Review Article

A comprehensive overview of pneumococcal vaccination recommendations for adults in South Africa, 2022

Charles Feldman[1]^, Sipho Dlamini[2]^, Guy A. Richards[3]^, John Black[4], India L. C. Butler[5]^, Clare Cutland[6]^, Eric Hefer[7], Bridget Hodkinson[2]^, Adri Kok[8], Pravin Manga[1], Susan Meiring[9]^, Muhangwi Molaudzi[10], Mahomed-Yunus S. Moosa[11]^, Salim Parker[12]^, Jonny Peter[13]^, Cloete van Vuuren[14]^, Estelle Verburgh[2]^, Gill Watermeyer[2]

[1]Department of Internal Medicine, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa; [2]Department of Medicine, Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa; [3]Department of Critical Care, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa; [4]Department of Internal Medicine, Walter Sisulu University, Gqeberha, South Africa; [5]Division of Geriatric Medicine, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa; [6]African Leadership in Vaccinology Expertise, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa; [7]General Practitioner in Private Practice, Forest Town, Johannesburg, South Africa; [8]Private Practice Physician and Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa; [9]Division of Public Health Surveillance and Response, National Institute for Communicable Diseases, a Division of the National Health Laboratory Service, Johannesburg, South Africa; [10]Phomolong Medical Centre, Tlhabane, Rustenburg, South Africa; [11]Division of Internal Medicine, Nelson R. Mandela School of Medicine, University of KwaZulu-Natal, Durban, South Africa; [12]Division of Infectious Diseases and HIV Medicine, University of Cape Town, Cape Town, South Africa; [13]Division of Allergy and Clinical Immunology, University of Cape Town, Cape Town, South Africa; [14]Department Internal Medicine, University of the Free State and Department of Internal Medicine, 3 Military Hospital, Bloemfontein, South Africa

Contributions: (I) Conception and design: C Feldman, S Dlamini, GA Richards; (II) Administrative support: C Feldman, S Dlamini, GA Richards; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: C Feldman, S Dlamini, GA Richards; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of the manuscript: All authors.

Correspondence to: Professor Charles Feldman. Department of Internal Medicine, University of the Witwatersrand Medical School, 7 York Road, Parktown 2193, Johannesburg, South Africa. Email: Charles.feldman@wits.ac.za.

Abstract: Pneumococcal infections remain a common global cause of significant morbidity and mortality. The first recommendations for adult pneumococcal vaccination, published in South Africa in 1999, contained information only on the 23-valent polysaccharide vaccine (PPV23). With the introduction of the 13-valent pneumococcal conjugate vaccine (PCV13) for use in adults and the perceived uncertainty that most clinicians had regarding use of these vaccines in adults, these vaccine recommendations were updated in 2022. A Working Group, which consisted of individuals in various fields of medical practice in South Africa, who were from different areas of the country, and included clinicians from both the public and private sectors, was assembled to revise the recommendations. The expertise of the participants varied widely, dependent on their training and specialty, and encompassed different organ systems, disease conditions, and/or practice types. Each participant was allocated a different section, based on their expertise, for which they were required to do an extensive review of the current literature and write their section. The entire working group then reviewed the complete document several times, following additional comments and recommendations. This update contains recommendations for the use of both PPV23 and PCV13, either alone, or in sequence, both in vaccine naïve and in previously vaccinated individuals. It includes both age and risk categories, and encompasses the elderly (≥65 years), as well as younger adults (<65 years) with comorbid conditions or with

^ ORCID: Charles Feldman, 0000-0002-6881-8314; Sipho Dlamini, 0000-0003-0582-5987; Guy A. Richards, 0000-0002-8893-3934; India L. C. Butler, 0000-0002-4417-2678; Clare Cutland, 0000-0001-8250-8307; Bridget Hodkinson, 0000-0001-5360-9483; Susan Meiring, 0000-0003-4508-5469; Mahomed-Yunus S. Moosa, 0000-0001-6191-4023; Salim Parker, 0000-0003-3386-0974; Jonny Peter, 0000-0002-2658-0723; Cloete van Vuuren, 0000-0002-9095-0039; Estelle Verburgh, 0000-0003-4657-7318.

high-risk conditions and/or immunocompromise. It is hoped that this review and its associated vaccine recommendations will clarify for clinicians, from all spheres of practice in South Africa, how, where, and when pneumococcal vaccines should be used in adults, with the ultimate goal of significantly increasing the appropriate use of these vaccines, in order to decrease the substantial morbidity and mortality associated with pneumococcal infections in adults in South Africa. Furthermore, it is hoped that this review of local epidemiological data and the manner in which this information was interpreted in the development of these local vaccine recommendations, could be used as an example for other regions of the world, to tailor their recommendations to locally available epidemiological data.

Keywords: Adult; pneumococcal; recommendations; vaccines

Submitted Mar 03, 2022. Accepted for publication Jul 28, 2022.
doi: 10.21037/jtd-22-287
View this article at: https://dx.doi.org/10.21037/jtd-22-287

Introduction

Worldwide, lower respiratory tract infections (LRTIs) continue to be associated with significant morbidity and mortality. The most recent Global Burden of Disease Study evaluated the global, regional, and national morbidity, mortality and aetiology of LRTIs [mainly community-acquired pneumonia (CAP) and bronchiolitis, with the latter predominantly in children] in 195 countries, between 1990 and 2016 (1). In 2016, LRTIs caused 2,377,697 deaths in people of all ages worldwide, with *Streptococcus pneumoniae* (pneumococcus) being the leading cause of LRTI morbidity and mortality globally, contributing to more deaths than *Haemophilus influenzae*, influenza virus and respiratory syncytial virus combined, and resulting in some 55.4% (1,189,937) of all deaths. LRTIs were found to be highest in sub-Saharan Africa and South/Southeast Asia. While the study noted that progress has been made globally in reducing the burden of LRTIs, particularly in younger children, it has not been equal across all ages and locations and the burden in the elderly, especially those older than 70 years of age (1,080,958 deaths), was increasing.

Furthermore, effective vaccines are available for a number of these infections, and their appropriate use could effectively reduce the burden of LRTI and pneumococcal infections, not only in children but also in the elderly and in high-risk cases (2). National recommendations for pneumococcal (and influenza) vaccination in adults in South Africa were initially published in 1999 (3); however, pneumococcal conjugate vaccines (PCV) were not available at that time and the document only described the use of the 23-polyvalent, polysaccharide vaccine (PPV23). In 2017, the adult CAP guideline in South Africa was updated and it included recommendations for use of both PPV23 and 13-valent pneumococcal conjugate vaccine (PCV13) in adults (4). The recommendations were largely based on those of the Centers for Disease Control and Prevention (CDC) in the United States (US).

With the introduction of PCV13 for use in adults in South Africa, it soon became evident that there was uncertainty among healthcare professionals regarding the efficacy, indications, and use of the different pneumococcal vaccines. Therefore, the aim of the current literature review and associated vaccination recommendations was to clarify all these issues for healthcare professionals in all spheres of practice in country, with the ultimate goal of encouraging use of these vaccines in adults, in order to decrease the significant morbidity and mortality associated with pneumococcal infections.

It is important for the authors to indicate initially some issues to the readers of this review and associated recommendations, with the hope of making the understanding of the manuscript text and *Tables 1-3* clearer.

Firstly, these recommendations do deviate in two small areas from the guideline that has been published by the CDC in the US in 2021, but not from similar recommendations from several other countries, for example, Belgium, Hong Kong, India, and parts of Italy, countries that have almost identical recommendations. The major differences from that of the CDC are that the current recommendations suggest the routine use of the PCV13 vaccine (in addition to PPV23 as described in the text and table) in adults 18 years and older with comorbid conditions. This differs from that of the CDC, who do not

Table 1 Recommendations for pneumococcal vaccination in vaccine-naive adults

Population	Initial pneumococcal vaccines recommended	Timing of additional PPV23 dose	Timing of possible third PPV23 dose
Adults aged ≥65 years with or without comorbid conditions (List A in *Table 2*) (level of evidence A II)	PCV13 first + PPV23 ≥1 year later	None	None
Adults <65 years with comorbid conditions (List A in *Table 2*) (level of evidence A III)	PCV13 first + PPV23 ≥1 year later	Consider additional PPV23 dose 5 years after last PPV23 dose at ≥65 years	None
Immunocompromised and high-risk adults (List B in *Table 2*) (level of evidence A II)	PCV13 first + PPV23 ≥8 weeks later	Additional PPV23 dose 5 years after last PPV23 dose if <65 years	Consider additional PPV23 dose at ≥65 years if 5 years after last PPV23 dose

The interval between administering PCV13 and PPV23 is recommended as 1 year for lower risk conditions, such as indicated in List A in *Table 2*, because this time interval is associated with optimal immunogenic responses to both vaccines. However, in patients with high-risk and immunocompromising conditions, as in List B in *Table 2*, who are at much higher risk of pneumococcal infections, a shorter interval of 8 weeks is recommended in order to broaden the potential serotype coverage as soon as possible. PCV13 alone does not give adequate serotype coverage for South African adults and if the cost of giving both vaccines, or likely compliance with the two-dose regimen is a concern, then PPV23 alone is an alternative in the elderly. In severely immune-compromised patients (post-HSCT and CAR-T cell therapy), a more intensive PCV13 administration is advised, as indicated in the section on haematology/oncology. Consider persons living in confined quarters, e.g., prison or barracks as potentially eligible for pneumococcal vaccination. PPV23, 23-valent pneumococcal polysaccharide vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; HSCT, haematopoietic stem cell transplant; CAR-T, chimeric antigen receptor T.

Table 2 List of chronic comorbid conditions and immunocompromising and or high-risk conditions

List	Details
List A: chronic comorbid conditions	Chronic lung disease
	Chronic liver disease
	Chronic heart disease
	Diabetes mellitus
	Smoking
	Alcoholism
	Long-term care facility resident
List B: immunocompromised and/or high risk	CSF leak
	Cochlear implant
	Previous IPD
	Impaired splenic function
	Major haemoglobinopathy
	HIV infection
	Chronic kidney disease/nephrotic syndrome
	Haematological malignancy
	Chemotherapy
	Metastatic cancer
	Organ or bone marrow transplant
	Immunosuppressive drugs
	Congenital/acquired immunodeficiency

CSF, cerebrospinal fluid; IPD, invasive pneumococcal disease; HIV, human immunodeficiency virus.

Table 3 Recommendations for pneumococcal vaccination in previously vaccinated adults

Previous pneumococcal vaccine received	Pneumococcal vaccine recommended	Timing of additional PPV23 dose	Timing of possible third PPV23 dose
PPV23 aged ≥65 years (level of evidence A II)	PCV13 ≥1 year later	None	None
PPV23 in adults <65 years with comorbid conditions (List A in *Table 2*) (level of evidence A III)	PCV13 ≥1 year later	Consider additional PPV23 dose at least 1 year after PCV13 and 5 years after last PPV23 dose at ≥65 years	None
PPV23 in immunocompromised and high-risk adults <65 years (List B in *Table 2*) (level of evidence A II)	PCV13 ≥1 year later	Additional PPV23 dose at least 1 year after PCV13 and 5 years after last PPV23 dose if <65 years	Consider additional PPV23 dose at ≥65 years if at least 1 year after PCV13 and 5 years after last PPV23 dose

The interval between administering PCV13 and PPV23 is recommended as 1 year for lower risk conditions, such as indicated in List A in *Table 2*, because this time interval is associated with optimal immunogenic responses to both vaccines. However, in patients with high-risk and immunocompromising conditions, as in List B in *Table 2*, who are at much higher risk of pneumococcal infections, a shorter interval of eight weeks is recommended in order to broaden the potential serotype coverage as soon as possible. PCV13 alone does not give adequate serotype coverage for South African adults and if the cost of giving both vaccines, or likely compliance with the two-dose regimen is a concern, then PPV23 alone is an alternative in the elderly. In severely immune-compromised patients (post-HSCT and CAR-T cell therapy), a more intensive PCV13 administration is advised, as indicated in the section on haematology/oncology. Consider persons living in confined quarters, e.g., prison or barracks as potentially eligible for pneumococcal vaccination. PPV23, 23-valent pneumococcal polysaccharide vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; HSCT, haematopoietic stem cell transplant; CAR-T, chimeric antigen receptor T.

recommend routine PCV13 use in adults with comorbid conditions. In addition, the current recommendations indicate that PCV13 should be given routinely (in addition to PPV23 as described in the text and table) in all adults 65 years of age and older, even those without high-risk and immuno-compromising conditions. This differs from that of the CDC, who recommend that PCV13 use in the elderly, outside of high-risk and immunocompromising conditions should be based on discussion and shared decision making with the patients. Reasons for this, which are based on significant differences in the current epidemiology of, and risk factors for, pneumococcal infections in South Africa and the US, are further described in the text, especially in the sections on Epidemiology, human immunodeficiency virus (HIV) and the Elderly.

