DETERMINING THE VALUE OF CORRELATES OF PROTECTION TO ASCERTAIN PNEUMOCOCCAL VACCINE EFFICACY IN ADULTS LIVING WITH HIV, A SCOPING REVIEW

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DECLARATION

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Determining the Value of Correlates of Protection to Ascertain Pneumococcal Vaccine Efficacy in Adults Living with HIV, Scoping Review.

I affirm that the above research report is my original study and all resources I have applied or cited have been shown and recognised with complete citations.

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ABSTRACT

Background

People Living With HIV(PLWH) remain susceptible to severe diseases caused by *Streptococcus pneumoniae*. In this scoping review, we synthesised existing evidence to determine the value of Correlates of Protection (CoP) to ascertain pneumococcal vaccines efficacy in adult PLWH and identify knowledge gaps.

Methods

Using the Joanna Biggs Institute framework (2022), our search strategy included 17 keywords across five databases. We retrieved 3123 studies gathered in the Covidence software. Two reviewers independently excluded 1549 duplicates. Of the 1574 remaining, 1274 articles were ineligible. Of the 300 studies with full-text reviews, 56 were included for data extraction.

Findings

9.3% of selected studies were from high-income countries, and 59.3% of included adult participants were males aged 18-84 years. Of the studies, 57.2% were high-quality randomised controlled trials (RCTs), supporting vaccination in adult PLWH with PCV followed by PPSV23 after 8 weeks, finding this regimen safe and cost-effective. Pneumococcal carriage in adult PLWH was 7.3% and mucosal IgA showed a 48-fold rise with vaccination, even in people with low CD4+ cell counts of <200 cells/mm^3. Serum pneumococcal IgG antibody titers against *S. pneumoniae – which predict protection - were* assessed by ELISA in 30 studies. PCVs perform better with a 2-7-fold increase in geometric mean concentration (GMC) after vaccination compared to a <2-4-fold increase for PPSV23 in adult PLWH. In 12 studies, a 2-4-fold rise in Opsonophagocytic killing Assay (OPA) GMT was reported versus a >4-fold increase in HIV negative people. MOPA, another way to identify CoP, showed adequate protection with an opsonic index of 5.6 after sequential PCV and then PPSV23 vaccination. Optimal immune responses for, PCV then PPSV23 occurred in people whose CD4 + count was > 200 cells/mm^3) and HIV viral load was <1000 copies/ml.

The number of memory B cells is associated with a higher antibody response following PCV13 vaccination, whereas PPSV23 vaccination is linked to a lower or impaired memory B cell response. No significant changes in memory B cells were observed after PCV7 vaccination. Both pneumococcal conjugate vaccines (PCVs) and PPSV23 are generally well

tolerated up to 60 days post-vaccination. However, antibody levels tend to wane by one year in adult PLWH, even among those with CD4+ counts above 200 cells/mm³, partially attributed to HIV-related B cell dysfunction, which includes shifts toward exhausted and atypical memory B cell subsets that impair long-term immune memory and vaccine responsiveness. There is limited data on vaccine responses in PLWH with additional comorbidities or other immunosuppressive conditions.

Conclusion

Concerns remain over the durability of the pneumococcal vaccines in PLWH and the best CoP in this population. OPA titres appear to better correlate with protection in PLWH, and being on ART at the time of vaccination improves immune response. There is a paucity of data on CoP among susceptible adult PLWH with other comorbidities. Limited clinical trials exist of pneumococcal vaccines and using correlates of protection as the outcome in PLWH in LMICs. While PCVs offer better long-lasting immunity, in PLWH, lower antibody concentrations and waning antibody titres remain concerning. More longitudinal studies are needed in adult PLWH in LMIC to assess whether a higher protective threshold is needed and possible additional doses or booster vaccinations.

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Lastly, my wife, Grace Absalom, for her love and support in managing our household during this demanding time.

DEDICATION

I devote this report to my daughters, Charity-Glory and Eunice. “Who you are tomorrow begins with what you do today”. The road to success is not easy to navigate, but with challenging work, drive, and passion.

ABBREVIATIONS

APC	Antigen Presenting Cells
ART	Antiretroviral therapy
CAP	Community-acquired pneumonia
CD	Cluster of Differentiation
CDC	Centres for Disease Control
CFU	Colony-Forming Unit
CoPs	Correlates of Protection
CPS13	Anti-pneumococcal Capsulated ELISA
CR	Cross-Protection for SPn Serotypes
CRM197	Carrier Proteins, Mutant of Diphtheria Toxin
CSF	Cerebrospinal Fluid
CSV	Comma Separated Values
ELISA	Enzyme-Linked Immunosorbent Assay
EPI	Expanded Programme on Immunisation
FDA	Food and Drug Administration
GMC	Geometric Mean Concentration for ELISA
HIC	High-Income Countries
GMT	Geometric Mean Titre for OPA
HREC	Health Research Ethics Committee
HVL	HIV Ribonucleic acid Viral load
ICH	International Council of Harmonisation
IgG/M	Immunoglobulin Gamma, mu

IL/CCL	Interleukins/Chemokines Ligands
IPD	Invasive pneumococcal disease
JBI	Joanna Biggs Institute
LytA	N-Acetylmuramoyl-L-alanine amidase
MBC	Memory B-Cells
MeSH	Medical Subject Headings
MOPA	Multiplex Opsonophagocytic assay
MZ	Marginal Zone antibodies
OPA	Opsonophagocytic Killing Assay
PCC	Population, Concept and Context
PCV	Pneumococcal Conjugate Vaccines
PLWH/WLWH	People or Women living with Human Immunodeficiency Virus
PPSV/PPV23	Pneumococcal Polysaccharide Vaccine
PRISMA-ScR	Preferred Reporting Items for Systematic Reviews and Meta-Analysis Extension for Scoping Reviews
RCT	Randomised Clinical Trials
RIS	Research Information System Files
RoB	Risk of Bias
RT/qPCR	Real-Time/Quantitative Polymerase Chain Reaction
QALY	Quality-Adjusted Life Year
SAE	Serious Adverse Events
SAGE	Strategy Advisory Group of Experts
SCR	Seroconversion Rate

sIgA	Salivary or Secretory Immunoglobulin Alpha
SoPs	Surrogates of Protection
Tfh	T-follicular helper T-Cells
SPn	*Streptococcus pneumoniae*
SSA	Sub-Saharan Africa
TB	Tuberculosis
Th	T-Helper Cells
VE	Vaccine's Efficacy/Effectiveness
WHO	World Health Organisation

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CHAPTER ONE

1. Introduction to the Study

Mortality due to invasive pneumococcal disease (IPD) in People Living with HIV(PLWH) remains unacceptably high despite the test and treat strategy with immediate initiation of combined anti-retroviral therapy (ART). Adult PLWH have 8-10 times higher risk of IPD and community-acquired pneumonia(CAP) caused by *Streptococcus pneumoniae* (SPn) compared to HIV-negative people (1,2). PLWH would benefit from the protection offered by pneumococcal vaccines, but it is unclear by how much.

PLWH have a weakened immune system and are expected to have different patterns of correlates of protection (CoP) (1,2). CoP of pneumococcal vaccines is a key immunological substitute endpoint or immune markers shown by serotype-specific IgG and T cell immunity (3–7). The pneumococcal vaccines include a quantity of vaccine-induced antibody titers of ≥0.35 μg/mL of non-mechanistic CoP, which has been associated with reduced risk of IPD and nasopharyngeal carriage (4–7). Of note, functional antibody activity reflects the ability of antibodies to promote phagocytosis and killing or clearance of bacteria, serving as a more direct mechanistic CoP (4,8). They directly determine and quantify the immune response by comparing vaccine-induced protection against an infectious pathogen in vaccinated versus unvaccinated individuals and serve as a proxy for predicting vaccine efficacy (VE) (9,10).

VE is the percentage by which the risk of a specific disease or its severity is reduced in vaccinated compared to unvaccinated individuals under ideal conditions or similar exposure in randomised clinical trials (RCT) (9,10). For a vaccine to be efficacious, it should have evidence of protection, either by trial data showing disease prevention, or it should induce a measurable immune response, like antibody and/ or cell-mediated immunity after vaccination, known as immunogenicity, thereby linking data to protection effectiveness (9). CoPs are established and validated in RCTs, which are costly and time-consuming to implement (9). In children, for whom pneumococcal vaccines are commercially available, trials of the new paediatric vaccines must be compared to the current effective vaccine (9,10). The sample sizes needed to show the superiority or non-inferiority have become prohibitively large (10).

Often, clinical end-points (infection or disease) in RCTs for vaccines are relatively rare or difficult to confirm (10). Hence, CoPs are key immunological substitute endpoints that directly determine and compare vaccine-induced protection against an infectious pathogen

(9,10). Evidence and the statistical measures that constitute a CoP are also required for the licensure process of vaccines, safety, effectiveness, and equivalence or improvement of the vaccines (**Annex 4: supplemental figure 1**) (9,10).

Additionally, a surrogate of protection (SoP) for SPn, "an immune response that substitutes clinical end-point for the true immunologic correlate of protection, which may be unknown or not easily measurable" (9). Surrogates can be assessed in individuals to predict VE in phase III RCTs (9,11). They assess VE against clinical or subclinical endpoints, such as pneumonia, meningitis, or carriage (Table 4C) (1,9). PLWH have depleted T-helper 1 (Th1) and T-helper cell defences, which are key in the protective immune response to IPD (2,12). For SPn, CoP involves antibodies and cytokines that directly protect against pneumococcal infections or reduce the severity of diseases (9,12). In contrast, SoP relies on markers that indirectly predict VE or decreased SPn nasopharyngeal carriage (9,12,13). However, although nasopharyngeal carriage reduction is a meaningful and measurable surrogate of vaccine impact at a population level, it is not a direct correlate of individual immune protection after pneumococcal vaccination (4,13).

1.1. Cellular and Humoral Immune Responses and Measurement Assays

Cellular immunity involves CD4+ and CD8+ cells, including follicular helper T-cells (Tfh), which activate B-cells to generate high-affinity antibodies (2,12). Humoral immune responses induced by pneumococcal vaccines include antibody production by stimulating B-cells to differentiate into plasma cells, which secrete specific immunoglobulin G (IgG) antibodies (2,14). Memory B-cells generated after vaccination with PCVs provide long-term immunity and a rapid response upon re-exposure to the pathogen (**Annexe 3; Table 4A-B)** (2,14).

1.2. Pneumococcal Vaccines, Induced Immunity and Vaccination Guidelines

PCV10-13-15 and PPSV23 are prophylactic vaccines and licensed (2). PCVs are recommended for children and adults (2,15). All forms of PCVs are conjugated to carrier proteins, namely a non-toxic mutant of diphtheria toxin (CRM197), which makes them more immunogenic (15). PCVs are classified by the number of SPn serotypes covered, including PCV7-10-13-15-20-21 (**Table 1**) (2,15). However, PCV21 does not include antigens for 10 serotypes contained in PCV20 (16). Next-generation vaccines such as PCV24-31 (**Table 1**) are still in the clinical trial phase and are highly immunogenic with CRM197 adjuvants (17). PCV24-31 are highly immunogenic and have been shown to reduce the risk of IPD by 54%, but no CoPs data in adult PLWH (17).

