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Impact of pneumococcal conjugate vaccines on hospitalizations for pneumonia in the United States

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Abstract

Introduction: Pneumonia is one of the leading causes of morbidity and mortality among children and older adults. Pneumococcal conjugate vaccines (PCVs) were introduced into the US routine infant vaccination schedule leading to substantial reductions of invasive pneumococcal diseases (IPD). PCVs introduction also led to reductions in all-cause pneumonia among US children, though the indirect impact of PCVs on pneumonia in adults is difficult to quantify, especially due to the recent US recommendation for direct PCV use in older adults.

Areas covered: We described the existing evidence for both the direct and indirect impact of PCVs on pneumonia among children and adults in the US since PCV introduction.

Expert opinion: The introduction of PCVs into the US routine infant vaccination schedule led to important reductions in the burden of IPD and non-invasive pneumonia among vaccinated and unvaccinated subjects. The impact of direct vaccination of older adults in the US since 2014, though difficult to quantify, is currently being evaluated. As pneumonia remains one of the leading causes of morbidity and mortality in the US, future evaluations of the direct and indirect effects of current and expanded valency PCVs in the US population are needed.

Keywords

pneumococcal conjugate vaccines; pneumonia; pneumococcal disease; *Streptococcus pneumoniae*; routine infant vaccination

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1.0 INTRODUCTION

1.1 Burden of pneumonia

Pneumonia is one of the leading causes of death among children and older adults.[1–5] Though young children are at a high risk of morbidity and mortality from pneumonia, the incidence of pneumonia and pneumonia-related mortality are highest among individuals 65 years of age and those with comorbidities.[4,6–8] The economic burden of pneumonia is substantial as well, with an estimated average cost for a hospitalization for pneumonia of \$11,000 in the US, with higher costs among those with chronic and immunocompromising conditions.[9–12] Across the world, over 10 billion dollars are attributable to pneumonia-related healthcare annually.[13] The disease and economic burdens of pneumonia are expected to grow as the global population continues to age.[14]

1.2 *Streptococcus pneumoniae* and pneumonia

Although multiple pathogens are recognized causes of pneumonia, it is difficult to ascertain the precise etiology of pneumonia in individual patients. *Streptococcus pneumoniae* is considered a leading bacterial cause of pneumonia yet determining its exact contribution to the burden of pneumonia is challenging.[1,15,16] Most pneumococcal pneumonias are non-invasive (e.g. the blood cultures, if performed, are negative) and difficult to identify with routine respiratory cultures due in part to the difficulty of obtaining high-quality respiratory specimens.[17]

1.3 The 23-valent pneumococcal polysaccharide vaccine (PPSV23): coverage and effectiveness among older US adults

The 23-valent pneumococcal polysaccharide vaccine (PPSV23) has been recommended for protection against invasive pneumococcal disease (IPD) and bacteremic pneumonia among older adults and subjects with high-risk conditions for several decades.[18] Although there is evidence from randomized and observational studies that PPSV23 can prevent IPD, several meta-analysis of randomized controlled trials have reported little or weak evidence supporting PPSV23 efficacy in preventing non-bacteremic pneumonia.[18–22] Though PPSV23 has been considered a cost-effective intervention for preventing IPD among immunocompetent individuals,[23] there are concerns regarding the decreasing immunogenicity of PPSV23 with age, its decreased efficacy among high-risk and at risk patients, the waning protection of PPSV23 against IPD over time, and the inability of PPSV23 for preventing pneumococcal nasopharyngeal colonization.[18,24,25]

In the US, before the PCV13 recommendation for use among those with immunocompromising conditions in 2013 and for all adults 65 years or older in 2014, around 60% of older adults reported having ever received a “pneumonia shot,” with similar coverage reported in more recent years since PCV13 introduction.[26–29] Using reimbursement data from the Centers for Medicare and Medicaid Services that focused specifically on claims for at least one dose of PPSV23 since 1999 in the Medicare population, the documented coverage was around 40% from 2009 to 2013 prior to PCV13 introduction among older adults.[30] The percentage of Medicare beneficiaries with at least one dose of PPSV23 since 1999 remained around 40% through 2017 even as the percentage

with claims for at least one dose of PCV13 increased from 0.9% in 2013 to 40.0% in 2016–2017. Overall, 59.3% of beneficiaries enrolled in 2016–2017 had 1 claim for any pneumococcal vaccine (PPSV23 or PCV13).[30]

1.4 PCVs introduction in the United States infant vaccination schedule and the impact on invasive pneumococcal disease

In 2000, the first pneumococcal conjugate vaccine (PCV) was licensed and recommended for use among young children in the US according to a 3+1 schedule (dose at 2, 4, 6 and a booster at 12–15 months). The 7-valent pneumococcal conjugate vaccine (PCV7) covered the seven most commonly detected serotypes (4, 6B, 9V, 14, 19F, 18C, and 23F) among children with IPD prior to 2000.[31] In addition to preventing IPD, PCV7 reduced the risk of nasopharyngeal carriage of vaccine serotypes among vaccinated children and thus targeted a known reservoir of pneumococcus in the community, enabling indirect protection of unvaccinated subjects.[32]

Vaccination coverage with PCV7 among infants increased rapidly after introduction.[33,34] Substantial declines in laboratory-confirmed IPD were documented among young children following PCV7 introduction, and concurrent declines were also observed among unvaccinated children and adults, indicating indirect protection derived from PCV7 vaccination.[35] Although the incidence rates of overall IPD remained consistently and substantially lower than historical rates before PCV7 introduction, surveillance in the decade after PCV7 introduction revealed increases in residual disease caused by serotypes not covered by PCV7, a phenomenon known as serotype replacement disease.[36] In particular, during the PCV7 years, serotype 19A became a commonly recognized cause of residual IPD.

In 2010, the 13-valent pneumococcal conjugate vaccine (PCV13) replaced PCV7 in the infant vaccination schedule to expand the serotype coverage (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 19A, 19F, 18C, and 23F) and to address the serotype replacement phenomenon. The switch from PCV7 to PCV13 was seamless and vaccination coverage remained >90% for 3 doses and around 80% for 4 doses.[33] Active laboratory-based surveillance systems documented further reductions in the incidence of IPD after the switch to PCV13.[35] As seen with PCV7, indirect protection of unvaccinated groups against IPD was demonstrated as well.[35]

Since the initial observed reductions after PCV13 introduction, the residual burden of IPD in the US has remained stable and substantially lower than prior to PCV13 introduction among both children and adults.[35] Among children <5 years in the US, the annual rate of IPD was 9 per 100,000 in 2016 (compared to 22 per 100,000 in 2009 prior to PCV13 introduction). The corresponding annual rates of IPD due to PCV13-serotypes were 2 and 13 per 100,000 for 2016 and 2009, respectively [35] Among adults 19–64 years of age, reductions in IPD and PCV13-serotype IPD were also demonstrated, when annual rates observed in 2016 (8 per 100,000 and 2 per 100,000, respectively) were compared to 2009 (12 per 100,000 and 6 per 100,000, respectively).[35] Furthermore, among older adults ≥65 years, all IPD and PCV13-serotype IPD remained significantly lower in 2016 (24 per 100,000 and 6 per 100,000, respectively) compared to pre-PCV13 introduction in 2009 (39 per 100,000 and 17 per 100,000, respectively).[35] This is in contrast to some reports from other countries

where reductions of IPD rates observed in all age groups are being eroded or negated by increases in non-PCV serotype disease, resulting in rates that are only minimally lower or not different after PCV introduction compared to the pre-PCV era.[37–39]

The underlying reasons for these differences among some countries are unclear, though there are known differences in vaccination schedules during the main period of comparison (e.g., US: 4 doses at 2, 4, 6, and 12 months, UK: 3 doses at 2, 4 and 12 months; Australia: 3 doses at 2, 4 and 6 months without a booster dose), catch-up recommendations (e.g., US: 1 dose for children 24–59 months with incomplete PCV13 vaccination, UK: 1 dose for children 12–24 months; Australia: 1 dose for children 12–59 months with incomplete PCV13 vaccination) and the timing and speed of vaccine introduction.[40] In addition, the underlying distribution of circulating serotypes before vaccine introduction could have contributed to these observed differences. Unlike the post-PCV7 years, in which serotype 19A emerged as a leading replacement serotype, no single dominant non-vaccine serotype has been consistently identified in the post PCV13 years.[35,41,42]

2.0 PCVs EFFICACY AGAINST PNEUMONIA AMONG ADULTS

Evidence of the benefit of PCVs on IPD, pneumococcal pneumonia and all-cause pneumonia among children is well documented in the pre-licensure clinical trials that led to the introduction of PCVs into the US infant vaccination schedule. Systematic reviews of clinical trials for PCVs have found that PCV vaccination was associated with reductions in the incidence of IPD, all-cause radiographically-confirmed pneumonia and clinically-diagnosed pneumonia among children.[43–47] [50–54] Although indirect protection derived from vaccination of infants has been well documented, whether direct vaccination of adults with PCVs would independently reduce the risk of pneumonia among adults was unclear. When evaluated among older adults, PCV7 and PCV13 vaccination produced a non-inferior or greater immunological response compared with the already licensed PPSV23. However, to approve the licensure of the new PCV13 for use in older adults, the US Food and Drug Administration required a demonstration of clinical efficacy against IPD and pneumococcal pneumonia in a randomized controlled clinical trial.

2.1 The CAPiTA trial

The CAPiTA trial, a large randomized, double-blind placebo-controlled trial enrolled nearly 85,000 individuals 65 years of age in the Netherlands from 2008 through 2010, with follow-up through 2013. CAPiTA was conducted to evaluate the efficacy of PCV13 on preventing vaccine-type IPD and noninvasive vaccine-type pneumococcal pneumonia among older adults.[48] For the trial, investigators identified pneumococcal infections using traditional diagnostics plus a novel serotype-specific urinary antigen detection assay to identify non-bacteremic pneumonia caused by serotypes included in PCV13.[48] In this study conducted by the University Medical Center Utrecht and Pfizer, the efficacy of PCV13 in the prevention of vaccine-type IPD and non-invasive pneumococcal pneumonia was demonstrated among older adults. However, the study did not demonstrate PCV13 efficacy for prevention of pneumonia from any cause, a secondary endpoint.[48] The trial reported a 45.6% (95% CI 21.8 – 62.5) vaccine efficacy in the prevention of first vaccine-type

community-acquired pneumonia in the per-protocol analysis, and a 37.7% (95% CI 14.3 – 55.1) efficacy against the same outcome in the modified intention-to-treat analysis. Similarly, the vaccine had a significant efficacy against vaccine-type IPD [VE: 75.0% (95% CI: 41.4% to 90.8%)] and against nonbacteremic vaccine type pneumonia [VE: 45.0% (95% CI: 14.2% to 65.3%)]. Efficacy against the first pneumococcal pneumonia with any pneumococcal strain was 30.6% (95% CI: 9.8% to 46.7%) in the per-protocol analysis and 22.4% (95% CI 2.3 – 38.5) in the modified intent-to-treat analysis. However, when the secondary endpoint of community-acquired pneumonia of any cause (pneumococcal and nonpneumococcal) was evaluated as the outcome, there was no statistically significant vaccine efficacy [VE: 5.1% (95% CI: –5.1 – 14.2%)]. [48]

