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A SELECTION OF TEN READINGS ON TOPICS RELATED TO COMBATING COMMON RESPIRATORY ILLNESSES: VACCINATION STRATEGIES IN SINGAPORE

FPSC 120: Saturday 6 July, 2.30-5.30 pm
All are available as PMC free full text

Selection of readings made by A/Prof Goh Lee Gan

READING 1 – RESPIRATORY SYNCYTIAL VIRUS (RSV), RECURRENT WHEEZE, AND ASTHMA IN CHILDREN: A NARRATIVE REVIEW

Binns E,[1,2] Tuckerman J,[1,3] Licciardi PV,[1,3] Wurzel D.[3-5] Respiratory syncytial virus, recurrent wheeze and asthma: A narrative review of pathophysiology, prevention and future directions. J Paediatr Child Health. 2022 Oct;58(10):1741-1746. PMID: 36073299.

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ABSTRACT
Globally, respiratory syncytial virus (RSV) is the leading cause of bronchiolitis and pneumonia in young children, and the association between severe RSV disease and later recurrent wheeze and asthma is well established. While a causal link between RSV and wheeze/asthma is not yet proven, immunological evidence suggests skewing towards a Th2-type response, and dampening of IFN-γ antiviral immunity during RSV infection underpins airway hyper-reactivity in a subset of susceptible children after RSV infection. Age at primary RSV infection, viral co-infection, and genetic influences may act as effect-modifiers. Despite the significant morbidity and mortality burden of RSV disease in children, there is currently no licensed vaccine. Recent advancements in RSV preventatives, including long-acting monoclonal antibodies and maternal vaccinations, show significant promise and we are on the cusp of a new era in RSV prevention. However, the potential impact of RSV preventatives on subsequent wheeze and asthma remains unclear.

The ongoing COVID-19 pandemic and associated public health measures have disrupted the usual seasonality of RSV. While this has posed challenges for healthcare services, it has also enhanced our understanding of RSV transmission. The near absence of RSV cases during the first year of the pandemic in the context of strict public health measures has provided a rare opportunity to study the impact of delayed age of primary RSV infection on asthma prevalence.

In this review, we summarise current understanding of the association between RSV, recurrent wheeze, and asthma with a focus on pathophysiology, preventative strategies, and future research priorities.

READING 2 – MODELLING THE HOUSEHOLD LEVEL IMPACT OF A MATERNAL RSV VACCINE IN MELBOURNE, AUSTRALIA

Campbell PT,[1,2] Geard N,[1,3] Hogan AB.[4] Modelling the household-level impact of a maternal respiratory syncytial virus (RSV) vaccine in a high-income setting. BMC Med. 2020 Nov 12;18(1):319. PMID: 33176774.

doi: 10.1186/s12916-020-01783-8. PMID: 33176774. Free full text.

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ABSTRACT

BACKGROUND: Respiratory syncytial virus (RSV) infects almost all children by the age of two years, with the risk of hospitalisation highest in the first six months of life. Development and licensure of a vaccine to prevent severe RSV illness in infants are public health priorities. A recent phase 3 clinical trial estimated the efficacy of maternal vaccination at 39% over the first 90 days of life. Households play a key role in RSV transmission; however, few estimates of population-level RSV vaccine impact account for household structure.

METHODS: We simulated RSV transmission within a stochastic, individual-based model framework, using an existing demographic model, structured by age and household and parameterised with Australian data, as an exemplar of a high-income country. We modelled vaccination by immunising pregnant women and explicitly linked the immune status of each mother-infant pair. We quantified the impact on children for a range of vaccine properties and uptake levels.

RESULTS: We found that a maternal immunisation strategy would have the most substantial impact in infants younger than three months, reducing RSV infection incidence in this age group by 16.6% at 70% vaccination coverage. In children aged 3-6 months, RSV infection was reduced by 5.3%. Over the first six months of life, the incidence rate for infants born to unvaccinated mothers was 1.26 times that of infants born to vaccinated mothers. The impact in older age groups was more modest, with evidence of infections being delayed to the second year of life.

CONCLUSIONS: Our findings show that while individual benefit from maternal RSV vaccination could be substantial, population-level reductions may be more modest. Vaccination impact was sensitive to the extent that vaccination prevented infection, highlighting the need for more vaccine trial data.

