day (factors that may be critical determinants for spread of mumps among vaccinated persons), we postulate that these factors did not vary sufficiently across the included yeshivas to allow significant differences to be discriminated. Nonetheless, the dynamics of prolonged face-to-face exposures with multiple chevrusas may have created a high enough force of infection to overwhelm vaccine-mediated

Table 1. Yeshiva class size, MMR vaccination coverage, attack rates, hours spent in the yeshiva, hours face-to-face with a chevrusa, daily mean density and number of chevrusas per day in Brooklyn yeshivas, 9/1/2009—3/30/2010

Yeshiva	Grade	Average Number of Students per class	Two Dose MMR Coverage (% by Grade)	Two Dose MMR Coverage (% by Yeshiva)	Grade Attack Rates (%)	Yeshiva Attack Rates (%)	Hours at School/Day ^a	Hours at School/Week	Hours Face-to-Face with Chevrusa(s)/Day ^a	Daily Mean Density (Average Number of Students per 100 Square Feet/Day) ^a	Number of Chevrusas/Day ^a
A	9	18.3	96	98	4	1	12.5	58.5	1	8	1.5
	10	20.3	100		0		12.5	58.5	3	9.8	1.5
	11	15.5	98		2		12.5	58.5	4	8.7	1.5
	12	19	98		0		12.5	58.5	9	6	1.5
B	9	34	97	97	6	8	12	64	6.25	4.1	3
	10	33	97		9		12	64	6.25	4.1	3
	11	33	93		3		12	64	6.25	4.2	3
	12	22	100		18		12	64	6.25	3.9	3
C	9	28	100	100	7	10	15.5	74.5	N.A.	N.A.	1
	10	25	100		4		15.5	74.5	N.A.	N.A.	1
	11	21	100		10		15.5	74.5	N.A.	N.A.	1
	12	25	100		20		15.5	74.5	N.A.	N.A.	1
D	9	24	96	95	8	11	13.5	67.5	3.75	3.1	3
	10	33	94		18		13.5	67.5	5.25	3.5	3
	11	37	100		6		13.5	67.5	5.25	3.6	3
	12	37	89		11		13.5	67.5	6.75	3	3
E	9	21.5	98	95	14	11	12	57	1.5	6.9	1
	10	24	96		10		12	57	3	9.2	1
	11	38	92		5		15	73	9.75	5.6	2.5
	12	24	92		17		15	73	10.25	4.7	2.5
F	9	28	82	90	7	16	14	74	11b	5.5	3
	10	38	92		18		14	74	11b	6.3	3
	11	40	93		18		14	74	11b	6	3
	12	40	90		18		14	74	11b	5.8	3
G	9	28	93	93	21	16	13	70	7	5	3
	10	23	96		22		13	70	7	4.7	3
	11	14	90		7		13	70	7	4.3	3
	12	51	94		12		13	70	7	6.3	3
H	9	40	95	98	20	17	9	49	1.5	6.3	4
	10	40	98		20		10.5	55	3.0	6	4
	11	18	100		19		13.5	67	8.5	3.4	4
	12	46	100		11		13.5	67	8.5	4.4	4
I	10	25.1	96	93	25	22	12.5	60	8	9.4	3
	11	27.5	87		14		12.5	60	8	9.3	3
	12	30.8	96		27		12.5	60	8	4.1	3
J	9	21	100	96	19	31	12.5	64	8b	4.3	2
	10	22	95		32		12.5	64	8b	4.6	2
	11	23	96		30		12.5	64	8b	4.5	2
	12	19	95		42		12.5	64	8b	4	2

N.A. means scheduling data not available. ^aA day is based off of the Monday–Thursday schedule (Fridays are half days, there is no school on Saturday and Sunday is a shortened day). ^bYeshivas F and J utilized the chevrusa system in the classroom, in addition to the beis midrash.

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Table 2. Univariate and multivariate analyses assessing independent factors associated with classroom mumps attack rates in Brooklyn yeshivas, 9/1/2009–3/30/2010

Yeshiva Characteristics and Environmental Factors ^a	Unadjusted Risk Ratio (95% CI)	P value	Adjusted Risk Ratio (95% CI) ^b	P value
Hours at school/day	0.92 (0.83– 1.01)	0.076	–	–
Mean density	0.01 (0– 105.87)	0.338	–	–
Hours face-to-face/day	1.10 (1.02– 1.18)	0.009	0.92 (0.81– 1.04)	0.165
Number of chevrusas/day	1.48 (1.15– 1.89)	0.002	1.46 (0.72– 2.94)	0.291

^a We excluded ventilation data because the outbreak occurred during winter when windows were closed and air conditioning was off. ^b Hours at school per day and mean density were not included in the final model because they were not significant in the univariate analysis.

protection and may have increased the likelihood of vaccine failure among yeshiva students.

Yeshiva students attended school on average 12.7 h/day with an average of 26.5 students per classroom, compared with an average of 6.7 h/day and 18.4 students per classroom for other private US secondary schools.^{12,13} Although neither school day duration nor density were significant risk factors in univariate analysis and are more indirect indices of close contact than face-to-face time or number of chevrusas/day, the yeshivas we evaluated had a school day that was approximately twice as long with 31% more students per classroom than other US private secondary schools which could have played a role in mumps transmission.^{12,13}

This paper describes class attack rates that were as high as 42%, despite high two-dose MMR vaccine coverage. Even with opportunities for mumps introductions in the surrounding non-Orthodox community, the exposures were likely less frequent and less intense than in yeshivas, so the high vaccination coverage generally provided adequate population immunity for protection.⁹ These findings are consistent with a large mumps outbreak in Israel in 2009 where most cases also occurred among well-vaccinated Orthodox Jewish adolescent males with minimal spread to the broader community, despite regular mixing with non-Orthodox Jews.¹⁴ Mumps outbreaks have also occurred in other international settings among highly vaccinated populations.^{15–17}

Two MMR vaccine doses provide 66–95% vaccine effectiveness against mumps.^{18,19} The two-dose policy has reduced mumps incidence by > 99% compared with the pre-vaccine era.² Despite high two-dose MMR vaccine coverage, the average yeshiva attack rate was 14.5% which was 10% higher than the 4.6% attack rate among two-dose vaccinated college students living in affected dormitories in the 2006 US mumps outbreak,²⁰ and almost as high as attack rates during the one-dose era.²¹ Although it is possible that lesser-vaccinated grades seeded the outbreak (3 [8%] grades had two-dose MMR coverage < 90%), none of these had the highest grade-level attack rates, nor were they in yeshivas with the highest attack rates.

Based on the age range of the students in the yeshivas included in this analysis (i.e., 13–18 y) and the ACIP guidelines for the standard age for receipt of the second MMR vaccine dose, it is likely that these students received their most recent dose between 7–14 y prior. Nonetheless, waning immunity did not seem to contribute to this outbreak,⁹ because the outbreak did not readily spread to older persons. Strain difference between the vaccine (genotype A Jeryl Lynn) and circulating mumps virus (genotype G) also did not seem to play a role, because generally, mumps

did not spread to the broader population.⁹ Opening windows and doors may help reduce mumps transmission.²² However, we excluded these factors in the model, because the outbreak occurred during winter when windows were closed.

This analysis had limitations. We did not evaluate schools with zero reported mumps cases as a comparison (e.g., public or girls schools), because our objective was to understand characteristics of schools with mumps transmission. Upon identifying yeshivas with reported cases on NYCDOH's list, we planned to compare yeshivas with high vs. low attack rates. However, after obtaining accurate case counts from surveying the included yeshivas, all but one had a high attack rate. The low attack rate school (Yeshiva A) had characteristics similar to high attack rate schools (e.g., long school days, multiple chevrusas, high density). We assessed whether there were differences between higher grades (11th and 12th) that generally had longer school days and spent more time face-to-face with chevrusas vs. lower grades (9th and 10th), but there was likely too much overlap in environmental conditions among grades to provide meaningful differences. A power analysis was not done at the onset, because this was deemed to be an outbreak response. Thus, we planned to enroll all yeshivas that met the inclusion criteria. As in any outbreak, tools are inadequate to monitor individual-level exposures to infectious respiratory agents, such as mumps; thus, this analysis was ecologic. However, due to the limitations of an ecological design, we were unable to report individual-level data, such as identify who the classroom index case-students were, report the severity of their illness (as a proxy for infectiousness), document who were linked as chevrusas, compare the attack rate among students who had zero or 1 dose of MMR vaccine, or identify who was uniquely exposed to whom. Yeshivas also did not provide mumps onset dates of case-students which limited our ability to assess transmission patterns (i.e., whether classrooms had one wave or several subsequent waves of mumps infection). We did not have age data on individuals to determine if older students were affected more frequently, potentially as a result of waning immunity; however, grade was considered a proxy for student age. To study risk factors for spread of mumps within yeshivas, it was necessary to restrict our analysis to yeshivas that had mumps exposure (i.e., any reported cases within a yeshiva). While this resulted in a limited number of included yeshivas, initial introduction of mumps was likely to be a primarily stochastic event, based on networks within the affected community. Nonetheless, we do not believe that this restriction introduced important bias. We potentially missed yeshivas, because healthcare providers may not have

reported all cases to the NYCDOH and schools were not always identified when cases were reported. Additionally, two yeshivas did not respond to our survey and 23 lacked contact information.

Despite these limitations, this evaluation is important given the paucity of literature providing detailed descriptions of settings where mumps transmission has occurred in two-dose vaccinated populations. Mumps outbreaks in two-dose vaccinated populations are an important phenomenon that have been reported in Western countries over the past 6 y,^{8,14,15,17} and their occurrence underscores the importance of this type of in-depth risk factor analysis. Additionally, this paper takes a novel approach to assessing mumps transmission risk factors, carefully measuring parameters relating to exposure at the yeshiva, grade and class levels. The negative findings in our investigation underscore the inadequacies of our current tools in measuring and understanding mumps transmission.

This investigation also highlights the challenges of mumps outbreak control with current vaccination policies in highly vaccinated two-dose populations. Yeshivas followed NYCDOH guidance and sent symptomatic students home for five days. However, mumps can spread before parotitis onset and from persons with asymptomatic infections (~30% of those infected are asymptomatic).¹ The Centers for Disease Control and Prevention (CDC) recommends reducing opportunities for close contact during mumps outbreaks in highly vaccinated populations.¹¹ However, this strategy might not always be effective in decreasing transmission, nor is it always feasible. Two MMR doses are sufficient to prevent mumps in most settings, as evidenced by the broader community remaining generally protected from mumps during this outbreak. The unique yeshiva setting, with the densely populated environment and prolonged face-to-face contact, may have led to a viral inoculum that overcame immunity, resulting in vaccine failure. However, had vaccination coverage not been so high, there would likely have been many more mumps cases, with disease that was more severe.^{9,23} Maintaining high MMR vaccination coverage remains the most effective way to prevent future outbreaks and limit their spread.

Methods

Inclusion criteria. We used mumps cases reported to NYCDOH to ascertain which yeshivas had mumps between 9/1/2009, when school resumed after summer break, and 3/30/2010, when school stopped for Passover. Since Brooklyn had the most reported cases, eligible all-male yeshivas were required to be located there and have: 1) at least one reported case in a student in the most affected age group (13–18 y in grades 9–12); 2) ≥ 80 students in grades 9–12; 3) ≥ 3 grades (i.e., 9th–11th or 10th–12th) to allow for comparison between upper and lower grades; and 4) two-dose MMR vaccine coverage $\geq 90\%$ prior to 9/1/2009. On the NYCDOH list of reported cases, school information was available for 238 (60%) male mumps case-students aged 13–18 y, but not all of them attended yeshivas that met the inclusion criteria.

Vaccination coverage assessments. Vaccination status was determined through school record reviews by NYCDOH.

Two-dose vaccination coverage was calculated by determining the number of students with ≥ 2 valid doses divided by the total number of students enrolled. MMR vaccine doses were considered valid if the first dose was given on or after the first birthday, the second dose at least 28 d later and if dates were recorded.⁷

Classroom survey. All yeshivas that met the inclusion criteria were sent classroom surveys that asked administrative staff to report the number of students, classrooms and grades in the yeshiva. Students were asked to self-report whether they had mumps-like illness, which was defined as fever and swelling in the jaw or cheeks, from 9/1/2009–3/30/2010; they also reported whether they saw a healthcare provider for mumps symptoms and stayed home from school for mumps.

School-based environmental factors survey. We documented average school day length; time spent in the classroom, beis midrash, cafeteria and prayers; room dimensions, which we calculated by measuring the length and width; room arrangement (i.e., face-to-face with a chevrusa or facing forward); mixing (e.g., number of chevrusas, integration of grades in school or on buses); type of school ventilation system; and school prevention measures. Dimensions of one classroom per grade were measured and used to impute dimensions for classes of similar enrollment within each school.

Data analysis. Data were analyzed in SAS 9.2 (SAS Institute Inc., Cary, NC). We calculated room density by dividing the number of students in the room by the square footage. To calculate daily mean density per class, we multiplied the density of each setting (e.g., classroom, study hall) by the proportion of hours the class spent in that room per day; we then summed the weighted density for each setting.

We examined the relationship between the mumps attack rate in each class, daily mean density, number of hours per school day, number of chevrusas a student had per day and total hours that students spent face-to-face with their chevrusas. Univariate analyses were conducted; variables significantly associated at the $p < 0.05$ level were used in multivariate analysis. We used generalized estimating equations to account for clustering of yeshivas and grades. Multicollinearity and interaction between variables were assessed.

Human ethics determination. The project titled “Environmental Factors Potentially Associated with Mumps Transmission in Yeshivas during a Mumps Outbreak among Highly Vaccinated Students—Brooklyn, New York, 2009–2010” was reviewed by the National Center for Immunization and Respiratory Diseases (NCIRD) Human Subjects Contact and determined to be Public Health Practice: Outbreak Response. Since the project was not considered to be research, no further action was required by CDC for human subjects protections in accordance with federal regulation for the protection of human subjects in research.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed. No external funding sources were used to gather the data, analyze the data or write up the findings.

Disclaimer

The findings and conclusions in this article are those of the authors and do not necessarily represent the views of the CDC, US (Department of Health and Human Services).

Previous presentations

This article has not been presented previously at a meeting or conference.

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EXHIBIT 415



Horizontal transmission of live vaccines

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Horizontal transmission of live vaccines

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Dear Editor,

Horizontal transmission has been rarely reported with many live attenuated vaccines. Different mumps vaccines have shown rarely such transmission.¹⁻⁵ A study in US reported evidence of the transmission of rubella vaccine virus from vaccinees to two susceptible contacts.⁶

With live varicella vaccines, there are at least three reports. The brother of a 3-y-old vaccinated girl developed fever and a rash; horizontal transmission of vaccine virus was later confirmed.⁷ A pregnant mother contracted the vaccine virus after her 12-mo-old boy received varicella vaccine.⁸ Horizontal transmission was reported in 15 (17%) susceptible healthy siblings after varicella vaccination of 156 children with leukemia.⁹ The package insert of live varicella vaccine (Varivax, Merck) states that “Post-marketing experience suggests that transmission of vaccine virus may occur rarely between healthy vaccinees who develop a varicella-like rash and healthy susceptible contacts. Transmission of vaccine virus from vaccinees who do not develop a varicella-like rash has also been reported.”¹⁰

There are two reports with rotavirus vaccines. A randomized, double-blind study on human rotavirus vaccine (Rotarix™, Glaxo) in 100 pairs of healthy twins found that the transmission rate among placebo recipients was 18.8%.¹¹ In another case, rotavirus vaccine (RotaTeq, Merck) transmission was reported from a vaccinated infant to an older, unvaccinated sibling, resulting in symptomatic rotavirus gastroenteritis.¹²

A study on live attenuated influenza vaccine (FluMist, MedImmune) in a Finnish day care showed that one child in the placebo group had transiently detectable vaccine virus, indicating transmission from a vaccinated child; the child remained asymptomatic.¹³

Despite these reports, these live vaccines are used in millions of doses across the world. Clearly, the benefit of vaccination outweighs the very low risk of vaccine virus transmission.

Conflict of Interest

All three authors are employed by Serum Institute of India Ltd.

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EXHIBIT 416



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INFECTIOUS DISEASES SOCIETY OF AMERICA

Infectious Diseases and Social Change**Edward H. Kass****From the Channing Laboratory, Thorndike Memorial Laboratory, Harvard Medical Unit, and Department of Medical Microbiology, Boston City Hospital; and Department of Medicine, Harvard Medical School, Boston, Massachusetts*

It is a happy privilege, extended annually to the President of the Infectious Diseases Society of America, to address this meeting at its opening session. My distinguished predecessors have each dealt with pertinent concerns, predictions, perceptions, and historical developments in the field of infectious diseases. The standards of the past throw a heavy burden on the present speaker, and not the least is the certain knowledge that the only time the whale gets harpooned is when he comes up to spout.

However, I am led to spout, despite the hazards, by the same concerns that beset us all. We are experiencing with much pain an almost revolutionary restructuring of the programs of support for medical care, medical investigation, and medical education. We find ourselves puzzled, frustrated, and often so angry that we are occasionally led to the brink over which some of our young people have fallen, in which we are tempted to use obscenity because we fear that rationality has failed. We resent the abrupt manipulations of our good intentions when all that we have asked for is to be able to continue our good works in an atmosphere that will put to effective social use the fruits of our earnest efforts.

Now there is basically nothing wrong with this charming scenario of the white-coated medical scientist distributing good works like free beer at a political picnic, although it does seem to have been written by the least sophisticated of writers for the Sunday supplements; nor is it necessary

that we abjure personal benefit in order to perform socially constructive work, for it is not at all clear how much would happen if there were not a combination of material reward and social motivation in our daily activities.

Where the scenario becomes distorted is in some of our assumptions and in some of our failures. We saw a grants system developing that virtually excluded education and direct application, and although we recognized the unbalanced system that was developing, we were not particularly effective (did we really try harder?) in reordering these directions. In part, at least, we were afraid of rocking the boat. We were further sustained by the thought that in the long run research would provide easier and more effective ways to deliver medical care and teaching.

Once again, these were not objectionable points of view at all. The views simply failed to anticipate the political tides and the changing political pressures. Most particularly, we failed to realize that not much was happening to the statistics of mortality, survival, chronic illness, or causes of death even while the costs of illness and medical care were rising steadily; and the public is now demanding what we said we were providing, and is deeply concerned over what it is getting for its money.

The cost of the fighting in Vietnam and the inflationary pressures that accompanied it were the precipitants that forced a national policy of re-examination of objectives and allocations in the medical area. It is my conviction, however, that without this precipitant the day of reckoning would have come soon anyway. And while I have no sympathy with the unplanned, unstructured, and almost chaotic way in which this reckoning is being conducted, I cannot find it in my conscience to blame all of our troubles on our unhappy in-

*President, Infectious Diseases Society of America.

This address was given at the joint meeting of the Infectious Diseases Society of America and the Tenth Interscience Conference on Antimicrobial Agents and Chemotherapy, sponsored by the American Society for Microbiology, October 19, 1970, Chicago, Illinois.

volvement in the problems of Southeast Asia. Nor can I state with any conviction the belief that without the Indochina war we would have reordered our priorities or have undergone searching re-examination of our allocations. We were like Mike falling from the top of a skyscraper and receiving solace from all the Pats distributed at each floor, each shouting out that everything was all right so far.

Why were we falling? First we had accepted some half truths and had stopped searching for the whole truths. The principal half truths were that medical research had stamped out the great killers of the past—tuberculosis, diphtheria, pneumonia, puerperal sepsis, etc.—and that medical research and our superior system of medical care were major factors in extending life expectancy, thus providing the American people with the highest level of health available in the world. That these are half truths is known but is perhaps not as well known as it should be.

Figure 1, for example, gives the data on deaths from tuberculosis in England and Wales. Similar data have been obtained in every industrialized country and throughout the United States, but these data are cited because they are reliable and begin in 1850. The data on deaths from tuberculosis show that the mortality rate from this disease has been declining steadily since the middle of the 19th century and has continued to decline in almost linear fashion during the past 100 years. There were increases in rates of tuberculosis during wars and under specified adverse local conditions. The poor and the crowded always came off worst of all in war and in peace, but the overall decline in deaths from tuberculosis was not altered measurably by the discovery of the tubercle bacil-

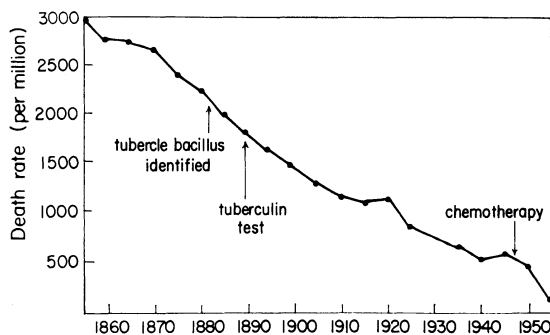


Figure 1. Mean annual death rate from respiratory tuberculosis, England and Wales.

lus, the advent of the tuberculin test, the appearance of BCG vaccination, the widespread use of mass screening, the intensive anti-tuberculosis campaigns, or the discovery of streptomycin. Only the advent of isoniazid changed the mortality patterns, and by then the rate of tuberculosis had fallen to but a small fraction of its levels 100 years earlier.

It is important that this point be understood in its completeness. The point was made years ago by Wade Hampton Frost, and more recently by René Dubos, and has been repeatedly stressed through the years by many observers of the public health. Our research efforts in dealing with tuberculosis have been of great value in the management of individual patients and in present-day public health practice, but they do not account for the linear decline in deaths during the past 100 years.

Similar trends in mortality have been reported with respect to diphtheria (figure 2), scarlet fever (figure 3), rheumatic fever, pertussis (figure 4), measles (figure 5), and many others. There are less reliably documented but suggestive similar trends with respect to carcinoma of the cervix, toxemia of pregnancy, stroke, and certain other disorders. This decline in rates of certain disorders, correlated roughly with improving socioeconomic circumstances, is merely the most important happening in the history of the health of man, yet we have only the vaguest and most general notions about how it happened and by what mechanisms socioeconomic improvement and decreased rates of certain diseases run in parallel. We know that for many infectious diseases, such as poliomyelitis and perhaps infectious hepatitis,

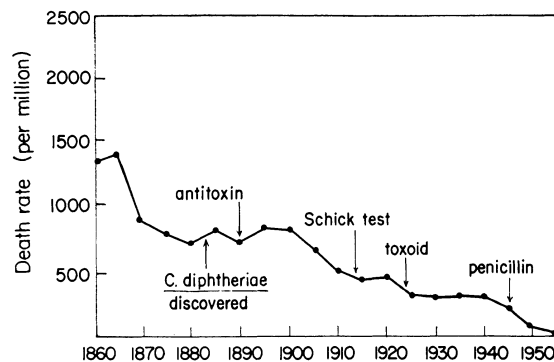


Figure 2. Mean annual death rate from diphtheria in children under 15 years of age, England and Wales.

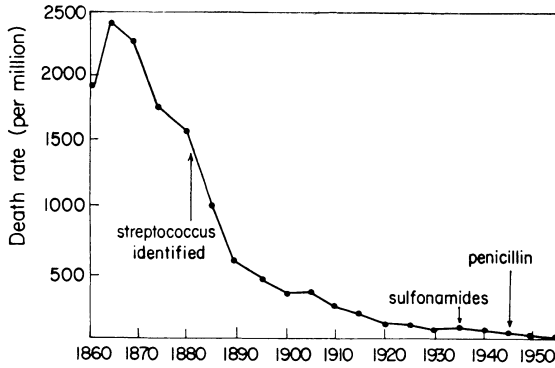


Figure 3. Mean annual death rate from scarlet fever in children under 15 years of age, England and Wales.

the trend is opposite, and for some there is little or no socioeconomic effect. This does not detract from the overriding relationship that has been seen in most common communicable diseases in which there is a strong relationship between socioeconomic status and rates of mortality and morbidity.

Currently fashionable is the view that nutritional improvements account for the decline in mortality from common infections and that nutritional inadequacy is a major factor in explaining the present predilection of the poor for certain communicable disorders. In fact, there is little useful evidence to support this view. Experimentally, the nutritional deficiencies that are needed to substantially affect resistance to infection are generally extreme, and in the case of certain viral disorders, such deficiencies may often *increase* resistance.

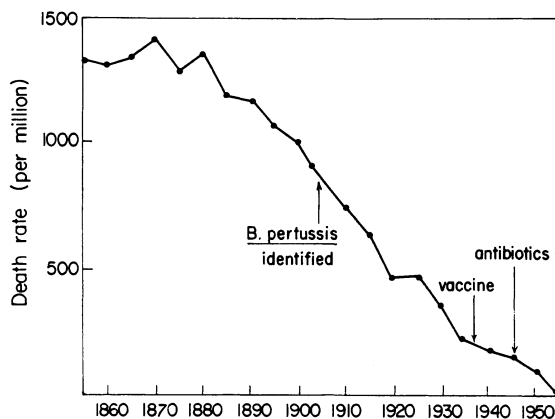


Figure 4. Mean annual death rate from whooping cough in children under 15 years of age, England and Wales.

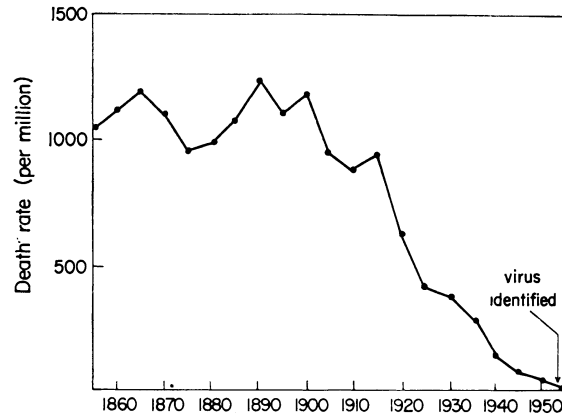


Figure 5. Mean annual death rate from measles in children under 15 years of age, England and Wales.

Clinically, there is not much evidence of manifest malnutrition in economically underprivileged populations in this or in other industrialized countries, if the available indices of malnutrition are used, even though it is evident that certain infectious diseases such as tuberculosis and rheumatic fever, are pretty much limited to the poor.

What other explanations are there for the effects of being poor? One explanation was developed in England more than 40 years ago (figure 6). It was shown that rates of rheumatic heart disease were almost linearly related to crowding in the home. This is understandable since spread by droplet infection is greatest in a narrow radius around an infected source and the home is, particularly for children, the place in which most prolonged contact will occur. Of course, this effect will be demonstrable in relation to any other locus for crowding.

Similar data were gathered during World War I by Glover, who showed that when beds in barracks were placed too close together rates of meningococcal infection among troops rose abruptly. In Peru, the Communicable Diseases Center gathered data relating attack rates of meningococcal disease to crowding in the home. Recently, Lilienfeld and his associates in Baltimore gained invaluable insight into this problem. They were distressed by the persistence of rheumatic fever in the black population of Baltimore and were puzzled because many of the black children with rheumatic fever came from homes that were middle class rather than ghetto in origin. Epidemiological analysis showed that the attack rates for rheumatic fever in these families were no longer related to low in-

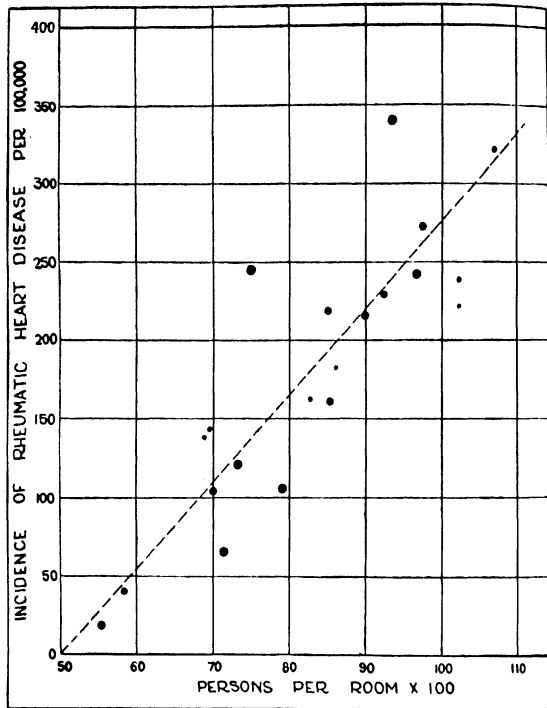


Figure 6. The correlation between the incidence of rheumatic heart disease per 100,000 and the number of persons per room ($\times 100$) as found by Perry and Roberts in various districts of the city of Bristol, England in 1927–1930. (The size of the dots indicates roughly the comparative population size of the districts.)

come or to lower educational levels, but were directly related to the number of people per bedroom. Evidently, in this group of families, when funds became more plentiful and the families began to move out of the ghetto, they tended to choose new dwellings which stretched their capacity to pay. Given a choice, they tended to select more space in living and dining rooms, putting added space for bedrooms at a lower priority.

I have referred to the increased longevity of our population as one of the indices of improved medical care. However, this is due almost completely to decreased infant mortality. The age of death of those who have lived to adulthood has been extended very little over the past 50 years, and in some populations it has actually declined. Infant mortality, due largely to gastrointestinal and respiratory infections, was at a rate of several hundred per 1,000 births during the 19th century, at a time when in royalty the rate was 12 per 1,000 births. That is, before antibiotics and before con-

temporary methods of control, the infant mortality rate in royal families was lower than that which is found in the best national rates now being recorded in any country of the world. Clearly, rich is better.

The lessons from these and from many similar observations are numerous. Among these are the responsibilities that we as experts in the field must face. We must face the need to assist or to bring about maximal control of disease even while we devote ourselves to new possibilities. Thus, while we develop vaccines or new anti-tuberculous drugs, we must be looking into more space per family unit or other ways of dealing with the spread of respiratory pathogens. While we try to determine why 50% of rheumatics drop out of programs of penicillin prophylaxis, we may need to use concepts of human engineering to calculate the cost and benefits of having better air-flow systems in industry, or better housing, and we shall then need to compare these costs with the cost of multiple specific approaches to control of many different diseases that may have common methods of spread.

Those of us who are interested in infectious disease are in the fortunate position of working with systems that are immediately relevant. Furthermore, even more than in most fields, we have seen the advantages of the continuous interdependence of applied and undirected investigation.

At an earlier stage in scientific history, scientists, and particularly those of the physical sciences, were enjoined to stay dissociated from the social consequences of their work. The general acceptance of this attitude of non-involvement by the scientist led to much powerful discovery, much of it used for the highest social purposes and much used to bring about more efficient ways of conquest, colonization, and the accumulation of wealth and power.

The present generation has questioned the wisdom of continuing a policy of advocacy of non-involvement and of dissociation from the social consequences and social objectives of scientific work. It no longer follows that all discovery is progress and that all technical achievements improve the lot of humanity. As this formidable questioning of the most fundamental drives of science goes on, we may wish to examine our posture in relation to our field of interest.

Is it conceivable that in conferring health and in

taking care of our infirm and elderly, we can supply a source of drive for progress that can rival successfully the immense and productive stimuli that have come from wars and from the exploration of geographical frontiers? Can we find drives in social welfare that will direct and harness our productive and creative energies? If not, we are surely doomed. If we fail to develop viable alternatives to violence and adventurism as a source of stimulus to maximal creative activity, perhaps we deserve to be doomed. Lorenz has told us that man is probably the missing link between the anthropoid ape and the civilized human being. Can we continue to evolve?

My belief is simple and hopeful. Our field shares with only a few the stature of being socially acceptable, patently useful, intellectually stimulating, and economically productive. It is our responsibility to examine our functions and to allocate a sufficient share of our resources and abilities to permit the bringing to society of the immediate benefits of what we have learned. We accept gladly the obligation to produce still further benefits within the limits of our capacities. We do these things in a framework that recognizes that the scientific method still offers the most valuable approach to the solution of problems, and that undirected investigation is a precious resource that must be preserved, but must be paid for by the prompt application of useful knowledge for the benefit of those who provide the basis for continuance.

It is depressing to contemplate, to cite but a small example, that for over 10 years it has been known how to prevent infection and death associated with indwelling catheterization of the urinary bladder, and yet we are still trying to convince

physicians, nurses, hospital administrators, and government officials that the simple and inexpensive methods involved should be applied uniformly.

It is exhilarating, on the other hand, to begin to see a possible infectious basis for some of the excess prematurity among the poor with the realization that T-strain mycoplasmas may account for excess prematurity in certain population groups, and that these may be susceptible to simple and inexpensive treatment.

Can it be that most diseases that preferentially attack the poor are infectious in origin? Can we be sure that common chronic diseases are not due to infectious agents? Can we convince our increasingly skeptical public of the desirability of our continuing to ask and to explore such questions? I believe we can, but believe we must convince the public not by slick advertising tricks of which they are inherently suspicious, however gullible they may be, but by acting promptly and critically, by showing that we will set social objectives and that we will not allow gaps to appear between discovery and application—that we will deal with the full social problem and not with the more convenient but often less useful small portions that happen to command our individual attentions. Here we must distinguish between incompetent or self-seeking passion in the glib who will use the right words but produce very little, and the thoughts of those who come to the problem with discipline and tough-minded capacity for analysis and action. As we recognize these distinctions and strike an effective balance between investigation and social action, we can look forward to continued support, continued satisfaction, and the realization that we have played a vital role in setting for our society new social goals.

EXHIBIT 417

The Questionable Contribution of Medical Measures to the Decline of Mortality in the United States in the Twentieth Century

JOHN B. McKINLAY AND SONJA M. McKINLAY

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“. . . by the time laboratory medicine came effectively into the picture the job had been carried far toward completion by the humanitarians and social reformers of the nineteenth century. Their doctrine that nature is holy and healthful was scientifically naive but proved highly effective in dealing with the most important health problems of their age. When the tide is receding from the beach it is easy to have the illusion that one can empty the ocean by removing water with a pail.”

*R. Dubos, Mirage of Health,
New York: Perennial Library, 1959, p. 23*

Introducing a Medical Heresy

The modern “heresy” that medical care (as it is traditionally conceived) is generally unrelated to improvements in the health of populations (as distinct from individuals) is still dismissed as unthinkable in much the same way as the so-called heresies of former times. And this is despite a long history of support in popular and scientific writings as well as from able minds in a variety of disciplines. History is replete with examples of how, understandably enough, self-interested individuals and groups denounced popular customs and beliefs which appeared to threaten their own domains of practice, thereby rendering them heresies (for example, physicians’ denunciation of midwives as witches, during the Middle Ages). We also know that vast institutional resources have often been deployed to neutralize challenges to the assumptions upon which everyday organizational activities were founded and legitimated (for example, the Spanish Inquisition). And since it is usually difficult for organizations themselves to directly combat threatening

“heresies,” we often find otherwise credible practitioners, perhaps unwittingly, serving the interests or organizations in this capacity. These historical responses may find a modern parallel in the way the everyday practitioners of medicine, on their own altruistic or “scientific” grounds and still perhaps unwittingly, serve present-day institutions (hospital complexes, university medical centers, pharmaceutical houses, and insurance companies) by spearheading an assault on a most fundamental challenging heresy of our time: *that the introduction of specific medical measures and/or the expansion of medical services are generally not responsible for most of the modern decline in mortality.*

In different historical epochs and cultures, there appear to be characteristic ways of explaining the arrival and departure of natural vicissitudes. For salvation from some plague, it may be that the gods were appeased, good works rewarded, or some imbalance in nature corrected. And there always seems to be some person or group (witch doctors, priests, medicine men) able to persuade others, sometimes on the basis of acceptable evidence for most people at that time, that they have *the* explanation for the phenomenon in question and may even claim responsibility for it. They also seem to benefit most from common acceptance of the explanations they offer. It is not uncommon today for biotechnological knowledge and specific medical interventions to be invoked as *the major reason* for most of the modern (twentieth century) decline in mortality.¹ Responsibility for this decline is often claimed by, or ascribed to, the present-day major beneficiaries of this prevailing explanation. But both in terms of the history of knowledge and on the basis of data presented in this paper, one can reasonably wonder whether the supposedly more sophisticated explanations proffered in our own time (while seemingly distinguishable from those accepted in the past) are really all that different from those of other cultures and earlier times, or any more reliable. Is medicine, the

¹It is obviously important to distinguish between (a) advances in knowledge of the cause and natural course of some condition and (b) improvements in our ability to effectively treat some condition (that is, to alter its natural course). In many instances these two areas are disjoint and appear at different stages of development. There are, on the one hand, disease processes about which considerable knowledge has been accrued, yet this has not resulted (nor necessarily will) in the development of effective treatments. On the other hand, there are conditions for which demonstrably effective treatments have been devised in the absence of knowledge of the disease process and/or its causes.

physician, or the medical profession any more entitled to claim responsibility for the decline in mortality that obviously has occurred in this century than, say, some folk hero or aristocracy of priests sometime in the past?

Aims

Our general intention in this paper is to sustain the ongoing debate on the questionable contribution of specific medical measures and/or the expansion of medical services to the observable decline in mortality in the twentieth century. More specifically, the following three tasks are addressed: (a) selected studies are reviewed which illustrate that, far from being idiosyncratic and/or heretical, the issue addressed in this paper has a long history, is the subject of considerable attention elsewhere, attracts able minds from a variety of disciplines, and remains a timely issue for concern and research; (b) age- and sex-adjusted mortality rates (standardized to the population of 1900) for the United States, 1900–1973, are presented and then considered in relation to a number of specific and supposedly effective medical interventions (both chemotherapeutic and prophylactic). So far as we know, this is the first time such data have been employed for this particular purpose in the United States, although reference will be made to a similar study for England and Wales; and (c) some policy implications are outlined.

Background to the Issue

The beginning of the serious debate on the questionable contribution of medical measures is commonly associated with the appearance, in Britain, of Talbot Griffith's (1967) *Population Problems in the Age of Malthus*. After examining certain medical activities associated with the eighteenth century—particularly the growth of hospital, dispensary, and midwifery services, additions to knowledge of physiology and anatomy, and the introduction of smallpox inoculation—Griffith concluded that they made important contributions to the observable decline in mortality at that time. Since then, in Britain and more recently in the United States, this debate has continued, regularly engaging scholars from economic history, demography, epidemiology, statistics, and other disciplines. Habakkuk

(1953), an economic historian, was probably the first to seriously challenge the prevailing view that the modern increase in population was due to a fall in the death rate attributable to medical interventions. His view was that this rise in population resulted from an increase in the birth rate, which, in turn, was associated with social, economic, and industrial changes in the eighteenth century.

McKeown, without doubt, has pursued the argument more consistently and with greater effect than any other researcher, and the reader is referred to his recent work for more detailed background information. Employing the data and techniques of historical demography, McKeown (a physician by training) has provided a detailed and convincing analysis of the major reasons for the decline of mortality in England and Wales during the eighteenth, nineteenth, and twentieth centuries (McKeown et al., 1955, 1962, 1975). For the eighteenth century, he concludes that the decline was largely attributable to improvements in the environment. His findings for the nineteenth century are summarized as follows:

. . . the decline of mortality in the second half of the nineteenth century was due wholly to a reduction of deaths from infectious diseases; there was no evidence of a decline in other causes of death. Examination of the diseases which contributed to the decline suggested that the main influences were: (a) rising standards of living, of which the most significant feature was a better diet; (b) improvements in hygiene; and (c) a favorable trend in the relationship between some micro-organisms and the human host. *Therapy made no contributions, and the effect of immunization was restricted to smallpox which accounted for only about one-twentieth of the reduction of the death rate.* [Emphasis added. McKeown et al., 1975, p. 391]

While McKeown's interpretation is based on the experience of England and Wales, he has examined its credibility in the light of the very different circumstances which existed in four other European countries: Sweden, France, Ireland, and Hungary (McKeown et al., 1972). His interpretation appears to withstand this cross-examination. As for the twentieth century (1901–1971 is the period actually considered), McKeown argues that about three-quarters of the decline was associated with control of infectious diseases and the remainder with conditions not attributable to micro-organisms. He distinguishes the infections according to their modes of transmission (air- water- or food-borne) and isolates three types of influences which figure during the period considered: medical measures (spe-

cific therapies and immunization), reduced exposure to infection, and improved nutrition. His conclusion is that:

the main influences on the decline in mortality were improved nutrition on air-borne infections, reduced exposure (from better hygiene) on water- and food-borne diseases and, less certainly, immunization and therapy on the large number of conditions included in the miscellaneous group. Since these three classes were responsible respectively for nearly half, one-sixth, and one-tenth of the fall in the death rate, it is probably that the advancement in nutrition was the major influence. [McKeown et al., 1975, p. 422]

More than twenty years of research by McKeown and his colleagues recently culminated in two books—*The Modern Rise of Population* (1976a) and *The Role of Medicine: Dream, Mirage or Nemesis* (1976b)—in which he draws together his many excellent contributions. That the thesis he advances remains highly newsworthy is evidenced by recent editorial reaction in *The Times* of London (1977).

No one in the United States has pursued this thesis with the rigor and consistency which characterize the work by McKeown and his colleagues in Britain. Around 1930, there were several limited discussions of the questionable effect of medical measures on selected infectious diseases like diphtheria (Lee, 1931; Wilson and Miles, 1946; Bolduan, 1930) and pneumonia (Pfizer and Co., 1953). In a presidential address to the American Association of Immunologists in 1954 (frequently referred to by McKeown), Magill (1955) marshalled an assortment of data then available—some from England and Wales—to cast doubt on the plausibility of existing accounts of the decline in mortality for several conditions. Probably the most influential work in the United States is that of Dubos who, principally in *Mirage of Health* (1959), *Man Adapting* (1965), and *Man, Medicine and Environment* (1968), focused on the non-medical reasons for changes in the health of overall populations. In another presidential address, this time to the Infectious Diseases Society of America, Kass (1971), again employing data from England and Wales, argued that most of the decline in mortality for most infectious conditions occurred prior to the discovery of either “the cause” of the disease or some purported “treatment” for it. Before the same society and largely on the basis of clinical experience with infectious diseases and data from a single state (Massachusetts), Weinstein (1974), while conceding there are some effective

treatments which seem to yield a favorable outcome (e.g., for poliomyelitis, tuberculosis, and possibly smallpox), argued that despite the presence of supposedly effective treatments some conditions may have increased (e.g., subacute bacterial endocarditis, streptococcal pharyngitis, pneumococcal pneumonia, gonorrhea, and syphilis) and also that mortality for yet other conditions shows improvement in the absence of any treatment (e.g., chickenpox). With the appearance of his book, *Who Shall Live?* (1974), Fuchs, a health economist, contributed to the resurgence of interest in the relative contribution of medical care to the modern decline in mortality in the United States. He believes there has been an unprecedented improvement in health in the United States since about the middle of the eighteenth century, associated primarily with a rise in real income. While agreeing with much of Fuchs' thesis, we will present evidence which seriously questions his belief that "beginning in the mid '30s, major therapeutic discoveries made significant contributions independently of the rise in real income."

Although neither representative nor exhaustive, this brief and selective background should serve to introduce the analysis which follows. Our intention is to highlight the following: (a) the debate over the questionable contribution of medical measures to the modern decline of mortality has a long history and remains topical; (b) although sometimes popularly associated with dilettantes such as Ivan Illich (1976), the debate continues to preoccupy able scholars from a variety of disciplines and remains a matter of concern to the most learned societies; (c) although of emerging interest in the United States, the issue is already a matter of concern and considerable research elsewhere; (d) to the extent that the subject has been pursued in the United States, there has been a restrictive tendency to focus on a few selected diseases, or to employ only statewide data, or to apply evidence from England and Wales directly to the United States situation.

How Reliable are Mortality Statistics?

We have argued elsewhere that mortality statistics are inadequate and can be misleading as indicators of a nation's overall health status (McKinlay and McKinlay, forthcoming). Unfortunately, these are the only types of data which are readily accessible for the examination of time trends, simply because comparable morbidity

and disability data have not been available. Apart from this overriding problem, several additional caveats in the use of mortality statistics are: (a) difficulties introduced by changes in the registration area in the United States in the early twentieth century; (b) that often no single disease, but a complex of conditions, may be responsible for death (Krueger, 1966); (c) that studies reveal considerable inaccuracies in recording the cause of death (Moriyama et al., 1958); (d) that there are changes over time in what it is fashionable to diagnose (for example, ischaemic heart disease and cerebrovascular disease); (e) that changes in disease classifications (Dunn and Shackley, 1945) make it difficult to compare some conditions over time and between countries (Reid and Rose, 1964); (f) that some conditions result in immediate death while others have an extended period of latency; and (g) that many conditions are severely debilitating and consume vast medical resources but are now generally non-fatal (e.g., arthritis and diabetes). Other obvious limitations could be added to this list.

However, it would be foolhardy indeed to dismiss all studies based on mortality measures simply because they are possibly beset *with known limitations*. Such data are preferable to those the limitations of which are either unknown or, if known, cannot be estimated. Because of an overawareness of potential inaccuracies, there is a timorous tendency to disregard or devalue studies based on mortality evidence, even though there are innumerable examples of their fruitful use as a basis for planning and informed social action (Alderson, 1976). Sir Austin Bradford Hill (1955) considers one of the most important features of Snow's work on cholera to be his adept use of mortality statistics. A more recent notable example is the study by Inman and Adelstein (1969) of the circumstantial link between the excessive absorption of bronchodilators from pressurized aerosols and the epidemic rise in asthma mortality in children aged ten to fourteen years. Moreover, there is evidence that some of the known inaccuracies of mortality data tend to cancel each other out.² Consequently, while mortality statistics may be unreliable for

²Barker and Rose cite one study which compared the ante-mortem and autopsy diagnoses in 9,501 deaths which occurred in 75 different hospitals. Despite lack of a concurrence on *individual* cases, the *overall* frequency was very similar in diagnoses obtained on either an ante-mortem or a post-mortem basis. As an example they note that clinical diagnoses of carcinoma of the rectum were confirmed at autopsy in only 67 percent of cases, but the incorrect clinical diagnoses were balanced by an almost identical number of lesions diagnosed for the first time at autopsy (Barker and Rose, 1976).

use in individual cases, when pooled for a country and employed in population studies, they can reveal important trends and generate fruitful hypotheses. They have already resulted in informed social action (for example, the use of geographical distributions of mortality in the field of environmental pollution).

Whatever limitations and risks may be associated with the use of mortality statistics, they obviously apply equally to all studies which employ them—both those which attribute the decline in mortality to medical measures and those which argue the converse, or something else entirely. And, if such data constitute acceptable evidence in support of the presence of medicine, then it is not unreasonable, or illogical, to employ them in support of some opposing position. One difficulty is that, depending on the nature of the results, double standards of rigor seem to operate in the evaluation of different studies. Not surprisingly, those which challenge prevailing myths or beliefs are subject to the most stringent methodological and statistical scrutiny, while supportive studies, which frequently employ the flimsiest impressionistic data and inappropriate techniques of analysis, receive general and uncritical acceptance. Even if all possible “ideal” data were available (which they never will be) and if, after appropriate analysis, they happened to support the viewpoint of this paper, we are doubtful that medicine’s protagonists would find our thesis any more acceptable.

The Modern Decline in Mortality

Despite the fact that mortality rates for certain conditions, for selected age and sex categories, continue to fluctuate, or even increase (U.S. Dept. HEW, 1964; Moriyama and Gustavus, 1972; Lilienfeld, 1976), there can be little doubt that a marked decline in overall mortality for the United States has occurred since about 1900 (the earliest point for which reliable national data are available).

Just how dramatic this decline has been in the United States is illustrated in Fig. 1 which shows age-adjusted mortality rates for males and females separately.³ Both sexes experienced a marked

³All age and sex adjustments were made by the “direct” method using the population of 1900 as the standard. For further information on this method of adjustment, see Hill (1971) and Shryock et al. (1971).

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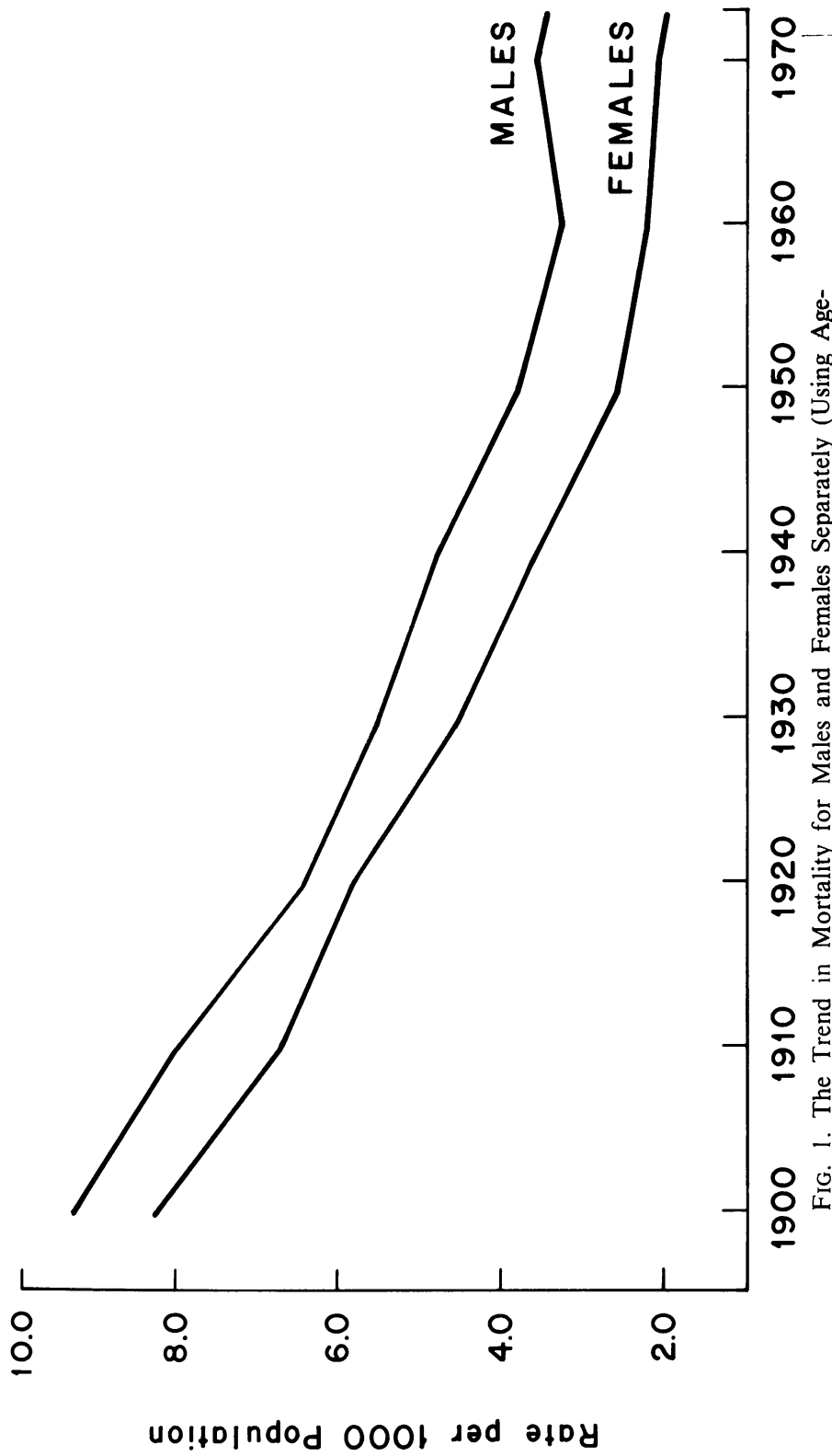


FIG. 1. The Trend in Mortality for Males and Females Separately (Using Age-Adjusted Rates) for the United States, 1900-1973.*

*For these and all other age-and sex-adjusted rates in this paper, the standard population is that of 1900.

decline in mortality since 1900. The female decline began to level off by about 1950, while 1960 witnessed the beginning of a slight increase for males. Figure 1 also reveals a slight but increasing divergence between male and female mortality since about 1920.

Figure 2 depicts the decline in the overall age- and sex-adjusted rate since the beginning of this century. Between 1900 and 1973, there was a 69.2 percent decrease in overall mortality. The average annual rate of decline from 1900 until 1950 was .22 per 1,000, after which it became an almost negligible decline of .04 per 1,000 annually. Of the total fall in the standardized death rate between 1900 and 1973, 92.3 percent occurred prior to 1950. Figure 2 also plots the decline in the standardized death rate *after* the total number of deaths in each age and sex category has been reduced by the number of deaths attributed to the eleven major infectious conditions (typhoid, smallpox, scarlet fever, measles, whooping cough, diphtheria, influenza, tuberculosis, pneumonia, diseases of the digestive system, and poliomyelitis). It should be noted that, although this latter rate also shows a decline (at least until 1960), its slope is much more shallow than that for the overall standardized death rate. A major part of the decline in deaths from these causes since about 1900 may be attributed to the virtual disappearance of these infectious diseases.

An absurdity is reflected in the third broken line in Fig. 2 which also plots the increase in the proportion of the Gross National Product expended annually for medical care. *It is evident that the beginning of the precipitate and still unrestrained rise in medical care expenditures began when nearly all (92 percent) of the modern decline in mortality this century had already occurred.*⁴

Figure 3 illustrates how the proportion of deaths contributed by infectious and chronic conditions has changed in the United States since the beginning of the twentieth century. In 1900, about 40 percent of all deaths were accounted for by eleven major infectious diseases, 16 percent by three chronic conditions, 4 percent by accidents, and the remainder (37 percent) by all other causes. By 1973, only 6 percent of all deaths were due to these eleven infectious

⁴Rutstein (1967), although fervently espousing the traditional view that medical advances have been largely responsible for the decline in mortality, discussed this disjunction and termed it "The Paradox of Modern Medicine." More recently, and from a perspective that is generally consistent with that advanced here, Powles (1973) noted the same phenomenon in England and Wales.

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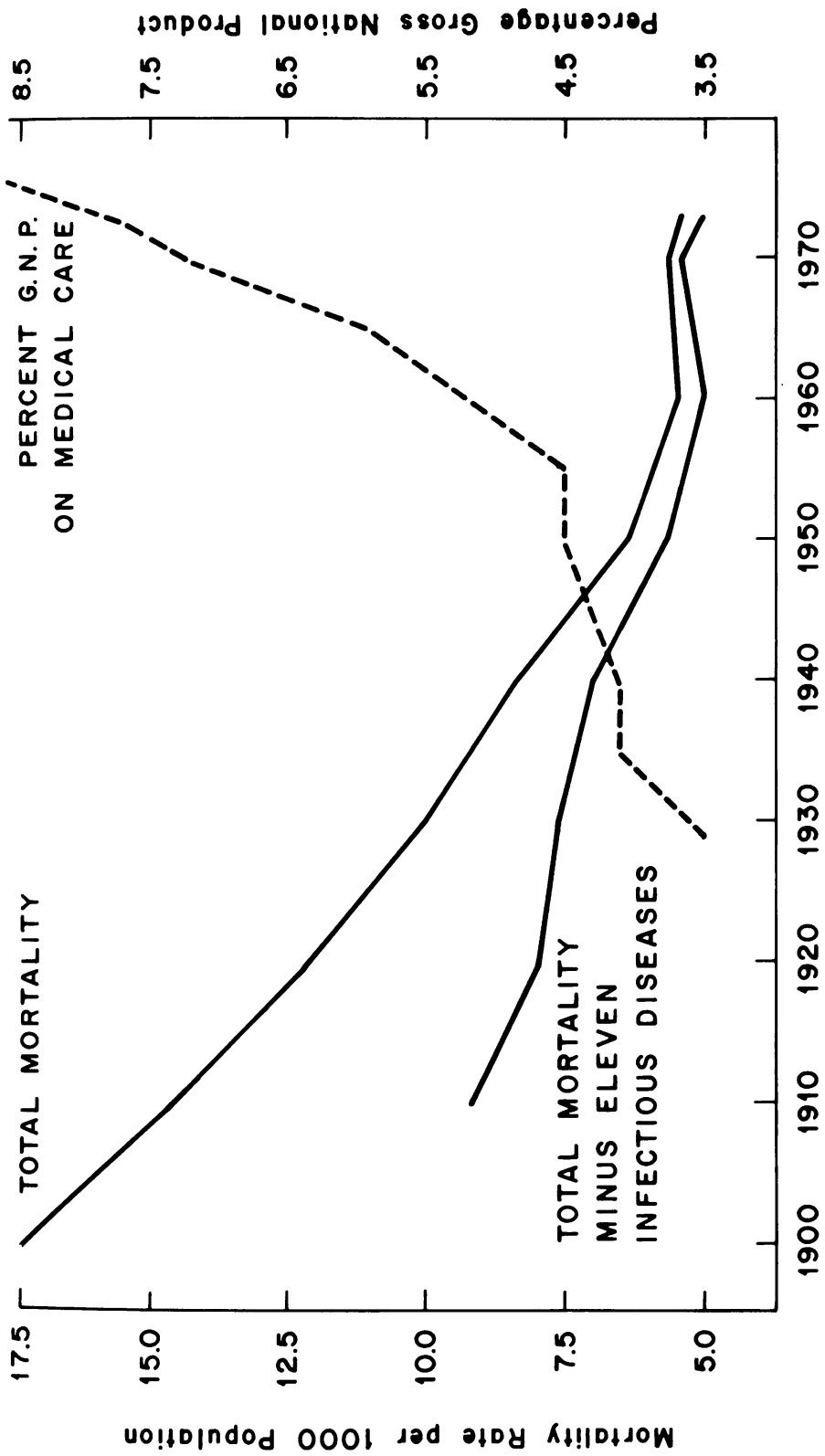


FIG. 2. Age-and Sex-Adjusted Mortality Rates for the United States 1900-1973, Including and Excluding Eleven Major Infectious Diseases, Contrasted with the Proportion of the Gross National Product Expended on Medical Care.

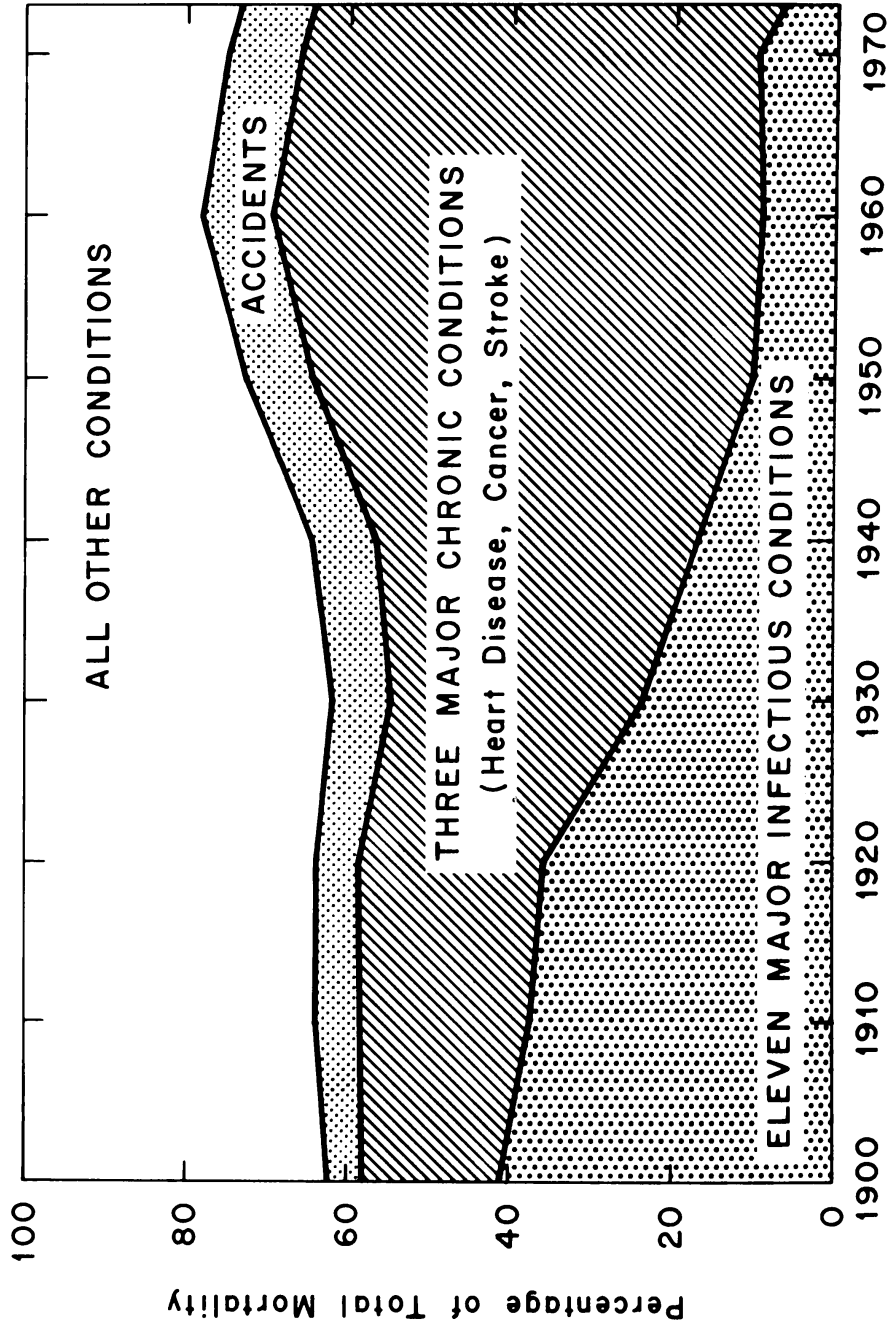


FIG. 3. Pictorial Representation of the Changing Contribution of Chronic and Infectious Conditions to Total Mortality (Age- and Sex-Adjusted), in the United States, 1900-1973.

diseases, 58 percent to the same three chronic conditions, 9 percent to accidents, and 27 percent were contributed by other causes.⁵

Now to what phenomenon, or combination of events, can we attribute this modern decline in overall mortality? Who (if anyone), or what group, can claim to have been instrumental in effecting this reduction? Can anything be gleaned from an analysis of mortality experience to date that will inform health care policy for the future?

It should be reiterated that a major concern of this paper is to determine the effect, if any, of specific medical measures (both chemotherapeutic and prophylactic) on the decline of mortality. It is clear from Figs. 2 and 3 that most of the observable decline is due to the rapid disappearance of some of the major infectious diseases. Since this is where most of the decline has occurred, it is logical to focus a study of the effect of medical measures on this category of conditions. Moreover, for these eleven conditions, there exist clearly identifiable medical interventions to which the decline in mortality has been popularly ascribed. No analogous interventions exist for the major chronic diseases such as heart disease, cancer, and stroke. Therefore, even where a decline in mortality from these chronic conditions may have occurred, this cannot be ascribed to any specific measure.

The Effect of Medical Measures on Ten Infectious Diseases Which Have Declined

Table 1 summarizes data on the effect of major medical interventions (both chemotherapeutic and prophylactic) on the decline in the age- and sex-adjusted death rates in the United States, 1900–1973, for ten of the eleven major infectious diseases listed above. Together, these diseases accounted for approximately 30 percent of all deaths at the turn of the century and nearly 40 percent of the total decline in the mortality rate since then. The ten diseases were selected on the following criteria: (a) some decline in the death rate had occurred in the period 1900–1973; (b) significant decline in the death rate is commonly attributed to some specific medical

⁵Deaths in the category of chronic respiratory diseases (chronic bronchitis, asthma, emphysema, and other chronic obstructive lung diseases) could not be included in the group of chronic conditions because of insurmountable difficulties inherent in the many changes in disease classification and in the tabulation of statistics.

