Vaccination, Underlying Comorbidities, and Risk of Invasive Pneumococcal Disease

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abstract

OBJECTIVES: Children with underlying conditions remain at increased risk for invasive pneumococcal diseases (IPD). This study describes the epidemiology, serotype distribution, clinical presentations, and outcomes of IPD in children with and without comorbidity.

METHODS: Cases of childhood IPD in Massachusetts were identified via enhanced surveillance from 2002 through 2014. Demographic and clinical data were collected via follow-up telephone interviews with parents and/or primary care providers. Underlying conditions were classified according to the 2012 Report of the Committee on Infectious Diseases and 2013 recommendations by the Advisory Committee on Immunization Practices.

RESULTS: Among 1052 IPD cases in Massachusetts children <18 years old, 22.1% had at least 1 comorbidity. Immunocompromising conditions (32.7%) and chronic respiratory diseases (22.4%) were most common. Children with comorbidities were older at the time of IPD diagnosis (median 54 vs 23 months, \(P<.001\)), had higher hospitalization (odds ratio 2.5; 95% confidence interval 1.7–3.6) and case-fatality rates (odds ratio 3.7; 95% confidence interval 1.5–8.9) compared with children without known underlying conditions after adjusting for age, gender, year of diagnosis, and pneumococcal vaccination status. During the last 2 years of the study, IPD among children with comorbidities was caused by non-pneumococcal conjugate vaccine 13 serotypes in 23-valent polysaccharide pneumococcal vaccine (6/12, 50%) or serotypes that are not included in any of the vaccines (6/12; 50%).

CONCLUSIONS: In children with comorbidity, IPD results in higher mortality, and a large proportion of disease is due to serotypes not included in current conjugate vaccines. Further research is needed, specifically to develop and evaluate additional strategies for prevention of IPD in the most vulnerable children.

WHAT’S KNOWN ON THIS SUBJECT: Universal use of conjugated pneumococcal vaccines has resulted in dramatic decline in vaccine-type invasive pneumococcal disease. However, disease is not evenly distributed, and children with underlying clinical conditions are disproportionately represented, especially among children >5 years of age.

WHAT THIS STUDY ADDS: Invasive pneumococcal disease among children with comorbidity results in higher morbidity and mortality, and a large proportion of disease is due to serotypes not included in current conjugate vaccines.

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Dr Yildirim conceptualized and designed the study, carried out the analyses, and drafted the initial manuscript; Dr Shea critically reviewed the manuscript; Dr Little and Ms Silverio carried out the laboratory testing, and reviewed and revised the manuscript; Dr Pelton conceptualized and designed the study, supervised the laboratory testing of the isolates, and critically reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

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Implementation of conjugated pneumococcal vaccine in the United States in 2000 led to dramatic reductions in invasive pneumococcal disease (IPD) burden not only among children targeted for vaccination, but also among unvaccinated children and adults through reductions in vaccine serotype nasopharyngeal colonization and reduced transmission from vaccinated children.\(^1\)\(^2\) However, after widespread uptake of the 7-valent pneumococcal conjugate vaccine (PCV7), we observed an increase in IPD incidence caused by serotypes not included in PCV7 (replacement disease), mainly by serotypes 19A and 7F.\(^3\)\(^4\) This resulted in the introduction of a second-generation, 13-valent conjugate vaccine (PCV13) targeting 6 additional serotypes in 2010.

More than a decade after introduction of the first PCV (in the United States), Streptococcus pneumoniae still remains the cause of substantial morbidity, mortality, and health care costs.\(^5\)\(^6\) Before the widespread use of conjugated pneumococcal vaccines, children younger than 2 years old, children of certain racial and ethnic groups, those who attend day care, and children within certain chronic medical conditions were recognized to be at higher risk for IPD. In the post-PCV7 era, IPD incidence in black children has been reported to approach that in white children,\(^7\) and group child care attendance was shown to no longer confer excess risk for vaccine type IPD in the United States.\(^8\) Nonetheless, children with certain chronic conditions remain at higher risk for IPD despite vaccine coverage exceeding 85% in young children.\(^9\) Post licensure studies demonstrated that PCV7 was 96% effective in healthy children and 81% effective in those with coexisting conditions against vaccine serotypes.\(^10\) This differential effect is also reflected in epidemiologic studies that reported PCV7 serotypes more frequently in children with underlying conditions compared with healthy children in the post-PCV7 era.\(^11\) Higher case-fatality rates also have been reported in children with an underlying chronic disease.\(^6\) As a result of these observations, in February 2013, the Advisory Committee on Immunization Practices extended the target age group and recommended routine use of PCV13 for children aged 6 to 18 years with immunocompromising conditions, functional or anatomic asplenia, cerebrospinal fluid leaks or cochlear implants, regardless of whether they received previous PCV7 or 23-valent polysaccharide pneumococcal vaccine (PPV23).