READING 3 – GLOBAL EPIDEMIOLOGY OF RSV IN COMMUNITY AND HOSPITALISED CARE, FINDINGS FROM 15 COUNTRIES

Staadegaard L,[1] Caini S,[1] Hooiveld M,[1] Summeren J,[1] Paget J,[1] van Dückers M,[1,24,25] Wangchuk S,[2] Thapa B,[2] de Almeida WAF,[3] de Carvalho FC,[3] Njouom R,[4] Fasce RA,[5] Bustos P,[6] Kyncl J,[7,8] Novakova L,[9] de Mora Coloma DJ,[10] Caicedo AB,[10,11] Meijer A,[12] Huang S,[13] Wood T,[13] Guiomar R,[14] Rodrigues AP,[14] Danilenko D,[15] Stolyarov K,[15] Lee VJM,[16,17] Ang LW,[16,18] Cohen C,[19,20] Moyes J,[19,20] Larrauri A,[21] Delgado-Sanz C,[21] Le MQ,[22] Hoang PVM,[22] Demont C,[23] Bangert M.[23] **The Global Epidemiology of RSV in Community and Hospitalized Care: Findings From 15 Countries. Open Forum Infect Dis. 2021 Mar 30;8(7):ofab159. PMID: 34337092.**

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ABSTRACT
BACKGROUND: Respiratory syncytial virus (RSV) is one of the leading causes of acute respiratory tract infections. To optimise control strategies, a better understanding of the global epidemiology of RSV is critical. To this end, we initiated the Global Epidemiology of RSV in Hospitalised and Community care study (GERi).

METHODS: Focal points from 44 countries were approached to join GERi and share detailed RSV surveillance data. Countries completed a questionnaire on the characteristics of their surveillance system.

RESULTS: Fifteen countries provided granular surveillance data and information on their surveillance system. A median (interquartile range) of 1,641 (552-2,415) RSV cases per season were reported from 2000 and 2020. The majority (55%) of RSV cases occurred in the <1-year-olds, with 8% of cases reported in those aged ≥65 years. Hospitalised cases were younger than those in community care. We found no age difference between RSV subtypes and no clear pattern of dominant subtypes.

CONCLUSIONS: The high number of cases in the <1-year-olds indicates a need to focus prevention efforts in this group. The minimal differences between RSV subtypes and their co-circulation implies that prevention needs to target both subtypes. Importantly, there appears to be a lack of RSV surveillance data in the elderly.

READING 4 – KNOWLEDGE, ATTITUDES, AND PRACTICES TOWARDS COVID-19 AMONG MULTIETHNIC ELDERLY ASIAN RESIDENTS IN SINGAPORE

Aravindhan A,[1] Gan ATL,[1] Lee EPX,[1] Gupta P,[1] Fenwick EK,[1] Man R,[2] Wong TY,[2] Lamoureux EL,[2] Cheng CY,[2] Ho KC,[3] Sung SC,[4] Ling ML,[5] Tan HK.[6] Knowledge, attitudes and practices towards COVID-19 among multiethnic elderly Asian residents in Singapore: a mixed-methods study. Singapore Med J. 2023 Nov;64(11):657-666. PMID: 34628802.

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ABSTRACT
INTRODUCTION: We investigated the knowledge, attitudes, and practice (KAP) towards coronavirus disease 2019 (COVID-19) and its related preventive measures in Singaporeans aged ≥60 years.

METHODS: This was a population-based, cross-sectional, mixed-methods study (13 May 2020-9 June 2020) of participants aged ≥60 years. Self-reported KAP about ten symptoms and six government-endorsed preventive measures related to COVID-19 were evaluated. Multivariable regression models were used to identify sociodemographic and health-related factors associated with KAP in our sample. Associations between knowledge/attitude scores and practice categories were determined using logistic regression. Seventy-eight participants were interviewed qualitatively about the practice of additional preventive measures and data were analysed thematically.

RESULTS: Mean awareness score of COVID-19 symptoms was 7.2/10. The most known symptom was fever (93.0%) and the least known was diarrhoea (33.5%). Most participants knew all six preventive measures (90.4%), perceived them as effective (78.7%), and practised "wear a mask" (97.2%). Indians, Malays, and participants living in smaller housing had poorer mean scores for knowledge of COVID-19 symptoms. Older participants had poorer attitudes towards preventive measures. Compared to Chinese, Indians had lower odds of practising three out of six recommendations. A one-point increase in score for knowledge and attitudes regarding preventive measures resulted in higher odds of always practising three of six and two of six measures, respectively. Qualitative interviews revealed use of other preventive measures, for example, maintaining a healthy lifestyle.