There are several considerations for the interpretation of the CAPiTA trial findings. Importantly, the trial was conducted in a setting with an existing, but relatively new, infant pneumococcal conjugate vaccination program (PCV7 was introduced in 2006 and it was replaced by PCV10 in 2011). This is important because the development of indirect protection of adults derived from vaccination of children depends on greatly reducing carriage of vaccine serotypes in both adults and children. This takes time, and in settings with more mature programs, with direct and indirect protection better established, the preventable burden of disease related to vaccine serotypes may be smaller.[41] Additionally, a major consideration is that the design of the per-protocol analysis systematically excluded subjects with immunosuppression at enrollment as well as those who developed immunosuppression during follow-up. Estimated efficacy was lower in the modified intention to treat analysis, and although numbers were small, secondary explorations did not demonstrate protection among patients with immunosuppression. In addition, the study did not demonstrate differences in all-cause mortality between groups.[18,49]

2.2 The 2014 ACIP recommendation for PCV13 use in older adults

Prior to the CAPiTA trial, a systematic review of PCV13 use found that 9 of 10 studies reported PCV13 as a cost-effective intervention in adults, though none of these were based on sufficient data regarding PCV13 efficacy or fully realized indirect protection derived from the infant vaccination programs.[50] In a separate cost-effectiveness study of PCV use among adults that incorporated evidence from the CAPiTA trial, several different scenarios were outlined for the assessment of PCV use in older adults without immunocompromising conditions (adding PCV13 to the existing PPSV23 recommendation for those aged 50 years, 60 years, or 65 years, and a separate strategy of PCV13 replacement for PPSV23 for those aged 65 years or older).[51] The pre-publication findings from this study were presented and discussed at the June and August 2014 ACIP meetings at which the recommendation for PCV13 use among adults aged 65 years or older was approved.[52] The study considered IPD rates of 8.62, 33.71 and 15.06 per 100,000 among adults 50–64 years, high-risk adults 65 years and healthy adults 65 years, respectively; vaccine effectiveness as per the CAPiTA trial (75.0% versus vaccine-type IPD and 45.0% versus vaccine-type non-bacteremic pneumonia); differential vaccine coverage (higher coverage in older age groups) with vaccination coverage levels similar to those attained with PPSV23 (~60%); and different costs per case (lower inpatient costs in older age groups) by age group.[51] Secondary analyses accounted for decreases in PCV13-type IPD and non-bacteremic

pneumonia and increases in non-PCV13 PPSV23 serotypes as well as the possibility for increasing indirect protection derived from the infant vaccination program over time.[51] The most cost-effective strategy identified was to either incorporate PCV13 in sequence with PPSV23 into the vaccination schedule for adults ≥ 65 years (\$62,065 per quality-adjusted life years (QALY); total cost of \$189 million) or to fully replace PPSV23 with PCV13 for adults ≥ 65 years (\$46,396 per QALY; total cost of \$64 million) compared to adding PCV13 at age 50 and 60 (\$333,200 and \$238,227 per QALY, respectively).[51] Although replacement of PPSV23 with PCV13 was estimated to be more cost-effective than using PCV13 in sequence with PPSV23 for adults ≥ 65 years in the first year of implementation, the cost of using PCV13 in sequence was lower than replacement of PPSV23 with PCV13 in subsequent years.[51] Importantly, the cost of using PCV13 in sequence with PPSV23 among adults ≥ 65 years was also substantially less cost effective in scenarios with greater herd protection over time through direct use and indirect protection from the childhood vaccination program (increased to \$272,621 per QALY by year 6).[51]

Based on the findings from the CAPiTA trial and previous assessments, the Advisory Committee on Immunization Practices (ACIP) recommended the use of PCV13 in sequence with PPSV23 among adults ≥ 65 years in the US in 2014.[41,49] The ACIP recommendation considered that PCV13 use in adults ≥ 65 years could meaningfully reduce the burden of pneumococcal disease due to PCV13 serotypes in addition to the indirect protection accruing from the childhood vaccination program that had transitioned from PCV7 to PCV13 in 2010.[41] Those estimates considered that the indirect protection among older adults derived from the PCV13 childhood vaccination program would be similar to that observed with the PCV7 infant vaccination program.[41] Yet, ACIP recognized that in a setting with fully realized indirect protection the expected benefits of direct vaccination of adults with PCV13 would be substantially lower and so made the recommendation with the intention of revisiting it in 2018.[41]

2.3 PCV coverage among adults in the US

Since 2014, the percentage of Medicare beneficiaries ≥ 65 years of age with evidence of PCV13 vaccination has increased from 14.8% in 2014–2015 to 40.0% in 2016–2017.[30] Laboratory-based surveillance has not demonstrated a clear change in the overall trends of IPD incidence rates (including bacteremic pneumonia) among older adults nor has there been a clear population-level change in the overall trend of all-cause pneumonia since the 2014 recommendation. Of note, the observed vaccination coverage with PCV13 among older adults is lower than the projected coverage used to support the 2014 recommendation for adult vaccination, which considered similar levels to those attained with PPSV23.

3.0 IMPACT OF PCVs INTRODUCTION ON PNEUMONIA IN THE US

3.1 Impact of PCVs introduction into routine infant vaccination programs on pneumonia in children

3.1.1 Direct impact of PCV7 introduction on pneumonia in children—Several studies have documented a significant reduction in the incidence of all-cause pneumonia hospitalizations among children following introduction of PCV7 in the US routine infant

vaccination schedule (Table 1).[53–61][42,55–62] Although the exact reduction varies somewhat across these prior studies, the estimates of PCV7 effectiveness against all-cause pneumonia have generally exceeded the initial expectations based on pre-licensure trials[63]. [62] Importantly, consistent reductions have been observed across several types of study populations (i.e., systematic samples of hospitalizations for the entire U.S., all payer hospitalizations databases from selected states, and private and commercial administrative databases) and using different analytical strategies (i.e., before and after assessments, interrupted time-series analyses, external and synthetic control analysis, and change point analyses). The observed declines in the incidence of childhood pneumonia in the US were sustained during the 9 years after PCV7 introduction in the US, with rates of 723, 360, and 93 per 100,000 among ages <2, 2–4, and 5–17, respectively, in 2007–2009, compared to 1,274, 411, and 97 per 100,000 in 1997–1999.[56,63] [57,64] Similar to what was observed for IPD, the rates of pneumonia hospitalization in the US remained consistently lower than the rates that existed before the introduction of PCVs. Prior to PCV13 introduction in 2010, PCV7 introduction into the US routine infant vaccination schedule was associated with reductions of 5% to 40% of all-cause pneumonia among different age groups of children.

3.1.2 Direct impact of PCV13 introduction on pneumonia in children—

Substantial reductions in pneumonia hospitalization rates were observed among children in the decade after PCV7 introduction, and PCV13 introduction in 2010 was associated with further declines. In a time-series analysis of a large private inpatient discharge database in the US, by the end of 2012, PCV13 introduction was associated with a 21% (95% CI: 14%–28%) and 17% (95% CI: 7%–27%) reduction of all-cause pneumonia among children <2 years and 2–4 years, respectively, with no change observed for children 5–17 years [–3% (95% CI: –20%–11%)]. [64]

These relative declines represented annual absolute reductions of 13,955 and 8,603 hospitalizations for all-cause pneumonia in children <2 years and 2–4 years, respectively. [64] In a smaller study among children enrolled in the Tennessee Medicaid program, PCV13 introduction in Tennessee (2010–2012) was similarly associated with a 27% reduction in annual pneumonia hospitalization rate compared to the 9-year PCV7 era (2001–2009).[65] Importantly though, disparities in hospitalizations for pneumonia were reduced but were not eliminated among racial/ethnic minorities compared to White children and among boys compared to girls in the US.[66–69] Overall, these studies provide consistent evidence that the coverage of six additional serotypes by PCV13 led to further reductions in all-cause pneumonia among young children.

3.2 Impact of PCVs introduction into routine infant vaccination programs on pneumonia in adults

3.2.1 Indirect impact of PCV7 introduction on pneumonia among adults—At 4 years after PCV7 introduction into the US infant vaccination schedule, the rate of hospitalizations for pneumonia had decreased significantly by 26% (95% CI: 4%–43%) among US adults 18–39 years, with more modest but non-significant reductions were observed among adults >40 years of age [40–64: 19% (95% CI: –3%–35%) and 65 years or older: 15% (95% CI: –2%–30%)]. [53] In additional studies with extended follow-up,

national hospitalization rates for all-cause pneumonia had decreased significantly across all adult age groups through 2009.[56] Annual pneumonia hospitalization rates declined significantly from 1997–1999 to 2007–2009 by 8, 85 and 360 per 100,000 in the 18–39, 65–74 and 75 years age groups, respectively.[56] The reduction was more substantial among adults 85 years of age, with a reduction of 1,301 hospitalizations per 100,000 in 2007–2009 compared to 1997–1999, and an estimated absolute reduction of around 73,000 hospitalizations in this age group annually.[56] Yet, in an analysis of hospitalization data from 8 state inpatient databases using a synthetic control method to estimate the impact of the program, no significant reductions in hospitalizations for pneumonia after PCV7 introduction were observed among adults, including those 65 years of age.[60] Similarly, a separate analysis of 10 statewide hospitalization databases reported no reduction of all-cause pneumonia among adults 24–59 years associated with PCV7 introduction by 2004, though a 6% decline was observed among those 12–23 years.[61]

Outside the US, some countries that evaluated the indirect protection against pneumonia derived from vaccination of infants with PCVs have reported similar significant declines among unvaccinated adults, though it has not been consistently observed in all countries.[70–72] The discrepancy in the quantification of PCV7 impact on the rate of hospitalizations for pneumonia across age groups, as well as the discrepancy in the findings in US populations compared to other countries, is thought to be related to differences in analytical approaches and comparison exposures and to different distributions of vaccine-serotype pneumococcal serotypes and non-vaccine serotypes before introduction of PCVs.[63,72] Additionally, differences in vaccine program factors (such as the specific schedule, timing of vaccine introduction, uptake of vaccine) and differences in the impact of the vaccine on pneumococcal nasopharyngeal carriage could have contributed to the observed differences in the observed impact of PCVs in different countries.[40,73,74]

3.2.2 Indirect impact of PCV13 introduction on pneumonia among adults—

Few studies in the US have examined the indirect protection derived from PCV13 introduction on pneumonia hospitalizations in adults.[16,63,64] One such study using administrative data from the Medical Expenditure Panel (MEP) Survey, 2007–2011, assessed changes one year post-PCV13 introduction in the infant vaccination program and found a non-significant 16% reduction in pneumonia hospitalizations across all-age groups (but did not report age-specific changes).[9] In a separate time-series analysis of a large inpatient database of privately insured subjects in the US, compared with PCV7 years, all-cause pneumonia hospitalization rates among adults 18–39 years of age had declined by 12% (95% CI: 6%–17%) within the first 2 years after PCV13 introduction (2011–2012), though a significant reduction was not observed among adults >40 years of age [40–64: 2% (95% CI: –2–6%) and among those 65 years or older: 3% (95% CI: –1%–6%)]. [64]

