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Public health impact and cost-effectiveness of 15-valent pneumococcal conjugate vaccine use among the pediatric population of the United States

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Abstract

Background: Although use of the 13-valent pneumococcal conjugate vaccine (PCV13) among children has reduced incidence of pneumococcal disease, a considerable burden of disease remains. PCV15 is a new vaccine that contains pneumococcal serotypes 22F and 33F in addition to serotypes contained in PCV13. To inform deliberations by the Advisory Committee on Immunization Practices on recommendations for PCV15 use among U.S. children, we estimated the health impact and cost-effectiveness of replacing PCV13 with PCV15 within the routine infant immunization program in the United States. We also assessed the impact and cost-effectiveness of a supplementary PCV15 dose among children aged 2–5 years who have already received a full PCV13 series.

Methods: We estimated the incremental number of pneumococcal disease events and deaths averted, costs per quality adjusted life-year (QALY) gained, and costs per life-year gained under different vaccination strategies using a probabilistic model following a single birth cohort of 3.9 million individuals (based on 2020 U.S. birth cohort). We assumed that vaccine effectiveness (VE) of PCV15 against the two additional serotypes was the same as the VE of PCV13. The cost of PCV15 use among children was informed from costs of PCV15 use among adults and from discussions with the manufacturer.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2023.03.045.

Results: Our base case results found that replacing PCV13 with PCV15 prevented 92,290 additional pneumococcal disease events and 22 associated deaths, while also saving $147 million in costs. A supplementary PCV15 dose among children aged 2–5 years who were fully vaccinated with PCV13 prevented further pneumococcal disease events and associated deaths but at a cost of more than $2.5 million per QALY gained.

Conclusions: A further decrease in pneumococcal disease in conjunction with considerable societal cost savings could be expected from replacing PCV13 with PCV15 within the routine infant immunization program in the United States.

Keywords

PCV15; PCV13; Cost-effectiveness; United States

1. Background

Streptococcus pneumoniae is a major cause of morbidity and mortality in the United States. Manifestations of pneumococcal disease include both invasive disease such as bacteremic pneumonia, septicemia, and meningitis as well as non-invasive disease such as non-bacteremic pneumonia and acute otitis media (AOM).

In 2000, a 7-valent pneumococcal conjugate vaccine (PCV7) was introduced into the routine infant immunization program in the United States as a 3 + 1 schedule (3 primary doses at 2, 4, 6 months of age, followed by a booster dose at 12–15 months of age) [1]. After PCV7 introduction, rates of invasive pneumococcal disease (IPD), pneumonia, and AOM due to PCV7 serotypes declined substantially [2–4]. In 2010, a 13-valent conjugate vaccine (PCV13) covering six additional pneumococcal serotypes replaced PCV7 and was associated with further declines in pneumococcal disease incidence [3,5]. Nevertheless, a considerable burden of pneumococcal disease remains in children and adults. This remaining pneumococcal disease burden appears to be due to a combination of pneumococcal serotypes not contained in PCV13 [6,7] as well as select PCV13 vaccine-type (VT) serotypes. In particular, despite being included as antigens in PCV13, serotypes 3 and 19F have been found to cause the majority of PCV13-VT-type IPD in U.S. children [8] and may be related to reports of reduced effectiveness of PCV13 against these serotypes [9].

In 2021, the United States Food and Drug Administration approved use of a 15-valent pneumococcal conjugate vaccine (PCV15) for adults aged 18 years and older, and in June 2022, use of PCV15 was approved for children aged 6 weeks through 17 years [10]. PCV15 has shown robust immunogenicity against the 13 serotypes shared with PCV13 and has shown statistically significantly higher immunogenicity against two additional pneumococcal serotypes (22F and 33F) compared to PCV13 [11].

To inform the Advisory Committee on Immunization Practices (ACIP) recommendation for PCV15 use among U.S. children, we conducted a study estimating the health impact and cost-effectiveness of using PCV15 instead of PCV13 within the routine infant immunization program in the United States. We also assessed the health impact and cost-effectiveness of a supplementary PCV15 dose among children aged 2–5 years who have already received a full

PCV13 series, similar to a “catch up” recommendation that was made in 2010 when PCV13 replaced PCV7 [12].

2. Methods

2.1. Overview

Similar to a previous cost-effectiveness analysis [13], we developed a probabilistic model to estimate the health impact and cost-effectiveness of replacing PCV13 with PCV15 in a hypothetical cohort of children. We used Monte Carlo simulation in spreadsheet-based software (@Risk 8.2; Palisade Corporation, Newfield, NY) to predict incremental cases of pneumococcal disease events and deaths averted, costs per quality adjusted life-year (QALY) gained, and costs per life-year gained under PCV15 vs. PCV13 schedules.

2.2. Model

We modelled the effects of PCV13 and PCV15 separately on VT IPD, VT pneumococcal pneumonia, and VT pneumococcal AOM. Our model tracked disease incidence for 15 years after the last PCV dose, although costs of sequelae, lost life-years, and quality-adjusted life-years were tracked through life expectancy. The general model structure is shown in Fig. 1. The population of the model represented the 2020 U.S. birth cohort (N = 3,939,295 in year 1) and used life expectancy and background mortality estimates by age from the National Vital Statistics System [14].

Disease burden incidence inputs in the model varied from 0 through 9 years of age and were constant from 9 through 20 years of age. Pneumococcal serotypes were classified into five categories that were not mutually exclusive: PCV13-serotypes (1, 3, 4, 5, 6A, 6B, 6C, 7F, 9 V, 14, 18C, 19A, 19F, 23F), serotype 3 alone, serotype 19F alone, PCV15-unique-serotypes (22F, 33F), and non-vaccine serotypes (NVT, all serotypes not in PCV13 or PCV15). Serotypes 3 and 19F were modeled separately based on reports of reduced PCV13 VE against these serotypes [9]. While serotype 6C is not included in PCV13, it was included within the PCV13-serotypes category due to reported cross protection from serotype 6A [15].

2.3. Parameters: Baseline disease incidence and case-fatality rates

IPD related parameters included incidence per 100,000 people; the proportion of IPD due to specified serotype groups; the proportion of IPD resulting in meningitis; and case fatality rates, all of which were obtained from the Centers for Disease Control and Prevention’s (CDC) Active Bacterial Core surveillance (ABCs) data during 2018–2019 [16]. Estimates of the proportion of individuals experiencing post-IPD meningitis sequelae of long-term disability or deafness, were informed from Olarte et al. [17], and Edmond et al. [18].

