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Should older adult pneumococcal vaccination recommendations change due to decreased vaccination in children during the pandemic? A cost-effectiveness analysis

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ABSTRACT

Background: The COVID-19 pandemic is causing declines in childhood immunization rates. We examined potential COVID-19-related changes in pediatric 13-valent pneumococcal conjugate vaccine (PCV13) use, subsequent impact on childhood and adult pneumococcal disease rates, and how those changes might affect the favorability of PCV13 use in non-immunocompromised adults aged ≥65 years.
Methods: A Markov model estimated pediatric disease resulting from decreased PCV13 use in children aged <5 years; absolute decreases from 10 to 50% for 1–2 years duration were examined, assuming no catch-up vaccination and that decreased vaccination led to proportionate increases in PCV13 serotype pneumococcal disease in children and seniors. Integrating pediatric model output into a second Markov model examining 65-year-olds, we estimated the cost effectiveness of older adult pneumococcal vaccination strategies while accounting for potential epidemiologic changes from decreased pediatric vaccination.
Results: One year of 10–50% absolute decreases in PCV13 use in <5-year-olds increased pneumococcal disease by an estimated 4–19% in seniors; 2 years of decreased use increased senior rates by 8–38%. In seniors, a >53% increase in pneumococcal disease was required to favor PCV13 use in non-immunocompromised seniors at a $200,000 per quality-adjusted life-year gained threshold, which corresponded to absolute decreases in pediatric PCV13 vaccination of >50% over a 2-year period. In sensitivity analyses, senior PCV13 vaccination was unfavorable if absolute decreases in pediatric PCV13 receipt were within plausible ranges, despite model assumptions favoring PCV13 use in seniors.
Conclusion: COVID-19-related decreases in pediatric PCV13 use would need to be both substantial and prolonged to make heightened PCV13 use in non-immunocompromised seniors economically favorable.

1. Introduction

The coronavirus disease (COVID-19) pandemic necessitated dramatic changes to medical practice. In-person medical visits were limited to those deemed essential, with mitigation practices that reduced in-office visits. Reduced onsite well-child visits resulted in significant declines in childhood immunizations; vaccinations in children <24 months of age decreased 45%-70%.[1] Decreased vaccination in children could result in increased vaccine-preventable illness in children and adults, particularly if children drive the spread of illness, as in influenza and other illnesses.[2] For example, decreases in adult pneumococcal disease over recent years were largely due to indirect (herd immunity) effects from childhood 13-valent pneumococcal conjugate vaccine (PCV13) vaccination, which began in 2010 in the US.[3,4] Thus, decreased PCV13 usage in children could increase pneumococcal illness in both children and adults. This potential for increased adult pneumococcal illness due to decreased pediatric PCV13 vaccination could prompt consideration of increased PCV13 use in US seniors.

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Prior to the pandemic, in 2019, CDC changed its PCV13 recommendations for seniors from routine use for all persons aged ≥65 years to routine use only in immunocompromised seniors, with an option for use in other seniors after a clinical shared decision making discussion.[3] This change was prompted by: no discernable direct population-level effects from senior PCV13 use; decreases in PCV13 serotype disease in seniors due to indirect effects from childhood vaccination; and cost-effectiveness analyses showing that PCV13-containing vaccination strategies cost > $560,000 per quality adjusted life year (QALY) gained in seniors, [5–7] an inefficient use of health care resources.[8]

Pediatric visits and vaccinations have rebounded somewhat as the pandemic continues.[1,9] However, it is not clear how changes in the course of the coronavirus pandemic will affect future pediatric medical visits and consequently pediatric PCV13 use, or whether catch-up vaccination in children will occur. In addition, it is not known how the population epidemiology of PCV13 serotypes will be affected by changes in pediatric PCV13 vaccine use or by COVID-19 itself, and whether such changes might influence the effectiveness and cost-effectiveness of PCV13 vaccination in older adults. To examine these issues, we used decision analysis techniques to estimate effects of decreased childhood pneumococcal vaccination due to COVID-19 and the resulting changes in pneumococcal disease epidemiology on the cost effectiveness of pneumococcal vaccination strategies in adults aged ≥65 years.