Secondly, it is important to be aware that there are few or limited clinical studies in many of the different comorbid medical conditions described in this document, on which to base the vaccine recommendations and so many of the recommendations are based on review of other guidelines, including those from the US, together with expert opinion. In this document, the recommendations are clearly outlined for ease of reference for each age-based and risk-based group of conditions in *Tables 1-3*, together with an indication of the strengths of each recommendation as per the tables to the following:

Strength of recommendation:

- A: strong recommendation for or against;
- B: moderate recommendation for or against;
- C: weak recommendation for or against.

Quality of evidence:

- I: evidence from at least one properly randomised, controlled trial;
- II: evidence from at least one well-designed clinical trial without randomisation, from cohort or case-controlled analytic studies (preferably from more than one centre), from multiple time-series, or from dramatic results from uncontrolled experiments;
- III: evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Thirdly, the authors are aware that both the vaccine types may not be routinely available in either the public or private sectors and if they are, they may not be reimbursed at all, or else only partly reimbursed. In those situations, where PCV13 is completely unavailable, or unaffordable for the patient, but PPV23 is, healthcare practitioners are advised still to use PPV23 in their patients on its own, in the same schedules as indicated in the tables.

The members of the Working Group and the Working Group methodology are shown in Appendix 1. We present the following article in accordance with the RIGHT reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-287/rc).

Overview of pneumococcal epidemiology in South Africa

Streptococcus pneumoniae, a gram-positive bacterium carried asymptomatically in the nasopharynx, is the causative agent of a broad range of diseases from non-invasive upper respiratory tract infections (URTI) to pneumococcal pneumonia, meningitis or bacteraemia (5). The isolation of the pneumococcus from a sterile site such as cerebrospinal fluid, blood, joints, peritoneum or pleura, is termed invasive pneumococcal disease (IPD). The pneumococcus is encased in a thick polysaccharide capsule, an important virulence factor, which protects the organism from phagocytosis. There are over 90 distinct pneumococcal serotypes based on the polysaccharide capsular antigens, which are the targets for the various pneumococcal vaccines. In South Africa, the currently available polysaccharide vaccine, PPV23, was registered for use in 1992. The conjugate vaccines were first registered for use in children, starting with PCV7 in April 2009, and replaced with PCV13 in April 2011. Registration of PCV13 for use in adults occurred in 2015.

Despite widespread use of pneumococcal infant vaccination programmes, IPD remains a common cause of morbidity and mortality in both children and adults (6,7). In a study published in 2016, IPD incidence amongst HIV-infected persons was 43 times higher than among HIV-uninfected persons (8). In 2018 in South Africa, IPD incidence was highest in infants (21 cases per 100,000 population) with a second peak occurring in adults 25 years and older (6 cases per 100,000 population) (9). Apart from HIV-coinfection, almost half (45%) of the persons with IPD had an underlying risk factor/condition predisposing them to infection. This included a history of smoking, underlying chronic lung disease or chronic renal disease (8). Overall, in-hospital mortality from IPD was 32%, with 23% of those presenting with pneumococcal meningitis suffering sequelae post discharge (8).

Following introduction of the PCV into the expanded programme on immunisation in 2009, antimicrobial non-susceptibility to penicillin decreased amongst young children with IPD (10). However, there has been no change in the proportion of penicillin susceptible isolates in the adult age groups over the past 10 years.

Within 4 years of the introduction of the PCV7 vaccine in South Africa, there was an overall reduction in IPD in adults aged 25–44 years, with a 57% decrease in PCV7-serotypes due to indirect herd protection (10). Unlike the US, whose elderly population experienced a dramatic decrease in IPD following vaccine introduction, overall IPD incidence in the South African population ≥65 years has largely remained unchanged (11-13). In 2018, 36% of IPD in persons ≥5 years was caused by serotypes in PCV13 and 79% in PPV23. Serotypes 8, 3, 19A, 12F and 4 were the top 5 serotypes causing IPD in this age group (8).

Since PCV introduction, South African children <5 years have experienced a 33% decline in mortality from all-cause pneumonia, but there has been no significant decline in all-cause pneumonia mortality in South African adults (14).

More than 10 years following PCV introduction, South Africa has seen some indirect effects of infant vaccination on the adult population with regard to decreased overall IPD incidence and PCV-specific serotype disease, but there is still a substantial proportion of vaccine preventable pneumococcal disease occurring in adults, particularly in those with underlying comorbidities or risk factors for developing respiratory infections.

More recently, many countries have reported a reduction in life-threatening invasive diseases including *S. pneumoniae*, likely attributable to coronavirus disease 2019 (COVID-19) containment policies, as well as public information campaigns (15). Social distancing efforts and mask wearing may not be sustainable measures for disease control, and therefore, vaccination of those at risk of IPD should still be prioritised.

Pneumococcal vaccines available for use in adults in South Africa

Two kinds of pneumococcal vaccines are available and registered for use in adults in South Africa. Although they have similar side effect profiles, they are different in their formulation, immunological responses, efficacies and costs (16-22) (*Table 4*).

Pneumococcal vaccination recommendations in different patient groups in South Africa

Pneumococcal vaccination recommendations for patients with cardiovascular (CV) diseases (CVD)

CVD are among the leading causes of morbidity and mortality in the world, especially among the elderly population (23). Well-known risk factors for ischaemic heart disease include smoking, hypertension, diabetes and dyslipidaemia, influenza and pneumococcal infections (24-26). There is considerable evidence suggesting that influenza and pneumococcal infections themselves can

Table 4 Summary of pneumococcal vaccines for use in adults in South Africa

Vaccine type	PCV13	PPV23
Vaccine name, Manufacturer	Pfizer Inc.: Prevenar 13® (PCV13)	Merck & Co., Inc.: Pneumovax®23 (PPV23)
Number of serotypes	13	23
Serotypes included	1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F	1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, 33F
Approximate costs	Single exit price (South Africa): PCV13 = R912.33	Single exit price (South Africa): PPV23 = R198.70
	Immunisation = R46.80	Immunisation = R46.80
		Doctor's script = R255.91
Volume and administration	0.5 mL; intramuscular	0.5 mL; intramuscular or subcutaneous
Vaccine properties/ conjugates	Capsular polysaccharides covalently linked (conjugated) to diphtheria CRM_{197} toxoid (16,17)	Purified capsular polysaccharides of the most common serotypes causes the majority of serious pneumococcal infections (17-19)
Age groups	Initially developed for infants and children but subsequently found to be efficacious in adults, including the elderly and high-risk patients (17-20)	Poor response in children less than 2 years of age; used in children >2 years of age and adults
Immunological response to vaccine	T-cell dependent (17)	T-cell independent (16)
	Potential for prolonged immunity (17,22)	Immunity may decline after 5 years, especially in the elderly and in those with comorbidities (17,21)
Efficacy	75% efficacy against IPD in the elderly (20)	60–70% efficacy against IPD (21)
	45% efficacy against vaccine-type non-bacteraemic pneumococcal pneumonia (20)	Less consensus on efficacy in preventing pneumococcal non-bacteraemic pneumonia (21)
Nasopharyngeal carriage	Reduces nasopharyngeal carriage, thus decreases spread of colonising serotypes to other individuals—"herd protection" (18)	No significant effects on pneumococcal nasopharyngeal carriage; therefore, does not reduce pneumococcal carriage or spread of infections in the population—no "herd protection" (21)
Side effects	Local—pain, swelling, induration, redness, which can be controlled with paracetamol (18)	
	Systemic—fever, chills, fatigue, headache, myalgias and arthralgias which can be controlled with paracetamol (18)	
	Severe systemic adverse events are rare (21)	
Contraindications	Severe allergic reactions to either vaccine or its components (18,21)	

PCV13, 13-valent pneumococcal conjugate vaccine; PPV23, 23-valent pneumococcal polysaccharide vaccine; IPD, invasive pneumococcal disease.

induce CV events, with the increased risk being due to a number of factors (27-29), which may lead to rupture of vulnerable atherosclerotic plaques leading to acute coronary syndromes (ACS).

Potential CV protective mechanisms of pneumococcal vaccination

The efficacy of pneumococcal vaccination in preventing acute myocardial infarction (MI) is not well established, mainly due to the lack of prospective randomized clinical trials and the negative results of many studies in this field (30,31). The recommendations for pneumococcal vaccination in patients with CVD are based on the consensus of experts' opinion and retrospective epidemiological studies.

Coronary heart disease (CHD)

In a cohort of over 21,000 patients, a fourfold higher risk of MI, stroke and fatal chronic heart failure (HF) has been described in the first 30 days after pneumonia hospitalization (32). In one meta-analysis of observational studies of patients 65 years and older, pneumococcal

vaccination was associated with a significantly lower risk of ACS events (33). However, other studies have failed to show any benefit and there have been no prospective randomized controlled trials evaluating the effect of pneumococcal vaccination on the clinical course of CVD (30).

Heart failure

In patients with HF, respiratory infection is associated with decompensation, hospitalisation and increased in-hospital mortality (34). In a study of CAP, it was found that most cardiac complications occurred in the first week after admission and more than 50% in the first 24 hours (35). In a multicentre study of 1,182 patients hospitalised with CAP, 32.2% had CV events in the following 30 days, and the 30-day mortality was 4 times higher in those who developed CV events compared to those who did not (36). Studies investigating cardiac complications during CAP hospitalization have clearly shown a much higher risk of HF compared with MI (37).

There is, overall, a paucity of good evidence with regard to the clinical outcomes of pneumococcal vaccination in HF patients, and this requires further research.

Pneumococcal vaccination recommendations for patients with respiratory diseases

Chronic obstructive pulmonary disease (COPD)

A number of causes, chief amongst which, are infections, can precipitate exacerbations of COPD. Although viruses are probably the most frequent aetiological agents, bacterial infections also commonly occur, inclusive of *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*, and other Gram-negative pathogens (38). Vaccination against the pneumococcus alone therefore is unlikely to eliminate exacerbations. The most comprehensive evaluation of the efficacy of the pneumococcal vaccine is from a 2017 Cochrane meta-analysis (39) in which no mortality benefit was demonstrated, but there was a reduction in all-cause CAP [odds ratio (OR) 0.59; 95% confidence interval (CI): 0.41 to 0.85; six studies, n=1,372; GRADE (quality of the evidence): moderate], with a number needed to treat (NNT) of 19, to prevent one episode. Most importantly, there was a significant reduction in exacerbations (OR 0.60, 95% CI: 0.39 to 0.93; 4 studies, n=446; GRADE: moderate) with a NNT of 8 (95% CI: 5 to 58). Despite this, there was no difference in hospitalization for any cause and comparison of the PCV13 and PPV23, which was assessed in only one study, found no differences between the two. In a more recent small, prospective, observational study of 121 patients, PCV13 was administered to 36.4%, 24% of whom were defined as exacerbators. PCV13 use reduced the number of hospitalisations from 32% to 18% with an adjusted OR of 2.77 for hospitalisation in those that were not vaccinated (40). In a large study of 596 elderly individuals with COPD, of whom 58 had an episode of CAP, prior use of PCV13 significantly reduced the occurrence of bacteraemia and severe IPD (41).

