

A SELECTION OF TEN READINGS ON TOPICS RELATED TO THE EVOLUTION OF PNEUMOCOCCAL VACCINES

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Selection of readings made by A/Prof Goh Lee Gan

READING 1 – VACCINE-PREVENTABLE HOSPITALISATIONS FROM SEASONAL RESPIRATORY VIRUSES. WHAT IS THE TRUE VALUE OF SUCH VACCINES?

Neri M,¹ Brassel S,¹ Steuten L,¹ Schirrmacher H,² Mendes D,³ Vyse A,³ Hamson E.³ Vaccine-Preventable Hospitalisations from Seasonal Respiratory Diseases: What Is Their True Value? Vaccines (Basel). 2023 May 4;11(5):945. PMID: 37243048.

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ABSTRACT

INTRODUCTION: Hospitals in England experience extremely high levels of bed occupancy in the winter. In these circumstances, vaccine-preventable hospitalisations due to seasonal respiratory infections have a high cost because of the missed opportunity to treat other patients on the waiting list.

This paper estimates the number of hospitalisations that current vaccines against influenza, pneumococcal disease (PD), COVID-19, and a hypothetical Respiratory Syncytial Virus (RSV) vaccine could prevent among older adults during winter in England.

METHODS: Their costs were quantified using a conventional reference costing method and a novel opportunity costing approach considering the net monetary benefit (NMB) obtained from alternative uses of the hospital beds freed up by vaccines.

RESULTS: The influenza, PD, and RSV vaccines could collectively prevent 72,813 bed days and save over £45 million in hospitalisation costs. The COVID-19 vaccine could prevent over 2 million bed days and save £1.3 billion. However, the value of hospital beds freed up by vaccination is likely to be 1.1-2 times larger (£48-93 million for flu, PD and RSV; £1.4-2.8 billion for COVID-19) when quantified in opportunity cost terms.

CONCLUSION: Considering opportunity costs is key to ensuring maximum value is obtained from preventative budgets, as reference costing may significantly underestimate the true value of vaccines.

READING 2 – PNEUMOCOCCAL CONJUGATE VACCINES REDUCE RISK OF RESPIRATORY DISEASE ASSOCIATED WITH CORONAVIRUS INFECTION

Dunne EM,¹ Nunes MC,^{2,3} Slack MPE,⁴ Theilacker C,⁵ Gessner BD.⁵ Effects of pneumococcal conjugate vaccines on reducing the risk of respiratory disease associated with coronavirus infection. Pneumonia (Nathan). 2023 May 25;15(1):10. PMID: 37226198.

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ABSTRACT

INTRODUCTION: Pneumococcal conjugate vaccines (PCVs) provide protection against vaccine-type pneumococcal disease in both children and adults. Growing evidence suggests that PCVs also reduce pneumonia and lower respiratory tract infections (LRTIs) more broadly, including protecting against viral-associated respiratory diseases.

METHODS: In this short narrative review, we highlight clinical studies investigating whether PCVs might have a role in reducing coronavirus disease, both those caused by endemic human coronaviruses (HCoVs) and severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2).

RESULTS: These studies include two randomised controlled trials assessing HCoV-associated pneumonia, one each in children and older adults, and two observational studies of PCV13 effectiveness against HCoV-associated LRTI and COVID-19 in adults.

DISCUSSION: We discuss possible mechanisms for PCV protection including preventing viral pneumococcal co-infections and the possibility that pneumococci in the upper respiratory tract might modify the host immune response to SARS-CoV-2.

CONCLUSION: Lastly, we identify knowledge gaps and further questions on the potential role of PCVs during the COVID-19 pandemic.

READING 3 – DETERMINANTS OF INFLUENZA AND PNEUMOCOCCAL VACCINE UPTAKE AMONG PRESCHOOL CHILDREN IN SINGAPORE

Zahari M,¹ Offeddu V,¹ Tam CC,^{1,5} Smith GJD.^{2,3,4} Determinants of influenza and pneumococcal vaccine uptake among preschool children in Singapore. *PLoS One*. 2023 May 17;18(5):e0285561. PMID: 37196045.