TABLE I
The Contribution of Medical Measures (Both Chemotherapeutic and Prophylactic) to the Fall in the Age and Sex-Adjusted Death Rates (S.D.R.) of Ten Common Infectious Diseases, and to the Overall Decline in the S.D.R., for the United States, 1900-1973

Disease	Fall in S.D.R. per 1,000 Population, 1900-1973 (a)	Fall in S.D.R. as % of the Total Fall in S.D.R. (b) = $\frac{(a)}{12.14} \times 100\%$	Year of Medical Intervention (Either Chemotherapy or Prophylaxis)	Fall in S.D.R. per 1,000 Population After Year of Intervention (c)	Fall in S.D.R. After Intervention as % of Total Fall for the Disease (d) = $\frac{(c)}{(a)} \times 100\%$	Fall in S.D.R. After Intervention as % of Total Fall in S.D.R. for All Causes (e) = $\frac{(d)}{(a)} \times 100\%$
Tuberculosis	2.00	16.48	Isoniazid/ Streptomycin, 1950	0.17	8.36	1.38
Scarlet Fever	0.10	0.84	Penicillin, 1946	0.00	1.75	0.01
Influenza	0.22	1.78	Vaccine, 1943	0.05	25.33	0.45
Pneumonia	1.42	11.74	Sulphonamide, 1935	0.24	17.19	2.02
Diphtheria	0.43	3.57	Toxoid, 1930	0.06	13.49	0.48
Whooping Cough	0.12	1.00	Vaccine, 1930	0.06	51.00	0.51
Measles	0.12	1.04	Vaccine, 1963	0.00	1.38	0.01
Smallpox	0.02	0.16	Vaccine, 1800	0.02	100.00	0.16
Typhoid	0.36	2.95	Chloramphenicol, 1948	0.00	0.29	0.01
Poliomyelitis	0.03	0.23	Vaccine, Salk/ Sabin, 1955	0.01	25.87	0.06

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TABLE 2
Pair-Wise Correlation Matrix for 44 Countries, Between Four Measures of
Health Status and Three Measures of Medical Care Input

Variable	Matrix of Coefficients							
	1	2	3a	3b	4a	4b	5	6
1. Infant Mortality Rate (1972)								
2. Crude Mortality Rate (1970-1972)	-0.14							
3.(a) Life Expectancy (Males) at 25 Years	-0.14	-0.12						
3.(b) Life Expectancy (Females) at 25 Years	-0.12	0.04	0.75					
4.(a) Life Expectancy (Males) at 55 Years	-0.01	0.10	0.74	0.93				
4.(b) Life Expectancy (Females) at 55 Years	-0.13	0.01	0.75	0.98	0.95			
5. Population per Hospital Bed (1971-1973)	0.64	-0.30	0.05	-0.02	0.17	0.0		
6. Population per Physician (1971-1973)	0.36	-0.30	0.11	0.04	0.16	0.07	0.70	
7. Per Capita Gross National Product: In \$U.S. Equivalent (1972)	-0.66	0.26	0.16	0.18	0.07	0.22	-0.56	-0.46
Variable (by number)	1	2	3a	3b	4a	4b	5	6

Sources:

1. *United Nations Demographic Yearbook: 1974*, New York, United Nations Publications, 1975. (For the Crude and Infant Mortality Rates).
2. *World Health Statistics Annual: 1972*, Vol. 1, Geneva, World Health Organization, 1975, pp. 780-783. (For the Life Expectancy Figures).
3. *United Nations Statistical Yearbook, 1973 and 1975*. New York, United Nations Publications, 25th and 27th issues, 1974 and 1976. (For the Population bed/physician ratios).
4. *The World Bank Atlas*. Washington, D.C., World Bank, 1975. (For the per capita Gross National Product).

measure for the disease; and (c) adequate data for the disease over the period 1900–1973 are available. The diseases of the digestive system were omitted primarily because of lack of clarity in diagnosis of specific diseases such as gastritis and enteritis.

Some additional points of explanation should be noted in relation to Table 1. First, the year of medical intervention coincides (as nearly as can be determined) with the first year of widespread or commercial use of the appropriate drug or vaccine.⁶ This date does *not* necessarily coincide with the date the measure was either first discovered, or subject to clinical trial. Second, the decline in the death rate for smallpox was calculated using the death rate for 1902 as being the earliest year for which this statistic is readily available (U.S. Bureau of the Census, 1906). For the same reasons, the decline in the death rate from poliomyelitis was calculated from 1910. Third, the table shows the contribution of the decline in each disease to the total decline in mortality over the period 1900–1973 (column b). The overall decline during this period was 12.14 per 1,000 population (17.54 in 1900 to 5.39 in 1973). Fourth, in order to place the experience for each disease in some perspective, Table 1 also shows the contribution of the relative fall in mortality after the intervention to the overall fall in mortality since 1900 (column e). In other words, the figures in this last column represent the percentage of the total fall in mortality contributed by each disease after the date of medical intervention.

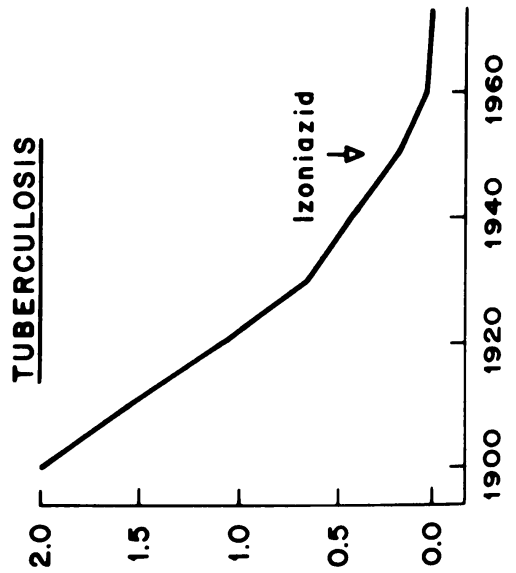
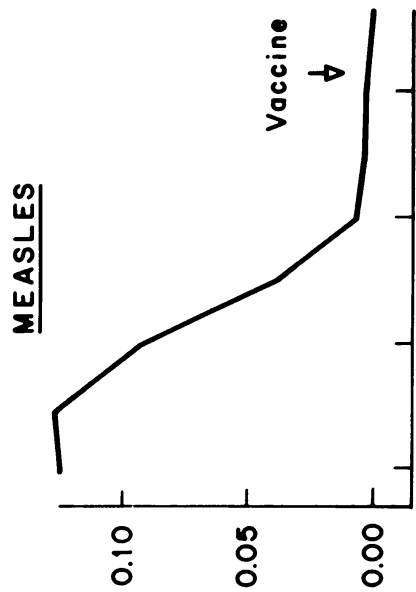
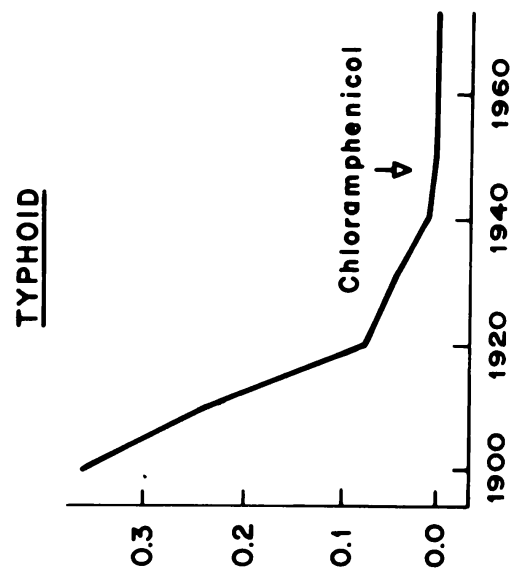
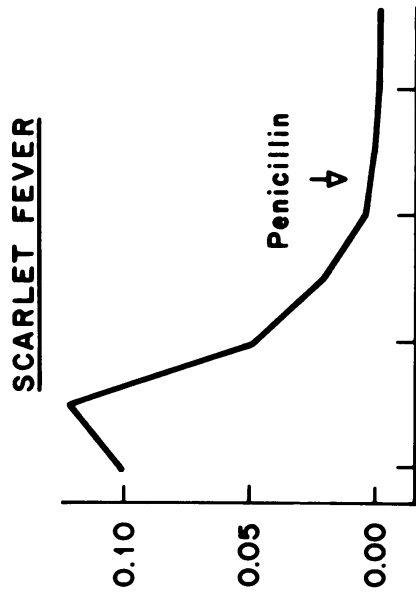
It is clear from column b that only reductions in mortality from tuberculosis and pneumonia contributed substantially to the decline in total mortality between 1900 and 1973 (16.5 percent and 11.7 percent, respectively). The remaining eight conditions *together* accounted for less than 12 percent of the total decline over this period. Disregarding smallpox (for which the only effective measure had been introduced about 1800), only influenza, whooping cough, and poliomyelitis show what could be considered substantial declines of 25 percent or more after the date of medical intervention. However, even under the somewhat unrealistic assumption of a constant (linear) rate of decline in the mortality rates, only whooping cough and poliomyelitis even approach the percentage which would have been expected. The remaining six conditions (tuberculosis, scarlet

⁶In determining the dates of intervention we relied upon: (a) standard epidemiology and public health texts; (b) the recollections of authorities in the field of infectious diseases; and (c) recent publications on the same subject.

fever, pneumonia, diphtheria, measles, and typhoid) showed negligible declines in their mortality rates subsequent to the date of medical intervention. The seemingly quite large percentages for pneumonia and diphtheria (17.2 and 13.5, respectively) must of course be viewed in the context of relatively early interventions—1935 and 1930.

In order to examine more closely the relation of mortality trends for these diseases to the medical interventions, graphs are presented for each disease in Fig. 4. Clearly, for tuberculosis, typhoid, measles, and scarlet fever, the medical measures considered were introduced at the point when the death rate for each of these diseases was already negligible. Any change in the rates of decline which may have occurred subsequent to the interventions could only be minute. Of the remaining five diseases (excluding smallpox with its negligible contribution), it is only for poliomyelitis that the medical measure appears to have produced any noticeable change in the trends. Given peaks in the death rate for 1930, 1950 (and possibly for 1910), a comparable peak could have been expected in 1970. Instead, the death rate dropped to the point of disappearance after 1950 and has remained negligible. The four other diseases (pneumonia, influenza, whooping cough, and diphtheria) exhibit relatively smooth mortality trends which are unaffected by the medical measures, even though these were introduced relatively early, when the death rates were still notable.

It may be useful at this point to briefly consider the common but dubious practice of projecting estimated mortality trends (Witte and Axnick, 1975). In order to show the beneficial (or even detrimental) effect of some medical measure, a line, estimated on a set of points observed prior to the introduction of the measure, is projected over the period subsequent to the point of intervention. Any resulting discrepancy between the projected line and the observed trend is then used as some kind of “evidence” of an effective or beneficial intervention. According to statistical theory on least squares estimation, an estimated line can serve as a useful predictor, but the prediction is only valid, and its error calculable, within the range of the points used to estimate the line. Moreover, those predicted values which lie at the extremes of the range are subject to much larger errors than those nearer the center. It is, therefore, probable that, even if the projected line was a reasonable estimate of the trend after the intervention (which, of course, it is not), the



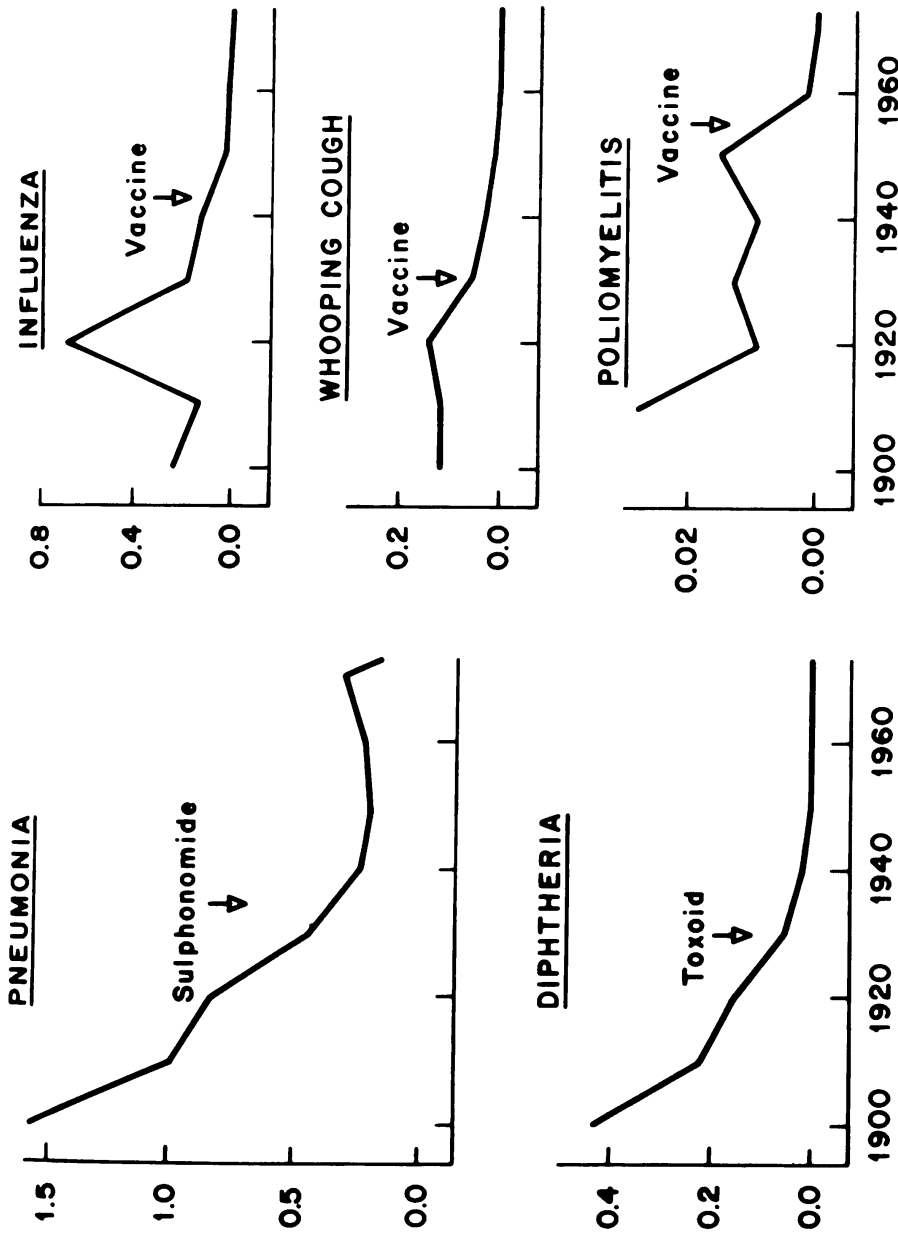


FIG. 4. The Fall in the Standardized Death Rate (per 1,000 Population) for Nine Common Infectious Diseases in Relation to Specific Medical Measures, for the United States, 1900-1973.

divergent observed trend is probably well within reasonable error limits of the estimated line (assuming the error could be calculated), as the error will be relatively large. In other words, this technique is of dubious value as no valid conclusions are possible from its application, and a relatively large prediction error cannot be estimated, which is required in order to objectively judge the extent of divergence of an observed trend.

With regard to the ten infectious diseases considered in this paper, when lines were fitted to the nine or ten points available over the entire period (1900–1973), four exhibited a reasonably good fit to a straight line (scarlet fever, measles, whooping cough, and poliomyelitis), while another four (typhoid, diphtheria, tuberculosis, and pneumonia) showed a very good quadratic fit (to a curved line). Of the remaining two diseases, smallpox showed a negligible decline, as it was already a minor cause of death in 1900 (only 0.1 percent), and influenza showed a poor fit because of the extremely high death rate in 1920. From Fig. 4 it is clear, however, that the rate of decline slowed in more recent years for most of the diseases considered—a trend which could be anticipated as rates approach zero.⁷

Now it is possible to argue that, given the few data points available, the fit is somewhat crude and may be insensitive to any changes subsequent to a point of intervention. However, this can be countered with the observation that, given the relatively low death rates for these diseases, any change would have to be extremely marked in order to be detected in the overall mortality experience. Certainly, from the evidence considered here, only poliomyelitis appears to have had a noticeably changed death rate subsequent to intervention. Even if it were assumed that this change was entirely due to the vaccines, then only about one percent of the decline following interventions for the diseases considered here (column d of Table 1) could be attributed to medical measures. Rather more conservatively, if we attribute some of the subsequent fall in the death rates for pneumonia, influenza, whooping cough, and diphtheria to medical measures, then perhaps 3.5 percent of the fall in the overall death rate can be explained through medical interven-

⁷For this reason, a negative exponential model is sometimes used to fit a curved line to such data. This was not presented here as the number of points available was small and the difference between a simple quadratic and negative exponential fit was not, upon investigation, able to be detected.

tion in the major infectious diseases considered here. Indeed, given that it is precisely for these diseases that medicine claims most success in lowering mortality, 3.5 percent probably represents a reasonable upper-limit estimate of the total contribution of medical measures to the decline in mortality in the United States since 1900.

Conclusions

Without claiming they are definitive findings, and eschewing pretensions to an analysis as sophisticated as McKeown's for England and Wales, one can reasonably draw the following conclusions from the analysis presented in this paper:

In general, medical measures (both chemotherapeutic and prophylactic) appear to have contributed little to the overall decline in mortality in the United States since about 1900—having in many instances been introduced several decades after a marked decline had already set in and having no detectable influence in most instances. More specifically, with reference to those five conditions (influenza, pneumonia, diphtheria, whooping cough, and poliomyelitis) for which the decline in mortality appears substantial after the point of intervention—and on the unlikely assumption that all of this decline is attributable to the intervention—it is estimated that at most 3.5 percent of the total decline in mortality since 1900 could be ascribed to medical measures introduced for the diseases considered here.

These conclusions, in support of the thesis introduced earlier, suggest issues of the most strategic significance for researchers and health care legislators. Profound policy implications follow from either a confirmation or a rejection of the thesis. If one subscribes to the view that we are slowly but surely eliminating one disease after another because of medical interventions, then there may be little commitment to social change and even resistance to some reordering of priorities in medical expenditures. If a disease *X* is disappearing primarily because of the presence of a particular intervention or service *Y*, then clearly *Y* should be left intact, or, more preferably, be expanded. Its demonstrable contribution justifies its presence. But, if it can be shown convincingly, and on commonly accepted grounds, that the major part of the decline in mortality is unrelated to medical care activities, then some commitment to social change

and a reordering of priorities may ensue. For, if the disappearance of *X* is largely unrelated to the presence of *Y*, or even occurs in the absence of *Y*, then clearly the expansion and even the continuance of *Y* can be reasonably questioned. Its demonstrable ineffectiveness justifies some reappraisal of its significance and the wisdom of expanding it in its existing form.

In this paper we have attempted to dispel the myth that medical measures and the presence of medical services were primarily responsible for the modern decline in mortality. The question now remains: if they were not primarily responsible for it, then how is it to be explained? An adequate answer to this further question would require a more substantial research effort than that reported here, but is likely to be along the lines suggested by McKeown which were referred to early in this paper. Hopefully, this paper will serve as a catalyst for such research, incorporating adequate data and appropriate methods of analysis, in an effort to arrive at a more viable alternative explanation.

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EXHIBIT 418



Review

Measuring the Benefits of Mass Vaccination Programs in the United States

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Abstract: Since the late 1940s, mass vaccination programs in the USA have contributed to the significantly reduced morbidity and mortality of infectious diseases. To assist the evaluation of the benefits of mass vaccination programs, the number of individuals who would have suffered death or permanent disability in the USA in 2014, had mass vaccination never been implemented, was estimated for measles, mumps, rubella, tetanus, diphtheria, pertussis, polio, *Haemophilus influenzae* type b (Hib), hepatitis B, varicella, and human papillomavirus (HPV). The estimates accounted for mortality and morbidity trends observed for these infections prior to mass vaccination and the impact of advances in standard of living and health care. The estimates also considered populations with and without known factors leading to an elevated risk of permanent injury from infection. Mass vaccination prevented an estimated 20 million infections and 12,000 deaths and permanent disabilities in 2014, including 10,800 deaths and permanent disabilities in persons at elevated risk. Though 9000 of the estimated prevented deaths were from liver cirrhosis and cancer, mass vaccination programs have not, at this point, shown empirical impacts on the prevalence of those conditions. Future studies can refine these estimates, assess the impact of adjusting estimation assumptions, and consider additional risk factors that lead to heightened risk of permanent harm from infection.

Keywords: vaccination; disease; mortality; disability; risk

1. Introduction

To measure the benefit of a mass vaccination program targeting an infectious disease, it is useful to assess what the risk of death or permanent injury would be from the disease in the absence of the mass vaccination program. There is an abundance of medical literature detailing the risks associated with infectious diseases; however, the information is scattered through dozens of sources that are often lengthy and consider only a narrow scope of the risks involved. For example, some sources describe the symptoms of a disease without specifying how many patients fully recover [1]; other sources describe the number of deaths from an infection without addressing permanent disability in survivors [2,3]. Moreover, some sources do not account for the pre-vaccine rates of decline in mortality for some infectious diseases [3–5]. We tried to address these challenges in our estimates.

2. Materials and Methods

We calculated rates of deaths and disabilities from infectious diseases, had mass vaccination never been implemented, using data principally from reports of the Centers for Disease Control and Prevention (CDC), complemented by reports from other federal entities such as the US Bureau of the Census and the US Public Health Service. We relied on data recorded in scientific journals (e.g., The Journal of the American Medical Association, Pediatrics, The Journal of Infectious Diseases, The New England Journal of Medicine, and The Journal of Clinical Oncology) in cases when data from

government sources were unavailable or incomplete. For example, although the impact of risk factors for many diseases is considered in CDC data, there are instances when measurements of risk factor relationships to outcomes are not provided. Other examples of information that is not always available in government records include estimates of the number of unreported cases and of permanent disability from certain diseases. In addition, when US data for measurements were unavailable, we relied on data from other developed countries.

Because we researched and gathered data for our estimates in 2016, when the latest available CDC mortality data were from 2014, we projected our estimates to 2014. When calculating the rates of deaths and disabilities corresponding to an infectious disease, we considered the trend in deaths and disabilities during a range of years just prior to the licensing of a vaccine or at the start of a nationwide mass vaccination program targeting the disease. This range of years is referred to as the “reference years.” The duration of each range was chosen by using the number of years between relative peaks of incidence of each disease.

Though <100% of the population is vaccinated and vaccines are <100% effective, mass vaccination programs have contributed to the significantly reduced morbidity and mortality of infectious diseases. There were fewer than two dozen deaths from diphtheria, tetanus, pertussis, polio, measles, mumps, rubella, *Haemophilus influenzae* type b (Hib), or varicella in 2014. Therefore, we counted all estimated cases projected to 2014 in the absence of mass vaccination as preventable.

We employed certain assumptions in our estimates. For example, we presumed that each vaccine neither reduced nor enhanced vulnerability to the incidence or outcomes of diseases that were not targeted by the vaccine. Throughout our text, we strive to be explicit whenever an assumption was made.

The rates of deaths or disabilities corresponding to various infectious diseases were computed using a denominator of 307 million individuals <80 years of age in 2014. We chose that age group because the life expectancy in 2014 was 79 years. In instances where age-specific counts of cases of infection were not available, case counts from the entire US population (319 million) were used. Moreover, we considered the broader population <80 years of age rather than the population of children, both because mass vaccination programs are intended to provide lifetime immunity to infection and because protecting against infection averts late complications of infection. For example, the polio mass vaccination program affected not only permanent injury from polio in children but also permanent injury from post-polio syndrome in adults.

To simplify and reduce the length of the report, we omitted analyses of certain mass vaccination programs that had marginal or unclear impacts on mortality. We excluded rotavirus and hepatitis A because each of those infections caused fewer than 100 annual pre-vaccine deaths [2,6]. We excluded influenza because its mass vaccination program has not made a clear impact on the trend of its pre-vaccine mortality rate [7–9]. Though there is an effective vaccine targeting meningococcal disease, the trend in the mortality rate for that infection after the introduction of its mass vaccination program has resembled the pre-vaccine trend [10]. Consequently, we excluded meningococcal disease because the matching mortality rate trends suggested that fewer than 100 annual deaths were prevented. We excluded pneumococcal disease for a similar reason. The CDC’s estimated decline in pneumococcal disease mortality after the introduction of the mass vaccination program matched the rate of decline in mortality from all pneumonia, including pneumonia caused by pathogens that are not targeted by the vaccine. From 2000 to 2009, the CDC estimated that pneumococcal disease mortality declined from 2.3 per 100,000 population to 1.6, a 30% decline [11,12]. During the same time period, the mortality rate of pneumonia from all causes declined from 22.6 to 16.6, a 27% decline [13]. The similar rates of decline suggested that the mass vaccination program prevented fewer than 100 deaths among individuals <80 years of age.

When accounting for risk factors leading to an elevated risk of permanent injury from an infection, we included only those factors that were observed in a high fraction of cases of permanent injury from the infection. To simplify the report, risk factors that were present in a small fraction of such cases

were excluded if accounting for those factors resulted in a rate of permanent injury that lay within the 95% confidence interval of the rate computed without those factors (i.e., did not make a statistically significant impact on the rate).

3. Results

It was estimated that 20 million infections and 12,000 deaths and permanent disabilities may have occurred in 2014 in the absence of mass vaccination, with 10,800 deaths and disabilities among individuals who have conditions or behaviors that would put them at higher risk of such outcomes and 1200 deaths and disabilities among persons without those conditions or behaviors. Tables 1 and 2 show the aggregated results for the infectious diseases examined in this report.

The following is a discussion of each disease. Recall that the “reference years” refer to the time period before the introduction of the corresponding mass vaccination program. Using data recorded during these years, we derived estimates of the expected number of deaths and permanent disabilities from each disease had mass vaccination not been introduced.

3.1. Measles

During the reference years of 1959–1962, before the introduction of mass vaccination, there were four million annual measles cases (equal in size to the birth cohort; Table S1A) that resulted in 402 deaths [2] mostly among the population <10 years of age [14]. Because the birth cohorts in the 1960s and in 2014 were the same size and the number of susceptible children was also the same [15,16], we estimated that these values would remain unchanged in the absence of mass vaccination. We also estimated 106 additional cases of measles that resulted in residual neurologic damage from complications of measles including measles encephalitis and subacute sclerosing panencephalitis (Table S1B).

Individuals with low levels of vitamin A are significantly more likely to suffer death or permanent disability from measles [17,18]; 92% of the most severe measles cases have had low levels of vitamin A (Table S1C) [19]. Therefore, we calculated 467 (=92% of 508) measles deaths and permanent disabilities at elevated risk.

Though the pre-vaccine measles mortality rate declined from 14.1 to 0.2 per 100,000 people (Figure S1), the measles fatalities recorded in the 1980s and 1990s suggested that the pre-vaccine decline may not have continued as rapidly in the absence of mass vaccination [17]. Consequently, we assumed that the measles mortality rate would have remained unchanged from the reference years.

3.2. Mumps

During the reference years of 1963–1966, before the introduction of mass vaccination, there were four million annual mumps cases (equal in size to the birth cohort; Table S2A) that resulted in 43 deaths [2], mostly among the population <30 years of age [20]. Because the birth cohorts in the 1960s and in 2014 were the same size and the number of susceptible children was also the same [15,16], we estimated that these values would remain unchanged in the absence of mass vaccination. We also estimated 11 additional cases of mumps resulting in permanent impaired hearing and 7 additional cases of mumps resulting in permanent impaired fertility (Table S2B).

Table 1. Estimated rates of death and permanent disability from various infectious diseases in the USA in the absence of mass vaccination among normal and high risk individuals <80 years of age, 2014.

Infection	Range of Reference Years Used for Estimates	Number of Cases (Morbidity) (A)	Population in 100,000 s (B)		Estimated Number of Cases of Death and Permanent Disability (C)		Rate: Deaths and Disabilities Per Number of Cases [C ÷ A]	Rate: Deaths and Disabilities Per 100,000 Population [C ÷ B] (95% C.I.)	
			Normal Risk ^a	High Risk ^a	Normal Risk ^a	High Risk ^a		Normal Risk ^a	High Risk ^a
Measles	1959-1962	4,000,000	2920	150	41	467	0.01%	0.014 (0.010-0.018)	3.11 (2.83 to 3.40)
Mumps	1963-1966	4,000,000	3070	0	61	0	0.002%	0.020 (0.015-0.025)	0
Rubella	1960-1968	4,000,000	3000	70	19	140	0.004%	0.006 (0.003-0.009)	2.00 (1.67-2.33)
Tetanus	1943-1945	1800	3070	0	113	0	6.3%	0.037 (0.029-0.043)	0
Diphtheria	1879-1945	560	3070	0	28	0	5%	0.009 (0.006-0.012)	0
Pertussis	1943-1945	1,300,000	3070	0	123	0	0.009%	0.040 (0.033-0.047)	0
Polio	1935-1954	72,500	2480	590	353	1149	2.1%	0.142 (0.127-0.157)	1.95 (1.83-2.06)
Hib	1980-1984	2800	1440	1630	66	208	9.8%	0.046 (0.035-0.057)	0.13 (0.11-0.14)
Hepatitis B	1988-1990	190,000	2610	460	106	3034	1.7%	0.041 (0.033-0.048)	6.60 (6.36-6.83)
Vaccella	1991-1994	4,000,000	3070	0	101	0	0.003%	0.033 (0.026-0.039)	0
HPV	2011-2014	2,800,000	1750	1320	198	5711	0.2%	0.113 (0.097-0.129)	4.33 (4.22-4.44)

^a "High risk" refers to individuals with specified factors linked to an elevated risk of permanent injury from the infection. "Normal risk" refers to individuals without those specific known factors and also refers to individuals with risk factors that were not identified or were excluded in our analysis. High risk factors, by infection, include: measles—insufficient vitamin A; rubella—woman who had not contracted rubella before pregnancy; polio—absence of tonsils and not resting after the onset of significant symptoms; *Haemophilus influenzae* type b (Hib)—breastfed for <13 weeks; hepatitis B—infant of an infected mother, dwelling with an infected partner, sex with an infected partner, sex with multiple partners, men having sex with men, injection-drug use, and dwelling in a community with an unusually large group of infected individuals; and human papillomavirus (HPV)—smoking, women not screened every 3 years, and men with ≥6 oral sex partners in their lifetime.

Table 2. Age groups that comprised the greatest proportion of deaths and permanent disabilities from various infectious diseases in the USA in the absence of mass vaccination.

Infection	Age Group	Proportion of Deaths and Permanent Disabilities
Measles	<10	91%
Mumps	<30	59%
Rubella	in utero	88%
Tetanus	<20	53%
Diphtheria	1–9	78%
Pertussis	<1	71%
Polio	<15	54%
Hib	<5	99%
Hepatitis B	≥50	79%
Varicella	≥20	54%
HPV	≥50	86%

3.3. Rubella (German Measles)

During the reference years of 1960–1968, before the introduction of mass vaccination, there were four million annual rubella cases (equal in size to the birth cohort; Table S3A) that resulted in 19 deaths [2]. CDC analyses of rubella have shown that permanent disability in rubella survivors was very rare [21]. However, mass vaccination was adopted because of congenital rubella syndrome (CRS) [21], which posed a threat to those infants whose mothers were infected by rubella during the first two trimesters of pregnancy. Therefore, we additionally considered the number of babies that contracted rubella in utero.

Using the government tracking of cases of rubella and CRS, we estimated that during the nine reference years, there were 1484 cases of CRS or 165 cases annually (Table S3B). Of those cases, we calculated 140 (=85% of 165) that resulted in death or permanent disability [21].

Because the birth cohorts in the 1960s and in 2014 were the same size and the number of susceptible children was also the same [15,16], we estimated that these values would remain unchanged in the absence of mass vaccination. Furthermore, most women in the 1960s contracted rubella before childbearing age [22], and the typical childbearing age of women in 2014 was greater than it was in the 1960s. Therefore, the estimated 165 cases of CRS for 2014 may be an overestimation.

3.4. Tetanus

Using the government tracking of cases of tetanus, we calculated that, during the reference years of 1943–1945, before the introduction of mass vaccination, one case of tetanus occurred in every 180,000 people (Table S4A). To estimate the number of tetanus cases for 2014 in the absence of mass vaccination, we multiplied the pre-vaccine incidence ratio of 1 in 180,000 by 2014's population (319 million) to obtain 1800 cases of tetanus.

CDC analyses of tetanus have shown that permanent disability in tetanus survivors was very rare [23]. As for deaths from tetanus, we used the most recent case fatality rates recorded among unvaccinated populations to account for significant improvements in health care and other factors influencing disease outcomes since the 1940s. From 2001 to 2008, we calculated a case fatality rate of 6.3% among unvaccinated individuals <80 years of age (Table S4B). We multiplied the estimated 1800 cases of tetanus for 2014 by the case fatality rate of 6.3% to obtain 113 fatal cases.

The pre-vaccine decline in the tetanus mortality rate from 2.4 to 0.5 tetanus deaths per 100,000 people (Figure S2) provided additional support for the projected decline in annual tetanus deaths from 626 in the 1940s (Table S4A) to 113 in 2014.

3.5. Diphtheria

During the reference years of 1879–1945, before the introduction of the national mass vaccination program, there was an exponential decline in diphtheria morbidity and mortality (Figure S3) [24–26]. This decline predated the introduction of antitoxin in the late 1890s, the introduction of toxin–antitoxin in the 1920s, and the gradual introduction of toxoid in the 1930s [27,28]. Furthermore, none of those events significantly altered the decline, suggesting that non-vaccine factors played important roles [27,28]. Laboratory testing revealed the protective effects of vitamin C [29], iron [30], and vitamin B3 [31] against diphtheria toxin. Studies also revealed that crowding and low levels of hygiene were associated with high incidences of diphtheria [32].

Because significant improvements in nutrition, sanitation, living conditions, and access to health care continued after the reference years, we estimated that the 65-year decline would have continued in the absence of the national mass vaccination program of the late 1940s, and we calculated 28 diphtheria deaths for 2014 (Table S5). Because the prevalence and severity of diphtheria risk factors required to put an individual at elevated risk have not been measured, we did not attempt to segregate cases at high risk from our results.

CDC analyses of diphtheria have shown that permanent disability in diphtheria survivors was very rare [28]. Additionally, given a case fatality rate of 5% for diphtheria [28], we estimated 560 (=28/5%) diphtheria cases for 2014.

3.6. Pertussis (Whooping Cough)

Using the government tracking of cases of pertussis during the reference years of 1943–1945, before the introduction of mass vaccination, we calculated 235,000 reported pertussis cases out of a total 1.3 million cases for 2014 in the absence of mass vaccination (Table S6A).

CDC analyses of pertussis have shown that permanent disability in pertussis survivors was very rare [33]. As for deaths from pertussis, we used the most recent case fatality rates recorded among unvaccinated populations to account for significant improvements in health care and other factors influencing disease outcomes since the 1940s. From 2012 to 2014, we calculated a reported case fatality rate of 0.7% among unvaccinated infants <3 months of age (Table S6B). We estimated 4500 reported pertussis cases for 2014 in that age group (Table S6C) and multiplied by the reported case fatality rate of 0.7% to obtain 32 fatal cases. Because infants <3 months of age comprised 26% of all pertussis deaths during the reference years (Table S6D), we calculated 123 (=32/26%) pertussis deaths among individuals of all ages.

The pre-vaccine decline in the pertussis mortality rate from 16.1 to 1.3 pertussis deaths per 100,000 people (Figure S4) and the mortality rate of one in eight million recorded in Sweden in the absence of mass vaccination in the 1980s [34] provided additional support for the projected decline in annual pertussis deaths from 2300 in the 1940s (Table S6D) to 123 in 2014.

3.7. Polio

During the reference years of 1935–1954, before the introduction of mass vaccination, there were an estimated 7260 annual cases of paralytic poliomyelitis (Table S7A), of which 1136 resulted in death or permanent disability (Table S7B,C). Since 95% of all polio infections were unnoticed or asymptomatic, and less than 1% of cases were paralytic [35], we estimated a total of 36,000 ($\approx 5\%$ of (7260/1%)) noticeable annual cases of polio. To estimate the number of noticeable cases of polio for 2014 in the absence of mass vaccination, we multiplied the pre-vaccine incidence ratio of 1 in 4400 ($\approx 36,000/160$ million) by the 2014 population (319 million) to obtain 72,500 cases.

Individuals without tonsils or who do not rest after the onset of significant symptoms are more likely to suffer permanent disability or death from paralytic poliomyelitis [36,37]. We calculated 1149 permanent disabilities and deaths among individuals at elevated risk and 353 among individuals at normal risk for 2014 in the absence of mass vaccination (Table S7D–H).

3.8. Hib (*Haemophilus Influenzae Type b*)

During the reference years of 1980–1984, before the introduction of mass vaccination, most children acquired immunity to Hib by five years of age through asymptomatic infection. In this report, we only considered identifiable cases of Hib-invasive Hib cases [38].

Using invasive *H. influenzae* data from the reference years and the government tracking of cases of invasive *H. influenzae*, we estimated an annual total of 3400 cases of invasive Hib for 1994–2000 in the absence of mass vaccination (Table S8A,B). Of those cases, we calculated 330 resulting in death or permanent disability from meningitis, bacteremia, or epiglottitis (Table S8C).

Children who were breastfed exclusively for ≥ 13 weeks were 2.8 times less likely to contract invasive Hib (Table S8D). On this basis, we used our estimates of invasive Hib incidence and permanent injury for 1994–2000 to calculate estimates for 2014 in the absence of mass vaccination: 66 cases of permanent injury among children breastfed exclusively for ≥ 13 weeks and 208 cases of permanent injury among children breastfed for < 13 weeks (Table S8E,F).

To estimate the number of all cases of invasive Hib for 2014, we divided the 274 cases of death and permanent disability by the percentage of Hib cases that resulted in such outcomes—9.8% ($= [60\% \times (11\% + 5\%)] + [15\% \times 1\%]$; Table S8C)—to obtain 2800 cases.

3.9. Hepatitis B

Using the government tracking of cases of hepatitis B during the reference years of 1988–1990, before the introduction of mass vaccination, we calculated 190,000 cases for 2014 in the absence of mass vaccination (Table S9A), including 300 cases of fatal fulminant hepatitis—nearly all of which occurred in adults and adolescents (Table S9B).

CDC analyses of hepatitis B have shown that permanent disability in hepatitis B survivors is very rare [39]. However, a portion of hepatitis B survivors can develop a chronic infection that can lead to fatal cirrhosis or liver cancer later in life, and 85% of those deaths occur in individuals < 80 years of age [40]. Using government chronic hepatitis B data, we estimated 1100 infections in adults and adolescents and 1740 infections in children resulting in chronic infection that led to death before age 80 for 2014 (Table S9C).

Individuals at high risk of exposure are more likely to contract hepatitis B (Table 3). Of the estimated 1400 deaths among adults and adolescents for 2014 in the absence of mass vaccination (300 from fulminant hepatitis + 1100 from chronic infection), we calculated 1300 deaths among individuals at elevated risk (Table S9D). Of the estimated 1740 deaths from infections in childhood, we calculated 1734 among children at elevated risk (Table S9E). Combining these totals resulted in 3034 ($= 1300 + 1734$) hepatitis B-related deaths among individuals at elevated risk and 106 ($= 100 + 6$) deaths among individuals at normal risk.

Table 3. Risk factors for elevated exposure to hepatitis B.

Age Group	Risk Factors
Children	Being born to a chronically infected mother, living with a chronically infected individual, and dwelling in a community that has a large number of infected individuals
Adults and adolescents	Having multiple sex partners, men having sex with men, injection-drug use, and dwelling in a community that has a large number of infected individuals

3.10. Varicella (Chicken Pox)

During the reference years of 1991–1994, before the introduction of mass vaccination, there were four million annual varicella cases (equal in size to the birth cohort; Table S10) that resulted in 101 deaths [2], mostly among the population ≥ 20 years of age [41]. Because the birth cohorts in the 1990s and in 2014 were the same size and the number of susceptible adults was also the same [16,42], we estimated that this value would remain unchanged in the absence of mass vaccination.

CDC analyses of varicella have shown that permanent disability in varicella survivors is very rare [43]. Though zoster (shingles) can occur later in life in individuals infected with varicella, death or permanent disability from zoster is also very rare [44]. Thus, we estimated no cases of varicella-related permanent disability for 2014.

3.11. HPV (Human Papillomavirus)

The CDC has estimated that there are 14 million annual cases of HPV of all types [45]. Of those 14 million cases, 20% (2.8 million) are targeted by vaccines [46]. Most HPV infections are unnoticed or asymptomatic. When there are symptoms from an HPV infection, such as genital warts, they very rarely cause death or permanent disability [45]. However, a small proportion of individuals infected with HPV can become persistently infected, and this condition can lead to various kinds of cancers later in life [45,47]. The first HPV vaccine was licensed in 2006, and the vaccination program targeted teenagers. Since HPV-attributable cancers rarely affect individuals < 30 years of age, it will take at least another decade before it is possible for mass vaccination to have a measurable effect on the incidence of those cancers. Here, we consider HPV-attributable cancer statistics during the reference years of 2011–2014.

Table 4 contains a list of HPV-attributable cancers and factors that lead to an elevated risk of dying from them. Among women < 80 years of age, we estimated 132 fatal HPV-attributable cancers occurring in women at normal risk and 5340 fatal cancers occurring in women at elevated risk (Table S11A). Among men < 80 years of age, we estimated 66 fatal HPV-attributable cancers occurring in men at normal risk and 371 fatal cancers occurring in men at elevated risk (Table S11B). Combining these totals resulted in 198 ($= 132 + 66$) HPV-related deaths among individuals at normal risk and 5711 ($= 5340 + 371$) deaths among individuals at elevated risk.

Table 4. Types of HPV-attributable cancer and factors that elevate the risk of dying from them.

Gender	HPV-Attributable Cancers	Risk Factors
Female	Cervix, vagina, vulva, anus, rectum, and oropharynx	No Pap or HPV screening every three years and smoking
Male	Oropharynx, penis, anus, and rectum	Smoking and having six or more oral sex partners in a lifetime

4. Discussion

Based on population data for 2014, it was estimated that mass vaccination programs against measles, mumps, rubella, tetanus, diphtheria, pertussis, polio, Hib, hepatitis B, varicella, and HPV could prevent 20 million infections and 12,000 deaths and permanent disabilities annually.

Individuals who have conditions or behaviors that would put them at higher risk of permanent injury from infectious diseases (e.g., insufficient vitamin A, absence of tonsils, breastfed < 13 weeks, injection-drug use, and smoking) were found to comprise 90% ($\approx 10,800/12,000$) of all the estimated cases of prevented death and permanent disability, with the remaining 1200 cases in persons at normal risk (or with risk factors excluded from this report). It is possible that the high risk conditions described in this report might expose individuals to permanent harm from other causes. More research in this arena would be useful.

Pre-vaccine declines in mortality rates recorded for measles, tetanus, diphtheria, and pertussis were not unique to those infections. In the early 20th century, significant declines in mortality rates were recorded for numerous infectious diseases that were not targeted by mass vaccination programs, such as those for tuberculosis, syphilis, typhoid fever, and dysentery [48]. The human immune system is evidently remarkably efficient when coupled with treatments for severe cases of diseases, such as antibiotics and when not hampered by factors like poor nutrition, poor sanitation, or limited access to health care.

Mass vaccination programs are best known for preventing deaths and permanent disabilities that occur a relatively short time after infection. However, 75% ($\approx 9000/12,000$) of the estimated cases of death and permanent disability prevented in this report would be from conditions occurring much later in life—liver cirrhosis and cancer. Though hepatitis B and HPV are the causes of these conditions, the hepatitis B and HPV mass vaccination programs have not, at this point, shown empirical impacts on the prevalence of liver cirrhosis and cancer. In spite of the significant reduction in acute cases of hepatitis B, the prevalence of chronic hepatitis B has remained practically unchanged since 1976 [49]. As for the HPV vaccine, although the prevention of HPV infections that are necessary for the potential development of cancer has been observed [45], cancer protection has not yet been empirically documented and uncertainties remain. Among these, a minimum protective antibody titer has not been determined [45], and the duration of antibody response has only been measured for eight-to-nine years [50]. Since most HPV-attributable cancers occur in the population >50 years of age, it may be that to most successfully prevent HPV-attributable cancer, either an HPV vaccine needs to provide lifetime immunity or booster doses need to be introduced into the mass vaccination program.

This report had other limitations. The accuracy of our estimates depended on the quality of the available evidence concerning the risks and effects of the diseases, which could have been imperfect. In many instances, we projected to 2014 from statistics recorded decades earlier. The accuracy of such projections could have been affected by changes in the organisms targeted by vaccines, changes in host resilience, or changes in health care practices deviating from pre-vaccine trends, among other factors. In addition, inaccuracies can propagate from one estimate to another when an estimate is used to derive the other. For example, the case fatality rate of a disease is sometimes used to estimate the total number of cases of that disease based on its estimated number of fatalities. Another limitation was related to the potential aggregate impact of risk factors that were not considered in generating our estimates, either because they are (individually) less commonly implicated or are undiscovered or inadequately studied. The comprehensive consideration of such factors might shift more of the vaccine-averted deaths and disability to the high-risk category. The same limitations might apply to the long term effects of some of the diseases. It is also possible that relevant information was missed in our literature review. We sought to convey the challenges surrounding some of the available data in the discussion of each disease and have tried to be explicit about assumptions made. We explained our choices in relation to the application of pre-vaccine trends and in gauging expected disease outcomes as a function of whether an individual is at higher risk. Furthermore, this study only estimated the number of deaths and permanent disabilities prevented by mass vaccination programs. It did not consider similar outcomes that may be caused by these programs.

Despite these limitations, we believe this report employed the best processes among the available data and studies for estimating the numbers of deaths and permanent disabilities that would have occurred (here estimated for 2014) in the absence of mass vaccination programs. Though other studies have presented estimates of the benefits of mass vaccination programs, they have not accounted for disease risk factors, cases of nonfatal permanent disability, pre-vaccine trends in mortality, post-vaccine improvements in factors tied to disease outcomes resulting in improved case fatality rates in unvaccinated populations (such as improved nutrition, sanitation, hygiene, indoor temperature control, health care, and the treatment of disease), and adjustments of pre-vaccine estimates using data recorded after vaccine licensure [3–5]. Furthermore, some studies have not provided an explanation

for the data used as the basis of their estimates [4,5]. We have tried to rectify these omissions in the present report.

5. Conclusions

Despite the decline in mortality rates of infectious diseases recorded since the late 19th century, the data in this report indicate that mass vaccination programs may still have prevented 20 million infections and 12,000 deaths and permanent disabilities in 2014. In addition, mass vaccination programs have reduced the burden on health services, hospitals, intensive care, and the economy caused by the diseases they target. Put another way, measuring the number of deaths and cases of permanent disability prevented by mass vaccination programs is not the only way to measure the benefit of those programs, as those benefits can also be measured by other outcomes such as hospitalizations or the economic burden associated with a disease. However, those outcomes may be more greatly influenced by a range of factors beyond the impact of the vaccine and the disease, such as shifts in approaches to and costs of hospitalization over time. Nonetheless, because such outcomes are generally a function of the morbidity and mortality of the disease, the data in this report might also be useful in generating estimates for those outcomes.

We believe this report provides a useful reference for the effect of mass vaccination programs on the most serious complications of the diseases they target. Future studies can seek to further refine these estimates, use these estimates in risk-benefit analyses, and assess how adjusting assumptions influences effect estimates.

Supplementary Materials: The following are available online at <http://www.mdpi.com/2076-393X/8/4/561/s1>: Table S1: Basis for figures concerning measles; A. Number of measles cases, 1959–1962; B. Estimated number of permanent disabilities from measles for 2014 in the absence of mass vaccination; and C. Percentage of severe measles cases that have low levels of vitamin A. Figure S1: Decline in measles mortality, 1900–1960. Table S2: Basis for figures concerning mumps; A. Number of mumps cases, 1963–1966; and B. Estimated number of permanent disabilities from mumps for 2014 in the absence of mass vaccination. Table S3: Basis for figures concerning rubella; A. Number of rubella cases, 1960–1968; and B. Estimated number of cases of CRS, 1960–1968. Table S4: Basis for figures concerning tetanus; A. Estimated incidence of tetanus, 1943–1945; and B. Tetanus case fatality rate among unvaccinated individuals <80 years of age, 2000–2008. Figure S2: Decline in tetanus mortality, 1900–1945. Table S5: Basis for figures concerning diphtheria. Figure S3: Decline in diphtheria mortality, 1879–1945. Table S6: Basis for figures concerning pertussis; A. Estimated number of cases of pertussis for 2014 in the absence of mass vaccination; B. Pertussis reported case fatality rate among unvaccinated infants <3 months of age, 2012–2014; C. Estimated number of cases of pertussis among infants <3 months of age for 2014 in the absence of mass vaccination; and D. Number of pertussis deaths and percentage that occurred among infants <3 months of age, 1943–1945. Figure S4: Decline in pertussis mortality, 1900–1945. Table S7: Basis for figures concerning polio; A. Estimated number of cases of paralytic poliomyelitis, 1935–1954; B. Estimated number of poliomyelitis cases resulting in permanent disability or death, 1935–1954; C. Estimated case fatality rate of paralytic poliomyelitis, 1935–1954; D. Estimated number of poliomyelitis cases resulting in death or permanent disability for 2014 in the absence of mass vaccination; E. Estimated risk of permanent disability or death from poliomyelitis in children <10 years of age based on tonsillectomy and rest status, 1935–1954; F. Estimated risk of permanent disability or death from poliomyelitis in individuals 10–39 years of age based on tonsillectomy and rest status, 1935–1954; G. Percentage of population that had no tonsils, 1935–1954; and H. Percentage of poliomyelitis cases that rested after significant onset of symptoms by type of paralysis and severity, 1935–1954. Table S8: Basis for figures concerning *Haemophilus influenzae* type b, A. Estimated number of cases of invasive Hib in the absence of mass vaccination, 1994–2000; B. Invasive *H. influenzae* tracking in children <5 years of age, 1994–2000; C. Estimated number of cases of invasive Hib resulting in death or permanent disability in the absence of mass vaccination, 1994–2000; D. Protective effect of breastfeeding against invasive Hib measured in 1997 Swedish study of children <6 years of age; E. Estimated number of cases of invasive Hib resulting in death or permanent disability for 2014 in the absence of mass vaccination based on breastfeeding status; and F. Estimated risk of invasive Hib based on breastfeeding status in the absence of mass vaccination, 1994–2000. Table S9: Basis for figures concerning hepatitis B; A. Estimated number of cases of hepatitis B for 2014 in the absence of mass vaccination; B. Estimated number of cases of fatal fulminant hepatitis B for 2014 in the absence of mass vaccination; C. Estimated number of hepatitis B cases leading to death from chronic infection before age 80 for 2014 in the absence of mass vaccination among various age groups; D. Estimated number of hepatitis B cases leading to death before age 80 for 2014 in the absence of mass vaccination among adults and adolescents at high risk of exposure; and E. Estimated number of hepatitis B cases leading to death before age 80 for 2014 in the absence of mass vaccination among children at high risk of exposure. Table S10: Basis for figures concerning varicella. Table S11: Basis for figures concerning human papillomavirus; A. Estimated number of HPV cases leading to death before age 80 for 2014 among women; and B. Estimated number of HPV cases leading to death before age 80 for 2014 among men.

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EXHIBIT 419

[Billing Code 3290-F8]

OFFICE OF THE UNITED STATES TRADE REPRESENTATIVE

Docket No. USTR-2018-0005

**Notice of Determination and Request for Public Comment Concerning Proposed
Determination of Action Pursuant to Section 301: China's Acts, Policies, and
Practices Related to Technology Transfer, Intellectual Property, and Innovation**

AGENCY: Office of the United States Trade Representative

ACTION: Notice of determination, request for comments, and notice of public hearing

SUMMARY: The U.S. Trade Representative (Trade Representative) has determined that the acts, policies, and practices of the Government of China related to technology transfer, intellectual property, and innovation covered in the investigation are unreasonable or discriminatory and burden or restrict U.S. commerce. The Office of the U.S. Trade Representative (USTR) is seeking public comment and will hold a public hearing regarding a proposed determination on appropriate action in response to these acts, policies, and practices. The Trade Representative proposes an additional duty of 25 percent on a list of products from China. The list of products, defined by 8-digit subheadings of the Harmonized Tariff Schedule of the United States (HTSUS), is set out in the Annex to this Notice.

DATES: To be assured of consideration, you must submit comments and responses in accordance with the following schedule:

April 23, 2018: Due date for filing requests to appear and a summary of expected testimony at the public hearing and for filing pre-hearing submissions.

May 11, 2018: Due date for submission of written comments.

May 15, 2018: The Section 301 Committee will convene a public hearing in the main hearing room of the U.S. International Trade Commission, 500 E Street SW Washington DC 20436 beginning at 10:00 am.

May 22, 2018: Due date for submission of post-hearing rebuttal comments.

ADDRESSES: USTR strongly prefers electronic submissions made through the Federal eRulemaking Portal: <http://www.regulations.gov>. Follow the instructions for submitting comments in sections F and G below. The docket number is USTR-2018-0005. For alternatives to on-line submissions, please contact Sandy McKinzy at (202) 395-9483.

FOR FURTHER INFORMATION CONTACT: For questions about the ongoing investigation or proposed action, contact Arthur Tsao, Assistant General Counsel, at (202) 395-5725. For questions on customs classification of products identified in the Annex to this Notice, contact Evan Conceicao at Evan.M.Conceicao@cbp.dhs.gov.

SUPPLEMENTARY INFORMATION:

A. Proceedings in the Investigation

On August 14, 2017, the President issued a Memorandum (82 FR 39007) instructing the Trade Representative to determine whether to investigate under section 301 of the Trade Act of 1974 (Trade Act) (19 U.S.C. 2411), laws, policies, practices, or

actions of the Government of China that may be unreasonable or discriminatory and that may be harming American intellectual property rights, innovation, or technology development.

On August 18, 2017, after consultation with the appropriate advisory committees and the inter-agency Section 301 Committee, USTR initiated an investigation into certain acts, policies, and practices of the Government of China related to technology transfer, intellectual property, and innovation. The notice of initiation (82 FR 40213) solicited written comments on, *inter alia*, four categories of acts, policies and practices of the Government of China:

1. The Chinese government reportedly uses a variety of tools, including opaque and discretionary administrative approval processes, joint venture requirements, foreign equity limitations, procurements, and other mechanisms to regulate or intervene in U.S. companies' operations in China, in order to require or pressure the transfer of technologies and intellectual property to Chinese companies. Moreover, many U.S. companies report facing vague and unwritten rules, as well as local rules that diverge from national ones, which are applied in a selective and non-transparent manner by Chinese government officials to pressure technology transfer.
2. The Chinese government's acts, policies and practices reportedly deprive U.S. companies of the ability to set market-based terms in licensing and other technology-related negotiations with Chinese companies and undermine U.S. companies' control over their technology in China. For example, the Regulations on Technology Import and Export Administration mandate particular terms for indemnities and ownership of

technology improvements for imported technology, and other measures also impose non-market terms in licensing and technology contracts.

3. The Chinese government reportedly directs and/or unfairly facilitates the systematic investment in, and/or acquisition of, U.S. companies and assets by Chinese companies to obtain cutting-edge technologies and intellectual property and generate large-scale technology transfer in industries deemed important by Chinese government industrial plans.

4. The investigation will consider whether the Chinese government is conducting or supporting unauthorized intrusions into U.S. commercial computer networks or cyber-enabled theft of intellectual property, trade secrets, or confidential business information, and whether this conduct harms U.S. companies or provides competitive advantages to Chinese companies or commercial sectors.

Interested persons filed approximately 70 written submissions. In addition, USTR and the Section 301 Committee convened a public hearing on October 10, 2017, during which witnesses provided testimony and responded to questions. The public submissions and a transcript of the hearing are available on www.regulations.gov in docket number USTR-2017-0016.

Based on information obtained during the investigation, including the public submissions and the public hearing, USTR and the Section 301 Committee have prepared a comprehensive report on the acts, policies, and practices under investigation. USTR posted the report on its website on March 22, 2018:

<https://ustr.gov/sites/default/files/Section%20301%20FINAL.PDF>. The report supports

findings that each of the four categories of acts, policies, and practices are unreasonable or discriminatory and burden or restrict U.S. commerce.

B. Determination on Acts, Policies, and Practices Under Investigation

Based on the information obtained during the investigation and the advice of the Section 301 Committee, and as reflected in the publicly-available report on the findings in the investigation, the Trade Representative has made the following determination under sections 301(b) and 304(a) of the Trade Act (19 U.S.C. 2411(b) and 2414(a)): the acts, policies, and practices covered in the investigation are unreasonable or discriminatory and burden or restrict U.S. commerce, and are thus actionable under section 301(b) of the Trade Act. In particular:

1. China uses foreign ownership restrictions, such as joint venture requirements and foreign equity limitations, and various administrative review and licensing processes, to require or pressure technology transfer from U.S. companies.
2. China's regime of technology regulations forces U.S. companies seeking to license technologies to Chinese entities to do so on non-market-based terms that favor Chinese recipients.
3. China directs and unfairly facilitates the systematic investment in, and acquisition of, U.S. companies and assets by Chinese companies to obtain cutting-edge technologies and intellectual property and generate the transfer of technology to Chinese companies.

4. China conducts and supports unauthorized intrusions into, and theft from, the computer networks of U.S. companies to access their sensitive commercial information and trade secrets.

C. Proposed Determination on Appropriate Action

Upon determining that the acts, policies, and practices under investigation are actionable, section 301(b) provides that the Trade Representative shall take all appropriate and feasible action authorized under section 301(c), subject to the specific direction, if any, of the President regarding such action, and all other appropriate and feasible action within the power of the President that the President may direct the Trade Representative to take under section 301(b), to obtain the elimination of that act, policy, or practice. In a Memorandum dated March 22, 2018 (83 FR 13099), the President directed the Trade Representative as follows:

Section 1. Tariffs. (a) The Trade Representative should take all appropriate action under section 301 of the Act (19 U.S.C. 2411) to address the acts, policies, and practices of China that are unreasonable or discriminatory and that burden or restrict U.S. commerce. The Trade Representative shall consider whether such action should include increased tariffs on goods from China.

(b) To advance the purposes of subsection (a) of this section, the Trade Representative shall publish a proposed list of products and any intended tariff increases within 15 days of the date of this memorandum. After a period of notice and comment in accordance with section 304(b) of the Act (19 U.S.C. 2414(b)), and after consultation with appropriate agencies and committees, the Trade Representative shall, as

appropriate and consistent with law, publish a final list of products and tariff increases, if any, and implement any such tariffs.

Pursuant to sections 301(b) and (c) and the March 22nd Memorandum from the President, the Trade Representative proposes that appropriate action would include increased tariffs on certain goods of Chinese origin. In particular, the proposed action is an additional duty of 25 percent on a list of products of Chinese origin identified in the Annex to this Notice. For example, if a good of Chinese origin is currently subject to a zero *ad valorem* rate of duty, the product would be subject to a 25 percent *ad valorem* rate of duty; if a good of Chinese origin were currently subject to a 10 percent *ad valorem* rate of duty, the product would be subject to a 35 percent *ad valorem* rate of duty; and so on.

To ensure the effectiveness of the action, any merchandise subject to the increased tariffs admitted into a U.S. foreign trade zone on or after the effective date of the increased tariffs would have to be admitted as “privileged foreign status” as defined in 19 CFR 146.41, and would be subject upon entry for consumption to the additional duty.

The list of products covered by the proposed action was developed using the following methodology:

Trade analysts from several U.S. Government agencies identified products that benefit from Chinese industrial policies, including Made in China 2025. The list was refined by removing specific products identified by analysts as likely to cause disruptions to the U.S. economy, and tariff lines that are subject to legal or administrative constraints. The remaining products were ranked according to the likely impact on U.S. consumers, based on available trade data involving alternative country sources for each product. The

proposed list was then compiled by selecting products from the ranked list with lowest consumer impact.

The value of the list is approximately \$50 billion in terms of estimated annual trade value for calendar year 2018. This level is appropriate both in light of the estimated harm to the U.S. economy, and to obtain elimination of China's harmful acts, policies, and practices.

D. WTO Dispute on Certain Discriminatory Technology Regulations

As noted above, the second category of acts, policies, and practices under investigation involve certain discriminatory technology regulations. The Presidential Memorandum provides the following regarding the Trade Representative's findings on this issue:

Section 2. WTO Dispute Settlement. (a) The Trade Representative shall, as appropriate and consistent with law, pursue dispute settlement in the World Trade Organization (WTO) to address China's discriminatory licensing practices. Where appropriate and consistent with law, the Trade Representative should pursue this action in cooperation with other WTO members to address China's unfair trade practices.

(b) Within 60 days of the date of this memorandum, the Trade Representative shall report to me his progress under subsection (a) of this section.

The Trade Representative has decided that certain acts, policies, and practices of China considered in the investigation may be appropriately addressed through recourse to WTO dispute settlement. Accordingly, on March 23, 2018, the Trade Representative initiated a WTO dispute by requesting consultations with the Government of China regarding

certain specific aspects of China's technology regulations considered in the investigation. You can find documents related to this dispute on the dispute settlement section of the WTO website under DS542: China — Certain Measures Concerning the Protection of Intellectual Property Rights. Because the Trade Representative intends to address these issues through recourse to WTO dispute settlement, the proposed tariff action does not relate to or take into account harm caused by these acts, policies, and practices.

E. Request for Public Comments

In accordance with section 304(b) of the Trade Act (19 U.S.C. 2414(b)), USTR invites comments from interested persons with respect to the proposed action to be taken in response to the acts, policies, and practices of China determined to be unreasonable or discriminatory, and to burden or restrict U.S. commerce. To be assured of consideration, you must submit written comments on the proposed action in response to China's acts, policies, and practices by May 11, 2018, and post-hearing rebuttal comments by May 22, 2018.

USTR requests comments with respect to any aspect of the proposed action, including:

- The specific products to be subject to increased duties, including whether products listed in the Annex should be retained or removed, or whether products not currently on the list should be added.
- The level of the increase, if any, in the rate of duty.
- The appropriate aggregate level of trade to be covered by additional duties.

In commenting on the inclusion or removal of particular products on the list of products subject to the proposed additional duties, USTR requests that commenters address specifically whether imposing increased duties on a particular product would be practicable or effective to obtain the elimination of China's acts, policies, and practices, and whether maintaining or imposing additional duties on a particular product would cause disproportionate economic harm to U.S. interests, including small- or medium-size businesses and consumers.

F. Hearing Participation.

The Section 301 Committee will convene a public hearing in the main hearing room of the U.S. International Trade Commission, 500 E Street SW Washington DC 20436, beginning at 10:00 am on May 15, 2018. You must submit requests to appear at the hearing by April 23, 2018. The request to appear must include a summary of testimony, and may be accompanied by a pre-hearing submission. Remarks at the hearing may be no longer than five minutes to allow for possible questions from the Section 301 Committee.

All submissions must be in English and sent electronically via www.regulations.gov. To submit a request to appear at the hearing via www.regulations.gov, enter docket number **USTR-2018-0005**. In the "Type Comment" field, include the name, address, email address, and telephone number of the person presenting the testimony. Attach a summary of the testimony, and a pre-hearing submission if provided, by using the "Upload File" field. The file name should include the name of the person who will be presenting the testimony. In addition, please submit a

request to appear by email to 301investigation@ustr.eop.gov. In the subject line of the email, please include the name of the person who will be presenting the testimony, followed by “Request to Appear”. Please also include the name, address, email address, and telephone number of the person presenting testimony in the body of the email message.

G. Procedures for Written Submissions

To assist in review of public comments submitted pursuant to Section E, the Section 301 Committee has prepared a public comment form that will be posted on the USTR website under “Enforcement/Section 301 investigations” and on the www.regulations.gov docket. USTR strongly encourages commenters to use the form to submit comments pursuant to Section E, though use of the form is not required. Please identify the specific good in question by the applicable HTSUS subheading.

All submissions must be in English and sent electronically via www.regulations.gov. To submit comments via www.regulations.gov, enter docket number **USTR-2018-0005** on the home page and click “search.” The site will provide a search-results page listing all documents associated with this docket. Find a reference to this notice and click on the link entitled “Comment Now!” For further information on using the www.regulations.gov website, please consult the resources provided on the website by clicking on “How to Use Regulations.gov” on the bottom of the home page. We will not accept hand-delivered submissions.

The www.regulations.gov website allows users to submit comments by filling in a “Type Comment” field or by attaching a document using an “Upload File” field. USTR

prefers that you submit comments in an attached document. If you attach a document, it is sufficient to type “see attached” in the “Type Comment” field. USTR prefers submissions in Microsoft Word (.doc) or Adobe Acrobat (.pdf). If you use an application other than those two, please indicate the name of the application in the “Type Comment” field.

File names should reflect the name of the person or entity submitting the comments. Please do not attach separate cover letters to electronic submissions; rather, include any information that might appear in a cover letter in the comments themselves. Similarly, to the extent possible, please include any exhibits, annexes, or other attachments in the same file as the comment itself, rather than submitting them as separate files.