Table 1: Pneumococcal Vaccines with Serotypes and How They Produce Antibodies (12,15–25)

No	Pneumococcal Vaccine	Covered Serotypes	Antibody Production	Vaccination schedule
1	PCV7 (15,20,21)	4,6B,9V,14,18C,19F,23F (6A CR)	Conjugated T-cell Dependent CRM197	1-3 Prime doses or Re-vaccination of paediatrics and adults
2	PCV10 (15,20,21)	1*, 4, 5*, 6B, 7F*, 9V, 14, 18C, 19F, 23F (19A CR)	Conjugated T-cell Dependent CRM197 Long-lasting Antibodies	
3	PCV13 (12,22)	PCV10 serotypes plus 3*, 6A*, 19A* (6A,6C,7A,19group CR)		
4	PCV15 (15,16,18,19)	1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F,22F*,23F, 33F*(6C-CR).		
5	PCV20 (15,16,18)	1,3,4,5,6A,6B,7F,8*,9V,10A*,11A*,12F*,14,15B*,18C,19A,19F,22F,23F,33F (6C-CR)		
6	PCV21 (15,16)	3,6A,7F,9N*,10A,15A**,15C**,16F**,17F**,20AF**, 23A**, 23B,24F**,31**,35B (29 CR)		
7	PCV24 (17)	PCV20 plus 2, 9N, 17F, 20B (6C-CR)		
8	PCV31 (17)	PCV20 plus 7C, 15A, 16F, 23A, 23B, 31, and 35B		

9	PPSV23 (22)	1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F and 33F	Polysaccharides T-Cell independent Short-lived antibodies	After 8 weeks or Revaccination after 5 years in adults only

Legend: CR-Cross Protection for other SPn serotypes; ** Subsequent difference for covered serotypes; * Additional covered serotypes; PCV20-21-24-31 are not yet recommended in routine vaccinations.

CRM197 adjuvant added in PCVs allows T-cells to recognise and activate B-cells by T-cell-dependent action to elicit robust and long-lasting immunity (**Figure 1**) (14). Upon vaccination, dendritic cells present the polysaccharide antigens to CD4+ T-helper cells and then activate B-cells (14). This process leads to improved plasma cells or memory B-cell formation, affinity maturation, and antibody change, resulting in high levels of IgG antibodies specific to the pneumococcal serotypes included in the PCVs (14). Antibody isotypes, especially IgM, occur during acute infection or vaccination, switch to IgG type in the chronic or protective phase, and produce immunoglobulins with long-lasting protection (14).

PPSV23, in contrast, produces antibodies by a T-cell independent mechanism and activates B-cells directly through B-cell receptors, mainly IgM type, with no class switching and memory formation occurring (14). Induced antibodies by PPSV23 generate a short-lived immune response despite covering a wide variety of SPn serotypes (**Table 1**) (12).

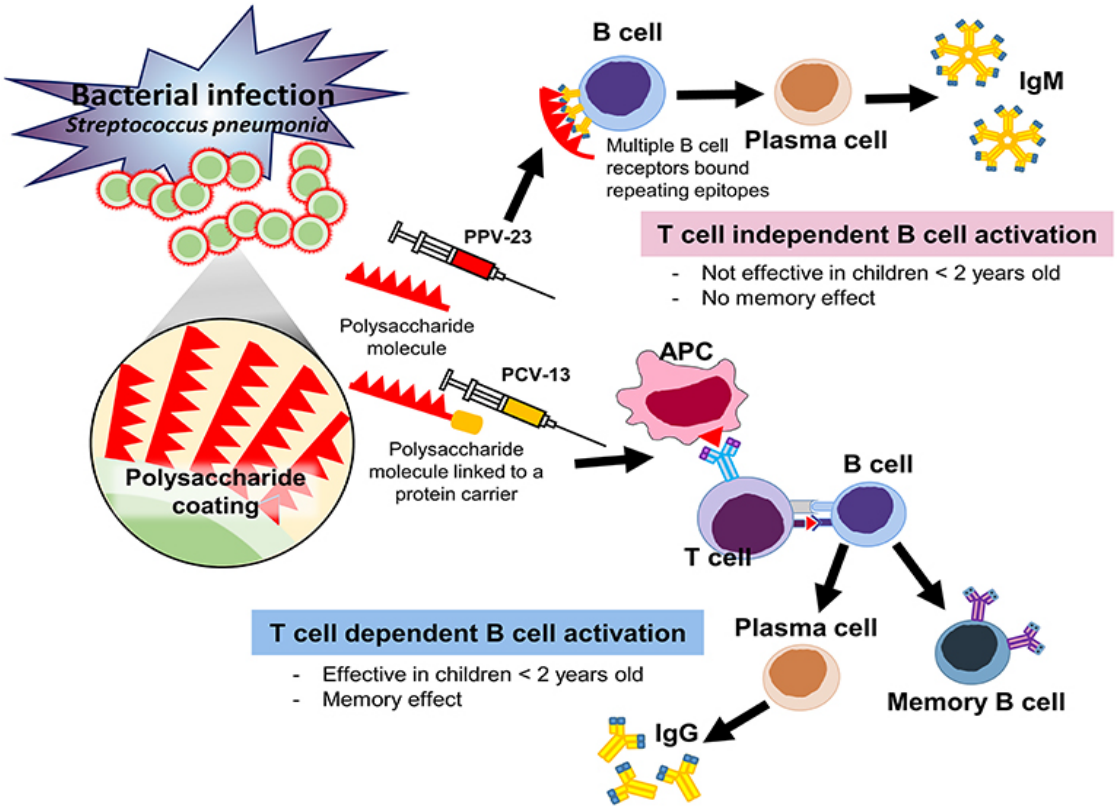

Figure 1: T-cell and B-cell antibody activation post-pneumococcal vaccination**.**

Source: Goonewardene et al., 2019 (14)

Vaccination against SPn forms part of most low-to-upper-middle-income countries' Expanded Program for Immunisation (EPIs) for children, including South Africa (26). In adults, the Southern African HIV Clinicians recommendations for pneumococcal vaccination guidelines (27) in PLWH have not been widely implemented. The most recent guideline recommends a first dose of PCV13 followed by a PPSV23 eight weeks later and revaccination with either PCV10-13 or PPSV23 after five years (19,27), regardless of CD4+ count, unlike the Center for Disease Control (CDC) recommendations, which suggest vaccination when the CD4+ count is >200 cells/mm^3 (28,29).

1.3. Pneumococcal Vaccine Type and Measurement Assays

Several methods to measure proxies for VE have been reported in the literature.

1.3.1. Enzyme-linked Immunosorbent Assay (ELISA)

The ELISA test is a highly sensitive and specific enzymatic assay that uses serum to detect antigen/antibody reactions (30,31). Optical density is measured following the addition of chromogenic reagent, leading to a colour development to assess the protective antibody titres in vaccinated individuals **(Figure 2)** (30,31). Serum pneumococcal IgG is the non-mechanistic surrogate immune marker. A geometric mean concentration (GMC) of 0.20-0.35 µg/ml is the accepted threshold needed to be achieved for protection.

Fig

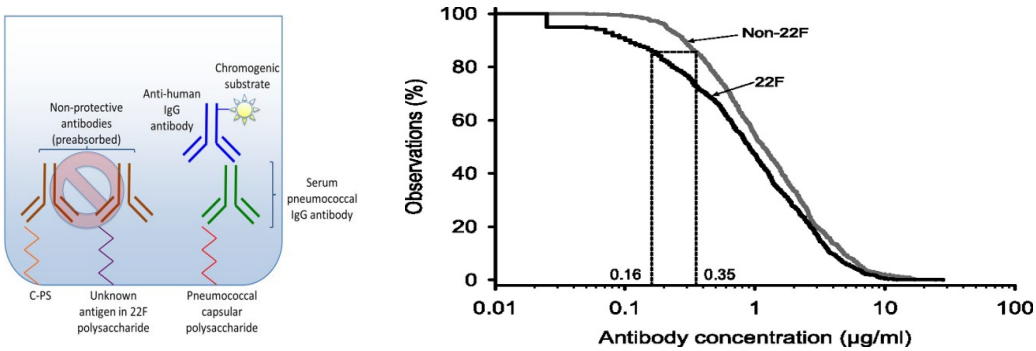

Figure 2a & b: Shows Serum Pneumococcal IgG antibodies measured with ELISA

Source: LaFon and Nahm., 2018; Poolman, Jan *et al*.,2010 (6,32)

1.3.2. Opsonophagocytic Killing Assay (OPA)

Measuring total IgG antibodies alone may not fully reflect the humoral response to pneumococcal vaccines (8). OPAs have been developed to assess antibody functionality. The OPA determines the geometric mean titre (GMT) of a mechanistic CoP type (4) antibody in serum, plasma, or whole blood-washed cells from vaccinated individuals **(Figure 3)** (8). A mixture of macrophages, complement, and specific serotype pneumococcus is added to a plate covered with standard agar (5,8). The growth of bacteriological colonies is measured to create a killing curve (5). OPAs assess the ability of antibodies or macrophages to engulf and eliminate SPn, providing a clearer picture of CoP post-vaccination (5,8,9). A significant increase in the killing curve in GMT of 1/8 or a 4-fold increased threshold, as defined by WHO, indicates protection in adult PLWH (5,8).

Studies of both children and adults validated OPA titres across laboratories, following key steps outlined by the International Committee for Harmonisation (ICH) and the Food and Drug Administration (FDA): specificity, linearity, accuracy, and robustness (10,32,33). Nine SPn serotypes showed over 80% agreement in OPA titres. The linearity of serotypes ranged from 0.98 to 1.00, confirming the test's suitability (10,32). The OPA test demonstrated 100% accuracy for seven serotypes, with serotypes 14 and 23F showing over 75% agreement (8). OPAs are thus reliable for determining CoPs and monitoring pneumococcal vaccines (8,9). They can also effectively assess past immune responses and reactions to subsequent boosters (8,9).

