

Estimating the Vaccine Effectiveness Against Serotype 3 for the 13-Valent Pneumococcal Conjugate Vaccine: A Dynamic Modeling Approach

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To cite this article:

Aaron Lucas, Michele Wilson, Heather L. Sings, Sarah Pugh, Dylan Jones, Raymond Farkouh, Bradford Gessner, Matthew Wasserman. Estimating the Vaccine Effectiveness Against Serotype 3 for the 13-Valent Pneumococcal Conjugate Vaccine: A Dynamic Modeling Approach. *International Journal of Infectious Diseases and Therapy*. Vol. 4, No. 4, 2019, pp. 56-66. doi: 10.11648/j.ijidt.20190404.12

Received: October 17, 2019; **Accepted:** November 14, 2019; **Published:** December 6, 2019

Abstract: Background: The 13-valent pneumococcal conjugate vaccine (PCV13) is the only PCV licensed to protect against serotype 3 in children. However, conflicting estimates exist of PCV13's direct and indirect protection vaccine effectiveness (VE) for serotype 3. Objective: Our study examined the of PCV13 for serotype 3 using different assumptions for PCV13 direct and indirect VE to model trends in serotype 3 invasive pneumococcal disease (IPD) and comparing these to observed data from the United Kingdom (UK). Methods: A dynamic transmission model of the spread of pneumococcal carriage and development of IPD was used to fit pre-PCV13-modeled IPD incidence with observed data. To allow for comparison across scenarios, post-PCV13-modeled IPD incidence was fit to observed data using assumptions for three different scenarios: (scenario 1) serotype 3 as a nonvaccine serotype, (scenario 2) VE against serotype 3 IPD of 63.5% based on a recent meta-analysis, and (scenario 3) a model-estimated VE against serotype 3. Results: Post-PCV13 introduction, modeled 2017 and average annual serotype 3 IPD incidence were within 20% and 59% of observed values for scenarios 2 and 3, respectively, but deviated by >100% for scenario 1. For adults aged ≥ 65 years, modeled 2017 IPD incidence in scenario 1 differed from observed data by 16% versus roughly 8% in scenarios 2 and 3. Conclusions: Observed data do not support a scenario of no serotype 3 VE, but rather a combination of direct protection among vaccinated children and a lower level of indirect protection among older adults. Policymakers should consider transmission dynamics when examining VE against covered serotypes.

Keywords: Pneumococcal Pneumonia, Vaccine, Dynamic Transmission Model, Invasive Pneumococcal Disease

1. Introduction

In 2000, a 7-valent pneumococcal conjugate vaccine (PCV7) was licensed to target pneumococcal disease due to the most common circulating serotypes at the time (4, 6B, 9V, 14, 18C, 19F, and 23F). Subsequently, 10-valent PCV (PCV10) and 13-valent PCV (PCV13) vaccines were licensed. PCV10 and PCV13 targeted the same serotypes as PCV7 in addition to three (1, 5, and 7F) or six (1, 3, 5, 6A,

7F, and 19A) additional serotypes, respectively. Both were licensed based on World Health Organization (WHO) recommendations whereby approval of new PCVs was based on the demonstration of immunologic noninferiority to PCV7. These PCVs have been highly effective in reducing incidence of diseases such as invasive pneumococcal disease (IPD), pneumococcal pneumonia, and acute otitis media due to the vaccine serotypes [1].

PCVs reduce the burden of pneumococcal disease through both direct and indirect protection [2, 3]. The latter occurs by

reducing nasopharyngeal carriage acquisition or density among vaccinated persons (primarily children) and thus reducing transmission of vaccine serotypes to unvaccinated persons.

Through these mechanisms, PCV13 has led to substantial reductions in IPD globally since its introduction [4]. However, although PCV13 is the only licensed PCV that contains serotype 3 in its formulation, authors have debated the presence and degree of vaccine effectiveness (VE) against this serotype [4, 5]. Given that there was no prelicensure efficacy study for PCV13 in infants, all estimates of PCV13 VE against IPD have been based on real-world observational studies, which have often found different estimates for direct or indirect PCV13 protection against serotype 3 by geography and time [3, 6-8]. For example, after the United Kingdom (UK) introduced PCV13 into the routine pediatric immunization schedule in 2010, vaccine-targeted serotype IPD incidence decreased for PCV13 serotypes other than 19A or plateaued for serotype 19A over the first 4 years following PCV13 introduction in both children and unvaccinated adults [9]. However, beginning in 2014, serotype 3 IPD incidence began to increase in both age groups, while other vaccine-type IPD incidence kept decreasing [5].

There is a large body of evidence from both randomized controlled trials and observational studies that PCV13 provides direct protection against serotype 3 in vaccinated children and adults. A recent meta-analysis of observational studies in infants [10] estimated VE against serotype 3 IPD of 63.5% (95% confidence interval, 37.3%-89.7%). In a study funded by the European Centre for Disease Prevention and Control (ECDC), PCV13 VE for serotype 3 IPD was 70% (95% confidence interval [CI], 44%-83%) for ≥ 1 dose and 57% (95% CI, 5%-81%) for children who were fully vaccinated [11]. In post-hoc analyses from a randomized controlled trial in The Netherlands [12], VE against serotype 3 was 60.0% (95% CI, 5%-85%) for chest X-ray-confirmed community acquired pneumonia (CAP) and 61.5% (95% CI, 18%-83%) for clinical CAP in the modified intention-to-treat population [13]. Finally, a recent meta-analysis of three studies in adults also found that PCV13 had a VE against serotype 3 for hospitalized CAP of 52.5% (95% confidence interval, 62% - 76%) [14]. However, there have also been published case control studies in children that have shown limited effectiveness against serotype 3 IPD, with some suggesting that VE against serotype 3 IPD wanes over time [1]. In addition, and as noted in a previous review of PCV13 impact on serotype 3 IPD in children [10], some prelicensure clinical trials showed that the immune response for serotype 3 following the booster dose was not increased above the levels seen after the infant vaccination series, suggesting potential hyporesponsiveness [16].