CONCLUSIONS: Elderly Singaporeans displayed high levels of KAP about COVID-19 and its related preventive measures, with a positive association between levels of knowledge/attitude and practice. However, important ethnic and socioeconomic disparities were evident, indicating that key vulnerabilities remain, which require immediate attention.

READING 5 – COVID-19 HOME RECOVERY PROGRAMME (HRP) IN SINGAPORE

Tan HYT,[1] Vasoo S,[1,5-7] Leo YS,[1,4,6-8] Yau JWK,[2] Toh MPHS.[3,4] Coronavirus disease and home recovery: a Singapore perspective. Western Pac Surveill Response J. 2023 Sep 30;14(5 Spec edition):1-7. PMID: 37969814.

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ABSTRACT
OBJECTIVE: At the beginning of the coronavirus disease (COVID-19) pandemic in Singapore, the strategy initially involved aggressive ring-fencing of infections, before pivoting towards managing recurrent local interspersed outbreaks of COVID-19. A key feature of Singapore's efforts to preserve healthcare capacity was the implementation of the nationwide Home Recovery Programme (HRP), whereby patients were allowed to recover at home as long as they met certain criteria. The programme was centrally coordinated by Singapore's Ministry of Health (MOH) and was supported by telemedicine providers, primary care physicians, and government agencies. This report aims to highlight Singapore's experience in coordinating and implementing the HRP, the challenges faced, and the outcomes.

METHODS: Published and internal data from MOH, along with policy documents, were reviewed together with a brief literature review of similar programmes conducted globally.

RESULTS: Implementation of the HRP led to the majority of patients (98%) recovering from COVID-19 in the outpatient setting, with similar mortality rates to inpatient settings. Hospitalisation rates for COVID-19 cases were reduced as compared to previously, alleviating strain on the healthcare system.

DISCUSSION: The HRP was largely successful at preventing healthcare capacities from being overwhelmed, while keeping fatalities to a minimum. Nonetheless, the risks of emergent variants of concern remain present, and heightened vigilance and potential modification of existing protocols based on fluctuations in virulence and infectivity are still needed. (c) 2023 The authors; licensee World Health Organization.

READING 6 – RETENTION OF IMMUNITY IN COVID-19 VACCINATED CANCER PATIENTS FOR AT LEAST FIVE MONTHS AFTER THIRD OR FOURTH DOSE

Tan WC,[1] Tan RYC,[1] Leong FL,[1] Lim ST,[1] IB,[1,14-16] Tan JYJ,[2] Malek MIBA,[2] Ong B,[2,5] Chiew CJ,[2,10] Tan KB,[2,16] SC,[3,4] Lim JSJ,[3-5] Chng WJ,[3-5] Tan Sundar R,[3,5,17-19] Lee Chai LYA,[3,6-8] Lee ARYB,[5] Tan TT,[9] Lye DC,[9-12] Bharwani LD.[13] COVID-19 Severity and Waning Immunity After up to 4 mRNA Vaccine Doses in 73 608 Patients With Cancer and 621 475 Matched Controls in Singapore: A Nationwide Cohort Study. JAMA Oncol. 2023 Sep 1;9(9):1221-1229. PMID: 37440245.

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ABSTRACT

IMPORTANCE: Despite patients with cancer being at risk of poor outcomes from COVID-19, there are few published studies for vaccine efficacy in this group, with suboptimal immunogenicity and waning vaccine efficacy described in small studies being a concern.

OBJECTIVE: To assess the incidence rate of severe COVID-19 disease outcomes associated with the number of vaccine doses received and the waning of protection over time.

DESIGN, SETTING, AND PARTICIPANTS: A prospective multicentre observational cohort study was carried out over two time periods (15 September 2021 to 20 December 2021 [delta wave], and 20 January 2022 to 11 November 2022 [omicron wave]) predominated by SARS-CoV-2 delta and omicron variants, respectively. Overall, 73,608 patients with cancer (23,217 active treatment, 50,391 cancer survivors) and 621,475 controls matched by age, sex, race and ethnicity, and socioeconomic status were included.