All-cause inpatient pneumonia incidence per 100,000 people and case fatality rates were obtained from National (Nationwide) Inpatient Sample (NIS) data during 2018–2019. The NIS dataset is the largest publicly available all-payer inpatient care database in the U.S. [19]. Age-stratified all-cause inpatient pneumonia incidence rates were obtained by identifying all inpatient hospitalizations among children aged < 18 years with a

pneumonia-related *International Classification of Diseases Diagnosis* ICD-10-CM code in any location (Supplementary Material S1). The proportion of all-cause inpatient pneumonia hospitalizations that were pneumococcal pneumonia was informed from CDC's Etiology of Pneumonia in the Community (EPIC) study by Jain et al. [20], and pneumococcal disease subject matter expert input. As the EPIC study reported no etiology in 20–30% of pneumonia hospitalizations, expert input considered the proportion of pneumococcal inpatient pneumonia reported in the study (4%) to be an underestimate, and thus recommended assumption of a higher proportion of 12% for the current analysis. This higher assumption was informed from studies among adults in North America, which found the proportion of pneumococcal pneumonia to range between 9 and 12% [21–24]. Data on serotype distribution of inpatient pneumococcal pneumonia was not available and was assumed to be the same as that for IPD.

All-cause outpatient pneumonia incidence per 100,000 was obtained from Tong et al., which used MarketScan Commercial Claims and Encounters data from 2014 [25]. We assumed no mortality from outpatient pneumonia. Based on pneumococcal disease subject matter expert input, the proportion of all-cause outpatient pneumonia events that were pneumococcal pneumonia was assumed to be half that of pneumococcal pneumonia in the inpatient setting (i.e., 6%). Similar to inpatient pneumonia, the serotype distribution for outpatient pneumonia was assumed to be the same as that for IPD.

All-cause AOM incidence per 100,000 was obtained from another study by Tong, et al., that also used MarketScan data from 2014 [26]. As the study by Tong et al. only reported the incidence of index AOM events, we estimated the incidence of recurrent AOM based on the proportion of recurrent episodes among AOM episodes, by age group, reported by Maron et al. [27]. We assumed no mortality from AOM. The proportion of children with AOM with consequent tympanostomy tube insertion surgery was obtained from Pichichero et al. [28]. As our estimates of all-cause AOM incidence were obtained from administrative data, we assumed that 60% of AOM events among children aged < 2 years and 70% of AOM events among children aged 2–5 years were true AOM diagnoses, of which 95% were bacterial infections; these proportions were informed by subject matter input. Additionally, in a study by Kaur et al., 24% of clinically diagnosed AOM cases were reported to be due to pneumococcus [7], as such, we assumed that 14% and 16% of AOM cases reported in administrative data were pneumococcal AOM events in children aged < 2 years and 2–5 years, respectively (Table 1). The study by Kaur et al. also reported serotype data on pneumococcal AOM cases and was used to inform the serotype distribution of pneumococcal AOM in this analysis.

2.4. Parameters: Vaccination

During 2018–2020, 92.4% of children had received 3 PCV13 doses and 82.3% had received at least 4 PCV13 doses by 24 months of age [29]. We assumed the same coverage rate for both the PCV13 and PCV15 strategies among infants. For the assessment of the supplementary PCV15 dose among children 2 years and older, we assumed a 50% vaccine uptake.

Vaccine effectiveness (VE) of PCV was modelled as a percentage reduction in incidence of IPD, pneumonia, and AOM due to VT serotypes. Estimates of PCV13 VE against IPD due to serotypes 3 and 19F were obtained from Andrew et al. [9] while estimates of VE against IPD due to remaining PCV13 serotypes were obtained from Moore et al. [30]. The VE of PCV13 against inpatient and outpatient VT-pneumococcal pneumonia was estimated by applying the ratio of VE against VT-IPD to VE against VT-non-bacteremic pneumococcal pneumonia observed in the CAPiTA trial (75%:45%) [31] to IPD VE estimates used in this study. The VE of PCV13 against VT-pneumococcal AOM was obtained from a study by Escola et al. [32]. In order to account for lower VE against AOM due to serotypes 3 and 19F, the ratio of VE estimates against IPD by serotype was applied to the VE against VT-AOM estimate. For all disease outcomes, the VE of PCV15 against serotypes 23F and 33F was assumed to be the same as the VE of PCV13 against serotypes other than 3 and 19F.

During the first year of life when children receive up to 3 PCV doses, we estimated that children would have 75.6% of the full VE. This estimate was informed from a study by Whitney et al. [33]. We assumed full protection from PCV in the second year of life once a child had received the complete 3 + 1 schedule [33]. As there are limited data on duration of protection provided my PCVs, we adopted a conservative estimate that VE started waning 5 years after completion of the 3 + 1 schedule, with linear waning to 0% effectiveness over the next 10 years. Since vaccine protection expired 15 years after last PCV dose in our model, the analytic horizon for the model was selected to be 15 years.

Finally, as previous pediatric PCV introductions have been associated with indirect effects resulting in declines in pneumococcal disease due to VT serotypes among those who are unvaccinated [34], we assumed a similar decline in disease due to serotypes 22F and 33F within our cohort following PCV15 introduction. This indirect effect was incorporated into the model by removing 7.8% of serotype 22F and 33F pneumococcal disease each year, consistent with indirect effect estimates used in a previous PCV cost-effectiveness analysis [13].

2.5. Parameters: Cost

Our analysis was performed from the societal perspective, including both medical and nonmedical costs. Medical costs were from MarketScan data [35] while nonmedical costs were informed from Ray et al. [36] and a Morbidity and Mortality Weekly Report [37]. For medical costs, conversions to 2021 dollars were done using the Consumer Price Index for medical care. For nonmedical costs, conversions to 2021 dollars were done using the Consumer Price Index for all items [38]. All outcomes were discounted by 3% annually. The public ($150.83) and private ($226.43) prices of a dose of PCV13 were obtained from CDC's 2021 vaccine price list [39] and were weighted by public (61%) and private (39%) purchase shares from Pfizer's (manufacturer of PCV13) internal sales data for 2021 (obtained through email communication). We assumed a vaccine administration cost of $15.04 [40] and travel/caregiver time cost as $33.30 [41]. At the time of this analysis, PCV15 (manufactured by Merck) did not have a published price for use within the pediatric population. Based on the price of PCV15 use among adults and following discussions

Merck, we assumed the private price for PCV15 was $216.09 and the public price was $150.83.