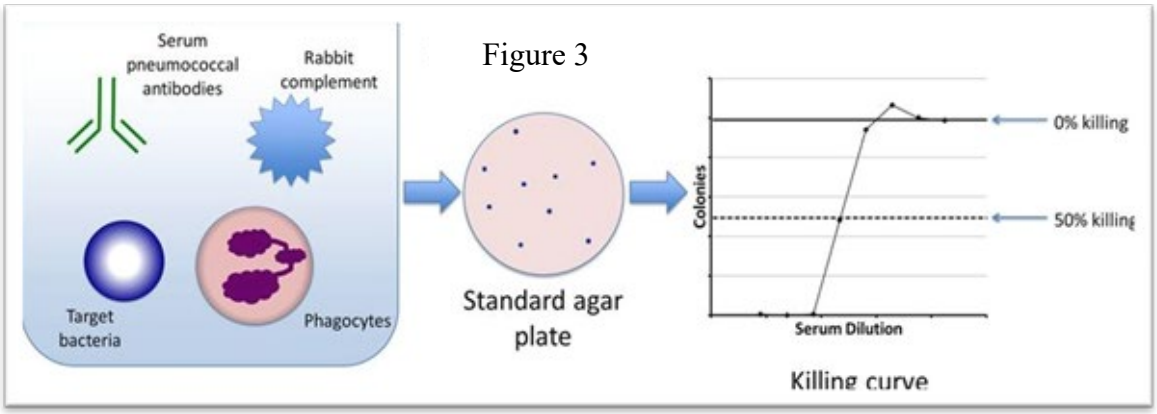

Figure 3: OPA, the gold-standard assay for SPn functionality.

Source: LaFon and Nahm., 2018; Poolman Jan et al.,2010 (6,32).

1.3.3. Multiplexed Opsonophagocytic Assays (MOPA)

The modified OPA (MOPA) can evaluate multiple serotypes in a single sample (8) and provides a more granular and functional assessment of anti-pneumococcal immunity (34). MOPA, a mechanistic CoP type (4), uses fluorescently labelled bacteria and polysaccharide beads to directly measure the efficiency of phagocytosis by immune cells after opsonisation with specific antibodies (35,36). WHO classifies the protective threshold of MOPA as an opsonic index of >4, which covers 70% of tested SPn serotypes in adult PLWH (34). The test distinguishes between opsonising and non-opsonising antibodies, providing a more accurate reflection of VE (34–37).

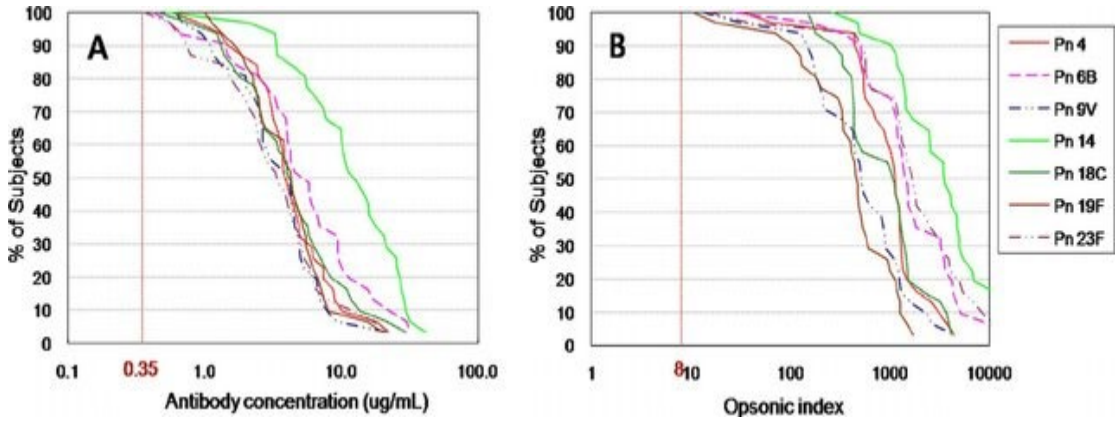

Figure 4C

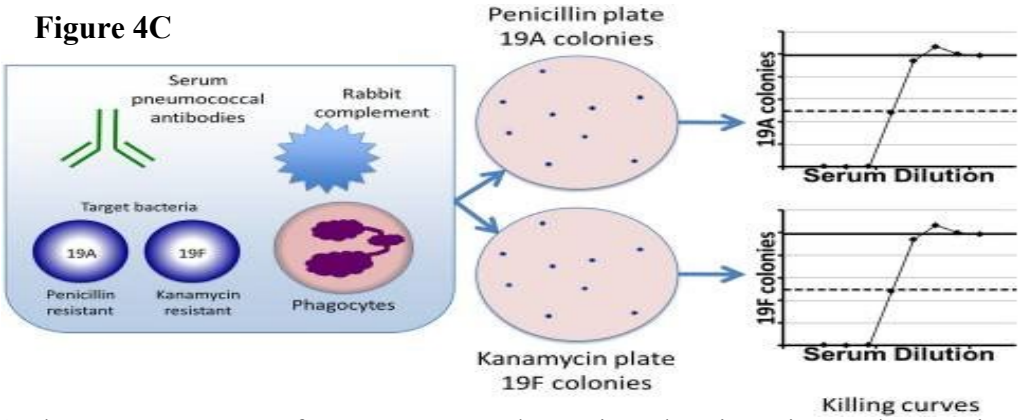

Figure 4a, b, c: MOPA Assay for Pneumococcal Vaccine Showing Titre and Opsonic Index**.**

Source: LaFon and Nahm., 2018; Lee *et al*., 2009 (32,37)

1.3.4. Novel assays applied in CoP for Pneumococcal Vaccines in PLWH

The combined use of immunological tools (Fluorospot, Western blot), molecular assays (RT-PCR, LytA PCR), and culture are additional assays that can be used to assess pneumococcal immune response.

The Fluorospot assay is a highly sensitive multiplex tool that quantifies B or T cell responses to S. pneumoniae in peripheral mononuclear cells by capturing secreted antibodies or cytokines on antigen-coated membranes, using fluorescent antibodies to detect multiple targets simultaneously and reported in spot-forming cells (38). Western blotting detects serum pneumococcal IgG against proteins, such as LytA, with high sensitivity and specificity, providing qualitative and semi-quantitative data for immune response characterisation and confirmation after screening (39).

Real-time PCR targeting genes such as ply and psaA sensitively detects pneumococcal DNA in clinical specimens, crucial for diagnosing active infection or carriage (13). LytA PCR is the gold standard for molecular pneumococcal identification due to its ability to detect low bacterial loads and improve specificity when combined with other targets (13). Culture remains the definitive method for identifying viable bacteria and serotype resistance patterns, but it is limited by lower sensitivity and longer turnaround (13). Despite novel assays for establishing correlates or surrogates of protection, OPA remains the best for testing functional serum pneumococcal IgG, especially in PLWH.

1.3.5. Pneumococcal Disease and Carriage in Adult PLWH

Worldwide, pneumococcal disease is predicted to cause more than 1 million deaths every year, with children <5 years being at high risk, together with PLWH (40). Due to depleted immunity, PLWH are thirty to three hundred times more susceptible to IPD and its complications (1,2). Inspite of being on ART, adult PLWH still have a 25% risk of recurring IPD and death yearly (13,22). PLWH are 10 times more likely to carry SPn asymptomatically. Immunocompromised T-helper cell defences in PLWH impair mucosal immunity, increasing susceptibility to pneumococcus (12). Vaccination stimulates IgG antibodies to prevent SPn colonisation (14). Studies in South Africa reported high pneumococcal carriage rates among PLWH and infants (13,30,41). Pneumococcal vaccines (PCV13 and PPSV23) are life-saving for adult PLWH by preventing IPD and reducing carriage by 80% (13,30).

1.4. Factors Affecting CoP and Induced Antibodies in Adult PLWH

CoPs that predict pneumococcal vaccine protection can be affected by age, immunosuppression, vaccine type and dose, geographical region, circulating serotypes, and antibiotic use (9). However, inadequate data exists on studies to report these factors. In adult PLWH, studies have shown an inadequate IgG antibody threshold observed only for SPn serotypes 4, 6B, and 19F in both PCV10-13 groups, which have noteworthy consequences for its efficacy (1,2,12). Antibody levels may also depend on the geographic area.

1.4.1. Challenges of CoPs for Pneumococcal Vaccines in Adults PLWH

PLWH, due to their weakened immunity, have different patterns of CoP with factors such as vaccine type, antibody waning, ethnicity, gene variation, infection rates per serotypes, immunity status on and off ART coming into play (9,10,42). Disease complexity, involving protection against pneumonia or meningitis, might also affect distinct immune mechanisms (13). Increased rates of breakthrough infections with carriage often occur in adult PLWH, particularly with advanced disease and residual immune dysfunction, hence affecting VE. Earlier studies have shown inconsistent CoPs to PCV13 and PPSV23, influenced by CD4+/CD8+ counts, viral load, and HIV, other comorbidities (2,9). Higher CD4+ counts were linked with better VE and vice versa. Now, no approved CoP exists specifically for adult PLWH since RCTs were done in children, mostly in HIC in the Northern hemisphere.

1.4.2. Waning of Pneumococcal Antibodies

Anti-pneumococcal IgG levels decline 30 days post-vaccination with PCVs and PPSV23 without serotype-specific exposure, but memory B-cells can rapidly produce antibodies upon re-exposure to protect against infection (43,44). Antibody thresholds vary by geographic area, infection site, and serotype, with more invasive SPn-types like (1,7F, 19A,19F) requiring increased titres of protection compared to less invasive ones (e.g., 6A, 6B, 18C, 23F) (2,12,43). No single immune marker titre guarantees complete protection, and maintaining antibody levels long-term is challenging due to transient immunosuppression or faster waning (44). In 2011, one RCT done in the Netherlands found a faster decline in IgG levels for specific serotypes in PCV10-13 groups after 5-12 months, with low levels observed for serotypes 4, 6B, and 19F in both pneumococcal vaccines (44). In adult PLWH, faster antibody decline occurs with CD4+ counts <200 cells/mm³ and unsuppressed HIV-RNA viral load (HVL) (44). While CD4+ counts and CD4/CD8 ratios are predictors of vaccine waning in adult PLWH, long-term data on viral load impact are lacking.

1.5. Statement of the Problem of CoPs to Pneumococcal Vaccines in PLWH

In countries with a high HIV burden, pneumococcal vaccines are not routinely administered to adult PLWH. Key concerns on administering vaccines to adult PLWH are the absence of CoP data to inform the optimal timing, dosage, efficacy, effectiveness, and tolerability of these vaccines, and whether to use combined PCVs with PPSV23 or alone to address depleted immunity in this population. The current literature lacks sufficient data on alternative endpoints for vaccine evaluation during the development and licensure phases for PLWH.

1.6. Study Hypothesis

We hypothesised that limited publications exist to inform up-to-date CoP induced by pneumococcal vaccines (PCVs and PPSV23) in adult PLWH as proxies for VE when measured using clinical outcomes.

1.7. Study Aims

We aimed to determine the value of CoPs to ascertain pneumococcal vaccine efficacy VE in adult PLWH of PCV7-10-13-15-20-21 and PPSV23.

1.7.1. Overall Objective

We aimed to review available literature globally on current CoP, especially serum pneumococcal quantity of antibodies and functionality, predicting efficacy and effectiveness of PCVs and PPSV23 in adult PLWH. We also assessed the gaps to make recommendations for future studies.