The Advisory Committee on Immunization Practices (ACIP) recommends PPV23 for all patients with chronic respiratory disease, including COPD (42), and the Global Initiative for Chronic Obstructive Lung (GOLD) also indicates that PPV23 reduces the incidence of CAP in younger patients with significant respiratory [forced expiratory volume in one second (FEV1) ≤40% of predicted] or CV comorbidity (43). The recommendation that PPV23 be administered to patients with COPD is based on the above Cochrane meta-analysis and some older evidence in which PPV23 reduced CAP in patients <65 years with an FEV1 <40% of predicted and on the fact that PCV13 shows similar immunogenicity (41,44).

The South African recommendations for the management of COPD mention that pneumococcal and influenza vaccines reduce exacerbations but do not make a recommendation as to who should receive the pneumococcal vaccine or which one(s) should be used (45), and the evidence as to the efficacy of the pneumococcal vaccine in patients with COPD is somewhat contradictory. However, as discussed in the introduction due to the lesser impact of infant vaccination on pneumococcal infection in the elderly, we would recommend PCV13 followed by PPV23 1 year later as in patients with other comorbidities.

Asthma

Asthma is an extremely common chronic illness with an increasing incidence in many parts of the world (46,47). Infections, particularly viral, are triggers for exacerbations (48) and bacterial co-infection, the most frequent of which is *S. pneumoniae*, may result in sinusitis, otitis media, infective bronchitis and pneumonia (49). There is however no good evidence that pneumococcal vaccination reduces exacerbations or improves asthma control (50).

High-risk adult asthmatics have been shown in some studies to have a 2- to greater than 6-fold increased risk of IPD and pneumococcal pneumonia (51-53) and some studies, particularly in children, indicate that vaccination may reduce corticosteroid and antibiotic use (54) but without an effect on

hospitalization for pneumococcal CAP (55,56).

Currently, the Global Initiative for Asthma (GINA) does not recommend pneumococcal vaccination for asthmatics whereas the World Health Organization (WHO) and ACIP do. (46,57). Vaccination is recommended in Australia for asthmatics that have frequent hospital visits or are on multiple medications, Canada recommends vaccination for those that have required medical care in the last year and the United Kingdom only if corticosteroids have been frequently administered (58).

In South African adults with asthma, PCV13 in addition to PPV23 1 year later, should be offered to those that are poorly controlled (e.g., those with daytime asthma symptoms, or need for reliever therapy ≥2 times a week, and those with any night time wakening due to symptoms) and/or require frequent need for oral corticosteroids (e.g., ≥2 courses in the past year), due to the lesser impact of infant vaccination on pneumococcal infection in adults (59,60).

Other respiratory conditions

In some publications, pneumococcal vaccines have also been recommended for use in other respiratory conditions, including suppurative lung conditions such as bronchiectasis and cystic fibrosis, interstitial and fibrotic lung conditions, as well as in smokers (current or immediate past) (61). Other reviews have specifically included conditions such as sarcoidosis, pulmonary hypertension and cor pulmonale (62). However, there is much less evidence for benefit for these conditions. In addition, certain occupations, such as welders (63) and those exposed to diesel exhaust particles (64), appear to be at risk of IPD, and might be suitable candidates for pneumococcal vaccination.

With regard to bronchiectasis, a Cochrane review in 2009 (65), found one randomised controlled open label study of 167 adults with chronic lung disease (bronchiectasis and other diseases associated with bronchiectasis) comparing PPV23 plus influenza vaccine, with influenza vaccine alone. It highlighted a significant reduction in acute infective exacerbations in the former (OR 0.48; 95% CI: 0.26 to 0.88) with the NNT for benefit being six over 2 years. The overall conclusion was that there was limited evidence for vaccinating adults with bronchiectasis.

In patients with cystic fibrosis, a 2016 Cochrane review found no randomised or quasi-randomised trials for evidence. The conclusion was that since most countries recommend routine childhood pneumococcal vaccination, future randomised trials in this setting are unlikely to occur (66).

In idiopathic pulmonary fibrosis (IPF), studies have documented that *S. pneumoniae* is one of the top four pathogens causing CAP in this condition, and therefore these studies and other reviews recommended pneumococcal vaccination be considered (62,67,68). In addition, animal studies have suggested that *S. pneumoniae* infection may possibly be associated with progression of fibrosis through the activity of its toxin, pneumolysin (69).

We would consider that all chronic respiratory disorders, irrespective of aetiology, are comorbid conditions associated with an increased risk of pneumococcal disease and therefore warrant the administration of pneumococcal vaccine, similar to that of patients with other comorbidities.

Pneumococcal vaccination recommendations for patients with inflammatory bowel disease (IBD)

The term IBD refers, largely, to two conditions, Crohn's disease and ulcerative colitis. Guidelines from the European Crohn's and Colitis Organisation advise that pneumococcal vaccination be considered for all patients with newly diagnosed IBD (70), the majority of whom will ultimately require immunosuppressive drug therapies, which significantly increase the risk of bacterial infection including IPD and pneumonia (71-73).

Ideally, pneumococcal vaccination should be given before initiation of immunosuppressive therapy in order to maximise the immune response, which is impaired in those on immunosuppressive drugs even after sequential administration of PCV13 followed by PPV23, with a seroconversion rate of 59% versus 81% (74). Combinations of different immunosuppressive medications resulted in a lower response to vaccination than monotherapies (75).

In patients already on any of the numerous immunosuppressive agents available, current guidelines from multiple societies and expert reviews recommend pneumococcal vaccination for all adult and paediatric IBD patients (70,76-79).

The recommended protocol for IBD in this setting is a single dose of PCV13 followed by PPV23 at least 2 months later, possibly with a second dose of PPV23 to patients on long-term immunosuppressive therapy, after 5 years, although there is little evidence to support the latter (76).

Recently monoclonal antibodies, ustekinumab and vedolizumab have been approved for management of IBD (80-82), as well as the small molecule JAK inhibitor, tofacitinib approved for ulcerative colitis (83). These molecules are less immunosuppressive (82,84), but despite this, it is reasonable to vaccinate as per the above strategies

for the immunosuppressed. The monoclonals do not appear to impact the immune response, but tofacitinib may (85).

Pneumococcal vaccination recommendations for patients with chronic liver disease

Chronic liver disease and liver transplantation (LT), and the use of immunosuppressive drugs significantly increases the risk of severe infection (86-89). IPD is more frequent and more severe with cirrhosis, and in these cases who develop meningitis, *S. pneumoniae* is responsible for 50% of the cases, and is also the major cause of primary peritonitis in those with ascites (88). Similarly, adults with liver disease are significantly more likely to be hospitalised with pneumococcal pneumonia than those without (89), and are significantly more likely to die during pneumococcal-related hospitalisation (90). LT recipients are at very high risk for pneumococcal diseases, with an incidence of 354/100,000 person-years compared to 11.5/100,000 in the general population (88).

Whereas large studies of pneumococcal vaccination in chronic liver disease are not available (91,92), in one small study of patients with alcohol-induced cirrhosis, antibody titres after pneumococcal vaccination were similar to those of healthy controls (91).

One recent position paper recommends that all patients with autoimmune liver disease, cirrhosis, and LT recipients should receive pneumococcal vaccination (93). Although for patients with chronic liver disease, who are not receiving immunosuppressive therapies, a single dose of PPV23 is commonly recommended (76,94), we would recommend the use of PCV13 initially, followed by PPV23 1 year later. In those receiving immunosuppressive therapies or following LT the single dose of PCV13 should be followed by PPV23 ≥8 weeks later. Re-vaccination with PPV23 after 5 years should be considered (76,88,94). If possible, vaccination should precede immunosuppressive therapy (74).

Patients already vaccinated with PPV23 should receive one dose of PCV13 at least a year after the PPV23 injection, and re-vaccination with PPV23 at 5 years should be considered (76,88,94).

Pneumococcal vaccination recommendations for patients with diabetes mellitus

Patients living with either type 1 or type 2 diabetes mellitus (T1DM, T2DM) are at increased risk of various infections including pneumococcal disease and IPD. Diabetics have a six times greater risk for hospitalisation and a three times greater risk of complications from influenza or pneumonia than non-diabetics (95).

Certain additional conditions occurring in patients with diabetes mellitus, put these patients at particularly high-risk, including age ≥65 years, and those with renal failure, CVD, nephrotic syndrome and renal transplant. Pneumococcal vaccine is indicated in all adult diabetics in a schedule similar to other risk groups (96). PCV13 vaccine is recommended for all diabetic adults followed by PPV23 1 year later unless there are compelling reasons for earlier administration of PPV23, such as in cases with associated high-risk and/or immunosuppressive conditions, as indicated above.

Pneumococcal vaccination recommendations in patients with chronic kidney disease and renal transplant

Patients with chronic renal disease are at increased risk for infections, especially IPD, and they have increased morbidity and mortality from IPD, as well as recurrent pneumococcal infections (97). Additional conditions and comorbidities (e.g., advanced age, diabetes mellitus) increase the risk further (97) and nephrotic syndrome on its own, poses a significantly increased risk due, among other factors, to loss of immunoglobulins, and use of immunosuppressive therapy (98). Renal transplant also increases risk significantly due to immunosuppressive therapy (99).

Pneumococcal vaccination does not increase the risk for acute or chronic rejection in solid organ transplants, nor lead to an increased production of donor specific antibodies in those with chronic renal disease (100,101).

Despite variable antibody response and inconclusive evidence for a durable response with pneumococcal vaccination (101,102), it is mostly recommended that patients with chronic renal disease and solid organ transplants preferably receive PCV13 first followed by PPV23 8 weeks later (101,102).

Pneumococcal vaccination recommendations for patients with autoimmune inflammatory rheumatic diseases (AIRD)

In patients with AIRD, infections, particularly LRTIs, are a major cause of hospital admission and death. Numerous studies and meta-analyses have shown that the rates of pneumococcal disease are significantly higher, frequently with a higher mortality, in patients with AIRD compared

Table 5 Risks for pneumococcal disease in patients with autoimmune inflammatory rheumatic diseases and with certain therapies used in AIRD

Risk factor	Details
Disease	
Chronic inflammatory arthritis	Rheumatoid arthritis, spondylarthritis including psoriatic arthritis, polymyalgia rheumatica
Connective tissue diseases	Systemic lupus erythematosus, Sjogren's syndrome, systemic sclerosis, mixed connective tissue disease, idiopathic inflammatory myositis, polymyalgia rheumatica, Behcet disease, relapsing polychondritis, periodic fever syndromes
Systemic vasculitis	Giant cell arteritis, Takayasu arteritis, ANCA-associated vasculitis, polyarteritis nodosa, cryoglobulinemic syndrome
Therapy	
Glucocorticoids	Moderate to high doses (≥7.5 mg/kg/day)
csDMARDs	Methotrexate, leflunomide, sulfasalazine
Immunosuppressive therapies	Azathioprine, cyclophosphamide, mycophenolate mofetil, calcineurin inhibitors
bDMARDs	Infliximab, etanercept, adalimumab, certolizumab, golimumab, abatacept, tocilizumab, rituximab, secukinumab, ustekinumab
tsDMARDs	Tofacitinib, baricitinib
Comorbidities	Older age, diabetes mellitus, chronic lung disease, smoking

Some of the therapies described are also used in conditions other than AIRD and the same recommendations for vaccinations in these conditions would pertain. AIRD, autoimmune inflammatory rheumatic diseases; ANCA, antineutrophil cytoplasmic antibody; csDMARD, conventional synthetic diseases modifying antirheumatic drug; bDMARD, biologic diseases modifying anti-rheumatic drug; tsDMARD, targeted synthetic diseases modifying anti-rheumatic drug.

with immunocompetent controls (103). This increased risk of all-cause pneumonia, pneumococcal pneumonia, and IPD may be due to the AIRD disease itself, to immunosuppressive therapies prescribed to treat these diseases, and to associated comorbidities (*Table 5*). "Risk-stacking" frequently occurs in AIRD patients where the risk of infection increases with increasing numbers of risk factors (104). Thus, the majority of patients with AIRD are at risk of pneumococcal disease, and vaccination should be strongly considered (105).