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ABSTRACT

INTRODUCTION: Young children are at increased risk of severe illness from influenza and pneumococcal infections. The World Health Organization (WHO) recommends vaccination with influenza and pneumococcal conjugate vaccine (PCV). However, in Singapore, vaccine uptake remains suboptimal relative to other routine childhood immunisations. Limited information exists regarding determinants of influenza and pneumococcal vaccine uptake in children.

METHODS: We estimated vaccine uptake and investigated factors associated with influenza and pneumococcal vaccination status by age group using data from a cohort study on acute respiratory infections in children attending preschools in Singapore. We recruited children aged two to six years at 24 participating preschools from June 2017 to July 2018. We determined the proportion of children immunised with influenza vaccine and PCV, and investigated socio-demographic factors associated with vaccine uptake using logistic regression models.

RESULTS: Among 505 children, 77.5 percent were of Chinese ethnicity, and 53.1 percent were male. History of influenza vaccination was 27.5 percent, of which 11.7 percent had been vaccinated within the past 12 months. In multivariable analyses, factors associated with influenza vaccine uptake were "children living in landed property" (aOR = 2.25, 95 percent CI [1.07-4.67]) and "history of hospitalisation due to cough" (aOR = 1.85, 95 percent CI [1.00-3.36]).

Nearly three-quarters of participants (70.7 percent 95 percent CI: [66.6-74.5]) reported prior PCV vaccination. PCV uptake was higher for younger children. "Higher parental education" (OR = 2.83, 95 percent CI [1.51,5.32]), "household income" (OR = 1.26, 95 percent CI [1.08,1.48]), and "smokers in household" (OR = 0.48, 95 percent CI [0.31,0.74]) were significantly associated with PCV uptake in univariable analyses. Only "smokers in household" remained significantly associated with PCV uptake (aOR = 0.55, 95 percent CI [0.33,0.91]) in the adjusted model.

CONCLUSION: Our results indicate that episodes of severe respiratory illness are a cue to influenza vaccination suggesting that doctors are more likely to recommend influenza vaccines to high-risk children. For PCV, our findings suggest that overall greater awareness and education on the benefit of PCV vaccination is required.

READING 4 – PNEUMOCOCCAL CONJUGATE VACCINES IN INFANTS ARE PROTECTIVE AGAINST RESPIRATORY SYNCYTIAL VIRUS HOSPITALISATIONS

Le H,¹ Blyth CC,^{1,6,7,8} Richmond P,^{1,8} Moore HC,^{1,9} Gidding H.^{2,3,4,5} Pneumococcal Conjugate Vaccines Are Protective Against Respiratory Syncytial Virus Hospitalizations in Infants: A Population-Based Observational Study. *Open Forum Infect Dis.* 2023 Apr 19;10(4):ofad199. PMID: 37125230.

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ABSTRACT

BACKGROUND: Pneumococcal conjugate vaccines (PCV) reduced the risk of respiratory syncytial virus (RSV) in a randomised clinical trial. We aimed to assess the real-world effectiveness of PCV on RSV-hospitalisations among Western Australian infants.

METHODS: We conducted a population-based cohort study of births during from 2000 to 2012, using probabilistically linked individual-level immunisation, hospitalisation, respiratory microbiology testing, and perinatal data. We performed Cox proportional hazard models with time-varying exposure (receipt of infant PCV doses) against the first RSV-confirmed hospitalisation 0-12 months adjusted for perinatal and sociodemographic factors.

RESULTS: From 360,994 children, 3-dose PCV coverage in Aboriginal infants ranged from 29 percent to 51 percent in 2001-2004 when PCV was funded for Aboriginal children only. Following universal funding in 2005, coverage increased to 85 percent for Aboriginal and 73 percent for non-Aboriginal infants. RSV-hospitalisation rates were highest in young infants aged 0-5 months (22.5/1,000 child-years) and >2 times higher in Aboriginal infants than in non-Aboriginal infants. Receipt of ≥3 PCV doses in the universal funded period was associated with a 30 percent reduction in RSV-hospitalisation in Aboriginal infants (adjusted hazard ratio, aHR 0.70 [95 percent confidence interval, CI 0.46-1.06]) and 21 percent reduction in non-Aboriginal infants (aHR 0.79 [95 percent CI 0.63-0.99]) compared with unvaccinated infants.

