Invasive Pneumococcal Disease Following the Introduction of 13-Valent Conjugate Vaccine in Children in New York City From 2007 to 2012

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IMPORTANCE Invasive pneumococcal disease (IPD) is a leading cause of pneumonia, meningitis, and bacteremia in children. In March 2010, a 13-valent pneumococcal conjugate vaccine (PCV13) was introduced to the routine childhood immunization schedule. The PCV13 contains 6 serotypes not included in the previously recommended 7-valent pneumococcal conjugate vaccine, including serotype 19A, the predominant cause of IPD prior to the introduction of PCV13.

OBJECTIVES To describe changes in the epidemiology and incidence of IPD in children younger than 5 years in New York City (NYC) after the introduction of PCV13 and assess PCV13 coverage in NYC.

DESIGN, SETTING, AND PARTICIPANTS Retrospective analysis of population-based IPD surveillance data of the general population residing in NYC between January 1, 2007, and December 31, 2012. Invasive pneumococcal disease cases were identified by laboratory reporting of positive pneumococcal cultures from a normally sterile body site in NYC residents younger than 5 years. Isolates were serotyped. Participants included 468 cases younger than 5 years with IPD reported through routine surveillance to the NYC Department of Health and Mental Hygiene.

MAIN OUTCOMES AND MEASURES Absolute differences and percentage changes in IPD incidence before and after the introduction of PCV13 by serotype grouping, age, and race/ethnicity. The number of PCV13 doses administered to children younger than 5 years was calculated using the NYC immunization information system.

RESULTS There were 468 IPD cases from 2007 to 2012. The incidence of IPD decreased by 69.6% (95% CI, −79.3% to −55.5%) from 21.0 cases per 100 000 (2007-2009 mean) pre-PCV13 to 6.4 cases per 100 000 (2011-2012 mean) post-PCV13. Estimates of disease caused by serotypes included in the PCV13 decreased by 82.5% (95% CI, −90.0% to −69.3%), including a 79.7% reduction in serotype 19A (95% CI, −89.0% to −62.4%). Reductions in IPD incidence were seen in all age groups, with the largest reduction in children younger than 12 months (80.4%; P = .005). Incidence decreased significantly in all racial/ethnic groups. The percentage of children younger than 5 years in NYC with 1 or more doses of PCV13 increased from 47.8% in 2010 to 89.8% in 2012.

CONCLUSIONS AND RELEVANCE The incidence of IPD in NYC children younger than 5 years and, particularly, the incidence of IPD caused by serotype 19A decreased dramatically following the introduction of PCV13, with reductions among all age and racial/ethnic groups. This represents a significant achievement for public health immunization programs and underscores the importance of achieving high immunization coverage.
Streptococcus pneumoniae is a leading cause of pneumonia, meningitis, and bacteremia in children worldwide. In June 2000, a 7-valent pneumococcal conjugate vaccine (PCV7 [Prevnar; Wyeth-Lederle Vaccines]) was introduced to the routine vaccination schedule in the United States for infants and children, with doses given at ages 2 months, 4 months, 6 months, and 12 months to 15 months. Substantial reductions in disease occurred soon after the introduction of PCV7, with a 76% decline in the incidence of invasive pneumococcal disease (IPD) among children younger than 5 years. This decline was driven by a reduction in serotypes included in PCV7. However, disease caused by serotypes not included in PCV7 increased, with serotype 19A causing most incidences of IPD in the post-PCV7 vaccine era. In February 2010, a 13-valent pneumococcal conjugate vaccine (PCV13 [Prevnar 13; Pfizer]) was licensed. On March 12, 2010, the Advisory Committee for Immunization Practices recommended that PCV13 replace PCV7 for all children and that a supplemental dose of PCV13 be given to children aged 14 to 59 months who completed the PCV7 series. The PCV13 contains the 7 serotypes included in PCV7, as well as an additional 6 serotypes, including serotype 19A. An estimated 64% of IPD cases in children younger than 5 years in 2007 were caused by serotypes contained in PCV13, with 42% of all IPD cases caused by serotype 19A.

We used data from the population-based IPD surveillance system in New York City (NYC) to describe changes in the epidemiology and incidence of IPD in children younger than 5 years. The population-level uptake of PCV13 in NYC after the introduction of PCV13 was also assessed.