EXPOSURE: Vaccine doses received, from zero to four doses, and time elapsed since last vaccine dose.

OUTCOMES: Competing-risk regression analyses were employed to account for competing risks of death in patients with cancer. Main outcomes were incidence rate ratios (IRRs) of COVID-19 infection, hospitalisation, and severe disease (defined as requirement for supplemental oxygen, intensive care, or death). The IRRs stratified by time from last vaccine dose served as indicators of waning of vaccine effectiveness over time.

RESULTS: The mean (SD) age of actively treated patients with cancer, cancer survivors, and controls was 62.7 (14.7), 62.9 (12.6), and 61.8 (14.7) years, respectively. Of 73,608 patients with cancer, 27,170 (36.9%) were men; 60,100 (81.6%) were Chinese, 7,432 (10.1%) Malay, 4,597 (6.2%) Indian, and 1,479 (2.0%) were of other races and ethnicities. The IRRs for the 3-dose and 4-dose vs the 2-dose group (reference) for COVID-19 hospitalisation and severe disease were significantly lower during both the delta and omicron waves in cancer and control populations. The IRRs for severe disease in the 3-dose group for active treatment, cancer survivors, and controls were 0.14, 0.13, and 0.07 during the delta wave and 0.29, 0.19, and 0.21 during omicron wave, respectively. The IRRs for severe disease in the 4-dose group

during the omicron wave were even lower at 0.13, 0.10, and 0.10, respectively. No waning of vaccine effectiveness against hospitalisation and severe disease was seen beyond five months after a third dose, nor up to five months (the end of this study's follow-up) after a fourth dose.

CONCLUSION: This cohort study provides evidence of the clinical effectiveness of mRNA-based vaccines against COVID-19 in patients with cancer. Longevity of immunity in preventing severe COVID-19 outcomes in actively treated patients with cancer, cancer survivors, and matched controls was observed at least five months after the third or fourth dose.

READING 7 – MAINTAINING POPULATION IMMUNITY AGAINST COVID-19 REINFECTIONS WITH OMICRON-ADAPTED BIVALENT VACCINES

Tan CY,[1] Chiew CJ,[2] Pang D,[3] Lee VJ,[4] Ong B,[5] Lye DC,[6] Tan KB.[7] Protective immunity of SARS-CoV-2 infection and vaccines against medically attended symptomatic omicron BA.4, BA.5, and XBB reinfections in Singapore: a national cohort study. Lancet Infect Dis. 2023 Jul;23(7):799-805. PMID: 36924786.

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ABSTRACT

BACKGROUND: Despite a large proportion of the population having been vaccinated and infected, Singapore had SARS-CoV-2 waves driven by the BA.5 and XBB sublineages of the omicron (B.1.1.529) variant. Data on the protective immunity against medically attended, symptomatic reinfections with omicron BA.4, BA.5, and XBB conferred by previous SARS-CoV-2 infections and vaccinations are scarce. We therefore aimed to derive information from Singapore's experience as one of the first countries with a XBB-driven wave.

METHODS: For this retrospective national cohort study, we used information from official databases of the Ministry of Health (MOH) of Singapore to assess hybrid immunity (obtained from previous infection and vaccination) against medically attended, symptomatic BA.4 and BA.5 reinfections from 1 Oct 2022 to 1 Nov 2022, and medically attended, symptomatic XBB reinfections from 18 Oct 2022 to 1 Nov 2022, among Singapore citizens and permanent residents aged at least 18 years. All individuals with acute respiratory symptoms who presented at any healthcare facility in Singapore between the stated dates were tested for SARS-CoV-2. Individuals were grouped into SARS-CoV-2-naive, pre-omicron, omicron BA.1, and omicron BA.2 groups according to their previous infection status. Data were also stratified by time from first infection to analyse the waning of immunity. Incidence rate ratios (IRRs) were measured by generalised linear Poisson regressions, with SARS-CoV-2-naive individuals as the reference group, and protective immunity was calculated as one minus the risk ratio multiplied by 100.