More problematic is the debate over the existence of indirect protection from PCV13 against serotype 3. As evidence of indirect protection among older unvaccinated persons, a study published by the ECDC [17, 18] found a statistically nonsignificant reduction in serotype 3 IPD

incidence in older unvaccinated adults across six PCV13 settings through 2014, followed by an increase through 2017, resulting in an overall 12% increase comparing 2017 to 2009. Conversely, in PCV10 countries, serotype 3 IPD incidence steadily increased from the time of PCV10 introduction, with a 56% increase in serotype 3 IPD comparing 2017 to 2009. In contrast, a randomized controlled trial of PCV7 versus PCV13 in children found no efficacy against serotype 3 carriage, although confidence limits were wide enough to allow for a potential effect [19].

In sum, some investigators [20, 21] have concluded that PCV13 has no direct or indirect protection against serotype 3, classifying the serotype as a nonvaccine serotype (NVT). For example, a recent modeling exercise by the Joint Committee on Vaccination and Immunization categorized serotype 3 as an NVT in estimating the impact on removing a priming dose in infant vaccination [22]. Furthermore, a number of cost-effectiveness studies also assume PCV13 provides no protection against serotype 3 [23-25]. If such an assumption is incorrect, it will underestimate the benefit of PCV13 vaccination. In this context, it is important to separate direct from indirect effects since a vaccine may provide the former without the latter. In this circumstance, effectiveness or efficacy studies may demonstrate direct protection while population-based surveillance shows no impact among unvaccinated age cohorts, or even target vaccine groups, if coverage remains sufficiently low.

The goal of the current study was to evaluate the validity of assumptions surrounding the VE of PCV13 against serotype 3. To do this, we compared the prospective trend in serotype 3 IPD incidence post-PCV13 introduction under different VE assumptions, using the observed UK IPD surveillance data as the backbone of the calculations. Many researchers have used mathematical models to carry out experiments, such as this one, that are impractical to conduct in the real world [26-28]. In carrying out this study, we used a previously published and validated model [29] of pneumococcal carriage and IPD that was calibrated to the UK.

2. Methods

2.1. Model Overview

To assess PCV13 VE against serotype 3 in the UK, we adapted a previously published dynamic transmission model that simulates the spread of pneumococcal carriage and development of IPD in a population over time [29]. The model stratifies individuals by the presence or absence of pneumococcal carriage, vaccine status, and age group. PCV13 vaccination in the UK, based on a 2+1 schedule (at 2, 4, and 12 months of age), is captured by transitioning eligible age groups through vaccine dose compartments based on dosing schedule and adherence.

In the model, individuals who acquire carriage may subsequently develop IPD. Entering a vaccine dose compartment protects against developing IPD by reducing

the probability of developing IPD (VE_{IPD}) or reducing the probability of acquiring carriage (VE_C) when exposed to a particular serotype for the duration of protection within the model. The reduction in circulating carriage afforded by the vaccine's VE_C lessens the probability of acquiring carriage for unvaccinated adults as well. The model tracks carriage acquisition, carriage duration, and development of IPD over time based on the individual's vaccination status and the population-level carriage prevalence for each serotype (force of infection). On the basis of Wasserman et al. [29], individuals who acquire serotype 3 carry for an average duration of 6.2 weeks and have a probability of IPD given carriage of nine cases per 100,000 acquisitions.

The model includes a fixed set of inputs derived from the published literature [29]. Given these inputs, the model estimates a set of unknown (calibrated) inputs by matching modeled IPD incidence as closely as possible to observed IPD incidence in the UK across five serotype groups (grouped PCV7 serotypes; serotype 3; serotype 19A; grouped serotypes 1, 5, 7F, and 6A; and grouped non-PCV13 serotypes) and seven age groups (0-<2, 2-4, 5-17, 18-34, 35-49, 50-64, and 65 years) [[5]]. Although some authors

consider 6A a PCV7 serotype due to cross-reactivity with 6B, for the purposes of this analysis, 6A was considered a PCV13 serotype.

The calibration procedure used to estimate the unknown parameters has been described previously [29]. Briefly, the model estimates a prevaccine-era "steady state" by solving a set of linear equations to calculate the force of infection parameters for each serotype and age group to initialize the model. The model then uses a simulated annealing approach to randomly draw values for the unknown (calibrated) parameters within certain bounds. The model is then run forward over all years of available IPD surveillance (in this case, 2001 to 2017). The calibration procedure is then repeated for a given number of iterations with the goal of minimizing the sum of squared deviations of the resulting yearly IPD incidence values produced from the model as compared with the actual IPD surveillance values by age and serotype group.

Table 1 shows the fixed and calibrated inputs for the VE_C and VE_{IPD} for each modeled serotype group excluding serotype 3. Details on other input parameter estimates can be seen in Supplementary Table 4.

Table 1. PCV13 Vaccine Effectiveness Against Serotype Groups.

Parameter	Direct Protection (VE_{IPD})			Indirect Protection (VE_C)		
	First Priming Dose	Second Priming Dose	Booster Dose	First Priming Dose	Second Priming Dose	Booster Dose
Serotype 19A	53%	75%	74%	Calibrated	Calibrated	Calibrated
Serotypes 1, 5, 7F, 6A	85%	94%	93%	Calibrated	Calibrated	Calibrated
PCV7-covered serotypes	56%	79%	93%	Calibrated	Calibrated	Calibrated
NVTs	0%	0%	0%	0%	0%	0%

IPD = invasive pneumococcal disease; NVT = nonvaccine serotype; PCV = pneumococcal conjugate vaccine; PCV13 = 13-valent PCV; VE = vaccine effectiveness; VE_C = vaccine effectiveness against carriage; VE_{IPD} = vaccine effectiveness against IPD.