2. Methods

The analysis used a 3-step procedure. First, a Markov model estimated changes in pediatric pneumococcal disease epidemiology resulting from decreased PCV13 use in children aged <5 years, with variation of the likelihood and duration of decreased pediatric vaccination. Next, using historic data on pneumococcal epidemiologic changes in children and adults occurring after pneumococcal conjugate vaccination with PCV7 began in 2000, we estimated changes in pneumococcal serotype epidemiology in seniors resulting from decreased pediatric vaccination. Finally, these changes were entered into a second (previously described[5,6]) Markov model that estimated the cost effectiveness and public health effects of competing pneumococcal vaccination strategies while accounting for those epidemiologic changes.

2.1. Step 1. Estimating epidemiologic changes due to reduced pediatric PCV13 vaccination (pediatric model)

The pediatric Markov model estimated yearly epidemiologic changes for children aged <5 years assuming proportionate increases in PCV13 serotype illness with decreases in PCV13 vaccination. Annual pediatric invasive pneumococcal disease (IPD) rates decreased by approximately 90 cases per 100,000 between 1999 and 2017, due to use of the 7-valent pneumococcal conjugate vaccine in children starting in 2000, switching to PCV13 use in 2010. [10,11] If the 0–1 year-old age cohort had a 10% absolute decrease in PCV13 vaccination without catch-up vaccination (decreasing from the current 91.6% to 81.6%, or a relative decrease of 11%), we assumed that their PCV13 serotype IPD rate would increase 11%, or by about 10 cases per 100,000 (i.e., 11% of 90 per 100,000). Thus, if pediatric PCV13 vaccination decreased by 10% for 1 year with no catch-up vaccination, then it was assumed that PCV13 serotype IPD rates increased by about 2 per 100,000 for the entire <5 year-old age cohort (10 cases divided by 5 one-year age cohorts) over the 5-year time horizon of the model; 2 years of 10% absolute reduction in vaccine use increased rates by about 4/100,000. Absolute decreases in PCV13 use ranging from 10 to 50% and of 1–2 years duration were modeled. We assumed that older children who already received PCV13 would not be affected by these changes in disease rates, but relaxed this assumption in sensitivity analyses. The assumption of no catch-up vaccination increased the resulting PCV13 serotype illness rates in both children and adults, thus favoring strategies using PCV13 in seniors. Pediatric model parameters are shown in Table 1.

2.2. Step 2. Estimating changes in senior pneumococcal illness epidemiology

We compared total and PCV13 serotype IPD rates before the introduction of routine childhood pneumococcal conjugate vaccination to contemporary rates (1998–9 to 2017), finding that for every decrease of 1 case per 100,000 children <5 years there was a corresponding decrease of 0.4–0.5 cases per 100,000 adults aged ≥65 years.[10,11] In the base case analysis, we used a 1:0.5 pediatric to senior ratio to calculate increases in total and PCV13 serotype IPD rates due to decreased receipt of pediatric PCV13. To allow for uncertainty in estimates, we also examined a 1:1 pediatric to senior ratio for increases in IPD rates in separate analyses, which would make PCV13 use in seniors more favorable in the analysis.

2.3. Step 3. Estimating cost-effectiveness of senior PCV13 vaccination (senior model)

We used a previously described Markov model (Supplemental Fig. 1) comparing two pneumococcal vaccination strategies in adults ≥65 years with no vaccination: the current CDC recommendations (23-valent pneumococcal polysaccharide vaccine [PPSV23] for all, PCV13 added for the immunocompromised and potentially for the non-immunocompromised after shared clinical decision making), and an alternative strategy (PPSV23 for all and PCV13 added only for the immunocompromised). The relative likelihoods of both IPD and nonbacteremic pneumococcal pneumonia (NBP) were assumed to increase identically. For example, with the previously described 10% absolute decrease in pediatric PCV13 vaccination that increased PCV13 serotype IPD rates by about 2 cases per 100,000 children, senior IPD rates would increase by about 1 case per 100,000 when a 1:0.5 pediatric to senior ratio was assumed. All-cause IPD rates in seniors, which were 26/100,000 in 2017, would increase to about 27/100,000, a relative increase of 3.8%. This 3.8% relative increase was then also applied to NBP case rates in seniors.