A recent study of data from two large US commercial insurance companies compared the incidence of all-cause pneumonia hospitalizations between 2007 and 2015 and reported significant declines among adults associated with the introduction of PCV13.[75] Reductions in the incidence of pneumonia hospitalizations were reported among adults younger than 75 years (though not among adults 75 years), with the bigger declines observed among those without underlying comorbidities relative to adults with

comorbidities or immunosuppressive conditions.[75] Importantly, PCV13 coverage among adults was low during the study period and thus it was not considered a major driver in these declines.[75]

Recent systematic reviews of indirect protection derived from switching to PCV13 vaccination programs from other PCV programs have been published.[76,77] Significant reductions in the incidence of all-cause pneumonia attributable to introduction of PCV13 were observed, including an estimated 14% reduction of community-acquired pneumonia (not limited to hospitalizations) among unvaccinated adults associated with the transition from to PCV13 across seven different US and non-US studies.[76] However, the data pooling in these reviews was challenging due to considerable heterogeneity in observed reductions across studies because of underlying differences in PCV coverage rates, data completeness and quality, analytical methodologies and the timing since PCV introduction across all of the studies.[77]

3.3 Direct impact of recommendation for PCV13 use in older adults

ACIP recommended the use of PCV13 in sequence with PPSV23 among adults 65 years in the US in 2014.[41,47] During the development of the current ACIP recommendation to directly vaccinate older adults with PCV13, a calculation of its projected impact estimated 230 IPD cases and approximately 12,000 cases of community-acquired pneumonia could be prevented over the lifetime of a single US cohort of persons aged 65 years or more.[41] This calculation assumed that the indirect protection from PCV13 would be similar to that observed after PCV7 introduction and that PCV13 coverage would be closer to 60% among older adults (i.e., similar to current PPSV23 coverage).[30] Although the national PCV13 coverage among older adults in the US has increased since 2014, it was around 40% in 2017.[30] Importantly, the current sequential vaccination recommendation may have hampered vaccine uptake as the recommendation has been reported as complicated to implement in routine clinical practice.[78–80] Therefore, although the increasing uptake since 2014 is encouraging, the relatively low PCV13 coverage attained thus far may be insufficient to allow a proper assessment of the impact of direct vaccination in older adults. Current and future assessments of the impact of direct vaccination of older adults with PCV13 will need to factor in the actual vaccination coverage among older adults.

A recent study assessed the effectiveness of PCV13 use among older adults using a test-negative design. Adults hospitalized with pneumonia with and without PCV13 serotype disease (identified using a serotype specific antigen detection assay for identification of PCV13 serotypes) represented cases and controls, respectively, and were identified from a population-level pneumonia surveillance program in Kentucky in 2015–2016.[81] The study reported that PCV13-serotype pneumonia cases were less likely to have received PCV13 compared to PCV13 serotype-negative pneumonia controls (4.4% vs. 14.5%).[81] The effectiveness of PCV13 in preventing serotype-specific pneumonia was estimated to be 70.1 (95% CI: 12.8–91.5) to 72.8 (95% CI: 4.1–90.7) for all-PCV type pneumonia and non-bacteremic PCV-type pneumonia, respectively.[81] These positive effectiveness findings are consistent with the findings from the large CAPiTA trial, but lacked precision because of the study size. Nevertheless, since this study occurred in the setting of evolving infant

vaccination, this type of study on the effectiveness of vaccination of adults does not allow for quantification of marginal benefits beyond what would be expected from full realization of indirect protection.[82]

4.0 ONGOING CHALLENGES IN THE PREVENTION OF IPD AND PNEUMONIA IN THE US

4.1 Remaining burden of pneumonia and pneumococcal nasopharyngeal carriage in the US

Despite the described changes, hospitalization rates for pneumonia remain high in the US. Additionally, though pneumonia hospitalization rates have declined substantially among children in the US, rates continue to be higher among racial/ethnic minorities compared to white children, and higher among young boys compared to girls.[66–69] Recent estimates among older adults also indicates that hospitalization for pneumonia continues to be a major problem, as the hospitalization rate for pneumonia among Medicare Advantage enrollees 65 years of age was 846.7 per 100,000 person-years in 2015 (5 years since PCV13 introduction in infants), which is higher than hospitalization rates for myocardial infarction, stroke and osteoporotic fractures.[7] Yet the high burden is not limited to older adults, as a prospective population-based cohort study of adults in a single city in Kentucky reported an age-adjusted incidence rate for hospitalizations with community-acquired pneumonia of 649 cases per 100,000 adults from June 2014 through May 2016.[83] Rates of community-acquired pneumonia increased with increasing age, with a rate of 69 per 100,000 in adults 18–24 years and higher rates of 1,507, 2,205, and 3,951 per 100,000 among adults 65–74, 75–84 and >84 years of age, respectively.[83]

As pneumococcal nasopharyngeal carriage among young children represents the main population reservoir of bacteria, examination of changes in carriage composition after introduction of PCV13 can be informative. Nasopharyngeal carriage data presented at the October 2017 ACIP meeting indicated that PCV13-serotype carriage has declined from >5% in 2010 to <1% in 2017 among children <5 years, and that carriage of PCV13 serotypes was very low among older adults as well (0.2%).[84,85] Overall pneumococcal carriage (not restricted to PCV13 serotypes) among young children in the US has remained relatively stable during the last years at around 30%, whereas overall pneumococcal carriage among older adults was substantially lower (1.8% or lower).[84,85] Despite these remarkable reductions in vaccine serotype carriage, a meaningful proportion of community-acquired pneumonia remains attributable to certain PCV13 serotypes and the proportion is relatively unchanged since the end of the PCV7 era (2006–2009), with around 65–70% of pneumococcal pneumonia cases attributable to 19A, 3 and 7F (estimated 30–50% due to 19A).[16,86–88]

4.2 The ongoing challenge in quantifying the burden of non-invasive pneumococcal pneumonia

As most pneumococcal pneumonia is non-invasive, the quantification of the burden of pneumococcal pneumonia has been challenging.[89] The design of a novel serotype-specific urinary antigen detection assay that identifies infection due to serotypes included in PCV13

has facilitated major steps forward in this quantification. In addition, a commercial urinary antigen detection test is available to detect pneumococcal antigens in urine specimens from patients with pneumococcal pneumonia, though testing is largely restricted to adults, as nasopharyngeal colonization, very common in children, is known to interfere with the tests.[86,90–92] This traditional urine test is the BinaxNOW diagnostic assay that identifies the presence of pneumococcal polysaccharide C, a capsular antigen common to all pneumococcal serotypes.[86,90–92] Furthermore, certain serotype-specific capsular antigens can be identified with highly sensitive and specific novel urinary assays allowing for the increased detection of pneumococcal infections compared to traditional diagnostic tests among adult patients with pneumonia.[86,92,93] However, these serotype-specific assays are currently limited to the detection of only a fraction of the more than 90 known distinct pneumococcal serotypes.[91]

Findings from a prospective multicenter study using one of these novel assays estimated that in 2011, 13.8% of hospitalizations for either community-acquired or healthcare-associated pneumonia were due to a pneumococcal serotype (of which 79.5% were PCV13 serotypes not originally covered by PCV7).[16,87] After accounting for potential interference of in-hospital vaccination with pneumococcal detection, the CDC Etiology of Pneumonia in the Community – EPIC study estimated that around 10% of community-acquired pneumonia hospitalizations were attributable to *S. pneumoniae* in 2010–2012 (with a non-significant reduction in cases due to PCV13 serotypes among adults from 6.4% in 2010 to 4.0% in 2012).[86,94]

Since 2013, the Centers for Disease Control and Prevention have been conducting surveillance for non-invasive pneumococcal pneumonia through the Active Bacterial Core Surveillance Program by monitoring adults hospitalized with radiographically-confirmed pneumonia and with a positive result from traditional urinary antigen detection tests.[95] This surveillance, which does not include IPD cases, provided initial comparisons of the incidence of non-invasive pneumococcal pneumonia between 2013–2014 and 2015–2016 and results were presented at the October 2018 ACIP meeting.[95] In a before and after comparison, a significant 35% decline (95% CI: 14%–49%) in non-invasive pneumococcal pneumonia was observed among adults ≥65 years in 2015–2016 (83 per 100,000) compared to 2013–2014 (128 per 100,000), with the largest decrease observed from 2013 to 2014 (i.e., likely attributable to indirect protection derived from the PCV13 infant vaccination program).[95] Furthermore, a significant 35% decline (95% CI: 28%–45%) among adults aged 18–49 years and a non-significant 12% decline (95% CI: –7% to 29%) among adults 50–64 was observed.[95] The observed decreases in those younger adult populations, along with the lack of further reductions in 2015–2016 compared to 2014 alone, are evidence against a decline in non-invasive pneumococcal pneumonia directly attributable to vaccination of older adults with PCV13. Nevertheless, these findings should be interpreted cautiously given the limited follow-up, limited ability to account for underlying trends, variability in testing practices, the sensitivity of the tests, and the changes in coding practices during this period. Although the analyses tried to account for some of these factors, the comparison remains challenging.

4.3 Residual pneumococcal disease after PCV13: the case of serotype 3

Of special note is that although PCV13 introduction has been associated with declines in IPD due to covered serotypes 19A and 7F, serotype 3 persists as a leading cause of IPD and pneumococcal pneumonia among both children and adults in the US despite being covered by PCV13.[96,97] Serotype 3 is particularly problematic due to its virulence.[98,99] Persistence of serotype 3 in the post-PCV13 years has been observed outside of the US as well.[100,101] The precise reasons for this persistence post-vaccination are unclear. Some studies suggest that immune protection against serotype 3 is lower than for other serotypes included in PCV13.[102] Interestingly, in the CAPiTA trial there were numerically more serotype 3 infections documented among placebo recipients than among PCV13 recipients, but the overall number of detections was small.[43] Furthermore, some studies indicate that serotype 3 releases capsular polysaccharide during bacterial growth, effectively interfering with the effectiveness of vaccine induced antibodies.[103] Other hypotheses include a recent antigenic change in serotype 3 with a rapid expansion of an antibiotic resistant variant.[104] Additional work is needed to understand the potential heterogeneity in PCV13 effectiveness against serotype 3, including how PCV13 effectiveness against serotype 3 may impact the direct benefits of PCV13 vaccination among adults.