For any comments submitted electronically containing business confidential information, the file name of the business confidential version should begin with the characters “BC”. Any page containing business confidential information must be clearly marked “BUSINESS CONFIDENTIAL” on the top of that page and the submission should clearly indicate, via brackets, highlighting, or other means, the specific information that is business confidential. If you request business confidential treatment, you must certify in writing that disclosure of the information would endanger trade secrets or profitability, and that the information would not customarily be released to the public. Filers of submissions containing business confidential information also must submit a public version of their comments. The file name of the public version should begin with the character “P”. The “BC” and “P” should be followed by the name of the person or entity submitting the comments or rebuttal comments. If these procedures are

not sufficient to protect business confidential information or otherwise protect business interests, please contact the USTR Tech Transfer Section 301 line at (202) 395-5725 to discuss whether alternative arrangements are possible.

USTR will post submissions in the docket for public inspection, except business confidential information. You can view submissions on the <https://www.regulations.gov> website by entering docket number USTR-2018-0005 in the search field on the home page.

Robert E. Lighthizer
United States Trade Representative.

ANNEX

Note: All products that are classified in the 8-digit subheadings of the Harmonized Tariff Schedule of the United States (HTSUS) that are listed in this Annex are covered by the proposed action. The product descriptions that are contained in this Annex are provided for informational purposes only, and are not intended to delimit in any way the scope of the proposed action. Any questions regarding the scope of particular HTSUS subheadings should be referred to U.S. Customs and Border Protection. In the product descriptions, the abbreviations “nesoi” and “nesi” mean “not elsewhere specified or included”.

HTS subheading	Product Description
28443010	Thorium compounds
28443020	Compounds of uranium depleted in U235
28443050	Uranium depleted in U235, thorium; alloys, dispersions, ceramic products and mixtures of these products and their compounds
28459000	Isotopes not in heading 2844 and their compounds other than heavy water
29146200	Coenzyme Q10 (ubidecarenone (INN))
29146921	Quinone drugs
29189914	2-(4-Chloro-2-methyl-phenoxy)propionic acid and its salts
29189930	Aromatic drugs derived from carboxylic acids with additional oxygen function, and their derivatives, nesoi
29214600	Amfetamine (INN), benzfetamine (INN), dexamfetamine (INN), etilamfetamine (INN), and other specified INNs; salts thereof
29214932	Fast color bases of aromatic monamines and their derivatives
29214938	Aromatic monoamine antidepressants, tranquilizers and other psychotherapeutic agents, nesoi
29214943	Aromatic monoamine drugs, nesoi
29221909	Aromatic amino-alcohols drugs, their ethers and esters, other than those containing > one kind of oxygen function; salts thereof; nesoi
29221990	Salts of triethanolamine
29221996	Amino-alcohols, other than those containing more than one kind of oxygen function, their ethers and esters and salts thereof, nesoi
29225013	Isoetharine hydrochloride and other specified aromatic drugs of amino-compounds with oxygen function
29225014	Other aromatic cardiovascular drugs of amino-compounds with oxygen function
29225017	Aromatic dermatological agents and local anesthetics of amino-compounds with oxygen function
29225019	Aromatic guaiacol derivatives of amino-compounds with oxygen function
29242905	Biligradin acid; 3,5-diacetamido-2,4,6-triiodobenzoic acid; and metrizoic acid
29242936	Naphthol AS and derivatives, nesoi
29242952	Aromatic cyclic amides for use as fast color bases
29242957	Diethylaminoacetoxylidide (Lidocaine)
29242962	Other aromatic cyclic amides and derivatives for use as drugs

HTS subheading	Product Description
29280010	Methyl ethyl ketoxime
29319010	4,4'-Diphenyl-bis-phosphonous acid, di(2',2'',4',4''-di-tert-butyl)phenyl ester
29329961	Aromatic heterocyclic compounds with oxygen hetero-atom(s) only described in additional U.S. note 3 to section VI, nesoi
29333915	Quinuclidin-3-ol
29339942	Acriflavin; Acriflavin hydrochloride; Carbadox; Pyrazinamide
29339951	Hydralazine hydrochloride
29339958	Droperidol; and Imipramine hydrochloride
29349901	Mycophenolate mofetil
29349905	5-Amino-3-phenyl-1,2,4-thiadiazole(3-Phenyl-5-amino-1,2,4-thiadiazole); and 3 other specified aromatic/mod. aromatic heterocyclic compounds
29349906	7-Nitronaphth[1,2]oxadiazole-5-sulfonic acid and its salts
29349947	Nonaromatic drugs of other heterocyclic compounds, nesoi
29349970	Morpholinethyl chloride hydrochloride; 2-methyl-2,5-dioxo-1-oxa-2-phospholan; and 1 other specified nonaromatic chemical
29371100	Somatotropin, its derivatives and structural analogues
29371900	Polypeptide hormones, protein hormones and glycoprotein hormones, their derivatives and structural analogues, nesoi
29372325	Estradiol benzoate; and Estradiol cyclopentylpropionate (estradiol cypionate)
29375000	Prostaglandins, thromboxanes and leukotrienes, their derivatives and structural analogues
29379005	Epinephrine
29379040	L-Thyroxine(Levothyroxine), sodium
30012000	Extracts of glands or other organs or of their secretions for organotherapeutic uses
30021100	Malaria diagnostic test kits
30021200	Antisera and other blood fractions including human blood and fetal bovine serum
30021300	Immunological products, unmixed, not put up in measured doses or in forms or packings for retail sale
30021400	Immunological products, mixed, not put up in measured doses or in forms or packings for retail sale
30021500	Immunological products, put up in measured doses or in forms or packings for retail sale
30021900	Blood fractions, nesoi
30022000	Vaccines for human medicine
30023000	Vaccines for veterinary medicine
30029010	Ferments, excluding yeasts
30029051	Human blood; animal blood prepared for therapeutic, prophylactic, diagnostic uses; toxins, cultures of micro-organisms nesoi & like products
30032000	Medicaments containing antibiotics, nesoi, not dosage form and not packaged for retail
30033100	Medicaments containing insulin, not dosage form and not packed for retail
30033910	Medicaments containing artificial mixtures of natural hormones, but not antibiotics, not dosage form and not packed for retail

HTS subheading	Product Description
30033950	Medicaments containing products of heading 2937, nesoi, but not antibiotics, not dosage form and not packed for retail
30034100	Medicaments containing ephedrine or its salts, not dosage form and not packed for retail
30034200	Medicaments containing pseudoephedrine (INN) or its salts, not dosage form and not packed for retail
30034300	Medicaments containing norephedrine or its salts, not dosage form and not packed for retail
30034900	Other medicaments containing alkaloids or derivatives thereof, nesoi, not dosage form and not packed for retail
30036000	Other medicaments containing antimalarial active principles described in subheading note 2 to this chapter, not dosage form and not packed for retail
30039001	Medicaments nesoi, not dosage form and not packed for retail
30041010	Medicaments containing penicillin G salts, in dosage form and packed for retail
30041050	Medicaments cont. penicillins or streptomycins, nesoi, in dosage form or packed for retail
30042000	Medicaments containing antibiotics, nesoi, in dosage form or packed for retail
30043100	Medicaments containing insulin, in dosage form or packed for retail
30043200	Medicaments, containing adrenal cortical hormones, in dosage form or packed for retail
30043900	Medicaments, containing products of heading 2937 nesoi, in dosage form or packed for retail
30044100	Medicaments containing ephedrine or its salts, in dosage form and packed for retail
30044200	Medicaments containing pseudoephedrine (INN) or its salts, in dosage form and packed for retail
30044300	Medicaments containing norephedrine or its salts, in dosage form and packed for retail
30044900	Other medicaments containing alkaloids or derivatives thereof, nesoi, in dosage form and packed for retail
30045010	Medicaments containing vitamin B2 synthesized from aromatic or mod. aromatic compounds, in dosage form or packed for retail
30045020	Medicaments containing vitamin B12 synthesized from aromatic or mod. aromatic compounds, in dosage form or packed for retail
30045030	Medicaments containing vitamin E synthesized from aromatic or mod. aromatic compounds, in dosage form or packed for retail
30045040	Medicaments containing vitamins nesoi, synthesized from aromatic or mod. aromatic compounds, in dosage form or packed for retail
30045050	Medicaments containing vitamins or other products of heading 2936, nesoi, in dosage form or packed for retail
30046000	Other medicaments containing antimalarial active principles described in subheading note 2 to this chapter, in dosage form and packed for retail
30049010	Medicaments containing antigens or hyaluronic acid or its sodium salt, nesoi, in dosage form or packed for retail
30049092	Medicaments nesoi, in dosage form and packed for retail
30051010	Adhesive dressings and other articles having an adhesive layer, coated or impregnated with pharmaceutical substances, packed for retail

EXHIBIT 420

Importing CBER-Regulated Products into the United States

What is the process for importing into the United States?

Generally, the process of importing into the United States is governed by Customs laws and regulations which are administered by the **U.S. Customs and Border Protection (CBP)**. CBP has primary responsibility for regulating and facilitating international trade, collecting import duties, and enforcing United States trade laws. All merchandise coming into the United States **clears CBP and is subject to duty unless specifically exempted by law**. CBP clearance involves a number of steps: entry, inspection, appraisal, classification, and liquidation. Information must be filed with CBP for all goods imported into the United States. This information, presented in an **"entry notice,"** must be filed with **CBP by the importer of record**. Frequently, a Customs broker files the entry notice on behalf of the importer of record. (The importer of record is the party holding the bond and is responsible for entry. The importer of record may be the broker, consignee, or true owner of the goods.) The person presenting entry information to CBP is known as the "filer." In order that the merchandise may be delivered to the importer or owner while review of the entry is taking place, a monetary bond is obtained. The bond contains a condition for the redelivery of an imported shipment, or any portion of it, upon demand of CBP.

What standards apply to imports that are regulated by the **Center for Biologics Evaluation and Research (CBER)**?

CBER regulates biological and related products, including blood and blood products (which includes certain kinds of devices), vaccines, allergenics, tissues, and cellular and gene therapies. CBER also regulates the medical devices involved in the collection, processing, testing, manufacture and administration of licensed blood, blood components and cellular products and all HIV test kits used both to screen donor blood, blood components, and cellular products and to diagnose, treat, and monitor persons with HIV and AIDs. In order to import a CBER-regulated product into the United States, **the product must meet FDA's regulatory requirements.** Foreign firms which manufacture products regulated by CBER that are directly or indirectly imported into the United States must comply with applicable FDA requirements before, during, and after importing into the United States. FDA does not recognize regulatory approvals from other countries.

Who directs and coordinates CBER's import program?

The Division of Case Management (DCM) within CBER's Office of Compliance and Biologics Quality (OCBQ) directs and coordinates CBER's import program (See the Resources for You box on the left-hand side for related links). You can send questions pertaining to the importation of

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CBER-regulated products to CBERImportInquiry@fda.hhs.gov
(mailto:CBERImportInquiry@fda.hhs.gov).

What role does FDA play when an FDA-regulated article is offered for import?

If the article being imported falls under FDA's jurisdiction, it is subject to FDA review. **Section 801 of the Federal Food, Drug, and Cosmetic Act (21 USC 381) sets out basic standards and procedures for FDA review of imports under its jurisdiction.** Section 801(a) provides for examination of imports and also authorizes FDA to refuse admission of imports that appear, from examination or otherwise, to violate FDA requirements. FDA regulations at 21 CFR 1271.420 set out the basic import standards and procedures for human tissues. As explained in more detail below, FDA and CBP have coordinated their efforts and work together to ensure the smooth processing of FDA-regulated imports.

Importing CBER-Regulated Products: Roles of Other Federal Agencies

The US Customs and Border Protection (CBP), Centers for Disease Control and Prevention (CDC), and the US Department of Agriculture (USDA), Animal and Plant Health Inspection Service (APHIS) may have regulations that may also apply to CBER-regulated products. Use the link below to learn more.

- [Importing CBER-Regulated Products: FDA Interactions with other Agencies \(/vaccines-blood-biologics/exporting-cber-regulated-products/importing-cber-regulated-products-fda-interactions-other-agencies\)](#)

Importing CBER-Regulated Products: FDA Product Codes

The FDA Product Code, a seven character set of letters and numbers, helps FDA classify and review imports. Use the link below to learn more.

- [Product Codes For Importing CBER-Regulated Products \(/vaccines-blood-biologics/exporting-cber-regulated-products/fda-product-codes-importing-cber-regulated-products\)](#)

Importing CBER-Regulated Products: Entry Review

To learn more about FDA's Entry Review programs for imported products, click on the resource links provided below.

- [PREDICT \(/industry/import-systems/entry-screening-systems-and-tools\)](#)

Importing CBER-Regulated Products: Entry Refusals

To learn more about FDA's Entry Refusal programs for imported products, click on the resource links provided below.

- [OASIS Report For Import Refusals \(/vaccines-blood-biologics/compliance-actions-biologics/exporting-cber-regulated-products\)](/vaccines-blood-biologics/compliance-actions-biologics/exporting-cber-regulated-products)
- [Import Alerts \(/industry/actions-enforcement/import-alerts\)](/industry/actions-enforcement/import-alerts)

Importing CBER-Regulated Products: Clinical Laboratories and Basic Scientific Research

Do you want to import biological specimens (e.g., blood, tissue, DNA) for testing in a clinical laboratory or for basic scientific research? Use the link below to learn more.

- [Importing CBER-Regulated Products: Clinical Laboratories and Basic Scientific Research \(/vaccines-blood-biologics/exporting-cber-regulated-products/importing-cber-regulated-products-clinical-laboratories-and-basic-scientific-research\)](/vaccines-blood-biologics/exporting-cber-regulated-products/importing-cber-regulated-products-clinical-laboratories-and-basic-scientific-research)

Importing CBER-Regulated Products: Compliance and Regulatory Resources

Additional compliance and regulatory resources related to importing CBER-regulated products are provided on the page below.

- [Compliance Program Guidance Manual - 7342.007: Imported CBER-Related Products \(/media/85664/download\)](/media/85664/download)
- [Compliance Program Guidance Manual - 7342.007 Addendum: Imported Human Cells, Tissues, and Cellular and Tissue-based Products \(HCT/Ps\) \(/media/73960/download\)](/media/73960/download)
- [FDA's Regulatory Procedures Manual, Chapter 9 - Import Operations and Actions \(/media/71776/download\)](/media/71776/download)
- [Import and Export Guidance Documents \(/regulatory-information/search-fda-guidance-documents/import-and-export-guidance-documents\)](/regulatory-information/search-fda-guidance-documents/import-and-export-guidance-documents)

Resources For You

- [Office of Compliance and Biologics Quality \(OCBQ\) \(/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/office-compliance-and-biologics-quality-ocbq\)](/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/office-compliance-and-biologics-quality-ocbq)
- [Division of Case Management \(DCM\) \(/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/division-case-management-dcm\)](/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/division-case-management-dcm)

EXHIBIT 421

FDA Product Codes For Importing CBER-Regulated Products

Product Codes For Importing CBER-Regulated Products

What is an FDA Product Code?

The FDA Product Code, composed of a seven-character set of letters and numbers, helps FDA classify and review imports. An FDA Product Code has five parts:

- The first part is the “Industry Code.” The Industry Code for all CBER-regulated products is the number “57,” so the FDA Product Codes for all CBER-regulated products begin with “57”.
- The second part of the FDA Product Code is the “Class Code.” For CBER-regulated products, the Class Code is a letter that describes, generally, what grouping the product falls into, for example, is it a viral vaccine, blood derivative, or human musculoskeletal (tissue) product.
- The third part of the FDA Product Code is the “Subclass Code”. For CBER-regulated products the Subclass Code is a letter that describes how the product will be used in the United States, for example, for further manufacturing, in final dosage form for patient use, or sample for product testing/assessment or FDA/CBER lot release.
- The fourth part of the FDA product Code is the “Process Indicator Code.” CBER-regulated products do not have a Process Indicator Code so in a FDA Product Code for a CBER-regulated product, this part is filled in with a hyphen (-).
- The fifth part of the FDA Product Code is the “Specific Product Code.” The Specific Product Code for CBER-regulated products is two numbers that specifically describes the particular kind of product, e.g., rabies vaccine.

How do I use this page to find the FDA Product Code to use when importing a CBER-regulated product?

To assist those importing CBER-regulated products, CBER has created two searchable tables in PDF format that match most CBER-regulated products to their FDA Product Codes: one table is organized by Product Class (product categories) and the other table is organized alphabetically by manufacturer name (if one is listed). Please note that these two tables are intended as a resource, but are not intended to be a complete list of every CBER-regulated product. If you are the import filer, you should review the information printed on product labeling, invoice papers, or entry documents that are provided by the manufacturer, exporter, and/or importer to identify possible search terms. Such information will help you select the best possible search term(s) to

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use to find the correct FDA Product Code. The bullets below summarize the most commonly used product codes for CBER-regulated products. If you still have questions about what the product is, contact the manufacturer, exporter, and/or importer for more information.

- For most biological drugs and devices that are licensed, approved, or cleared by CBER, the tables identify the **Industry Code (57)**, the **Product Class (e.g., C [Viral Vaccines])**, the **Specific Product Code (e.g., 02)**, the **product (e.g., influenza virus vaccine)**, **trade name (e.g., Flumist)**, and the **sponsor's (usually the manufacturer's) name (e.g., Medimmune)**.
- For blood and blood component (human) products that are licensed by CBER, we have not provided any trade names or manufacturers. The tables identify the **Industry Code (57)**, the **Product Class (D [Blood and Blood Components])**, the **Specific Product Code (e.g., 44)**, and the **product description (e.g., Source Plasma (Human))**.
- For certain CBER regulated drugs used in conjunction with blood banking and/or transfusions, we have not provided any trade names or manufacturer. The tables identify the **Industry Code (57)**, the **Product Class (e.g., Y)**, and the **Specific Product Code (e.g., 03)** for the **product description [e.g., Plasma Volume Expander (Dextran, Hetastarch, Pentastarch)]**.
- For medical devices approved or cleared by CBER, the tables identify the **Industry Code (73, 75, 80, 81, 82, or 83)**, the **Product Class (e.g., M)**, and the **Specific Product Code (e.g., VZ)** for the **product description [e.g., System, Test, Home, HIV-1]**.
- For human cells, tissue, and cellular or tissue-based products (HCT/Ps), we have not provided any trade names or manufacturers unless the product is licensed by CBER. For most HCT/Ps, the tables identify the **Industry Code (57)**, the **Product Class (J through T)**, the **Specific Product Code**, and the **product description**.

What should I do if I can't find a FDA Product Code for the product?

First, make sure you have enough specific information about the product. If you have enough specific information and searched using each applicable search term (e.g., product description, trade name, and/or manufacturer), and still cannot find the exact product you are searching for listed, there are two possible reasons: the product may have been licensed by CBER since the table was last updated or the product may be investigational.

If you found another product with the same product description as yours, just not the one manufactured by your manufacturer, then you should use that Specific Product Code for your product as FDA Product Codes are not specific to a particular manufacturer. For example, all rabies vaccines have the same Specific Product Code, so if you are importing a newly licensed, finished dosage form rabies vaccine, your vaccine would have the same Specific Product Code as an already licensed rabies vaccine, 57CH-15.

If you did not find any other product with a similar or identical product description to your product, then the product is likely the first of its kind and has not yet been assigned a Specific Product Code. If that is the case, you should determine what class of product it is and then use the “Not Elsewhere Classified” Specific Product Code, which is always “99”. For example, if you were importing a finished dosage form of new kind of bacterial vaccine that has not yet been assigned a Specific Product Code, the FDA product Code would be 57HH-99. For new kinds of products, FDA will assigned a Specific Product Code the next time it updates the table, so you should check the list each time you file an import entry for the product.

How do I find the FDA Product Code for importing an investigational (IND or IDE) product?

These tables do not include any investigational products by trade name or manufacturer so you will need to search by product description. First, make sure you have specific information about what the product is and what product class it falls into. If your search finds another product with the same product description as yours, but not manufactured by your manufacturer, then you should use that Specific Product Code for your product as FDA Product Codes are not specific to a particular manufacturer. For example, all rabies vaccines, even a rabies vaccine under investigation, should use the same Specific Product Code, so if you are importing an investigational rabies vaccine in finished dosage form, your vaccine would have the same Specific Product Code as an already licensed rabies vaccine (57CH-15).

If you did not find any other product with a similar or identical product description to your product, then product is likely be the first of its kind and has not yet been assigned a Specific Product Code. If that is the case, then you should determine what class of product it is and, then use the “Not Elsewhere Classified” Specific Product Code, which is always “99”. For example, if you were importing a new kind of bacterial vaccine in finished dosage form that has not yet been assigned a Specific Product Code, the FDA product Code would be 57HH-99.

Are FDA Product Codes different from CBER Biological Product Deviation (BPD) codes?

Yes, FDA Product Codes are different from CBER BPD product codes. When importing a CBER-regulated product, you should use the FDA Product Codes provided in the searchable tables. Do not use CBER BPD product codes to import your CBER-regulated products because this may cause a delay in FDA’s processing of your import.

Product Codes: Related Resources

- Product Code Builder (<http://www.accessdata.fda.gov/SCRIPTS/ORA/PCB/PCB.HTM>)
- CBER Import Product Codes Sorted Alphabetically by Manufacturer Name (</media/77814/download>)

- [Case 2:20-cv-02470-WBS-JDP Document 13 Filed 12/29/20 Page 187 of 406](#)
CBER Import Product Codes Sorted by Product Class (/media/77818/download)
- General Instructions for Completing the Biological Product Deviation Report (BPDR) - Form FDA 3486 (/vaccines-blood-biologics/biological-product-deviations/general-instructions-completing-biological-product-deviation-report-bpdr-form-fda-3486)
- Medical Device Classification Product Codes - Guidance for Industry and Food and Drug Administration Staff (/media/82781/download)
- Download Product Code Classification Files (/medical-devices/classify-your-medical-device/download-product-code-classification-files)

Resources For You

- PREDICT (/industry/import-systems/entry-screening-systems-and-tools)

EXHIBIT 422

Entry Screening Systems and Tools

- How are import entries screened?
- What is PREDICT?
- Can I get my PREDICT score?
- What is the Import Entry Review System?

How are import entries screened?

Automated systems help FDA employees speed their review of import entries while targeting FDA resources on the riskiest products.

These systems electronically review your entry and flag risky products or entries that are incomplete or contain inaccurate data. If each line of an entry is properly submitted, a lower-risk product may be allowed to enter domestic commerce without further FDA review.

When a system flags an entry for having incomplete or inaccurate data, FDA reviewers may ask for more information or request physical exam or sampling. For more information on entry review, please visit the entry review page (</industry/entry-submission-process/entry-review>).

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What is PREDICT?

PREDICT (Predictive Risk-based Evaluation for Dynamic Import Compliance Targeting) is a risk-based analytics tool FDA uses to electronically screen all regulated shipments imported or offered for import into the United States of America.

PREDICT improves import screening and targeting to prevent entry of adulterated, misbranded, or otherwise violative goods and expedites the entry of non-violative goods. PREDICT uses automated data mining, pattern discovery, and automated queries of FDA databases to determine the potential risk of a shipment. It takes into consideration the inherent risk of a product and also information about the previous history of importers, manufacturers and shippers.

PREDICT presents shipments for further review based on its analytical results. Shipments with lower risk ranks and no other potential risks may be processed through FDA review more quickly than higher risk lines.

- [Download the PREDICT slide presentation \(/media/83668/download\)](/media/83668/download)

Can I get my PREDICT score?

Since PREDICT is a key investigative tool for FDA's import program, PREDICT scores are not released to customs brokers/entry filers, importers, or the general public. System security controls protect the confidentiality of any proprietary trade information involved in these electronic industry-to-government transactions.

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What is the Import Entry Review System?

The Import Entry Review System is an FDA application used internally to view entry or line documentation, make initial admissibility decisions, and create field work assignments. The application allows FDA employees to effectively process entries in an efficient manner.

The application has the added functionality to quickly request additional specific information from the customs broker/entry filer when the information transmitted in an entry or line is insufficient to make an admissibility decision. Customs brokers/entry filers have the ability to upload the requested documents through the Import Trade Auxiliary Communication System (ITACS) (</industry/import-systems/itacs>), which can be viewed in the Import Entry Review System. With the additional information, the entry reviewer can update the data and rescreen the entry line with the new data, as needed. The entry reviewer can then issue a May Proceed or setup a work assignment. Updating entry information with more accurate and complete data helps PREDICT's screening results for future shipments.

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EXHIBIT 423

China Office



CHINA OFFICE

Established in November 2008, the China Office serves as the lead for the FDA's on-site presence in China. The mission of the Beijing-based office is to help ensure the safety, quality, and effectiveness of medical products and food produced in China for export to the United States.

The China Offices seeks to accomplish these objectives by:

- Promoting international health policy harmonization and regulatory convergence;
- Engaging with regulatory authorities, industry, academia, multilateral organizations, non-governmental organizations, and other relevant institutions to increase the FDA's understanding of China's regulatory framework and processes and share information about FDA science-based regulations and requirements;
- Conducting risk-based, commodity-specific inspections to meet the requirements of FDA legislative mandates; and
- Monitoring and reporting on regulatory trends, conditions, and emerging public health events that have the potential to impact the safety of FDA-regulated goods produced in China intended for U.S. consumption.

Focus on China

China ranks second among countries that export drugs and biologics to the United States. China also ranks first among countries that import devices to the U.S. The top three medical device imports from China are surgical drapes, non-absorbable gauze and surgical gowns.

Drugs and medical devices are overseen by the National Medical Products Administration, which reports to the State Administration of Market Regulation. NMPA is responsible for conducting drug registration and approvals and provides guidance to provincial authorities and works with provincial level investigators to assign inspections of clinical trial facilities and international inspections.

Imported and exported food are regulated by the General Administration of China Customs. GACC is also responsible for registering companies that export. Registration includes annual inspections to ensure the registered companies that export regulated products to the U.S. are compliant with U.S. requirements.

- FDA's Global Efforts to Protect Patients and Consumers from Unsafe Products (</news-events/fda-voices-perspectives-fda-leadership-and-experts/fdas-global-efforts-protect-patients-and-consumers-unsafe-products>)
- FDA's Global Efforts to Protect Patients and Consumers from Unsafe Products - CHINESE VERSION (</news-events/fda-voices-perspectives-fda-leadership-and-experts/fdazaiquanqiufanweineibaohuhuanzhexiaofeizhemianshoubuanquanchanpindeqinhai>)

Online Resources in Chinese

- Cosmetics - Chinese (</media/94777/download>)
- Drugs – SBIA Resources in Chinese (</drugs/cder-small-business-industry-assistance-sbia/sbia-resources-chinese-zhongwenxinxi>)
- Radiological Health – How to Get Your Electronic Product on the U.S. Market - in Chinese (https://v.youku.com/v_show/id_XNDA5MDAwNzcwOA==.html?spm=a2hzp.8253869.0.0) [↗](http://www.fda.gov/about-fda/website-policies/website-disclaimer) (<http://www.fda.gov/about-fda/website-policies/website-disclaimer>)

International Arrangements

- MOU between FDA, HHS and Certification and Accreditation Administration of the People's Republic of China Regarding Registration of U.S. Food Manufacturers Exporting to China (</international-programs/cooperative-arrangements/memorandum-understanding-between-food-and-drug-administration-department-health-and-human-services>) (June 2017)
- Implementing Arrangement with CFDA (</media/90544/download>) (November 2014)
- Implementing Arrangement with AQSIQ (</media/90562/download>) (November 2014)

- Case 2:20-cv-02470-WBS-JDP Document 13 Filed 12/29/20 Page 194 of 406
- [MOU between U.S. FDA and China's Center for Food Safety Risk Assessment \(/media/87744/download\)](#) (December 2013)
 - [FDA - SFDA China, Agreement on the Safety of Drugs and Medical Devices \(/international-programs/cooperative-arrangements/fda-sfda-china-agreement-safety-drugs-and-medical-devices\)](#) (December 2007)
 - [FDA - AQSIQ China, Agreement on the Safety of Food and Feed \(/international-programs/cooperative-arrangements/fda-aqsiq-china-agreement-safety-food-and-feed\)](#) (December 2007)

Resources For You

- [Contact Information: OGPS Offices \(/about-fda/office-global-policy-and-strategy/office-global-policy-and-strategy-offices\)](#)
- [FDA Globalization \(/international-programs/fda-globalization\)](#)
- [Imports and Exports \(/international-programs/imports-and-exports\)](#)
- [International Arrangements \(/international-programs/international-arrangements\)](#)
- [News, Speeches and Publications \(/international-programs/international-programs-news-speeches-and-publications\)](#)
- [Partnerships and Collaboration \(/international-programs/partnerships-and-collaboration\)](#)
- [President's Emergency Plan for AIDS Relief \(PEPFAR\) \(/international-programs/presidents-emergency-plan-aids-relief-pepfar\)](#)

EXHIBIT 424

FDA's China Offices Focus on Product Safety

More than three years after a series of safety scares involving Chinese exports, officials in the Food and Drug Administration's China office say the Chinese are on their way to developing an infrastructure that better ensures product safety.



FDA also trains Chinese regulators and manufacturers on techniques that promote safety. At a workshop in Zhejiang province, FDA's Daniel Geffin showed Chinese regulators how he inspects equipment used to sterilize canned foods.

Christopher Hickey, Ph.D., who leads FDA's 13-person staff in China, says the agency has trained more than 1,600 manufacturers and regulators on United States safety standards over the past two years.

"The FDA's China office represents a new era in cooperation between the United States and China on the safety of food and medical products," he says.

Michael Kravchuk, who served as deputy director in Beijing until he retired in September, says FDA has built solid relationships with Chi-

nese regulators and exporters since officially opening an office in the capital city of Beijing in November 2008. After a two-year stint in China, Kravchuk says he realized that FDA and their Chinese counterparts are working toward a common goal.

"What I realize is we are all trying to ensure quality products are on the market—regardless of where they are sold. They want to learn how we (approach product safety) and use as many of our techniques as possible," says Kravchuk.

Toward that end, FDA held a hands-

on workshop in the cities of Hangzhou and Zhoushan in September. The event included a half-day of classroom instruction and three full days of demonstrations at two plants that process low-acid canned foods—like mushrooms, sardines, artichoke hearts, and tuna.

Hickey says the workshop began with an FDA expert giving Chinese regulators step-by-step instructions on how their U.S. counterparts inspect facilities and products, covering everything from machinery maintenance to container specifications and labeling requirements.

On the second day, the workshop moved to a manufacturing plant where congee, a breakfast food similar to oatmeal, is made and packaged. Workshop participants watched an FDA investigator perform a mock inspection at the facility.

Past Problems

Some consumers have been wary of products made in China since a series of safety scares in 2007 and 2008. That's when contaminants in the blood thinner Heparin, pet food, toothpaste, seafood, and other products caused illnesses and some deaths in the United States and other countries.

The Chinese also suffered the consequences of contaminated products. In 2008, about 300,000 Chinese babies were sickened and six died from infant formula contaminated with the toxic chemical melamine, which is used to make concrete and plastics.

Some manufacturers purposely added melamine to formula because the chemical made it appear that the product contained more protein than it actually had. The incident resulted in numerous criminal prosecutions, and China executed two people connected to the scandal.

“The FDA’s China office represents a new era in cooperation between the United States and China on the safety of food and medical products.”

Hickey says the incidents underscored the need for FDA staff permanently stationed in Beijing, Shanghai, and Guangzhou.

“Our primary duties have been to build relationships with FDA’s regulatory counterparts and to work with Chinese firms that want to export products to the United States,” he says.

The office also aims to increase the number of inspections at manufacturing plants; boost collaboration on product safety with other U.S. government agencies; and monitor events—like an earthquake or other natural disaster—that could affect the safety or availability of FDA-regulated products.

Kravchuk says the China team is making progress, greatly increasing the number of inspections and investigations.

And the team may be getting reinforcements. **In his budget proposal for the 2013 fiscal year, President Obama has requested funding that will enable FDA to:**

- **strengthen its inspection and analytical capabilities by increasing its presence in China by sixteen inspectors and by adding three U.S.-based China analysts.**
- **broaden the range of its inspections. In addition to inspecting Chinese facilities that manufacture food and medical products for export to the United States, FDA will inspect sites of clinical trials and conduct follow-up inspections**

to ensure that firms continue to produce and manufacture food and medical products under safe conditions, and that they apply sound production practices.

Global Marketplace

Roughly 24 million shipments of FDA-regulated products were imported into the U.S. in the 2011 fiscal year—from Oct. 1, 2010, through Sept. 30, 2011—from 228 foreign jurisdictions. This represents a four-fold increase over the past decade.

This steadily increasing volume of imports has made it more important than ever for FDA to build relationships with regulators and industry abroad, says Murray Lumpkin, M.D., FDA’s senior advisor and representative on global issues.

Lumpkin says the foreign outposts give FDA a way to address safety issues before products leave the country of origin.

“By helping other nations develop stronger regulatory systems and helping industry to understand our expectations and realize they will benefit from them, we’re also helping ourselves and keeping U.S. consumers safe,” Lumpkin says.

In addition to China, FDA now has staff stationed permanently in New Delhi and Mumbai, India; Brussels, Belgium; London; Parma, Italy; San Jose, Costa Rica; Santiago, Chile; Mexico City; Pretoria, South Africa; and Amman, Jordan.

What the foreign offices are doing is

a key part of FDA’s new global strategy, which focuses on building coalitions with regulators in other countries, according to the FDA report Pathway to Global Product Safety and Quality. Working through these partnerships, FDA aims to develop an information network through which regulators worldwide can share knowledge about criminal enterprises, as well as cutting-edge investigative tools.

Deborah Autor, J.D., FDA’s deputy commissioner for Global Regulatory Operations and Policy, says the safety and quality of U.S. food and medical products is facing serious challenges in the era of global supply chains, international trade, and the foreign sourcing and manufacture of regulated products.

“This paradigm change in how FDA regulates will improve the quality and safety of FDA-regulated products and benefit consumers and industry through streamlined regulation and additional assurance of quality and safety,” she says.

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EXHIBIT 425



US FDA Compliance in China and India

HOW TO PREPARE FOR A GMP INSPECTION

IN THIS PAPER:

- Understanding the Basics of the US FDA
- Preparing for a Successful GMP Inspection
- Train Operations, QA, Management teams and more with UL's GMP Inspection Readiness Courses





Preparing for a GMP Inspection by the US FDA

The United States and European Union have historically been the largest and most heavily regulated markets for medical products. At the same time, the majority of medical products – generic drugs and active pharmaceutical ingredients (APIs) – have been produced in China and India, with the US alone relying on those two countries for up to 80% of the generic drugs sold in the US.

To meet the dynamic growth of the US and EU markets, both China and India experienced extremely rapid growth of their medical product sectors, especially among small- and medium-sized companies new to the industry and untrained in the quality requirements imposed by regulatory agencies in the US and EU. As a result, US and EU regulators have focused particular attention on the quality of products produced in these two countries that are destined for the US and EU markets. Resulting inspections of pharmaceutical manufacturing facilities in China and India, particularly by the US Food and Drug Administration (FDA) produced numerous Warning Letters and even product bans that prohibited entry of products into the US.

At the same time the North American and European demand for medical products skyrocketed, the need for those products increased rapidly inside China and India. Today, China and India account for more than ¾ of all drugs consumed by the US and EU. To meet the quality and regulatory requirements of those countries and to meet the escalating medical needs of their own citizens, both countries have enacted stringent new laws focused on assuring product quality, not only for exported products but also for those destined for in-country use.

The governments also began an important initiative to promote their domestic medical product sectors, control healthcare costs and secure their reputations as leading members of the global Life Science industry. Recent announcements are indicative of this assertive commitment to quality by both governments, including:



China Food and Drug Administration (CFDA) will be conducting unannounced inspections of drug and medical device facilities beginning September 1, 2015.



India's Central Drugs Standards Control Organization (CDSCO) has been equally aggressive, announcing its plan to test at least 42,000 drugs, hire new inspectors and place stringent work demands on existing staff.



To assist in their efforts to establish regulations consistent with global quality standards, both countries have initiated significant efforts to build greater cooperation with foreign regulators including the US FDA. Cooperative agreements between the FDA and the two countries have centered on the FDA's assignment of FDA investigators in each country.

The US has already assigned a number of investigators to work in China and India in cooperation with their in-country counterparts, but difficulties with visa applications have prevented the full number of FDA investigators, both domestic and US-based, from taking on their roles. The FDA has indicated that they are working foreign counterparts to resolving the difficulties causing the cooperative arrangements to move forward.

Although the quality regulations of each country reflect their unique national needs and approaches, the US' Current Good Manufacturing Practices (cGMPs) for pharmaceuticals and Quality System Regulations (QSR) for medical devices serve as the basis for many laws being enacted and implemented in other countries. In addition, the FDA has been ordered by the US Congress to increase its inspection of both foreign and domestic pharmaceutical and medical device facilities. As a result, regulators in countries ranging from Canada to Brazil, China and India are showing interest in working with the FDA to assist members of their domestic companies to improve their cGMP compliance and assure the consistent quality of their medical products, not only for export but also for domestic use. An important step in that process is helping companies understand and respond effectively to an FDA inspection.



The FDA has been ordered by the US Congress to increase its inspection of both foreign and domestic pharmaceutical and medical device facilities. As a result, regulators in countries ranging from Canada to Brazil, China and India are showing interest in working with the FDA to assist members of their domestic companies to improve their cGMP compliance and assure the consistent quality of their medical products, not only for export but also for domestic use.



Understanding the Basics of an FDA Inspection

Many companies, especially small- and medium-sized companies in countries with rapidly growing medical sectors, may never have experienced an FDA inspection. As a result, they may be confused or mistaken about their responsibilities before, during and after an FDA inspection. Just as important, many firms are unaware of how to use the information they learn during an inspection to improve their own productivity, quality and compliance.

Problems during an FDA inspection can be caused by several factors. Cultural and language differences may lead to misunderstandings about what is requested or noted. The purpose of the inspection may not be fully understood by employees, leading to unnecessary concern or distrust. Questioning techniques common in the US may seem intrusive or demanding in non-US cultures. A lack of familiarity with GMP requirements or FDA priorities can lead to confusion among employees about how they should respond to investigators' questions or requests.

All of these potential issues can be addressed by focused, well-developed training that empowers employees to undergo the inspection process with confidence and accuracy. Training should address key topics including the following:

- Overview of the US Food and Drug Administration and its mission
- FDA enforcement and types of inspections
- How plant inspections are conducted
- What to do – and not do – during an FDA inspection
- Interacting with FDA inspectors
- Questioning techniques
- Communication skills
- Cultural and language differences



Knowing the Rules

FDA investigators are likely to examine many different elements of a company's facility, operations and records. According to FDA's website, the GMP Inspection Checklist includes the following:

1. Buildings and facilities
2. Equipment and utilities
3. Qualifications of personnel
4. Raw materials
5. Production processes and procedures
6. Laboratory controls
7. Records and documentation
8. Labeling
9. Complaint management documentation
10. Failure investigations and change control

The Importance of Documentation

A common oversight by plant managers is FDA's priority focus on documentation and records. In fact, the lack of "data integrity," in which documentation and records have been falsified or improperly stored, has been one of the most frequent complaint noted by FDA investigators during their inspections in 2015. FDA has said many times, "If you don't document it, you didn't do it." Accurate, up-to-date documentation is so critical that an investigator will always ask for documentation during an inspection.

What type of documentation does FDA expect? Records must be maintained for the following:

- Raw materials and primary packaging materials
- Disposition of rejected materials
- Manufacturing of batches, documenting the following:
 - Lots and quantities of materials used
 - Processing, handling, transferring, holding and filling
 - Sampling, controlling, adjusting and reworking
 - Code marks of batches and finished products
- Finished products, documenting the sampling, individual laboratory controls, test results and control status
- Qualification of personnel
- Training records
- Standardized Operating Procedures (SOPs)

It is essential that these documents and records be up-to-date and accurate. It is also essential that they be easily accessible to investigators and employees if necessary. More than one violation has occurred when an investigator asks an employee to locate a specific SOP – only to learn that the employee has no idea where the SOP is stored. This situation could easily trigger additional questions by the investigator. Does management maintain records in compliance with GMP requirements? Are necessary documents, such as SOPs, readily accessible to employees for reference? Are documents completed by the appropriate personnel, stored in secure locations and reviewed as required? If the answers are "No," the investigator is likely to consider the possibility of additional issues at the facility.

FDA inspections can be stressful but they serve important roles, not only for patients but also for the facility being inspected. Often, an inspector will identify a potential issue that can be corrected easily and quickly before it becomes a serious problem. An inspector may provide a facility manager with a suggestion that produces positive results. A positive inspection not only assures access of the company's products to the US market, but reinforces the company's commitment to quality – and to the ongoing education of its employees. Passing an FDA inspection is a point of pride for employees who work very hard to ensure that the rules are followed, the laws are respected and the patients are protected.



Preparing for a Successful Inspection

Many companies have received violations because of inadequate preparation for an FDA inspection. Even if a company's GMP system is in good condition, it is important to prepare your employees for interacting with an investigator. Much of this information, such as overviews of FDA GMP requirements and the purpose of an FDA inspection, can be provided through well-designed on-line courses. Beyond these tools, the best approach for teaching employees how to work with investigators during an inspection is hands-on practice through role-playing.

Forward-thinking companies often stage realistic mock-audits that use many of the typical questions included in an inspection. Effective mock audits often begin with a one-day pre-class for a sampling of employees using a format as realistic as possible. Often, this is best accomplished by using an outside auditor who can conduct the mock audit and assess employee performance to set a baseline of competency. A 2-3 day class would then follow with multiple case study role-plays to illustrate the potential missteps and correct responses to investigator questions. Employees would then be tested with pre and post results compared. Any deficiencies can be readily identified and addressed through remedial training.

Mock audits, like employee preparation, are viewed by some companies as unnecessary. Nothing could be further from the truth. As attention on GMP compliance intensifies around the world and national regulators cooperate to standardize their information-sharing, GMP regulations and investigation procedures, companies will be held to a higher standard for product quality and regulatory compliance. Employee education is the best investment a company can make in achieving that standard of excellence and protecting both its reputation and market access.



Conclusion

Countries around the world are working hard to ensure a safe and effective drug supply. One of the most important tools in achieving that objective is consistent, globally accepted quality regulations. That consistent regulatory standard has not yet been achieved although it is under development by cooperative groups of national regulators from around the world. Until that regulatory standard is adopted, many countries will rely on the FDA's GMPs as the basis for their own regulations. Equally important, in addition to conducting their own global investigations of pharmaceutical and medical device facilities, the FDA will continue to work with their counterparts around the world to assure product quality, regulatory compliance and access to the large US market.

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For more than 30 years, UL has served corporate and government customers in the Life Science, Health Care, Energy and Industrial sectors. Our global quality and compliance management approach integrates ComplianceWire, training content and advisory services, enabling clients to align learning strategies with their quality and compliance objectives.

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EXHIBIT 426



MARKET NEWS

SEPTEMBER 28, 2018 / 11:34 AM / A YEAR AGO

CORRECTED-(OFFICIAL)-UPDATE 3-FDA halts imports from China's Huahai Chuannan plant

Alexandra Harney, Michael Erman



(FDA spokesman corrects information to show import ban only applies to a single Huahai factory. FDA's original statement on its website remains unchanged)

By Alexandra Harney and Michael Erman

SHANGHAI/NEW YORK, Sept 28 (Reuters) - The U.S. Food and Drug Administration said on Friday it will no longer allow imports of drug ingredients or medicines made with ingredients produced at China's Zhejiang Huahai Pharmaceuticals Chuannan factory, after a recall of one of its drugs that contained a probable carcinogen.

The Chinese bulk manufacturer of the high blood pressure treatment valsartan recalled the product from consumers in the United States in July because an impurity linked to cancer had been detected.

European authorities also said on Friday that they had found that Huahai did not comply with good manufacturing practices and that the company's factory in the Chuannan province, was no longer authorized to produce valsartan.

The European Medicines Agency said it was considering further action for other substances produced at the site.

On Sept. 28, the FDA posted a statement on its website that said: “The import alert stops all API made by ZHP and finished drug products made using ZHP’s API from legally entering the United States.”

On Oct. 10, FDA spokesman Jeremy Kahn said that the statement was incorrect, and the import ban only applies to the Chuannan factory. As of Oct. 10, the incorrect statement was still on the FDA’s website.

The FDA said it was halting imports from the plant after it found major manufacturing process issues during its inspection of Huahai’s plant. The agency said the freeze on the imports would remain in place until the Chinese manufacturer determines how the impurities were introduced and improves its quality control systems.

Huahai’s English-language website suggests that the company makes more than 50 drugs, active pharmaceutical ingredients and intermediate products used in a variety of medicines to treat high blood pressure, depression and other conditions. It was not immediately clear how many were from the Chuannan plant.

FDA spokesman Jeremy Kahn said the agency had no concern about additional drug shortages due to the import ban at this time.

In a heavily-redacted inspection report to Huahai posted on the FDA’s website on Sept. 20, the health regulator pointed out a range of serious problems, including with the company’s quality management system, how it evaluates the impact of changes to its manufacturing process, and its handling of products with impurities.

In all, the Aug. 3 report listed 11 problems based on an inspection by two investigators sent to the factory for about two weeks in late July and early August.

Huahai’s public relations department could not be reached for comment.

The company, which is based in eastern China’s Zhejiang province and makes bulk ingredients for drugmakers, told customers in late June that it had found N-nitrosodimethylamine, or NDMA, which is classified as a probable human carcinogen, in its valsartan.

In September, after a global recall of valsartan products, the FDA and the European Medicines Agency announced that another known carcinogen called N-Nitrosodiethylamine, or NDEA, had also been found in valsartan made by Huahai and by India's Torrent Pharmaceuticals, another manufacturer.

The FDA often redacts product-specific information in inspection reports, and the report released last week did not mention valsartan, NDMA or NDEA. However, the FDA wrote that Huahai's "change control system to evaluate all changes that may affect the production and control of intermediates or Active Pharmaceutical Ingredients (APIs) is not adequate."

Regulators and industry consultants say the NDMA was most likely introduced when Huahai changed the way it made valsartan in 2012. The FDA's Kahn told Reuters in an email in August that the change in valsartan manufacturing that was believed to have led to the introduction of NDMA occurred around December 2013.

Reporting by Michael Erman in New York and Alexandra Harney in Shanghai, Additional reporting by Ben Hirschler in London and the Shanghai newsroom; editing by Chizu Nomiyama and Bill Berkrot
Our Standards: The Thomson Reuters Trust Principles.

EXHIBIT 427

TESTIMONY**Exploring the Growing U.S. Reliance on China's Biotech and Pharmaceutical Products****JULY 31, 2019****Testimony of**

Mark Abdo

Associate Commissioner for Global Policy and Strategy - Food and Drug Administration

Before theU.S. - China Economic and Security Review Commission (<https://www.uscc.gov/>)**Introduction**

Chairman Bartholomew, Vice Chairman Cleveland, and distinguished Members of the Commission, thank you for the opportunity to submit written testimony to the Commission. We appreciate the Commission's thoughtful consideration of the national security implications and the opportunities that arise from the trade of products regulated by the Food and Drug Administration (FDA) between the United States and the People's Republic of China.

FDA is responsible for protecting public health by ensuring the safety, effectiveness, quality, and security of human and veterinary drugs, vaccines, and other biological products for human use, and medical devices. The Agency also is responsible for the safety and security of our nation's food supply, cosmetics, dietary supplements, and products that emit electronic radiation; and for regulating tobacco products. Imported products generally must meet the same standards as those produced domestically.

Sweeping economic and technological changes have revolutionized international trade over the last several decades creating a truly global marketplace for goods and services. Many of the challenges associated with globalization are observed in China and mirror the challenges we see in other countries. FDA has engaged in a variety of efforts to help address these challenges.

For example, in China, FDA conducts risk-based regulatory inspectional activities; capacity-building and confidence-building activities with Chinese regulatory authorities; and focused engagements with key in-country stakeholders, including regulatory counterparts, regulated industry, U.S. government agencies, multilateral organizations and academia. FDA monitors

and reports regulatory trends, conditions, and emerging public health events/incidents that have the potential to impact the safety of FDA-regulated products produced in China intended for U.S. consumption. FDA also coordinates with other agencies to support U.S. interests, including national security interests.

Scope of medical product & supplement manufacturing taking place in China

As of 2018, China ranks second among countries that export drugs and biologics to the United States by import line (13.4 percent). An import line is a distinct regulated product within a shipment through customs. A single shipment may include multiple lines of varying sizes. Approximately 83 percent of these Chinese import lines for drugs and biologics were human finished dosage forms (finished drugs) and 7.5 percent were active pharmaceutical ingredients (APIs), the remaining 10 percent were animal drugs and medicated animal feed. In addition to these import lines, APIs manufactured by China also come to the U.S. as part of finished drug products manufactured in other countries, for example, India. Therefore, the percentage of APIs produced by China for the United States marketplace is likely underrepresented by our numbers as China is a major supplier of APIs for other countries. It is important to note, FDA's Drug Shortages Staff continuously monitor drug supply chains for potential shortage issues, including for drugs and APIs sourced from China. With respect to registered foreign human drug manufacturing facilities that are subject to CGMP (current good manufacturing practices) surveillance inspections, approximately 22 percent of the API manufacturing facilities and 14 percent of finished dosage form manufacturing facilities are located in China.

China provides 39.3 percent of the medical device import lines, and ranks first among countries that export devices to the United States by import line. It is imperative FDA continues to ensure the quality and availability of FDA regulated medical products.

Risk-based Oversight

The Agency electronically screens imports using an automated risk-based system to determine if shipments meet identified criteria for physical examination or other review. To enhance our ability to target high-risk products, FDA developed the Predictive Risk-based Evaluation for Dynamic Import Compliance Targeting application, or PREDICT. This is a sophisticated screening application that uses information from many sources—such as intrinsic product risks, past inspection results, intelligence data, and even information about threats such as extreme weather that could spoil a shipment—to provide FDA entry reviewers with risk scores on every import line.

FDA maintains global vigilance of manufacturing facilities through a risk-based inspection strategy to focus inspectional resources on higher risk facilities and works closely with our international regulatory partners in Europe to avoid duplication of inspections. Among other

things, the number of inspections in any given country reflects our risk-based prioritization of our inspections and improvements in our targeting; our increasing ability to leverage inspectional work done by trusted partners, especially in Europe; and a higher number of foreign pre-approval inspections.

Our policy for prioritizing drug manufacturing surveillance inspections is based on factors such as a facility's compliance history, recall trends, time since last inspection, inherent risks associated with the drug being manufactured, processing complexity, and other factors, which are all carefully weighed and considered. FDA is maintaining global vigilance by concentrating inspections on higher risk facilities, both for routine surveillance and in evaluating new drug applications. As global compliance trends change – and standards in some sectors improve – we should expect to see an evolution in our inspection priorities.

In regard to food products, FDA recently published its Strategy for the Safety of Imported Food. FDA applies the same U.S. food safety requirements to all food consumed in the United States, regardless of whether the facility or farm that produces the food is located within the United States or half way across the globe. Because FDA's enforcement tools abroad differ from the Agency's tools domestically, Congress directed FDA to develop certain programs to ensure the safety of imported food. As with domestic oversight, FDA's strategy for overseeing the safety of imported food is to maximize agency public health impact by aligning resource allocation to risk level, tailoring the use of new and existing regulatory tools accordingly. FDA will work to optimize oversight of foreign firms and the portion of imported foods that receives FDA oversight, including leveraging the work of partners with strong regulatory systems or responsible parties in the food supply chain. However, based on our experience, the process of negotiating arrangements is time- and resource-intensive, requiring funding over a long period, and could potentially detract from resources for other inspection approaches and activities.

In addition, FDA also recently published the Plant and Animal Biotechnology Innovation Action Plan to implement and clarify risk-based policies with the goals of ensuring that developers know what they need to do to efficiently bring a plant or animal biotechnology product to market, and that consumers and the public understand how FDA's regulatory system helps ensure the safety of such products. FDA has already evaluated a genetically engineered crop (a rice variety) developed in China. The Agency anticipates other Chinese developers will engage FDA as part of the Agency's voluntary consultation process for biotechnology-derived plant varieties. FDA is well prepared to support a global marketplace focused on innovation in plant and animal biotechnology and to advance the Agency's public health mission.

On-going challenges

Substantial improvements have been made in the inventory of registered pharmaceutical manufacturing firms in recent years. However, there are remaining gaps in this inventory that should be addressed to ensure visibility of all Chinese manufacturers that produce drugs or

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active pharmaceutical ingredients of drugs that are ultimately shipped to the United States. The President's FY2020 budget includes a legislative proposal to address information gaps relating to foreign drug manufacturers. This full information on the drug supply chain, while available domestically, can be enhanced for foreign sites. Closing this gap will help ensure FDA has the information needed for effective shortage mitigation, provide more complete data for risk-based surveillance inspection planning, and help ensure prompt detection and intervention of unsafe drugs in the marketplace.

Coordination with other agencies

In addition to these efforts, FDA is also actively engaged in a number of collaborative efforts with other agencies. In general, for complicated issues that involve trade or scientific dispute, interagency (e.g., the Department of Homeland Security, the Office of the United States Trade Representative, the Department of Agriculture, and others as appropriate) coordination is pivotal in ensuring FDA's overall mission is advanced. While FDA depends on the major national security agencies and the Department of Health and Human Services' (HHS) broad national security efforts to protect our national security interests, FDA and the regulated industry at large have a vested interest in preventing unacceptable breaches of trust and confidentiality that can undermine the integrity of U.S. biomedical innovation and research. To that end, FDA has safeguards to prevent diversion of intellectual property in product applications to other entities, including other countries, and restricts the sharing of confidential information by FDA staff with others, including in some instances with foreign entities.

Foreign acquisitions, or investments by a foreign entity involving over 10 percent, of a U.S. company triggers a review of the transaction by the Committee on Foreign Investment in the United States (CFIUS) under 31 CFR § 800-806. While normally voluntary in nature, notices to CFIUS may be mandated (or even unilaterally filed by CFIUS) in the event a transaction not submitted to CFIUS but involving national security risk is identified. FDA provides input to the larger HHS response to CFIUS cases involving the Healthcare and Public Health, and Food and Agriculture, critical infrastructure sectors where FDA has a potential interest involved or may be impacted by the transaction. This includes, but is not limited to, acquisitions by Chinese entities. When applicable, CFIUS has the ability to refer the matter to the President, certify to Congress that the transaction does not present an unmitigated national security concern, or negotiate a risk mitigation agreement with the company that can require up to and including the complete, total, and permanent divestiture of the U.S. portions of the acquired or invested company. In the event of a mitigation agreement, CFIUS can also institute a mitigation monitoring agreement wherein compliance with the mitigation agreement is monitored by involved Federal agencies, generally with severe monetary damages imposed in the event of a breach of the mitigation agreement. CFIUS cases are not limited to any particular sector or industry; any transaction potentially involving national security risk and foreign control can be pulled into the process.

CFIUS controls are sufficient to address merger and acquisition risks when identified and applicable; they cannot cover transactions or company creation efforts that fall outside CFIUS' purview.

For dietary supplements, there are no formal agreements. For biotechnology, there are no formal agreements. However, the U.S. and China have a Biotechnology Working Group and a Technical Working Group that foster bilateral dialogue and are focused on trade and information sharing.

Another item of note is the Department of Defense's (DoD) access to FDA's Compliance Status Information System (COMSTAT) to evaluate a facility's ability to produce medical products in accordance with FDA's regulatory requirements. COMSTAT displays the status of medical product firm profiles using profile class codes based on categories of products produced by a firm. Profile class codes and statuses indicating if they are in accordance with FDA's regulatory requirements are determined during FDA inspections. Although COMSTAT requires an account for access and DoD personnel have accounts, COMSTAT does not have a reporting mechanism to determine when DoD accesses the system or what records are viewed.

Conclusion

Thank you for giving FDA the opportunity to describe the Agency's efforts to address the challenges of our globalized marketplace and to discuss our work in China. FDA is implementing a comprehensive strategy to enhance the safety of imported products and to establish an effective global safety net.

Our priorities in China are consistent with our priorities everywhere. The best way to ensure food safety and the integrity of medical products is to make sure firms consistently follow appropriate processes for safeguarding safety and quality in production. Manufacturers are best situated to ensure these processes, and regulatory bodies should hold companies accountable for lapses in the production process and not simply rely on testing after the fact to detect flaws.

Inspections and testing play an important role in that process, but they need to be used as part of a larger system that emphasizes a systematic, proactive, preventive approach to strengthen the production of safe food and safe and effective medical products produced in China for export to the United States. And in our globalized world, it is increasingly important that regulatory partners work together to ensure the safety of products as they move across borders. While many future challenges remain as we engage Chinese regulators and industry on these key issues, we will continue to expand on successes attained in recent years.


 More Congressional
Testimonies (/news-events/congressional-testimony)

EXHIBIT 428

US FDA Inspections in China: An Analysis of Form 483s from 2015

Posted 10 February 2016 | By [Zachary Brennan](#)

As the US becomes increasingly dependent on Chinese and Indian active



pharmaceutical ingredient (API) and drug manufacturing, a deeper look into the inspection reports from the US Food and Drug Administration (FDA) in China reveals a number of question marks that parallel the same sort of issues found in Form 483s issued after inspections in India.

A *Focus* review (thanks to use of the Freedom of Information Act (FOIA)) of eight FDA Form 483s for Chinese manufacturers in 2015 paralleled some of the same data integrity deficiencies listed in the 50 Form 483s *Focus* reviewed back in November.

Currently, 41 pharmaceutical manufacturing sites in China and five in Hong Kong are included on FDA's import alert list, which is a list of all the sites banned from shipping products to the US. China's Zhejiang Hisoar Pharmaceutical is the most recent addition (from 20 January) for good manufacturing practice deficiencies.

By comparison, there are 42 sites under import alert from India, though FDA notes that some of those facilities listed are only banned for certain products and not the entire site.

Unlike in India, it's become increasingly difficult for FDA to obtain visas for its inspectors in China and in 2014, FDA closed two of its offices in Shanghai and Guangzhou, China, and consolidated operations at its Beijing location.

As of 18 December, FDA told *Focus* the agency has 17 employees assigned to the Beijing office, including five new hires who have yet to deploy to China (only three of those five will work on drug-related issues). Six employees from the FDA's China office were scheduled to begin conducting inspections from January to March, FDA said, which would be a slight boost from a few months prior when FDA only had two inspectors overseeing the roughly 700 manufacturing facilities there.

Similarly in India, FDA has plans to double the number of its inspectors there – from about nine to 19, though even if that number is actualized the agency would still be tasked with inspecting more than 500 manufacturing sites exporting products to the US.

Concerns over how FDA can adequately track the drug and API supply chain is starting to worry Congress. In December, the House Committee on Energy & Commerce sent a letter to the US Government Accountability Office calling on the oversight office to investigate whether FDA can adequately monitor the manufacturers in India and China, which in the past have had a history of counterfeiting, adulteration, substandard manufacturing and data falsification.

And though both China and India have domestic pharmaceutical inspectors and regulators (China FDA and Central Drugs Standards Control Organization, respectively), the standards used for these inspections are not yet on par with FDA's.

Chinese Form 483s

Through the use of FOIA (Form 483s are not generally released publicly by FDA), *Focus* found that more than 80 Form 483s were issued to Chinese manufacturers in 2015 after 132 inspections by FDA staff. The 132 inspections is only 15 more than the number conducted in 2014, but up significantly from the paltry 19 inspections conducted in 2007, according to FDA.

By comparison, FDA conducted 203 inspections at Indian manufacturing sites in 2015, up significantly from the 114 inspections conducted in 2014, and the 66 inspections from 2007.

Unfortunately, because of delays in the FOIA system and the cost of obtaining the documents, *Focus* was only able to obtain eight of the 80 documents for review.

Observations

Zhejiang Hisoar Pharmaceutical Co., the most recent addition to FDA's import alert list, was cited in a 483 by the agency after a three day inspection in August with seven observations. Hisoar claims to manufacture four products for the US, four for the EU and three for Japan, and lists Pfizer, BASF, Sanofi and Novartis among its partners.

Among the most egregious observations are numerous data manipulation findings, in addition to the company's failure to locate a logbook documenting the manufacture of APIs, and individual equipment logs not including entries for uses of each piece of manufacturing equipment.

In addition, "sample raw data file names are altered in an attempt to hide deleted data files," FDA inspectors said, noting the history of raw data modifications could not be tracked. Case 2:20-cv-02470-WBS-JDP Document 13 Filed 12/29/20 Page 220 of 406

At **Chongqing Kangle Pharmaceutical Co.**'s manufacturing site in Chongqing, which the company claims is used mostly for producing anti-malarial APIs and is not included on FDA's import alert list, inspectors found that a fan blows outside air onto raw ingredients used for API manufacturing, which poses contamination issues. FDA also found "significant rust and flaking paint" in a wet chemistry quality control laboratory.

Another facility that's allowed to ship products to the US and claims to have customers in about 50 countries -- **Qilu TianhePharmaceutical**'s manufacturing site in Jinan, China -- was inspected by FDA twice back in May and June, with 15 observations cited.

During an inspection of the company's quality control lab, FDA found partially incomplete or "otherwise undesirable" gas chromatography results were moved into an auxiliary folder entitled "test." The large number of sample sets within this test folder "containing TNTC [too numerous to count] unreported sample injection results for finished APIs prevented our comprehensive review of the results," FDA said. These types of sample "tests" were also uncovered at Indian manufacturing sites last year.

FDA also found that the Qilu site failed to follow batch manufacturing instructions and lab control procedures, in addition to questions about the facility's design:

OBSERVATION 7

Facility design was found to be inadequate

Specifically, during our inspection of ongoing visual inspection activities for (b) (4) injection ((b) (4) / (4) ml vials) batch # (b) (4) on 05/28/15, we observed one operator stationed at the backside of the vial capping station within the grade B environment. According to your Workshop QA Lead, the operator crawled under the vial transport line in order to reach his operating station. Our visual examination found that due to the height of the vial transport line ((b) (4)) it would be considered unlikely that the operator could cross under the vial transport line without using his hands on the ground for stabilization.

FDA inspections at sites for Hangzhou Huadong Medicine Group Kangrun Pharmaceutical Co., Ferring Pharmaceutical, and Shanghai Desano Chemical Pharmaceutical Co. also revealed data integrity questions, particularly around the control of computer and software systems, incomplete lab records of instrumentation calibration and sampling plans not based on scientific principles.

At Shanghai Desano -- which is part of a group of five member companies making about 20 APIs and 15 finished products, mostly anti-virals, antibiotics and anti-malarials -- FDA inspected one site last May and "noted the presence of what appear to be too numerous to count instances of unreported incidents required to be reported as manufacturing deviations."

The eight 483s also include one for Pfizer's Dalian, China-based manufacturing site (though the 483 for another Pfizer manufacturing site in Fuyang City was not released by FDA to *Focus*). At the Dalian site, FDA officials found "the presence of uncontrolled records for a number of manufacturing records" which were supposed to be part of the company's document control program. Pfizer told Bloomberg in October that it addressed the issues **3**

EXHIBIT 429

COUNCIL *on*
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**U.S. Dependence on
Pharmaceutical Products
From China**

Blog Post *by* Yanzhong Huang

August 14, 2019



A technician works at a product line of the Inactivated H1N1 Influenza Vaccine in Sinovac Biotech Ltd., a Chinese vaccine making company, in Beijing, September 3, 2009. REUTERS/Jason Lee (CHINA BUSINESS HEALTH)

Last month, the U.S.-China Economic and Security Review Commission held a hearing on the United States' growing reliance on China's pharmaceutical products. The topic reminded me of a spirited discussion described in Bob Woodward's book, *Fear: Trump in the White House*. In the discussion, Gary Cohn, then chief economic advisor to President Trump, argued against a trade war with China by invoking a Department of Commerce study that found that 97 percent of all antibiotics in the United States came from China. "If you're the Chinese and you want to really just destroy us, just stop sending us antibiotics," he said.