Methods

Invasive pneumococcal disease was defined as the isolation of S. pneumoniae from a normally sterile body site in NYC residents younger than 5 years between January 1, 2007, and December 31, 2012. Cases of IPD were identified by laboratory reporting of positive pneumococcal cultures from invasive sites through the New York State Electronic Clinical Laboratory Reporting System mandated by NYC health code. Audits were routinely performed at clinical laboratories in NYC using randomly selected reports of reportable communicable diseases on a biennial basis to ensure appropriate reporting. Medical records were reviewed by the NYC Department of Health and Mental Hygiene staff for demographic and clinical information per routine surveillance. In this evaluation, data were collected as part of routine ongoing public health surveillance that does not require patient consent. This study was categorized as human participant research exempt per the NYC Department of Health and Mental Hygiene institutional review board.

The serotyping of isolates of S. pneumoniae was conducted at the Bacteriology Laboratory in the Wadsworth Center at the New York State Department of Health using the Quellung test method with capsular typing antiserum. Antiserum samples were prepared by the New York State Department of Health and Statens Serum Institut. Serotypes 4, 6B, 9V, 14, 18F, 19F, and 23F (included in PCV7) and serotypes 1, 3, 5, 6A, 19A, and 7F (included only in PCV13) were categorized as serogroup PCV13; all others were categorized as a nonvaccine type. One case in 2007 with both a PCV13-type disease and a non-PCV13-type disease isolated simultaneously was counted as one 0.5 case of PCV13-type disease and one 0.5 case of non-PCV13-type disease. The redistribution of unknown serotypes was performed where isolates with unknown serotypes were assigned a serotype grouping based on the proportion of PCV13 serotypes among isolates with known serotypes that year.

The incidence of IPD was calculated by serotype grouping, age, race/ethnicity, and year. Percentage change (relative risk − 1) × 100) in incidence with 95% CIs and absolute rate differences was calculated using the mean incidence of disease in the pre-PCV13 years (2007-2009) and post-PCV13 years (2011-2012). For all calculations, intercensal population denominator estimates for 2007 to 2009 and 2011 to 2012 were produced by the Department of Health and Mental Hygiene based on the US Census Bureau Population Estimate Program and housing unit data obtained from the NYC Department of City Planning available as of July 2013. The 2010 NYC data from the US Census Bureau were used for 2010 population estimates. Assignment of race and ethnicity of IPD cases was determined based on a hierarchy of available data from patient interviews (n = 57; 12.2%), medical record reviews (n = 429; 91.7%), and Electronic Clinical Laboratory Reporting System reports (n = 69; 14.7%). Cases with Hispanic ethnicity were considered Hispanic regardless of race; all other cases missing race or ethnicity variables (n = 31; 6.6%) were assigned values based on geocoding of address and US Census Bureau race data, using 5 multiple imputations taken from the racial distribution of the population younger than 5 years residing in the census tract of the case. The mean incidence by race/ethnicity was calculated using the mean of the 5 imputations and percentage change (relative risk − 1) × 100) and respective 95% CIs calculated across the 5 data sets. Overall
and pairwise differences in the incidence of IPD between race/ethnicity groups during the pre-PCV13 period (2007-2009) were calculated; the same method was used for comparison of incidence between race/ethnicity groups during the post-PCV13 period (2011-2012). In addition, Poisson regression models were constructed to estimate the overall reduction in IPD incidence in the post-PCV13 period and test whether race-specific incidence decreased at different rates. Age-by-race-specific counts for each year were modeled using age-by-race-specific population counts for each year; covariates included time, age, race, and race-time interactions. All analyses involving race accounted for multiple imputations. All analyses were conducted using SAS statistical software, version 9.2 (SAS Institute Inc). Results were considered statistically significant at P < .05.