1.7.2. The key goals

1.7.2.1. To define the present evidence on correlates of pneumococcal vaccine-induced protection in adult PLWH.

1.7.2.2. To summarise CoP and vaccine efficacy validation processes that have been used to show protection, or the absence of protection, against pneumococcal disease in adult PLWH.

1.7.2.3. To assess factors in PLWH reported in the literature that may affect CoP or antibody titres, such as CD4+ count, HVL or presence of comorbidity.

1.7.2.4. To report evidence gaps of current CoP in adult PLWH and make recommendations for future research into VE of SPn vaccines.

CHAPTER TWO

2. Scoping Review Methods

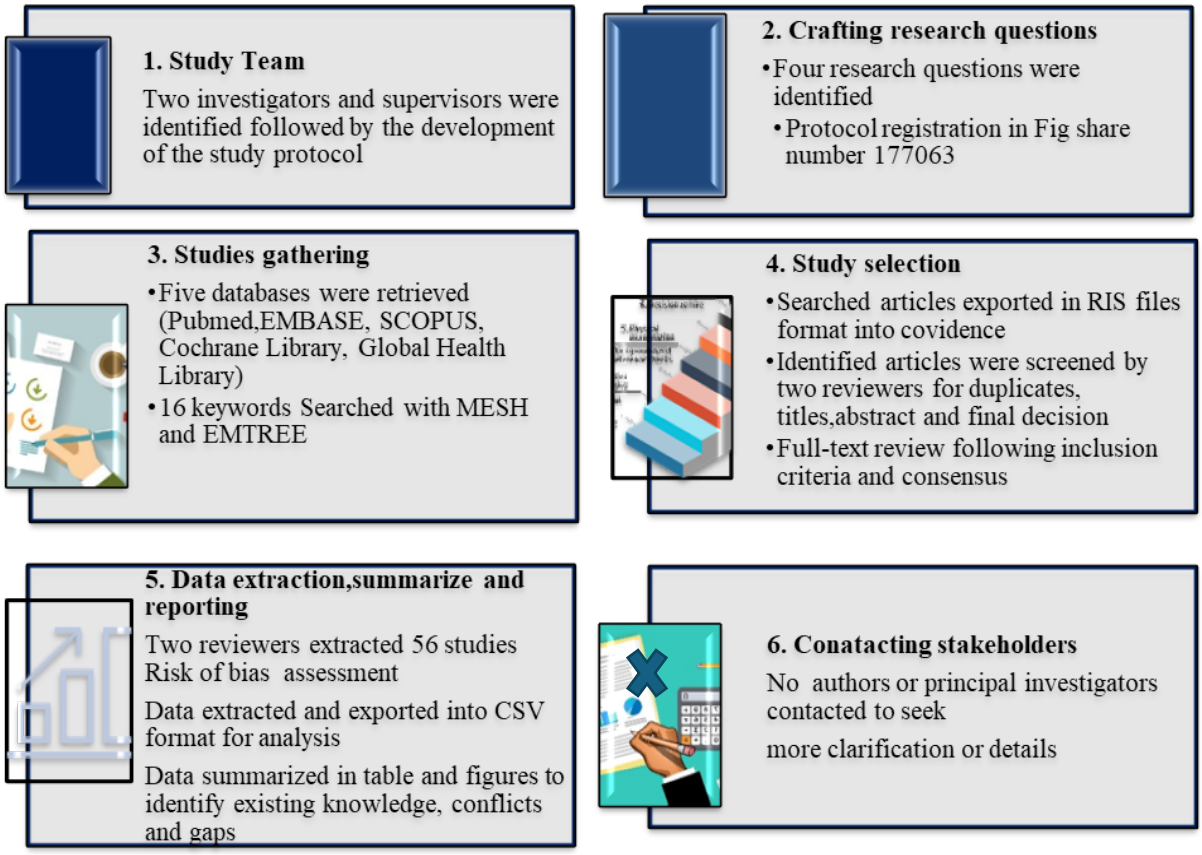

Figure 5: Summary of Five Steps on How to Conduct a Scoping Review: X=Represent step not conducted in scoping review

(Source: Mak and Thomas,2022) (45).

We followed five out of six steps to conduct scoping reviews (**Figure 5**) (45), the study team identification, crafting the research question, search strategy, study selection, data extraction and summarising in one report. However, enough details in the included articles were observed, and no consultation was done to seek more information from the author.

2.1.Development of Protocol, Research Questions, and Registration

A study protocol was developed and registered in the Figshare scoping review registry project number 77063 (46). The librarian from the University of the Witwatersrand and a public health specialist helped to develop and run a pilot search using 17 keywords in three databases. This approach enabled us to identify relevant studies on pneumococcal vaccines.

The study team formulated four key questions aligned with the study goals and pneumococcal vaccines CoP in adult PLWH. We included studies on the following vaccines: PCV7-10-13-15-20-21, and PPSV23.

The primary research question was, "**What is the current evidence on CoP relating to pneumococcal vaccine-induced immunity in adult PLWH**?" We retrieved meta-analyses, quantitative studies (RCTs), observational studies, expert reviews, and surveillance data supporting CoPs and reporting on VE in PLWH.

Our secondary review question was **"What are the current methods applied in the validation process of CoP of the pneumococcal vaccine in adult PLWH?"** We reported the validation process, the existing and novel methods for VE, and the effectiveness of PCV7-10-13-15-20-21, and PPSV23 in adults PLWH.

Also, we explored whether there is a changed antibody threshold and CoP for pneumococcal vaccines in PLWH. We described the current immune response induced by PCVs and PPSV23 by considering immune status and HVL. Additionally, we looked at the adverse events and tolerability of PCVs and PPSV23 stratified by CD4+ count, HVL, ART, and other comorbidities.

Finally, we summarised gaps in evidence from PCVs and the PPSV23-induced antibody threshold in adult PLWH and showed the extent of evidence on CoPs and gaps in knowledge.

2.2. Protocol Ethical Approval

Our study protocol received ethical approval (Ref W-PR-240527-05**), (Annexe 2A &B: Ethical Waiver Certificate)** from the Medical Human Research Ethics Committee at the University of the Witwatersrand.

2.3. Systematic Search Strategy

From June 2024 to December 2024(**Annexe 4: Supplemental Table 3: Gnat Chart**), we conducted a scoping review on the CoP of pneumococcal vaccines in adult PLWH. Following the JBI framework (2022) (45), we gathered articles from three databases: PubMed, SCOPUS, and EMBASE. Our search was based on the following 17 keywords "**adults with HIV", "Pneumococcal vaccines efficacy or effectiveness", "Immunogenicity", "PCV7", "PCV10", "PCV13" "PCV15", "PCV20", "PPSV23", "Opsonophagocytic Killing Assay", "Multiplex Opsonophagocytic Assay", "Correlate of Protection", "Pneumococcal carriage", "Anti-pneumococcal immunoglobulin", "Comorbidity" and "Pregnant mothers"**

In the full search phase, studies were retrieved using the above keywords from five databases: PubMed, EMBASE, Cochrane Library, SCOPUS, and Global Health Library **(Annexe 4: Supplemental Table 1: Search Strategy).** We applied the current Preferred Reporting Items for Systematic Reviews and Meta-Analysis with an extension for Scoping Reviews (PRISMA-ScR (**Figure 6**).

We used search term filters like Medical Subject Headings (MESH) and EMTREE for EMBASE linked to the study population (i.e., both sex and adults ≥18 years living with HIV, CD4+ count, HVL, and comorbidity, including participants who were pregnant and pneumococcal vaccines as an intervention (Table 2). Studies enrolling children, where no HVL were reported, pre-clinical studies, animal models, and/or people who had no comorbidities other than HIV, and adults who were HIV negative were excluded from retrieval. The duration of eligible studies was set as 01 January 2010 to 01 February 2024 in each database (**Annexe 4: Suppl Table 1: Search Strategy).** We only included studies that reported outcomes in PLWH aged over 18 years. The published articles relevant to pneumococcal disease, pneumococcal vaccines, and clinical endpoints following pneumococcal vaccination were also eligible. Our study included meta-analyses, systematic reviews, RCTs, observational studies, expert reviews, and guidelines. We excluded non-peer-reviewed publications and grey literature, or websites. We only searched for articles published in English with unrestricted access and available as full text.

2.4. Data Export, Studies Identification and Screening for Titles and Abstracts

All articles were exported using Covidence software (47) using the research information system (RIS) format generated from the five databases. Inclusion and exclusion criteria based on population, concept, context, intervention, and outcomes were linked in Covidence software (47) before the screening process (**Table 2**). Two independent reviewers were able to screen, select, and extract studies **(Annexe 4: Supplemental Figure 2; Overview of Data Extraction Tool**). As a first step, all identified studies were screened for relevance of titles and abstracts, year of publication, and whether the population was in adult PLWH. Any discrepancies were resolved by re-screening as a final decision based on the consensus reached.

2.5. Full-text Review for Eligibility Criteria

Both reviewers then screened the full text of all remaining articles. A final decision was made on which articles to include based on eligibility criteria (**Table 2**).

Table 2: Illustrates a Key Eligibility Criteria Used to Select Studies

Population Include Males and Females >18 years Adults PLWH ART use Pregnancy mother Tested for CD4 HIV Viral load Exclude Studies on PCVs and PPSV23 were done in Paediatrics and adolescents
Intervention / Exposure Include Meta-analysis and systematic review, Quantitative studies (randomised and non-randomised cohort, cross-sectional, case-control studies, and surveillance report SAGE reports, conference papers and abstracts Correlates of protection of PCV7, PCV10, PCV13, PCV15, PCV20 and PPSV23 Carriage or Surrogates of Protection of PCV7, PCV10, PCV13, PCV15, PCV20 and PPSV23 Exclude PLWH. Grey literature or Websites.
Comparator / Context Include People living with HIV in high-income and low-middle-upper-income countries (as classified by the World Bank) Exclude Pneumococcal vaccines done not in people living with HIV in high-income and low-middle-upper-income countries (as classified by the World Bank)
Outcome Include A scoping review on existing publications, and conference publications, including correlates of protection, and clinical practice (IPD, CAP) individuals Comorbidities Immunogenicity (titre) PCV7, PCV10, PCV13, PCV15, PCV20 and PPSV23 Dosing,Timing, Immunogenicity Vaccine efficacy or effectiveness Safety and Tolerability Pneumococcal carriage Exclude Duplicates of published articles from conferences or abstracts based on clinical practice, Laboratory immunogenicity data Epidemiological data to healthier individuals
Study Characteristics Include Articles published from 01 Jan 2010 to 01 Feb 2024 Published articles in English year of publication author(s), title and name of the journal DOI study design and population demographics, interventions or exposures outcomes of interest, and other relevant reports shown in publications Exclude Below 31 Dec 2009 Above 02 Feb 2024
Other Include Published articles in English Exclude Other languages rather than English

Source: Covidence 2025 (47)

2.6. Data Extraction and Charting

Before extraction, the data template in Covidence was updated (Covidence number, title, author, year, country, design, key intervention), and population characteristics (age, sex, sample size, CD4+, CD8+ count, HVL, ART status) were inserted. Also, data included assay names (ELISA, OPA, MOPA, Fluorospot, Western blot, RT-PCR, LytA, and Culture) and study outcomes. An inbuilt template with four key areas used to evaluate risk of biases, like study design, sample size, participant blinding, and other biases, and the risk of bias was rated as high, low, or unsure.