Cohn's words highlight a security concern associated with pharmaceuticals from China. As Rosemary Gibson noted in her testimony, centralization of the global supply chain of medicines in a single country makes it vulnerable to interruption, "whether by mistake or design." If we are dependent on China for thousands of ingredients and raw materials to make our medicine, China could use this dependence as a weapon against us. While the Department of Defense only purchases a small quantity of finished pharmaceuticals from China, about 80 percent of the active pharmaceutical ingredients (APIs) used to make drugs in the United States are said to come from China and other countries like India. For example, the chemical starting material used to make doxycycline, the recommended treatment for anthrax exposure, comes from China. When an influential Chinese economist earlier this year suggested that Beijing curb its exports of raw materials for vitamins and antibiotics as a countermeasure in the trade war with the United States, the worries surrounding our API dependence to China seemed to be vindicated. Concern about a disruption in the supply chain could explain why the tariffs on Chinese products proposed by the United States Trade Representative in May 2019, worth approximately \$300 billion, excludes "pharmaceuticals, certain pharmaceutical inputs, and select medical goods."

While the potential exposure to raw material supply disruptions drives part of our fear, concern about the safety and efficacy of Chinese-made pharmaceuticals is another component. In the summer of 2018, one of China's largest domestic vaccine makers sold at least 250,000 substandard doses of vaccine for diphtheria, tetanus, and whooping cough. It was the latest in a slew of scandals caused by poor quality drug products made in China over the last decade. In 2008, the contamination of a raw ingredient imported from China and used to make heparin, a blood-thinning drug, was associated with at least eighty-one deaths the United States. According to an investigative journalist, fraud and manipulation of quality data is still endemic in Chinese pharmaceutical firms.

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In order to address the growing security and safety concerns about Chinese-made pharmaceuticals, some suggest that the United States switch to India as an alternative API supplier. However, doing so would be no different from rearranging the deck chairs on the Titanic. It is true that many Indian pharmaceutical firms are leading API manufacturers but India depends on China for sourcing nearly three quarters of APIs in generic drug formulations. The disruption in the supply chain notwithstanding, switching to India for the supply of APIs would only make the drugs sold in the United States more expensive: APIs and chemical intermediates from China are 35 to 40 percent cheaper than Indian ones. Moreover, India has its own drug safety problems as well. In 2013, a generic drug maker in India pled guilty to drug safety charges, which included shipping batches of adulterated drugs, having incomplete testing records, and inadequate programs to assess drug quality. According to a former executive of the company, this was only a fraction of the safety issues the Food and Drug Administration (FDA) could identify in overseas plants.

Moreover, we could have overestimated our dependence on Chinese-made pharmaceutical products. As of 2018, China claimed 13.4 percent of all import lines—defined as distinct regulated products within a shipment through customs—among

countries that export drugs and biologics to the United States. Of these import lines for drugs and biologics, about 83 percent were finished drugs, and only 7.5 percent were APIs. We certainly underestimate the share of APIs from China given that Chinese-made APIs can come to the United States as part of the finished drug products from other countries like India. However, the lack of a reliable API registry makes it difficult to estimate the true market share of Chinese-made APIs.

In addition, when highlighting our dependence on Chinese-made pharmaceuticals, we could overlook the other side of the coin: China needs finished drugs made in the United States. China is facing a crisis of non-communicable diseases, including cancer, cardiovascular diseases, and diabetes. It is estimated that between 2002 and 2016, new cancer cases in China increased by more than 55 percent, from 2.19 million to 3.8 million. A majority of Chinese cancer patients, however, lack access to the most effective drugs. Partly because of this, cancer survival rate in China is less than half of the United States. Under the performance-based legitimacy in contemporary China, the government must justify its rule by continuously delivering public goods and services, like better healthcare, to meet people's wants. In an increasingly state-dominated political system, the link between performance and legitimacy becomes so tight that failure to deliver such goods could endanger the system itself. In the meantime, with the rapid improvement of material living standards, Chinese people are increasingly valuing things beyond basic earnings, such as good health. As President Xi Jinping stated in the 19th Party Congress, the "principal contradiction" in the society is "the contradiction between unbalanced and inadequate development and the people's ever-growing needs for a better life." In fact, in 2018, the government cut the import value-added tax on cancer drugs from 17 percent to 3 percent and reduced import tariffs on all common drugs and cancer drugs to zero. Essentially, regime legitimacy requires the state to deliver the most effective drugs, which are often patented and provided exclusively by multinational pharmaceutical companies. In May 2019, China unveiled a list of imported U.S. medical products to impose punitive tariffs upon. The list includes

commonly used drugs such as insulin, ibuprofen, as well as medical devices such as ultrasonic diagnostic apparatuses and endoscopes, which Chinese firms can manufacture themselves. Nevertheless, the list did not include anti-cancer drugs and other patented ones.

The same legitimacy concern also led the Chinese government to introduce incentives to improve the quality of its pharmaceutical products. In 2016, China's FDA introduced the Generic Consistency Evaluation (GCE), which required generic drugs approved for production prior to 2008 to pass the GCE in order to gain "equivalence" to branded drugs in terms of safety and efficacy. Failure to pass the GCE in a timely manner will lead to the revocation of registration licenses or ineligibility for government tendering. Since generic drugs approved before 2008 are prone to low quality problems, a significant number of drugs that have failed to pass GCE are expected to exit the public market. The measure will help weed out over half of the nation's 2,900 or so small, and often low-quality, domestic drug makers. Since early this year, nearly 20 pharmaceutical firms have either exited the industry or been reorganized.

So what does all this mean for a response from the United States? Before making any major decisions on this issue, it is important to collect as much information as possible for a full assessment of the risks we face. We should also nurture the development of alternative sources and capabilities to make critically essential drugs in the United States. At present, instead of looking at the issue from a national security perspective, the best approach is to work with China to ensure the safety and efficacy of their pharmaceutical products. As I argued in my testimony to the U.S.-China Commission, this involves expanding the FDA's inspection activities in China, helping to beef up the regulatory capacities of China's National Medical Products Administration in the drug development and review process, and making sure Chinese firms consistently follow the

appropriate process for safeguarding quality in production. Lastly, the U.S.-China Social and Cultural Dialogue, the only high-level forum to discuss U.S.-China cooperation after 2017, should be reopened as an institutional venue to discuss these issues.


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EXHIBIT 430



FDA Updates Plan for Mfg Inspections in China in Wake of Coronavirus Outbreak

February 27, 2020

The US Food and Drug Administration (FDA) is providing updated and more detailed information about the status of FDA inspections in China and the agency's oversight of imported products from China, which have been impacted by the novel coronavirus (COVID-19) outbreak. Earlier this month, the FDA outlined its supply-chain surveillance plan in the wake of the coronavirus (COVID-19) outbreak in China, including the steps the agency is taking to mitigate potential shortages and supply disruptions of products from China and how the agency is handling inspections of manufacturing facilities in China.

"While we are not able to conduct inspections in China right now, this is not hindering our efforts to monitor medical products and food safety," said FDA Commissioner Stephen M. Hahn and FDA Associate Commissioner for Regulatory Affairs Judith A. McMeekin in a joint statement issued February 25, 2020. "We have additional tools we are utilizing to monitor the safety of products from China, and in the meantime, we continue monitoring the global drug supply chain by prioritizing risk-based inspections in other parts of the world. The FDA is not currently conducting inspections in China in response to the US Department of State's Travel Advisory to not travel to China due to the novel coronavirus outbreak. We will continue to closely monitor the situation in China so that, when the travel advisory is changed, we will be prepared to resume routine inspections as soon as feasible."

The FDA says it is using other tools to help complement its inspections, including import screening, examinations, sampling, and import alerts, relying

on a firm's previous compliance history, and using information from foreign governments as part of mutual recognition agreements.

In response to the COVID-19 outbreak, the FDA says it will use, where appropriate, its authority to request records from firms "in advance or in lieu of" drug-surveillance inspections in China. The Federal Food, Drug, and Cosmetic Act, as amended by the FDA Safety and Innovation Act (FDASIA) of 2012, gives the FDA authority to request records "in advance of or in lieu of" on-site drug inspections. Congress enacted this provision to improve the effectiveness and efficiency of inspections, given the increasing globalization of drug production. Along with other FDASIA provisions, this inspection-record request authority was viewed as a way to "level the playing field" between foreign and domestic drug inspections by allowing the FDA to review records ahead of time and take a more risk-based approach to conducting both domestic and foreign inspections.

"These records will help the agency when we resume drug inspections in China. By applying the use of paper records in our risk-based inspection framework, we can prioritize our early inspections on those deemed most needed, based on the records," according to FDA's February 25 statement. "By doing so, we hope to rapidly assess what could become a backlog number of on-the-ground surveillance inspections this fiscal year if travel restrictions persist."

In addition to records requests, the FDA says it will continue working with US Customs and Border Protection to target products intended for importation into the US that violate applicable legal requirements for FDA-regulated products, which may come from a variety of sources, such as first-time importers unfamiliar with regulatory requirements or repeat offenders. The FDA has the ability, through its risk-based import screening tool (PREDICT), to focus its examinations and sample collections based on heightened concerns of specific products being entered into US commerce. The agency says the PREDICT screening continues to adjust risk scores as necessary throughout the COVID-19 outbreak. "We are keeping a close eye out for indications of port shopping or cargo diversion and will continue our oversight of shipments through potentially higher-risk venues such as International Mail Facilities," said the FDA in its statement. "We can refuse admission of products that fail sample testing or may violate other applicable legal requirements."

The FDA said in its statement that there is no evidence to support transmission of COVID-19 associated with imported goods and that there have not been any cases of COVID-19 in the US associated with imported goods.

Source: [US Food and Drug Administration](#)



The essential resource on pharmaceutical manufacturing, sourcing/procurement, and supply management provided by the ***Drug, Chemical & Associated Technologies Association (DCAT)*** a not-for-profit global business development association.

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EXHIBIT 431

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HEALTH

CONGRESS, GRAPPLING WITH TAINTED CHINESE DRUGS, IS BAFFLED BY LACK OF FDA OVERSIGHT IN U.S. PHARMACEUTICAL SUPPLY CHAIN

BY **BLAKE DODGE** ON 10/30/19 AT 2:50 PM EDT



HEALTH

PHARMACEUTICALS

BIG PHARMA

CHINA

Following major recalls of Chinese-manufactured medication that contained carcinogenic ingredients, Congress is taking a hard look at the U.S. supply chain of generic drugs.

About 80 percent of manufacturers that create key ingredients for the domestic drug market are located outside the United States, according to the U.S. Food and Drug Administration (FDA). But for some drugs, China is the only supplier.

At a congressional hearing on Tuesday, lawmakers expressed alarm, and sometimes disbelief, at the lack of oversight the FDA demonstrates over these foreign suppliers—despite the fact that U.S. drug firms are continuously outsourcing their manufacturing needs.

"There's a hidden health crisis in this country that will affect us all," Rep. Anna Eshoo of California, chair of the Health Subcommittee, said in the hearing. "The crippling inadequacy of the American drug supply."

Eshoo went on to say that the U.S. generic-drug industry's reliance on foreign agents creates shortages of life-saving medications as well as subpar manufacturing.

Indeed, in the past two years alone, the FDA has recalled three blood pressure drugs and the heartburn medication Zantac after they were found to contain potentially carcinogenic impurities that their Chinese manufacturer failed to report.

To the surprise of lawmakers in the room, regulators at the hearing said they cannot control or properly monitor these dangerous drugs until long after they've reached U.S. shores.

Active pharmaceutical ingredients (APIs) are the backbone of the generics industry. They make up the part of the drug that generics are supposed to share with their brand-name counterparts.

While the FDA maintains a "catalog" of foreign manufacturers, the sites are not required to tell the FDA whether they actually make APIs and in what quantities, according to Janet Woodcock, director of the Center for Drug Evaluation and Research at the FDA.

Unless Congress passes new legislation, the FDA can't demand this information from drug makers, either, Woodcock added.

A container used for clinical waste is seen at a private clinic that performs vaccinations in Hong Kong on July 24, 2018. At a congressional hearing on Tuesday, lawmakers expressed alarm about the lack of oversight the FDA demonstrates over some foreign suppliers.

ANTHONY WALLACE/AFP/GETTY IMAGES

"In short, we're overly reliant on China, we cannot trust the supply chains, and our national and economic security demand that we act," said Michael Wessel, commissioner of the U.S.-China Economic Security Review Commission.

Several lawmakers, concerned about drug shortages, asked Woodcock whether U.S. companies could be compelled to bring their manufacturing efforts back home.

While drug firms would be hard-pressed to abandon the cheaper labor markets in China and India, Woodcock said, the FDA is advocating for modernization such as automation and "continuous production" that could ease costs overall.

Current manufacturers may not have the resources to experiment in this fashion, but Woodcock said some new players have told the FDA that they're interested in branching out, technologically speaking, through nonprofit setups.

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EXHIBIT 432

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Coronavirus: All FDA Inspections Of Chinese Manufacturing Facilities Come To Screeching Halt

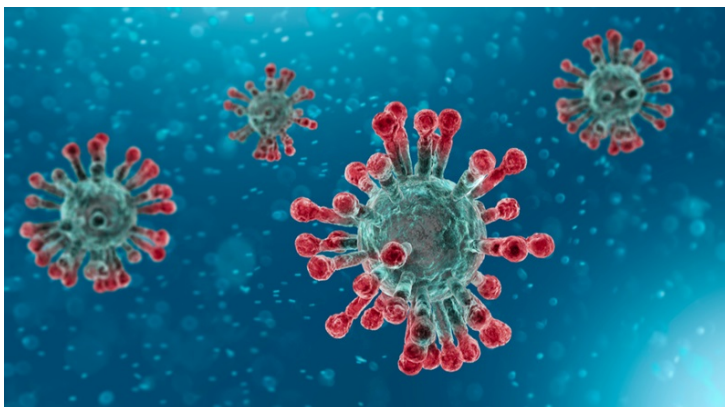
In a late Friday news statement, agency head Stephen Hahn also warned of possible “shortages of critical medical products”

14 Feb 2020 | NEWS

by Shawn M. Schmitt | @MedtechShawn | shawn.schmitt@informa.com

Executive Summary

The US agency has suspended all routine surveillance inspections in China through the end of March because of coronavirus fears, commissioner Stephen Hahn announced late on 14 February. Despite expecting medical product shortages, Hahn said the agency is being proactive: “We are not waiting for drug and device manufacturers to report shortages to us” before acting. The timing of Hahn’s statement – at 6 p.m. EST on a Friday, at the beginning of a three-day US holiday weekend – suggests he isn’t particularly excited to share the information.



The US Food and Drug Administration has abandoned all near-term plans to inspect Chinese manufacturing facilities in the wake of the coronavirus crisis, agency commissioner Stephen Hahn said late on 14 February.

“The FDA is not currently conducting inspections in China due to the State Department warning advising against travel to China,” Hahn wrote in a statement.

Inspections scheduled for the remainder of this month were either postponed by the agency, or it used “other information to inform decisions allowing the products to enter our US market,” he said.

Roughly 90% of canceled February inspections were routine surveillance audits, Hahn said. That means the other 10% – including high-risk for-cause inspections – won’t take place until March at the earliest.

Further, routine surveillance inspections scheduled for March in China also won’t move forward, he said: “At this time [they] are expected to be conducted at a later date.”

Hahn vowed that the FDA “will continue to closely monitor the situation in China so that as the situation improves, we will be prepared to resume routine inspections as soon as feasible.”

“We are not waiting for drug and device manufacturers to report shortages to us.”
– Stephen Hahn

Hahn pointed out that the agency conducts about 500 inspections in China in a given year.

The timing of Hahn’s statement – at 6 p.m. EST on a Friday, at the beginning of a three-day US holiday weekend – suggests he isn’t particularly excited to share the information.

Still, Hahn is adamant that “the robust and multi-layered compliance process at the FDA is helping to protect American patients and consumers even though we are not able to conduct inspections in China at this time.”

In his statement, the commissioner seeks to allay concerns about uninspected Chinese firms, noting that the audits are just “one of many tools that the agency uses to inform our risk strategy for imported FDA-regulated products and to help prevent products that do not meet the FDA’s standards from entering the US market.”

Those other “tools,” he said, include import alerts, increased import sampling and screening, records-requests, and company compliance histories with regulators in other countries, among other things.

“This process has a number of layers in place and is not solely reliant on boots-on-the-ground inspections,” Hahn claimed.

“While the outbreak is impacting our ability to conduct inspections in China, it’s important to underscore that the FDA’s regular risk-based process of surveillance testing of imported products, including those from China, which is based on a number of factors, continues,” he added. “We will continue to assess the need for additional examinations or analytical testing on FDA-regulated products from China as a result of the outbreak, and we will continue to look at inspections on a case-by-case basis.”

FDA Expects Supply Chain Troubles, Potential Shortages

Hahn also said the FDA expects that the coronavirus emergency will interfere with supply chains, “including potential disruptions to supply or shortages of critical medical products in the US.”

Chinese Device Exports, Supply Chains Holding Up In The Face Of Coronavirus – For Now

By Shawn M. Schmitt

06 Feb 2020

“We are not waiting for drug and device manufacturers to report shortages to us – we are proactively reaching out to manufacturers as part of our vigilant and forward-leaning approach to identifying potential disruptions or shortages,” he said.

A device industry expert in Shanghai told *Medtech Insight* on 4 February that Chinese exports and supply chains were holding – for now. (See sidebar story.)

If the agency identifies a potential shortage, it “will use all available tools” to “mitigate the impact” to patients and health care providers, Hahn said, pointing out that such tools “include closely working with manufacturers and expediting review of alternate supply to prevent shortages, among other measures.”

He added that “should the agency be alerted to a potential shortage of a critical medical product, we will be as transparent as possible in sharing updates as they develop.”

Exports of components and finished medical devices coming from coronavirus-stricken China will continue to flow to the US and other countries for now, but there could be trouble soon if government quarantines and international travel bans remain in place, an industry expert in Shanghai tells *Medtech Insight*.

[Read the full article here](#) ↗

EXHIBIT 433

F.D.A. Halts Overseas Inspections of Drugs and Devices, Citing Coronavirus

The agency said the spread of the virus globally prompted its decision. It had already pulled back from China, but this move will also affect India, a major generics manufacturer.

By Sheila Kaplan and Katie Thomas

March 10, 2020

The Food and Drug Administration said on Tuesday that it would stop routine inspections of food, drugs and medical devices overseas through April, citing the worldwide spread of the coronavirus.

The agency had already pulled back its inspectors from China, which is the largest source of raw ingredients for many drugs, like aspirin, ibuprofen and penicillin.

But this global action means that F.D.A. inspections would also be discontinued in India, the world's leading manufacturer of generic drugs. Last year, the agency said it conducted 3,103 inspections at overseas plants.

In addition to overseas inspections, the agency also screens samples of food, drugs, tobacco, veterinary products and cosmetics imported into the United States. In recent years, several types of drugs have had to be recalled because of contamination at the production level, many of which contained ingredients made in China. Those recalls prompted the F.D.A. to revamp some of its procedures.

The agency has also been monitoring the nation's drug supply chain, identifying several drugs that could face shortages if the epidemic in China and elsewhere lasts for months. It has said that at least one drug is currently in short supply in the United States because of difficulties related to the coronavirus, but has not said which one. Hospitals have struggled for years with hundreds of shortages of essential medicines, many of them generic products made overseas.

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“At a time when there are shortages of medicines — critical medicines — there’s a lot of untoward activity that can take place, like counterfeits and poor quality products,” said Rosemary Gibson, an expert on China’s drug supply who is a senior adviser at the Hastings Center, a nonpartisan bioethics research institute. “The bottom line is, who is going to be checking?”

Ms. Gibson said that while the agency does spot checks of imports, “the public needs assurance and transparency on what exact steps are being taken for every shipment of a prescription drug coming from China.”

Dinesh Thakur, a drug-safety advocate who exposed widespread quality problems as a former executive at the Indian drug maker Ranbaxy Laboratories, said Indian drug makers have been reporting that they still have about a six-month supply of active ingredients made in China. If they begin to run out, “Guess what’s going to happen?” he said. “You are going to have problems. They will happen in India. The question is, how do we enforce that?”

When the F.D.A. does cite pharmaceutical plants for problems, they frequently happen in India and China, according to a report by Barbara Unger, a consultant who tracks F.D.A. regulatory actions around the world. During the 2019 fiscal year, she found that the agency issued 16 warning letters to plants in India and 15 to facilities in China, accounting for a majority of the 43 warning letters issued that year to overseas drug manufacturing plants. It was not clear whether those warnings were issued after routine inspections — the type being halted because of the coronavirus outbreak — or after inspections for cause.

The F.D.A. has a staff of about 200 investigators who conduct overseas drug inspections, according to testimony before a House committee in December by Janet Woodcock, the director of the agency’s Center for Drug Evaluation and Research. Most of those inspectors are based in the United States and travel around the world to conduct anywhere from three to six inspections per year. Of those, about 12 are based in

Lower labor, transportation and energy costs have led many drug companies to gradually move their production overseas, especially for products' active ingredients. A 2011 report from the F.D.A. found that U.S. and European companies could reduce their costs by 30 to 40 percent.

Although there is no formal tracking of where active ingredients for drugs are made, experts have estimated that about 80 percent of such materials used in American drugs are made in India or China.

Since 2015 — reflecting this shift — the F.D.A. has conducted more foreign inspections than domestic ones. Although the agency continues to do routine inspections, its program is risk-based, meaning that it prioritizes inspection for facilities that are deemed higher-risk.

Thirty-two percent of vegetables, 55 percent of fruits and 94 percent of seafood consumed in the United States are now imported. Although there are nearly 109,000 foreign facilities that are registered with the F.D.A., the agency inspects only about 1,600 of them each year.

“The F.D.A. has always struggled to meet its foreign food inspection targets, and this is going to set them back even further,” said Sarah Sorscher, a deputy director of the Center for Science in the Public Interest.

In a statement announcing his decision, Dr. Stephen Hahn, the F.D.A.'s commissioner, said that most inspections would be postponed through at least April. He also said exceptions would be made for inspections that are deemed “mission critical,” generally facilities where evidence of violation of good manufacturing practices already exists.

He also said that the agency would adopt practices it had used in the past when inspections were impossible, including physical sampling and inspection of products at the U.S. border, and denying entry to companies with poor compliance histories and to new importers who might not be familiar with regulations.

EXHIBIT 434



Manufacturing

FDA anticipates disruptions, shortages as China outbreak plays out

by [Eric Palmer](#) | Feb 17, 2020 10:27am



The FDA has added resources to monitor for breaks in the drug supply chain but has had to suspend plant inspections in China for now. (Pixabay)

The FDA is bracing for drug and medical supply shortages in the U.S. as the COVID-19 outbreak from China continues to spread globally. The agency has contacted hundreds of drug and devicemakers, and, so far, the links of the supply chain have held but will take all available measures if disruptions appear.

The agency also has halted all plant inspections in China for now but says it can rely on facilities' compliance history and other information to determine whether drugs are safe for import.

"We are keenly aware that the outbreak will likely impact the medical product supply chain, including potential disruptions to supply or shortages of critical medical products in the U.S.," FDA Commissioner Stephen Hahn said in a [statement](#) late Friday.

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He said the agency is speaking with regulators globally and has added resources to quickly spot potential disruptions or shortages.”

“It’s worth noting that there are no vaccines, gene therapies, or blood derivatives licensed by the FDA that are manufactured in China,” Hahn said. “Raw materials used in manufacturing do come from China and other locations in Southeast Asia and we are in contact with biologics manufacturers to gauge any supply concerns regarding raw materials.”

RELATED: Concern for drug shortages grows as COVID-19 outbreak drags on

Other governments also are taking stock. EU Health Commissioner Stella Kyriakides last week said her group has a task force monitoring supplies, and, for now, no shortages are in evidence. In India, which produces about 40% of the generic drugs used by U.S. patients, a survey determined that manufacturers generally have about a two-month supply of ingredients from China on hand.

Because of the State Department warning against travel to and from China, inspections have been put on hold, Hahn said. The FDA estimates that only about 10% of pending inspections are for cause. Those, as well as routine inspections, have been postponed. Hahn said the agency can rely on its “risk-based model” to alert the agency to any serious concern that would require the agency to change its approach. He said the FDA has the authority to take actions, like seizing products already on the market, if they pose a danger to the public.

“(T)his is a dynamic situation that we are closely monitoring and will remain vigilant in this critical work,” Hahn said.

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HEALTH

FDA Cites Shortage of One Drug, Exposing Supply-Line Worry

China is key supplier of chemical and raw materials and other pharmaceutical ingredients for medicines



China is the world's biggest supplier of the raw materials that form the basis of medicines.

PHOTO: WANG JIANWEI/ZUMA PRESS

By Denise Roland and Jared S. Hopkins

Feb. 28, 2020 9:41 am ET

Factory shutdowns across China because of the new coronavirus have exposed an uncomfortable health-care reality: Many medicines rely on raw materials that are made in that country.

The U.S. Food and Drug Administration late Thursday said one drug has already gone into shortage because of difficulties obtaining a raw ingredient from a site affected by the coronavirus. It didn't disclose which drug or its manufacturer.

For several weeks, the FDA has been contacting more than 180 drug manufacturers, reminding them to provide notification of any expected supply shortages. That includes the makers of roughly 20 products the agency has identified as containing key pharmaceutical ingredients from China.

Most vulnerable are generic drugs, which make up some 90% of the medicines taken by Americans. Nongeneric, or branded, prescription medicines tend to have supply lines linked to other parts of the world.

Certain classes of drugs, too, are at special risk. **China is a key supplier of the chemical and raw materials for popular blood pressure medicines and several older antibiotics that are no longer manufactured in the U.S., such as doxycycline and penicillin.**

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Large drugmakers such as Teva Pharmaceutical Industries Ltd., one of the world's largest generic manufacturers, have said in statements before the shortage was announced that they were monitoring their supply chains and hadn't experienced any disruptions.

On Thursday's quarterly earnings call, Mylan NV said that it continues to monitor the situation and noted the company's diversified supply lines, but warned that shortages could occur in the future. The company's president, Rajiv Malik, said, "Our whole industry is in one way or other way connected with China, but you would expect us to be much better placed."

Experts believe China is also the only maker of key ingredients in a class of decades-old antibiotics known as cephalosporins, which treat a range of bacterial infections, including pneumonia.

"The antibiotic supply chain is becoming increasingly fragile, even without a global epidemic centered in the major manufacturing location," said Dan Diekema, director of infectious diseases at the University of Iowa Healthcare, a hospital. **"If we were to have major disruptions that caused shortages of several antibiotics at once, it would challenge our ability to adapt."**

Several generic manufacturers have seen prices on pharmaceutical raw materials grow by as much as 50%, including those for common products like cholesterol-lowering statins, according to research by Sanford C. Bernstein & Co.

Drugmakers are adjusting, including by looking for alternative suppliers and raising prices, according to industry experts and officials.

Some Chinese firms stopped shipping to manufacturers in India, said David Light, chief executive of Valisure, an online pharmacy that works with advisers in India. The Indian

generic-drug industry, which the FDA says supplies 40% of U.S. generic drugs, relies on China for much of its active ingredients.

With hundreds of manufacturing plants and other workplaces in China suspending operations in an effort to contain the spread of the coronavirus, more pressure on the pharmaceutical supply chain looms large. Yet details on the medicines supply lines into the U.S. are limited, hampering authorities' ability to anticipate which drugs are most vulnerable.

China is recognized as the world's biggest supplier of the raw materials—known as active pharmaceutical ingredients—that form the basis of medicines. That dependence on China makes shortages more likely should Chinese manufacturing be shaken, according to a 2019 U.S. government report. China's dominance is growing: the U.S. imported \$3.9 billion worth of pharmaceutical raw material from China in 2017, an increase of nearly one-quarter from the prior year, according to IHS Markit.

Even before the outbreak of the Covid-19 disease, experts for years have warned that overreliance on a single region posed risks to the U.S. health-care system. An explosion in 2016 at a plant in China led to a world-wide shortage of the antibiotic piperacillin.

“The pharma industry is pretty much bound hand and foot with manufacturers in China,” said Robert Walsh, whose company Samara Biopharma Consulting audits Chinese factories on behalf of Western drugmakers.

The industry has some cushion. Drugmakers tend to stock up in advance of China's Lunar New Year holiday, over which factories typically close for two weeks. They also order raw materials in bulk and maintain about six months of supply, according to industry officials.

“The question is, how far in time do these stockpiles go, and can we continue to rely as heavily as we do on manufacturing of these critical supplies offshore,” said Rita Numeroff, a health-care business strategist.

The intricacies of the supply chains for individual medicines—which companies keep under wraps for competitive reasons—remain hidden from the public. While the FDA requires manufacturers to report when there is a shortage of a specific product, companies that make the raw materials aren't subject to such demands. Nor must they disclose the size, or timing, of shipments being made to the U.S., limiting the ability of hospitals and other providers to plan for potential supply disruptions.

The FDA says it has no way to track API volume out of China.

“We technically have no idea what is actually manufactured in China,” said Soumi Saha, senior director of advocacy at Premier, one of the largest group-purchasing organizations in the U.S.

contracting for drugs and other supplies for hospitals. We're missing that upstream visibility.”

Trying to shed light on the medicines-supply chain is Mike Osterholm, director of the Center for Infectious Disease Research and Policy at the University of Minnesota. He is leading an effort to map out the supply chains for around 150 of the most important medicines and medical devices in the U.S., by piecing together information from shipping records, company disclosures and FDA data. Although the project started around 18 months ago, he said the coronavirus outbreak has put it “on steroids.”

“We have been asked to describe the inside of a large home, but we can’t go inside,” he said. “We’re looking in every window.”

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EXHIBIT 436

China enters the global vaccine market

China is gearing up to supply the world with affordable vaccines that fulfil all efficacy, safety and quality requirements. Jane Parry reports.

The global vaccine industry has long been dominated by a few multinational companies. But now that companies in China, India and other emerging economies are becoming major vaccine manufacturers and have started selling these vaccines on the international market, competition is set to increase and prices to come down.

For Jiankang Zhang, representative for PATH's China Programmes, the growth of China's vaccine industry is "a very positive development for global health, as governments and international procurement agencies will be able to afford more life-saving vaccines and thus protect more lives".

Since 1987, vaccine quality for international procurement has been assured through the prequalification system that is managed by the World Health Organization (WHO). The "prequalified" stamp of approval means that these vaccines are consistently safe, effective and of high quality, and thus recommended for bulk purchase by the United Nations Children's Fund (UNICEF) in 152 low and middle-income countries, the GAVI Alliance – which funds vaccines in 73 of these countries – and other agencies.

When WHO pre-qualified a Chinese-made vaccine for the first time last October, the move showed what Chinese vaccine manufacturers could potentially achieve and – in a sense – paved the way for others to follow suit.

"The prequalification of the Japanese encephalitis vaccine in China is a big step forward, and now several other Chinese producers are interested in obtaining prequalification for their vaccines," says Melissa Malhame, whose team at the GAVI Secretariat in Geneva works with vaccine manufacturers around the world to ensure sufficient supply of high quality vaccines at affordable prices.

This and other Chinese vaccines are licensed by the China Food and Drug Administration (CFDA) that is part of China's National Regulatory Authority (CNRA), which received WHO's seal of approval in March 2011, after finding that it met WHO standards for vaccine regulatory oversight.

In July, this status was renewed, after a successful WHO reassessment of the vaccine regulatory part of the CNRA. WHO Director-General Dr Margaret Chan welcomed the news saying: "As a result of this evaluation, WHO is confident in the quality, safety and effectiveness of vaccines that are made in China."

For Dr Lance Rodewald, head of WHO's expanded programme on immunization (EPI) in China, the two WHO programmes – prequalification and national regulatory authority strengthening – "are really terrific, as they have made it possible for the United Nations and other agencies to procure life-saving vaccines for countries without the ca-

capacity to make high quality vaccines or the resources to purchase them".

"More Chinese vaccine manufacturers will follow suit and apply for pre-qualification later this year or early next year," Rodewald says.

China has come a long way since 1978 when it introduced EPI and a largely state-run vaccine manufacturing industry grew up to meet the resulting demand.

Initially, the programme offered the country's children vaccines for polio, diphtheria, tetanus, pertussis (whooping cough), measles and tuberculosis. Later vaccines for hepatitis A and B, Japanese encephalitis, mumps, rubella and invasive meningococcal disease were added.

According to the CFDA, China has 34 vaccine manufacturers, of which four are international joint ventures, seven are state run and the rest are private. All 34, it says, have met the most recent (2010) Good Manufacturing Practices requirements.

"China is currently producing nearly all of the commonly-used vaccines for viral diseases such as influenza, measles, rabies (for humans), mumps, rotavirus, hepatitis A and B and for bacterial diseases, including typhoid, tetanus and diphtheria," says Dr Xu Ming, Vice President of the China Chamber of Commerce for Import and Export of Medicines and Health Products.

The dominant player in China's vaccine industry is state-owned Sino-pharm's subsidiary China National Biotechnology Group, comprising seven manufacturers – one of which is the Chengdu Institute of Biological Products, the producer of the Japanese encephalitis vaccine that was prequalified last year.

In 2010, the China National Biotechnology Group supplied over 740 million doses of 34 vaccines for 28 diseases, representing more than 85% of the vaccines used in China's immunization programme. The remaining vaccines are purchased by middle-class Chinese families.

China has been exporting vaccines for diphtheria, hepatitis B, measles, pertussis, polio, tetanus and yellow fever to poor countries for decades through bilateral aid programmes, says Xu, but



Children gather to be vaccinated for Japanese encephalitis in the Xiangkhouang province of Lao People's Democratic Republic

PATH/Aaron Joel Santos

PATH/Aaron Joel Santos



Japanese encephalitis vaccination campaign in the Xiangkhouang province of Lao People's Democratic Republic

“WHO prequalification of the Japanese encephalitis vaccine is a game changer.”

“As more Chinese companies obtain WHO prequalification, this will open the door to the export of Chinese vaccines,” Xu says.

The CFDA's role is vital to this process, as it looks at whether the clinical trials needed for licensing a vaccine are conducted ethically and meet international standards. The CFDA only licenses vaccine once it is satisfied with all the required data, including from clinical trials and technical reviews of production facilities and processes, provided by the manufacturer.

Once a new vaccine is licensed, every lot is chemically and biologically tested before it is released along the supply chain – a lot-release system that has been in place since the mid-2000s.

Having a national regulatory agency that meets international standards lets the purchasers and users of the vaccine know that the quality, safety and effectiveness of the vaccine are assured, Rodewald explains.

A major challenge for China's vaccine industry is to overcome concerns about product safety. China has been plagued in recent years by scandals over drug and food safety. In 2007, the former head of the Chinese State Food and Drug Administration was sentenced to death and executed, after being found guilty of taking bribes and failing to ensure the safety of drugs and devices approved during his tenure.

At home, the Chinese vaccine industry must overcome its image problems, especially with middle-class parents who can afford to pay out-of-pocket

for vaccinations and, therefore, exercise a choice about where they are from.

This is important – not just for the sake of confidence at home – but because domestic use will generate vital post-marketing data for vaccine-related adverse events, as these data are needed in countries ill equipped to do such surveillance. **There are always some adverse events and the knowledge gained from these enables manufacturers to improve their products.**

For Xu, several things are needed to restore public confidence. These include improved information sharing and communication between authorities to identify problems or risks, adjust and upgrade standards and improve the quality of vaccines. The industry also needs to step up its post-marketing surveillance while more stringent regulation is needed.

Betty Su, vice president for Asia Pacific, Boston Health care Associates, Inc., a firm specialized in global market access issues for the health-care industry, echoes Xu's point about post-marketing surveillance.

“The Chinese industry must realize that quality isn't just about releasing one batch of safe products but about safe transportation – something that is also important when China starts to supply the world with vaccines. This entails, among other things, establishing a tracking and monitoring system of the product's quality when it is out there being given to patients.”

But what would it take for more Chinese vaccines to be marketed outside China? Prequalification is one factor, but can be challenging for manufactur-

ers. The Chengdu Institute of Biological Products obtained WHO prequalification for its Japanese encephalitis vaccine after years of wide-ranging technical support from nongovernmental agency PATH, which is funded by the Bill & Melinda Gates Foundation.

The Clinton Health Access Initiative (CHAI) has been working with Chinese suppliers to support their applications for WHO prequalification for several vaccine candidates for the last two years, says Joshua Chu, CHAI's Director, Vaccines Markets.

The initiative also works with donors and other agencies to implement innovative market-based mechanisms, such as long-term volume guarantees, to make donor funds go further when purchasing vaccines. So far it has established volume guarantees with vaccine manufacturers in India and with other developing countries for other health products.

After Japanese encephalitis, there are plenty of good potential candidates for prequalification and purchase by United Nations agencies, says GAVI's Malhame. “These include pneumococcal conjugate, rotavirus, human papillomavirus, meningitis A, measles-rubella and inactivated polio virus (IPV) vaccines. China's vaccine industry should also be encouraged to enter international markets with WHO-prequalified products for other vaccines that are not supported by GAVI.”

Rodewald is also keen to see China's new IPV vaccine coming down the prequalification pipeline, since the Global Polio Eradication Initiative's Eradication and Endgame Strategic Plan 2013–18 calls for the vaccine to be introduced into immunization programmes by the end of 2015.

Last year GAVI said it would support the introduction of IPV in the 73 countries that are eligible for its support at about US\$ 1 a dose in 10-dose vials. For middle-income countries, UNICEF recently said it would offer the vaccine at between US\$ 2 and US\$ 3.30 per dose for the same 10-dose package.

“Twenty years ago China began a Sabin strain IPV development programme, and this is likely to be licensed by the CFDA this year,” says Rodewald. “This will be only the second Sabin IPV to be licensed worldwide and would be a very good candidate for WHO prequalification.” ■

EXHIBIT 437

China's emerging vaccine industry

Jan Hendriks,^{1*} Yan Liang² and Bing Zeng³

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The Chinese vaccine industry is developing rapidly due to an emerging and large market for current and new vaccines, a large potential for local vaccine manufacturing both in the public and private domain, and a governmental orientation towards national vaccine self-sufficiency. There are currently over 40 companies and institutions manufacturing a large variety of traditional (EPI) and some new vaccines.

The innovative development capacity of state vaccine institutions is stimulated by significant government investments. Various Chinese influenza manufacturers were in 2009 among the first worldwide to obtain national license for their pandemic H1N1 flu vaccines. It is of interest to note that private but also governmental entities are committed to raise manufacturing quality standards to reach WHO prequalification. It is expected that WHO prequalification for at least one product from a Chinese manufacturer will have been obtained by 2011. This will open the door to the global market for Chinese vaccines.

Introduction

The global human vaccine market is expected to grow rapidly in the coming decades, fueled by re-emerging vaccine preventable health threats such as pandemic influenza, an increasingly more coordinated international response thereto, and the availability of licensed new vaccines combined with several international philanthropically public private partnerships, such as GAVI. On top of this, countries with emerging economies are introducing these new vaccines in a more rapid pace than

ever. At the same time, equitable access to vaccines for the global community remains a subject of intensive international public health concern, as for example the recent case of pandemic influenza caused by the new H1N1 virus illustrates.¹ The importance of local or regional vaccine manufacturers, coordinated in the Developing Countries Vaccine Manufacturers' Network (DCVMN), to reduce this global vaccine inequity has been highlighted before.² The DCVMN (www.dcvmn.com) is a voluntary public health driven alliance of vaccine manufacturers in developing countries, under advocacy of WHO.² The members include vaccine manufacturers in developing countries, international organizations and resource institutions such as the Netherlands Vaccine Institute (NVI) and the Programme for Appropriate Technology in Health (PATH), based in Seattle, USA. The objective of the Network is to help the vaccine manufacturers in developing countries understand the most up-to-date status of vaccine development and assist them becoming a supplier to international markets, thereby improving the health of people in developing countries.^{2,3} Members of the DCVMN include public and private manufacturers mainly from countries with fast growing emerging economies, such as Brazil, India and China.

It is remarkable that at the international level, little is known about the vaccine situation in China, a country with a very large part of the world population. Due to China's impressive economic growth figures in latest years, the Chinese market is becoming very attractive for pharmaceutical companies. Because of its huge population, national vaccination policies in China are influenced by the ability of

Key words: China, national immunization program, pandemic influenza, developing country vaccine manufacturers' network (DCVMN)

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Table 1. The Chinese national immunization program (CNIP)

Abbreviation	Vaccine	Year of Introduction	Remarks
HBV	Hepatitis B Vaccine	2002	
BCG	BCG Vaccine	1978	
OPV	Oral Poliomyelitis Vaccine	1978	
DTP	Combined Vaccine of Pertussis, Diphtheria & Tetanus	1978	
MV	Measles Vaccine	1978	
DT	Combined Vaccine of Diphtheria & Tetanus	2008	Booster for 6 year olds
DTaP	Acellular DTP Vaccine	2008	To replace DTP
HAV	Hepatitis A Vaccine	2008	
MenA/MenAC	Meningococcus Vaccine	2008	
JE	Japanese Encephalitis Vaccine	2008	
MMR	Combined Vaccine of Measles, Mumps & Rubella	2008	
	Hemorrhagic Fever Renal Syndrome Vaccine	2008	
	Anthrax Vaccine	2008	Only for certain risk groups in endemic regions
	Leptospira Vaccine	2008	

domestic manufacturers to supply needed vaccines at an affordable price.

This commentary aims to give a recent overview of the emerging human vaccine industry in China in view of the increasing global awareness of the importance of regional or local vaccine manufacturing to tackle international vaccine availability issues.⁴ Although the focus of most Chinese vaccine manufacturers is at this moment their domestic market, they have a clear ambition and potential to play a role in the global market. This became apparent at the latest Annual Meeting of the DCVMN that was hosted by the China National Biotec Group (CNBG) in Beijing in September 2009. Currently 4 Chinese manufacturers are DCVMN members, including CNBG. CNBG's national status was actually reconfirmed end 2009, when China's State-owned Assets Supervision and Administration Commission (SASAC) announced a merger of the CNBG with the China National Pharmaceutical Corporation (Sinopharm). Sinopharm is one of China's largest pharmaceutical companies and is believed to become one of China's three giant pharmaceutical conglomerates over the next few years.⁵

The National Immunization Program and Vaccine Markets

China, with its 1.3 billion inhabitants and over 17 million newborns annually, is the world largest vaccine consuming

country. The current vaccine market in China was valued in 2009 to be around \$700 million with a compound annual growth rate expected to increase from around 15% now to 30% over the next few years, thanks to recently announced governmental healthcare reforms that emphasize prevention and aim to bring wider insurance coverage to the population.⁶

The Chinese government has traditionally over the years managed a successful vaccine-preventable disease programme. Polio-eradication was for example already achieved in 1994 and childhood immunization continues to be a high priority.⁷ A law was passed in 2005 ensuring provision of vaccines free of charge through the Chinese National Immunization Program (CNIP). The CNIP currently includes 14 (mainly pediatric) vaccines against 15 diseases (Table 1). Several new antigens including recombinant Hepatitis B were introduced since 2007.

Several vaccines in the CNIP are in short supply, for example the demand for Diphtheria-Tetanus-acellular-Pertussis vaccine (DTaP) was nearly 64 million doses in 2008, whereas manufacturers supplied only about 18 million doses, resulting in a market gap of 46 million doses in 2008. For MMR, the market gap is estimated at 23 million doses each year and there are also shortages for live attenuated hepatitis A vaccines, inactivated hepatitis A vaccines, and inactivated Japanese Encephalitis vaccines.⁸

The priority and cost-effectiveness of introduction of new vaccines such as conjugate Hib vaccine, pneumococcal and rotavirus vaccines, IPV replacement for OPV and combination vaccines to reduce the number of injections into this CNIP is currently actively being assessed in collaboration and consultation with international bodies such as WHO and GAVI.⁹ These studies are expected to lead in the coming years to the uptake of new vaccines in the CNIP. Currently, the introduction of a cHib vaccine (widely promoted by GAVI) is seriously being considered by the Chinese authorities and several domestic manufacturers have already started to develop and manufacture this conjugate vaccine.

Vaccines used outside the CNIP in the private market are produced by manufacturers based on market demand (Table 3). Examples are seasonal influenza vaccines and rabies vaccines. These may be purchased by consumers on a voluntary basis.

The Vaccine Regulatory Authority

Vaccines are regulated in China by the State Food and Drug Administration (SFDA). The SFDA with provincial FDA's supervises and controls throughout the country the entire vaccine supply chain, from production, trading, to supply and administration. Since China aims to produce and export vaccines, it is a prerequisite that China's regulatory authority,

the SFDA, is able to exercise the six regulatory functions that are recognized by WHO as essential to ensure that vaccines manufactured in China are of international assured quality. The Government has thus embarked since 2003 with WHO support on a programme to improve the vaccine regulatory capacity of the SFDA up to international standards.¹⁰ Currently WHO is preparing for a re-assessment of the SFDA which is expected to take place by the end of 2010. A successful outcome of this re-assessment will start the process of submission to WHO of pre-qualification dossiers of vaccines made by Chinese manufacturers, which will pave the way of China's entry into the global market. One of the first candidate vaccines for WHO pre-qualification will be the Japanese Encephalitis vaccine made by the Chengdu Institute for Biological Products in collaboration with PATH.

Vaccine Manufacturing in China

China ranks as the world's largest vaccine manufacturing country with an annual output of more than one billion doses.¹¹ The Chinese government has a policy to provide vaccines for the CNIP by Chinese manufacturers and, with the exception of BCG and OPV, does not encourage supply of CNIP vaccines by international vaccine manufacturers, according to a "Guidance Catalogue of Foreign Investment Industries" issued by the National Development and Reform Commission and the Ministry of Commerce in 2007.¹² Currently the website of the Chinese national regulatory authority (SFDA) lists 46 Chinese registered vaccine manufacturers, of public and private status, collectively manufacturing 24 licensed vaccines.¹³ Table 2 shows an overview with an indication of the number of vaccines they each manufacture and their legal status.

CNBG/Sinopharm. It is interesting to note from this list that the six subsidiary manufacturers of the CNBG group, located in Beijing, Changchun, Chengdu, Lanzhou, Shanghai and Wuhan, have the widest diversity of vaccines as compared to the private manufacturers. Collectively they provide 90% of the doses of the 14 CNIP vaccines (Table 3). To bolster

innovative development capacity, CNBG/Sinopharm established in Beijing in 2004 a corporate R&D centre to maximize the synergies of the 6 Institutions. The construction of a New National Vaccine Engineering Research Center, China's first national-level research, development and industrialization base for new vaccines started in 2009 in Beijing. The center will aim to upgrade traditional vaccines and solve technical problems occurring during the R&D and industrialization of new vaccines, focusing on R&D including pilot scale production of new vaccines and biomedicines.

CNBG/Sinopharm has also interests in several private companies, for instance CNBG/Sinopharm is a majority shareholder of Beijing Tiantan Biological Products Co., Ltd., (nr 43 in Table 3).

Recently, multinational vaccine companies show an increasing interest in expanding their presence and are entering the Chinese market by taking majority shares in Chinese companies. GSK announced in 2009 to take a 65% stake in a joint venture with the Chinese firm Walvax (nr 24 in Table 3) for the development, manufacture and supply to China's public vaccine market of MMR. This followed GSK's earlier announcement of a 40% stake in a JV with another Chinese company, Shenzhen Neptunus Interlong Biotech Co., Ltd., (nr 42 in Table 3) to develop and manufacture flu and rabies vaccines. Sanofi pasteur has a majority in Shenszen Sanofi (nr 36 in Table 3) and has announced investments of over \$94 million (RMB 700 million) in a flu vaccine facility with a 25 million doses annual capacity. Novartis obtained in November 2009 a majority (85% stake) in Zhejiang Tianyuan Bio-Pharmaceutical Co., Ltd., (nr 20 in Table 3), subject to government and regulatory approval in China.

Influenza Vaccines

Seasonal influenza vaccines. There is a big potential market for seasonal flu vaccines considering the current low vaccination rates and China's huge population. The overall seasonal flu vaccination rate in China was about 1.5% in the 2007–2008 season. For certain risk groups (the aged population) it was only about 0.3%.

Under the current SFDA regulation, provinces and municipalities can develop their own policies. This explains that regional differences on flu vaccination practices exist. For example, the Beijing municipality offered in the 2007/2008 season free flu vaccines to the registered elderly population, and half-price flu vaccines to students in primary and junior middle schools, totaling together over 1.5 million persons. Five flu manufacturers (Table 3; nrs: 9, 20, 26, 43 and 37) supplied seasonal influenza vaccines to this Beijing city programme. Obviously there is a marked interest by various manufacturers both domestically and internationally to obtain a market share of the influenza vaccine market in China, as is apparent from the relatively large number of influenza manufacturers in Table 3 as well as the interest of the international companies to get a stake in China's flu vaccine market.

Pandemic influenza vaccines. The recent global threat for a new avian flu pandemic and in particular the 2009 new (H1N1) influenza pandemic amplified galvanized the emerging Chinese flu vaccine industry. Due to very proactive pandemic vaccine preparedness decisions at the Government level, China made global headlines in 2009 becoming the first country to complete clinical trials for the new H1N1 pandemic flu, to approve domestically made pandemic flu vaccines and to start mass immunizations. The Chinese government's strategy was to vaccinate in 2009 five percent of the total population, or about 65 million people. By November 2009, SFDA had provided a national license to 10 Chinese manufacturers (see Table 3 nrs: 2, 3, 4, 7, 9, 20, 22, 26, 43 and 46). By February 2010, around 77 million people had received the vaccine. The Chinese vaccines were made in eggs with the NYMCMX-179A virus seed strain obtained from WHO. An extensive clinical study coordinated by the Chinese CDC in 7 provinces involving over 13,000 volunteers showed that a one dose regimen of a 15 ug split formulation without adjuvant yielded a protection of about 85%.¹⁴ The Chinese government purchase price was set to about 22 RMB (2.2 EUR) per dose. The vaccines were provided to the public (especially high risk groups: public health workers, students and patients

Table 2. Chinese vaccine manufacturers registered at SFDA¹³

	Vaccine Manufacturer	Location	Nr of products	Legal Entity
1	National Vaccine & Serum Institute (NVSI)	Beijing	2	Public; Sinopharm
2	Changchun Institute of Biological Products (CIBP)	Changchun, Jilin	7	Public; Sinopharm
3	Lanzhou Institute of Biological Products Co., Ltd., (LIBP)	Lanzhou, Gansu	13	Public; Sinopharm
4	Shanghai Institute of Biological Products (SIBP)	Shanghai	3	Public; Sinopharm
5	Wuhan Institute of Biological Products (WHIBP)	Wuhan, Hubei	4	Public; Sinopharm
6	Chengdu Institute of Biological Products (CDIBP)	Chengdu, Sichuan	6	Public; Sinopharm
7	Hualan Biological Engineering Inc., (Hualan)	Xinxiang, Henan	7	Private
8	Yunnan Yuxishangcheng Biotech Co., Ltd.	Yuxi, Yunnan	1	Private
9	Sinovac Biotech Co., Ltd., (SinoVac)	Beijing	3	Private
10	Rong'an Pharma Co., Ltd., (RongAn)	Ningbo, Zhejiang	2	Private
11	Guangzhou Nuocheng Bio-product Co., Ltd., (Nuocheng)	Guangzhou, Guangdong	1	Private
12	Beijing Qiweike Biotech Co., Ltd.	Beijing	1	Private
13	Shanghai Zerun Biotech Co., Ltd., (Zerun)	Shanghai	1	Private
14	Tianshili Jinna Biotech Co., Ltd.	Tianjin	1	Private
15	Shandong Hengye Biotech Co., Ltd.	Qingdao, Shandong	1	Private
16	Henan Puxin Bio-engineering Co., Ltd., (Puxin)	Zhengzhou, Henan	1	Private
17	Changchun Institute Co., Ltd., of Biological Products	Changchun, Jilin	2	Private
18	Zhejiang Pukang Biotechnology Co., Ltd., (Pukang)	Hangzhou, Zhejiang	1	Private
19	Changchun Wei-er-sai Pahrma Co., Ltd.	Changchun, Jilin	1	Private
20	Zhejiang Tianyuan Bio-Pharma Co., Ltd., (Tianyuan)	Hangzhou, Zhejiang	4	Private (85% Novartis)
21	Dalian Kunyang Pharma Co., Ltd.	Dalian, Liaoning	1	Private
22	Changchun Changsheng Life Science (Changsheng)	Changchun, Jilin	7	Private
23	Luoyi Bio-pharma Co., Ltd., (Luoyi)	Wuxi, Jiangsu	1	Private
24	Walvas Biotechnology Co., Ltd., (Walvax)	Yunnan	4	Private (65% GSK)
25	Shenzhen Kangtai Biological Products Co., (SKBP)	Shenzhen, Guangdong	1	Private
26	Jiangsu Yanshen Biological Tech Co., Ltd., (Yanshen)	Changzhou, Jiangsu	4	Private
27	Xinkexian Biotech Co., Ltd.	Fuyang, Anhui	5	Private
28	Liaoning Yisheng Pharma Co., Ltd., (Yisheng)	Shenyang, Liaoning	2	Private
29	Liaoning Chengda Bio-tech Co., Ltd., (Chengda)	Shenyang, Liaoning	1	Private
30	Fu'er Pharma Co., Ltd., (FuEr)	Hebei	2	Private
31	Zhejiang Weixin Pharma Co., Ltd., (Weixin)	Ningbo, Zhejiang	2	Private
32	Shenzhen Qinghuayuanxing Bio-pharma Tech Co., Ltd.	Shenzhen, Guangdong	1	Private
33	Beijing Hua-er-dun Bio-tech Co., Ltd.	Beijing	1	Private
34	Dalian Hanxin Pharma Co., Ltd., (Hanxin)	Dalian, Liaoning	2	Private
35	Beijing Lvzhu Phama Co., Ltd., (Lvzhu)	Beijing	3	Private
36	Institute of Medical Biology, Chinese Academy of Medical Science (IMBCAMS)	Kunming, Yunnan	2	Public
37	Shenzhen Sanofi Pasteur Biological Products Co., Ltd., (Pasteur)	Shenzhen, Guangdong	4	Private; (Stakeholder Sanofi)
38	Jilin Yatai Bio-pharma Co., Ltd., (Yatai)	Changchun, Jilin	1	Private
39	Jilin Maifeng Pharma Co., Ltd., (Maifeng)	Changchun, Jilin	1	Private
40	Beijing Wansai Bio-Pharma Co., Ltd.	Beijing	1	Private
41	Huabei Pharma Jintan Bio-tech Co., Ltd., (Jintan)	Shijiazhuang, Hebei	1	Private
42	Shenzhen Neptunus Interlong Biotech Co., Ltd.	Shenzhen, Guangdong	1	Private; (JV 40% GSK)
43	Beijing Tiantan Biological Products Co., Ltd., (BTBP)	Beijing	3	Private (holding company of Sinopharm)
44	Shanghai Rongsheng Pharma Co., Ltd.	Shanghai	1	Private
45	Shenzhen Weiwu Guangming Bio-product Co., Ltd.	Shenzhen, Guangdong	1	Private
46	Dalian Aleph Biomedical Co., Ltd., (Aleph)	Dalian, Liaoning	1	Private

Table 3. Major vaccine products in China¹³

	Product Name	Nr of Manufacturers	Reference nr in Table 2
1	Recombinant HBV	8	2, 3, 5, 6, 25, 34, 41, 43
2	BCG	5	1–4, 6
3	OPV	2	36, 43
4	DTP	6	1–6
5	MV	5	3–6, 43
6	DT	6	2–6, 43
7	DTaP	7	2–6, 22, 43
8	HAV	6	2, 9, 13, 18, 22, 36
9	Meningococcus A and A + C Vaccine	9	2–6, 20, 23, 24, 35, 43
10	JE	9	1–6, 20, 29, 43
11	MMR	1	4
12	Hemorrhagic Fever with Renal Syndrome Vaccine, Inactivated	6	2–4, 20, 23, 31
13	Anthrax vaccine	2	3, 6
14	Leptospira Vaccine	3	4–6
15	Adsorbed Tetanus Vaccine	6	2–6, 43
16	Combined Vaccine of Hepatitis A and B	1	9
17	Rabies Vaccine	14	2, 3, 5, 10, 11, 16, 22, 26, 28–30, 34, 38, 39
18	Tracheitis Vaccine	4	2, 4, 5, 26
19	Typhoid Vi Polysaccharide Vaccine	6	2–6, 43
20	Tick-borne encephalitis vaccine	1	2
21	Split A (H1N1) Influenza Vaccine	10	2–4, 7, 9, 20, 22, 26, 43, 46
22	Seasonal Influenza Vaccine	11	2–4, 7, 9, 20, 22, 26, 37, 42, 43
23	Pandemic (H5N1) Influenza Vaccine	1	9
24	Brucella Vaccine	2	2, 3

NB. The first 14 vaccines are used in the Chinese National Immunization Programme (see also Table 1).

with chronic diseases) free of charge. The estimated national flu vaccine production capacity was estimated by the first quarter of 2010 at around 100 million doses.

Concluding Remarks

The recent developments described here will lead to an increased uptake of traditional and new vaccines in the Chinese public immunization programme. In the years to come the domestic vaccine market in China will grow at an accelerated pace. Besides stimulating the domestic industry, this has attracted the interest of international manufacturers who are now engaging in China through different strategies, such as taking interests in Chinese private companies. This may lead to competitive supply of vaccines to Chinese markets including the EPI-markets. Because the Chinese regulatory authorities are striving to meet international criteria for vaccine

manufacturing and regulation, it may be expected that in the years to come the number of domestic vaccine companies will decrease, as they are forced to meet international quality standards. China's national policy to stimulate domestic vaccine manufacture is becoming more internationally oriented, as exemplified by the increasing presence of Chinese manufacturers in the DCVMN. Several Chinese manufacturers are making significant investments in their facilities to meet international GMP standards and regulations. CNBG/Sinopharm and others have embarked on an ambitious programme to meet WHO pre-qualification for one or more of their products opening the way to provide vaccines for the global market. The remarkable, very fast and significant up scaling of Chinese pandemic flu vaccine production capacity in 2009 illustrates the enormous potential and global relevance of the emerging Chinese vaccine

industry. This will in the near future no doubt benefit global access to vaccines.

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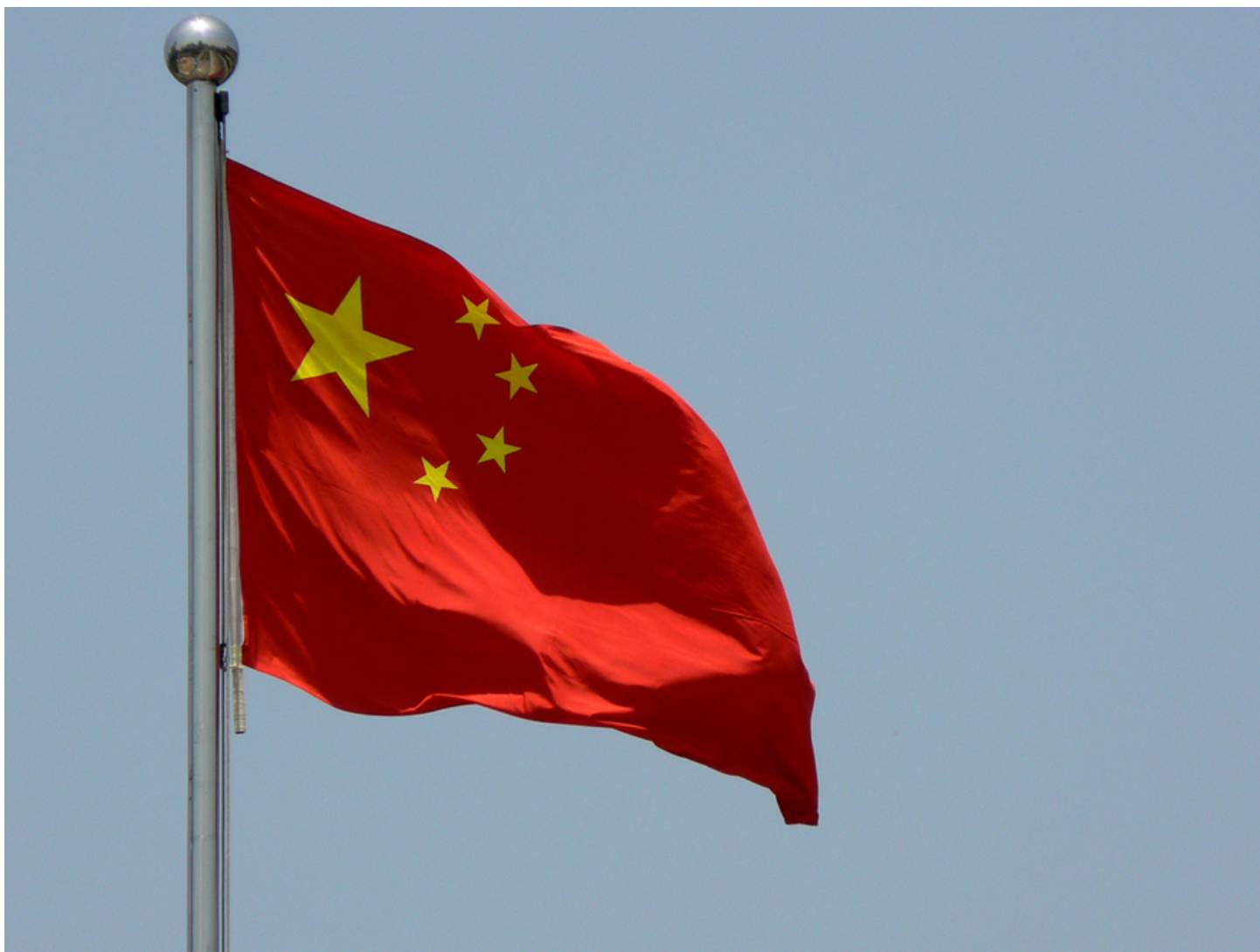
EXHIBIT 438



Manufacturing

China drug exports to U.S. rise but companies struggle with quality

by [Eric Palmer](#) | Aug 30, 2016 9:13am



Chinese companies now account for more than 50% of the global active pharmaceutical ingredient (API) market. It has more than 500 companies registered to sell in the U.S. and 10 times that many serving its own market. But many of those continue to struggle to meet international standards.

As an example, *Bloomberg* points to the fact that last year, Chinese authorities ordered about 700 Chinese firms to review pending drug applications and withdraw any that were false or incomplete in an effort to step up its drug

Case 3:20-cv-02470-WBS-JDP Document 13 Filed 12/29/20 Page 263 of 406
quality oversight. About three-quarters of the applications were voluntarily withdrawn or rejected by China's regulators, even though some of the drugs also were approved for sale in the U.S.

Several of the company's explained the disparity to *Bloomberg* by saying that their products sold in China were tested by Chinese labs that provided faulty information while those sold in the U.S. were certified by research firms in North American companies and, as a result, are safe. It was a sentiment that echoed China's regulators.

"Drugs approved in the past are still being used, but there may not be accurate data to prove that their efficacy reached international levels," Wu Zhen, vice minister of China's FDA explained at a press conference about its oversight, *Bloomberg* reports.

Of course, the U.S. FDA is not relying on its Chinese counterparts to ensure drug safety. It has upped its own staff dedicated to plant inspections there and has recently posted a steady stream of warning letters issued to Chinese drugmakers.

Some of those are operators like Concept Products, a Tianjin, China-based company that the FDA found lacking in some of the most basic GMP standards. A warning letter said the company did not write up or follow any processes for holding each lot for sampling. It never got the OK from the quality control people before release, and also didn't do stability testing to determine how the APIs should be stored and their appropriate expiration dates. The company also did not have established procedures for regularly cleaning and maintaining equipment.

Two weeks ago, the FDA issued a warning letter for two facilities operated by Xinxiang Tuoxin Biochemical in Xinxiang City, Henan, China for dirty equipment, holes in the facility that allowed insects into clean rooms and paint above API equipment that was chipping off the ceiling.

But some of the drugmakers that the FDA has cited, and that have had products banned from entry into the U.S., are large Chinese operations which supply some of the biggest western drug companies.

Those include Shanghai Desano Chemical Pharmaceutical and Chongqing Lummy Pharmaceutical, which were slammed in warning letters for manipulating testing and turning in falsified batch test results on APIs.

Shanghai Desano works with GlaxoSmithKline's (\$GSK) HIV med speciality group, ViiV Healthcare. ViiV said it did a review after being told of the warning letter and determined it should not affect the supply of any of its medications.