Vaccine effectiveness against IPD is based on Andrews et al. [38] and 2014 for all PCV13 serotypes, excluding serotype 3. For serotype 3, this value is scenario specific: in Scenario 1, serotype 3 is assumed to be an NVT; in Scenario 2, this value is derived from Sings et al. [10]; and in Scenario 3, this value is calibrated.

2.2. Approach to Modeling PCV13 VE Against Serotype 3

We conducted a series of scenario analyses to assess PCV13's VE against serotype 3. These scenarios included the following:

- Scenario 1: VE_{IPD} and VE_C against serotype 3 are both assumed to be 0, mimicking serotype 3 as an NVT.
- Scenario 2: VE_{IPD} against serotype 3 is assumed to be 63.5% following the booster dose [10]. VE_{IPD} against serotype 3 for the first and second priming doses followed the same procedure as described in Wasserman et al. [29]. VE_C against serotype 3 was a calibrated parameter.
- Scenario 3: VE_{IPD} and VE_C against serotype 3 were calibrated parameters.

The combination of these three scenarios provide for a broad perspective on evaluating PCV13 VE against serotype 3.

The model was first calibrated using the assumptions in Scenario 1. Then, to allow for comparison across scenarios, the pre-PCV13-calibrated inputs and initial conditions in Scenario 1 were also used for Scenarios 2 and 3. The post-PCV13-calibrated inputs were then reestimated for Scenarios 2 and 3 by initializing the calibration procedure at the start of PCV13's

introduction. For each scenario, the model was calibrated using the same observed data as in Wasserman et al. [29]. All other fixed inputs remained the same across scenarios. To assess the goodness of fit for each calibration, the sum of squared deviations between modeled and observed IPD incidence was compared between scenarios. Fit was assessed for all serotypes and serotype 3 IPD incidence separately.

2.3. Outcomes

The primary outcomes of the model were the trends in serotype 3 IPD incidence (from here forward referred to as IPD incidence). The study compared modeled annual IPD incidence rates in 2009 (the year preceding PCV13 introduction) and 2017 (the last year of observed data) with observed data. The study also examined the average annual IPD incidence post PCV13 introduction.

The study compared each scenario's outcome to the observed outcome. While all age groups were included in the model parameterization, results are presented for children aged 0-<2 years as well as adults aged ≥ 65 years, because these age groups represent the majority of IPD burden (calibration fit trends are presented in Supplementary

Material for each age group included in the model). Direct protection against serotype 3 IPD (VE_{IPD}) was therefore evaluated based on the best-fit scenarios for the vaccinated children aged 0-<2 years, while change in IPD incidence in the group aged ≥ 65 years was used to examine the existence of indirect protection (VE_C) against serotype 3.

3. Results

Following the calibration procedure for all scenarios, the

model found the best fit for observed data across all age groups in the model (both vaccinated and unvaccinated) with the estimated VE_{IPD} and VE_C against serotype 3 and goodness-of-fit estimates as presented in Table 2. In Scenario 2, the model estimated VE_C against serotype 3 to be 6% for the booster dose using a fixed 63.5% VE_{IPD} . In Scenario 3, the model estimated VE_{IPD} and VE_C against serotype 3 to be 31% and 19%, respectively. Scenario 3 had the best fit to observed data for all serotypes in addition to serotype 3.

Table 2. Vaccine Effectiveness Against Serotype 3 for Each Scenario.

Parameter	Scenario 1			Scenario 2		
	First Priming Dose	Second Priming Dose	Booster Dose	First Priming Dose	Second Priming Dose	Booster Dose
VE against IPD	0%	0%	0%	41%	65%	64%
VE against carriage	0%	0%	0%	4%	6%	6%
Goodness of fit ^a , all serotypes		795.2			859.9	
Goodness of fit ^a , serotype 3		31.2			19.1	

Table 2. Continued.

Parameter	Scenario 3		
	First Priming Dose	Second Priming Dose	Booster Dose
VE against IPD	15%	32%	31%
VE against carriage	10%	14%	19%
Goodness of fit ^a , all serotypes		793.0	
Goodness of fit ^a , serotype 3		16.3	

IPD = invasive pneumococcal disease; PCV = pneumococcal conjugate vaccine; VE = vaccine effectiveness.

^a Sum of squared deviations between modeled and observed IPD incidence for all serotype groups, age groups, and years.

^b Sum of squared deviations between modeled and observed serotype 3 IPD incidence, for all age groups and years.

Figures 1 and 2 illustrate the trends in IPD incidence for each scenario and for the observed data for children aged 0-<2 years and adults aged ≥ 65 years, respectively (results of the calibrated parameters and trends in IPD incidence for each age group included in the model are listed in Supplementary Table 1 and Figures 1 to 7). Pre-PCV13 (2001-2009) modeled IPD incidence aligned well with the observed data. From 2010 on, the fit (compared to observed data) and trend lines differed across scenarios due to the calibration. In observed data, IPD incidence decreased after 2009 and then immediately increased

(Figures 1 and 2). After the introduction of PCV13, modeled IPD incidence in Scenario 1 (assuming serotype 3 is an NVT) increased annually for both age groups. Conversely, for children aged 0-<2 years, scenarios allowing for direct and indirect protection against serotype 3 led to incidence decreasing before leveling off (Scenarios 2 and 3). For adults aged ≥ 65 years, Scenario 2 showed a lower increase in IPD incidence than Scenario 1 after 2009, and Scenario 3 resulted in IPD incidence roughly plateauing from the point of PCV13 introduction.