5.0 EXPERT OPINION

5.1 Initial summary of findings

There is a consistent body of evidence indicating a protective impact of PCVs against pneumonia among young children.[105] Recent systematic reviews of PCV impact among children reported that the transition from PCV7 to PCV13 was associated with further declines in IPD and hospitalizations for pneumonia in the US and in other settings.[66–69] Reductions in all-cause pneumonia have also been reported among adults through indirect protection derived from the switch from PCV7 to PCV13 in children.[16,63,64] Using nationally representative data sources, all-cause pneumonia rates were substantially lower in 2011–2012 for all adult age groups (18–39 years: 80.1 per 100,000, 40–64 years: 258.2 per 100,000, 65 years: 1375.2 per 100,000) compared to rates prior to PCV7 introduction (18–39 years: 107 per 100,000, 40–64 years: 336 per 100,000, 65–74, 75–84, 85 years: 1,293, 2,758 and 5,697 per 100,000 respectively).[63,64] However, in the early years following PCV13 introduction, there was still a residual amount of pneumococcal disease and even disease due to PCV13 serotypes. Two studies that assessed all-cause pneumonia hospitalizations in the year 2012 reported similar estimates of the remaining burden of pneumonia hospitalization attributable to any pneumococcal serotype (9.7% and 13.8%) and attributable to PCV13 serotypes (5% and 11%), with the majority of pneumococcal pneumonia hospitalizations attributable to PCV13-serotypes not covered by PCV7. Of note, a high burden of pneumococcal disease remains among those 65 years of age and those with underlying comorbidities.[86,87]

5.2 The impact of pneumococcal vaccination on pneumonia among US adults

PPSV23 is known to be effective in preventing IPD. However, few studies have assessed whether the PPSV23 vaccination program is associated with population level reductions in IPD and pneumonia.[25,106–109] Results from prior observational studies are challenging

to interpret due to low PPSV23 coverage and the difficulty in measuring non-bacteremic pneumonia as an outcome.[30,107,110–114] New clinical trials have not been considered for PPSV23 as these would be unfeasible and unpractical given existing recommendations for vaccination, and the relatively infrequent occurrence of IPD which would require very large studies to appropriately power those assessments. Future studies of the impact of PPSV23 vaccination among older adults in the US would be even more difficult to interpret with the introduction of PCV13 vaccination among older adults in 2014.

A major challenge for the ACIP recommendation to introduce PCV13 vaccination among older adults was the expectation that indirect protection derived from the PCV13 infant vaccination program in the US would ultimately render this recommendation for direct vaccination of adults redundant and of limited impact.[78] Pre-PCV13 data from active laboratory-based surveillance had demonstrated declining trends in IPD in both children and adults, which were anticipated to continue. However, at the time of the recommendation, there was a preventable burden of pneumococcal disease among older adults. The committee determined that waiting for the full materialization of indirect protection would allow for preventable occurrences of the disease in the meantime.

Currently, ACIP is evaluating the PCV13 recommendation among adults 65 years through ongoing monitoring of pneumococcal disease in the older adult population (including IPD and pneumonia). In addition to the difficulty in assessing the impact of the PCV13 recommendation among adults independent of impact of the routine infant PCV13 vaccination program that has been in place in the US since 2010, the evaluation will need to consider that the PCV13 coverage rate among older adults has been relatively low (40%), with an even lower coverage rate among those adults age 19–64 years with PCV13 indications.[30,84,115] Additionally, the evaluation will be impacted by the ongoing relatively stable prevalence of serotype 3, especially since the benefit of PCV13 vaccination against that serotype may be limited.[102] The upcoming ACIP decision regarding direct adult vaccination will need to balance the potential benefit of PCV13 vaccination among older adults against the cost and challenge of the currently recommended sequential PCV13 administration.

5.3 Key challenges and future research in the study of PCVs impact on pneumonia

Evidence regarding the impact of PCV13 introduction into the US routine infant vaccination schedule on pneumonia among adults is limited beyond 2014. It is difficult to distinguish the indirect protection derived from PCV13 use among infants from the direct protection derived from vaccination of adults with PCV13 starting in 2014. Studies with additional follow-up and extended observation times would be useful. Interestingly, most countries have not recommended direct vaccination of adults with PCV13. Therefore, subsequent comprehensive assessments of the indirect protection in adults derived from PCV vaccination of children in these settings will provide valuable information for evaluation of current vaccination recommendations.

Despite the ongoing reduction in the burden of pneumococcal diseases and the development of new high-valency conjugate vaccines, future questions about PCV use remain unanswered in the US. For one, it remains to be determined whether direct vaccination of adults with

PCVs provide substantial additional benefit on top of the indirect impact from infant vaccination (including any evidence of indirect protection in other adult age groups related to the older adult PCV13 recommendation), whether abbreviated vaccination schedules for children may be acceptable and appropriate in the US, and whether newer experimental higher valency conjugate vaccines would replace currently available pneumococcal vaccines. [57,116,117] In addition, the increase in drug-resistant *S. pneumoniae* documented in many regions and countries across the world further highlights the need for continued and expanded use of vaccine to prevent pneumococcal infections and pneumococcal pneumonia. [118]

5.4 Conclusion

In conclusion, the introduction of PCVs into the US routine infant immunization schedule has been associated with reductions in IPD among children and adults. PCV introduction has also been associated with declines in hospitalizations for pneumonia among young children. Yet the indirect protection derived from vaccination of children with PCV13 on pneumonia among older adults requires further study, as does the impact of the ACIP recommendation to directly vaccinate older adults with PCV13. These remaining questions regarding the impact of PCVs in the US highlight the importance of the ongoing evaluations of the US vaccination program, which includes the ongoing surveillance of both IPD and hospitalizations for pneumonia.

6.0 FIVE YEAR VIEW

The introduction of PCVs have led to large reductions in invasive and non-invasive pneumonia hospitalizations in the US. Whether or not the use of PCVs among older adults leads to additional reductions in pneumonia remains unclear. Additional evaluations of the direct and indirect effects of PCVs in the US population are needed, as pneumonia remains one of the leading causes of morbidity and mortality in the US and the world and continues to contribute to high healthcare costs.

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REFERENCES

Papers of special note have been highlighted as:

* of interest

** of considerable interest

1. File TM. Community-acquired pneumonia. *Lancet*, 362(9400), 1991–2001 (2003). [PubMed: 14683661]
2. File TM, Jr., Tan JS. Pneumonia in older adults: reversing the trend. *Jama*, 294(21), 2760–2763 (2005). [PubMed: 16333013]

3. Jackson ML, Neuzil KM, Thompson WW et al. The burden of community-acquired pneumonia in seniors: results of a population-based study. *Clin Infect Dis*, 39(11), 1642–1650 (2004). [PubMed: 15578365]
4. Jain S, Self WH, Wunderink RG et al. Community-Acquired Pneumonia Requiring Hospitalization among U.S. Adults. *N Engl J Med*, 373(5), 415–427 (2015). [PubMed: 26172429]
5. Rudan I, Boschi-Pinto C, Biloglav Z, Mulholland K, Campbell H. Epidemiology and etiology of childhood pneumonia. *Bulletin of the World Health Organization*, 86(5), 408–416 (2008). [PubMed: 18545744]
6. Stuckey-Schrock K, Hayes BL, George CM. Community-acquired pneumonia in children. *American family physician*, 86(7), 661–667 (2012). [PubMed: 23062094]
7. Brown JD, Harnett J, Chambers R, Sato R. The relative burden of community-acquired pneumonia hospitalizations in older adults: a retrospective observational study in the United States. *BMC geriatrics*, 18(1), 92 (2018). [PubMed: 29661135]
8. Wagenvoort GH, Sanders EA, de Melker HE, van der Ende A, Vlamincx BJ, Knol MJ. Long-term mortality after IPD and bacteremic versus non-bacteremic pneumococcal pneumonia. *Vaccine*, 35(14), 1749–1757 (2017). [PubMed: 28262334]
9. Park H, Adeyemi AO, Rascati KL. Direct Medical Costs and Utilization of Health Care Services to Treat Pneumonia in the United States: An Analysis of the 2007–2011 Medical Expenditure Panel Survey. *Clinical therapeutics*, 37(7), 1466–1476.e1461 (2015). [PubMed: 26001310]
10. De Graeve D, Beutels P. Economic aspects of pneumococcal pneumonia: a review of the literature. *PharmacoEconomics*, 22(11), 719–740 (2004). [PubMed: 15250750]
11. 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*, 18(1), 715 (2018). [PubMed: 30217156]
12. Weycker D, Farkouh RA, Strutton DR, Edelsberg J, Shea KM, Pelton SI. Rates and costs of invasive pneumococcal disease and pneumonia in persons with underlying medical conditions. *BMC Health Serv Res*, 16, 182 (2016). [PubMed: 27177430]
13. File TM, Jr., Marrie TJ. Burden of community-acquired pneumonia in North American adults. *Postgraduate medicine*, 122(2), 130–141 (2010). [PubMed: 20203464]
14. Welte T. Prevention is better than cure: time to change the focus of community-acquired pneumonia management. *The European respiratory journal*, 45(6), 1524–1525 (2015). [PubMed: 26028615]
15. Bartlett JG. Diagnostic tests for agents of community-acquired pneumonia. *Clin Infect Dis*, 52 Suppl 4, S296–304 (2011). [PubMed: 21460288]
16. Griffin MR, Grijalva CG. Distribution of pneumococcal serotypes in adult pneumococcal pneumonia cases: filling the evidence gap to inform vaccination policies. *J Infect Dis*, 208(11), 1734–1736 (2013). [PubMed: 24092844]
17. Yildirim I, Shea KM, Pelton SI. Pneumococcal Disease in the Era of Pneumococcal Conjugate Vaccine. *Infectious disease clinics of North America*, 29(4), 679–697 (2015). [PubMed: 26610421]
18. Weinberger DM, Shapiro ED. Pneumococcal conjugate vaccines for adults: reasons for optimism and for caution. *Human vaccines & immunotherapeutics*, 10(5), 1334–1336 (2014). [PubMed: 24763136]
19. Jackson LA, Neuzil KM, Yu O et al. Effectiveness of pneumococcal polysaccharide vaccine in older adults. *N Engl J Med*, 348(18), 1747–1755 (2003). [PubMed: 12724480]
20. Shapiro ED, Berg AT, Austrian R et al. The protective efficacy of polyvalent pneumococcal polysaccharide vaccine. *The New England journal of medicine*, 325(21), 1453–1460 (1991). [PubMed: 1944423]
21. Diao WQ, Shen N, Yu PX, Liu BB, He B. Efficacy of 23-valent pneumococcal polysaccharide vaccine in preventing community-acquired pneumonia among immunocompetent adults: A systematic review and meta-analysis of randomized trials. *Vaccine*, 34(13), 1496–1503 (2016). [PubMed: 26899376]
22. Kraicer-Melamed H, O'Donnell S, Quach C. The effectiveness of pneumococcal polysaccharide vaccine 23 (PPV23) in the general population of 50 years of age and older: A systematic review and meta-analysis. *Vaccine*, 34(13), 1540–1550 (2016). [PubMed: 26899372]