It found similar issues at Chongqing Lummy Pharmaceutical, and those problems have spilled onto clients in the U.S. The FDA this year rescinded its approval of an ANDA for temozolomide capsules, a chemo drug, that had been issued to Philadelphia-based Lannett after figuring out that it had been approved after the FDA had banned the Chinese API supplier. Lannett has sued the FDA.

Despite the regulatory issues, Chinese companies continue to build business in the U.S. *Bloomberg* reports that China's drug exports to the U.S. grew 4% last year.

- read the [Bloomberg story](#)
- here's the [warning letter](#) to Xinxiang Tuoxin Biochemical

Related Articles:

- [UPDATED: FDA warnings slam Chinese drugmakers, including ViiV partner](#)
- [FDA warns China's Concept Products: test your products](#)
- [Chinese API maker spanked in warning letter](#)

EXHIBIT 439

IMPACT & INNOVATION SERIES



Preparing for the Global Market: China's Expanding Role as a Vaccine Manufacturer

Reflections from a Gathering of Unlike Minds

At the 2011 Pacific Health Summit in Seattle, a workshop on China's global role in vaccines and immunization convened a lively, interactive panel of Chinese government and industry leaders. Key topics included the state of vaccine manufacturing in China today, domestic manufacturing and research and development (R&D) capacity, the evolution of regulatory systems as international standards become primary priorities, and areas for partnerships and collaborations with international partners. Workshop participants hailed from across many sectors and geographies. This report is a summary of the rich and thoughtful discussion that took place.

Inside

- 2 ... China's Vaccine Manufacturing Landscape
- 5 ... Updating China's Vaccine Regulatory System
- 11 ... Key Areas of Opportunity

Contributors

Sally Davies, Chief Medical Officer, UK National Health Service

Kewen Jin, General Manager, Aura Partners

Meng Li, Deputy Director of International Cooperation, China National Biotec Group (CNBG)

Rob Lin, Deputy Director of Financial Planning and Analysis, Global Health Program, Bill & Melinda Gates Foundation

Jilan Liu, Special Advisor, The National Bureau of Asian Research

Qi Shen, Director, Biological Products Testing at the National Institutes for Food and Drug Control, State Food and Drug Administration (SFDA)

Shi Li, CEO, Shanghai Zerun Biotechnology Co., Ltd

Yu Wang, Director General, China's Center for Disease Control and Prevention (CDC)

Yonglin Wu, Vice President, China National Biotec Group (CNBG)

Xiaoming Yang, President, China National Biotec Group (CNBG)

Jiankang (Jack) Zhang, Director, China Program, PATH



PACIFIC HEALTH SUMMIT
SEATTLE-LONDON

A 2011 Pacific Health Summit workshop report

The Current Vaccine Manufacturing Landscape in China

In March 2011 the World Health Organization (WHO) approved China's State Food and Drug Administration (SFDA) as a functional regulatory authority for vaccines. This approval means that the SFDA fulfills the WHO's criteria for international standards in vaccine regulation, and thus Chinese-made vaccines approved by the SFDA should ultimately meet internationally recognized standards and can apply for WHO prequalification status.¹

The WHO's major announcement comes at a time when China's vaccine manufacturing industry is arguably at its most robust. Today, China's 40 domestic vaccine manufacturers produce 49 types of vaccines that protect against 27 diseases. The industry's massive annual output totals nearly 1 billion doses, the world's highest yield in terms of a single national economy's vaccine output.

What are the forces behind China's recent enormous growth in this area? The answer: intense competition among domestic manufacturers, a surge of investment capital both from within the country and abroad, tremendous government support, the return of motivated and educated emigrants with experience in multinational pharmaceutical and biotechnology companies, and an eagerness to expand product sales to the international market. Placed against the backdrop

of SARS and avian flu outbreaks in recent years as well as a constantly advancing, cutting-edge domestic disease surveillance system run by the China CDC that reaches every township in China in real time, the boom in vaccine innovation and manufacturing is even more understandable.

"The concentration of players in China's vaccine industry is very low, so the competition is intense," remarked **Yonglin Wu**, Vice President, China National Biotec Group (CNBG). CNBG is China's largest biological products manufacturer and part of the state-owned Sinopharm Group, China's largest pharmaceutical company. China's vaccine industry as a whole comprises a mix of public, semi-private, and private firms of various sizes.

An additional factor that has contributed to the recent growth of China's pharmaceutical industry is a growing number of multinational pharmaceutical companies that have built a presence there in recent years, as well as the growing trend of collaborations between Chinese vaccine manufacturers and these multinational players.

"The concentration of players in China's vaccine industry is very low, so the competition is intense."

Yonglin Wu, Vice President,
China National Biotec Group (CNBG)

Xiaoming Yang, President, CNBG, noted a positive experience of collaborating with Merck concerning hepatitis B vaccine: "We've had very good experiences with them," said Yang. "About twenty years ago, they

¹ WHO prequalification ensures that vaccines used in national immunization services in different countries are safe and effective for target populations at the recommended schedules, and that they meet particular operational specifications. Every year, billions of U.S. dollars-worth of medicines and vaccines are purchased by international procurement agencies for distribution in resource-limited countries. Prequalification is intended to give these agencies the choice of a wide range of quality medicines for bulk purchase. For more information, see the WHO webpage, "A system for the prequalification of vaccines for UN supply," http://www.who.int/immunization_standards/vaccine_quality/pq_system/en/index.html.



Meng Li



Qi Shen, Kewen Jin (left to right)



Yu Wang

transferred the technology for hepatitis B vaccine. Then we manufactured the vaccine domestically and provided it to the whole country. This is a great example of a successful partnership between multinationals and local pharma.”

More recently, in July 2010 Merck and Sinopharm signed a cooperation agreement on HPV vaccine and several others, with a focus on marketing Merck products in China.

In addition to garnering the interest of multinationals, China’s domestic vaccine industry has also attracted Chinese expatriates. **Kewen Jin**, General Manager, Aura Partners, mentioned the arrival of returning Chinese professionals and the energy they bring to the industry. “Almost like an Internet start-up, these firms are often started by people who were born in China, went to the West for graduate school, worked there and learned the trade, and have now come back to China to take advantage of the healthy business climate,” he said.

Global health leaders have taken note of the recent boom of the vaccine industry in China. “I am terrifically impressed by how things have changed since I visited Shanghai four years ago,” said **Sally Davies**, Chief Medical Officer, UK National Health Service. “Back then, the vaccine manufacturers and the SFDA were clearly just beginning the ramp-up, and now industrial and regulatory efforts are progressing with the WHO prequalification. Progress is dramatic, and will have a big impact on global health.”

Making Products for Different Domestic Markets: Public and Private

In China the government is the primary purchaser of domestically produced vaccines, and purchases all of the vaccines covered under its Expanded Program on Immunization (EPI). This market is known as the

China’s Domestic Immunization Success

China’s Expanded Program on Immunization (EPI) is extraordinarily successful, with an immunization rate that regularly exceeds 90% at the township level, a hepatitis B infection rate of less than 1%, and the eradication of polio.[†] These figures are even more impressive when factoring in China’s diverse landscape as well as its population, the world’s largest, of 1.3 billion people.

What are the keys to the success of China’s national vaccine program, and is it possible to replicate in other countries? Participants discussed a myriad of interconnected factors, among them:

- Comprehensive immunization as a national priority—in practice as well as in policy;
- Providing EPI vaccines free of charge;
- Recognition that there is more to achieving immunization than just the vaccine itself; and
- Cross-discipline, collaborative efforts covering all aspects of the program.

China’s comprehensive national immunization program has continually been a top priority for the government since its inception in 1978, steered by the recognition that a healthy population equals a healthy economy. Leaders actively organized and built the necessary infrastructure and personnel, and the EPI has since expanded from its original

four vaccines to covering nearly all of the vaccine-preventable diseases found in China. EPI vaccines are mandatory for children to attend school and are given free of charge.

Active cooperation among stakeholders and a universal adherence to vaccination requirements are key factors to achieving high immunization rates, said **Yu Wang**, Director, China’s Center for Disease Control and Prevention (CDC). “A collaborative approach among those who share a stake in immunization is essential.” As such, China’s EPI workforce comprises 400,000 workers, including not only clinicians, but also CDC employees and other public health personnel whose roles are to inform, direct, and encourage immunization.

Yu Wang emphasized, “The development of safe, high-quality vaccines is a fundamental building block, but the delivery and service systems are also essential components of a successful immunization program.”

[†] Reports indicate that non-indigenous polio has been recently found within Chinese borders. In September 2011 ten cases of wild poliovirus type 1 (WPV1) were reported in China’s western Xinjiang Autonomous Uyghur Region. The viruses were found to be genetically related to the polio viruses currently spreading in Pakistan. Per the WHO, the last WPV case in China was reported in 1999, due to an importation from India. However, the last *indigenous* polio case occurred in China in 1994. For more information, see “Ongoing outbreak of wild poliovirus type 1 in China: WHO/Europe’s recommendations and response,” <http://www.euro.who.int/en/what-we-do/health-topics/disease-prevention/vaccines-and-immunization/news/news/2011/09/ongoing-outbreak-of-wild-poliovirus-type-1-in-china-who-europe-recommendations-and-response>.



Yonglin Wu, Meng Li
(left to right)

“public market.” Notably, the government not only purchases EPI vaccines, but also sets their prices, which are usually set very low. With the government as the sole purchaser in the public market, participants noted, those manufacturers concentrating on EPI vaccines are not subject to the same set of free market variables that often determine vaccine prices.

On the flip side of the public EPI market, the domestic private market comprises optional vaccines, those that are suggested but not required by the EPI. Chinese consumers pay for these vaccines, which cover diseases such as rabies and typhoid for example, out-of-pocket, and receive them of their own accord.

Since prices in the private market are not set by the government, manufacturers can charge far more for the vaccines that they sell there. Due to the higher

“Chinese innovation will go in the direction of the private market, toward new vaccines that are not covered in China’s EPI, toward vaccines aimed at the international market.”

Yonglin Wu, Vice President,
China National Biotec Group (CNBG)

profit margins, “Chinese innovation will go in the direction of the private market, toward new vaccines that are not covered in China’s EPI, toward vaccines aimed at the international market,” said Yonglin Wu.

Participants tied these public-private pricing complexities to the challenges that manufacturers face around upgrading technology and investing in R&D. As there is little to no profit potential in the public market, manufacturers continue to produce EPI vaccines using the old methods and equipment.

The Path to WHO Prequalification: Updating China's Vaccine Regulatory System

The March 2011 announcement by the WHO adds a new dynamic to the traditional Chinese marketplace. For Chinese manufacturers, the WHO's stamp of international approval on the SFDA means that they will be able to submit their vaccines for WHO prequalification for entry into the global public market—a market that includes international vaccine procurement bodies such as UNICEF and GAVI.

Coinciding with the March announcement, the Chinese government simultaneously rolled out new criteria for its Good Manufacturing Practices (GMP)² designed to align SFDA's regulations with the WHO's international standards for quality assurance in pharmaceutical manufacturing. Vaccines that meet these updated standards will be much better positioned to apply for and receive WHO prequalification.

Describing many of the goals and processes in the new GMP system, **Qi Shen**, Director, Biological Products Testing at the National Institutes for Food and Drug Control, SFDA, pointed to the SFDA's, significant regulation and monitoring of every level of vaccine production, noting its judicious restrictions on the use of antibiotics and preservatives in vaccine manufacturing.

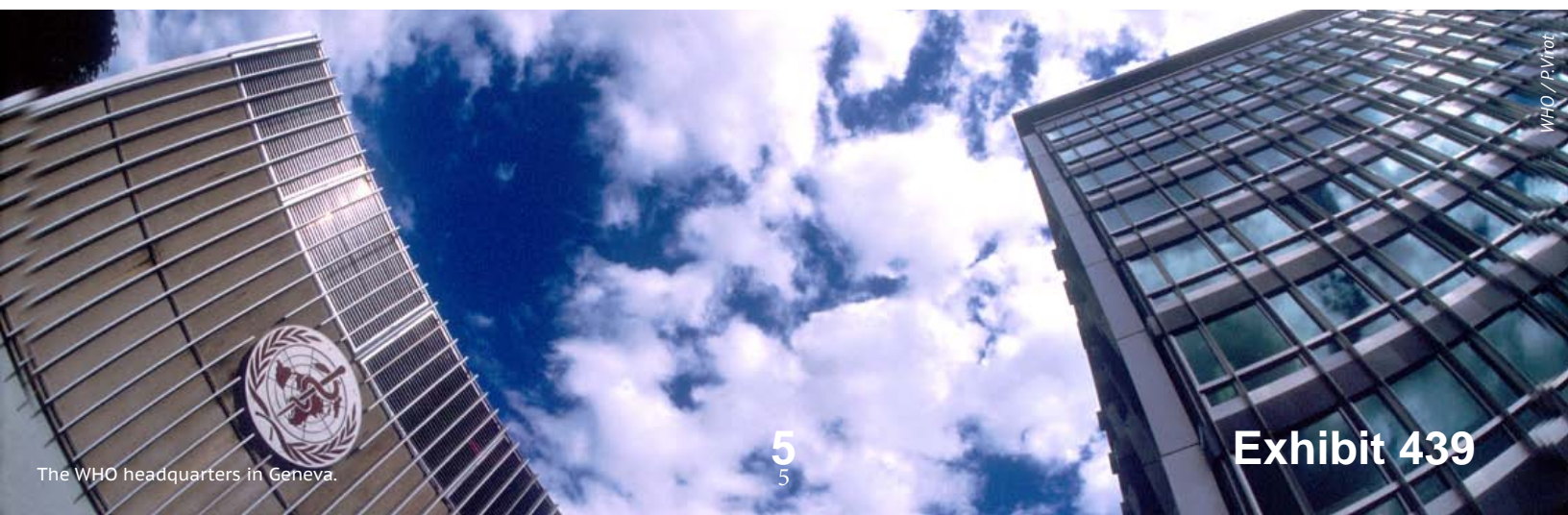
Meng Li, Deputy Director of International Cooperation, CNBG, reminded participants that regulation and

standards are certainly not new for China: "China's SFDA has very strict regulatory standards. They may even exceed international standards in some cases," she said.

The challenge, however, is matching practices with policies, and bringing China's vaccine industry fully up to speed with both new and international regulations. Participants acknowledged that considerable time and resources will be required for industry to comply with the Chinese government's latest GMP criteria and gear up for the WHO prequalification process. "There is a broad-based incentive in China to create new regulations and rules in order to harmonize with the international criteria," said Kewen Jin.

Emblematic of how significant a priority it is to the government that Chinese vaccine manufacturers meet international standards of quality and enter the global market, the SFDA's strict criteria stipulates the compliance of Chinese pharmaceutical companies to the updated GMP by the end of 2013. Manufacturers who are actively working toward meeting WHO prequalification receive government funding for the endeavor. If compliance is not reached by the end of 2013, manufacturers will lose their license to manufacture. Thus, participants noted, there is a huge sense of urgency within the industry to implement the necessary reforms to meet these most recent standards.

² Specific to pharmaceutical production, GMP (Good Manufacturing Practice) is the facet of quality assurance that ensures consistency and quality among drug products, including vaccines. For more information, see: http://www.who.int/medicines/areas/quality_safety/quality_assurance/production/en/.



The Industry Perspective

Implementing new vaccine regulatory criteria, agreed participants, is much easier said than done. Discussion explored the different factors that contribute to the unclear path between policy and implementation, with a focus on the view from industry.

“One key challenge in this process,” explained **Jilan Liu**, Special Advisor, The National Bureau of Asian Research, “is that sound policy is not always soundly implemented at the ground level.” In other words, this doesn’t mean that strict policies aren’t in place; on the contrary, they absolutely exist, but they can be exhibited and manifested in different ways than in, for example, many Western contexts.

Addressing regulatory complexities within such different contexts can create barriers to immediate cohesion with the new GMP and WHO prequalification standards.

Participants noted that many in China’s vaccine industry have never worked in an environment that is officially regulated by an outside overseeing body—that is, not the company itself but the SFDA and the WHO. It was acknowledged that preparing for the WHO prequalification will require a new mindset in many companies.

Pointing to her own experiences with hospital accreditation as a consultant for the Joint Commission International on Hospital Accreditation, however, Jilan Liu painted an optimistic picture of how large Chinese entities evolve to meet international criteria. “In the very beginning, it can be very hard to get an organization accredited,” she explained. “Going through the mindset change, process reengineering, and reorganization, and then having to incorporate policies and procedures into daily practice by everybody within the organization, is no small matter. But after one organization actually becomes accredited, many others quickly follow. The Chinese excel at learning from good examples—that’s the beauty of the Chinese model.”

Many companies have already taken significant, tangible steps to meet the WHO certification criteria. According to Xiaoming Yang, CNBG plans to invest about \$10 billion in the next five years to upgrade its manufacturing facilities to meet both the standards of the WHO and the Chinese government’s new GMP. The company applied for GMP inspection of its facility in June 2011. Under the new standards, CNBG intends to establish Japanese encephalitis (JE) as its first vaccine certified by the SFDA.



CNBG and PATH: Joining Forces against JE

While international markets have been relying on a three-dose Japanese encephalitis (JE) vaccine, China has been effectively immunizing its children with a single-dose JE vaccine for over twenty years. Compared to the internationally better-known JE vaccine, China’s JE vaccine is more practical and better-suited to the realities of lower-resource settings, where tracking and follow-up are among the many challenges.

Why isn’t China’s JE vaccine already more widely available outside of China? The safe, effective, and inexpensive vaccine has been virtually unknown to the rest of the world due to regulatory, language, and cultural barriers.

In close collaboration with PATH, CNBG began undertaking the important task of establishing JE as China’s first WHO-prequalified vaccine, a project that is slated for completion within the next two to three years. While CNBG provides the manufacturing capacity, capability, and knowledge, PATH provides the corresponding “soft infrastructure” support necessary to usher use of the Chinese JE vaccine into the parts of the world that would benefit most, via such means as funding, technical assistance, and international outreach and communication.

With SFDA approval already obtained, CNBG’s single-dose JE vaccine is on track to become the first Chinese-made vaccine to be prequalified by the WHO. The international availability of CNBG’s JE vaccine will create wider protection against a destructive disease that often afflicts the poorest and most marginalized. The CNBG-PATH partnership may serve as a model for how Chinese vaccine manufacturers can collaborate with international organizations and expand their markets while making a powerful contribution to global health.

Panelists discussed several areas where China's vaccine industry needs assistance to prepare for obtaining WHO prequalification and entering global public markets. Soft infrastructure, R&D, quality assurance, and new technologies were identified as key areas in which international collaboration would be most useful and invited.

Soft Infrastructure

While China's vaccine industry already possesses cutting-edge "hardware," or traditional infrastructural elements in terms of buildings and machinery, companies' "soft infrastructure" needs are growing rapidly—particularly regarding management policies and procedures.

Participants defined "soft infrastructure" or "software" in this context as institutional policies, procedures, processes, and management systems and philosophies (pertaining to both personnel and products). While all agreed that the appropriate facilities and technical knowledge are present, opportunities to implement and strengthen the aforementioned areas are great, especially when preparing to compete in global markets, which operate very differently from the Chinese domestic market. Manufacturers acknowledged that in many cases they need to adapt existing institutional structures in order to become significant players in those new and more diverse markets they hope to reach.

Often it is simply a question of practical experience. "In China's vaccine industry, there is a need for international market perspective," noted **Jiankang (Jack) Zhang**, Director, China Program, PATH.

"Chinese companies are open to guidance from external partners to help realign manufacturing and marketing philosophies to meet international

"The Chinese excel at learning from good examples—that's the beauty of the Chinese model."

Jilan Liu, Special Advisor,
The National Bureau of Asian Research

expectations, as well as navigate worldwide marketing and export standards, such as language and cultural norms, trade law, insurance, and distribution logistics," Jack Zhang continued.

Another "soft infrastructure" need concerns internal company procedures and systems. One example, said Yonglin Wu, is to "upgrade existing QMS [Quality Management Systems] to fall in line with WHO prequalification standards." Participants also discussed the need for training in developing or revamping SOPs [Standard Operating Procedure] to meet the SFDA's new GMP criteria.

"Lots of Chinese labs, buildings, hardware, and equipment are as good as those of multinationals, if not better, but it's the SOP that warrants improvement right now," emphasized Kewen Jin. "The SOP is what is needed for things to go right every day, every single day, even when your boss is not around. The culture of not running a red light in the middle of the night when there are no police around—I think that kind of culture needs time to be drilled down and made to stick."

Shi Li, CEO, Shanghai Zerun Biotechnology Co., Ltd., who spent nearly 25 years in the United States working for major multinational pharma companies, concurred. "In regard to hardware facility," he said. "I think that China is now much more advanced. ... The policies and guidance have in essence almost reached international



Jilan Liu, Qi Shen, Jiankang (Jack) Zhang
(left to right)



Buildings in Shanghai.

standards already. The missing parts are the team; the software, i.e. the management and practice; the people training; and the effective communication.”

“Now the challenge in communication between potential Chinese and foreign partners is not the language,” Shi Li continued. “The communication needs have to do with the understanding of social and business culture. Foreign partners need to understand Chinese communication and business culture, and people within China need more understanding of the business culture and operations in a multinational company. Bridging this kind of communication gap helps both sides understand each other’s business, expectations, and partnership potential.”

The workshop discussion overwhelmingly illustrated how Chinese manufacturers welcome and invite collaboration with external partners around

evolving soft infrastructure, particularly in terms of aligning specific industry niches like production line organization and international quality assurance. Participants pinpointed several key areas where international collaboration could enhance and support soft infrastructure improvements:

- Improve English and other foreign language competency to better communicate and conduct business with overseas markets, multinational firms, and international organizations
- Provide guidance around information technology tools to optimize the modern production process
- Advise on international trade laws and mechanisms to build domestic literacy around these issues
- Share technical knowledge of global distribution processes, insurance, and supply chain logistics
- Share intercultural communication knowledge to facilitate smooth partnerships with foreign firms and organizations
- Advise on guiding management structures and philosophies to account for the industry’s continuing brisk growth, and the influence and influx of returning migrants

“In the past, the major barrier hindering Chinese vaccines from going abroad was communication with the world,” said Yonglin Wu. “Working with the WHO, the Gates Foundation, PATH, and similar organizations are a great help to us—these types of partnerships are very important.”

In addition, the WHO is working closely with various manufacturers to provide training for inspectors and auditors. “I think that Chinese-made vaccines will become more widely available to the global market within five years,” said Jack Zhang.

“The missing parts are the team; the software, i.e. the management and practice; the people training; and the effective communication.”

Shi Li, CEO,
Shanghai Zerun Biotechnology Co., Ltd.

Reflections on Pricing: Effects on Public Confidence and Innovation in R&D

One major discussion thread explored how existing low vaccine price points in China impact quality perception of Chinese vaccines abroad, and influence manufacturers' investment capacity in innovation and R&D at home.

Low Prices and Perceptions of Quality

Participants acknowledged that the traditionally low price points of Chinese-made products have contributed to perceptions of poorer product quality. Participants also acknowledged that public confidence, both at home and abroad, regarding Chinese products has wavered in the wake of recent food, toy, and drug scares.

“Fair or unfair, perceived or real, there is certainly a perception about the quality of Chinese-made vaccines,” said Kewen Jin. “I think it’s up to us—the Chinese manufacturers—to show that our products are credible.”

How can Chinese manufacturers ably demonstrate the quality and efficacy of their vaccines given the complexity of vaccine pricing? Participants posited that the SFDA's attainment of vaccine regulatory approval by the WHO is one major step toward proving that China's regulatory standards for vaccines match international quality standards.

Yet the WHO prequalification does not address the pricing component of quality perception. As China is universally known for its low-priced products, many think that Chinese-made vaccines for the global public market will remain low in cost, thus offering the potential to bring more vaccines to more countries and more people.

“I think it’s up to us—the Chinese manufacturers—to show that our products are credible.”

Kewen Jin, General Manager, Aura Partners

However, as China's vaccine industry evolves, as the international market opens, and as domestic manufacturers build their soft infrastructure to promote vaccine innovation and meet international standards, participants acknowledged that rock-bottom prices will no longer be a safe assumption. They concurred that as Chinese-made vaccines become WHO-prequalified and enter the global market, their prices are likely to rise, given market dynamics. Acknowledging this tension, Jilan Liu asked the participants to consider not pushing too hard on prices, especially on current China prices.

“Even if manufacturers are willing to lower the prices in exchange for a contract, prices below a certain threshold would inevitably suppress innovation, and short-change safety and quality, which would eventually undermine public confidence,” she said. “There have been plenty of such examples in food and other sectors that we should try not to repeat.”

Thus, a key discussion conclusion was that the line of reasoning that China's entry to the international market will result in the incursion of cheap vaccines for the world is not necessarily accurate. It was acknowledged that higher quality vaccines will probably mean higher priced vaccines, despite the overall average price drop that may result from the entry of Chinese-made vaccines.

Participants emphasized that high-quality products, the utilization of the best technology and systems, and international credibility all surpass the maintenance of low pricing as their primary priorities in getting their vaccines out to the world. To bolster the vaccine industry's global competitiveness and reputation in innovation and production, industry leaders shared that China's manufacturers are reframing their price-based model, which emphasizes low prices, to a technology-based one, which prioritizes quality assurance.



Stock.xhng / Leonardini



Sally Davies



Qi Shen, Yonglin Wu (left to right)



Rob Lin

Low Prices and Incentives for Greater Innovation and R&D

Low prices also affect manufacturers' ability to invest in innovation and R&D, an issue which participants noted has become even more critical with the WHO prequalification now within reach, as well as for companies to remain competitive in an ever-globalizing world. However, all agreed that one common obstacle to deeper engagement by Chinese manufacturers in innovation and R&D has been the traditionally low price point of Chinese products as noted above.

present price point expectations may impede the industry's advances. With WHO prequalification in sight, however, there is much more motivation to invest in R&D due to the promise of global public markets. "In the past, our R&D strategy has been focused on the Chinese market," said Yonglin Wu. "Now we must focus on a much broader target market." He noted that many vaccines produced in China are replicas of ones that have existed for many years, with the initial innovation having originated in other countries. Marking a 21st century shift, many Chinese vaccine manufacturers now want to create brand new vaccines and carve out a respected international reputation as vaccine innovators.

"Modernizing our methods of vaccine research and assessment in order to give the public new vaccines that are safer and more convenient to deliver—this is more important than very low prices."

Yu Wang, Director General,
China's Center for Disease Control and Prevention (CDC)

Participants noted that Chinese manufacturers are experiencing a different kind of pressure than other big pharma, which do not have the same history of rock-bottom pricing. Chinese manufacturers have traditionally offered low prices, but maintaining those prices becomes difficult, if not unworkable, as they invest more in meeting new

sets of regulatory standards, upgrading hard and soft infrastructure, and innovating around new vaccines—all extremely costly ventures.

Since the Chinese government sets prices for the vaccines purchased for its EPI program, the prices for those vaccines are set very low. While the advantages to manufacturers are guaranteed customers and orders, the low prices reap comparatively little in profits, and thus less capital and drive to invest in R&D.

"I think we can all agree that vaccine manufacturers need to make money," said **Rob Lin**, Deputy Director of Financial Planning and Analysis, Global Health Program, Bill & Melinda Gates Foundation. "That creates incentives for them to produce quality products; it also puts in place incentives for them to create innovative products for future demand."

"With very low prices, we worry about how the industry will be able to adapt newer techniques to change old vaccines," explained Yu Wang. "So we view a low price as one consideration rather than the main consideration, because modernizing our methods of vaccine research and assessment in order to give the public new vaccines that are safer and more convenient to deliver—this is more important than very low prices."

Both the aspiration and the drive to make strides in vaccine innovation are clear among China's vaccine manufacturers, but as discussed above, the world's

Thus, they recognize the necessity of devoting more funding to R&D. Xiaoming Yang noted that CNBG is working to increase the percentage of its annual revenue invested back into R&D, from the current figure of 7%, to 15%.

International Partnerships to Advance Innovation and Reach Underserved Communities

International partnerships for R&D—with donors, foreign governments, multinational pharma, and other stakeholders—are one way that Chinese manufacturers are overcoming the obstacle of reconciling high R&D costs with the low profit margins of the global public market.

These collaborations have taken on various forms, including technology transfers, partnerships that share risk and costs, and product development partnerships. For example, CNBG, in partnership with PATH, is progressing on a promising new vaccine for multivalent rotavirus. “The Chinese vaccine industry is actively seeking opportunities in production line expansion and technological transfer,” said Yonglin Wu. “Our partnership with PATH is part of a larger effort we’re making to extend our reach to other countries.”

The joint CNBG-PATH project on rotavirus vaccine is one example of the Chinese vaccine industry’s interest in formulating vaccines for diseases that most often afflict impoverished countries and communities, where the promise of profit from vaccine sales is lacking. Xiaoming Yang mentioned that CNBG was also exploring the possibility of developing a cholera vaccine that may potentially benefit poor countries like Haiti.

Participants agreed that these kinds of international partnerships will be increasingly critical in the future.

Key Areas of Opportunity

Now that the path to obtaining WHO prequalification status and the promise of global markets is at hand, China’s vaccine manufacturers are more interested than ever in communicating and collaborating with international partners and organizations. Participants identified the following areas as key challenges to address and compelling opportunities for engagement and partnership.

R&D

Some manufacturers are already actively working to expand and reform their R&D operations. Technology transfer and co-ownership of projects in vaccine innovation are two areas ripe for new partnerships.

Soft Infrastructure

Chinese manufacturers are interested in “soft infrastructure”—international training and expert input in the areas of institutional processes, philosophies, and procedures, as well as in particular subjects and areas of competency that help them understand, and remain competitive in, foreign markets and to international vaccine procurement bodies.

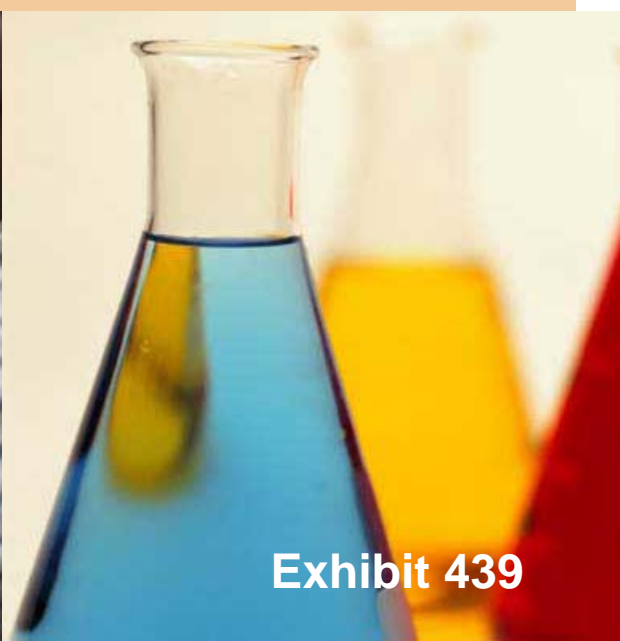
Cross-Cultural, Cross-Border Cooperation and Partnerships

Workshop participants agreed that there is an ongoing need for Chinese vaccine firms to enhance communication and cooperation efforts with other countries, companies, and organizations, both multinational and foreign.



UN Photo / Sophia Paris

Doctors administer diphtheria and tetanus vaccinations provided by the WHO to displaced children in Port-au-Prince, Haiti, following the 2010 earthquake.



Looking to the Future: China's Broader Role in Global Health

Participants discussed the tremendous potential impact that China's vaccine manufacturing capacity will have on the world once it is unleashed to global markets, following WHO prequalification of JE and other Chinese-made vaccines.

China has already demonstrated sound commitments to global health, as evidenced by the government's numerous financial pledges and aid projects for social and economic development in Africa, along with its efforts there to fight malaria. Building on this commitment, Xiaoming Yang noted, "CNBG is very interested in diseases specific to developing countries."

WHO prequalification for the country's vaccine industry will open the door for China to become even more of an important contributor to global health. Markets guaranteed to be impacted include GAVI-eligible countries, as GAVI is likely to be a high-volume purchaser of prequalified Chinese-made vaccines.

"China recognizes that it has a responsibility in global health and is willing to meet the challenge."

Jiankang (Jack) Zhang, Director,
China Program, PATH

Specifically, China's entry into the world vaccine market could result in two particularly game-changing turning points: lowering global procurement prices and reducing supply shortages. Even though the "China price" may eventually be a thing of the past, the combination of China's high-volume manufacturing levels, long experience producing EPI vaccines, and the flattening of vaccine prices for international vaccine procurement bodies like GAVI and UNICEF could make an enormous difference in helping the globe meet the Millennium Development Goal to reduce child mortality.

Flagging this potential, Jack Zhang stressed: "China recognizes that it has a responsibility in global health and is willing to meet the challenge."



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EXHIBIT 440

The New York Times | <https://nyti.ms/JqqMx2>

ASIA PACIFIC

China Investigates Vaccine Maker After Deaths of Infants

By DAVID BARBOZA DEC. 25, 2013

SHANGHAI — Health authorities in China are investigating one of the nation's biggest vaccine makers after eight infants died in the past two months following injections that were meant to immunize them against hepatitis B.

The government said this week that it had suspended the use of millions of doses of a hepatitis B vaccine produced by the manufacturer, Shenzhen Kangtai Biological Products. Government inspectors have been sent to examine the company's facilities.

Six of the deaths have been linked to vaccines produced by Shenzhen Kangtai; the two other infant deaths occurred recently after the use of a hepatitis B vaccine produced by another drug maker, Beijing Tiantan Biological Products. The government did not say whether any action had been taken against Beijing Tiantan or its vaccines. Investigators have not determined the cause of the deaths or linked them directly to the injections, but the cases come at a time of growing public concern in China about food and drug safety problems.

In recent years, China has been troubled by a series of scandals, including tainted rice and milk and the mysterious appearance of thousands of dead pigs floating in the Huangpu River in Shanghai. China has vowed repeatedly to crack down on food and drug safety violations and has moved to strengthen the powers of

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In the vaccine cases, the government is focusing on the role of Shenzhen Kangtai, a privately run drug maker formed in 1992 with government support and the cooperation of the American pharmaceutical company Merck.

Merck helped the company build its drug-manufacturing facility in the city of Shenzhen in the 1990s, and it gave the company the biological technology to produce a hepatitis B vaccine royalty free as part of an unusual joint venture aimed at improving health standards in China. At the time, up to two million Chinese children were being infected annually with hepatitis B.

Since then, China has made great strides in early vaccinations under a national program subsidized by the government. And Shenzhen Kangtai has become the country's biggest producer of hepatitis B vaccines, with a 60 percent market share, according to China's state-run news media. The company has also announced plans to build a \$140 million research and development and drug manufacturing center in Shenzhen.

A representative for Shenzhen Kangtai could not be reached Wednesday, although the company denied last week that its vaccines were at fault in the recent infant deaths.

Although the authorities have banned the use of Shenzhen Kangtai's hepatitis B vaccines at medical facilities, health experts say there are enough vaccines produced by five other Chinese drug makers to meet the demands of the national immunization program. In China, most hepatitis B vaccines are provided free to newborns.

Hepatitis B, which attacks the liver and can lead to death, is the most virulent form of hepatitis, according to the World Health Organization. Chronic forms of hepatitis affect about 500 million people a year worldwide.

A version of this article appears in print on December 26, 2013, on Page A15 of the New York edition with the headline: China Investigates Vaccine Maker After Deaths of Infants.

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Vaccine scandal and crisis in public confidence in China

Jie Qiu, Hengjing Hu, Shenghua Zhou, Qiming Liu

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In March, 2016, a vaccine scandal in Shandong province, eastern China, has led to the deaths of four children. According to state media, the prime culprit, a former pharmacist, was caught delivering vaccines on bicycles without approved storage conditions. The Shandong Food and Drug Administration made public a list of 25 problematic vaccines¹—including polio, mumps, measles, rubella, diphtheria, tetanus, pertussis, and meningococcal vaccines—that had been illegally sold in at least 10 provinces since 2011. Those vaccines are worth more than ¥570 million (ie, US\$88 million).

The vaccine scandal has caused public panic across China. Although relevant government departments have stressed that the improperly stored vaccines are unlikely to cause deaths directly,² public confidence in the health department was still hard hit. There is no doubt that the vaccine management system has a serious vulnerability, which permitted the improperly stored vaccines to be distributed across two-thirds of the country in the past 5 years. The problem of the public health management system has already been recognised since 2008, when toxic chemical melamine was discovered to have been added to formula milk, causing at least six infants to die. However, no effective reform in the system has been made in the past 5 years, and public health is still under threat.

The crisis was also fuelled by the news media's improper reporting. The key problem of those vaccines is ineffective immunity rather than lethality. Because of these exaggerated reports, the public is now questioning whether their children should be vaccinated, even though most vaccinations are mandatory in China. However, both the public and the media have missed the point: without vaccines, infectious diseases will take away many more lives.

The Chinese Government should address the shattered public confidence made worse by the vaccine scandal. The health management system should be improved to ensure that vaccines are properly stored and transported, and transparency of supervision should also be enhanced. Moreover, the government needs to ensure that communication to the public is accurate.

We declare no competing interests.

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Investigators in China have begun recalling defective vaccines produced by a Chinese drugmaker from domestic and overseas markets, health authorities said.

Investigators found Changchun Changsheng Life Sciences Ltd. had blended expired fluids in its vaccines and falsified records from as early as April 2014, the National Health Commission said in a statement Tuesday [Aug. 7].

The names of the overseas countries were not given, but the recall indicated the scandal gripping China may have spread to foreign markets, dealing a potentially heavy blow to the reputation of China's sprawling pharmaceutical sector.

The commission did not immediately respond to a fax Wednesday seeking comment.

Regulators ordered a production halt last month, but public anger soared after documents leaked online showed regulators had found inconsistencies in 2017 but failed to take immediate action.

President Xi Jinping and other top officials have reacted swiftly to contain outrage by condemning Changsheng and pledging improved regulation of food and medicine safety, two areas of perennial concern in China that could fuel anti-government sentiment among the growing urban middle class.

Regulators have launched nationwide spot checks on vaccine makers while the central government has set up a panel of experts to review vaccine safety in China's massive \$122 billion pharmaceutical industry. Changsheng was China's second-largest rabies vaccine manufacturer before the scandal hit.

Police in northeast China said last week they would seek the arrest of 18 Changsheng executives, including chairwoman Gao Junfang.

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Merck Opens New Manufacturing Facility in Hangzhou, China

New facility to deliver innovative, high-quality Merck medicines to Asia

Tuesday, April 16, 2013 8:00 am EDT

Merck (NYSE: MRK), known as MSD outside of the United States and Canada, announced the opening of its new pharmaceutical manufacturing facility in Hangzhou, China. The facility, located in the Hangzhou Economic and Technology Area (HEDA), will package Merck medicines for China and the Asia Pacific region and will become a critical part of Merck's global supply chain.

"This new facility helps Merck to achieve our mission of helping the world be well by bringing our innovative, high-quality medicines to more patients in China," said Willie A. Deese, executive vice president, and president of Merck Manufacturing. "It also extends our long-standing partnership with the Chinese government and our unequivocal commitment to help broaden access to quality healthcare throughout China."

The new facility – a nearly US\$120 million investment by Merck – deepens Merck's growing research and development (R&D), manufacturing and commercial presence in China. Merck also has an R&D Center in Beijing, three manufacturing facilities throughout the country, a marketing and sales organization headquartered in Shanghai, and employs more than 5000 employees in China.

"Merck built its first China plant in 1994 in Hangzhou," said Pam Cheng, president, MSD China. "Today, 20 years later, we are celebrating this new plant in Hangzhou that marks another milestone in our commitment to invest in China and further demonstrates the importance of China to Merck. We are pleased to witness the rapid growth in the country's healthcare system, and are proud to be part of the reform that is underway across China's healthcare industry."

Merck in China

Over the past two decades, Merck has successfully introduced more than 40 innovative medicines and vaccines in China. In addition, in the last ten years, Merck signed the C-MAP agreement with the Chinese government on HIV/AIDS prevention and treatment and donated US\$30 million toward the project.

In 2011, Merck established its Asia R&D headquarters in Beijing and committed to invest more than US\$1.5 billion in R&D in China over the next five years.

"Merck is looking to bring more innovative medicines and vaccines to the Chinese people, and to supporting China's efforts to meet its healthcare demands," commented Ms. Cheng. "With China's fast economic growth, rise in living standards, changing lifestyles, industrialization, urbanization and an aging population, more people across the country need quality health care and access to a strong medical system."

Facts about the new Merck manufacturing facility in HEDA

"The new facility in HEDA joins an integrated, interdependent network of 72 Merck facilities that supply medicines and vaccines to more than 140 countries," said Mr. Deese. "The HEDA facility is one of the most advanced and largest packaging facilities in China and the region."

The new facility is 75,000 m² and is capable of holding up to 16 high speed lines to package pharmaceutical tablets and sterile Merck medicines that are used to manage diabetes, cardiovascular, infectious, respiratory and bone diseases. Packaging capacity is currently estimated at more than 300 million packages annually. Products used in Merck's clinical studies and in its commercial activities to support future new product launches also will be packaged at the new HEDA plant.

The new facility is fully compliant with the rigorous quality, environmental, safety and compliance standards that all Merck manufacturing facilities worldwide meet. The HEDA facility received a current Good Manufacturing Practices (cGMP) certification in January 2013. Protecting the environment was also a critical consideration in the facility's construction – special air, waste and water management procedures and systems were built into the facility.

"Nothing is more important than the compliant, reliable supply of our medicines and vaccines. Our commitment to deliver to patients who rely on Merck for their health and well-being whether it be here in China, Asia Pacific or anywhere in the world is what drives us and defines us as a leading healthcare company," concluded Mr. Deese.

Today's Merck is a global healthcare leader working to help the world be well. Merck is known as MSD outside the United States and Canada. Through our prescription medicines, vaccines, biologic therapies, and consumer care and animal health products, we work with customers and operate in more than 140 countries to deliver innovative health solutions. We also demonstrate our commitment to increasing access to healthcare through far-reaching policies, programs and

partnerships. For more information, visit www.merck.com (<http://www.merck.com/>) and connect with us on Twitter (<http://www.twitter/Merck>), Facebook (<http://www.facebook.com/MerckBeWell>) and YouTube (<http://www.youtube.com/Merck>).

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EXHIBIT 444

Top-Selling Vaccine Made Cheap Shows Challenge to Merck: Health

Ketaki Gokhale

January 26, 2015, 11:00 AM EST



Asia's biggest vaccine maker is working on a string of new low-priced offerings that threaten to undercut brands from the world's biggest pharmaceutical companies.

Serum Institute of India Ltd., which makes vaccines injected in 65 percent of the world's children, is targeting newer vaccines, including one for the human papillomavirus that could be available in late 2018 and sell at a third of the price of Merck & Co.'s blockbuster Gardasil. Also in development are vaccines for types of severe diarrhea and pneumonia.

The version of the HPV vaccine will initially be launched in developing countries and Serum aims to later secure approval for the product in Europe, Suresh Jadhav, executive director of the Indian company, said in an interview. Gardasil is the world's second-best selling vaccine.

Fueled by the invention of advanced new products that command ever higher prices in western markets and a push to increase immunization for polio and measles in developing nations, vaccine sales are growing at double the rate of other pharmaceuticals, according to the World Health Organization.

The Ebola epidemic in West Africa has also lent urgency to the need for affordable versions of new vaccines for poor countries. The global market for vaccines has more than tripled to \$25.5 billion from \$7.4 billion in 2005, estimates Kalorama Information, a publisher of market research.

The world's biggest drugmakers -- including Merck, GlaxoSmithKline Plc, Sanofi and Pfizer Inc. -- dominate the market because of the heavy investments needed to develop vaccines and the high failure rate of potential candidates. Unicef procures their vaccines cheaply for the governments of the world's poorest countries, some on behalf of the Geneva-based GAVI Alliance, a charity that is the biggest provider of money for vaccines sent to developing countries.

In 2013, Unicef procured doses of vaccines for 100 countries, at prices that drug companies say represent their costs. Closely held Serum can undercut those prices because the Pune, India-based company has lower costs of production.

"This will result in creating much wider market access to HPV vaccines," said Jayant Singh, director of the healthcare practice at Frost & Sullivan in New Delhi, referring to the Indian company's planned product.

Most cervical cancers are caused by HPV, and the World Health Organization has recommended universal use of vaccines against the virus, creating an opening for vaccine makers in India and China to come up with cheaper alternatives. Xiamen Inovax Biotech Co., a pharma company based in southeast China, says it is working on an HPV vaccine against two strains of the virus.

Cervical cancer is responsible <http://www.who.int/reproductivehealth/topics/cancers/en/> for more than 270,000 deaths annually, 85 percent of which occur in developing countries, according to the WHO.

Building Stockpiles

Merck earned \$1.8 billion from sales of Gardasil in 2013, driven by approvals for use among boys, purchases for the U.S. Centers for Disease Control vaccine stockpiles and emerging market demand. Boys are vaccinated against HPV as a precaution against oral and anal cancer, which can be caused by the same virus.

Serum says it will initially run clinical trials in India and Africa for its alternative to Gardasil, and the first phase will start this year. Like Gardasil it would protect against four strains of HPV. London-based Glaxo also has an HPV vaccine called Cervarix, which protects against two strains. Glaxo via email said that each year around 80 percent of its vaccines, including Cervarix, go to developing countries at discounted prices.

Gardasil costs <http://www.cdc.gov/vaccines/programs/vfc/awardees/vaccine-management/price-list/> the U.S. Centers for Disease Control \$113.54 per dose. Unicef's website shows it has a contract to buy Gardasil from Merck at \$4.50 a dose this year.

While Serum hasn't yet agreed to a price, "it will be extremely affordable so that even the poorest of the poor countries can introduce it in their programs," Jadhav said. "We are looking at at least about one-third the price that it is currently being procured at by the UN agency."

Extremely Affordable

The presence of low-cost alternatives to Merck and Glaxo's vaccine may encourage developing countries to add HPV immunization to their routine schedules, creating a bigger market for all the manufacturers and eventually benefitting Merck and Glaxo, said Singh.

Merck said it is "premature" to talk of HPV vaccines under development. Low-cost HPV vaccines targeted at 53 low-income countries that are under a tie-up with GAVI wouldn't impact the company's income as it has already committed to no-profit pricing for Gardasil in those nations, Merck said in an e-mailed response to questions.

Getting copies of Gardasil approved in Europe as interchangeable with Merck's version will be challenging, if not impossible, said Richard Purkiss, an analyst at Atlantic Equities LLP in London. In many European Union countries, automatic substitution of biologics, or products like vaccines that are derived from living organisms, is prohibited or not recommended.

Serum has also been building its line-up of other vaccines. A vaccine it developed to target meningitis A in sub-Saharan Africa was this month approved for use in infants under one. It plans to sell a pentavalent rotavirus vaccine at \$2 to \$2.50 a dose to Unicef that will be available by the first quarter of 2018, Jadhav said. Unicef has agreed to pay Merck up to \$5 per dose this year for the U.S. company's RotaTeq vaccine. The virus can cause severe diarrhea.

Serum also has been developed for pneumonia vaccine which will be much cheaper than Merck's product and will be introduced by the first quarter of 2019. The product would compete with Glaxo's Synflorix, which Unicef has agreed to purchase this year for up to \$7 a dose.

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EXHIBIT 445

Merck & Co signs China vaccines alliance

27th July 2010

by

[Kevin Grogan](#)

Merck & Co is pushing on with its emerging markets strategy and linking up with China's Sinopharm Group Co.

The firms have signed "a statement of mutual intent" which will see them cooperate on human papillomavirus and other vaccine products in China. Merck currently markets the HPV treatment Gardasil and the companies added that they will also discuss the potential for promoting and marketing the US major's pharmaceutical products in the country.

Merck chief executive Richard Clark said "we look forward to furthering our discussions with Sinopharm to establish a joint venture to significantly increase the number of people in China who have access to important vaccines". He added that "expanding our business in emerging markets throughout the world is critical to the mission and growth" of the group "and innovative partnerships are a key element of our approach".

Sinopharm said that it has maintained a good relationship with Merck for many years, adding that the growing importance being put on public health and the development of the pharmaceutical industry in China "will be promoted through this strategic cooperation". Financial details of the pact have not been disclosed.

Merck has allied with a major player in China as Sinopharm is the largest state-owned pharmaceutical group. The Shanghai-based firm is China's largest bio-pharmaceutical manufacturing company and its biggest (and the world's third largest) drug distribution company, which is particularly useful given the government's desire to expand healthcare to the country's rural areas.

The New Jersey-headquartered giant recently stated that it expects the emerging markets to account for more than 25% of its global pharmaceutical and vaccine revenue in 2013, up from 17% at present.

EXHIBIT 446

WORLD REPORT | VOLUME 395, ISSUE 10225, P675, FEBRUARY 29, 2020

Indian pharma threatened by COVID-19 shutdowns in China

Patralekha Chatterjee

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As factories in China are closed, India is working to maintain supplies of active pharmaceutical ingredients.

Patralekha Chatterjee reports from New Delhi.

India supplies low-cost generic drugs to millions of people, both within and outside the country. But Indian pharmaceutical companies procure almost 70% of the active pharmaceutical ingredients (APIs) for their medicines from China, the world's leading producer and exporter of APIs by volume. As factories in China are closed to try to stem the coronavirus disease 2019 outbreak, pharmaceutical companies and the Indian Government are becoming concerned over the vulnerability of the Indian pharmaceutical supply chain.

“We see the pharmaceutical supply chain exported out of China under significant pressure. In addition to a manpower shortage due to more and more provincial governments adopting a mandatory 14-day quarantine policy for returning workers, the transportation and logistics apparatus is also getting clogged up due to various travel restrictions and difficult access to ports”, said Jim DeYonker of Centrient Pharmaceuticals, which has manufacturing facilities in India. He said that there were concerns specifically over the manufacture of statins and some antibiotics.

The Indian media has also carried reports about a recent surge in prices of paracetamol, vitamins, and penicillin. “Some of the scare is also due to [the] artificial shortage of APIs created by traders who started hoarding APIs as soon as they heard about the onset of the epidemic”, B R Sikri, chairman of the Federation of Pharmaceutical Entrepreneurs, an industry body, told *The Lancet*.

“There is no cause for panic, as yet”, said Sudarshan Jain, secretary general of the Indian Pharmaceutical Alliance. “The big pharma companies have enough API stocks for 2–3 months. We are currently doing an assessment of the stocks of API and finished formulations that [Indian Pharmaceutical Alliance] members and closely monitoring the situation in China.”



India's pharmaceutical industry has not always been so dependent on Chinese imports. In 1991, Chinese ingredients made up only 0.3% of India's bulk drug (API) imports. But as India's drug makers moved onto formulations, they started procuring APIs from China, where the cost of production is lower.

India's dependence on China for APIs is increasingly seen as a matter of health security. In 2018, the central government in India set up a taskforce to reviving the API sector.

Over the past fortnight, several high-level meetings between the Indian Government and key representatives of India's pharmaceutical industry have taken place to step up API manufacturing capacity within India. One such meeting, organised by NITI Aayog, a government think tank, raised suggestions such as speeding up approvals for building factories, including necessary clearances from the environment ministry, and for giving concessions on electricity, and the promotion of pharmaceutical manufacturing hubs.

 Figure thumbnail fx1

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“The government is very serious about encouraging India's API manufacturers to expand capacity. This is linked to our national security”, says Sikri.

In the long term, assuming that the government removes barriers to API production in India, it is unlikely to spur the industry into immediate action for ramping up production while APIs imported from China remain cheaper. For the industry involved in the formulation business, profit and turnover are key, says Sakthivel Selvaraj of the Public Health Foundation of India, a think tank.

Selvaraj says Indian companies still have an advantage in terms of wages, but fiscal and non-financial incentives and building infrastructure would be crucial to get domestic drug manufacturers to produce API.

“The only other option is to revive and revitalise the public sector drug makers”, Selvaraj told *The Lancet*.

EXHIBIT 447



Almost 40 Indonesian medical facilities procured fake vaccines

Katrina Megget, 12-Jul-2016

Ongoing investigations into the scale of the fake vaccine racket in Indonesia have uncovered counterfeits in 37 medical facilities across nine provinces.

The news follows the recent bust of a fake vaccine syndicate that had been operating in the country for more than a decade. At the time of the bust at the end of June, it was unclear how widespread the racket was, although 17 people were arrested and vaccines from nearly 30 health clinics were confiscated, while there were calls for children to be revaccinated.



Now Indonesia's Food and Drug Monitoring Agency (BPOM) says it has discovered fake vaccines procured by 37 medical facilities across nine provinces – South Sumatra, Lampung, Banten, Jakarta, West Java, East Java, Bangka Belitung, Riau and Riau Islands.

"We found 39 fake vaccines in all," said Arustiono, director for drugs distribution at BPOM.

Counterfeit vaccines so far discovered include Tripacel (combined vaccine for tetanus and diphtheria), Pediacel (combined vaccine for diphtheria, tetanus, whooping cough, polio and Hib infection), Engerix-B (hepatitis B vaccine), anti-tetanus serum, polyvalent anti-snake serum and Tuberculin PPD TR23. There have been calls to publically release the results from laboratory tests.

The investigation into the racket resulted from a tip off from a major pharma company that some of its products had been counterfeited. Brands produced by GlaxoSmithKline, Sanofi and Bio Farma are believed to have been subject to fake copies.

Health facilities in Indonesia are required to use vaccines that are provided by the government or distributed through official channels with rigorous safety procedures. But there is a demand for vaccines that come through unofficial channels, which then opens up the possibility of counterfeits flooding the market. The BPOM has also found that a number of internet sites may be operating as unofficial supply channels for fake vaccines.



negligence and has urged people affected by the fake vaccines to file a class action lawsuit against both institutions.

Meanwhile, the country's Health Ministry believes at least 197 children had been given fake vaccines and will now roll out a revaccination programme next week.

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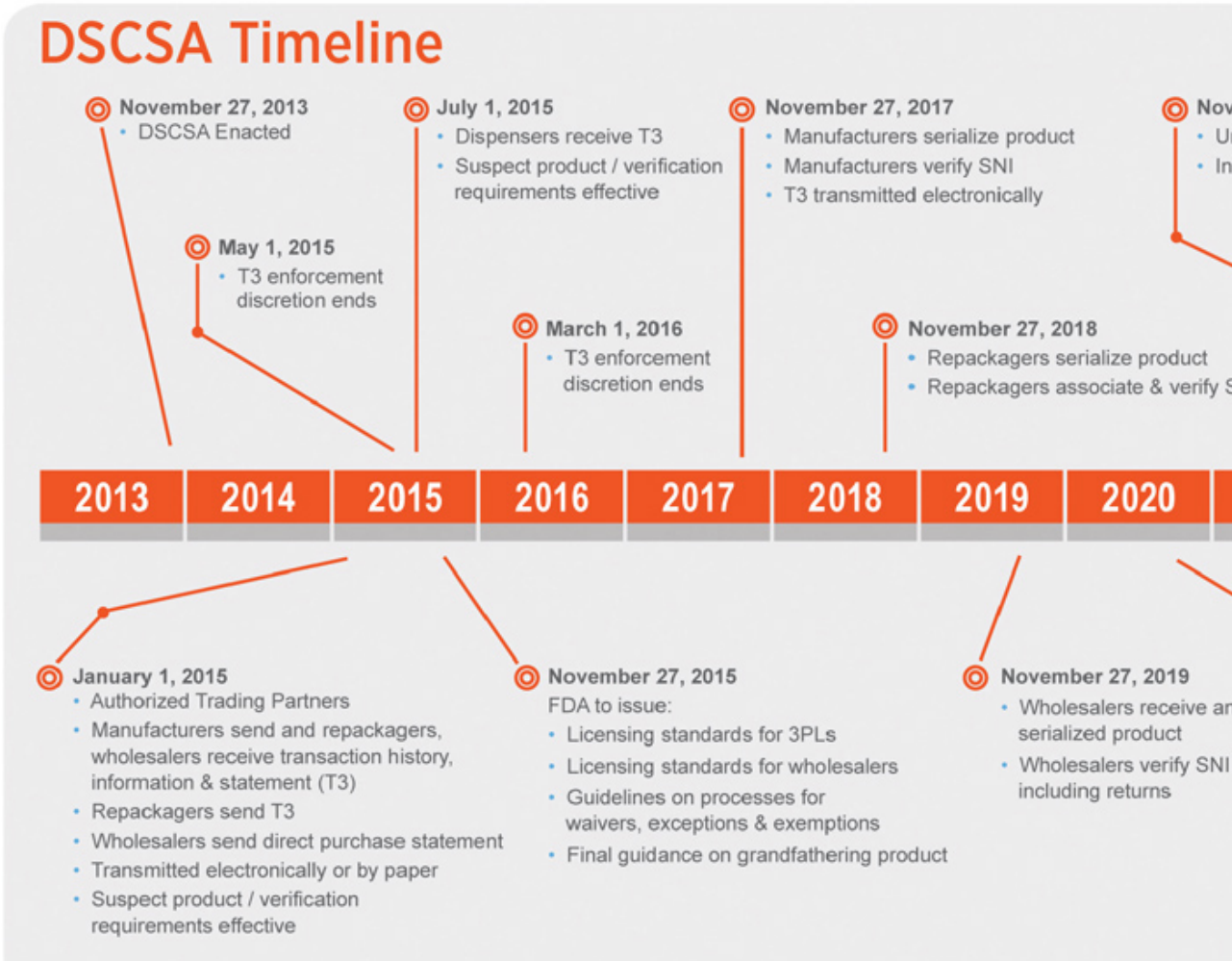
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EXHIBIT 448



**PHARMACEUTICAL
COMMERCE**
BUSINESS STRATEGIES FOR
BIO/PHARMA SUCCESS



2016 Product Security Report

May 5, 2016 | Updated: June 8, 2016

Pharma spends heavily to secure its supply chain, while politicians bring out the re-importation topic

Nicholas Basta

For the moment, let's all breathe a sigh of relief that no major counterfeiting scandal has erupted in the US in the past couple years; although there are always underpublicized cases of drug diversions or the improper purchase of prescription drugs from online, self-proclaimed "pharmacies," nothing on a par with the bogus anti-cancer drugs from the Middle East showing up in oncologists' offices in 2014 has occurred. Which is not to say that **counterfeiting, diversion and stolen pharmaceutical cargo are not global problems: the situation in Africa and other parts of the underdeveloped world is still dire, and counterfeiters and diverters still knock on the doors of national pharmaceutical supply chains around the world.**

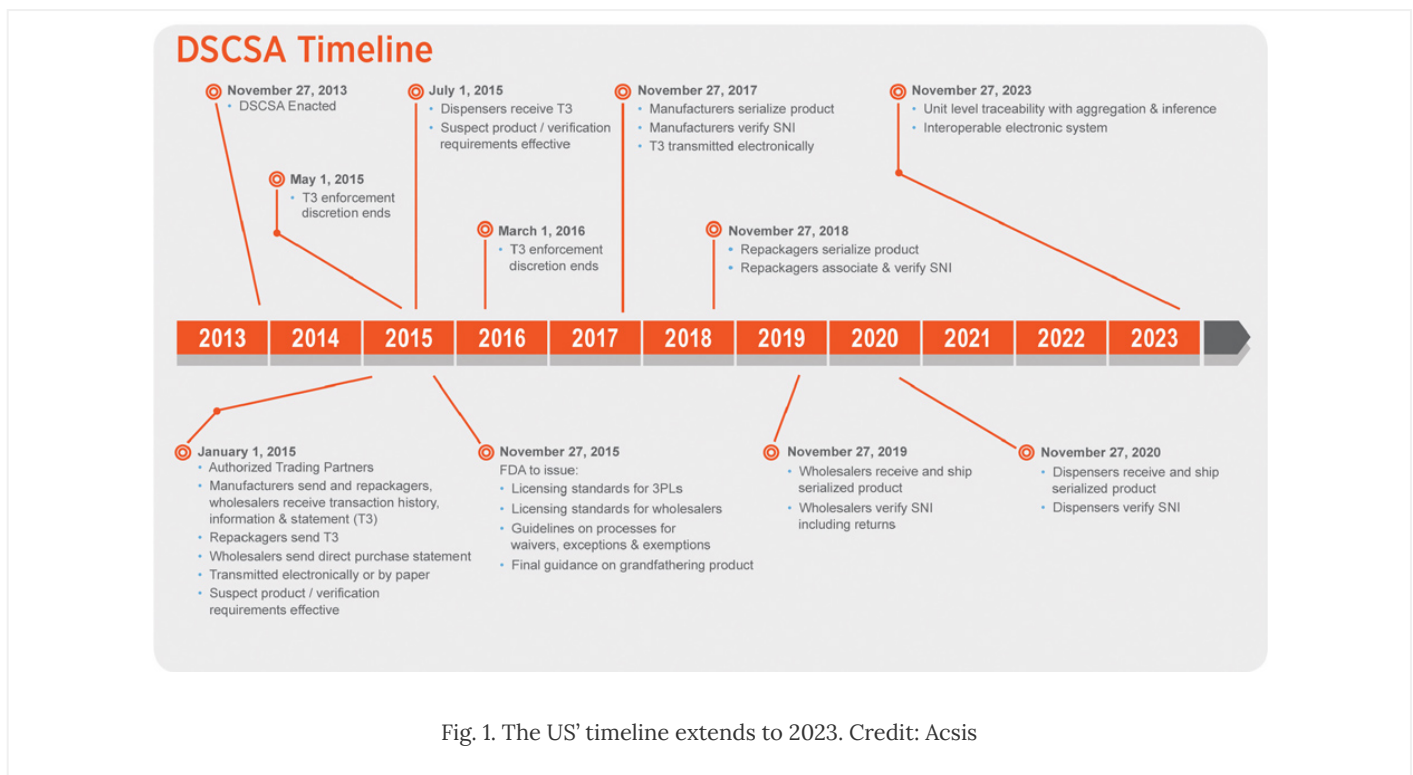


Fig. 1. The US' timeline extends to 2023. Credit: Acsis

And while counterfeiting remains the ultimate in evil criminal practices, product security needs to be looked at more broadly. As this story was going to press, news was breaking of **a major scandal in China, involving millions of doses of childhood vaccines that were improperly stored (and therefore inactivated) by a small group of traders who then sold the drugs to local pharmacies across the country.** The distribution apparently did not result in patient deaths (unlike earlier scandals involving adulterated infant formula), but is turning into a black eye for government regulators, who reportedly sat on the news for over a year and have now further eroded the Chinese public's trust in its healthcare system. Pharma supply chain managers know that improper storage can be as damaging as fake products; but that knowledge dwindles as drugs move into commercial distribution.

For brand-security and product-integrity managers in pharma, much of the attention is currently devoted to fulfilling the mandates of the US Drug Supply Chain Security Act (DSCSA). Operational managers in packaging and trade relations met, by and large, the January 2015 deadline for conveying lot-level data to trading partners along with the physical movement of the drugs in the

supply chain. The next step, for retail pharmacies to verify the incoming information and store that data for FDA inspection, was delayed twice during 2015, and is currently being complied with at the local pharmacy level.