Parameter values used in the senior model are shown in Supplemental Table 1. Assumptions used in the senior model were, as previously described:[5,6] hospitalized NBP was estimated as 3 times CDC Active Bacterial Core Surveillance (ABCs) bacteremic pneumonia rates, PCV13 serotype relative likelihood was assumed to be the same in IPD and NBP, outpatient NBP was estimated based on all-cause pneumonia rates, vaccine effectiveness was

Table 1
Pediatric model input parameter values and ranges.

Parameter	Value	Range	Source
Probabilities			
Receiving vaccination	91.6%	90.8%–92.4%	[15]
Baseline yearly IPD risk			
PCV13 serotypes	2.0 per 100,000	1.0–3.0	CDC ABCs
All serotypes	7.0 per 100,000	6.0–8.0	CDC ABCs
Absolute decrease in PCV13 use	10%	10%−50%	Model estimates
Duration of decreased vaccination	1 years	1–2 years	Model estimates

estimated based on clinical trial data and Delphi panel estimates, NBP case-fatality was assumed to be 50% (varied from 0 to 100%) of that seen with IPD, and PPSV23 was assumed ineffective in preventing NBP. In addition, it was assumed that pneumococcal disease rates would not change as a result of COVID-19, despite evidence of decreased IPD rates during the pandemic in the UK [12] and the US (personal communication, Lee H. Harrison, MD) during the pandemic. This assumption would again favor senior PCV13 use in the analysis. Further detail on pneumococcal vaccination effectiveness and pneumococcal disease risk values used in the senior model is shown in Supplemental Tables 2 and 3.

The Markov model for seniors estimated the cost-effectiveness of vaccination strategies as cost per quality adjusted life year (QALY) gained. We used $200,000/QALY gained as our cost-effectiveness benchmark. In the US, there is no accepted cost-effectiveness criterion; however, thresholds from $50,000 to $200,000 QALY gained are recommended as suitable benchmarks. [8] Use of a $200,000/QALY gained threshold, rather than lower recommended values, also favors senior PCV13 vaccination in the analysis.

3. Results

Absolute decreases in PCV13 receipt of 10%–50% over 1 year's duration in children <5 years old increased their PCV13 serotype IPD rates by an estimated 2.0–9.8 cases per 100,000, increasing senior IPD rates by a relative 3.8%-18.9% when a 1:0.5 pediatric to senior IPD case ratio was applied (Table 2). When decreases in pediatric vaccination were assumed to persist for two years, pediatric IPD rates increased by 3.9–19.7 cases per 100,000, increasing senior IPD rates by a relative 7.6%-37.8%.

Results from the Markov model examining senior adult pneumococcal vaccination strategies are shown in Fig. 1, depicting incremental cost-effectiveness ratios for strategies when increases in pneumococcal disease rates (i.e., both IPD and NBP) occur. Using a threshold of $200,000 per QALY gained, decreases in pediatric vaccination would have to result in a >53% increase in pneumococcal disease rates in seniors for current CDC pneumococcal vaccination recommendations to be favored compared to the alternative strategy. Increased disease rates of this magnitude correspond to absolute decreases in pediatric PCV13 vaccination of >50% over a 2 year period using a 1:0.5 IPD case ratio (Table 2). When considering longer durations of decreased pediatric PCV13 use, current senior pneumococcal vaccination recommendations were favored if pediatric PCV13 use decreased by: >40% over 3 years, >30% over 4 years, or >20% over 5 years. If it is assumed that all ages <5 years old are equally prone to decreased PCV13 use (instead of only the <1 year olds), then this scenario corresponds to results for 5 years of decreased use among <1 year olds, thus >20% decreases in all 1-year cohorts were similarly needed to favor PCV13 use in seniors. If a 1:1 pediatric to senior PCV13 serotype ratio is used, absolute decreases in pediatric PCV13 use would need to be >50% for one year or >30% for two years to favor senior PCV13 vaccination.