Each article was assigned a Covidence ID, with citation details (year, author(s), title, sample size, country, aims, abstract) and study characteristics (design, demographics, context, interventions/exposures, outcomes of interest, test names/markers). Duplicates were removed. Any discrepancies between reviewers 1 and 2 were resolved through discussion and repeated extraction. Extracted studies were exported as a Comma-Separated Values (CSV) file and summarised with figures and tables.

CHAPTER THREE

3. Scoping Review Results

3.1. Studies Identified and Selected

After a complete search, the *RIS* files for all studies were imported into the Covidence software developed by Veritas Health Innovation (Melbourne, Australia) (47). Of the identified 3123 articles from five databases, 1549 were excluded as duplicates. Two independent reviewers screened studies for the titles and abstracts based on eligibility; 1574 articles were eligible. Of these, 1274 ineligible studies reported data from healthy (HIV-negative) individuals. Also, we excluded studies done in children and adolescents, had no HVL reported, were pre-clinical, animal models, and/or had no people with comorbidities other than HIV.

Three hundred in full-text studies were reviewed, of which 244 studies were then determined to be ineligible. Finally, 56 selected studies remained to be extracted (PRISMA-ScR Steps-**Figure 6**).

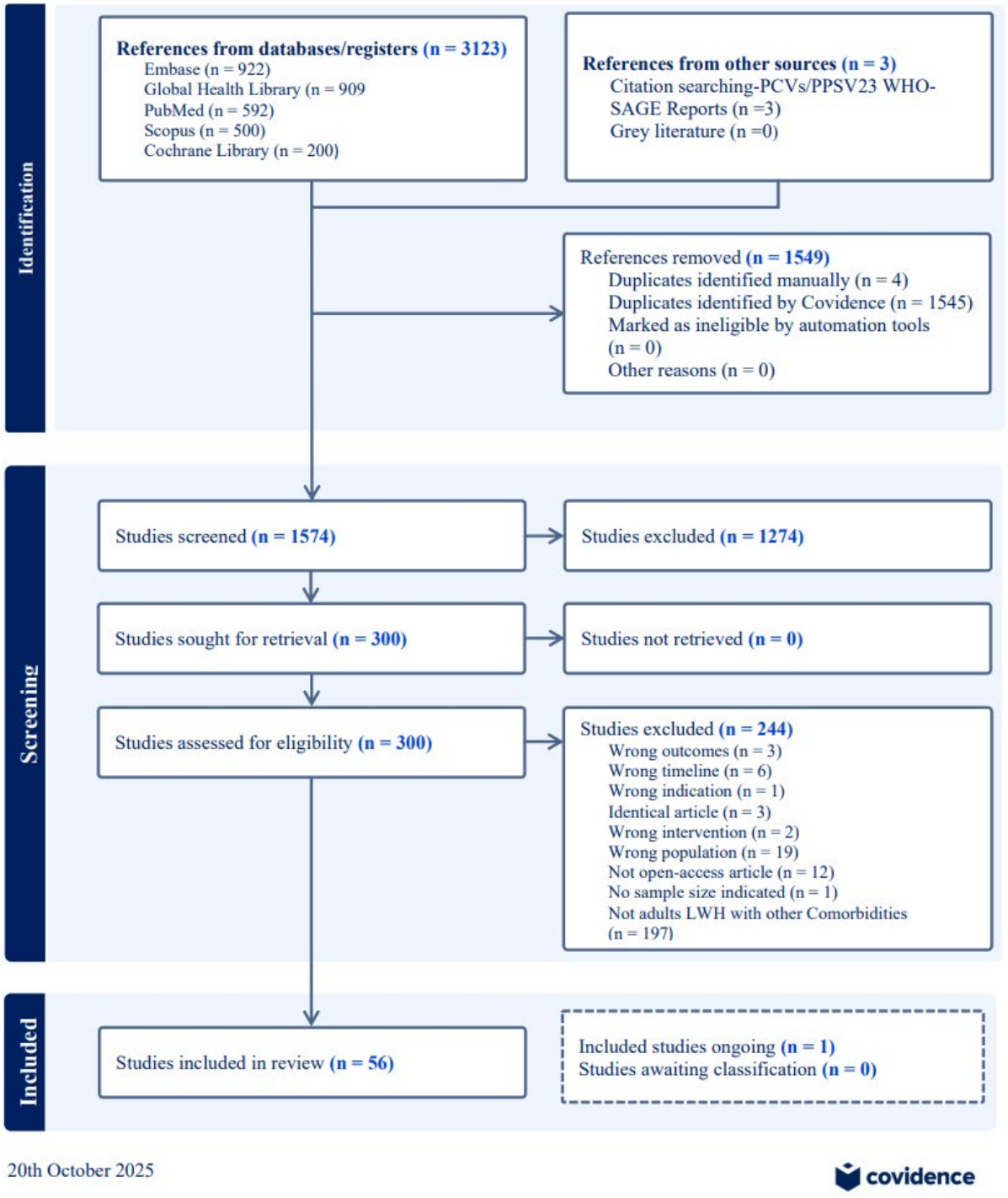

Figure 6: PRISMA-Scoping Review Steps on CoP for Pneumococcal Vaccines in PLWH

Source: Covidence 2025 (47).

3.2. Characteristics of Eligible Studies and Population

The selected 56 articles had 15,315 adult PLWH aged 18-84 years from 26 countries. The majority of the participants were male; 9315(59.5%). The age of participants in selected studies ranged from 18 to 84 years, except for one study that enrolled 346 pregnant women living with HIV aged 18 to 34 years (38). Their CD4+ counts ranged from 20 to 784 cells/mm³, and their HVL ranged from undetectable (<20) to 50,000 copies/µl. Among those on ART for two months to six years, 73% had an HVL of undetectable (<20) to 50,000 copies/µl. Approximately 73% were on ART for two months to six years, while others were on ART for 7-13 years. Of the studies, 89.3% (50/56) were from high-income countries, and only 6/56 (11.7%) originated in LMIC. Even so, 52 were single-country and 4 multi-centred studies in 13 countries. We stratified studies per country (**Table 3A**). The majority (16) were from the United States of America, (2,8–10,24–32) and Canada, including 2 studies (33,34).

Table 3A: Showing Selected Studies of COP/SOP, indicating the countries where the study was conducted, and References

Country	Number of countries where the study was conducted	Reference (N=56 Studies)
Australia	2*	(48,49)
Brazil	2	(21,50)
Belgium	1*	(49)
Canada	3	(49,51,52)
China	2	(53,54)
Chile	1*	(49)
Denmark	4	(31,55–57)
France	5*	(1,36,49,58,59)
Germany	2*	(23,49)
Ghana	1	(60)

Greece	2	(61,62)
Ireland	1	(22)
Italy	2	(63,64)
Japan	1*	(49)
Kenya	1	(65)
Malawi	3	(20,66,67)
Netherlands	2	(2,12)
Peru	1*	(1)
Romania	1*	(30)
Russia	2	(24,68)
South Africa	4*	(13,19,30,58)
Spain	3	(49,69,70)
Switzerland	1	(71)
Taiwan	6	(21,49,72–77)
Thailand	2*	(1,49)
United Kingdom	1*	(49)
United States of America	16	(1,15,16,43,49,64,65,78–85)

Legend: Light blue highlighted represents selected studies conducted in HIC.

Green colour: Shows selected studies from LUMIC

Asterix: Represent multi-country studies, expert reviews, or guidelines.

Out of 56 studies (32/56), 57.2% were clinical trials, 29 studies included placebo and controls, and 3 were non-randomised clinical trials in adult PLWH (1,16,20–23,31,38,43,51,53,55,56,58,61–64,66,72,73,75,78,79,81,82,86–93). Moreover, (16/56), 28.6% were observational studies (12,13,18,30,36,50,52,60,65,67,69,70,85,94–96), (2/56),

3.6% were cost-effectiveness analysis studies (24,85), and (2/56), 3.6% were systematic and meta-analyses (2,71). Of note, (6/56), 10.7% were expert reviews and guidelines for adult PLWH Table 4E (15,19,49,80,84,97)

3.3.Quality assessment of selected studies

We assessed the risk of bias based on reported bias, sample size, blinding and selection strategy of participants (**Table 3B**). A quarter of the studies (25%, 15/56) were of low quality due to selection bias (1,22,23,31,36,39,48,51,55–57,59,61,70,74,78,81,82,89,94,98), and 36% (21/56) of studies had small sample sizes of 40-104 individuals (**Table 3B**). Half (55%, 32/56) of the studies reported a blinded or randomised recruitment strategy to recruit participants. In addition, only one study reported high attrition rates due to lost follow-up (20)

Table 3B: Risk of Bias and Quality Assessment Tools for Selected Studies

Lead author	Country	Study design	Any type of bias	Sample size comments	Blinding of participants	Other sources of Bias
Abudulai 2019	Australia	Randomised controlled trial	Yes, Selection bias since no similar characteristics between HIV+ and HIV-	Yes, enough	Cohort and case-control	No
Cheng 2016	Taiwan	Non-randomised	Non, randomised study	yes, enough	Yes	sex bias only males participated in this study
Farmaki 2018	Greece	Randomised controlled trial	No	smaller size 40,35 males only	N/A	N/A
Glesby 2015	Germany	Randomised controlled trial	Yes, the majority were male's participants	Yes, Sufficient	Yes, randomized study design	Sex bias
Happe 2019	United States	Non-randomised	majority were male and small sample size	Yes, small sample size	blinded	N/A
HIV WorkingGroup 2010	United States	Randomised controlled trial	yes, biased males were dominant	Yes, enough	Blinded by Randomization	N/A
Ho 2013	Brazil	Randomised controlled trial	69.5% participants were males	Yes, enough	Blinded	Sex bias, 69.5% participants were males
Jensen 2020	Denmark	Randomised controlled trial	Smaller sample size	yes, smaller sample size	Blinded	N/A
Johannesson 2012	Denmark	Randomised controlled trial	Yes, sex bias	Yes, enough	Randomised study design	N/A
Lu 2013	Taiwan	Randomised controlled trial	Yes, sex bias	Yes, smaller sample size	N/A	Sex bias, males were dominant
Mohapi 2022	South Africa, USA, Peru, Thailand, and France	Randomised controlled trial	Yes, Bias multi-center	Yes, enough	Double blinded and randomized trial	Male participants were dominant
Rabian 2010	France	Randomised controlled trial	Sex Bias males were dominant	Enough	Blinded	N/A
Rodriguez-Barradas 2015	United States	Randomised controlled trial	No bias Reported	Moderate enough	Yes, blinded (control or placebo)	High attrition rate of participant
Romaru 2021	France	Cohort study	sex bias only 35 males	Smaller samples size	No blinding>type of study cohort	Selection bias>Overrepresentation PLWH
SÃ¸gaard 2010	Denmark	Randomised controlled trial	Gender bias males N=43 in Placebo vs control 49	Moderate sample size	Blinded control vs placebo	N/A
Sadlier 2016	Ireland	Randomised controlled trial	Yes, sex bias identified	Smaller sample size in one sex (male)	Blinded participants	No multivariate analysis was performed
Siemieniuk 2011	Canada	Cohort study	No bias	Enough	cohort and case control	Gender bias more males with high episodes in females
Slayter 2013	Canada	Randomised controlled trial	sex bias	Smaller sample size	Blinded in Randomized clinical trial	Sex bias
Tinggaard 2023	Denmark	Randomised controlled trial	Yes, sex bias	Yes, smaller sample size	Blinded	N/A
Vivancos-Gallego 2019	Spain	Case control	No Bias	Enough	Vaccination blinded	Selection bias less cases compared to control
Winckelmann 2013	United States	Randomised controlled trial	Gender bias more males in the placebo and control arm	smaller sample size	Blinded by randomization	N/A
Zou 2022	China	Case control	Selection bias> Antibody level evaluated in one year instead of years	Smaller sample size	blinded cases and controls for vaccination	Gender bias, more males in cases vs control