FINDINGS: 2,456,791 individuals were included in the study, contributing 53.1 million person-days of observation for the SARS-CoV-2-naive group, 3.4 million person-days for the pre-omicron group, 6.6 million person-days for the BA.1 group, and 13.7 million person-days for the BA.2 group between 1 Oct 2022 and 1 Nov 2022. Compared with SARS-CoV-2-naive individuals, first infections with pre-omicron variants did not confer protection against reinfection with BA.4 or BA.5 (IRR 0·87 [95% CI 0.73-1.05] for pre-omicron infection with booster vaccination) or XBB (IRR 1.29 [1.23-1.35] for pre-omicron infection with booster vaccination). Previous BA.2 infection with booster provided the greatest protection against reinfection, but this was lower against reinfection with XBB (protective immunity 51%; 95% CI 49-53) than against reinfection with BA.4 or BA.5 (78%; 74-82). Protection conferred by previous BA.2 infection against XBB

reinfection waned faster over time from first infection (from 74% [72-75] at 3-6 months to 49% [47-52] at 7-8 months) than protection against BA.4 or BA.5 reinfection (from 87% [82-90] at 3-6 months to 74% [66-80] at 7-8 months).

INTERPRETATION: Protection against XBB reinfection conferred by a previous omicron infection with vaccination was lower and waned faster than protection against BA.4 or BA.5 reinfection, which is indicative of the greater immune evasiveness of the XBB sublineage. Although severe COVID-19 is uncommon, populations remain vulnerable to future reinfection waves from emerging SARS-CoV-2 variants despite high rates of vaccination and infection, as reflected by substantially higher reinfection rates during Singapore's XBB wave than during the previous BA.5-driven wave. Policymakers could consider emerging public health interventions, such as omicron-adapted bivalent vaccines, to maintain population immunity against COVID-19.

READING 8 – PCV20 IS FOUND TO BE BOTH COST-SAVING AND MORE EFFECTIVE THAN PPSV23 FOR ADULTS AGED 65 YEARS AND HIGH-RISK ADULTS AGED 60-64 YEARS IN JAPAN

Nakamura S,[1] Mikami M,[2] Yonemoto N,[2] Kamei K,[2] Hayamizu T,[3] Moyon C,[4] Gouldson M,[5] Crossan C,[5] Vietri J.[6] Cost-effectiveness analysis of adult pneumococcal conjugate vaccines for pneumococcal disease in Japan. Expert Rev Vaccines. 2024 Jan-Dec;23(1):546-560. PMID: 38703180.

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ABSTRACT
BACKGROUND: The 23-valent pneumococcal polysaccharide vaccine (PPSV23) is used in the Japanese National Immunisation Program for older adults and adults with increased risk for pneumococcal disease; however, disease incidence and associated burden remain high. We evaluated the cost-effectiveness of pneumococcal conjugate vaccines (PCVs) for adults aged 65 years and high-risk adults aged 60-64 years in Japan.

RESEARCH DESIGN AND METHODS: Using a Markov model, we evaluated lifetime costs using societal and healthcare payer perspectives and estimated quality-adjusted life-years (QALYs), and number of prevented cases and deaths caused by invasive pneumococcal disease (IPD) and non-IPD. The base case analysis used a societal perspective.

RESULTS: In comparison with PPSV23, the 20-valent PCV (PCV20) prevented 127 IPD cases, 10,813 non-IPD cases (inpatients: 2,461; outpatients: 8,352) and 226 deaths, and gained more QALYs (+0.0015 per person) with less cost (-JPY22,513 per person). All sensitivity and scenario analyses including a payer perspective analysis indicated that the incremental cost-effectiveness ratios (ICERs) were below the cost-effectiveness threshold value in Japan (JPY5 million/QALY).

CONCLUSIONS: PCV20 is both cost-saving and more effective than PPSV23 for adults aged 65 years and high-risk adults aged 60-64 years in Japan.

READING 9 – A PCV20 CATCH-UP PROGRAMME IN US CHILDREN PREVIOUSLY IMMUNISED WITH PCV13 FOUND TO BE EFFECTIVE IN PREVENTING PNEUMOCOCCAL INFECTIONS, ANTIBIOTIC INFECTIONS, AND ANTIMICROBIAL-RESISTANT INFECTIONS

Rozenbaum MH,[1] Huang L,[1] Cane A,[1] Arguedas A,[1] Tort MJ,[1] Snow V,[1] Chilson E,[1] Farkouh R,[1] Chapman R,[2] Dillon-Murphy D.[2] Cost-effectiveness and impact on infections and associated antimicrobial resistance of 20-valent pneumococcal conjugate vaccine in US children previously immunized with PCV13. J Med Econ. 2024 Jan-Dec;27(1):644-652.

doi: 10.1080/13696998.2024.2339638. PMID: 38577742. Free full text.