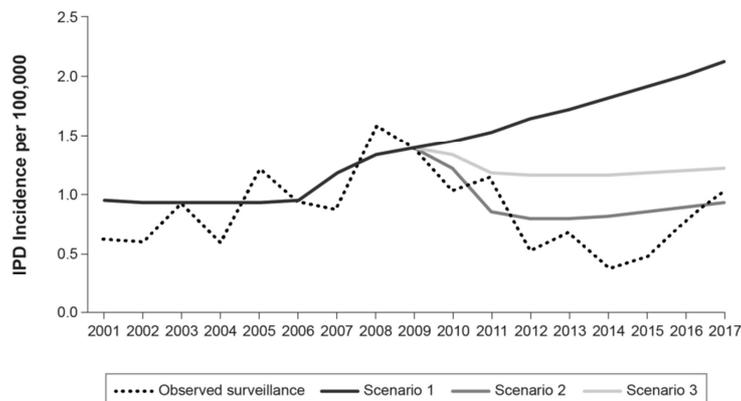


Figure 1. Modeled and Observed Serotype 3 IPD Incidence (Cases per 100000) From 2001 to 2017: Children Aged 0-<2 Years.

IPD = invasive pneumococcal disease; PCV13 = 13-valent pneumococcal conjugate vaccine.

Scenario 1 assumes serotype 3 is a nonvaccine serotype. Scenario 2 derives the PCV13 vaccine effectiveness against serotype 3 IPD from Sings *et al.* [10]. Scenario 3 assumes the PCV13 vaccine effectiveness against both serotype 3 IPD and carriage is unknown, and the model calibrates these values. Year refers to the latter epidemiological year (e.g., epidemiological year 2000/2001 is referred to as 2001).

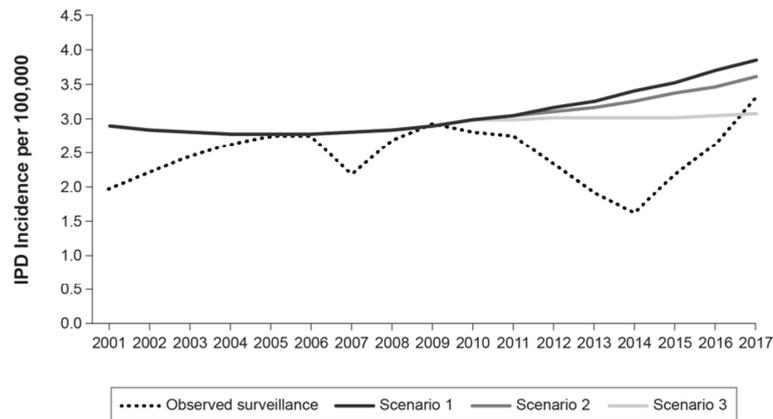


Figure 2. Modeled and Observed Serotype 3 IPD Incidence (Cases per 100000) From 2001 to 2017: Adults Aged ≥ 65 Years.

IPD = invasive pneumococcal disease; PCV13 = 13-valent pneumococcal conjugate vaccine.

Scenario 1 assumes serotype 3 is a nonvaccine serotype. Scenario 2 derives the PCV13 vaccine effectiveness against serotype 3 IPD from Sings et al. [10]. Scenario 3 assumes the PCV13 vaccine effectiveness against both serotype 3 IPD and carriage is unknown, and the model calibrates these values. Year refers to the latter epidemiological year (e.g., epidemiological year 2000/2001 is referred to as 2001).

Table 3 quantifies the results presented in Figures 1 and 2 and presents the modeled IPD incidence in 2009 (pre-PCV13) and 2017 (most recent year of observed data) and the average annual IPD incidence over the entire PCV13 era (2010-2017) for each scenario. In 2009, observed IPD incidence was 1.41 cases per 100,000 among children aged 0-2 years (Table 3). Modeled IPD incidence in 2009 was within 0.2% of observed data for the same age group. For children aged 0-2 years, following the introduction of PCV13, in Scenario 1, modeled 2017 IPD

incidence and the average annual IPD incidence in 2010-2017 deviated from observed IPD incidence by 107.7% (2.14 vs 1.03 cases per 100000) and 134.2% (1.79 vs 0.76 cases per 100000), respectively. By contrast, in scenarios 2 and 3, for children aged 0-2 years, modeled 2017 and average annual IPD incidence remained within roughly 20% (Scenario 2) and 60% (Scenario 3) of observed data. Scenario 2 resulted in the smallest average annual deviation from the observed data in 2017 and in the average annual IPD incidence.

Table 3. Serotype 3 IPD Incidence (Cases per 100000) Over the PCV13 Era.

Parameter	Serotype 3 IPD Incidence (Cases per 100000) (percentage deviation from observed)		
	2009	2017	2010-2017 (Average Annual)
Children aged 0-2 years			
Observed	1.41	1.03	0.76
Scenario 1		2.14 (107.7%)	1.79 (134.2%)
Scenario 2	1.41 (-0.2%)	0.94 (-8.7%)	0.90 (18.4%)
Scenario 3		1.23 (19.5%)	1.21 (58.7%)
Adults aged ≥ 65 years			
Observed	2.93	3.34	2.45
Scenario 1		3.88 (16.0%)	3.38 (37.7%)
Scenario 2	2.92 (-0.3%)	3.62 (8.3%)	3.26 (32.9%)
Scenario 3		3.09 (-7.6%)	3.03 (23.5%)

IPD = invasive pneumococcal disease; NVT = nonvaccine serotype; PCV = pneumococcal conjugate vaccine; PCV13 = 13 valent PCV.

Relative difference from the observed data (presented in parentheses) is estimated as the relative difference from the observed estimate. For example, a relative difference of -10% would suggest that the calibrated estimate is 90% of that of the observed data, while a relative difference of 100% would suggest that the calibrated estimate is twice that of the observed data.