23. Ogilvie I, Khoury AE, Cui Y, Dasbach E, Grabenstein JD, Goetghebeur M. Cost-effectiveness of pneumococcal polysaccharide vaccination in adults: a systematic review of conclusions and assumptions. *Vaccine*, 27(36), 4891–4904 (2009). [PubMed: 19520205]
24. Klugman KP. A tale of 2 pneumococcal vaccines. *Clin Infect Dis*, 58(7), 925–927 (2014). [PubMed: 24532545]
25. Andrews NJ, Waight PA, George RC, Slack MP, Miller E. Impact and effectiveness of 23-valent pneumococcal polysaccharide vaccine against invasive pneumococcal disease in the elderly in England and Wales. *Vaccine*, 30(48), 6802–6808 (2012). [PubMed: 23000122]
26. Williams WW, Lu PJ, O'Halloran A et al. Surveillance of Vaccination Coverage Among Adult Populations - United States, 2014. Morbidity and mortality weekly report. Surveillance summaries (Washington, D.C. : 2002), 65(1), 1–36 (2016).
27. Norris TVA, Cohen RA. Vaccination Coverage Among Adults Aged 65 and Over: United States, 2015. NCHS Data Brief, 281 (2017).
28. Williams WW, Lu PJ, O'Halloran A et al. Surveillance of Vaccination Coverage among Adult Populations - United States, 2015. Morbidity and mortality weekly report. Surveillance summaries (Washington, D.C. : 2002), 66(11), 1–28 (2017).
29. Williams WW, Lu PJ, O'Halloran A et al. Noninfluenza vaccination coverage among adults - United States, 2012. MMWR Morb Mortal Wkly Rep, 63(5), 95–102 (2014). [PubMed: 24500288]
30. CDC. Pneumococcal vaccination among U.S. Medicare beneficiaries aged 65 years, 2009–2017. AdultVaxView, <https://www.cdc.gov/vaccines/imz-managers/coverage/adultvaxview/pubs-resources/pcv13-medicare-beneficiaries.html> (2018).
31. Smith PJ, Singleton JA. County-level trends in vaccination coverage among children aged 19–35 months - United States, 1995–2008. Morbidity and mortality weekly report. Surveillance summaries (Washington, D.C. : 2002), 60(4), 1–86 (2011).
32. Hammitt LL, Bruden DL, Butler JC et al. Indirect effect of conjugate vaccine on adult carriage of *Streptococcus pneumoniae*: an explanation of trends in invasive pneumococcal disease. *J Infect Dis*, 193(11), 1487–1494 (2006). [PubMed: 16652275]
33. CDC. Pneumococcal Conjugate Vaccine (PCV) coverage among children 19–35 months by State, HHS Region, and the United States, National Immunization Survey-Child (NIS-Child), 2002 through 2017. ChildVaxView, <https://www.cdc.gov/vaccines/imz-managers/coverage/childvaxview/data-reports/pcv/trend/index.html> (2018).
34. National, state, and local area vaccination coverage among children aged 19–35 months - United States, 2008. MMWR Morb Mortal Wkly Rep, 58(33), 921–926 (2009). [PubMed: 19713881]
35. Emerging Infections Program Network, *Streptococcus pneumoniae* - Surveillance and Reporting, 1998–2016. Active Bacterial Core Surveillance, <https://www.cdc.gov/pneumococcal/surveillance.html> (2018).
36. Muhammad RD, Oza-Frank R, Zell E et al. Epidemiology of invasive pneumococcal disease among high-risk adults since the introduction of pneumococcal conjugate vaccine for children. *Clin Infect Dis*, 56(5), e59–67 (2013). [PubMed: 23155149]
37. Houseman C, Hughes GJ, Chapman KE, Wilson D, Gorton R. Increased Invasive Pneumococcal Disease, North East England, UK. *Emerg Infect Dis*, 23(1), 122–126 (2017). [PubMed: 27983490]
38. Ladhani SN, Collins S, Djennad A et al. Rapid increase in non-vaccine serotypes causing invasive pneumococcal disease in England and Wales, 2000–17: a prospective national observational cohort study. *Lancet Infect Dis*, 18(4), 441–451 (2018). [PubMed: 29395999]
39. Regev-Yochay G, Katzir M, Strahilevitz J et al. The herd effects of infant PCV7/PCV13 sequential implementation on adult invasive pneumococcal disease, six years post implementation; a nationwide study in Israel. *Vaccine*, 35(18), 2449–2456 (2017). [PubMed: 28342668]
40. Deloria Knoll M, Park DE, Johnson TS et al. Systematic review of the effect of pneumococcal conjugate vaccine dosing schedules on immunogenicity. *Pediatr Infect Dis J*, 33 Suppl 2, S119–129 (2014). [PubMed: 24336054]
41. Tomczyk S, Bennett NM, Stoecker C et al. Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine among adults aged ≥65 years:

- recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep*, 63(37), 822–825 (2014). [PubMed: 25233284]
42. Moore MR, Link-Gelles R, Schaffner W 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*, 15(3), 301–309 (2015). [PubMed: 25656600]
 43. Lucero MG, Dulalia VE, Nillos LT et al. Pneumococcal conjugate vaccines for preventing vaccine-type invasive pneumococcal disease and X-ray defined pneumonia in children less than two years of age. *The Cochrane database of systematic reviews*, (4), Cd004977 (2009). [PubMed: 19821336]
 44. Lucero MG, Dulalia VE, Parreno RN et al. Pneumococcal conjugate vaccines for preventing vaccine-type invasive pneumococcal disease and pneumonia with consolidation on x-ray in children under two years of age. *The Cochrane database of systematic reviews*, (4), Cd004977 (2004). [PubMed: 15495133]
 45. Licensure of a 13-valent pneumococcal conjugate vaccine (PCV13) and recommendations for use among children - Advisory Committee on Immunization Practices (ACIP), 2010. *MMWR Morb Mortal Wkly Rep*, 59(9), 258–261 (2010). [PubMed: 20224542]
 46. Updated recommendation from the Advisory Committee on Immunization Practices (ACIP) for use of 7-valent pneumococcal conjugate vaccine (PCV7) in children aged 24–59 months who are not completely vaccinated. *MMWR Morb Mortal Wkly Rep*, 57(13), 343–344 (2008). [PubMed: 18385642]
 47. Ewald H, Briel M, Vuichard D, Kreutle V, Zhydkov A, Gloy V. The Clinical Effectiveness of Pneumococcal Conjugate Vaccines: A Systematic Review and Meta-analysis of Randomized Controlled Trials. *Deutsches Arzteblatt international*, 113(9), 139–146 (2016). [PubMed: 26987462]
 48. Bonten MJ, Huijts SM, Bolkenbaas M et al. Polysaccharide conjugate vaccine against pneumococcal pneumonia in adults. *N Engl J Med*, 372(12), 1114–1125 (2015). [PubMed: 25785969] **Describes the findings from the CAPiTA trial, the largest trial evaluating the efficacy of PCV13 among older adults
 49. Gubbins PO, Li C. The Influence of Influenza and Pneumococcal Vaccines on Community-Acquired Pneumonia (CAP) Outcomes Among Elderly Patients. *Current infectious disease reports*, 17(12), 49 (2015). [PubMed: 26446610]
 50. Dirmesropian S, Wood JG, MacIntyre CR, Newall AT. A review of economic evaluations of 13-valent pneumococcal conjugate vaccine (PCV13) in adults and the elderly. *Human vaccines & immunotherapeutics*, 11(4), 818–825 (2015). [PubMed: 25933180]
 51. Stoecker C, Kim L, Gierke R, Pilishvili T. Incremental Cost-Effectiveness of 13-valent Pneumococcal Conjugate Vaccine for Adults Age 50 Years and Older in the United States. *Journal of general internal medicine*, 31(8), 901–908 (2016). [PubMed: 26976292] *Describes the findings from the primary cost-effectiveness study referenced to inform the ACIP recommendation for direct PCV13 use among older adults > 65 years of age in the US
 52. August 2014 ACIP Meeting. Summary Report, <https://stacks.cdc.gov/view/cdc/45918> (2014).
 53. Grijalva CG, Nuorti JP, Arbogast PG, Martin SW, Edwards KM, Griffin MR. Decline in pneumonia admissions after routine childhood immunisation with pneumococcal conjugate vaccine in the USA: a time-series analysis. *Lancet*, 369(9568), 1179–1186 (2007). [PubMed: 17416262]
 54. Chang DH, Bednarczyk RA, Becker ER et al. Trends in U.S. hospitalizations and inpatient deaths from pneumonia and influenza, 1996–2011. *Vaccine*, 34(4), 486–494 (2016). [PubMed: 26706275]
 55. Griffin MR, Grijalva CG. Hospitalizations after a decade of pneumococcal vaccination. *N Engl J Med*, 369(17), 1662–1663 (2013).
 56. Lee GE, Lorch SA, Sheffler-Collins S, Kronman MP, Shah SS. National hospitalization trends for pediatric pneumonia and associated complications. *Pediatrics*, 126(2), 204–213 (2010). [PubMed: 20643717]
 57. Grijalva CG, Griffin MR. Population-based impact of routine infant immunization with pneumococcal conjugate vaccine in the USA. *Expert review of vaccines*, 7(1), 83–95 (2008). [PubMed: 18251696]