3.4. Pneumococcal Vaccine Efficacy and Effectiveness in Adult PLWH and immunogenicity studies.

Most studies and three expert reviews or guidelines recommend a 0.5 µl initial dose of PCV10-13 vaccination when CD4+ counts are above 200 cells/mm^3 and a follow-up vaccination with PPSV23 after 8 weeks in adult PLWH **(Annexe 3; Tables 4A-E)** (15,19,36,49,58,66).

As shown in three studies, one prime dose of PCV10-13 in series with PPSV23 induces a higher titre of serum pneumococcal IgG compared to PPSV23 alone in adult PLWH with CD4+ count >200 cells/mm^3 at weeks 8 and 28 (36,58,66). Immunogenicity, as reported in

eighteen studies (**Annexe 3; Tables 4A-B),** shows that this regimen had a seroconversion rate (SCR) of 50% with coverage of serotypes 6B and 14 in adult PLWH (2). PCV10 was compared to PPSV23 when given to pregnant women living with HIV before and after delivery. Immunogenicity to both vaccines was similar, but timing of vaccination was the key difference, as post-partum vaccination generated a higher antibody response (38). In eighteen studies, which were quantified by ELISA, PCV vaccination in series to PPSV23 induced GMC of 0.2 to 0.35 µg/ml or SCR as a 2-fold increase of anti-pneumococcal IgG (1,2,12,15,16,18,22,30,31,38,39,56,59,62,64,66,79,82,94) compared to 1.3µg/ml or > 4-fold increase in healthy individuals (**Annex 3; Table 4A-B**). of note, high serum pneumococcal IgG antibody titres were produced in response to serotypes 7F, 14, 18C, 19F, 23 and 33F, while serotypes 3, 4, and 6B had the lowest GMCs (1,12). Two studies indicated that pre-vaccination GMCs below 100ug/ml correlated with increased non-responsiveness in adults with HIV (adjusted OR 8.7, p=0.0438) (1,2).

Out of 56 selected studies, nine used OPA (which is a mechanistic functional activity CoP) to quantify serum pneumococcal IgG (1,2,15,16,22,30,31,64,82) and three used MOPA to evaluate IgG functionality (36,64,99). OPAs aligned with ELISA results, showing that the prime PCV-booster dose of PPSV23 significantly increased GMT at weeks 8 and 28 (odds ratio of 1.71 and 1.6, respectively) in PLWH who are virally suppressed with CD4+ counts above 200 cells/mm^3 (1,2,15,16,22,30,31,64,82). In eight studies, GMTs after PCV vaccination increased by 2-7 times (2,9,10,17,25,26,61,79) while GMTs post PPSV23 exhibited a lower 2-4-fold increase (1,2,30). An opsonic index reached 5.6, above the threshold of greater than 4 by covering 70% of tested SPn serotypes as recommended by WHO for pneumococcal vaccines in adult PLWH (36).The GMT antibody threshold was lower for SPn serotypes 14 and 19A in the African American group vs. Caucasians, **Annex 3;Table 4A-C**(24).

The pneumococcal VE for PCV7-10-PPSV23 in 3 studies among adult PLWH ranged from 55-87.76% (54,58,66), and PPSV23 effectiveness in one study was 71.6% (94). In two studies, however, PCV7 alone did not provide significant protection, regardless of whether participants were on ART (20, 66. As identified in one study, when PCV7 is given in series to PPSV23, VE was 74% (95% CI: 30–90) but declined to 25% within a year in adult PLWH with CD4+ <200 cells/mm³ **(Annexe 3; Table 4A-B)** (66,75). Repeated vaccination with

PCV7 in series to PPSV23 did not affect CD4+ count and HVL (43,72). In adult PLWH with high HVL, PCV13 still demonstrated high efficacy with high antibody titre, contrary to PPSV23, which failed to protect adult PLWH (54).

Adjuvanted PCVs were superior, as they induced helper follicular CD4+ T-cells and improved the immune response (59). One meta-analysis reported that vaccination at higher CD4+ counts above 200 cells/mm^3 and HVL <40copies/ml induced a protective threshold titre of 0.35-1 µg/ml or a 2-fold rise, particularly when one dose of 0.5 µL of PCV was administered in series to PPSV23 at week 8 (OR=2.00, p<0.01) (2). In two studies, 0.5µl of PCV13 and PPSV23 was more immunogenic than PPSV23 alone, and a better regimen than the PPSV23 dose after PCV7, which did not induce an immune response (22,67). An Australian study found that CD4+ T-helper cells elicited robust responses following PCV13 and PPSV23 vaccination in adults PLWH (48). Antibody difference waned six months to one year post-vaccination and differed by race (2,100). Two studies applied Fluorospots and new anti-pneumococcal CPS13-IgG ELISA and reported that PCV10 had reduced immunogenicity compared to PPSV23 for serotypes 1, 6B, 7F, and 14, and was more immunogenic for serotype 4 **(Annex 3; Table 4A-B)** (38,63) Also, salivary IgA as a marker for mucosal carriage **(Annexe 3; Table 4A**) had a >48-fold rise in the vaccinated people (p <0.001) against a 35-fold increase in placebo group (p = 0.008) (63). PCV15-20-21 and PPSV23 (14.1%) were well tolerated and induced immune responses for all pneumococcal vaccine serotypes in adult PLWH (12,15,16,58).

Cellular immune response involving cytokines like IL2-6-13-12-17A was highly expressed compared to lower TfH cells for PCV10 in series to PPSV23 (**Annexe 3; Table 4A&B**) (38). In contrast, decreased IL-7 and chemokine ligands like (CCL)11-13-17 induced higher antibody (IgG) responses in adult PLWH with high CD4+, low HVL, underscoring the role of memory B-cells in post-vaccination responses (38). However, no significant cytokine expression was noted across racial groups in 33 gene expressions were observed between African American and Caucasian adult PLWH (100).

3.4.1. Pneumococcal colonisation and serotypes and risk of IPD in adult PLWH.

Pneumococcal carriage was reported in 5 studies using culture and sensitivity and 2 with LytA-RT-PCR to measure colonisation **(Annexe 3**; **Table 4C**). Out of 98% unvaccinated adult PLWH with unknown CD4+ counts and HVL, carriage prevalence ranged from 7.3-21.8% (13,18,31,50,60,67). Leading reported serotypes were 19F and 23F, with a prevalence of 15.4% (60). Pneumococcal vaccination significantly decreased carriage from 85% in the first year following vaccination to 25% (13,60).

Episodes of IPD were reported in the same studies, with 80% of IPD cases occurring in PLWH whose CD4+ counts were <200 cells/mm^3 at baseline and adult PLWH associated with a higher incidence of SPn for non-vaccine serotypes (13,18,31,50,60,67)**.** Immunocompromised patients with low CD4+ count also had a 7.1-fold greater risk of recurrent IPD(18,52)**.** SPn serotype 19A was commonly linked with resistance to penicillin, cotrimoxazole and tetracycline in IPD cases after a first dose of PCV13 boosted with PPSV23 (15). One dose of PCV13 reduced the IPD with an efficacy of 74% (95% confidence interval, 30-90) in adult PLWH (15)**.**

3.4.2. Immunological Memory B-cells

CoP, in adults PLWH, involves memory B cells and plasmablasts that reflect immune memory and activation dynamics, with memory B cells particularly critical for long-term protection (62). After PCV and PPSV23 vaccination in adult PLWH, memory B cells may wane or persist and reactivate quickly upon antigen re-encounter. Following vaccination, directly involve non-mechanistic serum pneumococcal IgG antibody titer (GMC) or mechanistic GMT that represents how the pathogen binds or facilitates opsonophagocytosis (killing or clearance) (4,6). For PCVs depend on the activation of memory B-cells and Ig class changes to induce antibodies (14), and different pneumococcal vaccines produce different responses. PCV13 vaccination through T-cell and B-cell interaction induced effective clearance of Spn, and long-lasting immune response by an increase of IgM+ memory B-cells (MBCs) and single Ig+ MBCs in adult PLWH (61,65,74). Diminished protection and phagocytosis were noted with PPSV23 vaccination, as evidenced by low IgM+ memory B-Cell levels, and single Ig+ MBC levels remained stable (61,65,74). However, patients not on ART with a depleted immune dysfunction had elevated transitional B-cell and plasma blast

concentrations compared to B-cells after PCV13 in series to PPSV23 (60). High transitional B-cells ensure the differentiation of IgM to plasma cells correlated with improved vaccine responses, while low levels predict poor responses (31).

3.5.Safety and Adverse Effects

Injection site or local reactions ranged from 10-52.2 % while systemic reactions occurred in 5-43.2% as adverse events AE post-vaccination with PCV+ PPSV23 were reported, **Annexe 3; Table 4A-C** (43). Two studies reported an incidence of severe adverse reactions associated with re-vaccination (16,43). PCV15 was well tolerated despite 13,2% SAE such as pain, erythema and swelling. Systemic reactions reported were myalgia and potentially life-threatening cases related to pyrexia, reported within two weeks for PCV15 and PPSV23 (16,43). Pyrexia was reported in one study, fourteen days after vaccination, as a life-threatening SAE in an adult PLWH (43).

3.6. Pneumococcal Vaccines in Adults PLWH with Other Comorbidities

There were no studies which included PLWH who had other comorbidities such as hypertension, diabetes, or chronic renal failure. PPSV23-antibody titres were higher in healthy elderly (not receiving any immunosuppressive drugs, or having any cancers, autoimmune and hepatitis B or C infection) with an age range of >60 years, associated with increases in plasma cells, but titres were significantly decreased in PLWH who had been recently cured of TB Table 4B (52).