The alternative vaccination strategy that eliminates PCV13 use for all seniors but the immunocompromised was favored at a $200,000/QALY gained threshold when the relative increase in senior pneumococcal disease rates is >10%, which corresponds to decreases in PCV13 use among children of >30% in one year and >20% over two years.

A sensitivity analysis examining potential decreased adult pneumococcal vaccination due to the pandemic found minimal changes in the cost-effectiveness of adult pneumococcal vaccination strategies. Proportionate decreases in costs offset decreased effectiveness associated with decreased adult vaccination rates.

4. Discussion

This analysis found that decreases in pediatric PCV13 use, which could increase pneumococcal disease incidence in both children and seniors, would need to be substantial and prolonged to influence the cost-effectiveness of the current pneumococcal vaccination recommendations for adults ≥65 years old. The cost-effectiveness of an alternative strategy that reserves PCV13 solely for the immunocompromised aged ≥65 years was economically reasonable at more plausible pandemic-related decreases in childhood PCV13 use. Our prior analyses[5,6] demonstrated that, in US seniors, this alternative strategy was economically more favorable than current pneumococcal vaccination recommendations.

Although pediatric vaccination rates have improved since their nadir in the early months of the pandemic,[1,9] the magnitude and duration of decreased pediatric vaccination that will occur is unclear. A surge in COVID-19 occurred during the winter of 2020–2021 and has abated in the US at present (May 2021), but potential effects on pediatric vaccination rates are unclear. To account for this uncertainty, we examined multiple potential vaccination decreases over 1 or 2 years' duration, while consistently biasing the analysis toward greater PCV13 disease rates in children (by assuming no catch-up vaccination after missed doses in children), resulting in greater pneumococcal illness rates in seniors. These assumption-related increases in PCV13 rates should make PCV13 use in seniors more economically favorable than it would be without those assumptions. Despite these assumptions, the incremental cost-effectiveness ratio of when PCV13 is used in non-immunocompromised seniors remained high. Additional

Table 2
Analysis results: increases in pneumococcal disease rates resulting from decreased pneumococcal vaccination in children.

Duration of decreased PCV13 use	Absolute decrease in PCV13 use	Increase in childhood IPD (cases per 100,000)	Relative increase in senior pneumococcal illness rates	
			Base case (1:0.5 ratio)*	Alternative case (1:1 ratio)*
1 year	10%	2.0	3.8%	7.6%
	20%	3.9	7.6%	15.1%
	30%	5.9	11.3%	22.7%
	40%	7.9	15.1%	30.2%
	50%	9.8	18.9%	37.8%
2 years	10%	3.9	7.6%	15.1%
	20%	7.9	15.1%	30.2%
	30%	11.8	22.7%	45.3%
	40%	15.7	30.2%	60.5%
	50%	19.7	37.8%	75.6%

PCV13 = 13-valent pneumococcal conjugate vaccine, IPD = invasive pneumococcal disease.
* Ratio of increases in pediatric to senior IPD cases resulting from decreased pediatric PCV13 vaccination.