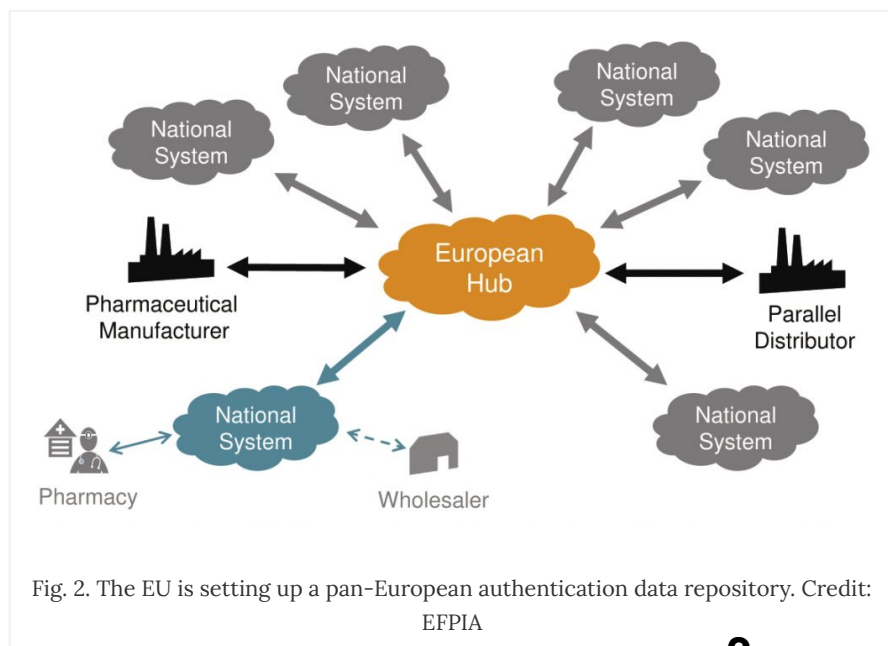
Pharmaceutical Commerce’s annual round-the-pharma-distribution-circle looks at the key areas of brand integrity:

- Serialization and traceability, now occurring globally
- Online pharmacies and online drug promotion to consumers
- Cargo security
- Anticounterfeiting technologies

Serialization milestones

At the very beginning of 2015, US wholesalers were mandated to begin recording lot-level data on shipments they receive from their pharma suppliers. That is one of the earliest deadlines to be met by the Drug Supply Chain Security Act (DSCSA) and, by most accounts, the mandate was met successfully. The next deadline was for that data to be on hand at retail pharmacies, but that deadline was delayed twice and only went into effect this spring. Industry observers say that the biggest pharmacy chains have been well equipped to receive this data; smaller chains or independents are relying on their distributors to keep the data on hand.

Manufacturer activity is ramping up rapidly for the next step—providing item-level serialization by November 2017. To accomplish this, manufacturers and their contract packagers need to install a 2D-barcoding device on their packaging lines (or, alternatively, to arrange for delivery of already-printed labels to be applied), and a machine-vision system to record the serial data and verify its placement.



A parallel development is occurring in Europe, where the Falsified Medicines Directive (FMD) was officially implemented in February by the European Union. A three-year timetable, to early 2019, is now the goal for the EU to have an authentication system in place whereby pharmacies can check with a national (or EU-wide) online database to verify the authenticity of a drug package prior to dispensing it to a patient. (Relative

Fig. 2. The EU is setting up a pan-European authentication data repository. Credit: EFPIA

to the US, this program is starting a little later and is scheduled to conclude a little sooner; from a packaging line perspective, the requirements are very similar.) A growing number of other nations, including China, South Korea, Brazil, Argentina, India and others, have their own timetables, although some of them seem to shift as their implementation date approaches.

Two North American companies—Systech International and Optel Vision—have been competing aggressively for the packaging-line equipment segment. Although neither company releases financial data, the momentum currently seems to belong to Optel, which opened a center in Ireland last year, is opening two additional centers—in Brazil and India—this year, and expects to employ nearly 50% more employees (to a total of almost 700) by year-end.

Both companies work with a variety of equipment vendors (cameras, barcode printers and scanners, as well as packaging equipment manufacturers of cartoners, bundlers and case-packing equipment). For its part, Systech has rebranded its software offerings as UniSolve and UniSecure; Darryl Brown, marketing manager, says that UniSecure, a proprietary method of using the optical image of a label itself as an authentication technology, is generating substantial interest in Europe. “UniSecure bridges a gap that enables consumers to connect directly with the pharma manufacturer,” by using a smartphone to authenticate the label with a manufacturer’s online database. “That can be important for communicating patient medication guides and the like, in the language that the patient prefers.”

Meanwhile, a number of European companies, including Antares Vision (from Italy) and Adents (from France) have opened offices in the US. Antares brings substantial experience from Turkey, where its systems serialize and verify 50% of the drugs being distributed in that country, according to Adriano Fusco, global marketing director at the firm. (Turkey was one of the first countries to establish a national drug-tracking system, both as protection against counterfeiting, and to digitize its health system reimbursement program.) The company also makes packaging line equipment; and its US facility is more than a sales office—it includes a sizable warehouse and production facility, which not only stocks units produced in Europe, but also manufactures several models on premises. The facility also features a laboratory for full solution testing, a team for technical support and a team of project managers.

Adents, which has experience in serializing food and cosmetics in Europe, opened a US office early last year, headed by Ed Cummings, an experienced systems integrator. He says that as opposed to his competitors, who provide their own cameras and visual-inspection equipment, Adents will work with nearly any equipment supplier—including working with vision equipment that might already be installed online. “We’re a pure-play software vendor,” he says, noting that the company is the pharma-serialization partner chosen by Siemens, a dominant industrial automation vendor, to provide packaging automation to the pharma industry.

Other players in the packaging automation field include Covectra, Seidenader (part of Körber Medipak), and Rockwell Automation.

Aggregation aggravation

The barcoding/serialization process itself is fairly straightforward; the main issue is selecting serial numbers and then applying them to each package (the verification part of this process, however, is another story).

But at the end of many packaging lines, individual packages go into cases or bundles, and those into pallets, and this “aggregation” step is a longstanding impediment to smooth packaging and distribution operations. Because

wholesalers and other pharma customers do not want to open each case of product

when it is received to verify its contents, they want a near-perfect accounting of what serialized items are in each case. The structure for doing this is to assign a “parent-child” relationship between the multiple barcodes of packages in a case, and a barcode for the case itself. (At this year’s HDMA Distribution Management Assn. conference and expo, one speaker alluded to a “grandparent-parent-child” relationship, including the barcode that would go with an entire pallet of product.)

Aggregation is expensive: industry experts agree that including aggregation more or less doubles the cost of a packaging line serialization project. Manufacturers know that the DSCSA does not specify aggregation in its mandates; however, most major wholesalers will insist on it as a term in their supplier contracts. “When you include aggregation, you have more control over what is happening in your packaging and warehousing operations,” says Antares’ Fusco. “For this reason many companies are going with aggregation, even if not expressly mandated.”

Antares and others provide automated, semi-automated and manual aggregation stations: either robotic equipment assembles a layer of packages, validates it with the camera and continues to fill up a case, or an operator performs either both the filling and the validation with a handheld scanner, or just the filling step. Systech’s Brown says that his company’s software has included process steps for aggregation for many years; it can also provide data on cases that might include both serialized and non-serialized product. (The issue of “grandfathering” pharmaceutical packages being made today, but which are not serialized, and will be in circulation for several years to come, is yet another worry of wholesalers.)

Jean-Pierre Allard, chief technology officer at Optel Vision, has presented data in company workshops that adding aggregation after a serialization project increases overall costs by 27%, as



Fig. 3. Antares All-in-One automated case packer handles aggregation.



Fig. 4. Antares Vision's manual casepacking station can be added into existing packaging lines.

compared to incorporating it at the same time as the serialization; but he also suggests that it is possible to approach the task stepwise, especially if there is an expectation that aggregation equipment will improve by the time it becomes necessary for a fully compliant traceability system.

Special mention should also be made of a key transfer that usually occurs within a pharma company's four walls: from the production area to warehousing. While some of the serialization vendors offer a dedicated warehouse tracking system, and big logistics software companies like JDA Software or Manhattan Research offer comprehensive warehouse and logistics IT systems, there are at least two vendors—Acsis and Roc-IT—that offer so-called “edge” systems that interact with the site-level serialization software and extend it into the warehouse. In the warehouse, serial data and location information—often collected by handheld scanners—can be compiled and stored. The systems provide a critical link between the output of the packaging lines, and the output of the

warehouse as product moves out from the manufacturer to its customers.

More standards

The great majority of this serialization activity is codified in standards established by the GS1 organization; its standards specify how a serial code is to be created and printed (both as a 2-D and a human-readable barcode), and the broader standards for global location numbers (GLNs) and a host of other codes. At a higher level, it has also established the EPCIS standard, which codifies how “events” are to be described in a traceability system. (An event is a step in the distribution process, such as a delivery of a shipment, stocking a case and the like. This event information ultimately becomes part of the “transaction history” required by DSCSA.) EPCIS 1.1 has been out for over a year; an updated ver. 1.2 is being released imminently, according to Peter Sturtevant, senior director in the GS1-US section. (Last July, EPCIS was accepted as ISO/IEC 19988 by the ISO organization, which gives it a broader applicability.) The GS1 Healthcare organization (a subset of GS1 for pharma and healthcare) conducts regular workshops, and maintains workgroups that continually refine the standards.

In theory, if everyone more or less agrees on the form of EPCIS data, packaging line equipment and plant-level IT systems should simply be able to process the data, right? In practice, however, most of the vendors (even those claiming GS1 certification) involved in serialization technology have their own methods of communicating these data, and transfers from, say, the plant floor to

the enterprise level require configuring interfaces at multiple steps. With five years or so of pilot projects, multiple already-installed lines, and the inherent competitive stance of vendors call for establishing a plant-automation communications standard.

Optel, joined by Systech and several other firms (with some pharma companies, who are paying for all this technology, coming along) have started an initiative to establish an open, global standard. And while its actual elements are still in flux, the direction the group, called the Open Serialization Communication Standard Work Group, is going in is to develop a standard in conjunction with ISA International (the former Instrument Soc. of America), and with the ISO organization in Europe. The standard is structured off the framework of ISA-95, a long-established standard in industrial automation, which specifies a “stack” of control (Level 1: sensors; Level 2: line controllers; Level 3: site automation; Level 4: enterprise data systems).

So far, a relatively small group of companies are either contributing funds to the effort, or providing internal resources to move the project forward. The progress has been slow: initial meetings were held in 2014, and a planning document was written last year by Charles Gifford, an industry consultant acting as executive director. That document looked to a June 2016 date for a draft standard, but the effort is still in the planning stage.

“It is not our core business to sell professional services to customize the IT connections from our packaging line and plant server platform to the various third-party platforms such as corporate serialization servers, MES and ERP systems,” says Louis Roy, Optel CEO. “For Optel Vision, having a single standard IT connection scheme with all our partners means that we will spend less time on every project and be able to deploy faster. For the manufacturers, it means that they are less vendor-locked with the interoperability such standard allows and, of course, they save money. Billions of dollars of integration can be saved for the industry with the Open-SCS standard.”

This initiative is a worthy one and could provide substantial savings to pharma manufacturers and their contract manufacturing partners; the problem is that developing a standard when the vendors in the field are competing heavily (think of the early days of Apple Computer and Microsoft); and because the clock is already ticking on serialization deadlines and thousands of packaging lines have already been converted, time could be running short for an effective standard.

Enterprise level

The vision for DSCSA is that pharmacies or doctors' offices can verify the authenticity of a drug package with an online data depository, and state pharmacy regulators can review the movement of a drug through the supply chain at a moment's notice. How data ultimately will be collected and made accessible remains to be determined; in the meantime, manufacturers need systems that can interact with their trading partners for at least that one-to-one data exchange.

At this enterprise level, companies like TraceLink, Axway, RFXcel, Frequenz (and System, with its UniSphere IT system solution) are offering or have installed systems to collect the massive amounts of data from a commercial-scale distribution perspective. The field is undergoing a step change as SAP introduced its Advanced Track and Trace for Pharma (ATTP) system late last year; previously, companies had been adapting existing SAP general-purpose tools (OER and AII) to meet the enterprise-level challenges, but the company, whose enterprise software is widely used in pharma, committed to an industry-specific system in ATTP.

Part of the problem these enterprise systems have to contend with is that each country or region has its own reporting requirements, so the systems have to be adapted to those nations with the addition of reporting modules. There are also capacity constraints; the data accumulated during, for example, daily warehousing operations at a wholesaler's distribution center are massive, and yet for the purposes of verifying the accuracy of a delivery, those data need to be accessible in almost real-time.

TraceLink committed to a full-blown cloud-based offering several years ago, and has benefitted from the flexibility that cloud-based computing offers (it partners with Amazon Web Services in this regard). Other companies offer both cloud-based and on-premises versions; SAP, which is putting more and more of its resources into cloud computing, offers its own hosting capacity.

In March, TraceLink announced that it had successfully managed commercial-scale data exchange—with full EPCIS compliance—with one of the Big 3 wholesalers and a leading pharma company in the US; the project started in 2015 and in February 2016, according to a company statement, “TraceLink processed more than 1,300 EPCIS events with more than 10,000 serialized units per event—and more than 230 EPCIS events with more than 100,000 serialized units per event. TraceLink can process these large-scale EPCIS events at operational speed, where traditional databases take hours to do the same. As a result, TraceLink customers are able to run their serialized operations and maintain the same level of productivity and efficiency they experienced prior to shipping products with serialization information.”

Safe online pharmacies?

One of the criticisms of DSCSA leading up to its passage was that it would barely make a dent on the trade going on with online “pharmacies” (many of which are pharmacies in name only, and which operate not only outside national pharmacy standards, but outside legal commerce). The National Assn. of Boards of Pharmacy (NABP), which has led a battle against these drug dealers for years, succeeded in getting the responsibility from the ICANN organization (which manages Internet domain names) to manage the “.pharmacy” name extension (technically, the “top level domain name”) last year, enabling it to at least prevent the online sites from using “.pharmacy” as part of their name.

As of October, NABP had authorized 227 entities (pharmacies as well as governmental boards and a handful of manufacturers) to use the .pharmacy name; most of them met NABP's criteria as

validated pharmacy sites, and there are discussions going on with other nations over the naming convention and how it is to be regulated.

The seriousness of the online pharmacy situation can't be understated. In its annual update of spurious online pharmacies, NABP reported in January that it had identified 10,668 websites operating outside US and NABP standards for pharmacy practice; more than half of them did not list a physical location, and a comparable number offer drugs not approved in the US for use. At the same time, reports are mounting of the sale of unapproved or counterfeit controlled substances; there was a rash of deaths in California recently from fake Xanax laced with fentanyl, a powerful analgesic. FDA, US Customs and Interpol, among others, run an "Operation Pangea" annually to crack down on illicit online pharmacies, shutting down thousands and confiscating fake drugs; the 2016 event has not yet occurred.

There was no little irony in an announcement, last August, that a federal indictment had been unsealed charging Ram Kamath, PharmD, and thirteen other organizations and individuals related to the sale of \$78 million worth of mislabeled and counterfeit drugs. Kamath, an Illinois resident, was also the director of pharmacy policy and international verifications for PharmacyChecker.com, a New York-based organization that promotes purchasing drugs from non-US sources. It also claims to provide a verification process of its own; however, one of the companies cited in the indictment, CanadaDrugs.com, as well as others in the past, have been shut down or had their executives arrested for counterfeit-drug distribution or selling controlled substances illegally.

"For years, millions of patients and physicians have relied upon PharmacyChecker.com and CanadaDrugs.com, believing they are getting genuine drugs from a real Canadian pharmacy," said Libby Baney, Alliance for Safe Online Pharmacies founder and executive director, in a statement. "The DOJ indictment evidences that these entities have been touting myths, giving US physicians and consumers a false—and consequently dangerous—sense of confidence."

The online pharmacy scene also highlights a related worry for pharma brand owners: improper use of their brand names for online sales or other purposes (one obvious example: a batch of drug being offered for sale on Ebay.com or elsewhere). Google, Bing and several other online information sites agreed to police the appearance of drug names and online pharmacy promotion on their sites several years ago (Google paid a \$500-million fine to the US government leading up to this effort). Another company, MarkMonitor, offers brand security services to pharma companies and other brand owners.

Security and resilience

Close observers of global pharmaceutical supply chains are aware of hot spots around the world where pharmaceutical shipments are being targeted by thieves, or where natural catastrophes can interrupt, for example, deliveries from a contract supplier. Within the US, elaborate tracking systems are managed by trucking companies to secure cargoes, with onboard cellular or satellite-

based systems tracking the shipments in real time to identify theft or diversion situations. (There's an arms race here: thieves have developed scanner-jamming devices; while security suppliers develop jamming-resistant technology.)

Charles Forsaith, a security director at Purdue Pharma and head of the Pharmaceutical Cargo Security Coalition, a volunteer group in the US, notes that truck thefts in the US have been declining for several years after his group and others began working to improve coordination between local law enforcement and trucking companies. "The spirit of cooperation, particularly within the pharma security groups, remains at a very high level," he says. More recently, a subgroup with PCSC has begun analyzing "last mile" incidents, frequently involving the vans used to deliver daily shipments to local pharmacies.

Several independent organizations, as well as the multinational logistics companies, can monitor shipments around the world, including ocean freighters and air cargo at airports (technology and regulations prohibit tracking aircraft in flight). FreightWatch International, a subsidiary of the cold-chain technology provider Sensitech, is one such service company; others include LoJack Supply Chain Integrity and CargoNet, a subsidiary of Verisk Analytics, a global fraud-protection and business continuity provider.

Last fall, in its eighth annual Pain in the (Supply) Chain survey, UPS Healthcare Logistics found that life sciences companies have made substantial progress over the past several years investing in IT systems and cargo protection, but that contingency and business-continuity planning was lagging, with only 60% of respondents considering this a priority. "Even as unplanned events have impacted healthcare supply chains over the past several years, a large percentage of supply chain decisionmakers still do not consider contingency planning important," the report concluded.

DHL came out with its own study this spring, Insight on Risk and Resilience,* in conjunction with a recently developed information and analytic service, Resilience360, which assesses global logistics threats (natural disasters, war, labor relations) for its clients. One of the offshoots of this service is the Supply Chain Risk Exposure Index, a customized assessment of manufacturers' business risks. "The life sciences industry has high-value products on which lives depend; in addition it has more stringent regulatory requirements than most industries," says Angelos Orfanos, president, DHL Life Sciences & Healthcare. "Outsourced logistics providers like us have invested heavily in resources to ensure product safety and risk reduction."

The public health aspects of pharma's supply chain integrity are the focus of a US organization, Healthcare Ready, which arose out of the follow-up to Hurricane Katrina in 2005 to coordinate private businesses and public health agencies (such as the Federal Emergency Management Administration) to prepare for natural disasters. "We've been working with state and federal public health and emergency response organizations to ensure that when the next natural disaster strikes, the medicine and healthcare supplies that affected people need will be available," says Emily Lord, executive director.

Too many silos

The centrality of serialization-based traceability systems to all these aspects of supply chain integrity is a key theme stressed by Andrew Stevens, an analyst for Gartner Group, the IT consulting firm. Besides noting the overlap among US, EU, and other nations' and regions' traceability initiatives, he puts the context of traceability in a business value context.

“One of the problems with traceability is that it is looked on only as a compliance issue, and focusing on making it work on packaging lines,” he says. “But once this data becomes available throughout supply chains and throughout pharma organizations, a very different perspective appears.” Even now, attention should be paid to how traceability will improve quality management in manufacturing, and soon will be of value to brand management teams, patient support services and a wide range of other functional areas (see Fig. 6).

INSIGHTON:



RISK & RESILIENCE

Fig. 5. DHL's Risk and Resilience report recommends a comprehensive view of business continuity

The Demand-Driven Network Roadmap

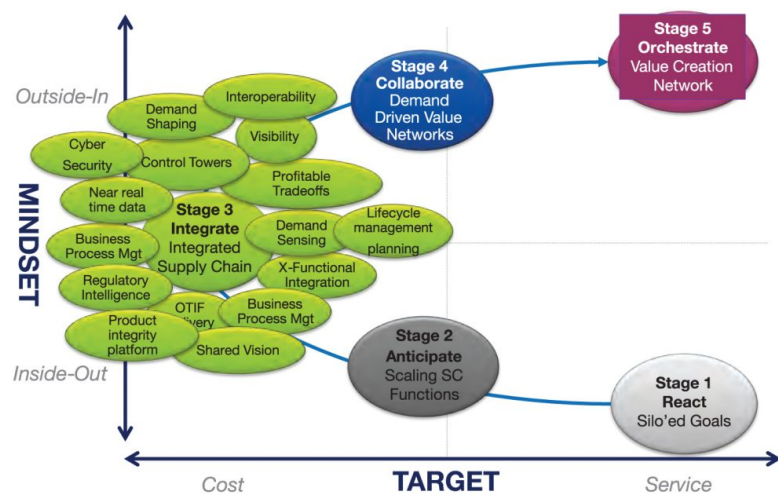


Fig. 6. Gartner envisions a future state where serialization data transforms supply chains into “value creation networks.” Credit: Gartner

As Stevens sees it, traceability will be a gateway to a future state of “digital business technology” that meshes well with where healthcare itself is going: value-based therapy management; connectivity with patients; and as-yet unrealized new business models. Improved supply chain performance—in the form of lower inventories, better visibility in distribution channels and more accurate forecasting—is just the first wave of change.

Greg Cathcart, president of Excellis Health Solutions, another IT consulting firm, sees a similar set of issues with how traceability is being handled now.

One example comes from health systems where, once the serial data that is to accompany the physical arrival of drug shipments is integrated into internal IT systems (which won't be a

EXHIBIT 449



DEEP DIVE

As India, China drug industries mature, FDA scrutiny an overhang

By Ned Pagliarulo

Published April 23, 2018

Sun Pharmaceutical Industries Ltd., India's largest generic drugmaker by market share, has spent the last two years stuck in a holding pattern.

Operations at a key factory in Halol have been hamstrung by the still-lingering effects of a warning letter Sun received from the U.S. Food and Drug Administration in December 2015. Despite the company's efforts to fix the manufacturing-related violations, U.S. regulators have yet to give an all clear — delaying the approval of new products made at the site.

It's a familiar story for dozens of other India- and China-based drug manufacturers flagged by the FDA for not keeping their operations up to code.

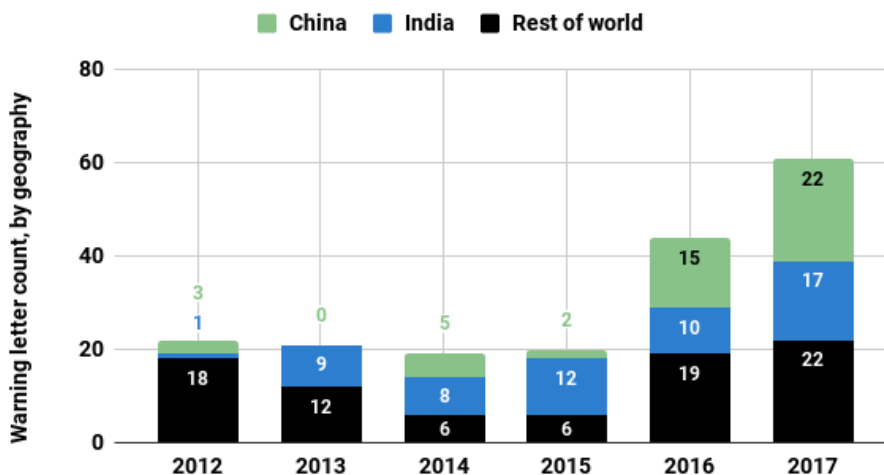
In recent years, the U.S. agency has issued warning letters to production plants in India and China at an increasing rate. Last year, for example, 39 of the 61 notices sent by the Office of Manufacturing Quality in the FDA's Center for Drug Evaluation and Research were to facilities in the two countries.

Observers say the stepped-up oversight isn't likely to wane any time soon — putting product quality in focus at a time when the domestic industry in both countries aims to move further into novel drug development.

"It is safe to say that the scrutiny is only going to increase in China over the next few years as well until that industry starts to mature," said Sam Verungopal, a principal at PwC, in an interview.

Enforcement actions like those faced by Sun also ups pressure on generic drugmakers abroad, just as falling prices and increasing competition threaten the wider industry's business model.

Manufacturing-related warning letters to China, India increase



* Letters issued by CDER's Office of Manufacturing Quality
 Ned Pagliarulo / BioPharma Dive, data from FDA

When inspectors knock

Many of the ingredients contained in medicines sold to U.S. consumers come from factories churning out pills and vials near Asian cities like Mumbai and Shanghai. Roughly 80% of active pharmaceutical ingredients and 40% of finished drugs are imported from abroad, according to the FDA, which has responded by opening offices in both India and China.

Given the reliance on foreign-sourced supply, it's not a surprise regulators have paid attention to drug factories overseas.

To better support inspection of the thousands of plants, the FDA opened offices in both India and China a decade ago. But, only in recent years have the number of warning letters issued to facilities in those countries surged.

That jump is particularly notable in the three years between 2015 and 2017. During that period, an office within the FDA's Center for Drug Evaluation and Research issued citations to nearly 80 Chinese and Indian plants for violations of Good Manufacturing Practices (GMP) — compared to 48 sent to facilities located elsewhere.

This uptick has occurred even as the number of inspections resulting in Form 483s, a notice of potential violations, has held steady. According to analysts at PricewaterhouseCooper LLP's Health Research Institute, this suggests an increased emphasis on quality during FDA inspections.

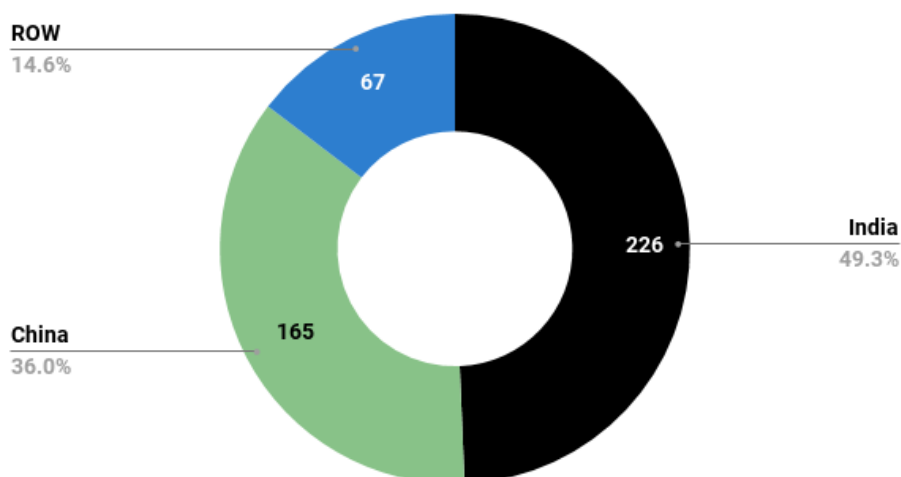
Of particular note, though, is the rapidly rising number of China-based plants flagged for GMP shortcomings.

"You could take a blueprint of the issues that were found across India and apply it to China. They are finding many of the same issues," PwC's Verungopal said, citing data integrity in particular as a key concern.

India, while still maturing, has seen a marked improvement in quality systems and employee capabilities, according to Verungopal.

The FDA isn't the only regulatory body probing manufacturing quality in India and China. Recently released data from an intra-agency program led by the European Medicines Agency showed the two countries were far and away the most frequent target of API-related inspections.

API inspections by international regulators, 2011 - 2016



Ned Pagliarulo / BioPharma Dive, data from EMA

Business abroad

For companies like Sun, shipping knockoff drugs into the U.S. has boosted business, fueling a string of acquisitions and licensing deals. In the fiscal year ending March 31, 2017, sales of generic medicines accounted for 45% of the Indian giant's \$4.5 billion. About half of revenues earned by Lupin Ltd., a rival, came from sales in the U.S.

With that much business at stake, Indian drugmakers are vulnerable to regulatory actions by the FDA and other agencies.

FDA scrutiny can have real consequences. Warning letters block the approval of new products made at the targeted facility. And unaddressed violations can lead to placement on import alert lists, allowing U.S. officials to turn back imports of drug products.

Sun says delays in securing approvals for products made at its Halol site have hurt sales and added remediation costs.

Pressured out?

Through warning letters and import alerts, the FDA can effectively shut out a non-compliant manufacturer from the all-important U.S. market.

But even for the many drugmakers that export to the U.S. with no issue, selling cheap generics isn't the business it used to be.

"Clearly we are in a situation where regulatory approvals for products are coming much faster than they used to and there are many more players in the market than historically there used to be," said Dilip Shanghvi, managing director at Sun Pharma, on an earnings call last November.

More powerful buyers, too, have put pressure on companies' pricing power.

Facing such challenges, some generic drugmakers may be tempted to diversify into higher-margin branded drug markets.

Just last month, Sun Pharma won U.S. approval of its first novel biologic drug — an IL-23 inhibitor called Ilumya (tildrakizumab) that the company had in-licensed from Merck & Co. in 2014.

Besides traditional generic players, other companies in the region are making strides in novel drug R&D as well. Hutchison China MediTech, Beigene Ltd. and Innovent Biologics Co., among others, are leading a rapidly emerging Chinese biotech field that aims to bring drugs developed in Chinese labs to markets domestically and overseas.

That growth will mean FDA inspectors more often visit India- and China-based plants in the context of evaluating New Drug Applications. U.S. approval of TaiMed Biologics Inc.'s new HIV medicine, for example, followed the FDA's first pre-license inspection of biologics contract manufacturer in China.

Moving up the value chain into novel drugs will keep the spotlight on manufacturing quality.

EXHIBIT 450



Register for the Fierce Coronavirus Virtual Series

Join us the week of March 30th for a series of virtual updates and expert panels discussing the coronavirus

Manufacturing

FDA halt of foreign inspections may delay some new product approvals

by [Eric Palmer](#) | Mar 11, 2020 10:40am



The FDA is halting foreign plant inspections, a move that has broad implications for drugmakers and consumers. (AGorohov)

The FDA has decided that the risk of inspectors crossing paths with COVID-19 is greater than the risk to consumers of drugmakers failing to meet FDA standards and putting poor quality drugs on the market. The agency has decided to halt inspections of all foreign drug manufacturers after earlier putting inspections in China on hold.

The FDA Tuesday **said** it will consider “mission critical” inspections on a case-by-case basis but otherwise is postponing foreign inspections in April. Instead, it will rely on help from regulators in other countries, testing products at the border for safety and wielding authority to deny entry to drugs considered defective or unsafe.

RELATED: Chinese heparin maker tried to sneak proof of its unapproved APIs out the back door

Already this year, the agency has banned drugs from manufacturers in Bulgaria, China, Denmark, Germany, India, Mexico and Venezuela. Just this week it banned drugs and products from a Chinese company called Hangzhou Linkeweier Daily Chemicals Co. that included faulty antibacterial wipes. But bans generally stem from plant inspections.

While the measures may provide some help in keeping defective drugs from the U.S., the FDA acknowledged it does nothing for drugmakers who are awaiting plant inspections to gain approval to launch new drugs for the U.S.

“We are aware of how this action may impact other FDA responsibilities, including product application reviews,” the agency said in a statement. “We will be vigilant and monitor the situation very closely and will try to mitigate potential impacts from this outbreak in lockstep with the whole of the federal government. We stand ready to resume foreign inspections as soon as feasible.”

Given the situation, the decision to halt inspection does not surprise lawyer Chad Landmon, chair of the FDA practice in Connecticut office of law firm Axinn. Assuming it is short-lived, he said in an email, there should not be a big concern over compliance and safety issues.

“That being said, FDA’s decision will likely delay approval of drug applications, particularly for generic pharmaceutical products,” given that many APIs and finished dosage forms are made overseas. And those delays “may have a negative impact on the overall cost of drugs given the important role that generic drug products play in reducing the overall costs of drugs,” he said.

RELATED: FDA anticipates disruptions, shortages as China outbreak plays out

The agency did not say how many inspections were on the books for the month, whether routine, new product or high-risk. When it announced last month that it was halting inspections in China, it said it averaged about 500 inspections a year in the country, an average of 41 a month, mostly for devices and food and drugs.

The FDA said it will get back at it just as soon as it is “feasible.”

“As this remains a dynamic situation, we will continue to assess and calibrate our approach as needed to help advance federal response efforts in the fight against this outbreak,” its statement said.

Read More On

EXHIBIT 451



United States Government Accountability Office
Report to the Committee on Energy and
Commerce

December 2016

DRUG SAFETY

FDA Has Improved Its Foreign Drug Inspection Program, but Needs to Assess the Effectiveness and Staffing of Its Foreign Offices

December 2016

GAO Highlights

Highlights of [GAO-17-143](#), a report to the Committee on Energy and Commerce

Why GAO Did This Study

Globalization has complicated FDA's oversight of drugs marketed in the United States. FDA reports that more than 40 percent of finished drugs and 80 percent of active pharmaceutical ingredients are produced overseas. FDA inspects drug manufacturing establishments to ensure that the safety and quality of drugs are not jeopardized by poor manufacturing practices. Beginning in 2008, FDA established foreign offices to obtain better information on products coming from overseas and perform inspections, among other things.

In 2008 and 2010, GAO examined FDA's foreign drug inspection program and recommended it conduct more foreign inspections. In another 2010 report, GAO recommended the agency develop strategic and workforce plans for its foreign offices. GAO was asked to update its work with a focus on FDA's oversight of foreign drug establishments. This study examines (1) enhancements FDA has made to its foreign drug inspection program; and (2) FDA's assessment of its foreign offices, and the challenges they face in ensuring drug safety. GAO analyzed FDA's inspection data from fiscal year 2007 through June 30, 2016; reviewed agency planning documents; and interviewed FDA officials, including former foreign office employees.

What GAO Recommends

GAO recommends that FDA assess the contributions of the foreign offices, and set a goal that distinguishes between the vacancy rates of staff in its foreign offices and those in its domestic international program office. HHS agreed with GAO's recommendations.

View [GAO-17-143](#). For more information, contact Marcia Crosse at (202) 512-7114 or crossem@gao.gov.

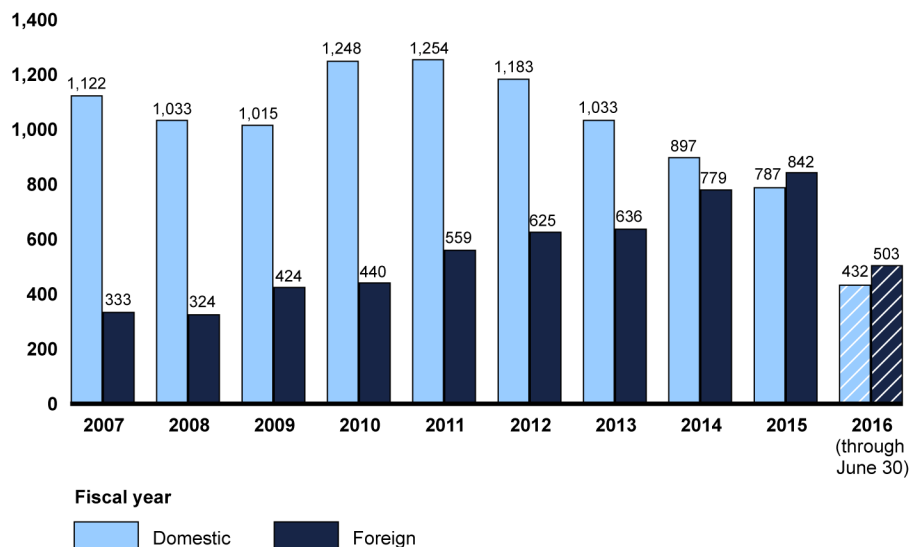
DRUG SAFETY

FDA Has Improved Its Foreign Drug Inspection Program, but Needs to Assess the Effectiveness and Staffing of Its Foreign Offices

What GAO Found

The Food and Drug Administration (FDA), an agency within the Department of Health and Human Services (HHS), has **increased its foreign drug inspections and enhanced its ability to prioritize drug establishments for inspection. The number of foreign inspections has consistently increased each year since fiscal year 2009. Beginning in fiscal year 2015, FDA conducted more foreign than domestic inspections. FDA has also improved the accuracy and completeness of information on its catalog of drug establishments subject to inspection. It has also reduced its catalog of drug establishments with no inspection history to 33 percent of foreign establishments, compared to 64 percent in 2010. However, the number of such establishments remains large, at almost 1,000 of the approximately 3,000 foreign establishments. FDA plans to inspect all of these establishments over the next 3 years.**

Total Number of Food and Drug Administration (FDA) Inspections of Domestic and Foreign Drug Establishments, Fiscal Year 2007 through June 30, 2016
Number of inspections



Source: GAO analysis of FDA data. | [GAO-17-143](#)

FDA has not yet assessed its foreign offices' contributions to drug safety. **FDA has made progress in its strategic planning for its offices in China, Europe, India, and Latin America, but the lack of an assessment is inconsistent with federal standards for internal controls. Though FDA uses two performance measures to assess the foreign offices—number of medical product inspections and number of collaborative actions—the collaborative action measure does not capture the offices' unique contributions to drug safety.** Moreover, the foreign offices face persistently high vacancy rates. As of July 2016, 46 percent of the foreign offices' authorized positions were vacant. Although FDA recently finalized a workforce plan, GAO identified several weaknesses with it. For example, the plan sets a workforce target that applies to both foreign and domestic international program offices, making it difficult to ascertain whether its goal of reducing foreign office staff vacancies is being met.

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Abbreviations

API	active pharmaceutical ingredient
CDER	Center for Drug Evaluation and Research
CGMP	current good manufacturing practice
D-U-N-S®	Data Universal Numbering System
eDRLS	electronic Drug Registration and Listing System
FACTS	Field Accomplishments and Compliance Tracking System
FDA	Food and Drug Administration
FDASIA	Food and Drug Administration Safety and Innovation Act
GDUFA	Generic Drug User Fee Amendments Act
HHS	Department of Health and Human Services
OIP	Office of International Programs
ORA	Office of Regulatory Affairs

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U.S. GOVERNMENT ACCOUNTABILITY OFFICE

441 G St. N.W.
Washington, DC 20548

December 16, 2016

The Honorable Fred Upton
Chairman
The Honorable Frank Pallone Jr.
Ranking Member
Committee on Energy and Commerce
House of Representatives

The Honorable Tim Murphy
Chairman
The Honorable Diana DeGette
Ranking Member
Subcommittee on Oversight and Investigations
Committee on Energy and Commerce
House of Representatives

Oversight of the nation’s drug supply chain has become increasingly complicated for the Food and Drug Administration (FDA), an agency within the Department of Health and Human Services (HHS). Much of the U.S. drug supply is manufactured overseas. FDA estimates that nearly 40 percent of finished drugs and approximately 80 percent of active pharmaceutical ingredients (API) are manufactured in registered establishments in more than 150 countries; yet, the agency is responsible for overseeing the safety and effectiveness of all drugs marketed in the United States, regardless of where they are produced.¹ As testing a drug at the border cannot reliably determine whether drugs were manufactured in compliance with current good manufacturing practice (CGMP) regulations, FDA conducts several types of inspections of establishments that manufacture drugs for the U.S. market.² FDA began opening offices

¹Drugs are defined to include, among other things, articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease, and include components of those articles. 21 U.S.C. §§ 321(g)(1)(B), (D). An API is any component that is intended to provide pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease. In this report, we refer both to drug products—drugs in their finished dosage forms—and to APIs as “drugs.” Establishments marketing their products in the United States are required to register annually with FDA.

²CGMPs provide for systems that assure proper design, monitoring, and control of manufacturing processes and facilities. See 21 C.F.R. pts. 210, 211, 212 (2016). FDA defines manufacturing to include the manufacture, preparation, propagation, compounding or processing of a drug. 21 C.F.R. § 207.3(a)(8) (2016).

around the world in 2008 to obtain better information on the increasing number of products coming into the United States from overseas, to build relationships with foreign stakeholders, and to perform inspections.

We have had long-standing concerns with FDA's role in the increasingly global pharmaceutical supply chain. In 1998, we reported that FDA had significant problems managing its foreign inspection data and conducted infrequent inspections of foreign establishments.³ Ten years later, in 2008, we determined that, because of inaccurate information in FDA's databases, the agency did not know how many foreign drug establishments were subject to inspection. In addition, we found that FDA continued to inspect relatively few foreign establishments, and that most such inspections were performed in response to an application to market a new drug in the United States, rather than to assess the continued quality of drugs already on the market.⁴ In January 2009, we added FDA's oversight of medical products (i.e., drugs and medical devices) to our High-Risk Series, citing FDA's inability to ensure the quality of medical products manufactured overseas as an area of particular concern.⁵ Although we found that FDA was conducting more inspections of foreign establishments in 2010, we also reported that many establishments may never have been inspected.⁶ We also identified shortcomings in the operations of the agency's foreign offices in that year and again in 2015, raising questions about their effectiveness.⁷

³See GAO, *Food and Drug Administration: Improvements Needed in the Foreign Drug Inspection Program*, [GAO/HEHS-98-21](#) (Washington, D.C.: Mar. 17, 1998).

⁴See GAO, *Drug Safety: Better Data Management and More Inspections Are Needed to Strengthen FDA's Foreign Drug Inspection Program*, [GAO-08-970](#) (Washington, D.C.: Sept. 22, 2008).

⁵See GAO, *High-Risk Series: An Update*, [GAO-09-271](#) (Washington, D.C.: January 2009).

⁶See GAO, *Drug Safety: FDA Has Conducted More Foreign Inspections and Begun to Improve Its Information on Foreign Establishments, but More Progress is Needed*, [GAO-10-961](#) (Washington, D.C.: Sept. 30, 2010). For a list of related reports, see the *Related GAO Products* page at the end of this report.

⁷See GAO, *Food and Drug Administration: Overseas Offices Have Taken Steps to Help Ensure Import Safety, but More Long-Term Planning Is Needed*, [GAO-10-960](#) (Washington, D.C.: Sept. 30, 2010); and *Food Safety: Additional Actions Needed to Help FDA's Foreign Offices Ensure Safety of Imported Food*, [GAO-15-183](#) (Washington D.C.: Jan. 30, 2015). Our 2010 report focused on the foreign offices' efforts to help ensure the safety of imported products, such as food and medical products, while our 2015 report specifically focused on their contributions related to the safety of imported food.

Given the persistent challenge of globalization for FDA, you asked us to provide an update on the agency's activities and accomplishments related to its foreign drug inspection program and the operations of its foreign offices. This report examines

1. the enhancements FDA has made to its foreign drug inspection program in recent years; and
2. FDA's assessment of its foreign offices, and the challenges the foreign offices face in ensuring drug safety.

To examine the enhancements FDA has made to its foreign drug inspection program in recent years, we reviewed FDA's process for prioritizing and selecting establishments for inspections, including whether it incorporated certain factors into its selection process as required in 2012 by the Food and Drug Administration Safety and Innovation Act (FDASIA).⁸ We also interviewed FDA officials about the sources of data the agency uses in this process, including any steps FDA may have taken to improve the completeness and accuracy of its data on foreign drug establishments. Additionally, we analyzed data from FDA's Field Accomplishments and Compliance Tracking System (FACTS), which contains information on the number of the agency's establishment inspections. Specifically, we examined FACTS data from fiscal year 2010 through June 30, 2016, to determine: (1) the number of foreign and domestic inspections conducted by FDA, (2) the type of inspections, and (3) the country in which the inspections took place. We also reviewed FACTS data presented in one of our prior reports on drug manufacturing establishment inspections conducted from fiscal years 2007 to 2009.⁹ To assess the reliability of the data from FACTS, we reviewed related documentation, interviewed knowledgeable agency officials, and compared the data to published information from the same database. On the basis of these steps, we found these data sufficiently reliable for the purposes of our reporting objectives. We also reviewed relevant documentation related to FDA's inspections of foreign drug establishments, including staffing and funding information. To learn more about FDA's foreign drug inspection program, including the agency's

⁸Pub. L. No. 112-144, § 705, 126 Stat. 993, 1066 (2012) (codified in pertinent part at 21 U.S.C. § 360(h)(4)).

⁹GAO-10-961 included information on drug manufacturing establishment inspections conducted from fiscal years 2007 to 2009. For this report, we focused on drug manufacturing establishment inspections conducted from fiscal years 2010 through June 30, 2016, which were the most recently available data at the time we did our work.

progress toward improving its information on foreign drug establishments and changes to the agency's approach to selecting and prioritizing drug establishment inspections, we interviewed officials from the Office of Regulatory Affairs (ORA), who are responsible for conducting inspections of foreign drug establishments, and from the Center for Drug Evaluation and Research (CDER), who are responsible for determining which establishments need inspection.

Our work focused on human drugs regulated by CDER and not on most biologics, medical devices, veterinary medicines, or other items or products for which FDA conducts inspections.¹⁰ Further, our work focused on activities related specifically to the foreign drug inspection program. As part of its oversight of imported drugs, FDA undertakes other activities, such as working toward international harmonization of regulatory requirements, which are beyond the scope of our review.

To examine FDA's assessment of its foreign offices and the challenges the foreign offices face in contributing to the safety of drugs entering the United States, we reviewed documents pertaining to the foreign offices and their activities provided by FDA's Office of International Programs (OIP), of which the foreign offices are a part and which is responsible for overseeing FDA's overseas activities. Specifically, we examined OIP's strategic plan and strategic workforce plan for the foreign offices to identify the offices' goals, mission, and desired long-term results. We also reviewed the operational plans of the foreign offices, which are completed quarterly by each office and include the performance measures and targets used to assess their activities.¹¹ We also reviewed the report of a

¹⁰Biologics are materials, such as viruses, therapeutic sera, toxins, antitoxins, vaccines or analogous products to prevent, treat, or cure human diseases or injuries, and are derived from natural sources, such as humans, animals, and microorganisms. See 42 U.S.C. § 262(i); 21 C.F.R. § 600.3(h) (2016). Medical devices include instruments, apparatuses, machines, and implants that are intended for use to diagnose, cure, treat, or prevent disease, or to affect the structure or any function of the body. 21 U.S.C. § 321(h). Our work focused on inspections related to the drug approval process or inspections conducted to determine an establishment's ongoing compliance with laws and regulations in the manufacture of human drugs already marketed in the United States. FDA conducts additional drug inspections that are beyond the scope of our review, such as inspections conducted to determine whether drug manufacturers are submitting to FDA, as required, complete and accurate data on adverse drug experiences associated with marketed drugs, inspections conducted for the President's Emergency Plan for AIDS Relief, and inspections of clinical trial sites, compounding pharmacies, and medical gas manufacturers.

¹¹A performance measure is a means of objectively assessing the outputs or outcomes of programs, products, projects, or services.

contractor retained by FDA to develop new performance measures for the foreign offices, as well as data from FDA's agency-wide performance tracking system, including some of the agency's performance measures and outcomes. We examined documentation pertaining to FDA's policies and procedures for staff deploying to and returning from the foreign offices, including materials related to the reintegration of staff into FDA's domestic offices upon their completion of their terms abroad.

Additionally, we analyzed the most recently complete FDA data on the number and type of authorized, filled, and vacant positions for each of OIP's foreign and domestic offices, as well as data on the number of staff assigned to the foreign offices on a temporary basis. This included data on the number of drug inspections conducted by foreign office personnel. To supplement this information, we interviewed FDA officials in OIP, which includes the China, India, Latin America, and Europe foreign offices, as well as officials in CDER and ORA, to obtain information on the foreign offices' contributions to drug safety and how these contributions are assessed by the agency. In addition, we interviewed 13 former foreign office staff who had responsibilities pertaining to drug safety—including those who were still with FDA and those who have since left the agency—about their experiences deploying to and working overseas, and, in some cases, returning to a domestic post with the agency. Finally, to identify criteria to evaluate FDA's assessment of its foreign offices' performances, we reviewed our previous reports on performance measures and standards for internal control in the federal government.¹²

We conducted this performance audit from February 2016 to December 2016 in accordance with generally accepted government auditing standards. Those standards require that we plan and perform the audit to obtain sufficient, appropriate evidence to provide a reasonable basis for our findings and conclusions based on our audit objectives. We believe that the evidence obtained provides a reasonable basis for our findings and conclusions based on our audit objectives.

¹²See GAO, *Human Capital: Key Principles for Effective Strategic Workforce Planning*, [GAO-04-39](#) (Washington, D.C.: Dec. 11, 2003). Strategic workforce planning is an essential tool to help agencies align their workforces with their current and emerging missions and develop long-term strategies for acquiring, developing, and retaining staff. See also GAO, *Standards for Internal Control in the Federal Government*, [GAO-14-704G](#) (Washington, D.C.: September 2014). Internal control is a process affected by an entity's oversight body, management, and other personnel that provides reasonable assurance that the objectives of an entity will be achieved.

Background

Several FDA centers and offices play key roles in helping to ensure the safety and effectiveness of drugs marketed in the United States:

- CDER establishes standards for the safety, quality, and effectiveness of and manufacturing processes for over-the-counter and prescription drugs.¹³
- OIP, which is part of FDA's Office of Global Regulatory Operations and Policy, leads, manages, and coordinates FDA's foreign offices' activities, such as performing inspections in the countries in which the offices reside. OIP also engages with international health and regulatory partners on a variety of issues, including establishing confidentiality agreements with regulatory counterparts for sharing information on regulated products, and collaborates with the staff in FDA's centers and ORA.
- ORA inspects establishments and reviews imported products offered for entry into the United States to ensure compliance with applicable laws and regulations, among other things. ORA is also part of FDA's Office of Global Regulatory Operations and Policy.

Types of Drug Inspections

FDA conducts several types of inspections of drug manufacturing establishments to protect the drug supply. Drugs manufactured overseas must generally meet the same statutory and regulatory requirements as those produced in the United States.¹⁴ CDER and ORA are primarily responsible for the agency's human drug inspection program. CDER requests ORA to inspect both domestic and foreign establishments to ensure that drugs are produced in conformance with federal statutes and regulations, including CGMP regulations. ORA investigators (based domestically and in the foreign offices) and, as needed, laboratory analysts are responsible for conducting the inspections.¹⁵ Investigators

¹³For purposes of this report, we consider drug quality to be a component of drug safety. Our references to drug safety are therefore meant to also encompass drug quality.

¹⁴FDA defines manufacturing to include the manufacture, preparation, propagation, compounding, or processing of a drug, and an establishment as a place of business under one management at one general physical location. 21 C.F.R. §§ 207.3(a)(7), (8) (2016). In this report, establishments may be engaged in the manufacture, preparation, propagation, or processing of drugs.

¹⁵ORA investigators lead inspections and are responsible for performing or overseeing all aspects of an inspection. ORA laboratory analysts are chemists or microbiologists and have expertise in laboratory testing. In some instances, staff from CDER may participate in inspections. ORA assists the agency's other product centers in planning establishment inspections of other FDA-regulated commodities, such as veterinary medicines and food.

generally conduct three types of drug manufacturing establishment inspections:

1. Preapproval inspections of domestic and foreign establishments may be conducted before FDA approves a new drug to be marketed in the United States. These inspections are triggered by FDA's receipt of a new drug application or an abbreviated new drug application, and focus on the manufacture of a specific drug. Preapproval inspections are designed to verify the accuracy and authenticity of the data contained in these applications to determine that the establishment is following commitments made in the application. Preapproval inspections also assess whether the establishment can manufacture the product in the application in conformance with CGMPs. FDA's decision to inspect a particular establishment listed on the application is based on multiple factors, including the establishment's compliance history—that is, the results of previous inspections, product recalls, and other compliance information—and the attributes of the product being proposed for manufacture.
2. Surveillance inspections are conducted at establishments after drugs are already marketed in the United States and focus on compliance with system-wide controls for ensuring that the manufacturing processes produce high-quality drugs. Establishments are prioritized for surveillance inspections through a process using a risk-based site selection model. Systems examined during these inspections include those related to materials, quality control, production, facilities and equipment, packaging and labeling, and laboratory controls. These systems may be involved in the manufacture of multiple drugs.¹⁶ FDA can use the results of a surveillance inspection to make decisions in the future if the establishment is listed on another application, as the results of a surveillance inspection can often be generalized to all drugs manufactured in a similar manner at a particular establishment.
3. For-cause inspections are conducted to investigate consumer complaints, reports of product quality defects submitted by consumers or health care professionals, or indications of potential manufacturing problems submitted by the manufacturers themselves through field alert reports, among other reasons. Additionally, these inspections

¹⁶Although surveillance inspections focus on system-wide controls, FDA considers nearly all drug establishment inspections to include an assessment of CGMPs.

may also be conducted as follow-up to warning letters or import alerts issued to manufacturers.¹⁷

While FDA may conduct a preapproval-only inspection or a surveillance-only inspection, FDA may also conduct an inspection that combines both preapproval and surveillance inspection components in a single visit to an establishment.¹⁸

FDA's Process for Prioritizing Establishments for Surveillance Inspection

FDA uses multiple databases to select foreign and domestic establishments for surveillance inspections, including

- The electronic Drug Registration and Listing System (eDRLS) contains information on foreign and domestic drug establishments that have registered with FDA to market their drugs in the United States. Establishments are required to register annually with FDA. Information in eDRLS includes the company's name, address, and the drugs they manufacture for commercial distribution in the United States, as reported by the establishment.
- FACTS contains information on domestic and foreign establishments inspected by ORA, the type of inspection conducted, and the outcome of those inspections. Investigators and laboratory analysts enter information into FACTS following completion of an inspection.

CDER relies on these and other databases to select establishments for surveillance inspections.¹⁹ CDER primarily uses data from eDRLS, which provides information on all registered establishments at a given point in time, and FACTS, which provides information about additional establishments that may not appear in eDRLS, to annually compile a

¹⁷A warning letter is a letter that notifies industry about violations that FDA has documented during its inspections. Warning letters are to be issued for violations of regulatory significance, i.e., those that may actually lead to an enforcement action if the documented violations are not promptly and adequately corrected. An import alert informs FDA field staff and the public that the agency has enough evidence to allow for detention without physical examination of products that appear to be in violation of FDA laws and regulations.

¹⁸Most combined inspections occur when FDA conducts a surveillance inspection at an establishment where a preapproval inspection was also being conducted.

¹⁹Other databases FDA uses to select establishments for inspection include the Operational and Administrative System for Import Support, which includes data on the number of establishments that have manufactured products that were shipped to the United States, and the FDA Inventory of Assets, which includes data on establishments producing products regulated by FDA.

catalog of establishments that are to be prioritized for inspection.²⁰ Because the establishments to be prioritized are continuously changing as they begin, stop, or resume marketing products in the United States, FDA does not maintain a single list of them; rather, the annual catalog provides a snapshot in time of such establishments. Based on these databases, as of June 2016, CDER's catalog consisted of approximately 2,000 domestic and 3,000 foreign drug establishments.

Until 2012, requirements governing FDA's selection of domestic and foreign establishments to inspect differed. Until then, FDA was required to inspect domestic establishments that manufacture drugs marketed in the United States every 2 years, but there was no comparable requirement for inspecting foreign establishments. However, FDASIA eliminated this distinction, instead directing FDA to take a risk-based approach to inspecting both domestic and foreign drug manufacturing establishments, consistent with a recommendation we made to FDA in 2008.²¹

To prioritize establishments for surveillance inspections, CDER applies its risk-based site selection model to its catalog of establishments each year to identify those establishments (both domestic and foreign) that, based on the characteristics of the drugs being manufactured, pose the greatest potential public health risk should they experience a manufacturing defect. This model analyzes three major factors—facility score, product score, and time since last inspection—to develop a list of establishments that FDA considers to be a priority for inspection.²² Establishments may also be selected for surveillance inspections for other reasons, such as FDA's focus on a particular product. Through this process, CDER develops a priority list of establishments selected for inspection that is then ranked and submitted to ORA. To be efficient with its resources, ORA staff may shift the order of establishments to be inspected on

²⁰In previous reports, we have referred to establishments that FDA identified as subject to inspection as an "inventory." FDA now refers to this compilation as a "catalog," a term we have adopted for the purposes of this report.

²¹Pub. L. No. 112-144, § 705, 126 Stat. 1066 (codified at 21 U.S.C. 360(h)(4)). For our previous recommendation, see [GAO-08-970](#).

²²The facility score includes information about the facility and its history, such as the type of establishment (for example, a manufacturer or a laboratory), number of products produced at the facility, and inspection history. The product score, meanwhile, captures information about a product itself, such as its therapeutic category (for example, an anti-fungal), its dosage form, and whether it is sterile.

CDER's prioritized list based on geographic proximity to other planned inspection trips.

FDA's Foreign Offices

FDA opened its foreign offices in 2008 to engage with foreign stakeholders to develop information that FDA officials can use to make better decisions about products manufactured in foreign countries for the U.S. market. To accomplish this, the foreign offices focus on the following activities:

1. establishing relationships with U.S. agencies located overseas and foreign stakeholders, including regulatory counterparts and industry, to facilitate collaborations that will streamline and enhance global drug development and regulation;
2. gathering better information locally on product manufacturing and transport to U.S. ports;
3. expanding FDA's inspectional capacity to include inspections of FDA-regulated commodities, such as drugs, medical devices, and food products, conducted by investigators based in the foreign offices; and
4. providing assistance to strengthen the regulatory systems of FDA's foreign counterparts to better assure the safety of the products manufactured and exported from their countries to the United States.²³

Currently, FDA has foreign offices in China, Europe, India, and Latin America. Some offices have more than one office location, also known as a post.²⁴ (See fig. 1.) FDA previously had foreign offices located in Africa and the Middle East, but these offices have since closed and been consolidated under the Office of Regional and Country Affairs, an OIP

²³FDA's capacity building, also known as technical cooperation, includes the provision of scientific, technical, regulatory, or inspection assistance, and education and training to help strengthen public health regulatory infrastructures abroad, especially for countries where exports to the United States are significant or increasing. FDA also engages with foreign industry to help assure their understanding of U.S. standards.

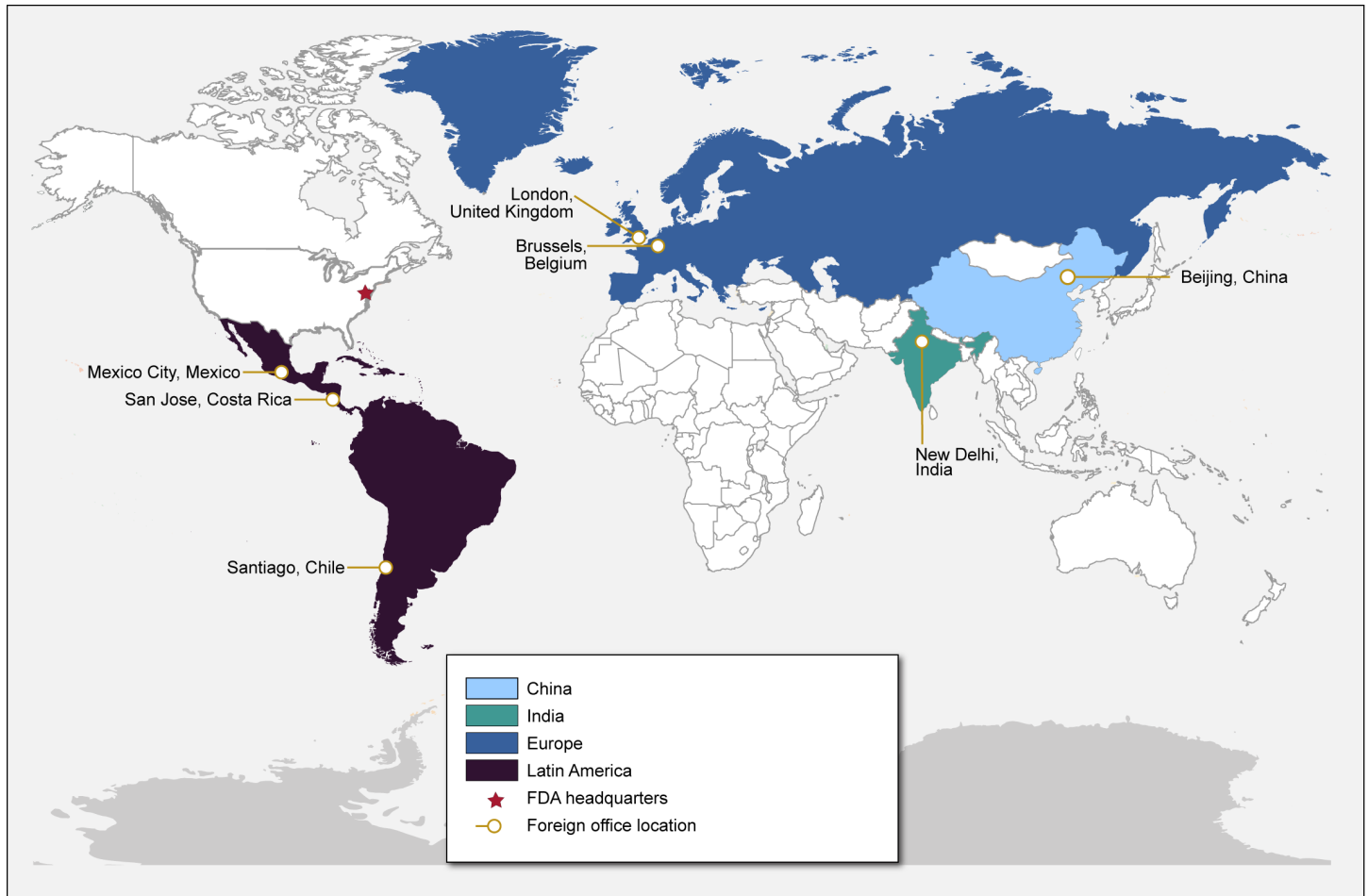
²⁴Specifically, the Latin America office has posts in Santiago, Chile; San Jose, Costa Rica; and Mexico City, Mexico. The Europe office has posts in Brussels, Belgium, and London, United Kingdom, and previously had a post in Parma, Italy that closed in 2012. Although the China office currently has one post in Beijing, it previously had posts in Guangzhou and Shanghai, which closed in 2014. Similarly, the India office currently has one post in New Delhi, but it previously had a post in Mumbai that closed in July 2016.

office based domestically in FDA's headquarters.²⁵ For fiscal year 2016, FDA budgeted approximately \$35.2 million for the China, Europe, India, and Latin America offices, an increase over the \$29.9 million budgeted for them in fiscal year 2009.²⁶

²⁵Specifically, FDA previously had foreign offices in Amman, Jordan, and Pretoria, South Africa, which closed in 2013 and 2015, respectively. Currently, the Office of Regional and Country Affairs manages FDA's activities in Asia and the Pacific (with the exceptions of India and China), the Middle East, Africa, and Canada. The office is responsible for fostering collaboration and the sharing of information and technical expertise with counterpart regulatory authorities throughout the regions, both directly and through their embassies in Washington, D.C. For the purposes of this report, we do not include this office when we refer to FDA's "foreign offices" since the office and its staff are based in the United States.

²⁶The \$29.9 million budgeted for the foreign offices in fiscal year 2009 included some posts for the China and India offices that have since closed. All staffing and administrative costs associated with the offices are included in budgeted amounts.

Figure 1: Geographic Responsibilities of the Food and Drug Administration’s (FDA) Foreign Offices, Including Their Locations, as of October 2016



Sources: GAO analysis of FDA information; Map Resources (map). | GAO-17-143

Note: The Latin America office encompasses three office locations, also known as posts, in Mexico City, Mexico; San Jose, Costa Rica; and Santiago, Chile. The Europe office includes two posts in London, United Kingdom, and Brussels, Belgium. FDA’s Office of International Programs (OIP) also has a domestic office that covers other regions in the world. Specifically, OIP’s Office of Regional and Country Affairs is responsible for agency interactions in other areas of the world, such as Canada, Australia, and the Middle East, which are not covered by one of FDA’s foreign offices.

As of July 2016, FDA had 29 staff members assigned to work in the foreign offices, including a director and deputy director in each office. The offices also have international program and policy analysts who analyze the impact of foreign issues on FDA programs and activities, and other staff who are responsible for engaging with foreign stakeholders and

gathering information. There are also investigators who conduct inspections of establishments manufacturing food or medical products in the China, India, and Latin America offices.²⁷ The offices also have locally employed staff, who are non-U.S. citizens employed by the FDA foreign offices.²⁸ Finally, OIP staff based in its domestic offices assist the foreign offices in addition to performing other duties related to advancing FDA's global mission.

FDA foreign office staff are posted overseas for two-year assignments. In addition, FDA may send staff to the foreign offices to perform temporary duty assignments of up to 120 days. HHS policy requires that its overseas staff commit to assignments of no more than 2 years per tour; however, staff have the option to renew in increments of one or two years, for up to a total of 6 years in one country, subject to strategic goals and management concurrence on performance. Staff can then rotate to a new country, but HHS requires that staff spend no more than 12 consecutive years overseas before returning to the United States for at least 1 year.

FDA Has Increased Its Foreign Drug Inspections and Enhanced Its Ability to Prioritize Drug Establishments for Inspection

Since fiscal year 2009, FDA has increased the number of all foreign drug inspections conducted each year. Additionally, the agency has taken steps to improve the accuracy and completeness of its catalog of foreign drug establishments, although FDA still lacks inspection history for 33 percent of this catalog. FDA has also strengthened the management of its process for prioritizing drug establishments for surveillance inspection, in particular its risk-based site selection model.

²⁷These investigators come from ORA, but are assigned to OIP for the duration of their terms abroad. While stationed overseas, FDA investigators are considered to be consumer safety officers. For purposes of this report, we refer to these staff throughout as investigators.