All therapies used to treat AIRDs, particularly the B cell-depleting therapy, rituximab, can reduce the efficacy of vaccination (106). To ensure the optimal response to vaccines, an early vaccination strategy is recommended before immunosuppressive therapy is started. In the case of rituximab, vaccination should ideally take place at least 4 weeks before the therapy. In cases when this time window for immunization is not possible, vaccination can be offered to patients already using immunosuppressive therapy, taking into consideration a potential suboptimal response to vaccine (107). This group should receive stepwise pneumococcal vaccination, with PCV13 followed by PPV23, 8 weeks later (108). Revaccination with PPV23 after 5 years is recommended.

Pneumococcal vaccination recommendations for patients with haematology/oncology diseases

Pneumococcal vaccination in splenectomised patients

Splenectomised patients are vulnerable to overwhelming sepsis by encapsulated organisms, and in particular the pneumococcus (109). It is routine practice to administer PPV23, where possible at least 2 weeks (but preferably 4–6 weeks) before performing a splenectomy although with access to the PCV13 this vaccine has become the agent of choice (110). If that is not possible, for example, in trauma cases, the recommendation is to vaccinate patients with PPV23 2 weeks post splenectomy. In patients who have not been exposed to PCV13, this should be given first, followed 8 weeks later by PPV23 and an additional PPV23 dose can be given 5 years later (110). Patients remain at life-long risk of pneumococcal sepsis and should be educated to insist upon prompt antibiotic treatment against *S. pneumoniae* upon developing a febrile illness.

Pneumococcal vaccination in patients with haemoglobinopathies, such as sickle cell disease (SCD)

Due to the hyposplenism that occurs in SCD, vaccination

against *S. pneumoniae* is necessary, because of the high risk for IPD (96). The recommendations would be the same as those described for patients with splenectomy. In addition, antibiotic prophylaxis is usually given in the young, which may be given life-long (111,112).

Pneumococcal vaccination in patients with haematological and oncological malignancies

Antibody responses after vaccination in these patients are significantly lower than those in the immunocompetent, yet may reduce the burden of pneumococcal disease (113). The vaccination is administered to stable cancer patients post-chemotherapy, usually with PCV13 followed by PPV23 at least 8 weeks later, with a repeat of the latter after 5 years (114).

Vaccination is seen as essential in cancer patients, although the evidence is based on other vulnerable populations (115). It is not known when the vaccine should be administered, or if it would be effective in patients on newer therapies, such as the immune checkpoint inhibitors, or those on chimeric antigen receptor T-cell (CAR T-cell) therapy. A 2021 position paper recommended that PCV13 should be administered even with B-cell aplasia, even though it would probably be of limited effectiveness, followed by PPV23 after B-cell recovery (116). Immunoglobulin replacement therapy, which is frequently co-administered to these patients, also impairs the immune response. The schedule for re-vaccination after CAR T-cells, should follow that recommended for haematopoietic stem cell transplant (HSCT).

Vaccination schedules in HSCT recipients

HSCT is intensely immunosuppressive, and immune-reconstitution can take months to years. Although the evidence for vaccination efficacy is low, it is nevertheless strongly recommended (76,115). Vaccination strategies against pneumococcal infection in HSCT recipients is as follows:

In phase 1, three consecutive doses of PCV13 are recommended, at least 1 month apart, initiated 3 to 6 months post HSCT (117). In patients with graft-versus-host disease, the schedule is typically delayed until immunosuppression has been weaned.

In phase 2, one dose of PPV23 is recommended 2 months after completion of phase 1. This schedule is immunogenic and well-tolerated; however, an optimal strategy to maintain long-term sero-protection remains to be established (118). This enhanced intensity vaccination schedule against pneumococcal and other infections needs to be administered, and monitored, in specialised units.

Pneumococcal vaccination recommendations for people living with human deficiency virus infection

Despite the increased uptake and access to antiretroviral therapy (ART), people living with HIV (PLHIV) are still susceptible to developing severe pneumococcal disease. This is despite $CD4^+$ cell count recovery on ART, possibly due to slow and incomplete recovery of anti-pneumococcal host defenses (119). This risk is increased by avoidable aspects of lifestyle, such as smoking, excessive alcohol consumption and intravenous drug abuse, which further intensify immunosuppression (119).

The availability and use of vaccines for children and adults has not substantially changed the incidence of IPD, with morbidity and mortality remaining high in both groups (7,119). Furthermore, a study in South Africa reported that PLHIV had an incidence of IPD that was 43 times higher than in HIV-uninfected persons, with ART use at the time of the study being 40% in those eligible, which had a relatively small impact on the IPD incidence (9). The risk for both IPD and CAP remains high for PLHIV even in those who have high $CD4^+$ cell counts and are virally suppressed (120). Despite longstanding international recommendations for pneumococcal vaccination, coverage remains low in many parts of the world.

Vaccination is recommended for all PLHIV regardless of their $CD4^+$ cell count but is best when the HIV viral load is <1,000 copies/mL, and the choice of either PCV13, or PPV23, or both, is a balance between the available resources, according to the South African HIV vaccination guideline (121). The "prime-boost" immunisation approach is favoured; first vaccinating with PCV13 followed by PPV23 8 weeks later (121). Alternatively, PCV13 could be given alone, while for those who are to receive PPV23 as the primary vaccine, this vaccine should be administered to those who have achieved virological suppression on ART regardless of the $CD4^+$ cell count (121).

Pneumococcal vaccination recommendations for patients with congenital/acquired immunodeficiency disorders, including complement deficiencies

Inborn errors of immunity (IEI), of which there are now 406 distinct disorders listed in the 2019 International Union of Immunological Societies (IUIS) classification, manifest with increased susceptibility to a broad or narrow spectrum of infections, as well as immune dysregulation phenotypes, e.g., autoimmunity, allergy or malignancy (122). Several

polygenic IEI, such as common variable immunodeficiency (CVID) manifest in a similar manner to monogenic diseases. Unlike live vaccines, which are contraindicated in many IEI, inactivated vaccines such as pneumococcal vaccines are generally safe and well tolerated. However, the immunogenicity, efficacy and hence recommended use, differ depending on the different groups of IEI (Table S1). In severe abnormalities of cellular and humoral immunity, e.g., severe combined immunodeficiency or agammaglobulinaemia with absent B-cells, there would be no response to the vaccines so they are not recommended. Furthermore, these patients are frequently receiving immunoglobulin replacement therapy, which contains pneumococcal antibodies, affording some protection without vaccination (123). In contrast, in certain IEI such as terminal complement deficiencies or innate immune defects there is a particular susceptibility to encapsulated bacterial infections, including *S. pneumoniae*. In this setting vaccination with both PCV13 and PPV23 for expanded serotype coverage is recommended as part of treatment, with boosting after 5 years with PPV23. In the diagnostic work-up of suspected functional antibody deficiencies, assessment of polysaccharide T-independent B-cell responses using PPV23 is recommended (123), with checking of serotype-specific pneumococcal antibody responses 4 weeks after vaccination; assessment of T-dependent B-cell responses to protein conjugates is usually performed to tetanus and diphtheria rather than PCV13. In other IEI groups, such as auto-inflammatory or immune dysregulation disorders, without B-cell defects, pneumococcal vaccination is recommended in line with that for the healthy population (124).

PCV13 should be administered initially followed by PPV23 8 weeks later (125). However, if PPV23 has been given prior to PCV13 as part of the diagnostic work-up of antibody deficiency, most groups recommend addition of PCV13 ≥1 year later (126).

Pneumococcal vaccination recommendations for adults 65 years of age and older

Older adults have complex needs and vaccination tends to be a neglected aspect of their care that should be integrated into a holistic healthcare program (127).

PPV23 and PCV13 are said to have similar effectiveness in preventing IPD in older adults (PPV23 50–80% versus PCV13 75%) (128). However, comparisons on prevention of mucosal disease, such as non-bacteraemic pneumonia, are challenging, due to differences in study techniques and the lack of validated and standardized diagnostic tests (19,129,130). PCV13 has been confirmed to be effective in reducing both bacteraemic (46%) and non-bacteraemic (45%) vaccine-type pneumococcal pneumonia. While some studies have documented PPV23 to be effective in preventing pneumococcal pneumonia in elderly people, this protection wanes over time and with increasing age (128,130).

The "prime boost" technique of administering the PCV13 followed sequentially by PPV23 in order to enhance and prolong the immune response, in other words enhanced immunogenicity, while at the same time adding potential cover for the additional serotypes contained in PPV23, has been studied, but the results have not been consistent (131). However, a recent real world effectiveness study (test-negative design) of pneumococcal vaccination with PCV13 versus PPV23, versus sequential PCV13/PPV23 in adults ≥65 years noted that for the group as a whole, there was no significant difference in vaccine effectiveness between PCV13 (40.0%; 95% CI: 15.9% to 95.4%) versus PPV23 (11.0%; 95% CI: –26.4% to 37.3%) (132). Furthermore, in the younger subset of patients (aged 65–74 years), sequential PCV13/PPV23 was associated with the highest adjusted vaccine efficacy (80.3%; 95% CI: 15.9% to 95.4%), compared with that of PCV13 (66.4%; 95% CI: 0.8% to 88.6%), and then PPV23 (18.5%; 95% CI: –38.6% to 52.0%).

An additional dose of PPV23 is used in some countries between 5 and 10 years after the preceding dose; however, the effectiveness wanes with age and the safety and benefits over the age of 75 years are uncertain (42). If the first dose of PPV23 was given before the age of 65 years, then a second dose can be given after the age of 65 years provided at least 5 years have passed. Addressing other co-morbidities may be more important in those aged >75 years (127).

Two early cost-effectiveness studies of use of PCV13 and/or PPV23 in different scenarios in adults, including cases without comorbidity, aged 50, 60, or 65 years old were conducted. Both noted that one dose of PCV13 in adults was cost-effective compared to other vaccine interventions, but the analyses in both these studies were sensitive to the anticipated progressive increase in indirect protection in adults from childhood immunization (133,134). However, based on a consideration of data from the CAPITA study, additional immunogenicity data, and the study by Stoecker and colleagues (134), the ACIP recommended in 2014 that PCV13 be used in series with PPV23 in all adults ≥65 years (135). However, the ACIP also noted that there would be a

reassessment of this recommendation in the future, based among other factors, on the anticipated increase in herd protection and its impact on the long-term utility of routine use of PCV13 in the elderly (135).

With regard to the indirect benefits of PCV13 vaccination, it has been demonstrated that childhood vaccination against pneumococcal disease with the conjugate vaccine has resulted, in many countries, in a substantial reduction in disease in older adults via herd protection, due to reduced nasal carriage; however, in South Africa, despite some herd protection, the impact on the age group >65 years has been limited, as mentioned in the introduction (10,136-138). In countries, such as the US, a maximal indirect benefit to older adults from vaccinating children has been reached that is not enhanced by subsequent direct vaccination with PCV13 in older adults, despite reasonable uptake (42). However, in South Africa, there is still considerable PCV13-serotype disease in both children and adults, including even younger adults, such that the IPD incidence has remained stable over 5 years up to 2019 (139).