For adults aged ≥ 65 years, observed IPD incidence was 2.93 cases per 100,000 in 2009, 3.34 per 100,000 in 2017, and an average of 2.45 cases per 100,000 in 2010-2017 (Table 3). Modeled 2017 IPD incidence in Scenario 1 differed from observed data by 16% in Scenario 1 versus roughly 8% in Scenarios 2 and 3. When considering the average annual IPD incidence in 2010-2017, the model differed from observed data by roughly 38% (Scenario 1), 33% (Scenario 2), and 24% (Scenario 3).

Observed IPD incidence rate ratios for adults aged ≥ 65 years from the ECDC [17, 18] were also compared with modeled IPD incidence rate ratios from Scenario 1 for the same age group

(Figure 3). Observed data from six sites with universal childhood PCV13 programmes showed a general decrease in serotype 3 IPD incidence rate ratios in 2011-2014, followed by an increase, whereas data from four sites with universal PCV10 programmes showed a general increase in serotype 3 IPD incidence rate ratios starting at the time of PCV10 introduction. When using the modeled IPD incidence rate ratios in Scenario 1 that assume serotype 3 is an NVT, the data were more closely aligned with the observed data from PCV10 sites but underestimated the observed increases. In addition, two PCV10 countries included regions that used PCV13, thus the ECDC data also may have underestimated IPD incidence in PCV10 countries.

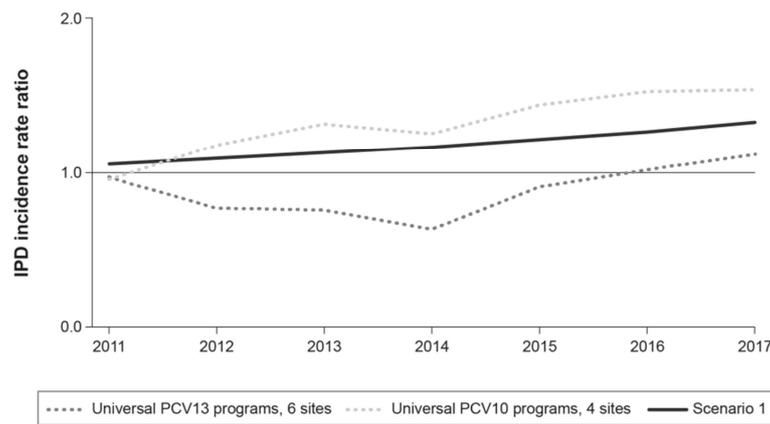


Figure 3. Serotype 3 IPD Incidence Rate Ratios from 2011 to 2017 for Adults Aged ≥ 65 s: Comparing Serotype 3 as an NVT to ECDC Data.

ECDC = European Centre for Disease Prevention and Control; IPD = invasive pneumococcal disease; NVT = nonvaccine serotype; PCV10 = 10-valent pneumococcal conjugate vaccine; PCV13 = 13-valent pneumococcal conjugate vaccine; VE = vaccine effectiveness.

IPD incidence rate ratios compare annual serotype 3 IPD incidence with that of 2009. Scenario 1 assumes serotype 3 is an NVT. Data for universal PCV13 and PCV10 programs taken from Figures 4a and 4b in Hanquet *et al.* [17], along with data from the February 2019 meeting of the Advisory Committee on Immunization Practices [18]. Year refers to the latter epidemiological year (e.g., epidemiological year 2000/2001 is referred to as 2001).

4. Discussion

Using a previously developed dynamic transmission model, we tested several scenario analyses to estimate PCV13 VE against serotype 3 assuming a 2+1 schedule in the UK. Of the three scenarios tested, modeled results produced the closest approximation to observed IPD incidence among children aged 0-2 years when assuming VE_{IPD} against serotype 3 was equal to 63.5%, a value taken from a previous meta-analysis of PCV13 VE against serotype 3 IPD in children [10]. This evidence further suggests that PCV13 provides direct protection against serotype 3 among vaccinated persons.

The evidence for PCV13 indirect protection against serotype 3 was mixed in our findings. Scenarios assuming non-zero VE_{IPD} and VE_C (Scenarios 2 and 3) exhibited better alignment with the average observed annual IPD incidence among adults aged ≥ 65 years post PCV13 introduction. However, these scenarios were not able to fully capture the immediate decrease in IPD incidence in the ≥ 65 -year age group that was observed in the UK. In contrast, assuming serotype 3 is an NVT resulted in markedly higher IPD incidence than was observed during this time period. However, the fits were generally better for the 0- to <2-year population (direct protection) than for the ≥ 65 -year population (indirect protection).

Modeled results for adults aged ≥ 65 years in Scenarios 2 and 3 were consistent with observed serotype 3 IPD incidence trends in countries with PCV13. Many countries with pediatric PCV13 immunization programmes have experienced a decrease and subsequent increase in serotype 3 IPD incidence among unvaccinated persons aged ≥ 65 years. If PCV13 does not provide sufficient protection against carriage of serotype 3, then, over time, cases of serotype 3 could increase if serotype 3 carriage and transmission

increase. Conversely, countries that have implemented pediatric PCV10 programmes have experienced an immediate and consistent upward trend in pediatric serotype 3 IPD incidence. As presented in Figure 3, compared to PCV10 countries, PCV13 countries also have experienced a markedly different serotype 3 evolution among unvaccinated older persons. Similarly, comparing the results of the model in Scenario 1 to the ECDC data from PCV10 countries demonstrated that if PCV13 VE_C against serotype 3 were 0%, then IPD incidence rates from PCV13 settings would be much higher and more closely aligned to PCV10 settings. In summary, these results highlight that a nontrivial, possibly low level of indirect protection against serotype 3 is conferred by PCV13 and could reflect impact against carriage acquisition, density, or duration. However, it should also be noted that several serotypes that are known to cause IPD, including serotype 3, undergo multiyear epidemic patterns that are independent of PCVs [30] and that may be due to a variety of factors. The observed differences in the PCV13 and PCV10 countries could also have been due to factors other than vaccine, including differences in the serotype distribution of nasopharyngeal carriage among children in the pre-PCV10 or PCV13 vaccine periods [31].