2.6. Parameters: Utilities

To obtain a composite measure that could combine mortality outcomes with less severe health outcomes, we applied QALY decrements to each episode of disease. QALY decrements were informed from Tang et al. [42] with the exception of tympanostomy tube insertions, which were from Delgleeize et al. [43]. No loss of health was indicated by a decrement of 0, movement from perfect health to death had a decrement of 1, and decrements for non-fatal disease episodes were between 0 and 1. The specific decrements per episode of disease are detailed in Table 3.

2.7. Sensitivity analyses

In the assessment of PCV15 vs. PCV13 among infants, we conducted two univariate sensitivity analyses. First, we assumed that the public price for PCV15 was 5% higher than PCV13 at $158.37. Second, we assumed no indirect effects of PCV15.

In the assessment of a supplementary PCV15 dose for children aged 2–5 years old, we also carried out two univariate sensitivity analyses. First, we assessed impact when assuming a higher proportion of pneumococcal AOM (19% among children aged < 2 years and 23% among children ≥ 2 years). This was done because the high burden of AOM was considered a key driver for PCV cost-effectiveness and a recent study demonstrated a higher proportion of pneumococcal AOM when using multiplex polymerase chain reaction instead of traditional culture methods to confirm diagnosis [44]. In the second univariate analysis, we assumed a higher proportion of sequalae after meningitis (20% among children aged < 5 years and 30% among children aged ≥ 5 years) because base case assumptions of sequalae following meningitis were informed from limited data.

Finally, we conducted multivariate sensitivity analysis using ranges for model inputs indicated in Tables 1–3. We randomly drew VE parameters from Beta-pert distributions over the indicated ranges. Disease and cost parameters were drawn from a normal distribution using the indicated 95% confidence interval around the sample mean. The 95% confidence interval around the sample mean for costs was calculated by bootstrapping the mean from a sample size equal to the total observations for AOM (n = 1,715,182), tympanostomy tube placement (n = 321), meningitis without IPD (n = 56), and meningitis with IPD (n = 41) over 5,000 repetitions with replacement. We drew QALY parameters from a uniform distribution to reflect the uncertainty surrounding QALY values. Our reported 95% confidence intervals for the main results are from 50,000 model iterations. The impact of the most important inputs identified during the multivariate sensitivity analysis were examined using a tornado diagram. A tornado diagram illustrates the impact range of inputs in the model on the cost per QALY gained and is sorted with the most influential (e.g., widest ranging) impacts at the top. The edges of each bar indicate the cost per QALY gained when the given input was drawn from the 10th or 90th percentile of possible values for that input.

3. Results

Under our base case assumptions, use of PCV15 vs. PCV13 was estimated to prevent an additional 183 non-meningitis IPD cases, 38 meningitis IPD cases, 6 cases of meningitis-related sequalae, and 13 deaths due to IPD during 17 years of a single birth cohort. Use of PCV15 vs. PCV13 prevented an additional 1,039 inpatient pneumococcal pneumonia cases, 9 inpatient pneumococcal pneumonia deaths, and 2,837 outpatient cases of pneumococcal pneumonia. Finally, use of PCV15 vs. PCV13 prevented an additional 80,588 outpatient AOM pneumococcal cases and 7,599 tympanostomy tube insertions per birth cohort (Table 4).

We estimated that use of PCV15 vs. PCV13 for children will result in a total of $147 million in savings in our base case scenario comprising $69 million in medical cost savings, $50 million in vaccine cost savings, and $27 million in additional savings for nonmedical costs per birth cohort. Because health outcomes were improved and costs were reduced, the use of PCV15 vs. PCV13 was considered cost saving. Univariate sensitivity analyses assuming a 5% higher public cost of PCV15 or removing indirect effects from PCV15 were also found to be cost saving (Table 4).

Introducing a supplementary PCV15 dose to children aged 2–5 years who are fully vaccinated with PCV13 prevented additional pneumococcal disease episodes and deaths, ranging from 29,143 pneumococcal disease episodes and 4 deaths prevented if a catch-up campaign was done at age 2 years to 539 pneumococcal disease episodes and 3 deaths prevented if a catch-up campaign was done at age 5 years. All scenarios resulted in additional costs ranging from $409–$421 million. As a result, the cost per QALY gained from this intervention was more than $2.5 million (Table 5). Univariate sensitivity analyses assuming a higher proportion of pneumococcal AOM resulted in additional costs ranging from $406–$416 million and the cost per QALY gained from this intervention was more than $2.5 million. Likewise, assuming a higher proportion of sequalae after meningitis resulted in additional costs ranging from $407–$419 million and the cost per QALY gained from this intervention was more than $2.6 million.

We explored the importance of different inputs via the multivariate sensitivity analysis described above and examined results in a tornado diagram (Supplementary material S2). All values in the tornado diagram were less than zero indicating that all model simulations including inputs drawn from the 10th or 90th percentile of values were still cost saving. The two most influential inputs in our model, in decreasing order, were the QALY decrements for AOM and the QALY decrements for tympanostomy tube insertions.

4. Discussion

We used a probabilistic model to estimate the health impact and cost-effectiveness of replacing PCV13 with PCV15 within the routine infant immunization program in the United States. Our base case results found PCV15 vs. PCV13 prevented additional IPD, pneumococcal pneumonia, and pneumococcal AOM cases, as well as deaths from pneumococcal disease, while also saving costs. Secondary analyses evaluating the impact

and cost-effectiveness of a supplementary PCV15 dose among children aged 2–5 years who are fully vaccinated with PCV13 found that such a scenario would prevent additional pneumococcal disease and deaths but at a cost of more than $2.5 million per QALY gained.

In the assessment of PCV15 vs. PCV13 among infants, we considered the pneumococcal disease burden and vaccine effectiveness inputs in our analysis to be conservative, yet we still found considerable cost savings when replacing PCV13 with PCV15. Importantly, as there are no data directly comparing the effectiveness of PCV15 vs. PCV13 against pneumococcal disease outcomes, we adopted a conservative approach for this input where we assumed that the VE of PCV15 against PCV15-serotypes was the same as the VE of PCV13 against PCV13-serotype pneumococcal disease, including the two additional serotypes unique to PCV15. Immunogenicity data have indicated a numerically higher immune response of PCV15 against serotype 3 compared to PCV13 [45]. If such immunogenicity data translates to PCV15 having greater effectiveness against serotype 3-associated pneumococcal disease compared to PCV13, the cost savings and disease prevented would be even greater than in our base case model results.