Defining the magnitude of the increased risk in children with comorbid conditions compared with healthy children and the spectrum of serotypes causing disease is needed to formulate new strategies for prevention of IPD in this population. To further this goal, we evaluated the epidemiology of IPD in Massachusetts children with selected comorbid illnesses and report trends over time in this population of children after the introduction of PCV.

METHODS
A population-based surveillance program for S pneumoniae infection in children was initiated in Massachusetts in October 2001.\(^12\) All clinical microbiology laboratories in Massachusetts submit isolates of S pneumoniae from blood, cerebrospinal fluid, or other normally sterile body sites collected from Massachusetts residents <18 years of age to the Massachusetts Department of Public Health (MDPH). Epidemiologists at the MDPH subsequently interview parents/guardians and/or primary care providers to obtain demographic and clinical information, including underlying comorbidities, about each case by using a standardized case report form. Based on a collaborative agreement between the MDPH and Boston University Medical Center and with approval of respective review boards, all available S pneumoniae isolates are transferred from the MDPH to the Maxwell Finland Laboratory for Infectious Diseases at Boston University Medical Center for analysis. The annual birth cohort in Massachusetts is stable and at approximately 80 000 children per each year. National Immunization Survey data indicate that PCV coverage with 3 or more doses approximates 90%, regardless of race/ethnicity.\(^13\)

The current study was restricted to IPD cases identified after April 1, 2002, and study years were defined as the 12-month period from April 1 of the first year until March 31 of the following year to examine the impact of PCV13 implementation, which occurred in April 2010. Study investigators (IY and SIP) independently reviewed the clinical information for each case, and classified identified comorbidities consistent with the 2012 Report of the Committee on Infectious Diseases and 2013 recommendations of the Advisory Committee on Immunization Practices.\(^14\)\(^15\) In addition, we also identified comorbidities that either had previously been shown to be associated with IPD or might plausibly be associated with infection with or impaired immune response to S pneumoniae, such as prematurity, trisomy 21.\(^9\)\(^16\)\(^17\)

Vaccination status was defined in 2 categories. A child was presumed to have complete vaccination if the child had received an adequate number of PCV immunizations to have had a protective immune response against the vaccine serotypes at least 14 days before the diagnosis of IPD. Otherwise, a child was categorized as having incomplete vaccination. Adequate number of immunizations for children <12 months of age was defined as 2 or more PCV doses. Children who received 0 or 1 PCV dose were presumed to have incomplete vaccinations. For children 12 months of age or older, complete vaccination
required at least 1 PCV dose after the age of 12 months; otherwise, it was incomplete vaccination.

The presence of \textit{S. pneumoniae} was confirmed by optochin sensitivity (≥5 mm inhibition) and bile solubility by using standard microbiologic methods according to guidelines from the Clinical and Laboratory Standards Institute and serotyped by Quelling reaction by using pneumococcal antisera (Statens Serum Institute, Copenhagen, Denmark). Serotypes were classified as follows: PCV7 included serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F; PCV13 included the serotypes found in PCV7 and serotypes 1, 3, 5, 7F, 6A, and 19A; PPV23 included the serotypes found in PCV7 and serotypes 1, 2, 3, 5, 7F, 8, 9N, 10A, 11A, 12F, 15B, 17F, 19A, 20, 22F, and 33F.