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ABSTRACT

AIM: The US Food and Drug Administration approved the 20-valent pneumococcal conjugate vaccine (PCV20) to prevent pneumococcal disease. In the context of routine PCV20 vaccination, we evaluated the cost-effectiveness and public health and economic impact of a PCV20 catch-up programme and estimated the number of antibiotic prescriptions and antibiotic-resistant infections averted.

MATERIALS AND METHODS: A population-based, multi-cohort, decision-analytic Markov model was developed using parameters consistent with previous PCV20 cost-effectiveness analyses. In the intervention arm, children aged 14-59 months who previously completed PCV13 vaccination received a supplemental dose of PCV20. In the comparator arm, no catch-up PCV20 dose was given. The direct and indirect benefits of vaccination were captured over a 10-year time horizon.

RESULTS: A PCV20 catch-up programme would prevent 5,469 invasive pneumococcal disease cases, 50,286 hospitalised pneumonia cases, 218,240 outpatient pneumonia cases, 582,302 otitis media cases, and 1,800 deaths, representing a net gain of 30,014 life years and 55,583 quality-adjusted life years. Furthermore, 720,938 antibiotic prescriptions and 256,889 antibiotic-resistant infections would be averted. A catch-up programme would result in cost savings of $800 million. These results were robust to sensitivity and scenario analyses.

CONCLUSIONS: A PCV20 catch-up programme could prevent pneumococcal infections, antibiotic prescriptions, and antimicrobial-resistant infections and would be cost-saving in the US.

READING 10 – PCV20 FOUND TO BE ABLE TO REDUCE PNEUMOCOCCAL DISEASE, SAVE LIVES, AND BE COST-EFFECIVE COMPARED TO STANDARD OF CARE VACCINATIONS FOR PREVENTION OF CAP AND IPD IN ADULTS

Kühne F,[1] Mahar E,[1] Friedrich J,[1] Sprenger R,[1] von Eiff C,[1] Achtert K,[2] Püschner F,[2] Urbanski-Rini D,[2] Schiller J,[2] Atwood M,[3] Vietri J,[4] Theilacker C.[4] Cost-effectiveness of use of 20-valent pneumococcal conjugate vaccine among adults in Germany. Expert Rev Vaccines. 2023 Jan-Dec;22(1):921-932. PMID: 37881844.

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ABSTRACT

OBJECTIVES: Despite national recommendations for use of pneumococcal vaccines, rates of community-acquired pneumonia (CAP) and invasive pneumococcal disease (IPD) remain high in Germany. New pneumococcal conjugate vaccines (PCVs) with expanded coverage have the potential to reduce the pneumococcal disease burden among adults.

METHODS: Using a Markov model, we evaluated the lifetime outcomes/costs comparing 20-valent PCV (PCV20) with standard of care (SC) vaccinations for prevention of CAP and IPD among adults aged ≥60 years and at-risk adults aged 18-59 years in Germany. PCV20 was also compared with sequential vaccination with 15-valent PCV (PCV15) followed by PPSV23 in a scenario analysis.

RESULTS: Over the course of a lifetime (82 years), use of PCV20 versus SC would prevent 54,333 hospitalisations, 26,368 outpatient CAP cases, 10,946 disease-related deaths, and yield 74,694 additional life-years (LYs), while lowering total medical costs by €363.2 M. PCV20 remained cost-saving (i.e., dominant) versus SC even in numerous sensitivity analyses, including a sensitivity analysis assuming moderate effectiveness of the SC pneumococcal polysaccharide vaccine against noninvasive pneumococcal CAP. In several scenario analyses and a probabilistic sensitivity analysis, PCV20 was also cost-saving compared to PCV15 PPSV23 vaccination.

CONCLUSIONS: One dose of PCV20 among adults aged ≥60 years and adults aged 18-59 years with moderate- and high-risk conditions would substantially reduce pneumococcal disease, save lives, and be cost-saving compared with SC.