Our analysis found routine use of PCV15 vs. PCV13 to be cost saving in sensitivity analyses that assumed a 5% higher public cost for PCV15, or assumed no additional indirect effects, and in multivariate sensitivity analyses where all available inputs were varied. In contrast, the supplementary PCV15 dose assessment estimated a substantial cost per QALY gained. Notably, the supplementary PCV15 dose assessment continued to have a substantial cost per QALY gained in sensitivity analysis when assuming a higher proportion of pneumococcal AOM or when assuming a higher proportion of sequalae after meningitis; these assumptions would have theoretically improved the incremental benefit of PCV15 use.

Our analysis relied on numerous assumptions that warrant attention. Firstly, there are limited data on the incidence of pneumococcal pneumonia and pneumococcal AOM among U.S. children, especially by pneumococcal serotype. Consequently, we relied on administrative data to obtain estimates of all-cause pneumonia and all-cause AOM health events and then applied specified proportions to these events to estimate pneumococcal disease burden. Additionally, we assumed the serotype distribution of pneumococcal pneumonia was the same as for IPD, while our serotype distributions for pneumococcal AOM were informed from a small study based in a single location. The proportion of IPD attributable to PCV15 unique serotypes (23F and 33F) was higher than the proportion of pneumococcal AOM attributable to these serotypes (18% vs 8%). Thus, by assuming the same serotype distribution as IPD for pneumococcal pneumonia, we may be overstating the positive effects of PCV15 against this disease outcome. However, there are no data to suggest that serotype distribution of pneumococcal pneumonia would be similar to pneumococcal AOM. Moreover, previous cost-effectiveness studies [13] have used similar serotype distribution assumptions, thus we chose this approach for consistency. Second, there are limited VE estimates of PCV13 against pneumococcal pneumonia in children. As such, we used clinical trial data among adults to extrapolate VE of PCV13 against IPD to obtain these estimates. Finally, our analysis relied on several assumptions regarding the cost of PCV15 for pediatric use, which were less expensive than or comparable to that of PCV13. The cost-effectiveness

of PCV15 will change if the cost of PCV15 is priced much higher than what we assumed in our model.

5. Conclusions

Using a probabilistic model, we showed that replacing PCV13 with PCV15 in the U.S. routine infant immunization program would prevent additional pneumococcal disease and deaths and would likely result in cost savings. Findings from the study helped inform the recent ACIP recommendation for PCV15 use among children aged 6 weeks through 18 years of age in the United States.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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

Data availability

The authors do not have permission to share data.

References

[1]. Preventing pneumococcal disease among infants and young children. Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 2000;49:1–35.

[2]. Pilishvili T, Lexau C, Farley MM, Hadler J, Harrison LH, Bennett NM, et al. Sustained reductions in invasive pneumococcal disease in the era of conjugate vaccine. J Infect Dis 2010;201:32–41. [PubMed: 19947881]

[3]. Hu T, Done N, Petigara T, Mohanty S, Song Y, Liu Q et al. Incidence of acute otitis media in children in the United States before and after the introduction of 7- and 13-valent pneumococcal conjugate vaccines during 1998–2018. BMC Infect Dis 2022;22:294. [PubMed: 35346092]

[4]. Zhou F, Kyaw MH, Shefer A, Winston CA, Nuorti JP. Health Care Utilization for Pneumonia in Young Children after Routine Pneumococcal Conjugate Vaccine Use in the United States. Arch Pediatr Adolesc Med 2007;161:1162–8. [PubMed: 18056561]

[5]. Moore MR, Link-Gelles R, Schaffner W, Lynfield R, Lexau C, Bennett NM, et al. Effect of use of 13-valent pneumococcal conjugate vaccine in children on invasive pneumococcal disease in children and adults in the USA: analysis of multisite, population-based surveillance. Lancet Infect Dis 2015;15:301–9. [PubMed: 25656600]

[6]. Balsells E, Guillot L, Nair H, Kyaw MH. Serotype distribution of Streptococcus pneumoniae causing invasive disease in children in the post-PCV era: A systematic review and meta-analysis. PLoS One 2017;12:e0177113. [PubMed: 28486544]

[7]. Kaur R, Fuji N, Pichichero ME. Dynamic changes in otopathogens colonizing the nasopharynx and causing acute otitis media in children after 13-valent (PCV13) pneumococcal conjugate vaccination during 2015–2019. Eur J Clin Microbiol Infect Dis 2022;41:37–44. [PubMed: 34432166]

[8]. Gierke R. Current Epidemiology of Pneumococcal Disease and Pneumococcal Vaccine Coverage among Children, United States. Presentation to Advisory Committee on Immunization Practices,. Available at: https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2022-02-23-24/02-Pneumococcal-Gierke-508.pdf. Accessed 08/15/2022.

[9]. Andrews NJ, Waight PA, Burbidge P, Pearce E, Roalfe L, Zancolli M, et al. Serotype-specific effectiveness and correlates of protection for the 13-valent pneumococcal conjugate vaccine: a postlicensure indirect cohort study. Lancet Infect Dis 2014;14:839–46. [PubMed: 25042756]

[10]. U.S. Food and Drug Administration. VAXNEUVANCE (Pneumococcal 15-valent Conjugate Vaccine). Available at: https://www.fda.gov/vaccines-blood-biologics/vaccines/vaxneuvance. Accessed 07/01/2022.

[11]. Merck Research Laboratories MC. Pneumococcal Polysaccharide 15-Valent Conjugate Vaccine (V114, VAXNEUVANCE). Presentation to Advisory Committee on Immunization Practices. Available at: https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2022-02-23-24/03-Pneumococcal-Bannietis-508.pdf. Accessed 07/19/2022.

[12]. Nuorti JP, Whitney CG. Prevention of pneumococcal disease among infants and children - use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine - recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWRRecomm Rep 2010;59:1–18.

[13]. Stoecker C, Hampton LM, Link-Gelles R, Messonnier ML, Zhou F, Moore MR. Cost-effectiveness of using 2 vs 3 primary doses of 13-valent pneumococcal conjugate vaccine. Pediatrics 2013;132:e324–32. [PubMed: 23821695]

[14]. Centers for Disease Control and Prevention. National Center for Health Statistics. National Vital Statistics Reports: United States Life Tables, 2017. Available at: https://www.cdc.gov/nchs/data/nvsr/nvsr68/nvsr68_07-508.pdf. Accessed 09/10/2021.

