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Forecasting invasive pneumococcal disease trends after the introduction of 13-valent pneumococcal conjugate vaccine in the United States, 2010–2020

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ABSTRACT

Introduction: Pneumococcal vaccines are highly effective at preventing invasive pneumococcal disease (IPD), a leading cause of global morbidity. Because pneumococcal vaccines can be expensive, it is useful to estimate what impact might be expected from their introduction. Our objective was to develop a statistical model that could predict rates of IPD following introduction of 13-valent pneumococcal conjugate vaccine (PCV13) in the U.S.

Methods: We used active surveillance data to design and validate a Poisson model forecasting the reductions in IPD observed after U.S. introduction of 7-valent pneumococcal conjugate vaccine (PCV7) in 2000. We used this model to forecast rates of IPD from 2010 to 2020 in the presence of PCV13. Because increases in non-PCV7-type IPD were evident following PCV7 introduction, we evaluated varying levels of increase in non-PCV13-type IPD ("serotype replacement") by sensitivity analyses.

Results: A total of 43,507 cases of IPD were identified during 1998–2009; cases from this period were used to develop the model, which accurately predicted indirect effects of PCV7 in adults, as well as serotype replacement. Assuming that PCV13 provides similar protection against PCV13 serotypes as PCV7 did against PCV7 serotypes, the base-case model predicted approximately 168,000 cases of IPD prevented from 2011 to 2020. When serotype replacement was varied in sensitivity analyses from 0 to levels comparable to that seen with serotype 19A (the most common replacement serotype since PCV7 was introduced), the model predicted 167,000–170,000 cases prevented. The base-case model predicted rates of IPD in children under five years of age decreasing from 21.9 to 9.3 cases per 100,000 population.

Conclusions: This model provides a "benchmark" for assessing progress in the prevention of IPD in the years after PCV13 introduction. The amount of serotype replacement is unlikely to greatly affect the overall number of cases prevented by PCV13.

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1. Introduction

Streptococcus pneumoniae (pneumococcus) is a leading cause of both mild and severe infections globally and in the United States [1,2]. In recent years, pneumococcus caused approximately 44,000 cases of invasive pneumococcal disease (IPD) annually in the United States, despite a substantial reduction due to introduction of seven-valent pneumococcal conjugate vaccine (PCV7) in 2000 [3]. PCV7 covers the seven serotypes which accounted for 82% of IPD in children under 5 years of age at the time of introduction [4]. Despite early fluctuations due to shortages, vaccine uptake was rapid and reached 83% for a 3-dose series by 2005 [5,6]. Rates of IPD quickly declined and have remained low amongst all age groups, likely due to both direct and indirect effects of the vaccine [7]. Simultaneously, a moderate increase in IPD caused by serotypes not included in PCV7, primarily serotype 19A, has been observed [8]. This so-called "replacement disease", in combination with reductions in PCV7-type IPD, appears to have led to a new equilibrium in overall IPD in the United States [7,9].

In February 2010, a 13-valent pneumococcal conjugate vaccine (PCV13) was licensed in the United States. PCV13 covers the seven serotypes included in PCV7, as well as six additional types, (1, 3, 5, 6A, 7F, and 19A). These types combined accounted for 44–64% of IPD in the United States in 2007 and 2008, depending on age group [10,11]. Going forward, it will be important to understand whether trends in IPD are similar to those observed after PCV7 introduction because such comparisons can help to quantify replacement disease in the presence of PCV13 and to consider the role of new, expanded-valency vaccines. To forecast the impact of PCV13, we modeled the effects of PCV7 coverage on incidence of IPD through

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Table 1
Assumptions for final model.

Assumption	Rationale	Reference(s)
PCV13 will have a similar impact on vaccine-type disease compared to PCV7	No effectiveness data currently available on PCV13 in the U.S.; however, recent reports indicate early declines in PCV13 serotype IPD the U.S. Additionally, immunogenicity studies indicate the PCV13 antigens are immunogenic	[19,20,25]
Vaccine coverage rates applied equally across all age groups	Due to indirect effects, increasing coverage among children affects rates among adults. In the current model, equal coverage across age groups substantially improved model fit	[7,26,27]
Vaccine coverage rates applied equally across all groups of serotypes	Increasing vaccination rates have been associated with an increase in IPD due to types not included in the vaccine, a phenomenon known as "serotype replacement". Again, equal coverage across serotype groups substantially improved the model fit	[7,9]

2009. We then made assumptions about potential indirect effects and serotype replacement following PCV13 introduction (Table 1).