3.7. Expert Review and Recommendations on Pneumococcal Vaccines in Adult PLWH

Vaccination guidelines from 26 countries recommend administering PCV13 to high-risk groups, followed by a PPSV23 booster after 8 weeks to enhance serotype coverage (15,19,49,75,80,84). Also, adult PLWH who have never been vaccinated with PPSV23 can be re-vaccinated with PCV13 after at least 5 years have passed. There is ongoing debate regarding the timing of pneumococcal vaccination based on CD4+ count and HVL levels, but a CD4+ count of 200 cells/mm^3 seems to be required, and viral load should be <1000

copies/ul (19,49). Pneumococcal vaccination is also recommended for smokers, residents of long-term care facilities, and individuals with comorbidities such as chronic lung, liver, heart disease, diabetes, and severe alcoholism (15,19). Other high-risk groups include cochlear implant recipients, individuals with intracranial shunts, sickle cell disease, asplenia, immunodeficiencies, hematopoietic stem cell transplant recipients and malignancies and people with adrenal failure, **Table 4E** (15,19).

CHAPTER FOUR

4. Discussion on Study Findings

In this first scoping review, significant gaps and conflicting data remain in the literature regarding CoPs and SoP in adult PLWH. Most studies were conducted in HIC and mostly enrolled male participants, highlighting the underrepresentation of adults living with HIV who are female and live in LUMIC.

4.1.Special considerations for vaccination in Adult PLWH

Expensive RCT studies remain the gold standard to support CoP validation and vaccination guidelines in adult PLWH. (15,19,62). Predominantly, ELISA is used in most studies to quantify serotype-specific serum pneumococcal IgG antibodies, and it appeared to show a lower protective threshold of <0.35µg/ml in PLWH, suggesting a need to re-evaluate this threshold in this population. Studies using OPA reported a 2-4 fold GMT increase (1,2,15,16,22,30,31,64,82) compared to 1.3µg/ml or > 4-fold increase in individuals without HIV (**Annexe 3; Table 4A-B).** Despite the widespread availability of ART, PLWH remain at high risk of IPD and hospitalisation even after immune recovery and viral suppression. Notably, a pneumococcal vaccine can minimise colonisation in adult PLWH with novel serotypes of SPn (13,50,60)**,** which theoretically could prevent the risk of contracting severe pneumococcal disease. Timing of vaccination in relation to ART and which vaccine to use appears to be crucial. PCV in series to PPSV23 should ideally be delayed until immune recovery (CD4+ >200 cells/mm^3) and HVL <1000 copies/ml in adult PLWH for optimal protection or immune response.

PCV10-13 had a higher efficacy compared to low PPSV23 effectiveness in IPD reduction and hospitalisation, **Annexe 3; Table 4A-C** (66), hence there is a need for more studies on high-valent PCV effectiveness. (35,41). The pneumococcal vaccines were reported to be immunogenic, safe and offered protection against IPD in adult PLWH (10,27,75). PCV7, though, did not provide a potential benefit in IPD prevention and hospitalisation (66).

As shown by Stanley Plotkin *et* al. and LaFon DC *et* al*,* the vital quantitative CoP immune responses are pneumococcal IgG, IgA in mucosal carriage and memory B-cells induced after PCVs and PPSV23 vaccination (4,6). recommends a priming dose of 0.5µl of PCV10-13-15

in series to PPSV23 eight weeks and repeated after 5 years, considering age (>65 years) with either PCVs or PPSV23 (15,19,62). For adult PLWH, PCV vaccination in series to PPSV23 induced low quantities of anti-pneumococcal IgG(non-mechanistic marker), as reported in several studies with GMC <0.35 µg/ml or SCR as a <2-fold increase and a limited number of studies for vaccine-covered serotypes (**Table 1, 4A-C)** (1,2,12,18,22,30,31,38,39,56,59,62,66,79,94). Previous studies had defined a threshold of > 1.3 µg/mL as protective in children, compared to a lower threshold of >0.35- 1 µg/mL or a 2-fold increase for GMC and a 4-fold rise for GMT(mechanistic functional activity marker) in adult PLWH (2, 15, 16, 24, 31, 37, 65. Adults with CD4+ counts above 200 cells/mm³ after a prime dose with PCV10 or PCV13 in series to PPSV23 were able to mount a more robust antibody response to the conjugate vaccine prime than those with lower counts. (36,58,66).

4.2.The best Assay to assess and validate CoP in PLWH

The WHO recommends OPA as the gold standard for assessing the functional activity and serotype-specific titres of serum pneumococcal IgG antibodies despite its limited application in adult PLWH (1,2,15,16,22,30,31,36,64,82,99). A significant increase in serum pneumococcal IgG antibody threshold, mainly tested by ELISA, in response to serotypes 7F, 14, 18C, 19F, 23 and 33F compared to serotypes 3, 4, and 6B had reduced GMCs (1,2,12,18,22,30,31,38,39,56,59,62,66,79,94).

OPAs showed consistent results with serum pneumococcal IgG antibodies **(Tables 4A-C)** (1,2,15,16,22,30,31,36,64,82,99). In virally suppressed adult PLWH with CD4+ counts above 200, a prime PCV dose followed by PPSV23 booster significantly increased antibody GMTs by 2-7 fold increase at weeks 8 and 28. (1,2,15,16,22,30,31,64,82). At different time points, antibody levels showed a moderate correlation with opsonophagocytic titers across all serotypes, whereas the correlation with overall protection at month 12 was weak and not statistically significant (36). However, for MOPA, the opsonic index reached 5.6—above the WHO threshold of 4 required for adequate protection (36). PLWH showed reduced opsonic indices versus healthy individuals in adult PLWH (36,101).

PCV10 and PPSV23 induced comparable antibody levels, although wide gene expression and ethnic disparities were observed in African Americans who had lower GMT thresholds for

serotypes 14 and 19A compared to Caucasians (24). This emphasises the need to enrol a representative study population per geographical area in future studies (78,100).

4.3. How CoP Predicted Pneumococcal Vaccine Efficacy and Effectiveness in Adult PLWH

As shown in several studies, PCV10-13 has been found to have superior efficacy compared to PPSV23 in reducing IPD and hospitalisation in adult PLWH, with even better results with the prime boost regimen (54,58,66,94). Only one study assessed PPSV23's effectiveness against PPSV23-serotype linked with pneumococcal pneumonia in adult PLWH (94). Expert reviews have recommended PCV13 vaccination in adult PLWH when VE is more than 74% and that is mainly achieved with PCVs. An exception was reported for PCV-10, which was less efficacious in antepartum women living with HIV compared to when given in the postpartum period (38). In pregnant women living with HIV(WLWH), it may be important to prioritise a booster dose after delivery to ensure robust and long-lasting immune responses. Also, it is vital to update specific pneumococcal vaccination guidelines for pregnant women. PCV15-20-21 were more immunogenic and provided adequate SPn serotype coverage. Until now, few clinical trials are underway for new generation higher valent PCV24-31 studies (17), which have similar immunogenicity and safety profiles to PCV20-21(15,16,98) in healthy individuals, with a 54% decrease in IPD episodes. The current higher valent PCVs are beneficial, covering more serotypes and reducing IPD, but lack CoP thresholds and need to be evaluated in adult PLWH.

In adult PLWH, evidence remains limited on VE and vaccine effect on nasopharyngeal carriage when stratified by CD4/8 and HVL (12,13,15,38,50,52,56,60,94)**.** Our scoping review suggests that, in childhood pneumococcal vaccination, adults are not protected, and high carriage and novel non-vaccine type serotypes have emerged and have been detected by methods like culture, real-time PCR(RT-PCR), Fluorospots, and LytA assays in adult PLWH (12,13,15,50,56,60,94).

4.4.SPn Serotypes Effect of CD4, HIV Viral load, and ART in Adult PLWH

The previous studies have shown that highly invasive serotypes (1,7F, 19A,19F) induced high antibody thresholds precluding the use of high-valent pneumococcal vaccines in adult PLWH to cover non-vaccine serotypes not covered in licensed pneumococcal vaccines (2,12,43) In contrast, a less invasive SPn includes 6A, 6B, and 23F, while serotypes 3, 4, and 6B had the lowest serum pneumococcal IgG antibody titre (2,12,43), suggesting that in PLWH, vaccines covering most pathogenic serotypes is necessary.

PCVs should ideally be delayed until immune recovery (CD4+ >200cells/mm³) in newly diagnosed PLWH for optimal response. In light of serum pneumococcal IgG or T-cell responses after PCVs in series to PPSV23 vaccination, studies suggested that vaccination of adults whose CD4+ cell counts are <200 cells/mm³ and HVL >1000 copies/µL does not induce optimal vaccine responses (2,10,68). Immunogenicity studies further show that in PLWH, SCR varies per serotype, like 6B,14, and 19F, and this in turn determines the pneumococcal vaccine effectiveness (2). Combining both vaccines, covering more serotypes and timing administration post-CD4+ recovery >200 cells/mm³ and having undetectable HVL improve protection in individuals with depleted immunity (2).

4.5.Pneumococcal Antibodies Decay in Adult PLWH

Of concern, antibodies appeared to wane from the sixth to twelve months post vaccination in adult PLWH despite CD4+ counts above 200 cells/mm^3 and undetectable HVL (2,12,43). This data warrants further research on the durability of protective immunity and the need for booster doses. As reported in immunosuppressed individuals on ART who received PCV10-13 in series to PPSV23 vaccines, a higher (4-fold) number of changed antibodies to memory B-cells to enhance more effectivity was linked to greater IgG antibody levels after vaccination (at 3, 4, and 9 months) (31,62). Additionally, salivary IgA serves as immune memory for mucosal immunity to prevent nasopharyngeal pneumococcal carriage post-vaccination, as shown in one study that had a higher level of salivary IgA in a combined PCV13 and PPSV23 vaccination (63). We should consider an optimal timing for pneumococcal vaccination to induce antibodies with a protective threshold. While CD4+ counts are well-studied, data on the impact of CD8 and HVL on long-term protection remain limited.

4.6.Cellular Immune Response and Safety in Adult PLWH

We examined the role of cytokines in adult PLWH after vaccination with PCVs and PPSV23. We found no reports on cytokines in other groups, except for antepartum women living with HIV (2,38). TfH cells influence the activation of IgG production post-vaccination with PPSV23, hence enabling better pneumococcal vaccine efficacy (48). This process drives effective maternal immune responses to pneumococcal vaccination, ensuring immediate and long-term protection for the mother and her offspring from IPD (38).