²⁸Locally employed staff are hired to work in the foreign offices to work on administrative issues or provide technical expertise as needed. As of July 2016, there were 19 locally employed staff located in the Europe, China, India, and Latin America offices. Adding these staff to the 29 FDA staff assigned to the foreign offices brings the total number of staff working in FDA's foreign offices to 48.

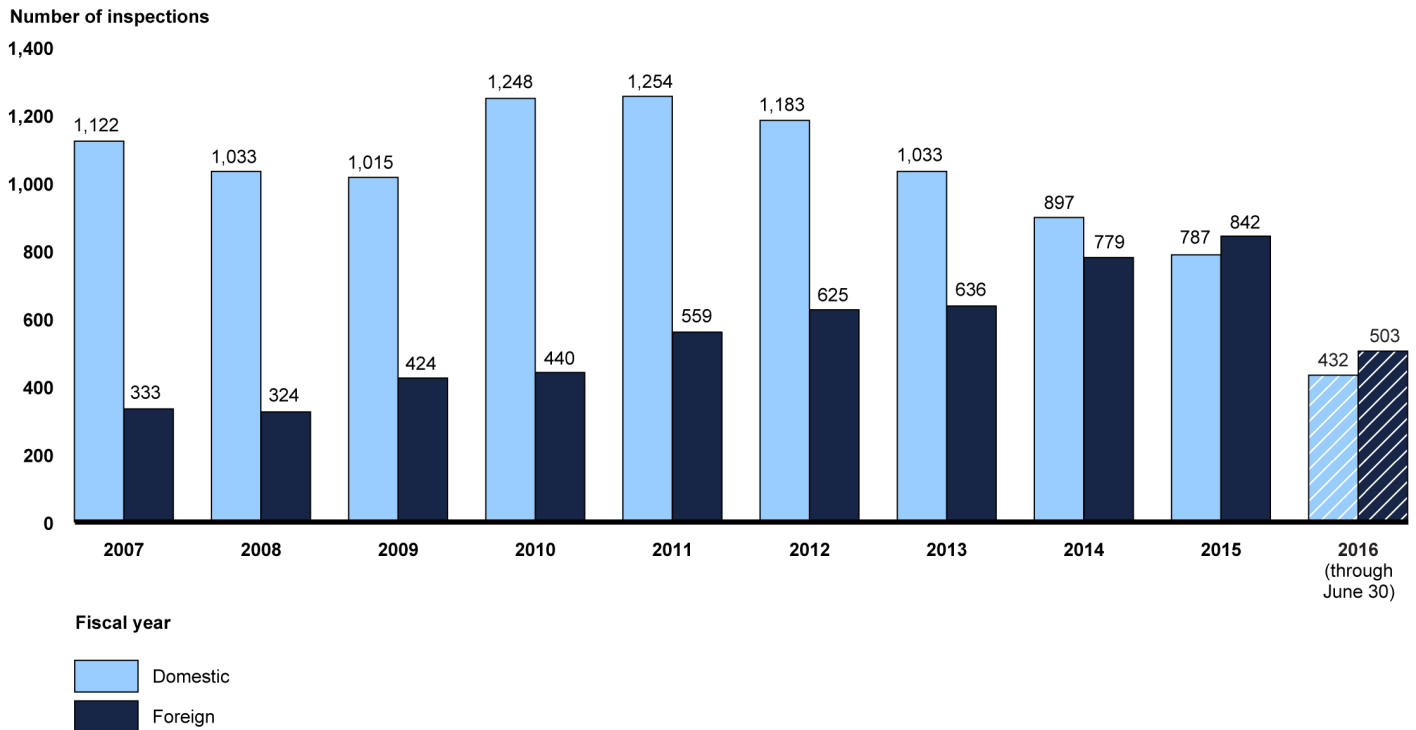
FDA Has Increased the Number of Foreign Drug Inspections Since Fiscal Year 2009

FDA has consistently increased the total number of foreign drug inspections—which include surveillance, preapproval, and for-cause inspections—conducted each year since fiscal year 2009, as shown in figure 2.²⁹ This is consistent with a recommendation we made in 2008, when we recommended that FDA conduct more inspections to ensure that foreign drug establishments are inspected at a frequency comparable to domestic establishments with similar characteristics.³⁰ Beginning in fiscal year 2015, FDA conducted more foreign than domestic inspections.

²⁹We are using the number of foreign drug inspections conducted in a fiscal year in our calculations, rather than the number of unique foreign drug establishments inspected. Although FDA can inspect an establishment more than once a year, during this time period there was not a sizeable difference between the number of foreign inspections conducted and the number of unique establishments inspected.

³⁰See [GAO-08-970](#).

Figure 2: Total Number of Food and Drug Administration (FDA) Inspections of Domestic and Foreign Drug Establishments, Fiscal Year 2007 through June 30, 2016



Source: GAO analysis of FDA data. | GAO-17-143

Note: This figure shows the number of foreign drug inspections conducted in a fiscal year, rather than the number of unique foreign drug establishments inspected. Although FDA can inspect an establishment more than once a year, during this time period there was not a sizeable difference between the number of foreign inspections conducted and the number of unique establishments inspected.

According to FDA officials, the agency has leveraged multiple staff resources to enable it to increase the number of foreign drug inspections conducted by the agency in recent years.

- ORA investigators based in FDA's domestic district offices continue to represent the majority of people participating in FDA's foreign inspections (approximately 49 percent of the total number of inspections conducted).
- As we previously reported, though, FDA established a dedicated foreign drug cadre in January 2009. The group of 15 domestically

based ORA staff exclusively participate in foreign drug inspections.³¹ FDA told us that the agency increased the number of staff assigned to the foreign cadre to 20 in 2012. Currently, the foreign cadre represents the next highest percent of staff participating in foreign inspections (approximately 31 percent of total inspections).

- Additionally, the Generic Drug User Fee Amendments Act (GDUFA) of 2012 authorized FDA to collect user fees from manufacturers of generic drugs, providing the resources to hire 80 additional investigators focused on inspecting generic drug manufacturers.³² FDA officials said that these investigators have primarily been assigned to foreign inspections, but during the period we reviewed, they participated in a relatively small percentage of the total number of foreign drug inspections conducted (approximately 8 percent of inspections).³³
- Investigators assigned full-time to FDA's foreign offices have also participated in inspections of foreign drug establishments (approximately 5 percent of inspections).
- Since fiscal year 2012, the foreign offices have also made use of temporary duty assignments from ORA to assist the foreign offices in completing their work priorities, including inspections. Staff on temporary duty assignments have participated in approximately 2 percent of foreign drug inspections.
- In addition, there are a variety of other FDA staff who, on occasion, may participate in an inspection if certain subject matter expertise is needed.

In addition to using various FDA staff to conduct foreign inspections, the agency has increased funding dedicated to conducting foreign inspections. According to FDA officials, the agency obligated approximately \$53 million to foreign inspections in fiscal year 2010. This amount has increased each year since, to \$92 million in fiscal year

³¹See [GAO-10-961](#).

³²Pub. L. No. 112-144, tit. III, 126 Stat. 1008 (codified in pertinent part at 21 U.S.C. § 379j-42).

³³The relatively low number of inspections conducted by the additional investigators hired using funds made available by GDUFA fees could be due to the fact that they only began conducting inspections in fiscal year 2014, when they participated in 3 inspections. The majority of their drug inspections occurred in fiscal years 2015 and 2016, when they participated in 172 and 179 inspections, respectively.

2015.³⁴ The average cost of a foreign drug inspection has slightly decreased over the years. FDA had estimated that the average cost of a foreign inspection was between \$60,000 and \$62,500 for fiscal year 2009; for fiscal year 2015, the average cost was \$57,600.

The locations where FDA has conducted foreign inspections have largely remained the same from what we previously reported. Specifically, FDA conducted drug inspections in 68 total countries from fiscal year 2010 and June 30, 2016, with 76 percent of these inspections conducted in 10 countries. Establishments in India were the most frequently inspected, followed by ones in China and Germany. (See table 1.) This mirrors what we previously found in 2010.³⁵

³⁴The agency has also increased its funding dedicated to conducting domestic inspections. According to FDA, the agency obligated approximately \$115 million in fiscal year 2010 for domestic drug inspections and increased the amount each year to eventually \$152 million in fiscal year 2015.

³⁵In 2010, we found that the 10 most frequently inspected countries were (1) India, (2) China, (3) Germany, (4) Canada, (5) United Kingdom, (6) Italy, (7) France, (8) Japan, (9) Ireland, and (10) Switzerland, followed by all other countries.

Table 1: Total Number of Food and Drug Administration (FDA) Drug Inspections of Foreign Establishments, by Country, Fiscal Year (FY) 2010 through June 30, 2016

Country	FY 2010	FY 2011	FY 2012	FY 2013	FY 2014	FY 2015	FY 2016 through June 30, 2016	Total	Estimated number of foreign establishments subject to surveillance inspection as of June 2016 ^a
India	72	99	140	110	114	204	101	840	572
China	48	89	59	74	113	129	81	593	535
Germany	50	35	59	60	72	68	37	381	191
Canada	24	43	49	51	39	52	30	288	166
Italy	33	36	38	45	50	41	34	277	146
Japan	23	22	49	28	47	31	39	239	162
France	32	24	25	36	44	45	22	228	146
United Kingdom	16	31	29	27	33	43	18	197	136
Switzerland	26	30	23	23	37	31	16	186	89
Ireland	12	17	14	21	26	17	14	121	60
All other countries	104	133	140	161	204	181	111	1,034	820
Total	440	559	625	636	779	842	503	4,384	3,023

Source: GAO analysis of FDA data. | GAO-17-143

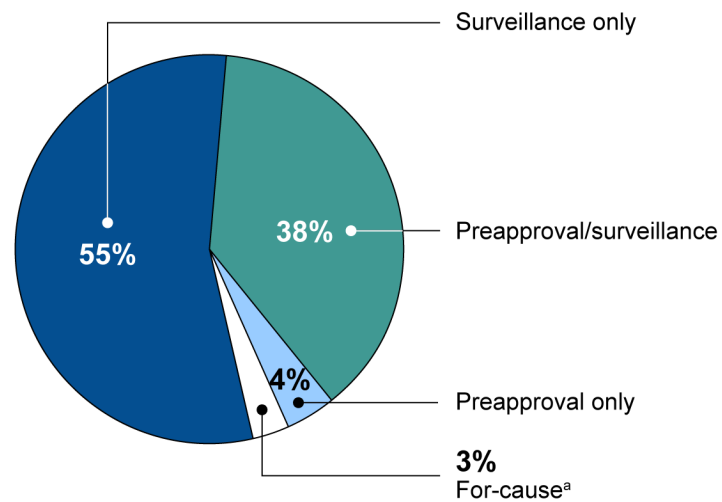
^aThe counts in this column represent the estimated number of foreign drug establishments that FDA will use for the fiscal year 2017 risk-based site selection model. FDA does not keep historical records reflecting the number of establishments subject to inspection each year. Agency officials told us they do not keep such records as the number of establishments subject to inspection frequently fluctuates as establishments begin, stop, or resume marketing products in the United States. As a result, we could not determine the estimated number of foreign establishments that were subject to inspection for fiscal year 2010 through fiscal year 2016.

Since 2009, FDA has changed the types of inspections it primarily conducts at foreign drug establishments. Specifically, more than half (55 percent) of all foreign inspections conducted from fiscal year 2010 through June 30, 2016, were surveillance-only inspections rather than preapproval inspections. (See fig. 3.) This is a significant increase since fiscal year 2009, when we found that 17 percent of foreign inspections were surveillance inspections, with the vast majority conducted in response to an application to market a new drug in the United States.³⁶ FDA officials acknowledged that foreign inspection priorities had previously been driven by pending applications for new drugs. However,

³⁶See [GAO-10-961](#). For fiscal year 2009, we found that the majority of foreign drug inspections FDA conducted contained both a preapproval and surveillance component (74 percent), followed by surveillance-only (17 percent), then preapproval only (9 percent).

this was prior to the enactment of FDASIA, when FDA was required to inspect all domestic establishments every 2 years, and also before an increase in funding available for foreign inspections provided for by generic drug user fees. FDA officials also said the agency eliminated a policy whereby inspections conducted for preapproval purposes often drove the selection of foreign establishments for inspections. As a result, FDA officials said that the selection of foreign establishments for routine surveillance inspections is now entirely driven by the risk-based site selection model. (See app. I for information on the number and types of foreign drug inspections conducted from fiscal year 2010 through June 30, 2016.)

Figure 3: Food and Drug Administration (FDA) Inspections of Foreign Drug Establishments by Type of Inspection, Fiscal Year 2010 through June 30, 2016



Source: GAO analysis of FDA data. | GAO-17-143

^aThis category includes any inspection that included a “for-cause” component. For-cause inspections are conducted to investigate consumer complaints, reports of product quality defects submitted by consumers or health care professionals, or indications of potential manufacturing problems submitted by the manufacturers themselves, among other reasons.

FDA Has Improved Information on Its Catalog of Foreign Drug Establishments, but Lacks Inspection History on One-Third of Them

Since 2010, FDA has taken steps to improve the accuracy and completeness of its catalog of foreign drug establishments. These steps are intended to address what FDA acknowledged as a challenge as early as 1988, following an internal evaluation that recommended that the agency develop a comprehensive catalog of all foreign establishments shipping drugs to the United States that could be used to improve long-range inspection planning and scheduling.³⁷ We also highlighted this challenge in our previous reports.³⁸ Most recently, in 2010, we found that a majority (64 percent) of foreign establishments in FDA's catalog may never have been inspected by the agency. Since then, FDA officials said that the agency has taken steps to improve the accuracy and completeness of its catalog by

- Requiring establishments to use a unique, numeric identifier. FDASIA required establishments to provide a unique facility identifier during their annual registration with FDA, and FDA elected to require establishments to use the Dun and Bradstreet Data Universal Numbering System (D-U-N-S®) number.³⁹ Using this number allows FDA to automatically validate data from every registration submission against the Dun and Bradstreet database to ensure the accuracy of the information. Any mismatch may result in rejection of a registration submission. The D-U-N-S® number also allows FDA to determine whether a firm has gone out of business or relocated. FDA officials said that it has also helped FDA improve the interoperability of the agency's data systems that collect or use registered facility information, as well as the interoperability of other agencies' systems.
- Adding two foreign inventory coordinators in 2013 tasked with incorporating foreign registrations and annual updates into FDA's master inventory. Additionally, these coordinators are responsible for updating FDA's inspection data to reflect accurate inventory updates.
- Establishing a data governance board to define standards, best practices, and policies for inventory data management. According to FDA officials, the governance board, which was created in May 2015, meets biweekly to examine the databases responsible for storing

³⁷Office of Regulatory Affairs, Program Evaluation Branch, "An Evaluation of FDA's Foreign Inspection Program," Rockville, Md., March 1988. This internal evaluation found that FDA did not maintain a catalog (previously referred to by FDA as an inventory) of all foreign drug establishments that were subject to FDA regulation.

³⁸See [GAO/HEHS-98-21](#); [GAO-08-970](#); and [GAO-10-961](#).

³⁹Pub. L. No. 112-144, § 702(b), 126 Stat. 1065 (codified at 21 U.S.C. § 360(i)).

information about drug establishments. Officials said the board has developed guidance for merging data processes and is working toward defining data metrics to determine whether they have improved on their reporting. The board has also defined data standards for storing key attributes of establishments, such as companies' names, and continues to examine best practices for sharing establishment data across FDA.

As a result of these steps, FDA has reduced its catalog of establishments that may never have had a surveillance inspection. Currently, FDA lacks information on the inspection history of 33 percent of the foreign establishments in its catalog, compared to the 64 percent for which it lacked inspection history in 2010. According to FDA officials, the establishments that are subject to inspections are continuously changing. For example, they said that some of the establishments without an inspection history may be newly registered with the agency, thus accounting for their lack of an inspection history; others could be establishments that are not subject to inspection, such as those that may have gone out of business or that have never shipped products to the United States. Although this may be the case for some—or even many—of these establishments, the fact remains that FDA does not know whether or for how long these establishments have or may have supplied drugs to the U.S. market, and has little other information about them. While the agency has made progress in reducing this knowledge gap, it is important to note that the overall number of foreign establishments with no surveillance inspection history (about 1,000 of the approximately 3,000) remains large.⁴⁰ (See app. II for information on the numbers and locations of the establishments for which FDA lacks an inspection history.)

To address this persistent concern, the agency plans to inspect all establishments in its catalog with no prior surveillance inspection history over the next 3 years (approximately one-third each year), beginning in fiscal year 2017. FDA will consider these establishments' risk scores as determined by the agency's risk-based site selection model to prioritize them for inspection, starting with those establishments having the highest risk scores. Some recent FDA inspections have uncovered significant issues at foreign drug manufacturing establishments, including raw material storage rooms that had never been cleaned and the presence of

⁴⁰The majority of these establishments are in China, India, and South Korea.

pests in a controlled processing area, underscoring the importance for FDA to fill this knowledge gap.

FDA Has Strengthened the Management of Its Risk-Based Site Selection Model

FDA has strengthened the management of its process for selecting drug establishments (domestic and foreign) for surveillance inspection. First, FDA generated a combined list of foreign and domestic establishments for use with the fiscal year 2016 risk-based site selection model. Using a combined list of establishments with the risk-based site selection model reflects the agency's full implementation of the 2012 FDASIA provision that directed FDA to take a risk-based approach to inspecting both foreign and domestic establishments. This is also consistent with a recommendation we made to the agency in 2008.⁴¹ For fiscal year 2016 and beyond, FDA officials said that ORA will only select establishments for surveillance inspection from the combined prioritized list—beginning with those establishments with the highest risk score, regardless of whether they are foreign or domestic—until they have exhausted their surveillance inspection capacity for that year. Prior to fiscal year 2016, foreign and domestic establishments were selected for inspection from separate prioritized lists, and in different manners.⁴² As a result, during this time, FDA officials said that a one-for-one match between the lists of foreign establishments prioritized for inspection and the final list of actual inspections conducted would be unlikely. Officials said that the prioritized lists of foreign establishments for fiscal year 2010 through fiscal year 2015 provided a framework for planning surveillance inspections, but that ORA was given discretion as to which specific establishments from the priority list would be inspected each year. Collectively, FDA officials said that the results from the priority list, the needs of the centers, and any unforeseen events dictated the final list of foreign establishments

⁴¹See [GAO-08-970](#).

⁴²Specifically, FDA officials said that investigators were required to first inspect domestic facilities with risk scores above a certain threshold (but allowing for substitutions as needed), before inspecting remaining domestic establishments. In comparison, according to FDA officials, inspecting foreign establishments with the highest risk scores was not a requirement; rather, ORA was given discretion in selecting foreign establishments from the priority list to account for logistical challenges associated with planning foreign inspection trips.

inspected prior to fiscal year 2016, and the final list could differ from the priority list generated by the risk-based site selection model.⁴³

Second, in 2015, the agency formalized its process for selecting establishments for inspection according to an establishment's known safety risks, based on certain risk factors specified by FDASIA. These factors are an establishment's compliance history, recall history, inherent product risk, inspection frequency and history, and whether the establishment has been inspected by a foreign government or agency.⁴⁴ FDA officials said that the agency has long considered certain FDASIA factors in selecting establishments to inspect, such as an establishment's inspection history. However, its risk-based site selection model has become increasingly sophisticated in factoring in specific details about establishments, the products they make, and other elements into the site selection process. Officials acknowledged that FDA cannot yet systematically determine whether an establishment has been subject to inspection by a foreign government or agency, because this requires the agency to negotiate agreements with foreign regulators to obtain meaningful foreign inspection results. Officials stated that FDA is in the process of doing so. However, FDA has been working on pursuing such agreements and determining how they may help the agency to assess the risk of foreign establishments when prioritizing them for almost a decade.⁴⁵ As they continue to explore these agreements, FDA officials said the agency does, on a case-by-case basis, review and exchange information with certain foreign regulators, which may result in the agency re-prioritizing its inspection schedule to address emergent issues.

Third, in fiscal year 2017, FDA plans for the first time to allow no more than 5 years to elapse between surveillance inspections at a specific establishment. That is, if an establishment included in FDA's catalog of

⁴³FDA officials explained that, at the beginning of each year, ORA would engage with the centers to discuss inspection priorities for the upcoming year. ORA would then consider its available resources before proceeding with inspections. In addition, unplanned events, such as a natural disaster, could affect the total number of inspections that could be conducted in a given year.

⁴⁴FDASIA also authorizes the Secretary of Health and Human Services to consider additional criteria deemed necessary and appropriate. Pub. L. No. 112-144, § 705, 126 Stat. 1066 (codified at 21 U.S.C. § 360(h)(4)).

⁴⁵GAO, *Drug Safety: Preliminary Findings Suggest Recent FDA Initiatives Have Potential, but Do Not Fully Address Weaknesses in Its Foreign Drug Inspection Program*, [GAO-08-701T](#) (Washington, D.C.: Apr. 22, 2008).

establishments subject to inspection has not been inspected in 4 years, the establishment is automatically included on the inspection list for the fifth year. According to FDA officials, the agency previously did not include a “hard stop” of a predetermined time in its model. For fiscal year 2017, after FDA inspects one-third of the establishments with no inspection history the agency will prioritize for inspection these establishments that have not had a surveillance inspection within the past 5 years. Once these inspections are completed, FDA plans to inspect establishments that were prioritized by the risk-based site selection model through its annual process. Should FDA complete inspections of all of the establishments prioritized through the risk-based site selection model, the agency plans to conduct additional inspections of as many of the remaining two-thirds of establishments with no inspection history as possible, given remaining inspection resources.

Fourth, FDA recently formalized its process for developing, evaluating, and documenting key decisions about its model each year. Prior to this effort, FDA lacked a formal approach to evaluating its model and documenting key decisions. As a result, in some cases, FDA was unable to recall or explain how the model—or the process to update it—had changed over time. Officials said that our prior reviews reinforced the need for a written procedure and a formal governance structure to support the development of the risk-based site selection model. In fiscal year 2016, FDA instituted a formalized process for developing and evaluating its fiscal year 2017 model and documenting key decisions made as a result of this evaluation. As part of this process, FDA created a review board that features multiple levels of input of the model’s design from FDA experts and senior management, and in October 2016 finalized a document that outlines roles and responsibilities related to the model, and that indicates how it is to be annually updated and implemented. FDA also incorporated best practices learned from its first experience using the review board to guide the development of the model. Officials said the document, going forward, will chronicle the decisions officials make regarding which factors were included in the model for a particular year and why. FDA’s formalized process for evaluating and updating its risk-based site selection model may improve the agency’s ability to monitor whether establishments that pose the greatest risk to public health, were they not to comply with CGMPs, are being selected for inspection. FDA is performing monitoring activities through its formalized process by annually updating the factors and weights included in the model through its newly formalized governance structure. This process allows subject matter experts to provide input each year on the relative importance of each factor and whether the factor should be included in the model.

FDA Has Not Yet Assessed Its Foreign Offices' Contributions to Drug Safety, and Their Efforts are Impeded by High Vacancy Rates

FDA has begun to take steps to enhance the agency's strategic planning for the foreign offices and has developed two performance measures. However, FDA could not readily cite the effectiveness of the offices' contributions, which began opening in 2008. High vacancy rates in the foreign offices threaten to impede the offices' efforts to ensure drug safety.

FDA Has Made Progress in Strategic Planning for Its Foreign Offices

FDA has made progress in its strategic planning efforts for its foreign offices since we last reported on them in 2010. For example, FDA has standardized how the foreign offices relay information about their activities. Specifically, each foreign office now completes an annual operational plan—updated quarterly—to ensure their activities are consistently reported and to facilitate tracking the outcomes of their efforts. Foreign office officials said that they worked closely together to align the core activities listed in the operational plans with OIP's strategic goals to improve officials' understanding of how each foreign office contributes to fulfilling OIP's mission of helping protect public health. For example, the plans include examples of activities related to data gathering, analysis, and information sharing, which support one of OIP's strategic goals of collecting and sharing intelligence and information. Officials said they use the operational plans to track whether the foreign offices' annual accomplishments are fulfilling OIP's goals, and noted that having a common operational plan across the offices allows for a common language amongst officials when discussing their efforts.

In addition, FDA officials noted they have taken the step of convening the foreign office directors and deputy directors at FDA headquarters at least once a year since 2010 to discuss their ongoing efforts and exchange best practices with each other, with the most recent convening occurring in April 2016. FDA officials also said that communication between the foreign offices and other FDA offices, including CDER and ORA, has increased over the years. For example, officials told us that OIP management and the foreign office directors and deputy directors have been meeting three times per month to ensure that the foreign offices are obtaining the types of information that would be most helpful in ensuring the safety of drugs entering the United States.

Since 2010, FDA Has Developed Two Performance Measures, but They Do Not Meaningfully Assess the Foreign Offices' Contributions to Drug Safety

FDA has begun to take steps in response to two recommendations we previously made to enhance the agency's strategic planning for the foreign offices. Specifically, we recommended in 2010 that FDA develop (1) performance goals and measures that can be used to demonstrate the offices' contributions to long-term outcomes related to imported FDA-regulated products; and (2) a strategic workforce plan for the foreign offices to help ensure that the agency is able to recruit and retain staff with the experience and skills necessary for the foreign offices, and to reintegrate returning staff from overseas into FDA's domestic offices.⁴⁶ Since then, OIP has developed two performance measures with established targets—number of inspections conducted by full-time medical product investigators at foreign offices and number of collaborative actions by OIP—that are used to assess the foreign offices' contributions.⁴⁷ According to FDA, the agency met its collective targets for these measures for fiscal year 2015.

First, regarding the number of inspections by foreign office staff, FDA set a performance measure in fiscal year 2016 for full-time medical product investigators assigned to the China, India, and Latin America offices for each to conduct 15 medical product inspections.⁴⁸ In other words, if there were two medical product investigators assigned to the China office, their target for the year would be 30 medical product inspections. Moreover, according to FDA, this goal applies to not only drugs, but all FDA medical product inspections, including medical devices and bioresearch monitoring inspections. There is not a specific "drug inspection" performance measure, although in practice, foreign office investigators are assigned a specific commodity (for example, food, drugs, or medical devices) to inspect. Depending on the current staffing composition, foreign office investigators could meet their target of 15 medical product inspections by inspecting establishments manufacturing medical products other than drugs.

Although FDA opened foreign offices abroad, in part, to help improve FDA's capacity to conduct foreign inspections, the staff in those offices

⁴⁶See [GAO-10-960](#).

⁴⁷FDA defines a collaborative action as concrete regulatory and public health actions, or initiatives that contribute toward supporting OIP objectives and outcomes.

⁴⁸The Europe office does not have investigators assigned to its office, although officials said it has assisted with planning for foreign drug inspections that are conducted by investigators based in the United States.

have conducted relatively few drug inspections since fiscal year 2010. Specifically, of the total number of drug inspections conducted between fiscal year 2010 and June 30, 2016 (4,384), investigators assigned full-time to the foreign offices participated in 241 (5 percent) of these inspections. The total number of drug inspections conducted each year by these full-time investigators ranged from 29 to 52, with the India office investigators conducting about two-thirds of the total number of inspections. See table 2 for more information on the number of drug inspections conducted by the foreign offices in India, China, and Latin America.

Table 2: Total Number of Food and Drug Administration (FDA) Drug Inspections in which Foreign Office Investigators Participated, Fiscal Year (FY) 2010 through June 30, 2016

FDA Foreign Office	FY 2010	FY 2011	FY 2012	FY 2013	FY 2014 ^a	FY 2015	FY 2016 through June 30, 2016	Total
India office	25	20	28	38	24	17	9	161
China office	8	11	1	11	2	9	15	57
Latin America office	0	0	0	3	4	11	5	23
Total	33	31	29	52	30	37	29	241^a

Source: GAO analysis of FDA data. | GAO-17-143

^aBetween fiscal year 2010 and June 30, 2016, FDA conducted a total of 4,384 foreign drug inspections. Foreign office investigators participated in 241 (5 percent) of these inspections.

We previously reported in 2010 that FDA did not have a goal for how many inspections it would like foreign office investigators to conduct—although this has since changed with its inspection targets—but that the agency would like to see overall increases in the number of inspections conducted in both China and India.⁴⁹ However, in the case of drug inspections, this goal has not yet been fully realized, as the number of inspections conducted by the India office has decreased since fiscal year 2013 and the number of inspections conducted by the China office has only just reached a new high in fiscal year 2016. We understand and previously reported that the China office had difficulty in obtaining visas from the Chinese government for its staff to deploy overseas for several years, which may have contributed to the low number of inspections conducted by the office during these years.⁵⁰ FDA appears to have been

⁴⁹See [GAO-10-960](#).

⁵⁰See [GAO-15-183](#).

able to overcome this particular challenge in 2014, and FDA officials told us there has been an overall increase in the total number of authorized foreign office staff who can perform foreign inspections since we reported in 2010. Specifically, in 2010 there were four investigators in the China office and three in the India office. As of July 2016, there were 11 of 18 authorized investigators in China, 3 of 13 authorized investigators in India, and 1 of 2 authorized investigators in the Latin America office, although these additional investigators may be conducting inspections of establishments that manufacture other FDA-regulated products, such as food. For example, according to FDA, in fiscal year 2015, foreign office investigators conducted 150 inspections of food establishments; 79 medical product inspections; and 8 veterinary medicine inspections; for a total of 237 inspections.⁵¹ FDA has also authorized 18 additional investigators for its foreign offices that the agency has yet to fill and of which at least 9 are intended to be assigned to performing drug inspections.

Drug inspections may also be conducted by temporary duty staff who are deployed to the foreign offices for 30-, 60-, 90-, or 120-day assignments to, in part, supplement the number of inspections conducted by the foreign offices. From fiscal year 2012, when staff began serving temporary duty in the foreign offices, through June 30, 2016, these staff participated in an additional 105 foreign drug inspections—bringing the total number of inspections in which full-time and temporary foreign office staff participated to 346. (For more information on the number of foreign drug inspections temporary duty staff have performed by year, see app. III.)

Regarding the second measure, collaborative actions, FDA set a target of completing 25 such actions for all of OIP for fiscal year 2016, according to FDA officials. The outcomes of this measure have been tracked internally by OIP since fiscal year 2014, when the measure was first implemented. OIP officials told us they use specific criteria to determine whether an activity qualifies as a collaborative action. For example, activities qualify only if they include collaboration with an external stakeholder or U.S. government agency other than FDA. Similarly, inspections conducted by foreign office investigators are excluded (as these are tracked separately) unless a foreign regulatory counterpart participates in the inspection with

⁵¹Of the 237 inspections completed by foreign office investigators in fiscal year 2015, 148 involved full-time foreign office investigators and 89 involved investigators on temporary assignment to the foreign offices.

FDA staff. In addition, activities are excluded if no tangible deliverable or result was identified. FDA reported exceeding its goal of 25 collaborative actions in fiscal year 2015 by 2, for a total of 27 collaborative actions.

We identified shortcomings with using the collaborative action measure to assess the foreign offices' performances. First, the measure and its target are not unique to the foreign offices. According to FDA officials, this measure applies to all of OIP's offices—both foreign and domestic. When asked about its decision to expand this target to all of OIP, rather than specifically focusing on the foreign offices, officials said that they prefer to adopt a holistic approach to assessing OIP's contributions. However, in adopting this approach, the measure does not reflect the unique contributions of the foreign offices as they are not distinguished from those made by OIP as a whole. Second, the target of 25 collaborative actions for all OIP does not necessarily target actions that are specific to drug safety-related efforts. FDA officials said the efforts could be focused on any commodity regulated by FDA, such as food and medical devices, meaning that the target could potentially be met without performing a single activity related to enhancing drug safety. Third, the measure is not expressed in terms of an end outcome. End outcomes are the results of programs and activities compared to their intended purpose.⁵² In this case, FDA's collaborative action measure is not expressed in terms of the foreign offices' purpose of enhancing drug safety. Furthermore, FDA officials—those in the foreign offices who engage in collaborative actions and those at FDA headquarters—acknowledge that it can be difficult to link the results of a foreign office's actions to enhanced drug safety.

Beyond the shortcomings of the collaborative action measure, FDA could not readily cite the overall effectiveness of the offices' contributions, and it has not completed a thorough assessment of their accomplishments, despite the implementation of the two performance measures within the last six years. Standards for internal control in the federal government call for agencies to have control activities that are designed appropriately to (1) conduct top-level reviews of actual performance, (2) review activities at the activity level, and (3) review performance measures and indicators.⁵³ While the foreign office staff may be engaged in meaningful

⁵²See GAO, *Managing for Results: EPA Faces Challenges in Developing Results-Oriented Performance Goals and Measures*, [GAO/RCED-00-77](#) (Washington, D.C.: Apr. 28, 2000).

⁵³See [GAO-14-704G](#).

activities, the activities cannot be systematically tracked by FDA using the two performance measures currently in place nor, according to officials, does the agency have a process in place to formally assess the offices' contributions. For example, FDA has not systematically tracked how information obtained from the foreign offices, and subsequently shared with FDA's centers and offices, contributed to increased drug safety, as such information would only be tracked if obtained in collaboration with foreign stakeholders. Additionally, FDA's two current performance measures do not capture a range of activities specifically undertaken by the foreign offices that resulted in drug safety related outcomes. Such outcomes could include additional inspections of foreign establishments in their host countries, warning letters to manufacturers in violation of CGMPs, or import alerts for products that appear in violation of FDA regulations. However, we found that the foreign offices were engaging in activities that produced potentially positive outcomes. When asked, FDA officials provided us with the following examples:

- In 2012, the India office discovered that an Indian establishment had manufactured and distributed API from one of its sites without fulfilling FDA's registration requirements. The India office shared this information with FDA's domestic offices and received concurrence to conduct an inspection at the firm's unregistered establishment, along with the firm's establishment that was registered with FDA. Inspections at both establishments revealed significant CGMP deficiencies. As a result, FDA issued a warning letter to the firm emphasizing the deficiencies and criticizing, among other things, its lack of oversight. Both establishments are on import alert.
- In 2013, the India office collected intelligence about an Indian company manufacturing APIs that had been linked to deaths in another country. The company and an affiliate were thought to be manufacturing sub-standard and fraudulent APIs, although FDA could not corroborate this through its own inspections since the U.S. embassy prohibited the agency from doing so due to security concerns. However, the India office followed up with the local government and obtained information about the company's establishments from the local government inspections. The local government in India had found the company not complying with CGMPs. As a result of the India office's intelligence gathering, the company and its affiliate were placed on import alert.

(See app. IV for examples of activities from each foreign office that may have helped ensure the safety of drugs entering the United States.)

However, positive examples such as these are not systematically tracked as they do not meet FDA's criteria of what constitutes a collaborative action. FDA's exclusion of activities that may enhance drug safety because they must be performed with a foreign counterpart or other U.S. government agency, for example, is not adequate as it does not include accomplishments made exclusively by foreign office staff, and leaves the agency with no reason to track them. While foreign office investigators have participated in for-cause inspections, for example, FDA officials said there is no tracking of the foreign offices' actions that led to such inspections in the first place. Therefore, if foreign office staff collect and share intelligence about an establishment in a host country with domestically based FDA staff that results in an action, which spurs a for-cause inspection or detaining a product at the border, this contribution is not assessed by any performance measure. An internal evaluation completed by FDA's Office of Planning in July 2016 similarly described the need for the foreign offices to make efforts to measure their benefits by recording instances of, for example, shortened recall time, signed FDA-relevant treaties, and other outcome measures. Without tracking how information collected by the foreign offices has resulted in these types of outcomes, FDA does not have reasonable assurance that the foreign offices' activities have helped ensure the safety of drugs entering the United States.

Furthermore, without evidence on the types of outcomes that resulted from information collected by the foreign offices, FDA cannot consider these outcomes and plan accordingly as the agency continues to test new performance measures for the foreign offices. FDA also cannot ensure that it has the correct number of staff deployed with the appropriate skills to perform such activities and enable the foreign offices to help fulfill FDA's mission overseas. FDA officials explained to us that the foreign offices have not existed for very long and that the changes and progress they have undergone since opening have been "remarkable." However, the limitations of FDA's two current performance measures to demonstrate such contributions reinforces the need for FDA to continue exploring new performance measures that will better assess the contributions of the foreign offices. FDA's July 2016 internal evaluation also described the need for OIP to establish performance measures that are aligned with selected outcomes for each foreign office, and that are tracked on a consistent basis to allow for continuous improvement and management oversight. FDA officials said they are considering using five other measures to assess the performance of its foreign offices that are currently included in the foreign offices' operational plans. However, these measures have not yet been adopted. FDA considered these measures

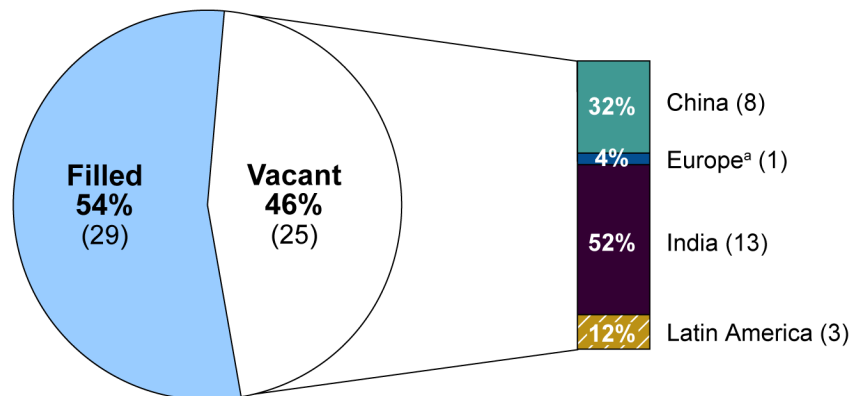
to be in the testing phase for fiscal year 2016, and said it plans to evaluate them in fiscal year 2017.

FDA Continues to Experience High Vacancy Rates in Its Foreign Offices, Limiting Its Ability to Ensure Drug Safety

Persistently high vacancy rates in FDA’s foreign offices threaten to impede the offices’ efforts to ensure drug safety. Our concerns extend back to 2010, when we reported that FDA had experienced challenges in staffing some of the foreign offices. For example, at that time, FDA had 2 vacant staff positions in the Latin America office out of a total of 14 positions (14 percent), and 4 vacancies in the India office out of a total of 15 positions (27 percent). In subsequent years, the number of vacancies in the foreign offices has increased. We later found that these rates were considerably higher—44 percent overall—as of October 2014.⁵⁴ This high vacancy rate has persisted. **As of July 2016, the foreign offices were authorized to have 54 full-time positions overseas, but 25 of these positions (46 percent) were vacant.** The India office has the highest vacancy rate at 68 percent (13 vacancies), followed by the Latin America office at 43 percent (3 vacancies), the Europe office at 33 percent (1 vacancy), and the China office at 32 percent (8 vacancies). (See fig. 4 for an analysis of vacancies by foreign office.)

Figure 4: Filled and Vacant Staff Positions at the Food and Drug Administration’s (FDA) Foreign Offices, as of July 2016

Percentage of approved positions (number of positions)



Source: GAO analysis of FDA data. | GAO-17-143

Notes: These numbers exclude approved and vacant positions for locally employed staff.

^aThis number excludes the Europe office’s staff who are based in the United States.

⁵⁴See [GAO-15-183](#).

Across all foreign offices, the position with the greatest proportion of vacancies is international program policy analysts, who analyze the impact of foreign issues on FDA programs and activities (6 of 10 authorized positions are vacant), followed by investigators, who conduct inspections (18 of 33 authorized positions are vacant). (See table 3.)

Table 3: Number of Authorized and Vacant Positions in the Food and Drug Administration’s (FDA) Foreign Offices, by Office and Position-Type, as of July 2016

		Director	Deputy Director	Supervisory Investigator	Investigator	International Program Policy Analyst	Total
China Office	Authorized	1	1	2	18	3	25
	Vacant	0	0	0	7	1	8
India Office	Authorized	1	1	1	13	3	19
	Vacant	0	0	1	10	2	13
Latin America Office	Authorized	1	1	0	2	3	7
	Vacant	0	0	0	1	2	3
Europe Office ^a	Authorized	1	1	0	0	1	3
	Vacant	0	0	0	0	1	1

Source: GAO analysis of FDA data. | GAO-17-143

Note: The Europe office has three staff members authorized to work overseas in Belgium and the United Kingdom: the director, deputy director, and one international program policy analyst. Additionally, the Europe office has two other international program policy analysts and one program support specialist assigned to it who are based in the United States.

Given that one of the reasons for opening the foreign offices was to conduct inspections, the large number of vacant investigators is concerning. FDA officials have stressed that there are significant benefits to having investigators stationed overseas. For example, officials noted that foreign office investigators can remain at an inspection site longer, if necessary, as they are not limited by travel arrangements to return to the United States. They can also initiate for-cause inspections more quickly than their domestic counterparts, as they are already in country. Former foreign office staff that we spoke with noted that the ability of foreign office investigators to conduct inspections quickly in response to emergencies is a great advantage of having FDA offices overseas. Former foreign office staff also said that it was valuable for investigators to be able to focus on their host country’s manufacturers, and to better understand how they satisfy CGMPs or their difficulties with doing so.

FDA acknowledged that recruiting and hiring staff for OIP, especially for the foreign offices, can be challenging, but that it is critical for achieving FDA's global mission. FDA's Office of Planning recently proposed a process for selecting foreign office locations and determining the correct mix of staffing and position types for them. However, the Office of Planning's proposal did not contain suggestions for overcoming high vacancy rates in the foreign offices. OIP has yet to implement this proposed process. OIP officials based in the United States and in the foreign offices cited several factors contributing to the foreign offices' persistently high vacancy rate. Although some of these factors may be beyond the agency's ability to resolve, others are issues we cited in our 2010 and 2015 reports that continue to challenge FDA.⁵⁵ Specifically, FDA officials said the following factors contribute to FDA's difficulty in filling its full-time positions overseas:

- Length of time to be cleared for deployment: Officials estimated that it takes approximately 9 to 12 months to complete the overseas deployment process, which includes, among other things, obtaining the appropriate security clearance for the employee, as well as medical clearances for the employee and any dependents who will be accompanying the employee overseas. Former foreign office staff that we spoke with confirmed that the deployment process could be quite lengthy, and two former staff specifically mentioned experiencing challenges navigating the process. We reported on these challenges in both 2010 and 2015.⁵⁶ FDA officials explained that there is little they can do to expedite this timeframe given the length of time involved to obtain necessary security and medical clearances required to work abroad. Furthermore, the process involves other government stakeholders, such as the Department of State, which is responsible for the medical clearances, limiting FDA's ability to control the deployment timeframe.
- Reintegration into FDA's domestic offices: Our discussions with former foreign office staff who have since returned to FDA's domestic offices or left the agency following their time spent overseas confirm that challenges reintegrating into FDA persist. For example, some former foreign office staff reported having to find a job in a domestic office on their own, or who faced considerable uncertainty about what their new role in the agency would be. Several also noted that the

⁵⁵See [GAO-10-960](#) and [GAO-15-183](#).

⁵⁶See [GAO-10-960](#) and [GAO-15-183](#).

skills they developed abroad were not being leveraged, and indicated that there was no effort by FDA management or OIP to debrief them upon their return. For example, a former policy analyst said he developed a unique set of skills for working with foreign regulators on potential drug safety issues that were no longer being leveraged by the agency once he returned to a domestic position. A former investigator, meanwhile, said he had developed a unique set of skills for determining whether establishments were falsifying their records, but it was unclear how he could best share these skills with other investigators upon his return to the United States. We reported on concerns about such challenges in both 2010 and 2015, and recommended in 2010 that FDA develop a strategic workforce plan to, in part, help ensure that the agency was able to reintegrate returning foreign office staff into FDA's domestic offices. FDA developed and finalized such a plan in 2016, and prior to this implemented a formal reintegration policy in 2015. However, FDA officials have not been formally debriefing returning foreign office staff. Of the 13 former foreign office staff we interviewed, only 3 of them reported being debriefed by OIP. When asked why OIP has not debriefed with returning foreign office staff, FDA officials said that they are developing a formal exit interview process for returning staff to be implemented in fiscal year 2017. However, officials also said that the offices are still "young and evolving," despite having been in operation for eight years. These challenges may discourage FDA officials from applying for a foreign office position and thus contribute to the foreign offices' vacancies.

- Financial concerns: Our discussions with former foreign office staff also show that financial concerns with working overseas persist. For example, FDA staff posted overseas do not receive locality pay, so staff may have a reduction in their purchasing power when they are assigned to a foreign office.⁵⁷ However, staff at certain locations may

⁵⁷Locality pay is a supplement to the rate of basic pay that is provided to federal employees within given localities in the continental United States to offset any gap between federal and nonfederal salaries. We previously reported that FDA officials said that HHS was considering locality pay to overseas staff. When asked for an update on this effort, FDA officials said HHS is still in the process of examining whether to do so. Notwithstanding the possibility that certain compensation adjustments and subsidies may be made for their benefit, the fact that FDA overseas employees do not receive locality pay increases concerns for individuals considering overseas employment.

receive hardship pay, a cost of living adjustment, and other benefits.⁵⁸ We reported on this challenge in 2010.⁵⁹ Additionally, staff may experience an increase in pay when they move overseas and may receive a promotion while abroad, but such pay increases and promotions are considered temporary and staff must return to their original salaries and roles when they return to the United States. Some former foreign office staff said that these temporary promotions were disincentives to working overseas. When asked about this issue, FDA officials said they are considering how the agency might be able to make the promotions permanent by taking into account experience gained while working overseas.

- Environmental and security concerns: FDA has noted that some of FDA's foreign offices are in countries that make recruitment difficult due to environmental concerns (such as poor air quality) or security concerns (such as dangerous locations). Although hardship pay accompanies some of these places, staff may still be hesitant to live in these locations for extended periods of time. We reported on this challenge in 2010.⁶⁰
- Personal reasons: Officials said that personal reasons affect the willingness of staff to spend time living overseas, such as whether spouses will be able to find a job abroad and concerns about the educational opportunities available for their children.
- Unfamiliarity with FDA's global mission: According to FDA officials, some FDA staff do not fully understand FDA's global mission and the importance of FDA's presence overseas. Over the years, FDA has been transforming from a domestically focused agency operating in a globalized economy to an agency operating in a regulatory environment that functions across borders. FDA noted that some agencies, such as the Centers for Disease Control and Prevention, have a longstanding foreign presence. In contrast, FDA's foreign posts are still relatively new, which presents a number of challenges, the agency noted. FDA officials described some of their recruitment

⁵⁸A cost of living adjustment is provided to federal employees posted at overseas locations where the cost of goods and services is more expensive, relative to Washington, D.C. In addition, FDA staff posted at overseas locations receive benefits that are not provided to domestic staff, such as subsidized housing and reimbursed private education for staff members' school age children. In October 2016, FDA officials said that they are considering other incentives, including incentive pay, for eligible foreign office employees.

⁵⁹See [GAO-10-960](#).

⁶⁰See [GAO-10-960](#).

efforts aimed at educating staff about its increasingly global mission. For example, the foreign offices have published blog postings highlighting the activities of their offices overseas and how they contribute to FDA's mission. FDA officials also told us they have met with selected FDA staff located across the country to advocate foreign offices as career considerations.

Another step FDA has taken to help reduce its vacancy rates in its foreign offices is to encourage staff to apply for a temporary duty rotation of 30-, 60-, 90-, or 120-days. In addition to helping the offices fulfill their mission, according to FDA, these rotations are a recruitment mechanism that allows staff to experience working overseas in the hope that they will eventually apply for a full-time position in a foreign office. Since 2011, 37 FDA staff have completed at least one drug-related temporary rotation in an FDA foreign office—some of these people completed more than one rotation. Of these 37 staff, 9 (24 percent) went on to work in a full-time position overseas.

In addition, to address these challenges, OIP finalized its strategic workforce plan in March 2016.⁶¹ The plan offers a strategic and long-term view of the challenges OIP faces, and addresses the agency's plan to recruit, hire, retain, and develop employees with the skills and abilities to fulfill the agency's global mission, consistent with a recommendation we made in 2010.⁶² We previously recommended that FDA develop a strategic workforce plan to help ensure that the agency was able to recruit and retain staff with the experience and skills necessary for the foreign offices, and to reintegrate returning foreign office staff into FDA's domestic offices. The plan outlines OIP's activities, performance measures, and timeline for addressing its workforce planning challenges. The activities are categorized by specific focus areas and include, for example, developing a hiring strategy, ensuring that employees separating from the agency participate in exit surveys to determine actions for improving retention, establishing a succession plan for anticipated vacancies, and working to maximize a returning foreign office employee's new skill set from his or her deployment.⁶³ FDA's workforce plan also addresses reintegration challenges and determining how the

⁶¹OIP has since updated its workforce plan in August 2016.

⁶²See [GAO-10-960](#).

⁶³The specific focus areas are (1) recruitment and hiring, (2) retention, (3) acclimation, (4) training and development, (5) deployment, (6) succession, and (7) reintegration.

agency can better leverage the skills staff develop while working abroad, which reflects concerns expressed to us by former foreign office staff. For example, one activity in the workforce plan is to evaluate FDA's new reintegration policy, which the agency issued in 2015, to determine whether it can be made more strategic and career enhancing for overseas deployment. Given that this plan has been recently developed, FDA has yet to evaluate it, but plans to do so in fiscal year 2017, and, if necessary, revise the activities or performance measures specified in the plan.

We reviewed OIP's workforce plan and identified concerns with some of the six performance measures OIP developed for the focus areas it plans to assess first.⁶⁴ For example, the recruitment and hiring performance measure calls for OIP to reduce its vacancy rate by 5 percent—taking it from 32 percent (its vacancy rate at the conclusion of fiscal year 2015) to 27 percent at the beginning of fiscal year 2017. However, this goal is not targeted to the vacancy rates in the foreign offices. Instead, the measure targets the OIP-wide vacancy rate. As of July 2016, OIP's domestic offices had a vacancy rate of 34 percent, in contrast to the foreign offices' collective vacancy rate of 46 percent. Because the 5 percent reduction to OIP's vacancy rate is a combined goal for both domestic and foreign offices, OIP could theoretically hire 8 new staff members in its domestic offices and achieve its goal without reducing any vacancies in the foreign offices.⁶⁵

⁶⁴The workforce plan includes six performance measures for select focus areas. Officials told us the performance measures may change upon assessment. Currently, the six performance measures (and their accompanying focus area) are (1) reduce the OIP vacancy rate by 5 percent from the baseline of 32 percent by the end of fiscal year 2016 (recruitment and hiring); (2) revise and implement a new employee orientation program by the second quarter of fiscal year 2017 (acclimation); (3) refine and document an acclimation program specifically for foreign assignments by the second quarter of fiscal year 2017 (acclimation); (4) evaluate and measure deployment processing time, monitor quarterly, and identify trends and areas for improvement that is within OIP's control, by the first quarter of fiscal year 2017 (deployment); (5) develop a system for tracking deployments by the third quarter of fiscal year 2017 (deployment); and (6) develop a concept paper on how FDA can better utilize the skills of employees returning from an overseas appointment by the first quarter of fiscal year 2017 (reintegration).

⁶⁵The workforce plan calls for a 5 percent reduction from the baseline vacancy rate of 32 percent (at the end of fiscal year 2015) to a vacancy rate of 27 percent. However, we based our calculations off of the most recent vacancy data available (as of July 2016), from which we found that OIP's vacancy rate had increased to 38 percent. Keeping consistent with the goal of a 5 percent reduction to the vacancy rate, our calculations were based off of a new goal of a 33 percent vacancy rate.

Meanwhile, the development of a concept paper on how FDA can better leverage the skills of employees returning from overseas, intended as the reintegration performance measure, is a positive step, but it does not constitute a performance measure. It may serve as a guide, but it does not measure FDA's outcomes in this area. Some of the other performance measures identified by FDA also do not measure outcomes. For example, the implementation of a new employee orientation program may help new foreign office staff better acclimate to their new positions, but such a program does not measure outcomes in this area.

A final concern with the workforce plan is that it does not take into account the recommendations of the 2016 internal evaluation of the foreign offices or the summaries of the operating states and workforce compositions of the China, Europe, India, and Latin American offices that were completed in 2014. For example, the workforce plan does not reflect the recommended foreign office staffing and position types specified in the 2016 evaluation, or address how these specifications might be achieved.

We have previously reported on the importance of workforce planning, which is utilized by agencies to align their workforce with current and emerging mission and program goals, and develop long-term strategies for acquiring, developing, and retaining staff. Workforce planning helps agencies think strategically about how to put the right people with the right skills in the right places at the right time. We have previously identified key approaches for effective strategic workforce planning. These approaches may vary with each agency's particular needs and mission, but should share certain principles, such as identifying skills and competencies to fill critical workforce gaps and the strategies needed to recruit them; developing specific strategies that are tailored to address gaps in number, deployment, and alignment of human capital; and monitoring and evaluating the agency's progress toward its human capital goals.⁶⁶ Similarly, federal internal control standards require agencies to establish and operate monitoring activities, evaluate results, and remediate deficiencies on a timely basis—which could be done when staff are returning from overseas deployments.⁶⁷ Without a specific focus on reducing the number and types of foreign office vacancies, OIP may find it difficult for the foreign offices to fulfill their mission. Furthermore, by not

⁶⁶See [GAO-04-39](#).

⁶⁷See [GAO-14-704G](#).

focusing specifically on the foreign offices' vacancies by position type FDA may be missing an opportunity to determine why particular positions are more difficult to fill than others and take appropriate action in response.

Conclusions

The United States' increasing dependence on global markets has been challenging for FDA. The rapid pace of globalization has complicated the agency's efforts to ensure the safety of our drug supply. Our concerns with FDA's response to globalization go back two decades. In that time we have made multiple recommendations to help the agency tackle this challenge. The enactment of FDASIA also provided the agency with new flexibility to help FDA cope with the growth of drug manufacturing overseas. To its credit, FDA has made important strides. It has implemented some of our 2008 and 2010 recommendations and is taking steps to address others. FDASIA has further enhanced the agency's efforts. To date, FDA has increased the number of foreign drug inspections, improved information on foreign establishments manufacturing drugs for the U.S. market, and opened offices overseas.

While FDA has made progress on some fronts, it has been incremental on others. FDA is now using a single risk-based model to select domestic and foreign establishments to inspect so that those that pose the greatest risk are prioritized for inspection, but the agency still lacks inspection history on approximately 33 percent of foreign establishments. While FDA has a plan to fill this knowledge gap over the next few years, this is an issue it has been aware of since at least 1988. Given the longevity of this issue, it will be important for the agency to fully execute its plan to inspect those remaining establishments for which it has no inspection history over the next three years.

FDA has also made progress in its strategic planning for the foreign offices, but despite these efforts, the agency has yet to determine whether the foreign offices meaningfully contribute to drug safety, because FDA has no formal process for assessing the offices' contributions. In 2008, the agency determined that opening foreign offices was an instrumental part of its response to globalization. Our recommendation that FDA develop performance goals and measures for these offices followed in 2010, two years after the first office was opened. We believe this recommendation has not been fully implemented. The two performance measures currently used to assess the foreign offices do not fully capture the specific contributions these offices have made. While FDA officials shared examples of the foreign offices' accomplishments, they do not systematically track such information, nor

have they fully assessed the extent to which the offices are helping to ensure drug safety. We believe it is important for FDA to track these types of results-oriented outcomes, and for the agency to determine how their performance measures—whether the existing ones or those currently being tested—can be used to demonstrate such results. Having performance measures that demonstrate results-oriented outcomes will better enable FDA to meaningfully assess the foreign offices' contributions to ensuring drug safety.

FDA should also consider including an examination of the appropriate staffing levels for its current foreign offices in its assessment of them. FDA's internal evaluation proposed a process for determining the correct mix of staffing and position types for the foreign offices, but as OIP has yet to implement and apply the process to the foreign offices, such an examination has not yet been completed. While the agency's progress overseas may be aggravated by the difficulties it faces in decreasing their vacancy rates, the agency must determine what outcomes it is working to achieve through these offices and then consider the appropriate staffing to reach those goals. Regardless, the current overall foreign office vacancy rate of 46 percent could easily undermine even the best strategic plan and precludes the offices from being as effective as possible. As we also recommended in 2010, FDA has now completed a strategic workforce plan for the foreign offices to help ensure that the agency is able to recruit and retain staff with the necessary experience. We recognize the value of the completion of this plan. However, FDA has not fully addressed our recommendation, because some of the reasons for the high vacancy rates in the foreign offices are not addressed. While FDA may not be able to address some of these reasons, such as time to deployment, it is all the more important that it addresses those within its span of control, such as addressing the financial concerns raised by staff and discussed in our 2010 report, as doing so may contribute to a decrease in its foreign office vacancy rate. It is also imperative that FDA fully implement its new reintegration program as outlined in the plan. The difficulties staff have experienced upon their return to domestic positions is one that former foreign office staff repeatedly shared with us when we prepared this and our 2010 reports. While the workforce plan contains goals and measures, the plan circumvents the high foreign office vacancy rate, rather than directly tackling it, by targeting a 5 percent reduction in OIP vacancies overall, rather than applying this goal exclusively to the foreign offices. The plan also does not target vacancies by specific position types. In essence, the current goal targeting OIP vacancies overall obscures the underlying challenges the agency faces of staffing people overseas and for particular positions. Without targeting the foreign

offices specifically or the types of positions most likely to have vacancies, FDA will not have a meaningful measure reflecting its true staffing position overseas.

FDA's response has been, in part, that the offices are still new and evolving, and it is too soon to expect more than it has already accomplished. We believe sufficient time has elapsed for the agency to address its remaining challenges. Otherwise, given their significance, FDA may not know the extent to which its foreign offices are actually assisting the agency in its efforts to ensure drug safety.

Recommendations for Executive Action

To help ensure that FDA's foreign offices are able to fully meet their mission of helping to ensure the safety of imported products, we recommend that the Commissioner of FDA take the following two actions as the agency continues to test performance measures and evaluate its OIP strategic workforce plan:

1. Assess the effectiveness of the foreign offices' contributions by systematically tracking information to measure whether the offices' activities specifically contribute to drug safety-related outcomes, such as inspections, import alerts, and warning letters.
2. Establish goals to achieve the appropriate staffing level for its foreign offices, which would include separating foreign office vacancies from the OIP-wide vacancy rate, and setting goals by position type.

Agency Comments and Our Evaluation

We provided a draft of this report to HHS for comment. In its written comments, reproduced in appendix V, HHS concurred with our two recommendations and said it is taking immediate steps to address them. For example, starting in fiscal year 2017, FDA plans to conduct internal reviews of its foreign offices' performances annually, review the offices' programs and efforts at the activity level, and review performance indicators. To accomplish this, HHS said that OIP has recently hired two designated full-time employees to work on strategic planning, operational plans, and performance measures. HHS also said that OIP plans to, among other things, adjust its performance measures to track the foreign offices' measures separately from its domestic offices, and characterize the offices' contributions by type of commodity, including drugs. Additionally, HHS said that OIP's strategic workforce plan will be updated to reflect the disaggregation of performance measures that track foreign office vacancy rates and targets by position type. Furthermore, FDA said it is developing recruitment, hiring, retention, and reintegration strategies

to enable the agency to utilize the unique experiences that foreign office employees develop overseas. HHS also provided technical comments, which we incorporated as appropriate.

As agreed with your offices, unless you publicly announce the contents of this report earlier, we plan no further distribution until 30 days from the report date. At that time, we will send copies to the Secretary of Health and Human Services and the appropriate congressional committees. In addition, the report will be available at no charge on the GAO website at <http://www.gao.gov>.

If you or your staff have any questions about this report, please contact me at (202) 512-7114 or crossem@gao.gov. Contact points for our Offices of Congressional Relations and Public Affairs may be found on the last page of this report. GAO staff who made key contributions to this report are listed in appendix VI.



Marcia Crosse
Director, Health Care

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EXHIBIT 452

TESTIMONY

Securing the U.S. Drug Supply Chain: Oversight of FDA's Foreign Inspection Program

DECEMBER 10, 2019

Testimony of

Janet Woodcock, M.D.

Director - Center for Drug Evaluation and Research

Before the

House Committee on Energy and Commerce, Subcommittee on Oversight and Investigations

<https://energycommerce.house.gov/subcommittees/oversight-and-investigations-116th-congress>

Chair DeGette, Ranking Member Guthrie, and Members of the Subcommittee, I am Dr. Janet Woodcock, Director of the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA or the Agency), which is part of the Department of Health and Human Services (HHS).

Today I will provide the Committee with an overview of the history of FDA's foreign drug inspection program, and the ways it has evolved in response to the industry's globalization and changes in law and regulation. I will also explain our approach when our inspections indicate that a facility does not operate in keeping with established quality standards. These standards are known as current good manufacturing practices (CGMPs). I will also describe some potential enhancements that would enable FDA to complement our foreign drug inspection program. The Agency believes that over the longer term, we should encourage investment in advanced manufacturing technology and in strengthening the approach by which manufacturers assure the quality of their products. This approach, which we call quality management maturity, would provide a safer and more secure drug supply because it can help prevent many quality problems from occurring in the first place. Advanced technology, which can be more cost-effective and environmentally friendly than traditional manufacturing technology, may also enable the United States to play a larger role in pharmaceutical manufacturing.

The Globalization of Pharmaceutical Manufacturing

Over the past 30 years, pharmaceutical manufacturing has become an increasingly global enterprise. Beginning in the 1970s, industry moved away from the mainland United States, first to Puerto Rico in response to tax incentives, and then to Europe and developing nations such as China and India. Developing nations can provide significant cost savings to pharmaceutical companies because of their lower labor, energy, and transportation costs. In addition, they often have weaker environmental regulations than more developed countries. A World Bank study estimated that in 2004, China and India held a cost advantage of about 40 percent when compared with the United States and Europe. [1] FDA’s 2011 report, “Pathway to Global Product Safety and Quality,” also noted that both China and India enjoy a labor cost advantage and that manufacturing active pharmaceutical ingredients (APIs) in India can reduce costs for U.S. and European companies by an estimated 30 percent to 40 percent.[2]

As the U.S. drug market shifted toward lower-priced generic drugs, manufacturers came under increasing cost pressure and found these efficiencies compelling reasons to locate more of their facilities overseas, particularly in developing parts of the world. **This shift is reflected in the CDER’s Site Catalog (“Catalog”), which lists all drug manufacturing facilities worldwide that are subject to routine FDA inspections. [3] As of August 2019, 28 percent of facilities manufacturing APIs and 47 percent of the facilities producing finished dosage forms (FDFs) of human drugs for the U.S. market were located in the United States. (See Figures 1 and 2)**

Percentage of Active Pharmaceutical Ingredient Manufacturing Facilities for All Drugs by Country or Region, August 2019

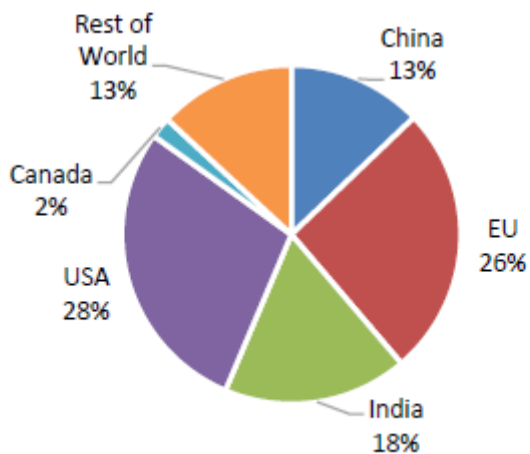


Figure 1: For all FDA-regulated drugs, 28 percent of manufacturing facilities producing active pharmaceutical ingredients (APIs) are located in the United States.

Percentage of Finished Dosage Form Manufacturing Facilities for All Drugs by Country or Region, August 2019

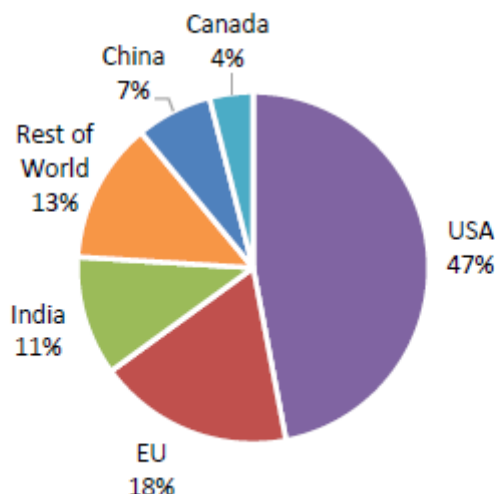


Figure 2: For all FDA-regulated drugs, 47 percent of manufacturing facilities producing finished dosage forms (FDFs) are located in the United States.