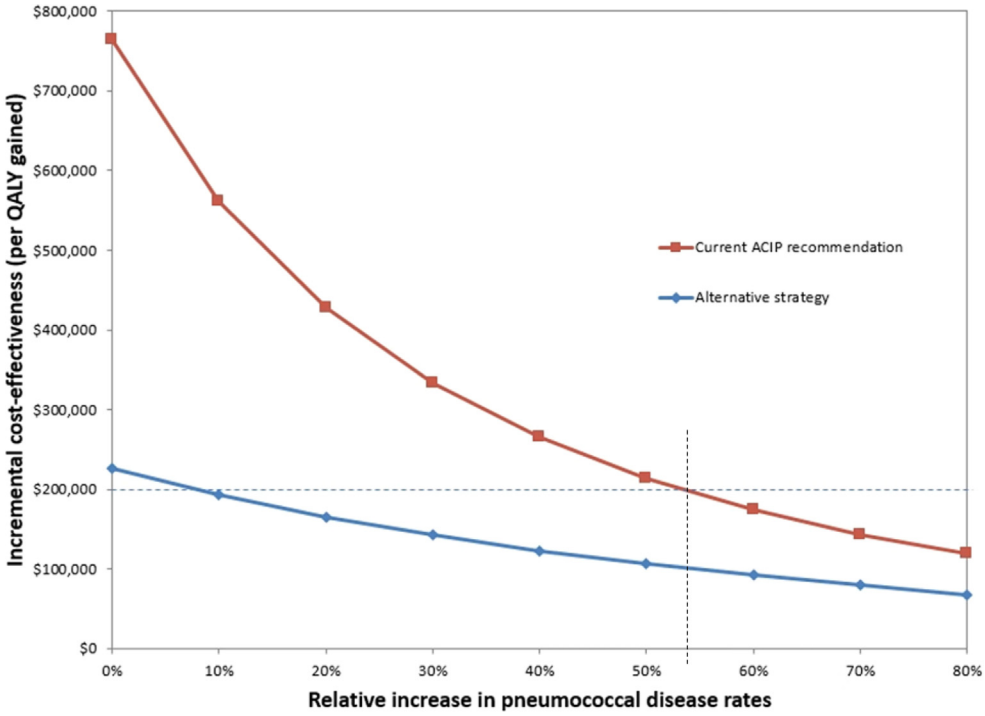

Fig. 1. One-way sensitivity analysis varying the relative increase in pneumococcal disease rates (combining both invasive pneumococcal disease and nonbacteremic pneumonia) in US seniors resulting from decreased pneumococcal vaccination in children. The dotted horizontal line depicts the $200,000 per quality adjusted life year (QALY) threshold and the vertical dashed line depicts the relative increase in pneumococcal disease where the current recommendation curve crosses that threshold. Curves depict the current CDC recommendation for pneumococcal vaccination in seniors (the 23-valent pneumococcal polysaccharide vaccine [PPSV23] for all, with the 13-valent pneumococcal conjugate vaccine [PCV13] added for the immunocompromised and potentially for the non-immunocompromised after shared clinical decision making) and an alternative strategy (PPSV23 for all, adding PCV13 only for the immunocompromised).

biases toward greater PCV13 use in seniors, i.e., a higher pediatric to senior ratio of increased IPD cases and no IPD rate decreases due to the pandemic (unlike the observed decreases),[12] would make current senior pneumococcal vaccination recommendations less unfavorable in the analysis, but decreased pediatric PCV13 use would still need to be large and of extended duration to make PCV13 use in non-immunocompromised seniors economically favorable.

4.1. Strengths and limitations

This study builds upon a previously published Markov decision analysis that demonstrated the cost-effectiveness of the current CDC pneumococcal vaccination recommendations for U.S. seniors.[5,6] Data from definitive sources, such as the CDC ABCs, on 2020 pneumococcal disease rates are not yet available. In this absence, modeling can help inform public health officials of the risks of pneumococcal resurgence and consider strategies that might mitigate those risks. The results of this analysis suggest that CDC recommendations that currently do not advocate routine PCV13 use in non-immunocompromised seniors will not need to be modified based on plausible projections of COVID-19-related decreases in pediatric PCV13 vaccination.