Vaccination histories of IPD cases were ascertained through medical record reviews and NYC's population-based immunization information system, the Citywide Immunization Registry (CIR). The proportion of children younger than 5 years with 1 to 4 doses of PCV13 was calculated using doses reported to the CIR at the end of each year from 2010 through 2012. In 1997, the health code in NYC required immunizing professionals to report immunizations given to all children aged younger than 8 years in the CIR; in 2005, the requirement was expanded to include immunizations administered to all children younger than 19 years. The CIR is one of the more mature immunization information systems in the United States in data completeness and timeliness.13-16

**Results**

Between January 1, 2007, and December 31, 2012, 468 cases of IPD were identified in children in NYC younger than 5 years, with 329 cases from 2007 to 2009, 70 cases in 2010, and 69 cases from 2011 to 2012. The proportion of IPD cases with serotyped prior to redistribution was 48.7% in 2007, 60.2% in 2008, 89.9% in 2009, 90.0% in 2010, 85.7% in 2011, and 96.3% in 2012. Cases with unknown or other race/ethnicity reported were assigned race/ethnicity based on multiple imputations.

<table>
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<th>Variable</th>
<th>Average No. of Cases per Year</th>
<th>Incidence per 100 000 Persons</th>
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<td>19A</td>
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<td>12.26</td>
<td>11.19</td>
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Abbreviations: IPD, invasive pneumococcal disease; PCV13, 13-valent pneumococcal conjugate vaccine.

- Mean case counts and incidence rates were estimated based on those with known serotypes and redistributed case counts. The percentage of cases serotyped prior to redistribution was 48.7% in 2007, 60.2% in 2008, 89.9% in 2009, 90.0% in 2010, 85.7% in 2011, and 96.3% in 2012.

- Cases with unknown or other race/ethnicity reported were assigned race/ethnicity based on multiple imputations.

Changes in IPD by Serotype Grouping

The overall incidence of IPD decreased significantly from a mean of 21.0 cases per 100 000 (2007-2009) to a mean of 6.4 cases per 100 000 (2011-2012; Table 1). There was a 69.6% reduction in overall IPD (95% CI, −79.3% to −55.5%) and an estimated 82.5% reduction in PCV13-type disease (95% CI, −90.0% to −69.3%; Figure 1). The reduction in PCV13-type IPD was driven by a reduction in the 6 additional serotypes included in PCV13 but not PCV7. The incidence of IPD attributable to serotypes included in PCV7 was negligible both before and after the introduction of PCV13, accounting for only 1.2% (n = 4) of all serotyped IPD cases from 2007 to 2012. The incidence of PCV13-type disease decreased from a mean of 15.3 cases per 100 000 (2007-2009) to 2.7 cases per 100 000 (2011-2012; Table 1). The PCV13-type disease accounted for an estimated 82.5% reduction in PCV13-type disease (95% CI, −79.3% to −55.5%).
In the pre-PCV13 era, an estimated 72.3% of PCV13-type cases were serotype 19A (n = 115). The incidence of serotype 19A decreased by 79.7% (P = .001); however, it has remained the most prevalent individual serotype since the introduction of PCV13. The incidence of non–PCV13-type disease did not change significantly.

Changes in IPD by Age
The mean age of cases did not change significantly in the pre- and post-PCV13 years (25.0 months vs 27.4 months, respectively; P = .29). Children younger than 12 months had the highest incidence of cases before the introduction of PCV13 (28.1 cases per 100,000) and experienced the greatest reduction in incidence (80.4%; 95% CI, −91.6% to −54.4%) after the introduction of PCV13 (Table 1; Figure 2). Incidence of cases aged 12 to 35 months and 36 to 59 months also decreased significantly by 67.6% (95% CI, −81.9% to −41.8%) and 62.0% (95% CI, −80.0% to −27.8%), respectively.

Changes in IPD by Race and Ethnicity
Before the introduction of PCV13 (2007-2009), there were significant differences in the incidence of IPD between racial/ethnic groups overall (P = .001), with the incidence of IPD significantly higher in non-Hispanic black individuals (30.4 cases per 100,000; P = .005) compared with non-Hispanic white individuals (17.3 cases per 100,000; Table 1). Each racial/ethnic group had a significant percentage reduction in the incidence of IPD, with the greatest reduction in incidence in non-Hispanic black individuals (67.6% [95% CI, −81.9% to −41.8%]) and 62.0% (95% CI, −80.0% to −27.8%), respectively.

After the introduction of PCV13 (2011-2012), there was no significant difference in incidence of IPD between racial/ethnic groups (P = .89). However, race-specific incidence did not decrease at significantly different rates (P = .78). However, race-specific incidence did not decrease at significantly different rates (P = .78).