[15]. Cooper D, Yu X, Sidhu M, Nahm MH, Fernsten P, Jansen KU. The 13-valent pneumococcal conjugate vaccine (PCV13) elicits cross-functional opsonophagocytic killing responses in humans to Streptococcus pneumoniae serotypes 6C and 7A. Vaccine 2011;29:7207–11. [PubMed: 21689707]

[16]. Centers for Disease Control and Prevention. Active Bacterial Core Surveillance (ABCs). Available at: https://www.cdc.gov/abcs/index.html. Accessed 05/17/2022.

[17]. Olarte L, Barson WJ, Barson RM, Lin PL, Romero JR, TQ Tan et al. . Impact of the 13-valent pneumococcal conjugate vaccine on pneumococcal meningitis in US children. Clin Infect Dis 2015;61:767–75. [PubMed: 25972022]

[18]. Edmond K, Clark A, Korczak VS, Sanderson C, Griffiths UK, Rudan I. Global and regional risk of disabling sequelae from bacterial meningitis: a systematic review and meta-analysis. Lancet Infect Dis 2010;10:317–28. [PubMed: 20417414]

[19]. Overview of the National (Nationwide) Inpatient Sample (NIS). Available at: https://www.hcup-us.ahrq.gov/nisoverview.jsp. Accessed 06/08/2022.

[20]. Jain S, Williams DJ, Arnold SR, Ampofo K, Bramley AM, Reed C, et al. . Community-acquired pneumonia requiring hospitalization among U.S. children. N Engl J Med 2015;372:835–45. [PubMed: 25714161]

[21]. World Health Organization. Strategic Advisory Group of Experts on Immunization 5-7 October 2020. Available at: https://terrance.who.int/mediacentre/data/sage/SAGE_eYB_October_2020.pdf?ua=1. Accessed 12/7/2022.

[22]. Isturiz RE, Ramirez J, Self WH, Grijalva CG, Counselman FL, Volturo G, et al. . Pneumococcal epidemiology among us adults hospitalized for community-acquired pneumonia. Vaccine 2019;37:3352–61. [PubMed: 31072732]

[23]. RL Sherwin, Gray S, Alexander R, McGovern PC, Graepel J, Pride MW, et al. . Distribution of 13-valent pneumococcal conjugate vaccine Streptococcus pneumoniae serotypes in US adults aged ≥50 years with community-acquired pneumonia. J Infect Dis 2013;208:1813–20. [PubMed: 24092845]

[24]. Wunderink RG, Self WH, Anderson EJ, Balk R, Fakhran S, Courtney DM, et al. . Pneumococcal Community-Acquired Pneumonia Detected by Serotype-Specific Urinary Antigen Detection Assays. Clin Infect Dis 2018;66:1504–10. [PubMed: 29342250]

[25]. Tong S, Amand C, Kieffer A, Kyaw MH. Trends in healthcare utilization and costs associated with pneumonia in the United States during 2008–2014. BMC Health Serv Res 2018;18:715. [PubMed: 30217156]

[26]. Tong S, Amand C, Kieffer A, Kyaw MH. Trends in healthcare utilization and costs associated with acute otitis media in the United States during 2008–2014. BMC Health Serv Res 2018;18:318. [PubMed: 29720156]

[27]. Marom T, Tshori S, Shefer G, Pitaro J. Pneumococcal conjugated vaccines decreased acute otitis media burden: a population-based study in Israel. J Pediatr 2021;235:233. [PubMed: 33894263]

[28]. Pichichero ME, Casey JR, Almudevar A. Reducing the frequency of acute otitis media by individualized care. Pediatr Infect Dis J 2013;32:473–8. [PubMed: 23340550]

[29]. Hill HA, Yankey D, Elam-Evans LD, Singleton JA, Sterrett N. Vaccination Coverage by Age 24 Months Among Children Born in 2017 and 2018 - National Immunization Survey-Child, United States, 2018–2020. MMWRMorb Mortal Wkly Rep 2021;70:1435–40.

[30]. Moore MR, Link-Gelles R, Schaffner W, Lynfield R, Holtzman C, Harrison LH, et al. . Effectiveness of 13-valent pneumococcal conjugate vaccine for prevention of invasive pneumococcal disease in children in the USA: a matched case-control study. LancetRespir Med 2016;4:399–406.

[31]. Bonten MJ, Huijts SM, Bolkenbaas M, Webber C, Patterson S, Gault S, et al. . Polysaccharide conjugate vaccine against pneumococcal pneumonia in adults. N Engl J Med 2015;372:1114–25. [PubMed: 25785969]

[32]. Eskola J, Kilpi T, Palmu A, Jokinen J, Haapakoski J, Herva E, et al. . Efficacy of a pneumococcal conjugate vaccine against acute otitis media. N Engl J Med 2001;344:403–9. [PubMed: 11172176]

[33]. Whitney CG, Pilishvili T, Farley MM, Schaffner W, Craig AS, Lynfield R, et al. . Effectiveness of seven-valent pneumococcal conjugate vaccine against invasive pneumococcal disease: a matched case-control study. Lancet 2006;368:1495–502. [PubMed: 17071283]

[34]. Shiri T, Datta S, Madan J, Tsertsvadze A, Royle P, Keeling MJ, et al. . Indirect effects of childhood pneumococcal conjugate vaccination on invasive pneumococcal disease: a systematic review and meta-analysis. Lancet Glob Health 2017;5:e51–9. [PubMed: 27955789]

[35]. MarketScan Research Databases. Available at: https://www.ibm.com/downloads/cas/OWZWJ0QO. Accessed 08/10/2022.

[36]. Ray GT, Whitney CG, Fireman BH, Ciuryla V, Black SB. Cost-effectiveness of pneumococcal conjugate vaccine: evidence from the first 5 years of use in the United States incorporating herd effects. Pediatr Infect Dis J 2006;25:494–501. [PubMed: 16732146]

[37]. Centers for Disease Control and Prevention. Economic costs associated with mental retardation, cerebral palsy, hearing loss, and vision impairment-United States, 2003. MMWR Morb Mortal Wkly Rep. 2004;53:57–9. [PubMed: 14749614]

[38]. U.S. Bureau of Labor Statistics. Consumer Price Index–all urban consumers. Available at: https://data.bls.gov/cgi-bin/surveymost. Accessed 06/13/2022.