Given our model's difficulty in fitting observed incidence in adults aged ≥ 65 years, it is likely that other nonvaccine exogenous factors play a role in serotype 3 dynamics and NVT replacement in the UK, and several hypotheses exist. First, as with influenza infection, pneumococcal carriage density may increase logarithmically with use of live attenuated influenza vaccine (LAIV), which, in the UK, is the primary influenza vaccine used among young children, the age group most likely to transmit infection [32]. Several lines of evidence are consistent with but do not confirm this hypothesis. A randomized clinical trial of 151 children found that pneumococcal carriage density was 2.68 times higher in children aged 2-4 years who received LAIV compared with those who

did not [33]. A second study in mice found that LAIV increased bacterial transmigration and could increase the risk of otitis media [34]. Given that the UK has a pediatric influenza vaccine uptake of 60%-80% [32], a relatively modest protection from PCV13 against serotype 3 could be overwhelmed by stimulation of pneumococcal proliferation among heavy transmitters immediately before the season of greatest pneumococcal disease risk. Second, there may be additional carriage reservoirs outside of children that may lead to increases in disease caused by NVT and serotype 3, as vaccine serotype carriage is reduced at a population level. By using pediatric carriage-testing methodology (e.g., a focus on the nasopharynx versus saliva and oropharynx), recent studies have reported that adult pneumococcal carriage has been underestimated multiple-fold [35]. Third, a recent report on global serotype 3 genotypes and genetic evolution reported that a new antimicrobial-resistant clade of serotype 3 emerged in 2014 [36], and that emergence did not correlate with the use or timing of introduction of PCV13 at a population level. As with the LAIV hypothesis, this finding raises the possibility that PCV13 impact is being overwhelmed by a new clade for which community antibiotic pressure is no longer providing sufficient synergy. Fourth, serotype 3 may actually represent a serogroup with multiple related serotypes, similar to those identified in the recent separation of serotypes 6A and 6C [37]. In this scenario, PCV13 may have greater impact against one form of serotype 3, which then is replaced by a second form less susceptible to vaccine-induced immunity. However, further effectiveness or immunogenicity studies are required to support this theory. Fifth, there may be changes in antibiotic pressure with rational antibiotic use policies, or temporal changes may have occurred in risk factors for pneumococcal disease, including those that favor serotype 3, such as aging of the population, increased prevalence of chronic diseases, changes in breastfeeding or child group care practices, or changes use of extended care facilities for older adults. Finally, there are aspects of pneumococcal disease that are still not fully understood. For example, NVT IPD incidence in the UK increased approximately linearly following the introduction of PCV13 [5]. Starting in 2014, however, NVT incidence substantially increased [5]. Further research is recommended to better understand these phenomena and to better capture the dynamics of a very complex disease.

As with any modeling study, this analysis is subject to several limitations. The most notable limitation is the limited availability of data on VE and duration of protection for each dose. Similarly, real-world data on carriage of each serotype over time is extremely limited. The results are thus subject to

uncertainty. A further limitation is that the results are based on only one country, and as such our findings may or may not be generalizable to other settings. This question could be explored in other countries for which PCV13 was introduced to better assess the consistency of evidence of PCV13 against serotype 3. However, few countries have sufficiently robust data available to model complex serotype dynamics before and after vaccine introduction. Additionally, for computational reasons and lack of data, the model does not consider the impact of immigration/emigration or transient travel on carriage and IPD incidence. These factors could influence the transmission of disease carriage, as individuals traveling from countries without PCV13 may affect the carriage rate within the UK population. Finally, implications of LAIV or other population-level impacts that could be driving increases in serotype 3 IPD incidence in more recent years, as discussed above, were not addressed in the model. These structural limitations would require a substantially more computationally intensive model, and that combined with the absence of data to estimate key parameters may render accounting for them infeasible.

5. Conclusions

Using a dynamic transmission model parameterized with the best available evidence and calibrated to the UK surveillance system, our results support the hypothesis that PCV13 provides direct protection against serotype 3 for vaccinated persons and may provide additional protection against some aspect of serotype 3 carriage, whether acquisition, density, or duration. Policymakers should consider direct and indirect effects of conjugate pneumococcal vaccines when interpreting changes in disease incidence rates, including those for specific serotypes. Additionally, policymakers should recognize that PCVs represent only one of many potentially competing factors that can influence pneumococcal disease epidemiology. Further research is necessary to better understand the complexity of disease transmission dynamics and the evolution of serotype epidemiology.

6. Supplementary Material

6.1. Calibrated Parameter Estimates

All non-calibrated parameters are taken from Wasserman et al., 2018. All parameters that varied across scenarios are listed in Table 4.

Table 4. Calibrated Parameters for Each Scenario.

Parameter	Scenario 1			Scenario 2		
	First Priming Dose	Second Priming Dose	Booster Dose	First Priming Dose	Second Priming Dose	Booster Dose
Indirect protection (VE against carriage)						
Serotype 19A	15%	22%	73%	14%	34%	74%
Serotype 3	0%	0%	0%	4%	6%	6%
Serotypes 1, 5, 7F, and 6A	17%	47%	71%	7%	21%	21%
PCV7-covered serotypes ^a	29%	54%	79%	29%	54%	79%
Duration of immunity (PCV7 and PCV13) ^a	14 years	4 years	17 years	14 years	4 years	17 years

Parameter	Scenario 1			Scenario 2		
	First Priming Dose	Second Priming Dose	Booster Dose	First Priming Dose	Second Priming Dose	Booster Dose
Indirect protection (VE against carriage)						
Duration of carriage among carriers (NVT) ^a	2 weeks			2 weeks		
Probability of IPD given carriage acquisition (NVT) ^a	2 per 100000 acquisitions			2 per 100000 acquisitions		

IPD = invasive pneumococcal disease; PCV = pneumococcal conjugate vaccine; VE = vaccine effectiveness; NVT = nonvaccine serotype.
^a To allow for comparison across scenarios, the pre-PCV13 calibrated inputs and initial conditions in Scenario 1 were also used for Scenario 2 and 3.