Our analysis has limitations. Projections of pneumococcal epidemiology in children and senior adults resulting from decreased PCV13 use in children were based on changes that occurred when pneumococcal conjugate vaccines were introduced and assume proportionately similar increases in PCV13 serotypes when vaccination decreases. It is not clear that this will be the case. When pediatric PCV7, then PCV13, were introduced, rapid changes in vaccine serotypes in all ages occurred due to decreased carriage of those serotypes. It is not clear how rapidly those serotypes would reappear with decreased pediatric PCV13 use. In our analyses, we attempted to account for this uncertainty by consistently assuming greater increases in pneumococcal illness rates in children and seniors that would result from decreased pediatric vaccination than might occur in a more conservative analysis. Despite these assumptions, such as no catch-up vaccination in children and greater increases in senior pneumococcal disease due to childhood vaccination indirect effects, plausible decreases in pediatric PCV13 use resulting from the pandemic likely will not make heightened PCV13 use in non-immunocompromised seniors more economically reasonable. We also assume that COVID-19 infection will not substantially increase pneumococcal disease rates in seniors. If the presence of COVID-19 on its own increases pneumococcal illness or if more recent US national data suggests increasing pneumococcal disease rates, then our findings will be less robust; decreased IPD rates observed thus far in the pandemic suggest that this will not be the case. Another limitation is our assumption that PPSV23 is not effective in preventing nonbacteremic pneumococcal pneumonia, which is a point of controversy.[13,14] However, if PPSV23 does prevent nonbacteremic pneumococcal pneumonia, the case against heightened PCV13 use in non-immunocompromised seniors is strengthened.[5,6] Finally, other factors could have contributed to decreased adult pneumococcal disease rates over time, such as decreased cigarette smoking or increased adult PPSV23 use. If so, our analysis overestimates the effects of changes in pediatric vaccination on adult disease.

5. Conclusions

The public heath impact of the COVID-19 pandemic has reached well beyond the direct effects of viral infection, treatment and recovery. Interruptions to medical care, including missed well-child visits and vaccines and the indirect protection they confer, have potential implications outside of those whose care is directly

affected by the pandemic. However, disruption of childhood pneumococcal vaccination is unlikely to require reconsideration of PCV13 recommendations in non-immunocompromised seniors.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dr. Zimmerman has no current conflicts of interest but within 3 years had research grants from Sanofi Pasteur on unrelated topics. Dr. Nowalk has an active research grant from Merck & Co. on an unrelated topic, and had research grants within 3 years from Pfizer and Sanofi Pasteur on unrelated topics that are no longer active. Dr. Schaffner is a member of a data safety monitoring board (DSMB) for Pfizer, former member of a DSMB for Merck, and has served as a consultant to Roche Diagnostics. Dr. Harrison has served as a consultant to GSK, Merck, Pfizer, and Sanofi Pasteur. Other authors have no competing interests to disclose.

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Conflicts of interest. Dr. Zimmerman has no current conflicts of interest but within 3 years had research grants from Sanofi Pasteur on unrelated topics. Dr. Nowalk has an active research grant from Merck & Co. on an unrelated topic, and had research grants within 3 years from Pfizer and Sanofi Pasteur on unrelated topics that are no longer active. Dr. Schaffner is a member of a data safety monitoring board (DSMB) for Pfizer, former member of a DSMB for Merck, and has served as a consultant to Roche Diagnostics. Dr. Harrison has served as a consultant to GSK, Merck, Pfizer, and Sanofi Pasteur. Other authors have no competing interests to disclose.

Author contributions: Drs. Smith, Zimmerman, and Nowalk conceived and designed the study, Dr. Smith and Ms. Wateska programmed and calibrated the model and interpreted its results, assisted by Drs. Zimmerman, Nowalk, Lin, Harrison, and Schaffner. Ms. Wateska and Drs. Smith, Zimmerman, and Nowalk prepared the manuscript, with critical revisions by Drs. Harrison, Lin, and Schaffner.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2021.06.037.

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