CONCLUSIONS: Prior to the introduction of RSV vaccines, our study suggests that universal childhood PCV vaccination may result in a reduction in severe RSV infections in children and may be important for countries that are yet to consider PCV programmes.

READING 5 – UNDERSTANDING PARENTAL VACCINE HESITANCY WITH PCV13

Ni YH,¹ Xu ZH,¹ Wang J.¹ **Understanding vaccine hesitancy with PCV13 in children: Results of a survey in Shanghai, China. PLoS One. 2023 Apr 27;18(4):e0284810. PMID: 37104479.**

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ABSTRACT

A questionnaire survey for parents of children under five years of age was conducted to analyse vaccine hesitancy with the 13-valent pneumococcal conjugate vaccine (PCV13) in Shanghai, China.

A total of 892 valid questionnaires were collected. Descriptive statistical methods, Chi-square tests, and effect size of Cohen were used.

Among participants, 421 (48.8 percent) had children who had been vaccinated with PCV13 before the survey while 227 (26.73 percent) planned vaccination with PCV13 in the future. The main reasons for not receiving vaccination were the fear of adverse reactions (79, 26.7 percent), beyond vaccination age (69, 23.3 percent), and no need to vaccinate (44, 14.9 percent).

Reducing vaccine hesitancy and increasing vaccination willingness can be achieved through health interventions, lower vaccine prices, and the adjustment of vaccination strategies.

READING 6 – HISTORICAL POPULATION-LEVEL IMPACT OF INFANT PCV13 NATIONAL IMMUNISATION PROGRAMMES

Perdrizet J,¹ Horn EK,² Huang L,² Hayford K,³ Grant L,³ Barry R,³ McDade C,⁴ Wilson M.⁴ **Historical Population-Level Impact of Infant 13-Valent Pneumococcal Conjugate Vaccine (PCV13) National Immunization Programs on Invasive Pneumococcal Disease in Australia, Canada, England and Wales, Israel, and the United States. Infect Dis Ther. 2023 May;12(5):1351-1364. PMID: 37079175.**

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ABSTRACT

INTRODUCTION: This study estimates the annual population-level impact of 13-valent pneumococcal conjugate vaccine (PCV13) infant national immunisation programmes (NIPs) on vaccine-type and non-vaccine type invasive pneumococcal disease (IPD) incidence across all ages using national surveillance data.

METHODS: We identified countries (Australia, Canada, England, Wales, Israel, and the US) with national IPD active surveillance data that introduced the seven-valent PCV (PCV7) followed by PCV13, which also reported annual serotype- and age group-specific incidence. We extracted IPD incidence by serotype groupings [PCV13 minus PCV7 (PCV13-7) serotypes; PCV13-7 serotypes excluding serotype 3; non-PCV13 serotypes; and the 20-valent (PCV20) minus PCV13 (PCV20-13) serotypes] and by age groups (<2 years, 2-4 years, 5-17 years, 18-34 years, 35-49 years, 50-64 years, and ≥65 years). For each country, we calculated the annual relative change in IPD incidence (percent change) and the corresponding incidence rate ratio (IRR) for seven years post-introduction compared to the year prior to PCV13 programme initiation.

RESULTS: PCV13-7 vaccine-type IPD incidence consistently decreased over time following the introduction of PCV13 across countries, reaching an approximate steady state after 3-4 years in ages <5 years, with roughly 60-90 percent decrease (IRRs = 0.1-0.4) and after 4-5 years in ages ≥65 years with approximately 60-80 percent decrease (IRRs = 0.2-0.4). Incidence declines were more substantial for the PCV13-7 grouping when excluding serotype 3.

Non-PCV13 serotype incidence was variable by country and age group, ranging from virtually no serotype replacement compared to the PCV7 period across ages in the US to increases for other countries ranging from 10 to 204 percent (IRRs = 1.10-3.04) in children <5 years and 41 percent to 123 percent (IRRs = 1.41-2.23) in ages ≥65 years.