58. Nelson JC, Jackson M, Yu O et al. Impact of the introduction of pneumococcal conjugate vaccine on rates of community acquired pneumonia in children and adults. *Vaccine*, 26(38), 4947–4954 (2008). [PubMed: 18662735]
59. 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*, 161(12), 1162–1168 (2007). [PubMed: 18056561]
60. Bruhn CA, Hetterich S, Schuck-Paim C et al. Estimating the population-level impact of vaccines using synthetic controls. *Proceedings of the National Academy of Sciences of the United States of America*, 114(7), 1524–1529 (2017). [PubMed: 28154145]
61. Kurum E, Warren JL, Schuck-Paim C et al. Bayesian Model Averaging with Change Points to Assess the Impact of Vaccination and Public Health Interventions. *Epidemiology (Cambridge, Mass.)*, 28(6), 889–897 (2017).
62. Black S, Shinefield H. Safety and efficacy of the seven-valent pneumococcal conjugate vaccine: evidence from Northern California. *European journal of pediatrics*, 161 Suppl 2, S127–131 (2002). [PubMed: 12494258]
63. Griffin MR, Zhu Y, Moore MR, Whitney CG, Grijalva CG. U.S. hospitalizations for pneumonia after a decade of pneumococcal vaccination. *N Engl J Med*, 369(2), 155–163 (2013). [PubMed: 23841730] *Important article highlighting the impact of PCV7 introduction in the US in 2000 on hospitalizations for pneumonia in children and adults through the end of the PCV7 era and before PCV13 introduction in 2010
64. Simonsen L, Taylor RJ, Schuck-Paim C, Lustig R, Haber M, Klugman KP. Effect of 13-valent pneumococcal conjugate vaccine on admissions to hospital 2 years after its introduction in the USA: a time series analysis. *Lancet Respir Med*, 2(5), 387–394 (2014). [PubMed: 24815804] *Demonstrates the indirect protection against pneumonia hospitalizations among adults 18–39 years of age (12% decline) observed within 2 years after PCV13 introduction into the US childhood routine vaccination program in 2010
65. Griffin MR, Mitchel E, Moore MR, Whitney CG, Grijalva CG. Declines in pneumonia hospitalizations of children aged <2 years associated with the use of pneumococcal conjugate vaccines - Tennessee, 1998–2012. *MMWR Morb Mortal Wkly Rep*, 63(44), 995–998 (2014). [PubMed: 25375070]
66. Segal N, Greenberg D, Dagan R, Ben-Shimol S. Disparities in PCV impact between different ethnic populations cohabiting in the same region: A systematic review of the literature. *Vaccine*, 34(37), 4371–4377 (2016). [PubMed: 27443591]
67. Wiese AD, Grijalva CG, Zhu Y, Mitchel EF, Jr., Griffin MR. Changes in Childhood Pneumonia Hospitalizations by Race and Sex Associated with Pneumococcal Conjugate Vaccines. *Emerg Infect Dis*, 22(6) (2016).
68. de St Maurice A, Schaffner W, Griffin MR, Halasa N, Grijalva CG. Persistent Sex Disparities in Invasive Pneumococcal Diseases in the Conjugate Vaccine Era. *J Infect Dis*, 214(5), 792–797 (2016). [PubMed: 27247342]
69. Kornetsky R, Greenberg D, Falup-Pecurariu O. Disparities in Effectiveness of Pneumococcal Vaccine in Industrialized and Developing Countries: Is Vaccination Closing the Gap? *Antibiotiki i khimioterapii = Antibiotics and chemotherapy [sic]*, 61(11–12), 63–67 (2016).
70. Baldo V, Cocchio S, Gallo T et al. Impact of pneumococcal conjugate vaccination: a retrospective study of hospitalization for pneumonia in North-East Italy. *Journal of preventive medicine and hygiene*, 57(2), E61–68 (2016). [PubMed: 27582630]
71. Baldo V, Cocchio S, Baldovin T et al. A population-based study on the impact of hospitalization for pneumonia in different age groups. *BMC Infect Dis*, 14, 485 (2014). [PubMed: 25192701]
72. Menzies RI, Jardine A, McIntyre PB. Pneumonia in Elderly Australians: Reduction in Presumptive Pneumococcal Hospitalizations but No Change in All-Cause Pneumonia Hospitalizations Following 7-Valent Pneumococcal Conjugate Vaccination. *Clin Infect Dis*, 61(6), 927–933 (2015). [PubMed: 26066319]
73. Conklin L, Loo JD, Kirk J et al. Systematic review of the effect of pneumococcal conjugate vaccine dosing schedules on vaccine-type invasive pneumococcal disease among young children. *Pediatr Infect Dis J*, 33 Suppl 2, S109–118 (2014). [PubMed: 24336053]

74. Loo JD, Conklin L, Fleming-Dutra KE et al. Systematic review of the indirect effect of pneumococcal conjugate vaccine dosing schedules on pneumococcal disease and colonization. *Pediatr Infect Dis J*, 33 Suppl 2, S161–171 (2014). [PubMed: 24336058]
75. Pelton SI, Bornheimer R, Doroff R, Shea KM, Sato R, Weycker D. Decline in Pneumococcal Disease Attenuated in Older Adults and Those with Comorbidities Following Universal Childhood PCV13 Immunization. *Clin Infect Dis*, [Epub ahead of print] (2018). *Demonstrates the reduction of pneumonia hospitalizations among healthy adults 18–74 years of age associated with the indirect protection after 5 years of use in US children
76. Vadlamudi NK, Chen A, Marra F. Impact of 13-pneumococcal conjugate vaccine among adults: a systematic review and meta-analysis. *Clin Infect Dis*, [Epub ahead of print] (2018). *Recent meta-analyses of the impact of PCV13 introduction in routine childhood vaccination programs on invasive pneumococcal disease and pneumonia that demonstrated a reduction in all-cause pneumonia associated with the transition from PCV7 to PCV13 in the US
77. Tsaban G, Ben-Shimol S. Indirect (herd) protection, following pneumococcal conjugated vaccines introduction: A systematic review of the literature. *Vaccine*, 35(22), 2882–2891 (2017). [PubMed: 28449971]
78. Musher DM, Rodriguez-Barradas MB. Why the recent ACIP recommendations regarding conjugate pneumococcal vaccine in adults may be irrelevant. *Human vaccines & immunotherapeutics*, 12(2), 331–335 (2016). [PubMed: 26606172]
79. Black CL, Williams WW, Warnock R, Pilishvili T, Kim D, Kelman JA. Pneumococcal Vaccination Among Medicare Beneficiaries Occurring After the Advisory Committee on Immunization Practices Recommendation for Routine Use Of 13-Valent Pneumococcal Conjugate Vaccine and 23-Valent Pneumococcal Polysaccharide Vaccine for Adults Aged ≥ 65 Years. *MMWR Morb Mortal Wkly Rep*, 66(27), 728–733 (2017). [PubMed: 28704347]
80. Hurley LP, Allison MA, Pilishvili T et al. Primary Care Physicians' Struggle with Current Adult Pneumococcal Vaccine Recommendations. *Journal of the American Board of Family Medicine : JABFM*, 31(1), 94–104 (2018). [PubMed: 29330244]
81. McLaughlin JM, Jiang Q, Isturiz RE et al. Effectiveness of 13-Valent Pneumococcal Conjugate Vaccine Against Hospitalization for Community-Acquired Pneumonia in Older US Adults: A Test-Negative Design. *Clin Infect Dis*, [Epub ahead of print] (2018). **Important study demonstrating that PCV13 is effective against hospitalizations for non-bacteremic pneumonia among older adults
82. Pilishvili T. Estimating PCV13 direct and indirect effects on IPD among adults ≥ 65 years; Advisory Committee on Immunization Practices, CDC, February 2018 Meeting; 2018. <https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2018-02/Pneumo-03-Pilishvili-508.pdf>
83. Ramirez JA, Wiemken TL, Peyrani P et al. Adults Hospitalized With Pneumonia in the United States: Incidence, Epidemiology, and Mortality. *Clin Infect Dis*, 65(11), 1806–1812 (2017). [PubMed: 29020164]
84. Lee G. Pneumococcal Vaccines; Advisory Committee on Immunization Practices, CDC, June 2018 Meeting; 2018. <https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2018-06/Pneumo-01-Lee-508.pdf>
85. Loughlin AM, Hsu K, Silverio AL, Marchant CD, Pelton SI. Direct and indirect effects of PCV13 on nasopharyngeal carriage of PCV13 unique pneumococcal serotypes in Massachusetts' children. *Pediatr Infect Dis J*, 33(5), 504–510 (2014). [PubMed: 24670957]
86. Wunderink RG, Self WH, Anderson EJ et al. Pneumococcal Community-Acquired Pneumonia Detected by Serotype-Specific Urinary Antigen Detection Assays. *Clin Infect Dis*, 66(10), 1504–1510 (2018). [PubMed: 29342250]
87. Sherwin RL, Gray S, Alexander R 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*, 208(11), 1813–1820 (2013). [PubMed: 24092845]
88. Olarte L, Barson WJ, Barson RM et al. Pneumococcal Pneumonia Requiring Hospitalization in US Children in the 13-Valent Pneumococcal Conjugate Vaccine Era. *Clin Infect Dis*, 64(12), 1699–1704 (2017). [PubMed: 28199482]

89. Said MA, Johnson HL, Nonyane BA et al. Estimating the burden of pneumococcal pneumonia among adults: a systematic review and meta-analysis of diagnostic techniques. *PloS one*, 8(4), e60273 (2013). [PubMed: 23565216]
90. Bellew S, Grijalva CG, Williams DJ et al. Pneumococcal and Legionella Urinary Antigen Tests in Community-acquired Pneumonia: Prospective Evaluation of Indications for Testing. *Clin Infect Dis*, [Epub ahead of print] (2018).
91. Weinberger DM, Malley R, Lipsitch M. Serotype replacement in disease after pneumococcal vaccination. *Lancet*, 378(9807), 1962–1973 (2011). [PubMed: 21492929]
92. Huijts SM, Boersma WG, Grobbee DE et al. Predicting pneumococcal community-acquired pneumonia in the emergency department: evaluation of clinical parameters. *Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases*, 20(12), 1316–1322 (2014).
93. Pride MW, Huijts SM, Wu K et al. Validation of an immunodiagnostic assay for detection of 13 *Streptococcus pneumoniae* serotype-specific polysaccharides in human urine. *Clinical and vaccine immunology : CVI*, 19(8), 1131–1141 (2012). [PubMed: 22675155]
94. Grijalva CG, Wunderink RG, Zhu Y et al. In-Hospital Pneumococcal Polysaccharide Vaccination Is Associated With Detection of Pneumococcal Vaccine Serotypes in Adults Hospitalized for Community-Acquired Pneumonia. *Open forum infectious diseases*, 2(4), 135 (2015).
95. Gierke R. Estimating impact of 13-valent pneumococcal conjugate vaccine (PCV13) on pneumococcal pneumonia among adults; Advisory Committee on Immunization Practices, October 2018 Meeting; 2018. <https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2018-10/Pneumococcal-03-Gierke-508.pdf>
96. Matanock A. Invasive Pneumococcal Disease in the US - 2008–2016; Advisory Committee on Immunization Practices, October 2017 Meeting; <https://stacks.cdc.gov/view/cdc/57593107>
97. 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*, 12(5), e0177113 (2017). [PubMed: 28486544]
98. Grabenstein JD, Musey LK. Differences in serious clinical outcomes of infection caused by specific pneumococcal serotypes among adults. *Vaccine*, 32(21), 2399–2405 (2014). [PubMed: 24637174]
99. Weinberger DM, Harboe ZB, Sanders EA et al. Association of serotype with risk of death due to pneumococcal pneumonia: a meta-analysis. *Clin Infect Dis*, 51(6), 692–699 (2010). [PubMed: 20715907]
100. Harboe ZB, Dalby T, Weinberger DM et al. Impact of 13-valent pneumococcal conjugate vaccination in invasive pneumococcal disease incidence and mortality. *Clin Infect Dis*, 59(8), 1066–1073 (2014). [PubMed: 25034421]
101. Weinberger DM, Warren JL, Dalby T et al. Differences in the impact of pneumococcal serotype replacement in individuals with and without underlying medical conditions. *Clin Infect Dis*, [Epub ahead of print] (2018).
102. De Wals P Commentary on paradoxical observations pertaining to the impact of the 13-valent pneumococcal conjugate vaccine on serotype 3 *Streptococcus pneumoniae* infections in children. *Vaccine*, 36(37), 5495–5496 (2018). [PubMed: 30077481]
103. Choi EH, Zhang F, Lu YJ, Malley R. Capsular Polysaccharide (CPS) Release by Serotype 3 Pneumococcal Strains Reduces the Protective Effect of Anti-Type 3 CPS Antibodies. *Clinical and vaccine immunology : CVI*, 23(2), 162–167 (2016). [PubMed: 26677201]
104. Sings HL, De Wals P, Gessner BD et al. Effectiveness of 13-Valent Pneumococcal Conjugate Vaccine Against Invasive Disease Caused by Serotype 3 in Children: A Systematic Review and Meta-Analysis of Observational Studies. *Clin Infect Dis*, [Epub ahead of print] (2018).
105. Principi N, Esposito S. Prevention of Community-Acquired Pneumonia with Available Pneumococcal Vaccines. *International journal of molecular sciences*, 18(1) (2016).
106. Andrews RM, Counahan ML, Hogg GG, McIntyre PB. Effectiveness of a publicly funded pneumococcal vaccination program against invasive pneumococcal disease among the elderly in Victoria, Australia. *Vaccine*, 23(2), 132–138 (2004). [PubMed: 15531029]