Table 4. Continued.

Parameter	Scenario 3		
	First Priming Dose	Second Priming Dose	Booster Dose
Indirect protection (VE against carriage)			
Serotype 19A	28%	40%	47%
Serotype 3	10%	14%	19%
Serotypes 1, 5, 7F, and 6A	21%	41%	65%
PCV7-covered serotypes ^a	29%	54%	79%
Duration of immunity (PCV7 and PCV13) ^a	14 years	4 years	17 years
Duration of carriage among carriers (NVT) ^a	2 weeks		
Probability of IPD given carriage acquisition (NVT) ^a	2 per 100000 acquisitions		

IPD = invasive pneumococcal disease; PCV = pneumococcal conjugate vaccine; VE = vaccine effectiveness; NVT = nonvaccine serotype.
^a To allow for comparison across scenarios, the pre-PCV13 calibrated inputs and initial conditions in Scenario 1 were also used for Scenario 2 and 3.

6.2. Modeled and Observed Serotype 3 IPD Incidence for All Age Groups

Figures 1 to 7 illustrate the trends in IPD incidence for each scenario and for the observed data for each age group

included in the model. Results were inconclusive in analyzing the fit and primary outcomes of interest for people aged 2 – 64 years, as IPD incidence was very close to zero for this population.

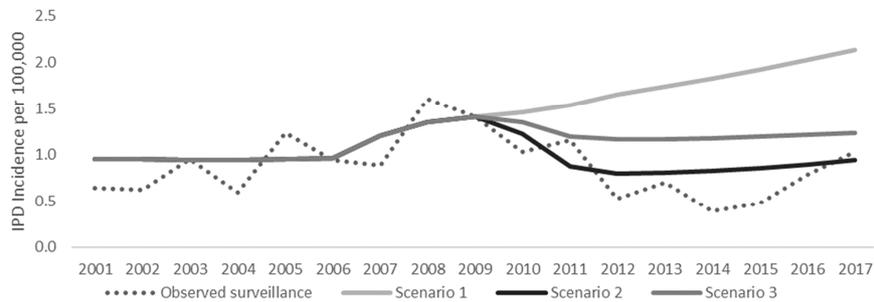


Figure 1. Modeled and Observed Serotype 3 IPD Incidence (Cases per 100000) From 2001 to 2017: 0-<2 Years.

IPD = invasive pneumococcal disease; PCV13 = 13-valent pneumococcal conjugate vaccine. Scenario 1 assumes serotype 3 is a nonvaccine serotype. Scenario 2 derives the PCV13 vaccine effectiveness against serotype 3 IPD from Sings *et al.*, 2018 [10]. Scenario 3 assumes the PCV13 vaccine effectiveness against both serotype 3 IPD and carriage is unknown, and the model calibrates these values.

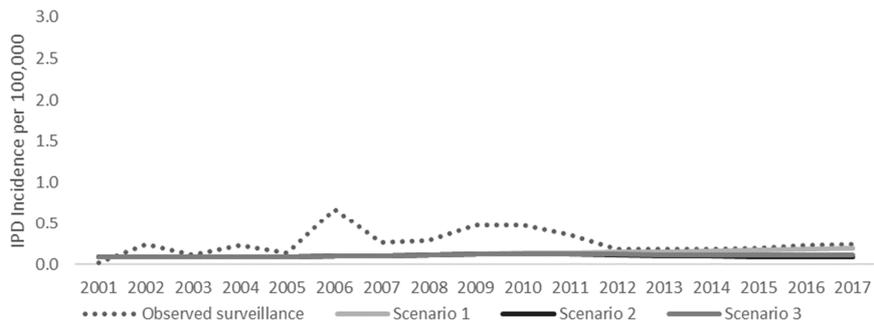


Figure 2. Modeled and Observed Serotype 3 IPD Incidence (Cases per 100000) From 2001 to 2017: 2-<5 Years.

IPD = invasive pneumococcal disease; PCV13 = 13-valent pneumococcal conjugate vaccine. Scenario 1 assumes serotype 3 is a nonvaccine serotype. Scenario 2 derives the PCV13 vaccine effectiveness against serotype 3 IPD from Sings *et al.*, 2018 [10]. Scenario 3 assumes the PCV13 vaccine effectiveness against both serotype 3 IPD and carriage is unknown, and the model calibrates these values.

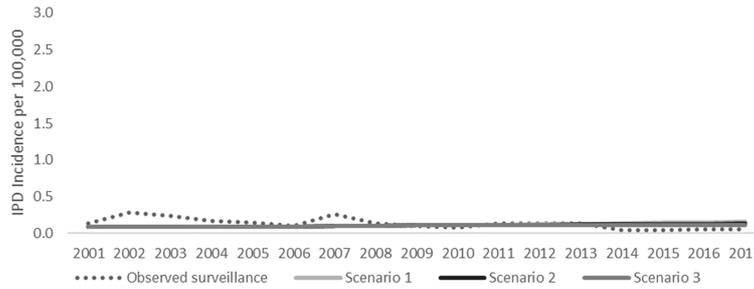


Figure 3. Modeled and Observed Serotype 3 IPD Incidence (Cases per 100000) From 2001 to 2017: 5-<18 Years.

IPD = invasive pneumococcal disease; PCV13 = 13-valent pneumococcal conjugate vaccine.

Scenario 1 assumes serotype 3 is a nonvaccine serotype. Scenario 2 derives the PCV13 vaccine effectiveness against serotype 3 IPD from Sings et al., 2018 [10]. Scenario 3 assumes the PCV13 vaccine effectiveness against both serotype 3 IPD and carriage is unknown, and the model calibrates these values.