In the light of all these data, we recommend the routine use of both PCV13 and PPV23, sequentially, for all South Africans ≥65 years. If patients are vaccine-naïve, without immunocompromise or high-risk conditions, they should routinely be given PCV13 followed by PPV23 1 year later. Therefore, this recommendation differs from that of the US, which recommends routine PPV23 in this group of patients and only consideration of the additional use of PCV13 based on additional discussions (shared-decision making) with the patients (132,140). In vaccine-naïve elderly with immunocompromising conditions, or with cerebrospinal fluid leak (CSF) leak or cochlear implant, PPV23 should be given 8 weeks after the PCV13. PCV13 should not be given as a standalone vaccine for elderly South Africans due to limited serotype coverage, and if cost or compliance with a two-dose regimen is an issue, PPV23 alone can be given to immunocompetent patients.

Other indications for pneumococcal vaccination

In patients with the following clinical situations, not necessarily included in previous sections, pneumococcal vaccination is recommended (140,141).

CSF and cochlear implants

Any condition associated with a CSF leak, particularly of long duration, increases the risk of meningitis (142).

A cohort study in 2003 estimated the incidence of pneumococcal meningitis post insertion of cochlear implants to be greater than 30 times that of age-matched controls (143).

For these indications, the recommendation for vaccination in vaccine-naïve individuals is PCV13 followed by PPV23 8 weeks later. A subsequent dose of PPV23 is recommended 5 years after the first PPV23 dose, and consideration can be given to an additional dose at age >65 years if 5 years have elapsed since the last dose.

Solid organ transplant recipients (SOT)

SOT patients experience higher incidence and mortality rates from IPD compared to the general population, with a variable rate depending on the organ transplanted (102,144,145). Risk of death from IPD is up to 3 times higher in an undifferentiated immune-suppressed population (24%) compared to the general population (9%) (146).

Vaccine response rates may be lower in SOT recipients, with limited evidence evaluating clinical outcomes with either vaccine. Both PPV23 and PCV13 vaccines produce measurable sero-responses (147), although less so than those in healthy controls, with limited evidence of benefit from "prime boosting" and less durable response rates (102). Concerns that vaccination may increase the risk of adverse allo-responses such as rejection and generation of donor specific antibodies are not supported by safety studies (102). Solid organ transplantation candidates (pre-transplant) are more likely to develop vaccine-induced immunity compared with SOT who are receiving immunosuppressive agents (post-transplant), and as such, the latter should receive vaccination in line with the transplant recommendations and/or guidelines (148,149).

Pneumococcal vaccination recommendations for travellers

Respiratory tract infections occur commonly in travellers, even to first world destinations. This is particularly the case in those ≥65 years of age and those with comorbid conditions, or with immunocompromise from whatever cause. As such, these groups should ensure that their vaccination schedules are up to date (150-155). Mass gatherings such as the annual Hajj in Saudi Arabia and the soccer world cup (which is held every 4 years) have been associated with increased respiratory infections. During the Hajj over 50% of pilgrims have reported respiratory symptoms in some studies and pneumonia has been documented as the most frequent cause of hospital admissions from communicable disease (154). A significant

percentage of pilgrims are older than 60 (more than one third from certain countries), with a number of them having comorbid conditions such as diabetes, and influenza and pneumococcal vaccination have been strongly advised for both groups (154,155).

Pneumococcal vaccination, especially in older travellers with comorbid conditions, would provide protection against this infection and potentially reduce the acquisition of multidrug-resistant vaccine serotypes from countries where they are prevalent (156,157). Immunocompromised patients account for 1–2% of travellers seen in US travel clinics, and, interestingly, tend to have itineraries similar to those of their immunocompetent counterparts. This is a heterogenous group that includes those on immunosuppressants due to organ transplantation, inflammatory and autoimmune disorders, and HIV infected individuals, all of whom would benefit significantly from pneumococcal vaccination, as discussed previously (158).

Perspective of pneumococcal vaccination recommendations for healthcare practitioners in general practice or working in primary care clinics

A General Practitioner (GP) or primary care clinic consultation offers the ideal opportunity to promote and administer the pneumococcal vaccine. Most GP or primary care clinic consultations are problem-based and the focus is on the acute complaints, history taking, examination and thereafter provision of a prescription or referral for specialist consultation. The GP or primary care practitioner should always consider who amongst their patients would benefit most from pneumococcal (and other) vaccines. The administration of the annual influenza vaccination offers a very good opportunity to suggest a pneumococcal vaccination at the same time, as they are safe to administer simultaneously. Routine vaccination should not be neglected during the COVID-19 pandemic, particularly in high-risk cases.

High-risk patients are described in each of the sections above. With an aging population, who more regularly consult with their GP or primary care practitioner for follow-up and monitoring of chronic conditions and for repeat of chronic medication prescriptions, vaccination should be discussed on each visit and the opportunity taken to educate patients and their families.

Many patients are apprehensive about vaccination as they are concerned that they may actually contract the infection from the vaccine. A brief explanation of the types of vaccines and their immunological responses is required, and an explanation that the pneumococcal vaccine does not contain either live or killed microorganisms.

Remember to get consent prior to administration of any vaccine and record the vaccination in the patient's file. A good idea is to remove the vaccine vial wrapper from the glass vial and stick this into the patient file. Patients taking warfarin or novel oral anticoagulants require careful injection to reduce bleeding at the injection site.

It also needs to be recognised that patients with multiple comorbid conditions (a condition termed "risk stacking") is not uncommon in older and aging patients (104). These patients have an even greater risk of pneumococcal infections that may be as high as, or even higher than, those adults with high-risk and immunocompromising conditions and this is often not considered in vaccination recommendations (104). In South Africa, in addition, as indicated previously, HIV remains a major driver of ongoing pneumococcal infections, despite the comprehensive roll-out of ART (121), while a recent modelling study indicated the cost-effectiveness of PCV13 versus PPV23 in adults in South Africa, particularly in those with HV (137)

Additional potential risk factors for CAP and/or pneumococcal infection, some not mentioned above, include cigarette smoking, excessive alcohol consumption, obesity, sleep apnoea, occupations such as welding and gold mining, and people living in confined areas, such as barracks and prisons, and it may be advisable to consider pneumococcal vaccination in these groups of patients, for some of whom specific recommendations exist (159-164).

Barriers, knowledge gaps and vaccine advocacy

Vaccinations are recommended throughout life to prevent the acquisition and spread of vaccine-preventable diseases (165). Although older adults are at risk for vaccine-preventable diseases, the primary focus of medical care for adults has focused on prevention and/or treatment of chronic comorbid conditions. The primary focus of vaccination programs, therefore, has been directed at childhood immunisation and for that reason the uptake of routine vaccinations in adults has remained very low (165).

The common barriers to use of vaccinations in adults are numerous and include, among others (165):

(I) Lack of recognition of the importance, benefits and safety of vaccination in adults;
(II) Lack of healthcare provider knowledge and/or recommendations about vaccination;

(III) Missed opportunities for vaccination at office, clinical or hospital visits;
(IV) Lack of publicly-funded vaccines and of reimbursement to vaccine providers and patients;
(V) Lack of coordinated vaccine programs, records systems, and registries for adults.

Vaccines are effective tools for the support of adults as they age, alongside healthy diet and physical exercise; these contributing to so-called "healthy ageing" (166,167). Important steps that healthcare practitioners can take to promote vaccination include (167):

(I) At every visit assess patients' vaccination status;
(II) Recommend vaccination strongly to each patient at every opportunity. To do this use the 4Rs as a way of remembering to do this. These are Recommend, Repeat, Remind and Review;
(III) Have a program in your practice for vaccine administration;
(IV) If not, refer patients to healthcare professionals who do administer vaccines;
(V) Document vaccine administration and submit to registries.

It is important to remember that the healthcare professional is the patients' best health advocate (167).

However, there are some knowledge gaps noted when developing vaccine recommendations. The most important issue is that not all vaccines have had their efficacy or effectiveness studied in randomized clinical trials in each and every medical condition, since in many conditions, proof of immunogenicity in those cases is adequate for registration of vaccines. For some medical conditions, no studies exist and this could be an avenue for future research.

In its broadest sense, advocacy is the use of information, evidence and arguments to bring about change. Vaccine advocacy is best defined as: the promotion of the best scientific knowledge, moral attitudes, and public health practice with regard to vaccination (168). This is a change, which includes but is not limited to, attitude, behaviour, policies, practices and bridging the gap from problem to solution. Improving access to vaccines for vaccine preventable infections (VPI) such as pneumococcal disease has become important in South Africa. Vaccine advocacy is an important strategy to improve access for PCV13 for adolescents and adults. The use of PCV13 for adolescents and adults is not readily available in the public health system in South Africa though the vaccine is registered for use in adults.

This document presents evidence and information advocating for the use of PCV13 and PPV23 as a vaccination strategy in adolescents and adults at high risk for invasive pneumococcal infection in South Africa. This document bridges a gap that exists in the absence of a national adult vaccination programme to support the use PCV13 for adolescents and adults. This document presents evidence that supports the use of PCV13 therefore providing an opportunity to improve policy and programs to reduce the burden of this disease in adults. The only vaccine programme supported by the National Health Department for adolescents and adults is the yearly influenza vaccine. The COVID-19 and human papillomavirus (HPV) vaccine programmes are supported by the national health department but are also supported through special access programmes. This document whilst advocating for greater access for PCV13 for adults intends changing the behaviour, practice and attitude of health care workers with respect to the use of pneumococcal vaccines in adults. Evidence suggests that increased or improved access to vaccines for adolescents and adults, includes, amongst others, having national permissive recommendations in low and middle income countries such as South Africa (169). Having a national recommendation allows for or increases awareness for vaccination, which should lead to bridging the gap that is needed to effect greater use of vaccines. This in itself may not be sufficient but are important steps in advocacy, as advocacy takes a long-term view of an issue, recognising that it takes time to effect change.

Future pneumococcal vaccines

While newer conjugate vaccines, including PCV15 and PCV20, have recently been licensed and recommended for use in the US and in parts of Europe (170), these are still some way from being licensed and recommended for use in South Africa; however, as soon as they are, this document will be updated.

Conclusions

It is hoped that this document will clarify for healthcare professionals in all spheres practice, how, where, and when pneumococcal vaccines should be used in adults in South Africa, and potentially beyond that, with the ultimate goal of substantially increasing their use, in order to reduce the significant morbidity and mortality associated with pneumococcal infections.

Acknowledgments

The authors wish to thank Dr. Mark Sonderup and Wendy Spearman for consultant support. This document has been endorsed by the following Societies/Boards: Faculty of Consulting Physicians of South Africa (FCPSA), Federation of Infectious Diseases Societies of Southern Africa, South African Clinical Haematology Society (SACHas), South African Geriatrics Society (SAGS), South African HIV Clinicians Society, South African Society of Travel Medicine (SASTM), South African Stem Cell Transplant Society (SASceTS), and South African Thoracic Society (SATS).

Funding: The development of this document with its recommendation was funded by an unrestricted educational grant from Pfizer to the Federation of Infectious Diseases Societies of Southern Africa (FIDSSA), an umbrella organization encompassing most of the individual infectious diseases societies in the South Africa. The funders played no role, whatsoever, in the design, writing, reviewing, or finalizing of the manuscript.