CONCLUSIONS: Countries with longstanding PCV13 infant NIPs have observed substantial direct and indirect benefits, which are demonstrated in this study by the reduction in PCV13-7 IPD incidence compared to PCV7 period in all age groups. Over time, non-PCV13 serotypes have emerged in response to the reduction of incidence of PCV13-unique serotypes. Higher-valent PCVs are needed to address this emerging pneumococcal disease burden as well as the direct vaccination of both pediatric and adult populations against the most prevalent circulating serotypes.

READING 7 – EFFICACY AGAINST PNEUMOCOCCAL CARRIAGE

Temple B,¹ Tran HP,² Nguyen TV,² Dai VTT,³ Smith-Vaughan H,⁴ Licciardi PV,⁵ Satzke C,⁶ Mulholland K,⁷ VPT-II Collaborator Group. Efficacy against pneumococcal carriage and the immunogenicity of reduced-dose (0 + 1 and 1 + 1) PCV10 and PCV13 schedules in Ho Chi Minh City, Viet Nam: a parallel, single-blind, randomised controlled trial. *Lancet Infect Dis.* 2023 Apr 13;S1473-3099(23)00061-0. PMID: 37062304

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ABSTRACT

BACKGROUND: Interest in reduced-dose pneumococcal conjugate vaccine (PCV) schedules is growing, but data on their ability to provide direct and indirect protection are scarce. We evaluated 1 + 1 (at two and 12 months) and 0 + 1 (at 12 months) schedules of PCV10 or PCV13 in a predominately unvaccinated population.

METHODS: In this parallel, single-blind, randomised controlled trial, healthy infants aged two months were recruited from birth records in three districts in Ho Chi Minh City, Vietnam, and assigned (4:4:4:4:9) to one of five groups: PCV10 at 12 months of age (0 + 1 PCV10), PCV13 at 12 months of age (0 + 1 PCV13), PCV10 at two months and 12 months of age (1 + 1 PCV10), PCV13 at two months and 12 months of age (1 + 1 PCV13), and unvaccinated control. Outcome assessors were masked to group allocation, and the infants' caregivers and those administering vaccines were not. Nasopharyngeal swabs collected at six months, 12 months, 18 months, and 24 months were analysed for pneumococcal carriage. Blood samples collected from a subset of participants (200 per group) at various timepoints were analysed by ELISA and opsonophagocytic assay. The primary outcome was the efficacy of each schedule against vaccine-type carriage at 24 months, analysed by intention to treat for all those with a nasopharyngeal swab available. This trial is registered at ClinicalTrials.gov, NCT03098628.

FINDINGS: 2,501 infants were enrolled between 8 March 2017, and 24 July 2018 and randomly assigned to study groups (400 to 0+1 PCV10, 400 to 0+1 PCV13, 402 to 1+1 PCV10, 401 to 1+1 PCV13, and 898 to control). Analysis of the primary endpoint included 341 participants for 0+1 PCV10, 356 0+1 PCV13, 358 1+1 PCV10, 350 1+1 PCV13, and 758 control.

At 24 months, a 1+1 PCV10 schedule reduced PCV10-type carriage by 58 percent (95 percent CI 25 to 77), a 1+1 PCV13 schedule reduced PCV13-type carriage by 65 percent (42 to 79), a 0+1 PCV10 schedule reduced PCV10-type carriage by 53 percent (17 to 73), and a 0+1 PCV13 schedule non-significantly reduced PCV13-type carriage by 25 percent (-7 to 48) compared with the unvaccinated control group. Reactogenicity and serious adverse events were similar across groups.

INTERPRETATION: A 1+1 PCV schedule greatly reduces vaccine-type carriage and is likely to generate substantial herd protection and provide some degree of individual protection during the first year of life. Such a schedule is suitable for mature PCV programmes or for introduction in conjunction with a comprehensive catch-up campaign, and potentially could be most effective given as a mixed regimen (PCV10 then PCV13). A 0+1 PCV schedule has some effect on carriage along with a reasonable immune response and could be considered for use in humanitarian crises or remote settings.