[39]. Centers for Disease Control and Prevention. CDC Vaccine Price List. Available at: https://www.cdc.gov/vaccines/programs/vfc/awardees/vaccine-management/price-list/index.html. Accessed 06/13/2022.

[40]. Glazner JE, Beaty B, Berman S. Cost of vaccine administration among pediatric practices. Pediatrics 2009;124(Suppl 5):S492–8. [PubMed: 19948580]

[41]. Maciosek MV, Edwards NM, Coffield AB, Flottemesch TJ, Nelson WW, Goodman MJ, et al. . Priorities among effective clinical preventive services: methods. Am J Prev Med 2006;31:90–6. [PubMed: 16777547]

[42]. Tang Z, Matanock A,Jeon S, Leidner AJ. A review of health-related quality of life associated with pneumococcal disease: pooled estimates by age and type of disease. J Public Health (Oxf) 2022;44:e234–40.

[43]. Delgleize E, Leeuwenkamp O, Theodorou E, Van de Velde N. Cost-effectiveness analysis of routine pneumococcal vaccination in the UK: a comparison of the PHiD-CV vaccine and the PCV-13 vaccine using a Markov model. BMJ Open 2016;6:e010776.

[44]. Kaur R, Adlowitz DG, Casey JR, Zeng M, Pichichero ME. Simultaneous assay for four bacterial species including Alloiococcus otitidis using multiplex-PCR in children with culture negative acute otitis media. Pediatr Infect Dis J 2010;29:741–5. [PubMed: 20335823]

[45]. Platt HL, Greenberg D, Tapiero B, Clifford RA, Klein NP, Hurley DC, et al. . A Phase II Trial of Safety, Tolerability and Immunogenicity of V114, a 15-Valent Pneumococcal Conjugate Vaccine, Compared With 13-Valent Pneumococcal Conjugate Vaccine in Healthy Infants. Pediatr Infect Dis J 2020;39:763–70. [PubMed: 32639460]

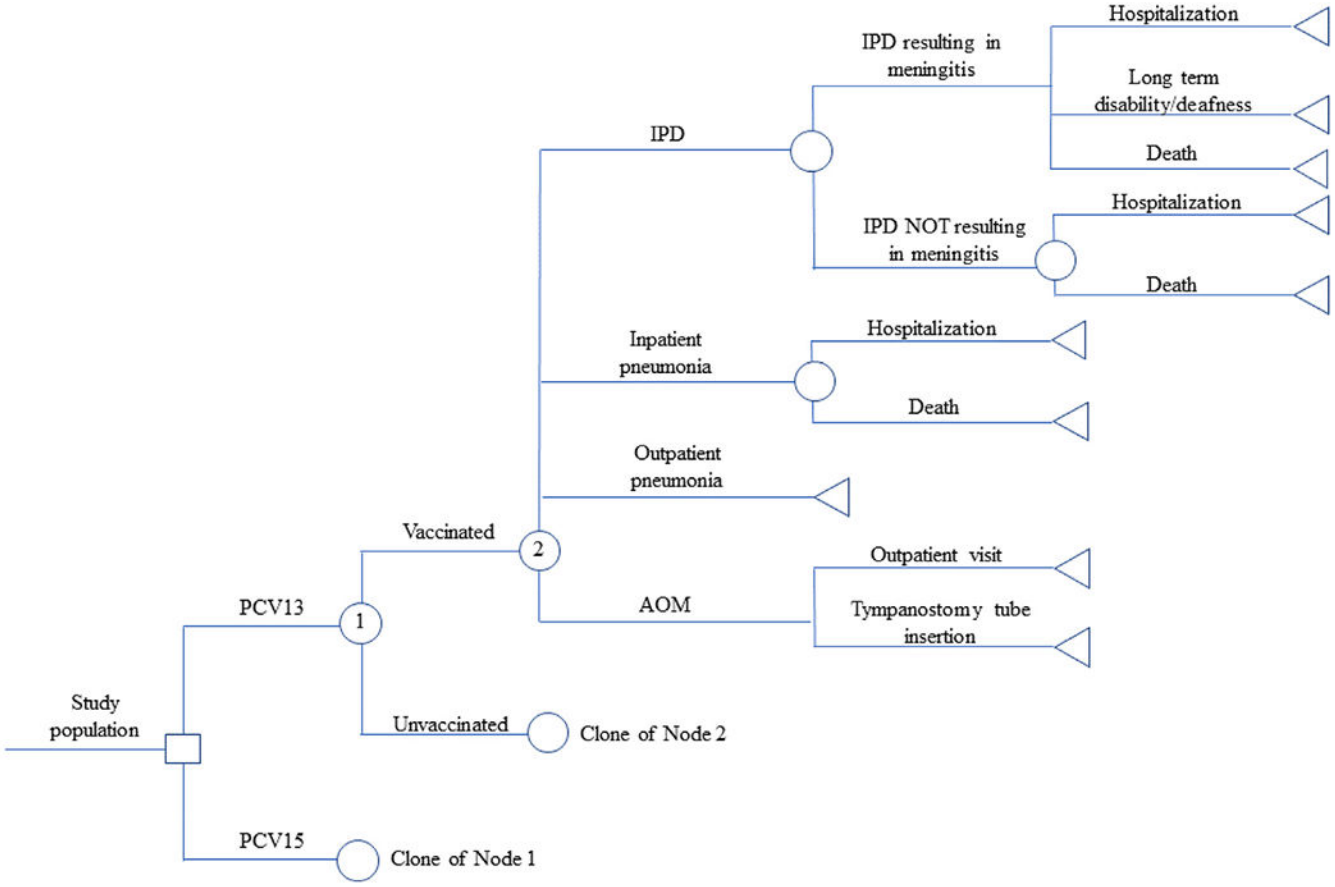

Fig. 1.

Model structure, Abbreviations: PCV13; 13-valent pneumococcal conjugate vaccine, PCV15; 15-valent pneumococcal conjugate vaccine, AOM; acute otitis media, IPD; invasive pneumococcal disease. For the assessment of a supplementary PCV15 dose among children who had received a full PCV13 series, the comparator arm was represented by no additional vaccination.

Table 1

Pneumococcal Disease Incidence by Indicated Age Used in the Cost-Effectiveness Model.