Footnote

Reporting Checklist: The authors have completed the RIGHT reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-287/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-287/coif). CF has received honoraria for participation in Advisory Boards and Speaker's Bureaus for MSD and Pfizer. CF reports that the development of this document and its recommendations was funded by an unrestricted educational grant from Pifzer to the Federation of Infectious Diseases Societies of Southern Africa. SD has received payment for Speaker's Bureaus for the following organizations in the last 36 months, Pfizer, MSD, ABBVIE, and SANOFI. All these speaker activities were for educational meetings or conferences. In addition, SD has participated in Advisory Board for the following organizations, MSD, ViiV, Health/GSK, Adcock Ingram and Jansen. GAR has received honoraria for Speaker's Bureaus from Pfizer and MSD-None recently however. MM has acted on the speaker's bureaus of MSD, Pfizer, J&J, Aspen, Mylan and Cipla, and on the Advisory Boards of Pfizer, MSD, J&J and Mylan, has also received fully paid travel expenses to international conferences and advisory boards, and had leadership or fiduciary roles in SAHIVSOC and AVCS. MYSM has received consulting fees from Johnson & Johnson, Cipla, MSD, ViiV, 360 pharmaceuticals and Mylan, and participated on data safety monitoring boards or advisory boards for EnACT, NTZ versus SOF/DCV Study, and The CARES Study, and acts on the Southern African HIV Clinicians Society. JP has received speaker's fees from Sanofi, Novartis and Janssen, and participated on the advisory board for Sanofi. CvV has acted on the Speaker's Bureaus of Mylan and Viatris. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. GBD 2016 Lower Respiratory Infections Collaborators. Estimates of the global, regional, and national morbidity, mortality, and aetiologies of lower respiratory infections in 195 countries, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Infect Dis 2018;18:1191-210.
2. Available online: https://www.cdc.gov/pneumococcal / vaccination.html (last accessed 26 September, 2020).
3. Adult pneumococcal vaccination guideline. SAMA-SA Pulmonology Society Working Group. S Afr Med J 1999;89:1222-30.
4. Boyles TH, Brink A, Calligaro GL, et al. South African guideline for the management of community-acquired pneumonia in adults. J Thorac Dis 2017;9:1469-502.
5. Bennett JE, Dolin R, Blaser MJ. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. Elsevier Inc., 2014.
6. Drijkoningen JJ, Rohde GG. Pneumococcal infection in adults: burden of disease. Clin Microbiol Infect 2014;20 Suppl 5:45-51.

7. Wahl B, O'Brien KL, Greenbaum A, et al. Burden of *Streptococcus pneumoniae* and *Haemophilus influenzae* type b disease in children in the era of conjugate vaccines: global, regional, and national estimates for 2000-15. Lancet Glob Health 2018;6:e744-57.
8. Meiring S, Cohen C, Quan V, et al. HIV Infection and the Epidemiology of Invasive Pneumococcal Disease (IPD) in South African Adults and Older Children Prior to the Introduction of a Pneumococcal Conjugate Vaccine (PCV). PLoS One 2016;11:e0149104.
9. National Institute for Communicable Diseases. GERMS-SA Annual Report 2018. 2019. Available online: http://www.nicd.ac.za/publications/archives/
10. von Gottberg A, de Gouveia L, Tempia S, et al. Effects of vaccination on invasive pneumococcal disease in South Africa. N Engl J Med 2014;371:1889-99.
11. Whitney CG, Farley MM, Hadler J, et al. Decline in invasive pneumococcal disease after the introduction of protein-polysaccharide conjugate vaccine. N Engl J Med 2003;348:1737-46.
12. Feikin DR, Kagucia EW, Loo JD, et al. Serotype-specific changes in invasive pneumococcal disease after pneumococcal conjugate vaccine introduction: a pooled analysis of multiple surveillance sites. PLoS Med 2013;10:e1001517.
13. von Gottberg A, Kleynhans J, de Gouveia L, et al. Trends in invasive pneumococcal disease among adults aged >=15 years, South Africa, 2005-2016. In: ISPPD-11, Melbourne. 2018. Available online: http://isppd2018.kenes.com/
14. Kleynhans J, von Gottberg A, Cohen C, et al. Impact of the pneumococcal conjugate vaccine on pneumonia mortality in South Africa, 1999-2016: a retrospective observational study. In: ISPPD-12, Toronto. 2020. Available online: https://cslide.ctimeetingtech.com/isppd20/attendee/confcal/session/calendar?q=Kleynhans
15. Brueggemann AB, Jansen van Rensburg MJ, Shaw D, et al. Changes in the incidence of invasive disease due to *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Neisseria meningitidis* during the COVID-19 pandemic in 26 countries and territories in the Invasive Respiratory Infection Surveillance Initiative: a prospective analysis of surveillance data. Lancet Digit Health 2021;3:e360-70.
16. Feldman C, Anderson R. Review: current and new generation pneumococcal vaccines. J Infect 2014;69:309-25.
17. Musher DM. Pneumococcal vaccination in adults. UpToDate 2020. Available online: https://www.uptodate.com/contents/pneumococcal-vaccination-in-adults
18. Jarvis S. Pneumococcal vaccination. Available online: https://patient.info/doctor/pneumococcal -vaccination
19. Bonten MJ, Huijts SM, Bolkenbaas M, et al. Polysaccharide conjugate vaccine against pneumococcal pneumonia in adults. N Engl J Med 2015;372:1114-25.
20. Pink Book. Pneumococcal Disease. Available online: https://www.cdc.gov/vaccines/pubs/pinkbook/pneumo.html (accessed 9 September, 2022)
21. de Roux A, Schmöle-Thoma B, Siber GR, et al. Comparison of pneumococcal conjugate polysaccharide and free polysaccharide vaccines in elderly adults: conjugate vaccine elicits improved antibacterial immune responses and immunological memory. Clin Infect Dis 2008;46:1015-23.
22. Pollard AJ, Perrett KP, Beverley PC. Maintaining protection against invasive bacteria with protein-polysaccharide conjugate vaccines. Nat Rev Immunol 2009;9:213-20.
23. Lopez AD, Mathers CD, Ezzati M, et al. Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data. Lancet 2006;367:1747-57.
24. Wong ND. Epidemiological studies of CHD and the evolution of preventive cardiology. Nat Rev Cardiol 2014;11:276-89.
25. Warren-Gash C, Smeeth L, Hayward AC. Influenza as a trigger for acute myocardial infarction or death from cardiovascular disease: a systematic review. Lancet Infect Dis 2009;9:601-10.
26. Liu C, Yavar Z, Sun Q. Cardiovascular response to thermoregulatory challenges. Am J Physiol Heart Circ Physiol 2015;309:H1793-812.
27. Vardeny O, Solomon SD. Influenza vaccination: a one-shot deal to reduce cardiovascular events. Eur Heart J 2017;38:334-7.
28. Yende S, D'Angelo G, Kellum JA, et al. Inflammatory markers at hospital discharge predict subsequent mortality after pneumonia and sepsis. Am J Respir Crit Care Med 2008;177:1242-7.
29. Pothineni NVK, Subramany S, Kuriakose K, et al. Infections, atherosclerosis, and coronary heart disease. Eur Heart J 2017;38:3195-201.
30. Siriwardena AN, Gwini SM, Coupland CA. Influenza vaccination, pneumococcal vaccination and risk of acute myocardial infarction: matched case-control study. CMAJ 2010;182:1617-23.
31. Ochoa-Gondar O, Vila-Corcoles A, Rodriguez-Blanco T, et al. Evaluating the clinical effectiveness of pneumococcal vaccination in preventing myocardial infarction:

The CAPAMIS study, three-year follow-up. Vaccine 2014;32:252-7.
32. Corrales-Medina VF, Alvarez KN, Weissfeld LA, et al. Association between hospitalization for pneumonia and subsequent risk of cardiovascular disease. JAMA 2015;313:264-74.
33. Ren S, Newby D, Li SC, et al. Effect of the adult pneumococcal polysaccharide vaccine on cardiovascular disease: a systematic review and meta-analysis. Open Heart 2015;2:e000247.
34. Fonarow GC, Abraham WT, Albert NM, et al. Factors identified as precipitating hospital admissions for heart failure and clinical outcomes: findings from OPTIMIZE-HF. Arch Intern Med 2008;168:847-54.
35. Corrales-Medina VF, Musher DM, Wells GA, et al. Cardiac complications in patients with community-acquired pneumonia: incidence, timing, risk factors, and association with short-term mortality. Circulation 2012;125:773-81.
36. Violi F, Cangemi R, Falcone M, et al. Cardiovascular Complications and Short-term Mortality Risk in Community-Acquired Pneumonia. Clin Infect Dis 2017;64:1486-93.
37. Santos-Gallego CG, Badimon JJ. Cardiac Complications After Community-Acquired Pneumonia. Am J Cardiol 2016;117:310.
38. Wedzicha JA, Seemungal TA. COPD exacerbations: defining their cause and prevention. Lancet 2007;370:786-96.
39. Walters JA, Tang JN, Poole P, et al. Pneumococcal vaccines for preventing pneumonia in chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2017;1:CD001390.
40. Figueira-Gonçalves JM, Bethencourt-Martín N, Pérez-Méndez LI, et al. Impact of 13-valent pneumococcal conjugate polysaccharide vaccination in exacerbations rate of COPD patients with moderate to severe obstruction. Rev Esp Quimioter 2017;30:269-75.
41. Alfageme I, Vazquez R, Reyes N, et al. Clinical efficacy of anti-pneumococcal vaccination in patients with COPD. Thorax 2006;61:189-95.
42. Matanock A, Lee G, Gierke R, et al. Use of 13-Valent Pneumococcal Conjugate Vaccine and 23-Valent Pneumococcal Polysaccharide Vaccine Among Adults Aged ≥65 Years: Updated Recommendations of the Advisory Committee on Immunization Practices. MMWR Morb Mortal Wkly Rep 2019;68:1069-75.
43. Available online: https://goldcopd.org/ (2021).
44. Dransfield MT, Harnden S, Burton RL, et al. Long-term comparative immunogenicity of protein conjugate and free polysaccharide pneumococcal vaccines in chronic obstructive pulmonary disease. Clin Infect Dis 2012;55:e35-44.
45. Abdool-Gaffar MS, Calligaro G, Wong ML, et al. Management of chronic obstructive pulmonary disease-A position statement of the South African Thoracic Society: 2019 update. J Thorac Dis 2019;11:4408-27.
46. GINA: Global Strategy for Asthma Management and Prevention 2020 Update. Available online: https://ginasthma.org/gina-reports/ Accessed 1/9/20
47. World Health Organisation Asthma 2020. Available online: https://www.who.int/news-room/q-a-detail/asthma Accessed 1/9/20
48. Jackson DJ, Johnston SL. The role of viruses in acute exacerbations of asthma. J Allergy Clin Immunol 2010;125:1178-87; quiz 1188-9.
49. World Health Organisation. Pneumococcal disease. Available online: https://www.who.int/ith/diseases/pneumococcal/en/ Accessed 1/9/20
50. Kwak BO, Choung JT, Park YM. The association between asthma and invasive pneumococcal disease: a nationwide study in Korea. J Korean Med Sci 2015;30:60-5.
51. Talbot TR, Hartert TV, Mitchel E, et al. Asthma as a risk factor for invasive pneumococcal disease. N Engl J Med 2005;352:2082-90.
52. Juhn YJ, Kita H, Yawn BP, et al. Increased risk of serious pneumococcal disease in patients with asthma. J Allergy Clin Immunol 2008;122:719-23.
53. Klemets P, Lyytikäinen O, Ruutu P, et al. Risk of invasive pneumococcal infections among working age adults with asthma. Thorax 2010;65:698-702.
54. Eisenlohr CP, Chartrand EM, Barzaga MR, et al. Impact of pneumococcal vaccine response on asthma exacerbation frequency in young children. Immun Inflamm Dis 2020;8:493-6.
55. Lee TA, Weaver FM, Weiss KB. Impact of pneumococcal vaccination on pneumonia rates in patients with COPD and asthma. J Gen Intern Med 2007;22:62-7.
56. Castro-Rodriguez JA, Abarca K, Forno E. Asthma and the Risk of Invasive Pneumococcal Disease: A Meta-analysis. Pediatrics 2020;145:e20191200.
57. Centers for Disease Control and Prevention. Recommended Adult Immunization Schedule by Medical Condition and Other Indications, United States, 2020. Available online: https://www.cdc.gov/vaccines/schedules/hcp/imz/adult-conditions.html (Ac-cessed 1/9/20).