PCV13-Type Disease After the Introduction of PCV13
Following the introduction of PCV13 (2011-2012), 26 cases of IPD caused by PCV13 serotypes were identified, of which 24 were caused by the 6 additional serotypes not included in PCV7 (Table 2). Fifteen cases (57.7%) with PCV13-type disease had
not received any dose of PCV13, including 9 cases (1 with PCV7-type disease and 8 with IPD caused by the 6 additional serotypes in PCV13) who had received the full 4-dose PCV7 series but had not received the supplemental PCV13 dose. There were no cases of PCV13-type disease in children who were too young to be eligible for vaccination. The remaining 11 PCV13-type cases received 1 or more doses of PCV13, including 1 serotype 19A case who received the full PCV13 4-dose series. Serotype 19A accounted for most PCV13-type cases (84.6%), both among those who received 1 or more doses of PCV13 (81.8%) and those without any PCV13 doses (86.7%). The mean age of the PCV13-type cases was 34.1 months compared with 23.5 months among all non-PCV13 cases in the corresponding period (P = .01).

PCV13 Vaccination Uptake
The proportion of children younger than 5 years in NYC with 1 or more doses of PCV13 increased from 47.8% at the end of 2010 to 89.8% at the end of 2012. Several groups of children younger than 5 years were only eligible to receive 1 dose of PCV13 to be considered up-to-date, including those who were previously vaccinated with PCV7. Coverage with 3 or more doses of PCV13 increased from 4.3% to 40.7% and coverage with 4 doses increased from 0.4% to 19.2% from the end of 2010 to the end of 2012. Early uptake of PCV13 coincided with decreases in the case counts of PCV13-type IPD (Figure 3).

Discussion
Incidence of IPD in NYC decreased significantly in 2011 to 2012 after the introduction of PCV13. This reduction in disease was largely attributable to the decrease in disease caused by additional serotypes included in PCV13, including an estimated 79.7% reduction in disease caused by serotype 19A, the dominant replacement serotype that emerged after the introduction of PCV7. The timing of the decline in disease mirrors the rapid replacement of PCV7 with PCV13 in NYC children. The largest decrease in disease incidence was seen in children younger than 12 months, the group born after the introduction of PCV13 who were eligible for the full vaccine series by the end of 2011. More than half the cases with PCV13-type disease after the introduction of PCV13 did not receive any doses of PCV13. Thirty-one percent of cases with IPD caused by the 6 additional serotypes included in PCV13 received the primary 4-dose PCV7 series but no supplemental PCV13 dose, representing a potentially preventable disease.

Declines in the incidence of IPD occurred in each racial/ethnic group after the introduction of PCV13. Significant differences in incidence between racial/ethnic groups before the introduction of PCV13 were not seen after the vaccine introduction. The largest decline was seen in non-Hispanic black individuals. This result may be owing to higher IPD incidence in non-Hispanic black individuals prior to vaccine introduction, allowing for a larger decrease. It has been suggested previously that the effect of vaccine-induced herd immunity could potentially differ by racial/ethnic group or that race-based vaccine targeting may occur at the healthcare–professional level. However, the 2012 National Immunization Survey estimated that the mean vaccination coverage of 3 or more doses of any PCV in NYC children aged 19 to 35 months was not significantly different in non-Hispanic black individuals (90.4%; ±8.2%) and non-Hispanic white individuals (93.9%; ±4.8%).

The emergence of nonvaccine replacement serotypes remains a concern. However, in the 2 years after the introduction of PCV13, the incidence of disease caused by non-PCV13 serotypes has not increased. Continued surveillance of IPD and monitoring for replacement serotypes is critical.