107. Moberley S, Holden J, Tatham DP, Andrews RM. Vaccines for preventing pneumococcal infection in adults. The Cochrane database of systematic reviews, (1), Cd000422 (2013). [PubMed: 23440780]
108. Djennad A, Ramsay ME, Pebody R et al. Effectiveness of 23-valent polysaccharide pneumococcal vaccine and changes in invasive pneumococcal disease incidence from 2000 to 2017 in those aged 65 and over in England and Wales. *EClinicalMedicine*, [in press] (2019).
109. Huss A, Scott P, Stuck AE, Trotter C, Egger M. Efficacy of pneumococcal vaccination in adults: a meta-analysis. *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne*, 180(1), 48–58 (2009).
110. Black CL, Williams WW, Arbeloa I et al. Trends in Influenza and Pneumococcal Vaccination Among US Nursing Home Residents, 2006–2014. *Journal of the American Medical Directors Association*, 18(8), 735.e731–735.e714 (2017). [PubMed: 28623156]
111. Lu PJ, Nuorti JP. Pneumococcal polysaccharide vaccination among adults aged 65 years and older, U.S., 1989–2008. *Am J Prev Med*, 39(4), 287–295 (2010). [PubMed: 20837278]
112. Pneumococcal Polysaccharide Vaccine (PPV) coverage report, England, April 2017 to March 2018. Public Health England, https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/730029/hpr2718_ppv-vc2.pdf (2018).
113. Lindenauer PK, Lagu T, Shieh MS, Pekow PS, Rothberg MB. Association of diagnostic coding with trends in hospitalizations and mortality of patients with pneumonia, 2003–2009. *JAMA*, 307(13), 1405–1413 (2012). [PubMed: 22474204]
114. van de Garde EM, Oosterheert JJ, Bonten M, Kaplan RC, Leufkens HG. International classification of diseases codes showed modest sensitivity for detecting community-acquired pneumonia. *Journal of clinical epidemiology*, 60(8), 834–838 (2007). [PubMed: 17606180]
115. Fedson DS. PCV13 vaccination for older adults: Another view. *Vaccine*, 34(38), 4466 (2016). [PubMed: 27553745]
116. Swanson DS, Harrison CJ. Playing “Whack-a-Mole” With Pneumococcal Serotype Eradication. *Pediatrics*, 140(5) (2017).
117. McLaughlin JM, Utt EA, Hill NM, Welch VL, Power E, Sylvester GC. A current and historical perspective on disparities in US childhood pneumococcal conjugate vaccine adherence and in rates of invasive pneumococcal disease: Considerations for the routinely-recommended, pediatric PCV dosing schedule in the United States. *Human vaccines & immunotherapeutics*, 12(1), 206–212 (2016). [PubMed: 26376039]
118. Arancibia F, Ruiz M. Risk Factors for Drug-Resistant Cap in Immunocompetent Patients. *Current infectious disease reports*, 19(3), 11 (2017). [PubMed: 28251510]

ARTICLE HIGHLIGHTS

- Pneumococcal conjugate vaccines have proven effective against invasive pneumococcal disease and non-invasive pneumonia among young children in the US
- The quantification of indirect protection against non-invasive pneumonia among adults requires additional study.
- The impact of the recommendation for direct PCV13 vaccination among older adults in the US remains unclear as ACIP continues to re-evaluate the current recommendation
- New pneumococcal conjugate vaccines with expanded valency are under development and their licensure and use may lead to a greater impact against invasive pneumococcal disease and non-invasive pneumonia

Table 1.

Characteristics of key studies evaluating the impact of PCVs introduction on pneumonia in the United States

	Publication Year	Population	Data source	Years in study	Relevant Outcome	Main evaluation of interest	Relevant findings to PCV impact on all-cause pneumonia
Grijalva et al. <i>Lancet</i> [53]	2007	Children <2 years	National Inpatient Sample	1997–2004	<ul style="list-style-type: none"> • All-cause pneumonia hospitalizations • Dehydration (control) 	Compared hospitalization rates before and after PCV7 introduction ¹ using time-series analysis	<ul style="list-style-type: none"> • Children <2 years: All-cause pneumonia declined 39% for children <2 years (rate difference: 506 per 100,000)
Zhou et al. <i>Arch Pediatr Adolesc Med</i> [59]	2007	Children <2 years	Claims database encompassing 40 employer-based insurance programs	1997–2004	<ul style="list-style-type: none"> • All-cause pneumonia • Pneumococcal pneumonia 	Compared hospitalization and ambulatory visits rates before and after PCV7 introduction ¹	<ul style="list-style-type: none"> • Children < 2 years: All-cause pneumonia hospitalizations declined 52.4% decline (11.5 to 5.5 per 1,000) and pneumonia ambulatory visits declined 41.1% (99.3 to 58.5 per 1,000) in 2001–2004 compared to 1997 to 1999
Nelson et al. 2008. <i>Vaccine</i> [58]	2008	All ages	Group Health (privately insured) database	1998–2004	<ul style="list-style-type: none"> • Presumptive pneumonia hospitalizations and outpatient encounters • Confirmed pneumonia hospitalizations and outpatient encounters 	Compared hospitalization rates before and after PCV7 introduction ¹	<ul style="list-style-type: none"> • Children <1 year: Non-significant reductions in confirmed hospitalizations [aIRR: 0.90; absolute risk reduction: 0.4 per 1000py]) • Children 1–2 years: Non-significant reductions in confirmed hospitalizations [aIRR: 0.91, absolute risk reduction: 0.3 per 1000py]) compared to pre-PCV7 rate 0.91 per 1000 py • Children 3–4 years: Non-significant reductions in confirmed hospitalizations [aIRR: 0.90, absolute risk reduction: 0.1 per 1000py]) compared to pre-PCV7 rate 0.90 per 1000 py • Children 5–17 years: Non-significant reductions in confirmed hospitalizations [aIRR: 0.84, absolute risk reduction: 0.0 per

Publication Year	Population	Data source	Years in study	Relevant Outcome	Main evaluation of interest	Relevant findings to PCV impact on all-cause pneumonia
						<p>1000py)] compared to pre-PCV7 rate 0.84 per 1000 py. Significant 18% increase in outpatient pneumonia compared to pre-PCV7.</p> <p>• Adults 18–64: Significant 17% increase in confirmed hospitalizations for pneumonia compared to pre-PCV7. Significant 34% increase in outpatient pneumonia compared to pre-PCV7</p> <p>• Adults 65–74: Significant 30% increase in confirmed hospitalizations for pneumonia compared to pre-PCV7</p> <p>• Adults >=65 years: Significant 47% increase in confirmed hospitalizations for pneumonia compared to pre-PCV7</p>
Lee et al. <i>Pediatrics</i> [56]	2010	Children <18 years	Kids Inpatient Databases	1997, 2000, 2003, 2006	• All-cause pneumonia hospitalizations	<p>Compared rates before and after PCV7 introduction¹</p> <p>• Children <18 years: Overall rates of community-acquired pneumonia did not change after PCV7 introduction (199.1 per 100,000 in 1997 and 201.2 per 100,000 in 2006)</p> <p>• Children <1 year: A 22% decrease in community-acquired pneumonia was observed in 2006 compared to 1997 before PCV7 introduction (1,169 versus 912.9 per 100,000)</p> <p>• Children 1–5 years: No significant change was observed in community-acquired pneumonia after PCV7 introduction</p> <p>• Children 5–12 years: A 21.9% increase in pneumonia hospitalizations</p>

Publication Year	Population	Data source	Years in study	Relevant Outcome	Main evaluation of interest	Relevant findings to PCV impact on all-cause pneumonia
						(rate difference: 15.2 per 100,000) in 2006 compared to 1997 • Children 13–18 years: A 40.5% increase in pneumonia hospitalizations (rate difference 18.1 per 100,000) in 2006 compared to 1997
Griffin et al. <i>NEJM</i> [63]	2013	All ages	National Inpatient Sample	1997–2009	<ul style="list-style-type: none"> • All-cause pneumonia hospitalizations (primary and secondary) 	Compared hospitalizations rates before and after PCV7 introduction ¹ • Children <2 years: PCV7 associated with absolute rate reduction of 551.1 per 100,000 (95% CI: 445.1 to 657.1)] • Adults ≥85 years: PCV7 associated with absolute rate reduction of 1,300.8 per 100,000 (95% CI: 984.0 to 1617.6)] • Children 2–17 years: No observed changes associated with PCV7 • Adults 18–84 years: No observed changes associated with PCV • All ages: Overall reduction was 54.8 fewer hospitalizations per 100,000 (95% CI: 41.0 to 68.5) associated with PCV7 introduction
Griffin et al. <i>MMWR</i> [65]	2014	Children <2 years	Tennessee Hospital Discharge Data System	1998–2012	<ul style="list-style-type: none"> • All-cause pneumonia hospitalizations • Fractures (control) 	Compared hospitalization rates before and after PCV7/PCV13 introduction ¹ • Children <2 years: Absolute number of pneumonia hospitalizations declined by around 1,400 cases • Children <2 years: The rate of pneumonia hospitalizations declined from 14.5 per 1,000 in the pre-PCV7 era to 8.6 in the PCV7 years • Children <2 years: The rate of hospitalizations declined to 4.1 per 1,000 after PCV13 introduction compared to PCV7 years • Children <2 years: No

Publication Year	Population	Data source	Years in study	Relevant Outcome	Main evaluation of interest	Relevant findings to PCV impact on all-cause pneumonia
						meaningful reduction in the rate of fractures was observed
Loo et al. <i>Pediatr Infect Dis J</i> [74]	2014	All ages	7 population-based pneumonia studies (5 with 3+1 schedule, 1 with 3+0 and 1 with 2+1)	n/a	<ul style="list-style-type: none"> • IPD • Nasopharyngeal carriage • Pneumonia² 	Systematic review examining the impact of PCV7 introduction ¹ • Non-vaccinated age groups (varied across studies: 44.4% of studies (n=9) provided evidence of a significant reduction of pneumonia in non-vaccinated age groups (2 in the US with 3+1, 1 in Taiwan with 3+1, 1 in Australia with 3+0) with no reduction observed in the other 2 studies (1 in Poland with 2+1 and 1 in US with 3+1 schedule) • Children 5–17 years: Two studies demonstrated PCV7 introduction was associated with significant reductions in pneumonia • Adults 18–38 years: Two studies demonstrated PCV7 introduction associated with significant reductions in pneumonia, one study did not demonstrate a reduction (18–49 years age group used) • Older adults >65 years: One study demonstrated an increase in pneumonia after PCV7 introduction
Simonsen et al. <i>Lancet Respir Med</i> [64]	2014	All ages	IMS Charge Data Master Hospital Database	2005–2015	<ul style="list-style-type: none"> • Invasive pneumococcal disease • Pneumococcal syndromes • All-cause pneumonia • Empyema • Urinary tract infections (control) • Total number of admissions (control) 	Compared hospitalization rates before and after PCV13 introduction ¹ • Children <2 years: PCV13 associated with 21% (95% CI: 14 to 28; estimated n=13,955) reduction in all-cause pneumonia within 2 years after PCV13 introduction and reduction observed for non-invasive confirmed pneumococcal pneumonia • Children 2–4 years: PCV13 associated with 17% (95% CI: 7 to 27;