58. Immunisation Advisory Centre. Acdm Rev 2016 Pneumo_highrisk_finaledit_V2.pdf Available online: https://www.immune.org.nz/sites/default/files/publications/Acdm%20Rev%202016%20Pneumo_highrisk_finaledit_V2.pdf (Accessed 1/9/20)
59. Weinberger DM, Pitzer VE, Regev-Yochay G, et al. Association Between the Decline in Pneumococcal Disease in Unimmunized Adults and Vaccine-Derived Protection Against Colonization in Toddlers and Preschool-Aged Children. Am J Epidemiol 2019;188:160-8.
60. Yildirim I, Shea KM, Pelton SI. Pneumococcal Disease in the Era of Pneumococcal Conjugate Vaccine. Infect Dis Clin North Am 2015;29:679-97.
61. List. Risk conditions for pneumococcal disease. Australian Immunisation Handbook. Available online: https://immunisationhandbook.health.gov.au/resources/handbook-tables/list-risk-conditions-for-conditions-for-pneumococcal-disease
62. Mirsaeidi M, Ebrahimi G, Allen MB, et al. Pneumococcal vaccine and patients with pulmonary diseases. Am J Med 2014;127:886.e1-8.
63. Wong A, Marrie TJ, Garg S, et al. Welders are at increased risk for invasive pneumococcal disease. Int J Infect Dis 2010;14:e796-9.
64. Shears RK, Jacques LC, Naylor G, et al. Exposure to diesel exhaust particles increases susceptibility to invasive pneumococcal disease. J Allergy Clin Immunol 2020;145:1272-1284.e6.
65. Chang CC, Singleton RJ, Morris PS, et al. Pneumococcal vaccines for children and adults with bronchiectasis. Cochrane Database Syst Rev 2009;(2):CD006316.
66. Burgess L, Southern KW. Pneumococcal vaccines for cystic fibrosis. Cochrane Database Syst Rev 2016;9:CD008865.
67. Oda K, Yatera K, Fujino Y, et al. Respiratory comorbidities and risk of mortality in hospitalized patients with idiopathic pulmonary fibrosis. Respir Investig 2018;56:64-71.
68. Lee JS, McLaughlin S, Collard HR. Comprehensive care of the patient with idiopathic pulmonary fibrosis. Curr Opin Pulm Med 2011;17:348-54.
69. Knippenberg S, Ueberberg B, Maus R, et al. Streptococcus pneumoniae triggers progression of pulmonary fibrosis through pneumolysin. Thorax 2015;70:636-46.
70. Rahier JF, Magro F, Abreu C, et al. Second European evidence-based consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. J Crohns Colitis 2014;8:443-68.
71. Kantsø B, Simonsen J, Hoffmann S, et al. Inflammatory Bowel Disease Patients Are at Increased Risk of Invasive Pneumococcal Disease: A Nationwide Danish Cohort Study 1977-2013. Am J Gastroenterol 2015;110:1582-7.
72. Bonovas S, Fiorino G, Allocca M, et al. Biologic Therapies and Risk of Infection and Malignancy in Patients With Inflammatory Bowel Disease: A Systematic Review and Network Meta-analysis. Clin Gastroenterol Hepatol 2016;14:1385-1397.e10.
73. Long MD, Martin C, Sandler RS, et al. Increased risk of pneumonia among patients with inflammatory bowel disease. Am J Gastroenterol 2013;108:240-8.
74. Kantsø B, Halkjær SI, Thomsen OØ, et al. Immunosuppressive drugs impairs antibody response of the polysaccharide and conjugated pneumococcal vaccines in patients with Crohn's disease. Vaccine 2015;33:5464-9.
75. van Aalst M, Garcia Garrido HM, van der Leun J, et al. Immunogenicity of the Currently Recommended Pneumococcal Vaccination Schedule in Patients With Inflammatory Bowel Disease. Clin Infect Dis 2020;70:595-604.
76. Rubin LG, Levin MJ, Ljungman P, et al. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. Clin Infect Dis 2014;58:309-18.
77. Dezfoli S, Melmed GY. Vaccination issues in patients with inflammatory bowel disease receiving immunosuppression. Gastroenterol Hepatol (N Y) 2012;8:504-12.
78. Ardura MI, Toussi SS, Siegel JD, et al. NASPGHAN Clinical Report: Surveillance, Diagnosis, and Prevention of Infectious Diseases in Pediatric Patients With Inflammatory Bowel Disease Receiving Tumor Necrosis Factor-α Inhibitors. J Pediatr Gastroenterol Nutr 2016;63:130-55.
79. Farraye FA, Melmed GY, Lichtenstein GR, et al. ACG Clinical Guideline: Preventive Care in Inflammatory Bowel Disease. Am J Gastroenterol 2017;112:241-58.
80. Bye WA, Jairath V, Travis SPL. Systematic review: the safety of vedolizumab for the treatment of inflammatory bowel disease. Aliment Pharmacol Ther 2017;46:3-15.
81. Hanauer SB, Sandborn WJ, Feagan BG, et al. IM-UNITI: Three-year Efficacy, Safety, and Immunogenicity of Ustekinumab Treatment of Crohn's Disease. J Crohns Colitis 2020;14:23-32.
82. Harrington JE, Hamilton RE. Ganley-Leal L, et al. The immunogenicity of the influenza, pneumococcal, and hepatitis B vaccines in patients with inflammatory bowel disease treated with Vedolizumab. Crohn's & Colitis 2020;360:otaa082.
83. Sandborn WJ, Panés J, D'Haens GR, et al. Safety of

Tofacitinib for Treatment of Ulcerative Colitis, Based on 4.4 Years of Data From Global Clinical Trials. Clin Gastroenterol Hepatol 2019;17:1541-50.
84. Brodmerkel C, Wadman E, Langley RG, et al. Immune response to pneumococcus and tetanus toxoid in patients with moderate-to-severe psoriasis following long-term ustekinumab use. J Drugs Dermatol 2013;12:1122-9.
85. Winthrop KL, Silverfield J, Racewicz A, et al. The effect of tofacitinib on pneumococcal and influenza vaccine responses in rheumatoid arthritis. Ann Rheum Dis 2016;75:687-95.
86. Ekpanyapong S, Reddy KR. Infections in Cirrhosis. Curr Treat Options Gastroenterol 2019;17:254-70.
87. Bonnel AR, Bunchorntavakul C, Reddy KR. Immune dysfunction and infections in patients with cirrhosis. Clin Gastroenterol Hepatol 2011;9:727-38.
88. Valour F, Conrad A, Ader F, et al. Vaccination in adult liver transplantation candidates and recipients. Clin Res Hepatol Gastroenterol 2020;44:126-34.
89. Gil-Prieto R, Pascual-Garcia R, Walter S, et al. Risk of hospitalization due to pneumococcal disease in adults in Spain. The CORIENNE study. Hum Vaccin Immunother 2016;12:1900-5.
90. van Hoek AJ, Andrews N, Waight PA, et al. The effect of underlying clinical conditions on the risk of developing invasive pneumococcal disease in England. J Infect 2012;65:17-24.
91. Pirovino M, Lydick E, Grob PJ, et al. Pneumococcal vaccination: the response of patients with alcoholic liver cirrhosis. Hepatology 1984;4:946-9.
92. McCashland TM, Preheim LC, Gentry MJ. Pneumococcal vaccine response in cirrhosis and liver transplantation. J Infect Dis 2000;181:757-60.
93. Boettler T, Marjot T, Newsome PN, et al. Impact of COVID-19 on the care of patients with liver disease: EASL-ESCMID position paper after 6 months of the pandemic. JHEP Rep 2020;2:100169.
94. Strikas RA; Centers for Disease Control and Prevention (CDC); Advisory Committee on Immunization Practices (ACIP), et al. Advisory committee on immunization practices recommended immunization schedules for persons aged 0 through 18 years-United States, 2015. MMWR Morb Mortal Wkly Rep 2015;64:93-4.
95. CDC. Flu and pneumonia vaccinations decrease relative morbidity risk for people with diabetes. Available online: http://www.cdc.gov/diabetes/projects/pdfs/hpNewsletter.pdf (accessed February 25, 2015).
96. CDC. Vaccine-Specific Recommendations. 2018. Available online: http://www.cdc.gov/vaccines/hcp/acip-recs/vaccspecific/index.html (accessed July 10, 2018).
97. Baxter R, Yee A, Fireman B, et al. Chronic kidney disease and invasive pneumococcal disease in adults. ID Week, Poster 1105. Available online: https://idsa.confex.com/idsa/2014/webprogram/Paper45859.html (last accessed 9 September 2022).
98. Crew RJ, Radhakrishnan J, Appel G. Complications of the nephrotic syndrome and their treatment. Clin Nephrol 2004;62:245-59.
99. Roca-Oporto C, Pachon-Ibanez ME, Pachon J, Cordero E. Pneumococcal disease in adult solid organ transplantation recipients. World J Clin Infect Dis 2015;5:1-10.
100. Mulley WR, Dendle C, Ling JEH, et al. Does vaccination in solid-organ transplant recipients result in adverse immunologic sequelae? A systematic review and meta-analysis. J Heart Lung Transplant 2018;37:844-52.
101. Dendle C, Stuart RL, Polkinghorne KR, et al. Seroresponses and safety of 13-valent pneumococcal conjugate vaccination in kidney transplant recipients. Transpl Infect Dis 2018;20:e12866.
102. Dendle C, Stuart RL, Mulley WR, et al. Pneumococcal vaccination in adult solid organ transplant recipients: A review of current evidence. Vaccine 2018;36:6253-61.
103. Furer V, Rondaan C, Heijstek M, et al. Incidence and prevalence of vaccine preventable infections in adult patients with autoimmune inflammatory rheumatic diseases (AIIRD): a systemic literature review informing the 2019 update of the EULAR recommendations for vaccination in adult patients with AIIRD. RMD Open 2019;5:e001041.
104. Shea KM, Edelsberg J, Weycker D, et al. Rates of pneumococcal disease in adults with chronic medical conditions. Open Forum Infect Dis 2014;1:ofu024.
105. Furer V, Rondaan C, Heijstek MW, et al. 2019 update of EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases. Ann Rheum Dis 2020;79:39-52.
106. Rákóczi É, Szekanecz Z. Pneumococcal vaccination in autoimmune rheumatic diseases. RMD Open 2017;3:e000484.
107. Dell' Era L, Esposito S, Corona F, et al. Vaccination of children and adolescents with rheumatic diseases. Rheumatology (Oxford) 2011;50:1358-65.
108. Paradiso PR. Pneumococcal conjugate vaccine for adults: a new paradigm. Clin Infect Dis 2012;55:259-64.
109. Landesman SH, Schiffman G. Assessment of the antibody response to pneumococcal vaccine in high-risk