Isolates found to be unencapsulated were confirmed to be \textit{S. pneumoniae} by \textit{lytA} gene amplification by using real-time polymerase chain reaction.\textsuperscript{16} Antibiotic susceptibility to penicillin, ceftriaxone, azithromycin, and trimethoprim/sulfamethoxazole (1/19) was determined by E-tests (BioMerieux, Durham, NC), according to manufacturer guidelines, and minimum inhibitory concentration (MIC) interpretations were based on the Clinical and Laboratory Standards Institute 2012 guidelines.\textsuperscript{19} In these guidelines, penicillin resistance is defined by MIC values between 0.12 and 1.0 μg/mL and high resistance is defined as MIC ≥2.0 μg/mL.

Annual IPD incidence rates were calculated by dividing the number of IPD cases by the population of Massachusetts residents <18 years of age as identified from the US Census Bureau estimates.\textsuperscript{20} IPD incidence rates also were estimated for children with hematomic malignancies and sickle cell disease (SCD), because these were among the most prevalent comorbidities identified in our population, and because we were able to estimate population denominators necessary for risk calculations. Information used to estimate population denominators for population groups with each comorbid condition came from the following sources. First, we used information from the National Cancer Institute’s Surveillance, Epidemiology, and End Results Program\textsuperscript{21} to estimate the total number of Massachusetts children with hematomic malignancies (leukemia and lymphoma for the purpose of this study). Next, we used a previously described approach\textsuperscript{22,23} to estimate the number of incident cases of SCD in Massachusetts children by using data obtained from the New England Newborn Screening Program, and to estimate the total number of patients with SCD in each year by adjusting each birth cohort population by estimated mortality rates published in the literature.\textsuperscript{24} Statistical analyses were conducted in SAS version 9.3.1 software (SAS Institute, Cary, IN).

We used $\chi^2$ and t-tests to compare variables, and the Cochran Mantel-Haenszel $\chi^2$ test to compare antibiotic susceptibility and clinical presentations over time; 2-sided $P$ values <.05 were considered statistically significant. Logistic regression was used to estimate associations between underlying clinical conditions and IPD controlling for age, gender, year of diagnosis, and immunization status when appropriate. Approval for this study was granted by the institutional review boards of both Boston University Medical Center and Massachusetts Department of Public Health.

**RESULTS**

Between April 2002 and April 2014, 1052 cases of IPD were reported in Massachusetts children <18 years of age. Demographic and clinical...
characteristics of IPD cases are presented in Table 1. The incidence of IPD in children younger than 2 years old declined more than 70% during this time period, from 32.7 cases/100 000 (95% confidence interval [CI] 23.8–41.6/100 000) to 9.6 cases/100 000 (95% CI 4.6–14.6/100 000), and IPD incidence in children 5 to 18 years reached an all-time low of 1.2 cases/100 000 in 2012/2013 (Fig 1).

Comorbidities
Information on comorbidities was available for 1008 (95.8%) of 1052 children (Table 2). Of these, 223 (22.1%) cases were found to have at least 1 underlying clinical condition. The most common conditions included immunosuppression due to primary immunodeficiency or immunosuppressive or radiation therapies (32.7%), and chronic respiratory diseases including asthma (22.4%).

In our population, IPD cases with underlying clinical conditions were older than IPD cases without comorbidities. The mean age at IPD diagnosis among children with at least 1 clinical condition was 54.0 months (interquartile range [IQR] 19–101 months) compared with 23.0 months (IQR 11–52 months) in children without any clinical conditions. More than 40% of the cases among children with comorbidity were older than 5 years of age, and among all IPD cases reported in children older than 5 years of age, 35.7% had a reported underlying condition. In a logistic regression model, the odds of an IPD case having comorbidity was 2.8 (95% CI 2.0–3.7) times higher in children 5 years or older compared with children younger than 5 years after adjusting for gender, year of diagnosis, and pneumococcal immunization. The proportion of IPD cases with underlying conditions did not change significantly by study year, gender, or race.

Clinical Presentations
Bacteremia was the most frequent presentation and reported in more than half of the cases (56.1%), followed by pneumonia, which was reported in one-third (34.8%) of all cases (Table 1). Clinical presentation of IPD was similar for cases with and without underlying conditions. Bacteremic pneumonia was observed more often in children with asthma (58.6%) compared with children

FIGURE 1
without asthma (34.6%); however, this difference was not statistically significant when adjusted for age, gender, year of diagnosis, and pneumococcal immunization (adjusted odds ratio [aOR] 2.1; 95% CI 0.9–4.7).