Publication Year	Population	Data source	Years in study	Relevant Outcome	Main evaluation of interest	Relevant findings to PCV impact on all-cause pneumonia
						<p>estimated n=8,603) reduction in all-cause pneumonia within 2 years after PCV13 introduction</p> <p>• Adults 5–17 years: No reduction in pneumonia observed associated with PCV13 introduction, though reduction observed for non-invasive confirmed pneumococcal pneumonia</p> <p>• Adults 18–39 years: PCV13 associated with 12% (95% CI: 6 to 17; n=9,484) reduction in all-cause pneumonia within 2 years after PCV13 introduction and reduction observed for non-invasive confirmed pneumococcal pneumonia</p> <p>• Adults 40–64 years: No reduction in pneumonia observed associated with PCV13 introduction, though reduction observed for non-invasive confirmed pneumococcal pneumonia</p> <p>• Adults >=65 years: No reduction in all-cause pneumonia observed associated with PCV13 introduction, though reduction observed for non-invasive confirmed pneumococcal pneumonia</p>
Park et al. <i>Clin Ther</i> [9]	2015	All ages	Medical Expenditure Panel Survey Database	2007–2011	• All-cause pneumonia hospitalizations	<p>Compared hospitalization rates before and after PCV13 introduction¹</p> <p>• All ages: PCV13 associated with 16% decrease in pneumonia from 16.5 per 1,000 patients before PCV13 (2007–2009) to 13.9 per 1,000 after PCV13 (2011), although the finding was not significant</p>
Chang et al. <i>Vaccine</i> [54]	2016	All ages	National Inpatient Sample	1996–2011	• All-cause pneumonia and influenza hospitalizations	<p>Compared trend of hospitalization rate before and</p> <p>• All ages: Total decline in pneumonia and influenza was 95 per</p>

Publication Year	Population	Data source	Years in study	Relevant Outcome	Main evaluation of interest	Relevant findings to PCV impact on all-cause pneumonia
					after PCV7/ PCV13 introduction ¹	100,000 from 1996 to 2011 • Children <2 years: Decline of 228 per 100,000 observed associated with PCV7 and PCV13 introduction • Adults >=65 years: Largest decline observed among older adults 65 years (487 per 100,000)
Kornetsky et al. <i>Antibiot Khimioter</i> [69]	2016	All ages	22 original publications and 1 review	n/a	• IPD • Pneumonia ²	Systematic review of the impact of PCV7/PCV13 introduction ¹ • Children <5 years: The impact of PCV introduction in the US on pneumonia hospitalizations among children <5 years is comparable to other industrialized and developing countries
Stoecker et al. <i>J Gen Intern Med</i> [51]	2016	Older adults	Probabilistic cohorts of 50+, 60+ and 65+ adults with different vaccination coverage and disease incidence rates	n/a	• Cost per quality-adjusted life year gained	Estimation of cost-effectiveness of direct PCV13 introduction in adults • Adults >=65 years: Evidence supports PCV13 use in adults at 65 years of age (either adding to series with PPSV23 or in replacement of PPSV23) due to higher value relative to PCV13 use at an earlier age than recommending PCV13 use at an earlier age • Adults >=65 years: The cost of recommending PCV13 use in adults >=65 years of age was \$62,065 per quality-adjusted life-year in 2013 (at the time of the recommendation), with substantial increases in cost per quality-adjusted life-years after 6 years of projected herd protection (\$272,621/QALY).
Wiese et al. <i>Emerg Infect Dis</i> [67]	2016	Children <18 years	Tennessee Hospital Discharge Data System	1998–2013	• Primary hospitalization for pneumonia • All-cause hospitalization for pneumonia	Compared hospitalization rates before and after PCV7/PCV13 introduction ¹ • Children <18 years: Overall decline in pneumonia hospitalization rate from 4.0 per 1,000 children in 1998–1999 to 2.0 per 1,000 children in 2011–2013.

Publication Year	Population	Data source	Years in study	Relevant Outcome	Main evaluation of interest	Relevant findings to PCV impact on all-cause pneumonia
						<p>Absolute differences in rate across Whites and Blacks declined significantly and substantially during the study period (especially for children 2–4 years), though meaningful differences in pneumonia rates still exist by sex (higher rates in males within race and age categories)</p> <p>• Children <2 years: Largest absolute (–18.6 and –13.6 per 1,000 reduction in rate for Black males and females, respectively) and relative reduction (RR: 0.31 and 0.32 for Black males and females) in the PCV13 years compared to the pre-PCV7 years</p>
Bruhn et al. <i>Proc Natl Acad Sci USA</i> [60]	2017	All ages	10 US State Inpatient Databases	1994–2005	• All-cause pneumonia hospitalizations	<p>Synthetic control analysis to examine trend of hospitalization rates before and after PCV7 introduction¹</p> <p>• Children <1 year: PCV7 associated with 14% reduction (95% CI: 0.77 to 0.96) compared to pre-PCV7 counterfactual</p> <p>• Children 1–17: PCV7 not associated with a significant reduction in pneumonia hospitalizations</p> <p>• Adults 18–39 years: PCV7 associated with 14% increase in pneumonia among those 18–39 years (95% CI: 1.00 to 1.31)</p> <p>• Adults 40–79 years: PCV7 not associated with a significant reduction in pneumonia hospitalizations</p> <p>• Adults ≥80 years: PCV7 not associated with a significant reduction in pneumonia hospitalizations</p>
Kurum et al. <i>Epidemiology</i> [61]	2017	Children <5 years	10 US State Inpatient Databases	1996–2010	<p>• IPD</p> <p>• Pneumococcal pneumonia</p> <p>• All-cause pneumonia</p>	<p>Changepoint analysis to examine the trend of hospitalizations</p> <p>• Children <12 months: All-cause pneumonia declined 26% and 33% at 2</p>

Publication Year	Population	Data source	Years in study	Relevant Outcome	Main evaluation of interest	Relevant findings to PCV impact on all-cause pneumonia	
					before and after PCV7/PCV10 introduction ¹	and 4 years after PCV7 introduction • Children 12–23 months: All-cause pneumonia declined 10% at both 2 and 4 years after PCV7 introduction • Children 2–5 years: All-cause pneumonia did not significantly decrease among children 24–59 months of age at any time	
McLaughlin et al. <i>Clin Infect Dis</i> [81]	2018	Older adults >= 65 years of age	Population-based surveillance study in Louisville, Kentucky	2015–2016	• Vaccine-type community-acquired pneumonia	Compared vaccine effectiveness of direct receipt of PCV13 versus no PCV13	• Adults >=65 years: Pneumonia cases with positive test for PCV13 serotypes were less likely to have received PCV13 [4.4% (3/68) versus 14.5% (285/1966)] • Adults >=65 years: Adjusted vaccine efficacy after controlling for patient characteristics, immunosuppression, BMI, and history of prior influenza and PPSV23 vaccination, VE range was 71.1% to 73.3%
Pelton et al. <i>Clin Infect Dis</i> [75]	2018	All ages	Patients identified from two US private healthcare claims repositories	2007–2015	• IPD • Pneumococcal pneumonia hospitalizations • All-cause pneumonia hospitalizations	Compared hospitalization rates before and after PCV13 introduction ¹	• Adults 18–49 years: PCV13 introduction in children associated with 11% (95% CI: 8–13; 39 per 100,000py) reduction in all-cause pneumonia after 2 years and 19% reduction in all-cause pneumonia after 5 years (95% CI: 16%-21%; 35 per 100py) compared to 2007–2010 (PCV7 era; 44 per 100,000py) • Adults 50–64 years: PCV13 introduction in children associated with 9% (95% CI: 6–11; 90 per 100,000py) reduction in all-cause pneumonia after 2 years and 11% reduction in all-cause pneumonia after 5 years (95%

Publication Year	Population	Data source	Years in study	Relevant Outcome	Main evaluation of interest	Relevant findings to PCV impact on all-cause pneumonia
						<p>CI: 9–13%; 88 per 100py) compared to 2007–2010 (PCV7 era; 99 per 100,000py)</p> <p>• Adults 65–74 years: PCV13 introduction in children associated with 8% (95% CI: 3–12; 204 per 100,000py) reduction in all-cause pneumonia after 2 years and 13% reduction in all-cause pneumonia after 5 years (95% CI: 10–17%; 191 per 100py) compared to 2007–2010 (PCV7 era; 220 per 100,000py)</p> <p>• Adults >=75 years: PCV13 introduction in children associated with 4% (95% CI: 2% to 7% increase; 918 per 100,000py) increase in all-cause pneumonia after 2 years and 9% increase in all-cause pneumonia after 5 years (95% CI: 6% to 11% increase; 957 per 100py) compared to 2007–2010 (PCV7 era; 880 per 100,000py)</p>
Vadlamudi et al. <i>Clin Infect Dis</i> [76]	2018	All ages	29 observational studies (7 of which assessed pneumonia as an outcome)	<ul style="list-style-type: none"> • IPD • Non-invasive pneumococcal disease (including pneumonia²) • Hospitalizations • Mortality 	Systematic review of the impact of PCV13 introduction ¹	<p>• All ages: Pooled rates from 7 observational studies (n=76,337) indicated a moderate 14% risk reduction for pneumonia associated with PCV13 introduction [IRR: 0.86 (95% CI: 0.77–0.96)]</p> <p>• All ages: Pooled rates from 2 observational studies (n=4,364) indicated no significant reduction in non-invasive pneumococcal diseases (including pneumonia, sinusitis, otitis media, pharyngitis and others [IRR: 1.13 (95% CI: 0.72–1.78)])</p> <p>• All ages: Of note, pooled mortality</p>

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Publication Year	Population	Data source	Years in study	Relevant Outcome	Main evaluation of interest	Relevant findings to PCV impact on all-cause pneumonia
						rates from 5 studies indicated a 30% reduction in pneumonia-related mortality after PCV13 introduction [n=20,437; IRR: 0.71 (95% CI: 0.54–0.93) for those >=65 years and IRR: 0.68 (95% CI: 0.56–0.83) for those under 65 years]

¹Introduction in US routine childhood vaccination schedule (PCV7 introduced in 2000 and PCV13 introduced in 2010)

²In systematic reviews and meta analyses the definitions of the outcome varied across each study

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