	Age in years									
	0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9–20**
All-cause AOM burden [a]	64,770 (58293–71247)	62,218 (55996–68440)	38,974 (35077–42871)	38,974 (35077–42871)	38,974 (35077–42871)					
% of AOM with tympanostomy tube insertion [b]	12% (6–15)	12% (6–15)	8% (4–15)	8% (4–15)	8% (4–15)					
% Pneumococcal AOM [c]	14%	14%	16%	16%	16%					
% PCV13 (+6C-3-19F)	3%	3%	3%	3%	3%					
% Serotype 3	3%	3%	3%	3%	3%					
% Serotype 19F	3%	3%	3%	3%	3%					
% PCV15 unique (22F, 33F)	8%	8%	8%	8%	8%					
% NVT	83%	83%	83%	83%	83%					
All-cause outpatient pneumonia [d]	1409	2841	2705	1405	1144	1069	907	1121	563	504
% Pneumococcal outpatient pneumonia [f]	6% (1–10)	6% (1–10)	6% (1–10)	6% (1–10)	6% (1–10)	6% (1–10)	6% (1–10)	6% (1–10)	6% (1–10)	6% (1–10)
All-cause inpatient pneumonia [e]	684 (635–733)	485 (448–521)	453 (410–497)	235 (214–257)	192 (175–208)	160 (146–173)	136 (124–147)	167 (147–188)	84 (76–92)	75 (69–81)
% All-cause inpatient pneumonia resulting in fatality	1.3% (1.02–1.59)	0.53% (0.37–0.70)	0.40% (0.23–0.58)	0.42% (0.21–0.64)	0.61% (0.32–0.91)	0.39% (0.15–0.63)	0.32% (0.06–0.59)	0.78% (0.35–1.20)	0.51% (0.13–0.89)	1.72% (1.42–2.01)
% Pneumococcal inpatient pneumonia [f]	12% (2–20)	12% (2–20)	12% (2–20)	12% (2–20)	12% (2–20)	12% (2–20)	12% (2–20)	12% (2–20)	12% (2–20)	12% (2–20)
IPD incidence [g]	14 (11–16)	10 (7–12)	5 (3–6)	5 (3–6)	3 (2–4)	5 (3–6)	3 (1–4)	2 (1–3)	1 (0–2)	1 (1–1)
% of IPD resulting in meningitis	16%	16%	16%	16%	16%	20%	20%	20%	20%	20%
% Meningitis resulting in long-term disability [h]	7% (4–11)	7% (4–11)	7% (4–11)	7% (4–11)	7% (4–11)	11% (8–18)	11% (8–18)	11% (8–18)	11% (8–18)	11% (8–18)
% Meningitis resulting in deafness	9% (7–13)	9% (7–13)	9% (7–13)	9% (7–13)	9% (7–13)	14% (11–22)	14% (11–22)	14% (11–22)	14% (11–22)	14% (11–22)
% Meningitis hospitalized	100%	100%	100%	100%	100%	97%	97%	97%	97%	97%
% Meningitis resulting in fatality	10%	10%	10%	10%	10%	0%	0%	0%	0%	0%

	Age in years									
	0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9–20**
% IPD NOT resulting in meningitis	84%	84%	84%	84%	84%	84%	84%	84%	84%	84%
% Non-meningitis that are hospitalized	82%	82%	82%	82%	82%	83%	83%	83%	83%	83%
% Non-meningitis cases resulting in fatality	4%	4%	4%	4%	4%	4%	4%	4%	4%	4%
% PCV13 (+6C-3-19F)	4%	1%	10%	10%	10%	10%	11%	11%	11%	11%
% Serotype 3	12%	4%	11%	11%	11%	11%	14%	14%	14%	14%
% Serotype 19F	7%	7%	6%	6%	6%	6%	9%	9%	9%	9%
% PCV15 (22F, 33F)	17%	21%	15%	15%	15%	15%	14%	14%	14%	14%
% NVT	60%	67%	59%	59%	59%	59%	52%	52%	52%	52%

Abbreviations: PCV13: 13-valent pneumococcal conjugate vaccine, PCV15: 15-valent pneumococcal conjugate vaccine, AOM: acute otitis media, IPD: invasive pneumococcal disease, NVT: non-vaccine type.

[a] All-cause AOM rates were estimated from index AOM visits from Tong et al. 2018 plus the proportion of recurrent AOM visits from Maron et al. 2021.

[b] Proportion of children with AOM with consequent tympanostomy tube insertion were from Pichichero et al. 2013.

[c] The proportion of all-cause AOM that were pneumococcal AOM, and serotype distributions were estimated by expert input and from Kaur et al. 2022.

[d] All-cause outpatient pneumonia rates were from Tong et al. 2018.

[e] All-cause inpatient pneumonia rates were estimated from 2018 to 2019 averages in the National (Nationwide) Inpatient Sample (NIS).

[f] The proportion of inpatient pneumonia hospitalizations that were pneumococcal pneumonia was informed from Jain et al. 2015 and expert input. The proportion of outpatient pneumonia visits that were pneumococcal pneumonia was assumed to be half that of pneumococcal pneumonia in the inpatient setting.

[g] IPD incidence, syndrome distribution, case fatality rates, and serotype distribution were estimated from 2018 to 2019 averages from the Centers for Disease Control and Prevention's Active Bacterial Core surveillance.

[h] The proportion of children experiencing post-IPD meningitis sequelae, in the form of long-term disability or deafness, were obtained from Olarte et al. 2015 and Edmond et al. 2010.

Table 2

Vaccine Effectiveness (VE) (%) Assumptions by Vaccine, Outcome, and Age Group.

Disease outcomes by vaccine and serotype	<12 months (range) [e]	≥12 months (range)
PCV13		
IPD, PCV13 serotypes (+6C, −3, −19F) [a]	65 (58–70)	86 (76–92)
IPD, serotype 3 [a]	20 (0–52)	26 (0–68)
IPD, serotype 19F [a]	57 (28–68)	75 (37–90)
Pneumonia, PCV13 serotypes (+6C, −3, −19F) [b]	39 (35–42)	52 (46–55)
Pneumonia, serotype 3 [b]	12 (0–31)	16 (0–41)
Pneumonia, serotype 19F [b]	34 (17–41)	45 (22–54)
AOM, PCV13 serotypes (+6C, −3, −19F) [c]	41 (31–48)	54 (41–64)
AOM, serotype 3 [c]	12 (9–15)	16 (12–19)
AOM, serotype 19F [c]	36 (27–42)	47 (36–56)
PCV15 [d]		
IPD, PCV15 unique serotypes (22F, 33F)	65 (58–70)	86 (76–92)
Pneumonia, PCV15 unique serotypes (22F, 33F)	39 (35–42)	52 (46–55)
AOM, PCV15 unique serotypes (22F, 33F)	41 (31–48)	54 (41–64)

Abbreviations: PCV13: 13-valent pneumococcal conjugate vaccine, PCV15: 15-valent pneumococcal conjugate vaccine, AOM: acute otitis media, IPD: invasive pneumococcal disease.