Although the observational nature of the data in this evaluation limited the ability to make causal inferences between the introduction of PCV13 and declines in IPD, an association is highly likely given that significant declines were specific to the additional serotypes included in PCV13. Further, the reduction in IPD incidence mirrored the rapid PCV13 uptake and high coverage, as documented in the CIR. Rapid uptake of PCV13 in NYC in 2010 was achieved through the Department of Health and Mental Hygiene notifications to pediatricians citywide, which instructed health care professionals to immediately replace PCV7 with PCV13 and administer a PCV13 supplemental dose as indicated. The notifications also included the return policy for unused doses of PCV7 that were privately purchased and publicly funded through Vaccine for Children. Approximately 75% of children aged 0 to 6 years in NYC were eligible for publically funded vaccines in 2010, according to Jane R. Zucker, MD, MSC, NYC Department of Health and Mental Hygiene, Bureau of Immunization (written communication, January 26, 2015). Among NYC children aged 19 to 35 months, the 2012 National Immunization Survey estimated coverage for 3 or more doses of either PCV vaccine (PCV7 or PCV13) in 2012 (87.4%; ±4.7%), similar to coverage with 3 or more doses of PCV7 in 2009 (92.4%; ±4.2%). However, these coverage estimates are not directly comparable with the CIR coverage pre-
sented in this article, which included only PCV13 doses administered to all children younger than 5 years.9

There was a 35% reduction in incidence of non-PCV13-type disease during the analysis. Factors such as secular trends in IPD, blood culturing practices, or surveillance artifact could have accounted for the change in non-PCV13-type IPD and such factors could similarly have affected PCV13-type disease. However, the 35% reduction in non-PCV13-type disease was not statistically significant and represented a small absolute decrease in the incidence of 1.99 cases per 100 000 relative to the 82% reduction and absolute reduction of 12.64 cases per 100 000 in PCV13-type IPD.

This analysis had limitations. Serotype group–specific incidence rates were calculated using redistributed case counts. If the yearly distribution of serotypes differed in those isolates without serotyping information, the incidence rate estimates may have been biased. However, this method of calculating incidence rates for IPD is well documented in the literature.3,4,20 In addition, the proportion of cases serotyped in the post-PCV13 period (2011-2012) was high at 89.9% (n = 62 of 69), so misclassification of serotype grouping after the introduction of PCV13 was likely to be low during this period. The proportion of cases serotyped in the pre-PCV13 period (2007-2009) was lower (66.9%; n = 220 of 329); however, cases resided in different neighborhoods throughout NYC and were reported from different facilities. In a sensitivity analysis, if all isolates without serotyping information prior to the introduction of PCV13 were classified as non-PCV13 type and all those after the introduction of PCV13 were classified as PCV13 type, the percentage reduction in PCV13-type incidence would decrease to 70.0% (10.2 cases per 100 000 in 2007-2009 vs 3.1 cases per 100 000 in 2011-2012). If all isolates without serotyping information prior to the introduction of PCV13 were classified as PCV13 type and all those after the introduction of PCV13 were classified as non-PCV13 type, the percentage reduction in PCV13-type incidence would increase to 86.0% (17.2 cases per 100 000 in 2007-2009 vs 2.4 cases per 100 000 in 2011-2012). Such differential rates of serotyping by serotype group in the pre- and post-PCV13 eras are unlikely; however, even the lowest estimate would show a 70% reduction in PCV13-type disease. While race/ethnicity data were available for 93.4% of cases, self-reported race/ethnicity was only available for 12.2% of cases and it has been suggested previously that race/ethnicity data obtained from administrative sources may be less accurate than self-reported data.21,22 However, in those cases where multiple data sources were available for review, there was a 94.1% (n = 48 of 51) concordance between race/ethnicity reported by interviews and medical record reviews and a 72.7% (n = 8 of 11) concordance between race/ethnicity reported by interviews and electronic laboratory records. Assignment of missing race/ethnicity based on geographical location of residence may have been inaccurate. Further, if cases of a particular race/ethnicity group were more likely to be recorded as unknown, these estimates may have been biased. However, race/ethnicity was missing for only 6.6% of cases and multiple imputations of missing race/ethnicity were performed to improve estimates. If these analyses are restricted to only those with known race/ethnicity, there is still a statistically significant percentage reduction in the incidence of IPD in each race/ethnicity group postvaccine introduction, except for Asian/Pacific Islander individuals.

Conclusions

These surveillance data show a significant decline in IPD after the introduction of PCV13 among NYC children younger than 5 years. Significant reductions were seen for all age and racial/ethnic groups. These reductions represent a substantial achievement for public health immunization programs in the 21st century. Maintaining a strong immunization infrastructure as well as ensuring access to pediatric vaccines through the Vaccines for Children program and achieving the Healthy People 2020 objectives for PCV13 coverage should remain a priority for the health of children in the United States.

REFERENCES