2. Methods

2.1. Case ascertainment

Cases of invasive pneumococcal disease (IPD) were identified through the Active Bacterial Core surveillance (ABCs) system, an active, laboratory- and population-based surveillance system for selected invasive bacterial pathogens. Data were included from all sites participating in a given year, starting in 1998 (unless otherwise noted): California, San Francisco County (1998-present) and Alameda and Contra Costa counties for children under 5 years (2001-present); Colorado, 5 county Denver area (2001-present); Connecticut; Georgia, 20 county Atlanta area; Maryland, 6 county Baltimore area; Minnesota, 7 county Minneapolis/St. Paul area (1998-present), entire state (2003-present); New Mexico (2004-present); New York, 7 county Rochester area (1998-present), 8 county Albany area (1999-present), and Erie County for children under 5 years (2005-present); Oregon, 3 county Portland area; Tennessee, 4 urban counties (1998–1999) and 7 additional urban counties (1999-present). Methods for case ascertainment and isolate collection have been described previously [12]. The total surveillance population for IPD in 2009 was 29.2 million (Table 2).

2.2. Immunization coverage

In 2000, PCV7 was recommended on a 4-dose schedule in the United States, with doses at 2, 4, 6 and 12–15 months of age. Shortly thereafter, vaccine shortages caused the Advisory Committee on Immunization Practices (ACIP) to temporarily suspend the recommended 4th dose for children, and later, suspend the recommended 3rd and 4th doses for healthy children [5,13]. As a result, uptake of both the 3rd and 4th doses was somewhat delayed and varied greatly by state, giving us wide-ranging data points for modeling the variation in rates across ABCs sites. Coverage rates for 3+ and 4+ doses were based on estimates from the National Immunization Survey (NIS) of coverage in children aged 19–35 months [14,15]. State-level NIS estimates were used for ABCs states, regardless of the size of the ABCs catchment area in a particular state. *Model* A model was specified and estimated using disease case counts from ABCs data from 1998 to 2009 (pre-PCV13 period) as the dependent variable. Population denominators were obtained from postcensal population estimates, using single-race "bridged" estimates [16]. Candidate models included vaccine coverage rates as continuous, non-transformed variables for 3 and 4 doses, 8 age groups (<2 years, 2–4, 5–17, 18–34, 35–49, 60–64, 65–79, 80+), 3 race groups (White, Black, other), and 4 serotype groups. Serotype groups were as follows:

(1) PCV7 types (plus 6A cases due to their cross-reactivity and decline similar to PCV7 types) [17]
(2) Serotype 19A
(3) PCV4 types (types included in PCV13, but not PCV7, minus types 6A and 19A)
(4) Non-vaccine types (all non-PCV13 types)

The model was constructed using a number of alternate specifications, including both negative binomial and Poisson distributions, using actual rates from 1998 to 2009. Additionally, different iterations of the model included fewer age and serotype groups; however since disease rates and trends varied substantially within the broader strata, finer age and serotype strata were chosen to allow flexibility. Based on goodness of fit tests, the Poisson and negative binomial models did not differ substantially. In the absence of clear differentiation in favor of the negative binomial assumption, Poisson is the appropriate distribution for count data; hence, a Poisson model, with adjustment for overdispersion, was specified and estimated. The model-predicted estimates of disease, by age and serotype group, were then extended through 2020.

The 1998–2009 portion of the model was estimated twice. In the first scenario, PCV7 coverage rates were set to zero for children ≥5 years of age and serotypes not included in the vaccine. This model structure conforms to only the direct effects of vaccine, meaning indirect (herd) effects for age groups ≥5 years and replacement disease were not considered. Under these assumptions, we would not expect to see a decline in disease rates over time in older children and adults and instead, would expect model predictions to be a *de facto* average of disease rates over the course of the study through the "averaging" effect of regression modeling. This model confirms that the dramatic decline in rates post-2000 was not due to changes in the underlying population or other basic demographic parameters. Fig. 1(a) shows the predictions from this model for adults ≥65 years of age. Presence or absence of a secular trend is not accounted for, nor relevant in view of the overwhelming vaccine impact (see Fig. 1(b)). Under the second scenario, PCV7 coverage rates acted as a primary driver for the vaccinated age groups and as a surrogate for indirect effects and replacement disease, allowing us to include these effects in the model and therefore conduct sensitivity analyses. In this scenario, PCV7 coverage rates by state were applied evenly, regardless of age or serotype group, allowing us to consider the effect of coverage rates on all ages and all serotype groups. For example, in California in 2003, NIS estimated 72.7% of children under 5 had received 3 doses of PCV7. Therefore, in the second scenario, age groups ≥5 years and non-PCV7 serotype groups were artificially assigned a coverage rate of 72.7%. The models were compared using both goodness-of-fit statistics and predictive ability for rates of disease from 1998 to 2009, as compared to actual rates in ABCs areas. Based on goodness-of-fit criteria, the second model, which allowed for estimation of indirect effects and replacement disease, was determined to be superior (Fig. 1).

Once the model was constructed, it was used to forecast future rates of disease and cases prevented by age group. Scenarios with differing amounts of replacement disease after PCV13 introduction were simulated by including a fictional "serotype X", which