[a]VE of PCV13 against IPD due to serotype 3 and serotype 19F were obtained from Andrews et al. 2014 while VE against IPD due to remaining PCV13 serotypes were obtained from Moore et al. 2016.

[b]VE of PCV13 against pneumonia were estimated by applying to ratio of VE against IPD to VE against pneumonia (75%: 45%) observed in the CAPiTA trial to VE against IPD estimates used in this study.

[c]VE of PCV13 against AOM was obtained from Escola et al. 2001. To account for lower VE against AOM due to serotype 3 and 19F, the ratio of VE estimates against IPD by serotype were applied to the VE against vaccine-type AOM estimate.

[d]The VE of PCV15 against serotypes 23F and 33F was assumed to be the same as the VE of PCV13 against serotypes other than 3 and 19F.

[e]During the first year of life when children receive up to 3 PCV doses, we estimated that children would have 75.6% of the full VE, informed from a study by Whitney et al. 2006 in which VE was 0% for the first 2 months, 73% for the next 2 months after dose 1, 96% for the next two months after dose 2, and 95% after dose 3 for the last 6 months.

Table 3

Cost and Quality-Adjusted Life-Year (QALY) Inputs Used in the Cost-Effectiveness Model.

Disease outcome	Medical cost, $ [a]	Nonmedical cost, $	QALY Decrement, $ [d]
AOM	80 (64–95)	228[b]	0.0016 (0–0.1461)
Tympanostomy tube insertion	3449 (2759–4138)	228[b]	0.0016 (0–0.1461)
Outpatient Pneumonia	335 (268–402)	420[b]	0.0004 (0.0001–0.0329)
Inpatient Pneumonia	10,475 (8380–12570)	562[b]	0.0105 (0.0001–0.0155)
Non-meningitis IPD	18,339 (14671–22007)	562[b]	0.0016 (0.0013–0.007)
Meningitis IPD	24,544 (19635–29453)	2947[b]	0.0165 (0.0001–0.0166)
Disability	246,563 (197250–295875)	1,273,447[c]	0.2456 (0.16–0.49)
Deafness	46,195 (36956–55434)	525,465[c]	0.2137 (0.07–0.72)

Abbreviations: PCV13: 13-valent pneumococcal conjugate vaccine, PCV15: 15-valent pneumococcal conjugate vaccine, AOM: acute otitis media, IPD: invasive pneumococcal disease.

[a] Medical costs were from MarketScan data inflated to 2021 US dollars using the Consumer Price Index for medical care.

[b] From Ray et al. 2006.

[c] From Centers for Disease Control and Prevention, Morbidity and Mortality Weekly Report 2004.

[d] QALY decrements are from Tang et al. 2021 with the exception of tympanostomy tube insertions which are from Delgleeize et al. 2016.

Table 4

Net Effects and Cost-effectiveness Results of Replacing PCV13 with PCV15 in a U.S. Birth Cohort Model.

Model results	Base Case (2.5% – 97.5%)	5% higher public cost for PCV15	No additional indirect effect
Cases prevented			
AOM	80,588 (98951–62070)	80,588	72,562
Tympanostomy tube insertion	7599 (10873–5081)	7599	6957
Outpatient Pneumonia	2837 (5153–62)	2837	1995
Inpatient Pneumonia	1039 (1873–23)	1039	783
Deaths due to Pneumonia	9 (16–0)	9	6
IPD Non-Meningitis	183 (202–150)	183	164
IPD Meningitis	38 (41–31)	38	33
Deafness	3 (4–1)	3	2
Disability	3 (5–2)	3	3
Deaths due to IPD	13 (15–11)	13	12
QALYs gained	759 (658–7155)	759	622
Life-years gained	664 (377–880)	664	532
Savings [Additional costs], $ millions			
Total Cost	147 (175–115)	89	133
Medical Costs	69 (94–40)	69	58
Nonmedical Costs	27 (33–22)	27	24
Vaccine Costs	50 (51–50)	[7]	50
Cost-effectiveness Ratios ($)			
Cost/QALY	Cost-Saving	Cost-Saving	Cost-Saving
Cost/Life-year	Cost-Saving	Cost-Saving	Cost-Saving

Abbreviations: PCV13: 13-valent pneumococcal conjugate vaccine, PCV15: 15-valent pneumococcal conjugate vaccine, AOM: acute otitis media, IPD: invasive pneumococcal disease, QALY: Quality-adjusted life-year.

All outcomes, QALYs gained, life-years gained, and costs were discounted. All savings [costs] are reported in $US2021.

Table 5

Net Effects and Cost-effectiveness Results of a Supplemental PCV15 dose, among Children Aged 2 years and Older who have Already Received a Full PCV13 series, by Specific Age Cohort.

Model results	Age 2 years	Age 3 years	Age 4 years	Age 5 years
Cases prevented				
AOM	26,110	18,349	9681	0
Tympanostomy tube insertion	2089	1468	774	0
Outpatient Pneumonia	677	503	438	391
Inpatient Pneumonia	218	158	135	117
Deaths due to Pneumonia	1	1	1	1
IPD Non-Meningitis	39	34	27	24
IPD Meningitis	8	7	6	6
Deafness	1	1	0	0
Disability	1	1	1	1
Deaths due to IPD	3	2	2	2
QALYs gained	158	129	101	77
Life-years gained	120	104	90	82
Savings [Additional costs], $ millions				
Total Cost	[409]	[413]	[417]	[421]
Medical Costs	17	13	9	4
Nonmedical Costs	8	6	4	1
Vaccine Costs	[434]	[432]	[429]	[426]
Cost-effectiveness Ratios ($)				
Cost/QALY	2,595,642	3,198,991	4,136,984	5,490,205
Cost/Life-year	3,402,561	3,952,575	4,622,636	5,111,949

Abbreviations: PCV13: 13-valent pneumococcal conjugate vaccine, PCV15: 15-valent pneumococcal conjugate vaccine, AOM: acute otitis media, IPD: invasive pneumococcal disease, QALY: Quality-adjusted life-year. All outcomes, QALYs gained, life-years gained, and costs were discounted. All savings [costs] are reported in $US2021.