READING 8. PCV VACCINATION IN CHILDREN FOLLOWING EPI REDUCES FUTURE DEATHS FROM PNEUMONIA

Shahid ASMSB,¹ Rahman AE,¹ Afroze F,¹ Sarmin M,¹ Nuzhat S,¹ Alam T,¹ Chowdhury F,¹ Ackhter MM,¹ Parvin I,¹ Saha H,¹ Islam SB,¹ Shahrin L,¹ Ahmed T,¹ Chisti MJ,¹ Shahunja KM,² Sultana MS.³ Vaccination following the expanded programme on immunization schedule could help to reduce deaths in children under five hospitalized for pneumonia and severe pneumonia in a developing country. *Front Pediatr.* 2023 Mar 27;11:1054335. PMID: 37051437.

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ABSTRACT

BACKGROUND: Worldwide, pneumonia is the leading cause of mortality in children under the age of five. An expanded programme on immunisation (EPI) is one kind of evidence-based tool for controlling and even eradicating infectious diseases.

OBJECTIVES: This study aimed to explore the impact of EPI vaccination, including BCG, DPT-Hib-Hep B, OPV, IPV, and PCV-10, among children from the age of 4-59 months hospitalised for pneumonia and severe pneumonia. Additionally, we evaluated the role of 10 valent pneumococcal conjugate vaccines alone on clinical outcomes in such children.

METHODS: In this retrospective chart review, children from the age of 4-59 months with WHO-defined pneumonia and severe pneumonia admitted to the Dhaka Hospital of the International Centre for Diarrheal Disease Research, Bangladesh (icddr,b) between August 2013 and December 2017 who had the information on immunisation as per EPI schedule by four months of age were included in the analysis.

A comparison was made between the children who were fully immunised (immunisation with BCG, DPT-Hib-Hep B, OPV, and IPV from 2013 to 2015 and PCV-10 from 2015 to 2017) and who were not immunised (consisting of partial immunisation and no immunisation) during the study period.

RESULTS: A total of 4,625 children had pneumonia and severe pneumonia during the study period. Among them, 2,605 (56.3 percent) had received the information on immunisation, 2,195 (84.3 percent) were fully immunised by four months of age according to the EPI schedule, and 410 were not immunised.

In the log-linear binomial regression analysis, immunisation of children from 4-59 months of age was found to be associated with a lower risk of diarrhoea ($p=0.033$), severe pneumonia ($p=0.001$), anaemia ($p=0.026$), and death ($p=0.035$). Importantly, the risk of developing severe pneumonia (1,054/1,570 [67 percent] vs 202/257 [79 percent], $p<0.001$) and case-fatality rate (57/1,570 [3.6 percent] vs 19/257 [7.4 percent], $p=0.005$) was still significantly lower among those who were immunised with PCV-10 than those who were not.

CONCLUSION: Children immunised as per the EPI schedule were at a lower risk of diarrhoea, severe pneumonia, anaemia, and death, compared to unvaccinated children. In addition, PCV-10 was found to be protective against severe pneumonia and deaths in vaccinated children. The overall results underscored the importance of the continuation of immunisation, scrupulously adhering to the EPI schedule to reduce the risk of morbidities and mortalities in children, especially in resource-limited settings.

READING 9 – FACTORS ASSOCIATED WITH PNEUMOCOCCAL NASOPHARYNGEAL CARRIAGE

Neal EFG,^{1,2} Chan J,^{1,2} Nguyen CD,^{1,2} Russell FM.^{1,2} Factors associated with pneumococcal nasopharyngeal carriage: A systematic review. *PLOS Glob Public Health*. 2022 Apr 11;2(4):e0000327. PMID: 36962225.

doi: 10.1371/journal.pgph.0000327. PMID:36962225. Free full text.

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ABSTRACT

Pneumococcal disease is a major contributor to global childhood morbidity and mortality and is more common in low- and middle-income countries (LMICs) than in high-income countries. Pneumococcal carriage is a prerequisite for pneumococcal disease. Pneumococcal conjugate vaccine reduces vaccine-type carriage and disease. However, pneumococcal carriage and disease persist, and it is important to identify other potentially modifiable factors associated with pneumococcal carriage and determine if risk factors differ between low, middle, and high-income countries.