This movement accelerated in the 2000s, but due to mandates for domestic inspections and limited staffing, FDA's inspectorate remained focused on domestic manufacturing. Until passage of the Food and Drug Administration Safety and Innovation Act (FDASIA) in 2012 (P.L.112-144), the Agency was legally required to inspect manufacturing facilities in the United States every two years but had no similar mandate for the inspection frequency of foreign facilities. This resulted in more frequent inspections for domestic facilities and created an unequal playing field that was exacerbated by resource constraints.

The Globalization of FDA's Drug Inspection Program

In response to the move from domestic to global manufacturing and the passage of FDASIA, FDA's drug inspection program shifted from one focused heavily on U.S.-based facilities through the early 2000s to a program that, since 2015, has conducted more foreign than domestic drug inspections. **(See Figure 3)** FDA's drug inspection program is now risk-based. FDA prioritizes for inspection facilities deemed higher-risk based on specific, defined criteria.

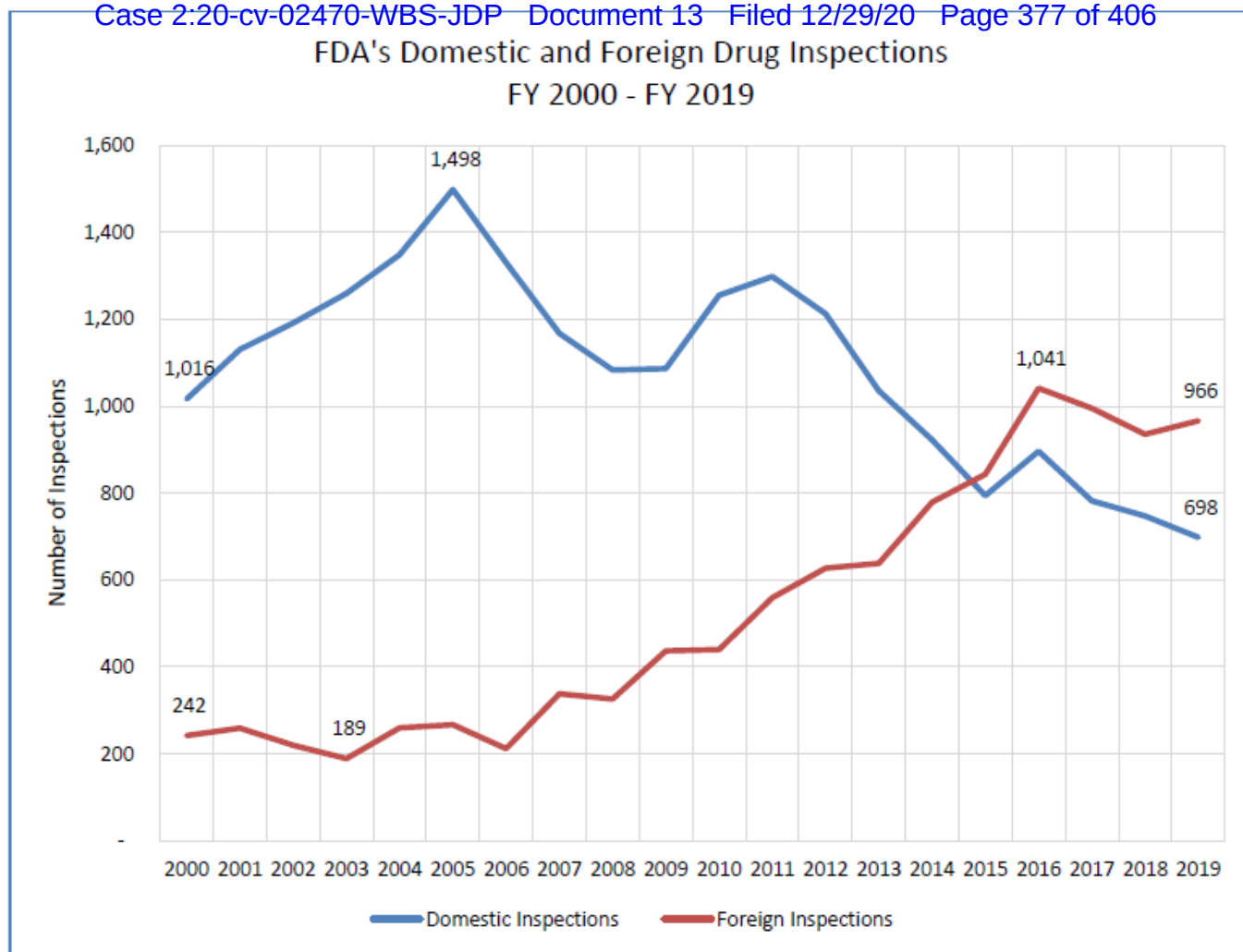


Figure 3: FDA's Inspections of Foreign Drug Manufacturing Facilities Increased Sharply After 2006 and Have Exceeded Inspections of Domestic Drug Facilities Since 2015

Types of Inspections

The types of inspections performed in both domestic and foreign facilities include *pre-approval*, *surveillance*, and *for-cause inspections*.

- *Pre-approval inspections*: conducted as part of the review of an application to market a new brand or generic drug.
- *Surveillance inspections*: Used to monitor the manufacturing process and, periodically, the quality of distributed drugs. FDA uses the findings to evaluate whether a manufacturer is complying with CGMPs. In general, the Agency does not announce domestic surveillance inspections to the company in advance but announces international surveillance inspections. [4] Whether inspections are announced often depends on particular cases and the history of specific facilities.
- *For-cause inspections*: Triggered when FDA has reason to believe that a facility has serious manufacturing quality problems or when FDA wants to evaluate corrections that

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have been made to address previous violations. For-cause inspections can be announced or unannounced, whether domestic or international, depending on the specific situation.

The Site Selection Model

To address the need to prioritize use of limited resources, in 2005 FDA implemented a risk-based approach to drug facility surveillance inspections. A mathematical model, the Site Selection Model (SSM), was designed to select facilities with the greatest potential for public health risk should they not comply with established manufacturing quality standards. FDA uses results of the model to prepare a prioritized list of facilities for inspection.

The passage of FDASIA ratified our risk-based approach and removed the requirement to inspect domestic facilities on a fixed biennial schedule. FDASIA also enhanced our inspectional authority by requiring facilities to provide, upon request, records or other information in lieu of or in advance of an inspection. Additionally, under another provision added by FDASIA, if the owner or operator of a foreign facility delays, denies, or refuses to permit inspection, all drugs manufactured at that facility would be deemed “adulterated.” [5] The Agency thanks this committee and Congress for your support in enacting this law.

In 2007, FDA began to shift its investigator workforce to cover foreign facilities and to rebalance allocation between domestic and foreign inspections. Still, the Agency did not have adequate staffing and financial resources for foreign inspection coverage. Both the Generic Drug User Fee Amendments (GDUFA) of 2012 and its reauthorization in 2017 provided new resources to FDA for inspecting foreign facilities, which are often the source for APIs and FDFs of generic drugs.

With new resources, FDA has been able to inspect some facilities that previously had not been inspected. CDER's Catalog showed that as of July 2016, there were 965 foreign manufacturing facilities that had never been inspected by FDA. By the end of FY 2019, FDA had inspected 495 or 51 percent of these previously uninspected facilities (**See Figure 4**). An additional 359 facilities (37 percent) were removed from the Catalog because they were no longer part of FDA's inspection obligations for a number of reasons: e.g., they had gone out of business, were not serving the U.S. market, or had been registered with FDA erroneously. In addition, 52 or six percent of the facilities had refused inspection; [6] 37 or four percent of the facilities were inaccessible to FDA investigators because they were unable to travel to them (e.g., as a result of travel warnings); and 22 or two percent had no drug shipments.

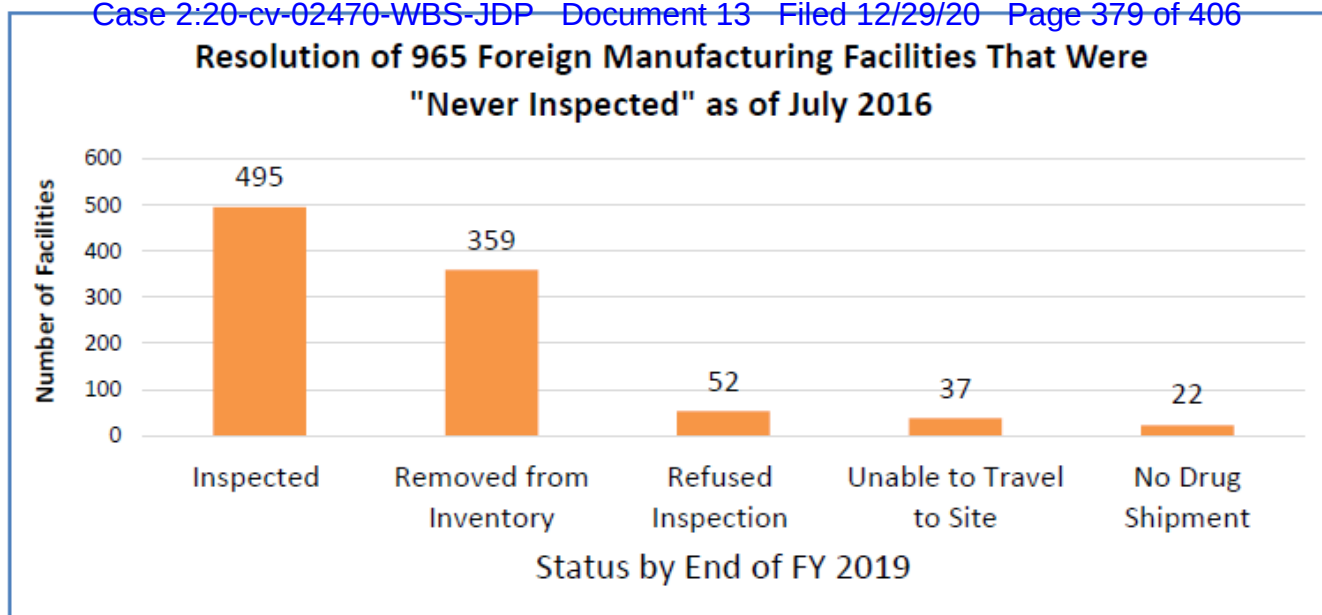


Figure 4. FDA has now inspected 495 (51%) of the 965 foreign manufacturing facilities that had never been inspected, as of July 2016.

The SSM is at the core of FDA's surveillance inspection prioritization program and ensures a uniform approach for domestic and foreign facility inspections. The Agency uses the model to calculate a score for every facility in its Catalog using risk-based factors. Factors in the SSM include:

- **Inherent product risk.** Different types of products carry different levels of risk based on characteristics such as dosage form, route of administration, or whether the product is intended to be sterile. For example, a manufacturing facility that makes sterile injectable drug products will have a higher inherent product risk than a facility that makes oral capsules.
- **Facility type.** Risk levels can vary depending on the operations that a facility performs. A facility that manufactures drug product or active ingredients is higher in risk than a facility that only packages drug product.
- **Patient exposure.** The more products a facility manufactures, the more likely a patient is to encounter products made at that facility. This refers to both number and types of products manufactured. A facility that manufactures many products will have a higher exposure factor than a facility that makes few products.
- **Inspection history.** A facility that has not met established quality standards when previously inspected is considered higher risk than those that have met standards in the past.
- **Time since last inspection.** As the time since a facility was last inspected increases, the risk that it may not meet established quality standards increases, as does the need for re-inspection.

- **Hazard signals.** Events such as product recalls or manufacturers' or patients' reports of quality problems associated with a facility increase the risk score when compared with facilities that have fewer or no major hazard signals.

FDA compares a facility's score to others in the Catalog and ranks them by risk, with the highest risk assigned for inspection regardless of location.

If the three factors that are fairly static for a facility (inherent product risk, facility type and patient exposure) are used to risk rank facilities, for inspections conducted from December 2011 to June 2019, the median time between inspections was 2.1 years for high-risk facilities. In general, all high-risk facilities were inspected with about the same frequency regardless of location. (See Figure 5)

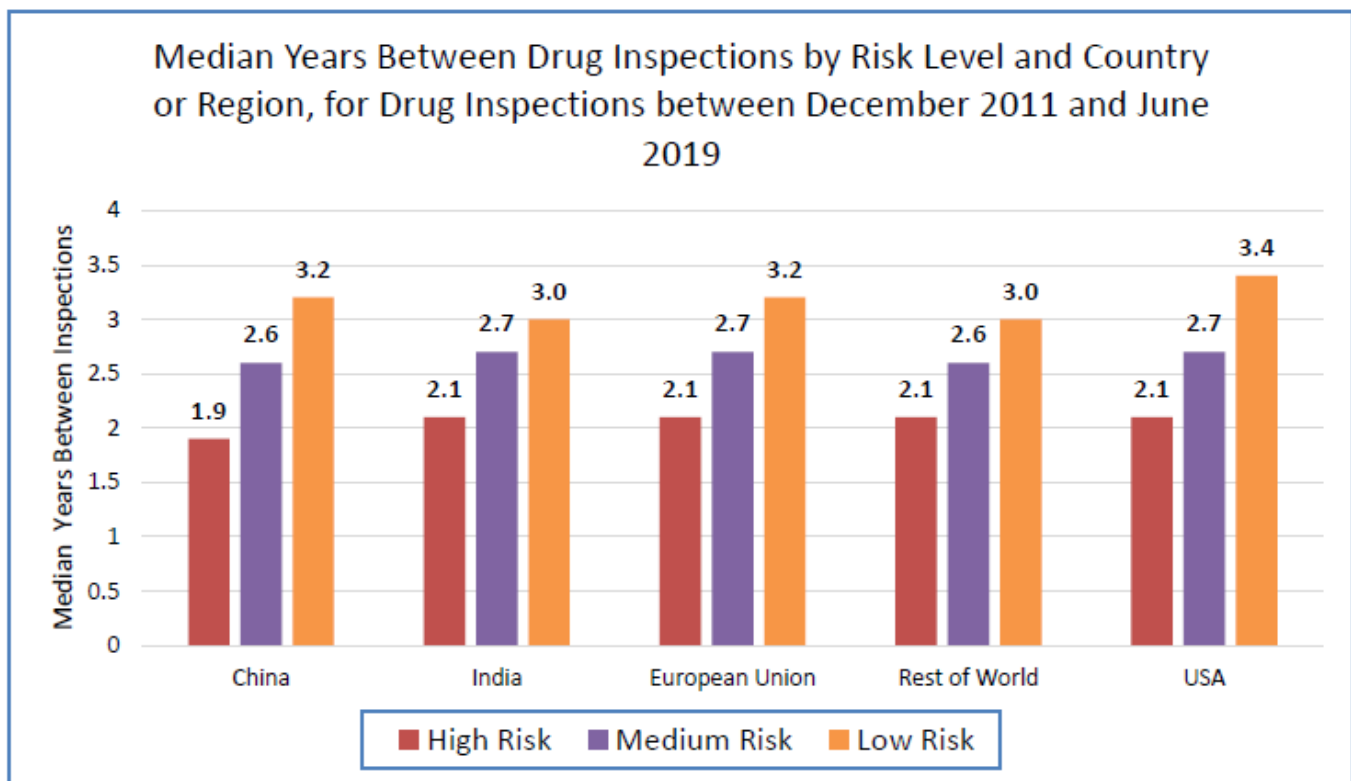


Figure 5. FDA inspected high-risk manufacturing facilities more frequently than medium- or low-risk facilities, and medium-risk facilities more frequently than low-risk facilities, across all countries or regions. In general, all facilities in a risk category were inspected with about the same frequency, regardless of location.

Inspection Outcomes

Following inspection of a manufacturing facility, FDA classifies the inspection as “no action indicated” (NAI), “voluntary action indicated” (VAI), or “official action indicated” (OAI).

- **No Action Indicated (NAI)** means that no objectionable conditions or practices (e.g., quality problems) were found during the inspection (or they were minor problems that do

- **Voluntary Action Indicated (VAI)** means objectionable conditions or practices were found but the Agency is not prepared to take or recommend any administrative or regulatory action.
- **Official Action Indicated (OAI)** means regulatory and/or administrative actions will be recommended. [7]

Not surprisingly, with more frequent inspections directed to higher-risk facilities since 2012, FDA uncovered some deficiencies, particularly in foreign facilities that had not been inspected as frequently as domestic ones prior to the inception of FDASIA and GDUFA. Nevertheless, 90 percent or more of the final outcomes of inspections were acceptable (NAI or VAI) in all countries or regions except India (**See Figure 6**).

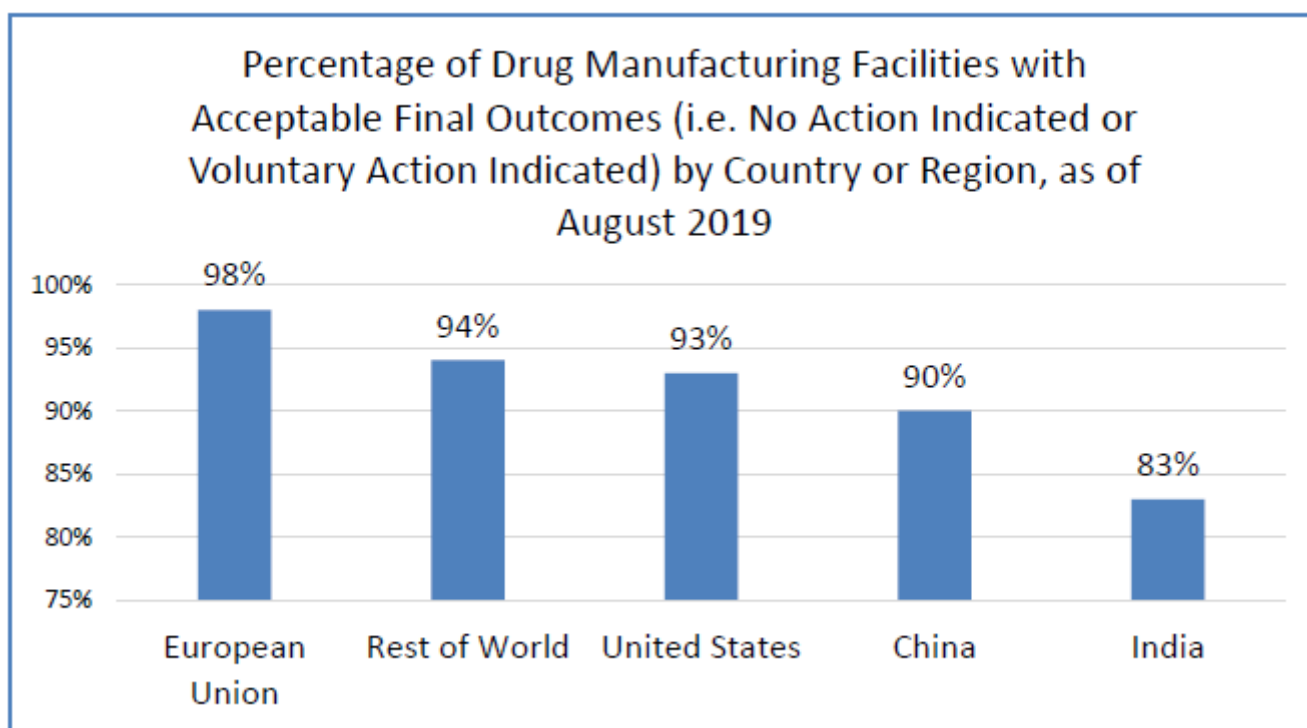


Figure 6. The majority of final inspection outcomes for manufacturing facilities making human drugs were acceptable, meaning that they were classified as having No Action Indicated or Voluntary Action Indicated. However, India had a lower percentage of acceptable outcomes than other countries and regions. (These were outcomes as of August 2019 for the most recent inspection of facilities that were in the Catalog as of July 2019.)

Both foreign and domestic drug manufacturers must meet the same regulatory requirements in terms of complying with established quality standards (CGMPs). If a facility doesn't meet CGMP standards upon inspection, FDA has an array of regulatory tools it can use to encourage a company to remediate their manufacturing processes and achieve compliance. These tools

include warning letters, import alerts, injunctions, and seizures. [8] If the Agency observes on a follow-up inspection that a facility still does not meet CGMP standards, it can escalate the matter as appropriate.

If a foreign facility is found to have quality problems serious enough for FDA to classify it as OAI, the Agency can place a facility on Import Alert to prevent drugs from the facility from legally entering the United States. Generally FDA will remove a facility from a CGMP-related Import Alert after an onsite re-inspection demonstrates that the problems have been remediated and the firm is in compliance with CGMP.

Despite the tools at FDA's disposal, we still face some challenges in ensuring the safety of imported drugs entering our drug supply. Under our current authorities, foreign-based manufacturers of certain drugs can legally ship drugs to the United States without ever having been inspected by FDA. Drugs in this category typically include OTC monograph drugs and APIs used in pharmacy compounding. This increases the risk of exposing American patients to unsafe or ineffective drugs and requires resource-intensive efforts on FDA's part to identify and respond to any problems that arise subsequently. For example, last month, we issued a warning letter to a discount retailer for receiving OTC drugs produced by foreign manufacturers with serious violations of CGMPs. The majority of the foreign facilities involved had distributed drugs to the United States prior to FDA inspections. [9]

FDA's Program Alignment Initiative and Concept of Operations Agreement

The inspection of drug manufacturing facilities relies on the collaboration of two organizations within FDA: the Office of Regulatory Affairs (ORA), which contains the field force of investigators who conduct the inspections, and CDER, which includes compliance officers who review inspection reports that are initially recommended as OAI and for-cause inspections to determine the final classification and whether appropriate regulatory action is required. CDER also includes reviewers who evaluate applications for marketing approval and post-marketing changes. ORA has recently completed a multi-year effort to implement a specialized inspectorate focused on human drugs.

On June 6, 2017, CDER and FDA's Office of Regulatory Affairs (ORA) entered into a Concept of Operations [10] (ConOps) agreement to better integrate facility evaluations and inspections for human drugs. The planning for this integration began in 2013 in a Program Alignment initiative. [11] The ConOps is designed to improve the collaboration between ORA and CDER and enhance the efficiency and effectiveness of FDA's oversight of drug manufacturing facilities. As part of this effort, FDA redesigned processes to enhance the efficiency and effectiveness of classifications of inspection classifications **(See Figure 7)**. If ORA initially recommends classifying the inspection report as OAI, CDER's Office of Compliance then reviews the report

and the manufacturing facility may submit a remediation plan to rectify any quality problems that were noted. CDER evaluates the evidence supporting inspection observations, impacts to patient safety, the company's responses to the observations, and the adequacy of proposed corrective actions. Depending on the particular circumstances, including remediation efforts made at the facility, CDER may reclassify the inspection.

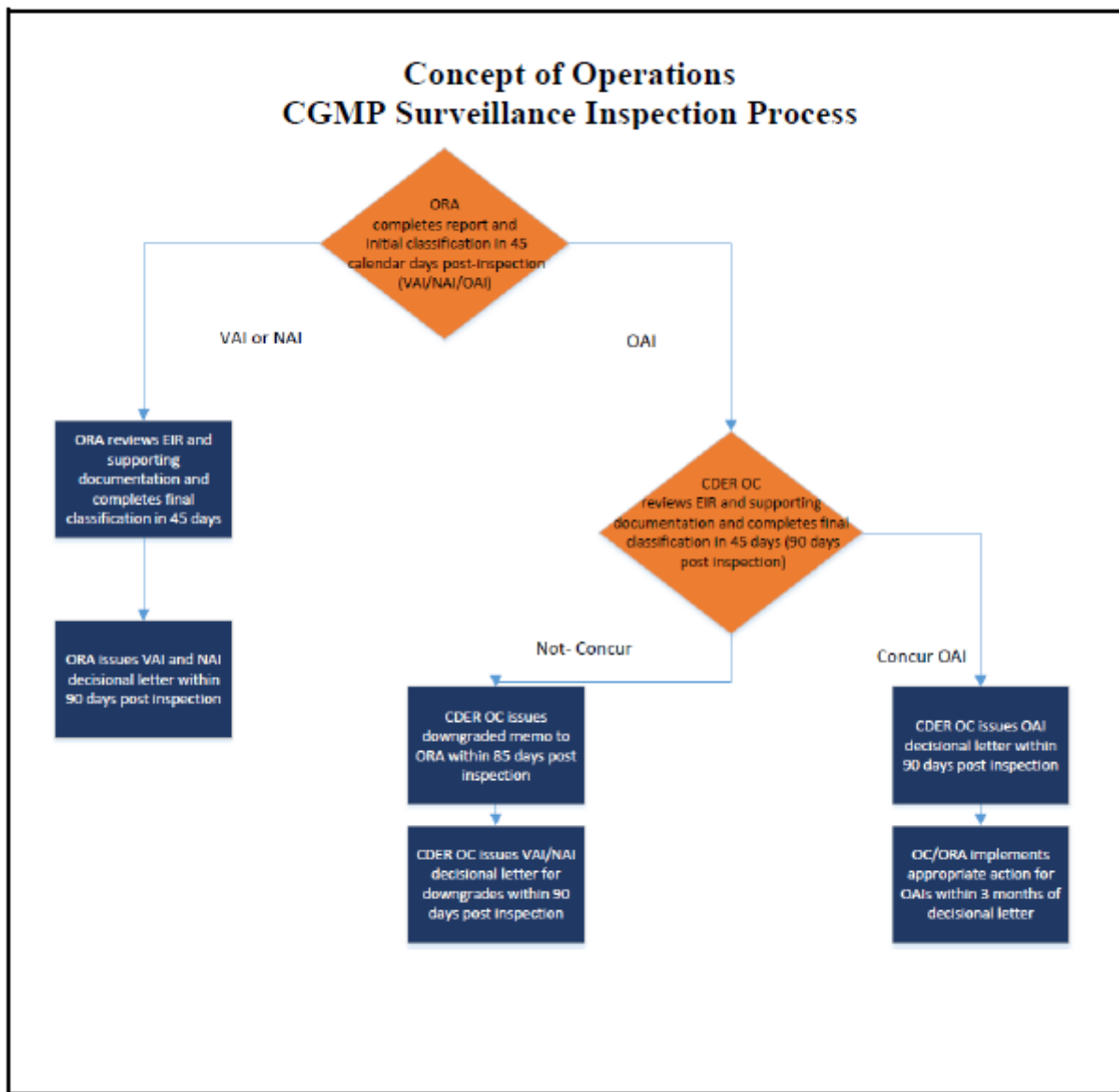


Figure 7. Process for classifying surveillance inspection outcomes after implementation of the ConOps.

Implementation of the ConOps has helped improve consistency in evaluation of inspection observations, classification of the inspection, and has reduced the time frames for taking enforcement action. The percentage of cases in which CDER concurs with ORA's initial recommendation is known as the "concurrence rate" (See Figure 8). In 2019, the concurrence rate had risen to 73 percent.

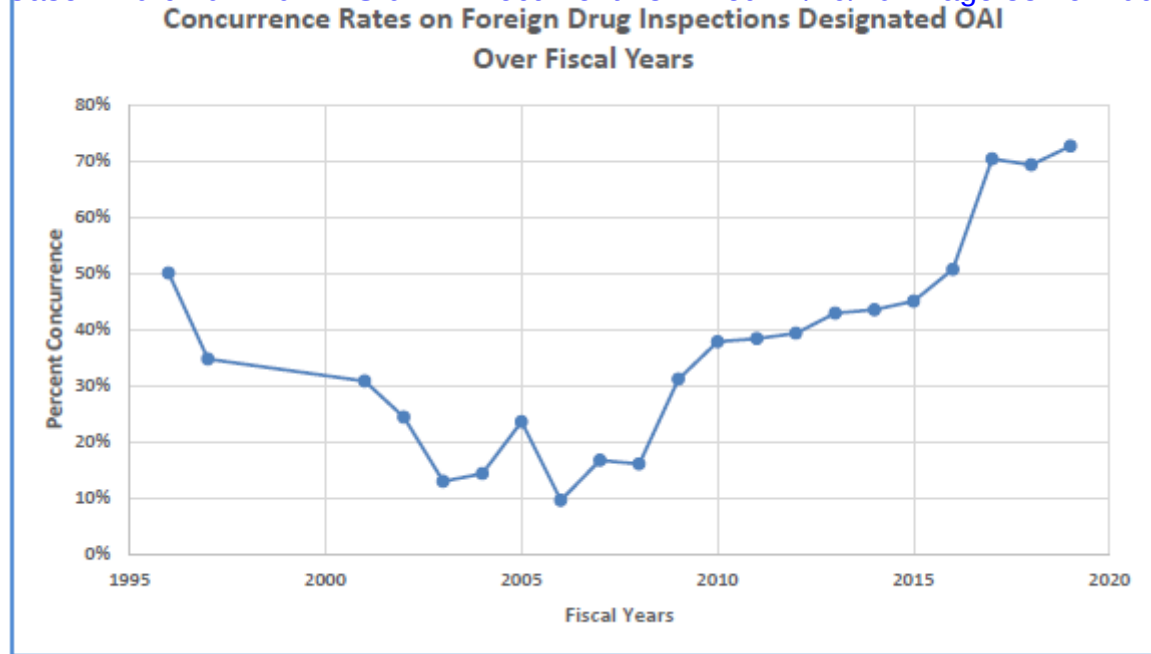


Figure 8. Concurrence rates on foreign drug inspections designated OAI were 50% in 1996 and rose to 73% in 2019. (FY 1996-1997 based on GAO data, all other data from FDA compliance database.)

The median time for FDA to issue a warning letter for drug manufacturing issues has decreased since ConOps was implemented, even though the number of warning letters FDA has issued has increased during that same time period (See Figure 9).

Agency Progress Toward Six-Month Compliance Actions

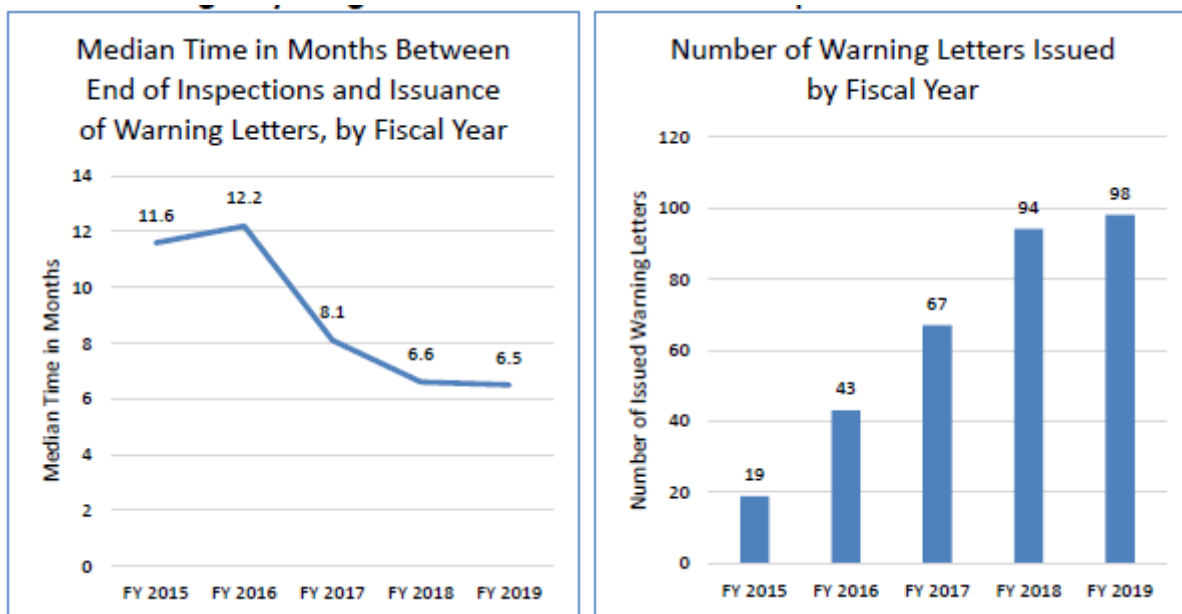


Figure 9. From FY 2015 to FY 2019 there has been an overall median 44% improvement in median time between the end of an inspection and issuance of a warning letter. During the same time, the number of warning letters increased.

Building an Investigator Work Force

FDA has performed more foreign than domestic inspections since 2015. The Agency utilizes a risk-based site selection model to identify firms for inspection. FDA has achieved this level of foreign coverage by using a mixed investigator work force consisting of (1) U.S.-based investigators who perform both domestic and foreign inspections; (2) a dedicated foreign cadre of U.S.-based drug investigators who conduct foreign inspections exclusively; and (3) foreign office-based investigators who inspect facilities manufacturing human drugs (**See Table 1**). The majority of foreign inspections are performed by domestically based staff in the first two categories.

Type of Investigator	Number of Qualified Foreign Drug Investigators in FY 2019	Number of Foreign Inspections Each Investigator is Expected to Perform Each Year	Estimated Percentage of All Foreign Inspections Performed in FY 2019
U.S.-Based Investigators Performing Foreign and Domestic Inspections	188	3-6 Foreign inspections per year	90%
Dedicated Foreign Drug Cadre	12 (included in the 188 listed above)	16 -18 inspections per year	16% (part of the 90% above)
Foreign Office-Based Investigators	12	15 inspections per year	10%

Table 1. FDA's Investigator Work Force for Inspections of Foreign Facilities Producing Human Drugs, FY 2019

By the end of this calendar year we expect 20 pharmaceutical investigators will be onboarding, and with our new direct hire authority we anticipate filling all our pharmaceutical investigator vacancies in 2020. In recent years, FDA has made progress in developing the foreign office-based inspectorate. At the same time, FDA's participation in the Mutual Recognition Agreement with the European Union has enabled us to focus more of our investigator work force on higher-risk facilities around the world.

However, the Agency continues to face challenges in developing the investigator work force due to the rigorous nature of the job (e.g., foreign travel restrictions and hardship). Competition for qualified candidates in a low-unemployment economy adds to our challenge in hiring. Even if the Agency succeeds in hiring a new investigator, it can take 1.5 to 2 years of training to bring them to a fully proficient level. Beyond these general issues, FDA faces specific challenges to achieving optimum staffing levels, such as negotiated agreements with host countries that affect the number of investigators who can be permanently attached to a foreign office.

FDA's Sampling and Testing Program

Although application assessments and inspections are a foundation of FDA's efforts to maintain a safe, reliable drug supply, the safety and effectiveness of drugs depends on a multipronged approach, of which quality checks by FDA and manufacturers are a part. To help ensure that safe and effective drugs are sold in the United States, we test selected drugs in state-of-the-art FDA laboratories and through research contracts and grants. This testing program includes APIs and finished drug products. We test using the same standards that are part of the drug approval process for identity, strength, and purity.

Some have raised the question of why we do not test every drug product before it enters the United States. FDA performs thousands of tests a year pre- and post-market. Only a small percentage (about one percent) of drugs that are tested fail to meet the established quality specifications. [12] Testing by FDA or third parties of each batch of drug product in U.S. commerce, which amounts to millions of batches and trillions of individual tablets, capsules, and other dosage forms, before they enter the U.S. market would not be feasible at a practical level (in 2018, there were almost 186 trillion tablets and capsules on the U.S. market [13]) and the current approach is effective and efficient.

FDA Encourages Industry to Invest in Mature Quality Management Systems and Advanced Manufacturing Technology

FDA inspects manufacturing facilities and takes action, if needed, to enforce CGMP quality standards and applicable regulations. The Agency's investigators look for deficiencies in meeting CGMP standards, but these assessments do not measure how far the facility is above the minimum CGMP. Simple adherence to CGMP standards does not indicate that a firm is investing in improvements or planning or deploying advanced quality control techniques that could better enable it to prevent quality problems leading to supply disruptions.

Even when a firm does invest in such improvements, it may be difficult to identify measures of quality that could be used to predict major quality issues that can lead to shutdowns of manufacturing lines resulting in supply disruptions. Even if these measures were readily available, FDA might not have access to the needed data regarding the performance of the manufacturing facility.

This is why it is critical that industry evolve from meeting the minimum manufacturing quality threshold to achieving quality management maturity. Some pharmaceutical firms have been slow to implement robust, mature quality systems and the accompanying quantitative measures of quality that have been the foundation of success in other industries, such as automotive and aerospace. [14] These industries exercise quality oversight by continuously monitoring quality in

real time during manufacturing of their products, and promptly correcting operations when needed. Numerous organizations and quality experts have worked to develop conceptual models and standards for advancing the maturity of industrial quality management systems. These models could be used more broadly in the pharmaceutical industry to improve the quality and reliability of the drug supply.

Many pharmaceutical manufacturers, whether domestic or foreign, have been slow to invest in these mature quality management systems because the market currently has no visibility into manufacturing facilities' quality. This lack of transparency reinforces competition based solely on price and disincentivizes companies from making investments in upgrading their facilities and quality practices until problems become frequent and severe enough to result in supply disruptions and drug shortages. As we have stated in our recent report, "Drug Shortages: Root Causes and Potential Solutions", [15] a way to create incentives for manufacturers to invest in product quality is to develop and implement a rating system for quality management maturity that is based on objective criteria. Such a rating system could enable purchasers to compare differences in quality and choose whether to reward more reliable manufacturers financially and with increased market share.

In addition to quality management maturity, the Agency encourages pharmaceutical manufacturers to invest in advanced manufacturing technology to improve their products and processes. Although widely used in some other industries, such as automotive, aerospace, and semiconductors, advanced manufacturing is now just beginning to be used by pharmaceutical companies. New technologies include "continuous manufacturing" (CM), wherein the finished drug product or active pharmaceutical ingredient is produced as a continuous stream, as opposed to traditional batch manufacturing where breaks or stops exist between different processing steps. In some examples of advanced pharmaceutical manufacturing, production can be continuous from chemical synthesis of the active ingredient through production of the tablets or other dosage forms. Product quality can be precisely controlled with modern automation and control systems and can be closely monitored during production by using highly sensitive analytical tools.


Conclusion

Over the past 20 years, the pharmaceutical industry that supplies American patients with drugs has, to a significant degree, moved offshore, so that today the majority of API and FDF manufacturing facilities are located outside the United States. In response, FDA has developed a risk-based approach to surveillance inspections that ensures equal treatment of foreign and domestic facilities. We believe that this is an effective and efficient approach for ensuring that American patients have access to a supply of safe and effective drugs. We thank the committee

for the legislation that has made this transition possible. At the same time, the reliability of our drug supply chain could be further strengthened by investment in modern manufacturing technology and in establishing mature quality management systems in manufacturing facilities.

Footnotes

1. Bumpas, Janet; Betsch, Ekkehard. *Exploratory study on active pharmaceutical ingredient manufacturing for essential medicines (English)*. Health, Nutrition and Population (HNP) discussion paper. Washington, DC: World Bank: 12 – 13, Figure 2.
<http://documents.worldbank.org/curated/en/848191468149087035/Exploratory-study-on-active-pharmaceutical-ingredient-manufacturing-for-essential-medicines>
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2. U.S. Food and Drug Administration, “Pathway to Global Product Safety and Quality,” A Special Report, p. 20. Accessed October 4, 2019 at <https://www.hsdl.org/?view&did=4123> (<https://www.hsdl.org/?view&did=4123>) ↗ (<http://www.fda.gov/about-fda/website-policies/website-disclaimer>).
3. The Agency updates the Catalog continually, so the information it provides is a snapshot in time.
4. FDA usually announces international surveillance inspections in advance, partly due to logistics such as arranging travel and access to facilities, and securing visas, and partly because of the high costs of conducting foreign inspections. When a surveillance inspection is announced, some manufacturers conduct a self-inspection or hire an independent inspector to ensure that manufacturing processes meet requirements.
5. The Federal Food, Drug, and Cosmetic Act (FD&C Act) describes different circumstances in which a drug may be considered adulterated. For example, a drug might be adulterated where it is contaminated with filth, where its purity departs from certain compendial standards, or where the conditions of its manufacturing are not consistent with current good manufacturing practice (CGMP).
6. Under the FD&C Act, as amended by FDASIA, a drug product will be deemed adulterated if a drug has been manufactured, processed, packed, or held in any factory, warehouse, or establishment which delays, denies, or limits an inspection, or refuses to permit entry or inspection. In such a case, FDA typically will place the firm on import alert.

7. See "What Is A Classification:" at <https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-references/inspections-database-frequently-asked-questions> (<https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-references/inspections-database-frequently-asked-questions>).
8. Import Alert: Import alerts inform the FDA's field staff and the public that the agency has enough evidence to allow for Detention Without Physical Examination (DWPE) of products that appear to be in violation of the FDA's laws and regulations. These violations could be related to the product, manufacturer, shipper and/or other information.
9. <https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/greenbrier-international-inc-dba-dollar-tree-574706-11062019> (<https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/greenbrier-international-inc-dba-dollar-tree-574706-11062019>).
10. See <https://www.fda.gov/media/107225/download> (<https://www.fda.gov/media/107225/download>).
11. See <https://www.fda.gov/about-fda/office-regulatory-affairs/program-alignment-and-ora> (<https://www.fda.gov/about-fda/office-regulatory-affairs/program-alignment-and-ora>).
12. These are established by USP, see <https://qualitymatters.usp.org/what-usp-standard> (<https://qualitymatters.usp.org/what-usp-standard>)  (<http://www.fda.gov/about-fda/website-policies/website-disclaimer>).
13. IQVIA. National Sales Perspective. 2014-2018. Extracted: August 2019.
14. Fuhr, Ted, et al., 2015, Flawless-from Measuring Failure to Building Quality Robustness in Pharma, McKinsey & Company.
15. <https://www.fda.gov/drugs/drug-shortages/agency-drug-shortages-task-force> (<https://www.fda.gov/drugs/drug-shortages/agency-drug-shortages-task-force>).


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EXHIBIT 453

HOUSE COMMITTEE ON ENERGY & COMMERCE

CHAIRMAN FRANK PALLONE, JR.

(/)

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HEARING ON "SECURING THE U.S. DRUG SUPPLY CHAIN: OVERSIGHT OF FDA'S FOREIGN INSPECTION PROGRAM"

Date: Tuesday, December 10, 2019 - 10:00am

Location: 2123 Rayburn House Office Building

Subcommittees: 116th Congress (/subcommittees/116th-congress)

Energy and Commerce (116th Congress) (/subcommittees/energy-and-commerce-116th-congress)

Oversight and Investigations (116th Congress) (/subcommittees/oversight-and-investigations-116th-congress)

The Subcommittee on Oversight and Investigations of the Committee on Energy and Commerce held a hearing on Wednesday, December 10, 2019, at 10:00 a.m. in the John D. Dingell Room, 2123 of the Rayburn House Office Building. The hearing is entitled, "Securing the U.S. Drug Supply Chain: Oversight of FDA's Foreign Inspection Program."

Key Documents

Memorandum from Chairman Pallone

(/sites/democrats.energycommerce.house.gov/files/documents/OI%20Briefing%20Memo_Hearing_2019.12.10_FDA%20Foreign%20Drug%20Inspections to the Subcommittee on Oversight and Investigations)

Opening Statement of Chairman Pallone (/sites/democrats.energycommerce.house.gov/files/documents/OI%20Pallone%202012.10.19.pdf) as prepared for delivery

Opening Statement of Subcommittee Chair DeGette (/sites/democrats.energycommerce.house.gov/files/documents/OI%20DeGette%202012.10.19.pdf) as prepared for delivery

Livestream



Witnesses

Mary Denigan-Macauley, Ph.D.
Director, Health Care
Government Accountability Office

Testimony (</sites/democrats.energycommerce.house.gov/files/documents/Testimony%20-%20Denigan-Macauley%20%28GAO%29%2020191210.pdf>)

Janet Woodcock, M.D.
Director, Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Testimony (</sites/democrats.energycommerce.house.gov/files/documents/Updated%20Testimony%20-%20Woodcock%20%28FDA%29%2020191210.pdf>)

EXHIBIT 454

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Outsourcing in the digital age

Pharma's increased reliance on contract manufacturers magnifies the risks of delayed digitalization

By Cathal Strain President, Neo PLM

Feb 19, 2020



Unlike most products they purchase, consumers have no way to readily assess the quality of the drugs they take. For example, a consumer can immediately see that a tablet computer purchased online is faulty if it arrives with a cracked screen. Detecting impurities in medicinal tablets is not so simple.

In decades past, pharmaceutical companies essentially assured the marketplace of their product quality with the message: “We make what we sell, and we sell what we make.” In other words, consumers could be confident in the quality of a drug because the same company managed the end-to-end product lifecycle, from R&D through manufacturing and marketing.

If asked now, most consumers would likely say they believe every drug they take is still made by the company whose name is on the label. They would almost certainly expect all drugs to be manufactured and quality controlled using the best available technologies.

In reality, upwards of 60 percent of pharma manufacturing is outsourced. And while the industry has shifted dramatically in that respect, it has not changed in other areas. Pharma — including drug companies, generics makers and contract manufacturing organizations (CMOs) — lags far behind other industries in the use of modern control and information technologies to improve quality and efficiency.

Regulatory requirements and good manufacturing practices (GMPs) have evolved somewhat over time, but have not changed significantly at their core. They were conceived before outsourced manufacturing became the norm, at a time when commercially available technology was generally much less advanced. Today, pharma companies and CMOs continue to rely on disjointed, document-based processes rather than integrated digital systems to manage product knowledge and manufacturing. (The myriad reasons for this phenomenon have been discussed elsewhere at length.)

The industry’s delayed digitalization poses significant risks — to pharma companies and, more importantly, their consumers. Those risks are compounded in multiple areas by outsourcing production, from initial tech transfer to troubleshooting to ongoing process analysis and improvement.

However, the time is rapidly approaching when the entire industry must move forward. Pharma companies will demand their CMOs provide much more robust production data — in electronic form — whether it’s due to the growing momentum toward Pharma 4.0 or tightened regulations. Tech vendors to the industry will need to be prepared with the innovative new systems required to support that sea change.

CMOs that transition now to a more automated and digitized operation will enjoy a significant competitive advantage in the short term, demonstrably reducing risk for their clients. That advantage will only become greater when stakeholders across the industry finally commit to a more connected approach to manufacturing and knowledge management.

The shift to outsourcing

External manufacturing was practically unheard of some 30 years ago. However, around the early to mid-1990s, the landscape began to change as pharma companies increasingly gravitated toward

CMOs. There were — and still are — compelling advantages to these partnerships. The business of manufacturing can be challenging. Outsourcing production allows pharma companies to concentrate on their core competencies, R&D and marketing, while leveraging the focused expertise of a CMO.

On the other hand, CMOs have different business objectives than pharma companies, and tend to be even more reluctant to embrace technology as a result. They generally provide only paper batch records to “prove” to clients that drugs were manufactured as specified.

What’s more, external manufacturing often takes place in locations where meaningful oversight is simply not possible. Outsourcing production is expected to continue increasing, but industry observers raise legitimate questions about just how well CMO clients can monitor quality in these partnerships.

Pharma companies currently seek to mitigate their risks by completing a reasonably extensive due diligence process when selecting a CMO. **The clear business imperatives are that the CMO has:**

- **The required talent in its organization**
- **The manufacturing capacity necessary to produce and deliver product on time**
- **A proven quality system that ensures product can be manufactured as specified**

To evaluate whether a prospective manufacturing partner meets these criteria, pharma companies typically take an audit-based approach to due diligence. This includes reviewing previous audits, particularly any conducted by regulators.

There is nothing technically wrong with this approach to due diligence, which is considered perfectly acceptable by regulatory bodies. That said, regulators often uncover deficiencies — which can be significant — when poring over a manufacturing facility’s procedures and records.



The global pharmaceutical contract manufacturing market was valued at \$92.314 billion in 2017 and is expected to reach \$146.41 billion by 2023

(Source: Market Reports World)

Are quality systems sufficient?

Regulators exercise oversight over manufacturing facilities — both internal to drug companies and external — by requiring them to maintain an acceptable pharmaceutical quality system (PQS). Adherence to these systems is monitored through regulatory inspections and, for CMOs, customer audits.

However, industry observers raise valid questions about the effectiveness of this approach given pharma's general resistance to increasing automation and digitalization. Remember, current regulatory guidelines and GMPs were developed when pharma products were manufactured almost exclusively in-house and paper was the only viable way to convey manufacturing instructions and capture process data.

Regulators constructed their requirements to ensure accountability to the extent possible in that environment. Even today, a pharmaceutical manufacturer can operate a completely paper-based facility while maintaining total regulatory compliance. Given that fact, and pharma's typically high margins relative to other industries, there is no immediate incentive for drug manufacturers to modernize. Some may even oppose greater transparency for fear it could expose issues that now go undetected due to the deficiencies of a paper- and audit-based approach to quality control.

The luxury of avoiding change in this way is exceedingly rare. In most industries, ongoing innovation is required across an organization — not only in R&D — to remain competitive and meet consumers' ever-growing quality expectations.

Exploring the risk factors

Pharma's digital deficit in the manufacturing and supply chain presents myriad risks, which are heightened dramatically when outsourcing is added to the equation. Anyone who has worked in a drug manufacturing facility knows that each day brings new challenges. When a production problem occurs, the first step is to understand precisely what happened. In more modern plants, with high levels of instrumentation and automation, piecing together the story becomes much easier — a matter of analyzing process history, not interviewing eyewitnesses. In a paper-based world, manually recorded data is of little to no use, regardless of how many signatures it bears. Without ubiquitous shop-floor process measurements (not just laboratory-based control point measurements) there is simply no way to verify that a process was manufactured as intended.

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The technology deficit in pharma goes well beyond a lack of shop-floor measurement and process automation. There are several other key areas where the use of digital tools could significantly reduce risk and improve quality assurance, particularly for outsourced manufacturing:

Quality systems: Pharma companies must move from a paper- and audit-based approach to continuous electronic monitoring of all manufacturing data associated with manufacturing processes.

Tech transfer: Document-based tech transfer does not support effective process knowledge management — or the central goal of ensuring the receiving party understands the process sufficiently for successful implementation. This is especially true when the transfer takes place between organizations rather than internal departments.

Process design and production planning: Manufacturing optimum-quality products begins with sound engineering. That means undertaking comprehensive process design and simulation prior to making production commitments. This approach fosters more informed equipment selection decisions and a better understanding of productivity, resulting in vastly improved planning, production efficiency and predictability of asset utilization.

Analytics and continuous improvement: If a facility lacks sophisticated measurement and control capabilities, clearly there isn't much substrate for the application of advanced analytical tools. As the famous Peter Drucker quote goes, "If you can't measure it, you can't improve it."

Process knowledge management: Under today's document-based paradigm, managing process knowledge across the product lifecycle is difficult even with in-house manufacturing. Outsourcing magnifies this challenge substantially, as the client pharma company sacrifices full access to critical production information. Over time, companies stand to lose more organizational or corporate memory on a critical component of the business: Manufacturing.

Looking to the future: traceability throughout the process

Regardless of where it occurs, consumers should reasonably expect the drugs they take are manufactured using the best available technologies. Most of the information technologies that make up today's typical stack — including systems for ERP, manufacturing, process control and lab information — have been available since the 1980s. Add the explosion in capabilities the "digital revolution" has delivered in the interim and one would think that pharma, an industry whose lifeblood is innovation, would be at the forefront of technological advancement.

The reality is far different, and the risks of adhering to an antiquated paradigm are magnified by increased outsourcing. Partnering with CMOs offers many benefits, but at the same time exacerbates information silos, further distancing key stakeholders from the details of how their products are

manufactured. This is especially true because CMOs have generally invested much less in automation and digital technologies than pharma companies.

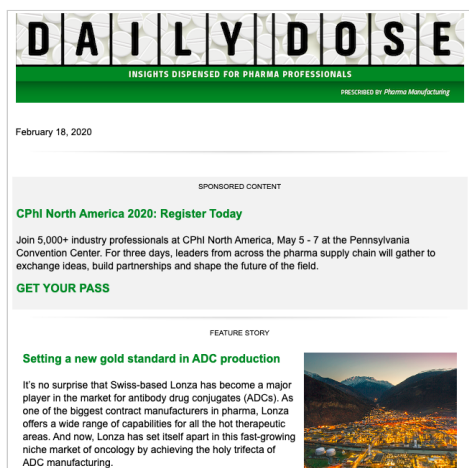
That said, CMOs have not spent more in those areas largely because their clients haven't demanded it. The industry's expanding discussion of Pharma 4.0 is an encouraging sign in this regard. For pharma companies, reaping the full benefits of IIoT will require a long-overdue digitalization, both internally and for their partners. This reality is among the reasons paper manufacturing records and business processes appear likely to become obsolete. Although drug companies are leading the Pharma 4.0 conversation, it won't be long before CMOs are pulled in.

To be sure, however, pharma companies and CMOs are not completely to blame for the current state of manufacturing. Even those using all of the most current technologies would still lack the integration between systems that IIoT demands. Tech vendors to pharma must do their part by innovating new systems that digitize critical data and facilitate interconnectivity across organizations.

In this digital age, there is no reason pharma should not have the technology in place to ensure complete visibility into every aspect of manufacturing — whether it occurs in-house or thousands of miles away. Along with drums of product, pharma companies should require their CMOs to deliver a comprehensive electronic dataset that includes each and every operating detail.

Of course, Pharma 4.0 still represents a huge challenge. The industry has not yet achieved Pharma 3.0, which would require drug companies to significantly modernize their own facilities while insisting their CMOs do the same. That means the industry must essentially implement Pharma 3.0 and Pharma 4.0 simultaneously. The transformation must begin in R&D's process development group and extend to a digital thread that provides complete traceability throughout the drug production lifecycle, whether the manufacturing assets are in-house or outsourced.

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EXHIBIT 455

[HEALTH NEWS](#)

Tainted drugs: Ex-FDA inspector warns of dangers in U.S. meds made in China, India

Massoud Motamed says the FDA struggles to police the sprawling number of overseas drug manufacturers who may hide problems in their production lines.



[Ex-FDA inspector sounds alarm about overseas factories producing medications for U.S.](#)

MAY 10, 2019 04:09

May 10, 2019, 1:01 PM EDT

By Didi Martinez, Brenda Breslauer and Stephanie Gosk

The notice arrived at the home of Denise Schreck, a New Jersey woman who suffers from high blood pressure, last July.

"URGENT PRODUCT RECALL," blared the words at the top of the letter from her pharmacy.

The blood pressure medication used by Schreck and millions of other Americans was tainted. The culprit? A chemical with the potential to cause cancer.

[Privacy - Terms](#)

Schreck went online to learn more and discovered that the generic drug, valsartan, was in fact found to contain a contaminant formerly used in the production of rocket fuel, according to a government fact sheet.

"I was just really blown away," Schreck, 51, told NBC News. "It's shocking to know that you've been taking a probable carcinogen for four years."

Denise Schreck is one of millions of Americans who have been prescribed the blood pressure medication, valsartan.

NBC News

[The valsartan recall](#) came as little surprise to Massoud Motamed, a former inspector with the U.S. Food and Drug Administration (FDA). More than a year before the notices went out, Motamed had tried to sound the alarm on what he flagged as potential systemic problems at two facilities in China and India that produce the active ingredients in generic valsartan and other blood pressure medications.

Speaking out publicly for the first time, Motamed told NBC News that the FDA ultimately overruled his recommendation to crack down on one of the plants. Perhaps more alarming, he says the issues at the two overseas drug production facilities are hardly unique.

"This is only the tip of the iceberg," Motamed said in an exclusive interview.

The valsartan case underscores a new reality in the pharmaceutical industry – a growing reliance on foreign manufacturers to provide the raw ingredients for drugs sold in the U.S. According to FDA data, roughly 85 percent of the facilities manufacturing the ingredients in American drugs are located overseas, many from China and India where production costs are low and experts say local government oversight is less stringent.

The shift has contributed to a flood of recent recalls and fueled escalating concerns about the safety of medicines consumed in the U.S.

Since last summer, drug companies have announced a total of 45 recalls of generic lifesaving blood pressure medications. They include certain versions of valsartan and two other blood pressure drugs, losartan and irbesartan, as well as other blood pressure medications that contain the recalled drugs in their formulations. The raw ingredients were all traced to overseas manufacturing sites where drugs can be processed at a lower cost than at U.S. facilities.

"Growing up, we had this saying, 'You get what you pay for,'" Motamed said. "We have that belief for everything except pharmaceuticals. If we want to drive competition and drive the price down, it comes at the cost of quality."

Massoud Motamed NBC News

For Motamed, the recalls tell only part of the story. He says a more systemic issue has largely gone unreported: FDA inspectors struggling to keep up with foreign drug manufacturers that may bury or hide problems in their production.

Last year, the FDA inspected only one in five registered human drug manufacturing facilities abroad, according to agency data.

With U.S. inspectors scrambling to review a sprawling network of overseas drug production plants, the FDA is left to rely on the word of the facility managers, Motamed said.

Privacy - Terms

"I believe it would surprise Americans how much we rely on the manufacturer and whatever they tell us to say that a drug is good or bad," the former inspector told NBC News.

The FDA also inspected only about one in five domestic drug manufacturing facilities last year, according to agency data. But unlike inspections at U.S. plants, where investigators can show up without warning and ask for more time to examine conditions if they identify potential issues, Motamed said the foreign site reviews are often hobbled by language barriers and time constraints.

"Say I'm at a domestic facility and I tell my supervisors that I'm finding all these problems and I need more time to inspect. That happens – no issue," Motamed said.

"The same is not true of a foreign facility. I've had inspections where I really could have benefited from the extra time and I knew there were problems to be uncovered, but I had to leave the country."

Motamed spent three years as an FDA investigator, working mainly overseas to inspect foreign manufacturing facilities. A Texas native with a Ph.D. in biochemistry, Motamed, 34, joined the agency driven by a desire to contribute to the field of public health.

He had been in the role for more than two years when he went to inspect the Zhejiang Huahai Pharmaceutical plant in Linhai, China – the company that produced the tainted ingredients in Schreck's recalled medication – in May 2017.

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Motamed's four-day inspection turned up a series of alarming issues that he later outlined in official reports. Facilities and equipment not maintained. Anomalies in testing not investigated. And "unknown impurities" dismissed as laboratory error.

After his visit, and as first reported by [Bloomberg](#), Motamed recommended that a warning letter be sent to the firm – an official action that bars the company from gaining the approvals to produce new U.S. drugs at the facility, until it resolves the issues.

But three months later, he was overruled by FDA management. The FDA decided to allow Zhejiang Huahai to voluntarily fix the problems on its own, the agency wrote in an official document obtained by NBC News, citing the firm's compliance history and mostly "adequate responses" to impurities in their testing.

"There are many factors that inform the FDA's decisions at a given time regarding what action to take following an inspection," the FDA said in a statement to NBC News. "We make those decisions in the interest of patient safety based on all information available to us, including evidence collected during an FDA inspection and a manufacturer's proposed corrective actions."

After facing criticism over its handling of the case, the FDA said it would have been "unlikely" to catch the impurities at the source of the recall during a routine inspection.

"Nonetheless, our inspections did reveal systemic problems of supervision that could have created the conditions for quality issues to arise," reads a January 2019 FDA press release.

In a statement to NBC News, Zhejiang Huahai said it's "working closely with regulators here and abroad to evaluate the source of the impurities that resulted in the recall" and is determining if "any modifications to its manufacturing processes are necessary."

Denise Schreck got the notice from her pharmacy in July that her blood pressure medication was being recalled due to an "unexpected impurity" in her medication in the form of a probable human carcinogen. [NBC News](#)

The problems were not confined to the facility in China. While investigating a drug production factory in India, Hetero Labs Limited, in December 2016, Motamed discovered what appeared to be a brazen attempt to cover up issues at the plant.

"I was going to the bathroom and I kept seeing that people were going into an archival room. And that's not generally typical," Motamed said.

He decided to review the firm's closed circuit TV footage. What the inspector saw next shocked him.

Motamed watched footage of individuals shredding company documents four days before his arrival, [the inspection report](#) says.

"They were staying up all night shredding extensive amounts of documents right before our audit," Motamed said. "...It means there are systemic issues."

"It's one of the more concerning findings I've had over the years," the former inspector added.

The FDA eventually sent a warning letter to Hetero in August 2017, citing "significant violations of current good manufacturing practice." Some 19 months after Motamed first flagged suspicious activity at the plant, Hetero was found to be one of the sources of the contaminated drug ingredients for sale in the U.S.

Hetero did not respond to several requests for comment by NBC News.

In the case of valsartan products, the FDA said last August that [more than half](#) of all the medication sold in the U.S. was being pulled from store shelves.

While it's unknown exactly how many people have been impacted by the recalls, the sheer demand for the drugs suggest it could reach into the millions. In 2016, 1.6 million people purchased valsartan and 9.2 million bought losartan, according to data provided by the U.S. Department of Health and Human Services.

The recalls create a vexing challenge for consumers like Don Grybb, who said he struggled to find a suitable alternative after finding out that his valsartan medication was being pulled from store shelves.

"Almost from prescription to prescription, I would find significant changes in my blood pressure," said Grybb, 68, of Michigan.

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Don Grybba said he was made aware of the recall in 2017, but when he got a call from his pharmacy telling him that they couldn't refill his medication. Courtesy of Don Grybba

The FDA and outside healthcare professionals have warned consumers against suddenly stopping their medication due to the recall, saying that the short-term risks outweigh the potential impact of consuming the recalled medication.

The uncertainties surrounding the medications also pose challenges to doctors.

"It's hard to know what to prescribe patients," said Dr. Randall Zusman, a cardiologist at Massachusetts General Hospital Heart Center in Boston. "You want to assume it's safe and effective. You don't want to feel like you are prescribing something that causes harm."

The FDA says the overall risk posed by the impurities is small. For valsartan, FDA testing found the pills contained somewhere between three and 210 times the agency's acceptable level for NDMA, the probable carcinogen at the center of the recall. If 8,000 people took the highest dose of the contaminated drug daily for four years, the FDA estimates, there may be one additional case of cancer over the lifetimes of those people.

"This is troubling to us and we know it's troubling to the public," the FDA said in a statement. "The concern is appropriate."

Experts said the contaminants are still powerful at low levels. "This is well beyond the risk that government agencies typically deem acceptable," said Lisa Lefferts, senior scientist at the Center for Science in the Public Interest. "While most people won't get cancer from the contaminants in these pills, it's an unacceptable risk, and avoidable."

The FDA has [issued a list](#) of medications free of the probable carcinogens and says it has been working to mitigate and prevent shortages.

"Our first action was to immediately undertake a major operation to investigate and to identify the root causes of the presence of these impurities and to work with companies to address the risks that the impurities posed to patients," Dr. Janet Woodcock, the FDA director for the Center for Drug Evaluation and Research, said in a statement to NBC News.

Dozens of consumers have now gathered to sue nearly every company involved in the recall through a consolidated multidistrict litigation case in New Jersey.

"There are a lot of things that could have been done to prevent something like this," Daniel Nigh, an attorney for the plaintiffs, told NBC News.

The Association for Accessible Medicines, the trade group for generic drug manufacturers, said its "member companies with affected products voluntarily recalled their medicines containing valsartan and have worked closely with the FDA.

"Patients in the United States can be confident that the medicines they take are safe and effective," the group added. "Manufacturers of generic medicines and the Food and Drug Administration work to ensure that prescription drugs meet the same high-quality standards regardless of where they're manufactured."

Motamed left the FDA in 2017, disillusioned over his experience trying to police a sprawling industry in what he described as a "cat and mouse" game where companies do what they can to conceal problems from the FDA. He believes the agency needs to hire more qualified investigators and needs to conduct more inspections of the facilities producing drug ingredients.

Now working for the private pharmaceutical sector in India, Motamed said he's speaking out to raise awareness about the risk of tainted drugs.

"I think there's a significant portion which, if we test it here in the U.S., would not pass," Motamed said.

As for Schreck, the anxiety brought on by the valsartan recalls has prompted her to stash her bottle of pills in a small brown cabinet above her kitchen sink.

Why? She sees it as evidence that could be used in a court of law in the event that cancer were to infect her body one day.

"I hate to think that because of this I run an extra risk of developing cancer," Schreck said. "But it is my proof."

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