Outcome

Compared with IPD cases with no comorbidities, patients who had underlying conditions were more than twice as likely to be hospitalized (aOR 2.5; 95% CI 1.7–3.6), and 3 times as likely to die (aOR 3.7; 95% CI 1.5–8.9) after adjusting for age, gender, year of diagnosis, and pneumococcal immunization (Table 1). Overall, there were 23 IPD-related deaths, 10 of which occurred in children with bacteremia; 7 and 6 deaths occurred in children with meningitis and pneumonia, respectively. Children diagnosed with meningitis had sixfold higher case fatality rates compared with children with isolated bacteremia (aOR 6.1; 95% CI 2.1–17.9), even after adjusting for presence of comorbidity, age, gender, year of diagnosis, and immunization status.

Pneumococcal Vaccination and Serotypes

Approximately one-third of all IPD cases (29.9%) had incomplete pneumococcal vaccination at the time of IPD diagnosis (Table 1). Children with comorbidities were more likely to have incomplete vaccination (45/128; 35.2% of children with comorbidity versus 128/497; 25.8% of children without comorbidity); however, this difference was not statistically significant after adjusting for age, gender, and year of diagnosis (aOR 1.0; 95% CI 0.6–1.7). Among those with comorbidity and complete vaccination information, children with primary immunodeficiency (71.4%, 5/7) and children with SCD (57.1%, 4/7) had higher proportions of incomplete immunization, but there was no statistical significance after adjusting for age, gender, and year of diagnosis.

Pneumococcal isolates were available for 855 (81.3%) of the 1052 IPD cases and 806 (80.0%) of 1008 IPD cases with complete comorbidity information. The availability of serotypes did not differ by presence of underlying conditions. There were 5 (0.6%) S pneumoniae isolates that were nontypeable. The proportion of PCV7-IPD cases declined during the study period, whereas the proportion of cases caused by the 6 additional serotypes included in PCV13 increased until 2010, then declined after introduction of PCV13 (Fig 2). Comorbidity was less prevalent among cases caused by the additional 6 serotypes included in PCV13 (78/418, 18.7%) compared with cases caused by PCV7 (23/72, 31.9%) serotypes, additional 11 serotypes in PPV23 (34/143, 23.8%), and other serotypes (50/173, 28.9%). However, after adjusting for age, gender, year of diagnosis, and immunization status,
the prevalence of comorbidity was comparable in all serotype groupings. During the last 2 years of the study, 4 years after the implementation of PCV13, IPD cases among children with comorbidities were caused by either additional serotypes in PPV23 (6/12, 50%) or other serotypes that are not included in any of the vaccines (6/12; 50%) (Fig 2). In addition, children with comorbidities were more likely to have IPD caused by serotypes with lower invasive capacity (ie, 6C, 23A, 11A, 35B, 19F, 15A, and 15B/C) compared with children with no known underlying condition (32.1% vs 18.3%; P < 0.001); this difference remained statistically significant after multivariate analysis (aOR 2.1; 95% CI 1.3–3.2) (Fig 3).

**Antibiotic Susceptibility**

Results for antibiotic susceptibility testing were available for 787 (97.6%) of 806 isolates obtained from IPD cases with complete comorbidity information. The proportion of penicillin nonsusceptible isolates was similar among children with and without comorbidity (12.8% vs 8.9%). Among all cases, 77 strains (9.5%) exhibited intermediate (68; 8.4%) or high resistance (9; 1.1%) to penicillin; serotypes 19A (n = 59), 19F (n = 7), 9V (n = 2), 7F (n = 2), 6B (n = 2), 14 (n = 2), 35B (n = 2), and 6A (n = 1) were identified among the penicillin intermediate and resistant isolates. Only 3 children with IPD caused by strains with high penicillin resistance had comorbidity (1 transplant, 1 nephrotic syndrome, and 1 neuromuscular disease). The prevalence of cephalosporin and macrolide resistance was comparable between 2 groups as well (data not shown).

**Risk of IPD in Selected Groups**

During our study period, 14 (1.4%) children diagnosed with IPD also had SCD, and 19 (1.9%) had a hematologic malignancy. Comparing the average annual risk of IPD in these cohorts to the average annual risk in children without such conditions identified an approximately 50-fold higher risk in children with SCD (relative risk [RR] 49.1; 95% CI 29.3–89.0), and an ~33-fold higher risk in children with hematologic malignancies (RR 33.8; 95% CI 21.6–53.0) (Table 3).