This information may help inform pneumococcal disease prevention programmes. This systematic literature review describes factors associated with pneumococcal carriage stratified by country income status and summarises pneumococcal carriage rates for included studies.

We undertook a systematic search of English-language pneumococcal nasopharyngeal carriage studies up to 30 June 2021. Peer-reviewed studies reporting factors associated with overall pneumococcal nasopharyngeal carriage in healthy, community-based study populations were eligible for inclusion. Two researchers independently reviewed studies to determine eligibility.

Results are presented as narrative summaries. Eighty-two studies were included, and 46 (56 percent) were conducted in LMICs. There was heterogeneity in the factors assessed in each study.

Factors positively associated with pneumococcal carriage in all income classification were young age, ethnicity, symptoms of respiratory tract infection, childcare attendance, living with young children, poverty, exposure to smoke, season, and co-colonisation with other pathogens. Breastfeeding and antibiotic use were protective against carriage in all income classifications.

Median (interquartile range) pneumococcal carriage rates differed by income classification, ranging from 51 percent (19.3-70.2 percent), 38.5 percent (19.3-51.6 percent), 31.5 percent (19.0-51.0 percent), and 28.5 percent (16.8-35.4 percent) ($P = 0.005$) in low-, lower-middle, upper-middle, and high-income classifications, respectively.

Our findings suggest that, where measured, factors associated with pneumococcal nasopharyngeal carriage are similar across income classifications, despite the highest pneumococcal carriage rates being in low-income classifications.

Reducing viral transmission through vaccination and public health interventions to address social determinants of health would play an important role.

This review is registered with PROSPERO, CRD42020186914.

READING 10 – PNEUMOCOCCAL VACCINATION IN ADULTS

Dunne EM,¹ Cilloniz C,² von Mollendorf C,³ Lewnard J,⁴ Grant LR,⁵ Jodar L,⁵ Theilacker C,⁵ Gessner BD,⁵ Slack MPE.⁶ Pneumococcal Vaccination in Adults: What Can We Learn From Observational Studies That Evaluated PCV13 and PPV23 Effectiveness in the Same Population? *Arch Bronconeumol.* 2023 Mar;59(3):157-164. PMID: 36681604.

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ABSTRACT

INTRODUCTION: Fifteen and 20-valent pneumococcal conjugate vaccines (PCV15; PCV20) were recently licensed to prevent pneumococcal disease in adults. In the absence of efficacy or effectiveness data for these new vaccines, studies comparing 23-valent pneumococcal polysaccharide vaccine (PPV23) and PCV13 might help inform decision-making on how to best implement expanded-valency PCVs. Comparing PPV23 and PCV13 is problematic, as no head-to-head clinical trials evaluated efficacy. Comparing effectiveness results across observational studies that vary by population, design, and outcomes is difficult. To address these limitations, we undertook a narrative review of studies that assessed PPV23 and PCV13 vaccine effectiveness (VE) in the same adult populations.

METHODS: We conducted a literature search in PubMed and Google Scholar and screened 525 studies using a standardised evaluation framework.

RESULTS: Nine studies met inclusion criteria, all from high-income countries. None evaluated invasive pneumococcal disease (IPD) alone. VE against vaccine-type pneumococcal pneumonia ranged from 2 to 6 percent for PPV23 and 41 to 71 percent for PCV13. VE against pneumococcal pneumonia or severe pneumococcal disease (IPD or pneumococcal pneumonia) ranged from -10 to 11 percent for PPV23, 40 to 79 percent for PCV13, and 39 to 83 percent for sequential PCV13/PPV23. VE against all-cause pneumonia or lower respiratory tract infection ranged from -8 to 3 percent for PPV23 and 9 to 12 percent for PCV13.

CONCLUSIONS: Overall, PCV13 demonstrated better protection than PPV23 against pneumococcal disease and all-cause respiratory outcomes in the included studies. Where evaluated, sequential PCV13/PPV23 vaccination showed little benefit over PCV13 alone. Results support the use of PCVs to protect against pneumococcal disease and respiratory infections in adults.