populations. Rev Infect Dis 1981;3 Suppl:S184-97.
110. Rubin LG, Schaffner W. Clinical practice. Care of the asplenic patient. N Engl J Med 2014;371:349-56.
111. Cannas G, Merazga S, Virot E. Sickle Cell Disease and Infections in High- and Low-Income Countries. Mediterr J Hematol Infect Dis 2019;11:e2019042.
112. Howard J, Hart N, Roberts-Harewood M, et al. Guideline on the management of acute chest syndrome in sickle cell disease. Br J Haematol 2015;169:492-505.
113. Kamboj M, Shah MK. Vaccination of the Stem Cell Transplant Recipient and the Hematologic Malignancy Patient. Infect Dis Clin North Am 2019;33:593-609.
114. Rieger CT, Liss B, Mellinghoff S, et al. Anti-infective vaccination strategies in patients with hematologic malignancies or solid tumors-Guideline of the Infectious Diseases Working Party (AGIHO) of the German Society for Hematology and Medical Oncology (DGHO). Ann Oncol 2018;29:1354-65.
115. Weber T, Ljungman P. Stringent vaccination of cancer patients: is it that important? Ann Oncol 2018;29:1348-9.
116. Los-Arcos I, Iacoboni G, Aguilar-Guisado M, et al. Recommendations for screening, monitoring, prevention, and prophylaxis of infections in adult and pediatric patients receiving CAR T-cell therapy: a position paper. Infection 2021;49:215-31.
117. Cordonnier C, Labopin M, Chesnel V, et al. Randomized study of early versus late immunization with pneumococcal conjugate vaccine after allogeneic stem cell transplantation. Clin Infect Dis 2009;48:1392-401.
118. Cordonnier C, Labopin M, Robin C, et al. Long-term persistence of the immune response to antipneumococcal vaccines after Allo-SCT: 10-year follow-up of the EBMT-IDWP01 trial. Bone Marrow Transplant 2015;50:978-83.
119. Feldman C, Anderson R, Rossouw T. HIV-related pneumococcal disease prevention in adults. Expert Rev Respir Med 2017;11:181-99.
120. Garcia Garrido HM, Mak AMR, Wit FWNM, et al. Incidence and Risk Factors for Invasive Pneumococcal Disease and Community-acquired Pneumonia in Human Immunodeficiency Virus-Infected Individuals in a High-income Setting. Clin Infect Dis 2020;71:41-50.
121. Dlamini SK, Madhi SA, Muloiwa R, et al. Guidelines for the vaccination of HIV-infected adolescents and adults in South Africa. Southern African Journal of HIV Medicine 2018;19:a839.
122. Bousfiha A, Jeddane L, Picard C, et al. Human Inborn Errors of Immunity: 2019 Update of the IUIS Phenotypical Classification. J Clin Immunol 2020;40:66-81.
123. Bucciol G, Schaballie H, Schrijvers R, et al. Defining Polysaccharide Antibody Deficiency: Measurement of Anti-Pneumococcal Antibodies and Anti-Salmonella typhi Antibodies in a Cohort of Patients with Recurrent Infections. J Clin Immunol 2020;40:105-13.
124. Sobh A, Bonilla FA. Vaccination in Primary Immunodeficiency Disorders. J Allergy Clin Immunol Pract 2016;4:1066-75.
125. Kobayashi M, Bennett NM, Gierke R, et al. Intervals Between PCV13 and PPSV23 Vaccines: Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Wkly Rep 2015;64:944-7.
126. Froneman C, Kelleher P, José RJ. Pneumococcal Vaccination in Immunocompromised Hosts: An Update. Vaccines (Basel) 2021;9:536.
127. Boyd C, Smith CD, Masoudi FA, et al. Decision Making for Older Adults With Multiple Chronic Conditions: Executive Summary for the American Geriatrics Society Guiding Principles on the Care of Older Adults With Multimorbidity. J Am Geriatr Soc 2019;67:665-73.
128. Falkenhorst G, Remschmidt C, Harder T, et al. Effectiveness of the 23-Valent Pneumococcal Polysaccharide Vaccine (PPV23) against Pneumococcal Disease in the Elderly: Systematic Review and Meta-Analysis. PLoS One 2017;12:e0169368.
129. Smith KJ, Zimmerman RK, Lin CJ, et al. Alternative strategies for adult pneumococcal polysaccharide vaccination: a cost-effectiveness analysis. Vaccine 2008;26:1420-31.
130. Berild JD, Winje BA, Vestrheim DF, et al. A Systematic Review of Studies Published between 2016 and 2019 on the Effectiveness and Efficacy of Pneumococcal Vaccination on Pneumonia and Invasive Pneumococcal Disease in an Elderly Population. Pathogens 2020;9:259.
131. Lazarus R, Clutterbuck E, Yu LM, et al. A randomized study comparing combined pneumococcal conjugate and polysaccharide vaccination schedules in adults. Clin Infect Dis 2011;52:736-42.
132. Heo JY, Seo YB, Choi WS, et al. Effectiveness of Pneumococcal Vaccination Against Pneumococcal Pneumonia Hospitalization in Older Adults: A Prospective, Test-Negative Study. J Infect Dis 2022;225:836-45.
133. Smith KJ, Wateska AR, Nowalk MP, et al. Cost-effectiveness of adult vaccination strategies using pneumococcal conjugate vaccine compared with pneumococcal polysaccharide vaccine. JAMA 2012;307:804-12.
134. Stoecker C, Kim L, Gierke R, et al. Incremental Cost-

Effectiveness of 13-valent Pneumococcal Conjugate Vaccine for Adults Age 50 Years and Older in the United States. J Gen Intern Med 2016;31:901-8.
135. 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 2014;63:822-5.
136. Meiring S, Cohen C, De Gouveia L, et al. GERMS-SA annual surveillance report for laboratory-confirmed invasive meningococcal, *Haemophilus influenzae* and pneumococcal disease, South Africa, 2018. NICD Bull 2019. Available online: https://www.nicd.ac.za/wp-content/uploads/2018/09/GERMS-SA-annual-surveillance-report-for-laboratory-confirmed-invasive-meningococcal-Haemophilus-influenzae-and-pneumococcal-disease-South-Africa-2017.pdf (last accessed 9 September 2022).
137. Feldman C, Dlamini SK, Madhi SA, et al. The cost-effectiveness of using pneumococcal conjugate vaccine (PCV13) versus pneumococcal polysaccharide vaccine (PPSV23), in South African adults. PLoS One 2020;15:e0227945.
138. Kwambana-Adams BA, Mulholland EK, Satzke C, et al. State-of-the-art in the pneumococcal field: Proceedings of the 11th International Symposium on Pneumococci and Pneumococcal Diseases (ISPPD-11). Pneumonia (Nathan) 2020;12:2.
139. GERMS-SA Annual Surveillance Review, SOUTH AFRICA, 2019. Available online: http://www.nicd.ac.za/
140. Freedman MS, Bernstein H, Ault KA, et al. Recommended Adult Immunization Schedule, United States, 2021. Ann Intern Med 2021;174:374-84.
141. Vaccines and Immunizations (CDC). Available online: https://www.cdc.gov/vaccines/index.html (accessed 1 March 2021).
142. Oh JW, Kim SH, Whang K. Traumatic Cerebrospinal Fluid Leak: Diagnosis and Management. Korean J Neurotrauma 2017;13:63-7.
143. Reefhuis J, Honein MA, Whitney CG, et al. Risk of bacterial meningitis in children with cochlear implants. N Engl J Med 2003;349:435-45.
144. Kumar D, Humar A, Plevneshi A, et al. Invasive pneumococcal disease in solid organ transplant recipients--10-year prospective population surveillance. Am J Transplant 2007;7:1209-14.
145. van Aalst M, Lötsch F, Spijker R, et al. Incidence of invasive pneumococcal disease in immunocompromised patients: A systematic review and meta-analysis. Travel Med Infect Dis 2018;24:89-100.
146. Lopez A, Mariette X, Bachelez H, et al. Vaccination recommendations for the adult immunosuppressed patient: A systematic review and comprehensive field synopsis. J Autoimmun 2017;80:10-27.
147. Eckerle I, Rosenberger KD, Zwahlen M, et al. Serologic vaccination response after solid organ transplantation: a systematic review. PLoS One 2013;8:e56974.
148. Chong PP, Avery RK. A Comprehensive Review of Immunization Practices in Solid Organ Transplant and Hematopoietic Stem Cell Transplant Recipients. Clin Ther 2017;39:1581-98.
149. Danziger-Isakov L, Kumar D; AST ID Community of Practice. Vaccination of solid organ transplant candidates and recipients: Guidelines from the American society of transplantation infectious diseases community of practice. Clin Transplant 2019;33:e13563.
150. Gautret P, Gaudart J, Leder K, et al. Travel-associated illness in older adults (>60 y). J Travel Med 2012;19:169-77.
151. Alon D, Shitrit P, Chowers M. Risk behaviors and spectrum of diseases among elderly travelers: a comparison of younger and older adults. J Travel Med 2010;17:250-5.
152. Sand M, Bollenbach M, Sand D, et al. Epidemiology of aeromedical evacuation: an analysis of 504 cases. J Travel Med 2010;17:405-9.
153. Drewett G, Leder K. Infectious disease following travel to developed regions: a snapshot of presentations to an Australian travel medicine clinic. J Travel Med 2016;23:taw053.
154. Parker S, Hoosen AA, Feldman C, et al. Respiratory infections due to Streptococcus pneumoniae and the influenza virus in South Africans undertaking the Hajj. Southern African Journal of Infectious Diseases 2018;33:a137.
155. Woś M, Korzeniewski K. The older traveller. Int Marit Health 2018;69:285-96.
156. Schwartz KL, Morris SK. Travel and the Spread of Drug-Resistant Bacteria. Curr Infect Dis Rep 2018;20:29.
157. Schroeder MR, Chancey ST, Thomas S, et al. A Population-Based Assessment of the Impact of 7- and 13-Valent Pneumococcal Conjugate Vaccines on Macrolide-Resistant Invasive Pneumococcal Disease: Emergence and Decline of *Streptococcus pneumoniae* Serotype 19A (CC320) With Dual Macrolide Resistance Mechanisms. Clin Infect Dis 2017;65:990-8.
158. Cotton CN, Kroger AT, Freedman DO. Approach to the immunocompromised traveler. Center for Disease Control

and Prevention, Travelers' Health, Chapter 5. Available online: https://wwwnc.cdc.gov/travel/yellowbook/2020/travelers-with-additional-considerations/immunocompromised-travelers (downloaded 01 October 2020).
159. Maccioni L, Weber S, Elgizouli M, et al. Obesity and risk of respiratory tract infections: results of an infectiondiary based cohort study. BMC Public Health 2018;18:271.
160. Fernandez C, Manuel A. Obesity, respiratory disease and pulmonary infections. Ann Res Hosp 2017;1:38.
161. Chiner E, Llombart M, Valls J, et al. Association between Obstructive Sleep Apnea and Community-Acquired Pneumonia. PLoS One 2016;11:e0152749.
162. Nuorti JP, Butler JC, Farley MM, et al. Cigarette smoking and invasive pneumococcal disease. Active Bacterial Core Surveillance Team. N Engl J Med 2000;342:681-9.
163. Palmer KT, Cosgrove MP. Vaccinating welders against pneumonia. Occup Med (Lond) 2012;62:325-30.
164. Sequera VG, Valencia S, García-Basteiro AL, et al. Vaccinations in prisons: A shot in the arm for community health. Hum Vaccin Immunother 2015;11:2615-26.
165. Mehta B, Chawla S, Kumar V, et al. Adult immunization: the need to address. Hum Vaccin Immunother 2014;10:306-9.
166. Doherty TM, Connolly MP, Del Giudice G, et al. Vaccination programs for older adults in an era of demographic change. Eur Geriatr Med 2018;9:289-300.
167. Aging and Immunity: The Important Role of Vaccines. Available online: https://www.acponline.org/system/files/documents/clinical_information/resources/adult_immunization/aging_and_immunity_guide.pdf (accessed 9 September 2022).
168. Balinska MA. What is vaccine advocacy? Proposal for a definition and action. Vaccine 2004;22:1335-42.
169. Das JK, Salam RA, Arshad A, et al. Systematic Review and Meta-Analysis of Interventions to Improve Access and Coverage of Adolescent Immunizations. J Adolesc Health 2016;59:S40-8.
170. Kobayashi M, Farrar JL, Gierke R, et al. Use of 15-Valent Pneumococcal Conjugate Vaccine and 20-Valent Pneumococcal Conjugate Vaccine Among U.S. Adults: Updated Recommendations of the Advisory Committee on Immunization Practices - United States, 2022. MMWR Morb Mortal Wkly Rep 2022;71:109-17.

Cite this article as: Feldman C, Dlamini S, Richards GA, Black J, Butler ILC, Cutland C, Hefer E, Hodkinson B, Kok A, Manga P, Meiring S, Molaudzi M, Moosa MYS, Parker S, Peter J, van Vuuren C, Verburgh E, Watermeyer G. A comprehensive overview of pneumococcal vaccination recommendations for adults in South Africa, 2022. J Thorac Dis 2022;14(10):4150-4172. doi: 10.21037/jtd-22-287