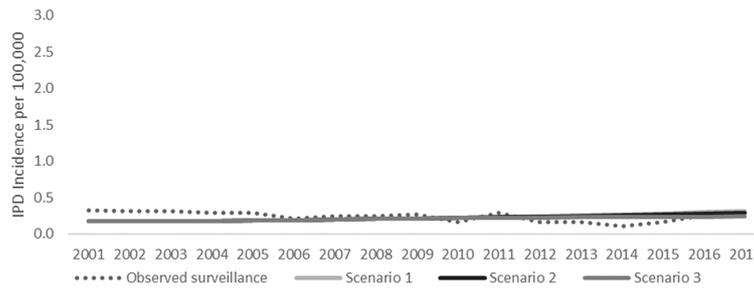


Figure 4. Modeled and Observed Serotype 3 IPD Incidence (Cases per 100000) From 2001 to 2017: 18-<35 Years.

IPD = invasive pneumococcal disease; PCV13 = 13-valent pneumococcal conjugate vaccine.

Scenario 1 assumes serotype 3 is a nonvaccine serotype. Scenario 2 derives the PCV13 vaccine effectiveness against serotype 3 IPD from Sings et al., 2018 [10]. Scenario 3 assumes the PCV13 vaccine effectiveness against both serotype 3 IPD and carriage is unknown, and the model calibrates these values.

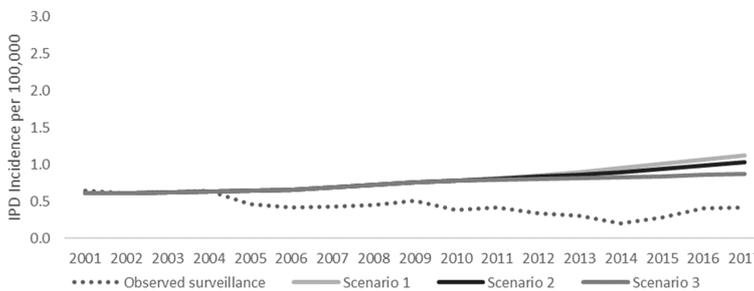


Figure 5. Modeled and Observed Serotype 3 IPD Incidence (Cases per 100000) From 2001 to 2017: 35-<50 Years.

IPD = invasive pneumococcal disease; PCV13 = 13-valent pneumococcal conjugate vaccine.

Scenario 1 assumes serotype 3 is a nonvaccine serotype. Scenario 2 derives the PCV13 vaccine effectiveness against serotype 3 IPD from Sings et al., 2018 [10]. Scenario 3 assumes the PCV13 vaccine effectiveness against both serotype 3 IPD and carriage is unknown, and the model calibrates these values.

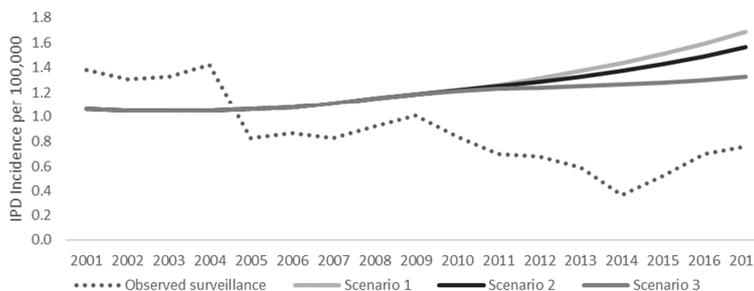


Figure 6. Modeled and Observed Serotype 3 IPD Incidence (Cases per 100000) From 2001 to 2017: 50-<65 Years.

IPD = invasive pneumococcal disease; PCV13 = 13-valent pneumococcal conjugate vaccine.

Scenario 1 assumes serotype 3 is a nonvaccine serotype. Scenario 2 derives the PCV13 vaccine effectiveness against serotype 3 IPD from Sings et al., 2018 [10]. Scenario 3 assumes the PCV13 vaccine effectiveness against both serotype 3 IPD and carriage is unknown, and the model calibrates these values.

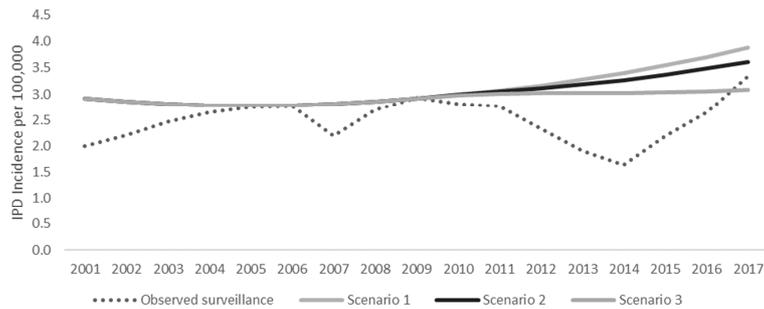


Figure 7. Modeled and Observed Serotype 3 IPD Incidence (Cases per 100000) From 2001 to 2017: ≥ 65 Years.

IPD = invasive pneumococcal disease; PCV13 = 13-valent pneumococcal conjugate vaccine.

Scenario 1 assumes serotype 3 is a nonvaccine serotype. Scenario 2 derives the PCV13 vaccine effectiveness against serotype 3 IPD from Sings *et al.*, 2018 [[10]]. Scenario 3 assumes the PCV13 vaccine effectiveness against both serotype 3 IPD and carriage is unknown, and the model calibrates these values.

Acknowledgements

Financial support: This work was funded by Pfizer Inc., Collegeville, United States.

Conflict of Interest

Dr. Lucas and Mr. Wilson are employees of RTI Health Solutions. Mr. Wasserman, Dr. Sings, Dr. Pugh, Dr. Gessner, and Dr. Farkouh are employees of Pfizer Inc. Dr. Jones is an employee of Pfizer Ltd.

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