**DISCUSSION**

Our surveillance identified that children with underlying clinical conditions comprise a substantial portion of IPD cases. In our study population, every fifth child with IPD...
overall, and every third child among cases in children >5 years of age, had an underlying chronic condition. Children with comorbidity had higher rates of hospitalization and excess mortality. Serotypes not included in conjugated vaccines were more prevalent, suggesting that new strategies will be needed to prevent IPD in this population. Our findings are supported by published reports that children with comorbidity are at excess risk for pneumococcal disease compared with otherwise healthy children.8,11,27 Higher hospitalization rates can be due to increased vigilance by parents or physicians and a greater propensity to observe and initiate early treatment in patients with chronic conditions, but may also reflect the severity of the disease. The latter rationale is also supported by the fact that the outcome of infection is less favorable in children with underlying conditions, reflected as a fourfold higher mortality.

Although the effectiveness of PCV7 was reported to be lower in children with coexisting conditions compared with healthy children, increasing penetration of conjugated pneumococcal vaccines provides protection against vaccine serotypes as a result of herd immunity.10 However, as shown in our study, serotypes that are not included in the conjugate vaccines, and known to be less virulent in healthy children, cause a significant proportion of IPD in children with an underlying condition. In our study, no PCV7 or PCV13 serotype was identified as a cause of IPD in children with comorbidity.
during the last 2 years. PPV23 is currently recommended for children aged ≥2 years with increased risk of IPD. Our data on serotypes causing IPD indicate a high burden of IPD caused by serotypes in PPV23 but not in PCV13, further supporting recommendations for broader protection by using both PCV13 and PPV23. Unfortunately, in our study, pneumococcal vaccination (both PPV23 and PCV13) coverage was very low in children with comorbidity, which also is consistent with other published studies. It follows that there is a need for education of both health care providers and the families regarding the importance of vaccination in high-risk children.

Children with certain clinical conditions have been well known to be at increased risk for IPD; however, data describing the magnitude of these increased risks are lacking in the PCV era. One reason is lack of information about the prevalence of clinical conditions in the general population, which is necessary to estimate incidence rates or relative incidence to healthy individuals. We were able to estimate the risk of IPD for children with 2 different underlying conditions; children with SCD and hematologic malignancies had significantly higher risk of IPD compared with children without such conditions. Our data provide further insight into the susceptibility of such children, define the magnitude of the excess risk of IPD among children with an underlying condition in the post-PCV era, and call for the development of new strategies for prevention of pneumococcal disease. Our study has a number of limitations. All surveillance programs are prone to underreporting; however, we believe that our surveillance system captures most laboratory-confirmed IPD in Massachusetts, as the same surveillance system has been in place longer than a decade and providers are very familiar with the process. Next, although we were able to ascertain the presence of comorbidity in nearly 96% of our study population, we had to rely on information collected via case report forms rather than complete medical records. Because most clinical data captured in case report forms were obtained from patients’ physicians for each case, we are confident that we appropriately captured the presence of existing comorbidity, but we did not have detailed information about severity of comorbid conditions (eg, we were unable to evaluate steroid use in asthma cases), potentially leading to misclassification. However, our surveillance system lacks detailed data, such as rapidity of disease onset, severity of the comorbid condition (ie, we were unable to evaluate steroid use in asthma cases), potentially permitting misclassification. Also because the number of children living with certain clinical conditions was not known, we relied on different datasets and assumptions to identify the prevalence of individuals with particular underlying conditions in the Massachusetts population. We used statewide newborn screening data to estimate incident cases of SCD, and Surveillance, Epidemiology, and End Results data for the estimated prevalence of hematologic malignancies in Massachusetts. These estimates do not account for immigration in and out of the catchment area.

CONCLUSIONS
Our study found a significantly increased risk of IPD and of a fatal outcome among children with comorbidities compared with otherwise healthy children. Serotypes that are not included in currently available conjugate vaccine are more prevalent and cause disease in such children. We need more insight into the role of PPV23 in protecting children with underlying conditions, and new strategies to provide broader coverage among children who are at highest risk for pneumococcal infection and fatal outcomes.

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