4.6.1. Safety of vaccines in PLWH

Generally, both PCV10-13 and PPSV23 are safe and tolerable in adult PLWH. Several studies documented reasonable and acceptable safety assessments and proved that the vaccines are safe in adults PLWH (10,27,75). However, some SAEs have been reported with the high-valent vaccines like PCV15-20 and PPSV23 in adult PLWH, which need to be taken into consideration. Most SAEs reported, though, were non-life-threatening (10). In a RCT with PCV20-21, 0.6% of deaths occurred following vaccination, but they were deemed not associated with pneumococcal vaccines (10). The importance of continuous monitoring, reporting and post-licensure safety assessments in adult PLWH receiving PCVs is also needed.

4.7.CoPs in Adult PLWH With Other Comorbidities

No specific studies have reported CoPs and SoPs in patients with other comorbidities such as hypertension, diabetes, or chronic renal failure, with no data on latent or active tuberculosis.

4.8.Pneumococcal Vaccines: Vaccination Compliance

Compliance with pneumococcal vaccination and low perceptions affect CoP in adult PLWH, influenced by low uptake with coverage, incomplete vaccination schedules, and hence low pneumococcal antibodies associated with hesitancy due to concerns about vaccine efficacy, side effects, and reduced trust in healthcare providers (69,96). It is potentially important to consider these factors during rollout and continued pneumococcal vaccination surveillance with monitoring and promoting awareness in vaccination confidence.

4.9.Gaps in Current CoP and Future Opportunities for Pneumococcal Vaccines

This study summarised gaps in the literature regarding the CoP in adults living with HIV who have received pneumococcal vaccination. To our knowledge, no scoping review on this topic has been published in peer-reviewed journals before.

4.9.1. Higher-valent vaccines with adjuvant should be validated with OPA or MOPA to evaluate directly immune function activity, per WHO recommendations, and included in post-licensure surveillance for adult PLWH. Of note, novel technologies are beneficial to detect SPn antibody titers with serotypes, hence pneumococcal vaccine modelling and vaccinomics can predict long-term CoP to proxy efficacy and effectiveness for prevention of IPD, CAP with hospitalisation in adults with PLWH

4.9.2. We found no effectiveness studies on IPD and CAP on PCVs and efficacy for PPSV23, warranting further studies in adult PLWH. More studies are needed to generate data on safety profiles, gene expression diversity, carriage, serotypes and should include PLWH with other comorbidities such as TB. Studies with longer follow-up are required in PLWH.

4.9.3. Studies have been done that assessed B-cell subsets considering CD4+, HVL, ART status with colonisation, long-term immune responses and antibody decay post-vaccination beyond one year, calling for studies with longer duration.

Limitations

More than half of the published studies were of high-quality RCTs conducted in adults with PLWH. Despite the use of blinding and randomisation to reduce selection biases, our findings show a notable trend of male dominance in the studied populations.

One of the strengths of this study was that two independent reviewers screened the selected articles to minimise the risk of bias. However, there are several weaknesses, especially in the search strategy. The restriction to 17 search terms may have missed relevant articles, and we

did not include case series studies and only included articles published in English and open-access papers. We may have missed papers in other languages which could have been translated to offer important insights. Additionally, we found selection bias in 22 studies due to non-random sampling methods, reducing their statistical power. Also, we did not include any articles published in 2024, which may have had relevant current findings that could affect our understanding of the pneumococcal vaccine continuum of care in adult PLWH. Cytokines in other groups were not explored, except for antepartum women living with HIV, in whom elevated IL-2-6-12 supported the theory of immune response in controlling disease severity (38).

Conclusion

In the first scoping review, the paucity of data on CoP and carriage studies among adult PLWH is evident in our setting. RCT studies emanating from HIC remain the gold standard to support CoP validation and vaccination guidelines, and determination of protection thresholds specific to our population is needed. PCVs offer better protection than PPSV alone, with long-lasting immunity, with PCV13 appearing to be the best option in the prime boost regimen with PPSV23 in adult PLWH. OPA titers correlate with ELISA but reflect actual protective immune responses, especially in HIV, where antibody function is compromised. More research needs to be done to determine OPAs in adult PLWH, including women, in longitudinal studies with long-term follow-up beyond one year.

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Annexes 3: Table 4A: CoP in Selected Studied PCV in series to PPSV23 and Re-vaccination 3-8 years (1,2&3 Doses) (n=32

Lead author , Year	**Country**	**Vaccine and Period**	**Study design**	**Age**	**Sample Size**	**CD4 cells/ mm3**	**HVL (copies/ ml**	**ART**	**Assay type**	**Overall Results**	**Key outcomes+ Summary**	**Type of Bias**
Bhorat et al, 2015 (30)	South Africa, Romania	Combined 3PCV13 doses + 1 PPSV23	Cohort study 0,1Month, IgG	18-41.2	151: 44M	537.3	<50	On ART	IgG GMCs+ GMTs)	IgG GMCs and OPA GMTs were observed for all serotypes after dose 1 of PCV13 compared with pre-vaccine levels. GMCs and GMTs were the same in PCV13 doses 2 and 3 and after PPSV23.	3 doses of PCV13+PPSV23 were well tolerated in naive, HIV	No Bias
Cho 2013 (85)	United States	PCV13+ PPSV23 + Cost-E with other Comorbidities	Cohort study	-	Not Reported	Not reported	Not reported	Not reported	Program costs, medical costs, non-medical costs, and disease burden	PCV13 prevent 57 IPD, averts 93 deaths and saves 1360 QUALY per cohort.	PCV13 + PPSV23 reduces both disease and costs of 16 $million (in 2009$) + savings of $21 million per cohort.	No Bias
C-L Lu et al.,2014 (72)	Taiwan	Combined Revaccination PCV7+1dose PPSV23 compared to 5years	NRCT	>18	127	350	<50	on ART	ELISA to measure IgG GMC	Revaccination with one dose of PCV7 (AOR, 4.57), two doses of PCV7 (AOR, 22.66), CD4 >350 cells/mm3 (AOR, 3.24), Low HVL (AOR, 3.87) give better response in 48WKS	Revaccination with PCV7+ PPSV23 gives a better serologic response in 5 years.	No Bias
Crum-Cianflone et al 2010 (43)	United States	Ethnicity IgG+PCV7 + PPSV23, Serotypes 4, 9V, 14, and 19F)	RCT	18-60	204: 180 males	<500	<50	on ART	ELISA+ IgG +Serotypes	2-fold rise in IgG 1 µg/mL, at day 60 post-vaccination, 2 of 4 serotypes.	Revaccination PCV7+PPSV3 +Similar IgG AA and Caucasian PLWH	Sex Bias Against Males
Crum-Cianflone et al.,2010 (100)	United States	Re-vaccination 3–8-year PCV7+PPSV23	RCT	18-64	131	381-701	50	on ART 6.3 years	ELISA IgG level with a post-vaccination	SCR for PCV+PPV (57% vs 36%) (P = .004) IgG GMT change 60 for serotypes 4, 9V, and 19F (P < .05, for all), except 14. No effect on CD4+HVL in revaccination	O.5ul of PCV was more immunogenic than PPSV23 and tolerable at day, and waned by day 180 Severe adverse reaction associated with re-vaccination	No Bias
Duarte et al., 2022 (38)	United States	Combined PCV10+ PPSV23 Titre, Cyto + MeB in ante/postpartum women LWH	RCT	18-36	346F: 106P: 230Antp	>590, CD8 >778	<40 Ante/postpartum	on ART	ELISA/ chemiluminescence/ Fluorospot	Overall, PCV-10 was less immunogenic than PPSV-23 for serotypes 1, 6B, 7F, and 14, except 4 Higher CD4+ lower CD8+ HVL associated with higher antibody responses to 6 of 8 serotypes (1, 4, 7F, 14, 23F, and 33F). IL-2, IL-6, IL-13, IL-12p70, and/or IL-17A and negative loadings for IL-7, CC chemokine ligand 11 (CCL-11), CCL-13, and CCL-17	PCV10 +PPSV23 higher IgG in postpartum VS antepartum. PCV10 and PPSV23 are not specifically recommended in pregnancy	No Bias

										were associated with higher antibody responses		
Farmaki et al.,2019 (61)	Greece	Combined PCV13+PPSV23 MBCs	RCT in 1 Year	18-63	40: 35M	<200	50	on ART	ELISA for IgG and Flowcytometry for IgM MBCs	PCV13, IgM+ MBCs were unchanged Levels of sIg+ MBCs increased significantly. PPSV23 levels of IgM+ MBCs reduced levels of sIg+ MBCs remained stable.	Combined PCV13 induce high IgM + MBCs vs Low in PPSV23 at month 12	small sample size
French et al.,2010 (66)	Malawi	PCV7 +PPSV23	RCT	18-74	486	>200	<25	on ART 337 days	TB PCV7 protected a PLWH pneumonia (75.4) (79.0)0.74 Meningitis	Vaccine efficacy of 74% (95% confidence interval A low CD4+ is associated with IPD death. Lower adverse reactions were observed	PCV7 protect against Recurrent IPD vaccine serotypes or serotype 6A	small sample size
Garrido et al.,2020 (2)	Netherlands	PCVs+PPSV23	Systematic and Meta-analysis	>18	39	>100	Not reported	on ART	ELISA IgG level, serotypes 6	IgG antibodies+ Serotypes 6B, 14, had SCR (50-70% in PCV+ PPSV23, or a combination of PCV/PPSV23, in adult PLWH.	Combined PCV13+PPSV23+ ART=Immunogenic Recovery delayed until (CD4>200) + unknown schedule	No Bias
Glesby et al.,2015 (23)	Germany	PPSV23 + PCV13 after 6months	RCT, 6 Months	>18	329	<200	<50	on ART 6 months	ELISA and OPA IgG Safety	PCV13+PPSV23 Antibody levels were generally similar after 1 or 2 doses of PPSV23. Safety Pain at the injection site was the most common local reaction. Severe injection site or systemic events were uncommon.	PCV13+ PPSV23 Induce IgG and OPA CD4 200 cells/mm3. Ig 1 month after doses 2 and 3. IgG declined and remained above baseline.	Sex Bias Against Males
H.M. Garcia Garrido, J.L. Schnyder, B. Haydari et al. 2022 (12)	Netherlands	combined PCV13 +PPSV23 PLWH on ART and HIV-Neg controls	Cohort study 0.2 Months	18-70	140:1 20M	<200	<20	on ART	ELISA IgG GMC titre, Serotypes, BMI, Alcohol User,	PPSV23+ PCV13 increased IgG GMC increases except serotypes 3 and 5 CD4 count <500 cells/mm3 vs 500 cells/mm3 Four serious AEs occurred, none related to the study.	serotypes observed PCV13 (40%), PPSV23 58 2months Low CD4 nadir <200 cells/mm + Protective immunity waned rapidly	Selection Bias
Happe et al.,2019 (78)	United States	Combined PCVs+PPSV23 high IPD with poor immune response to	NRCT	44-62	28 M	>400	<200	on ART, 1 year	ELISA +OPA IgG level, serotypes 14, 19A and 23F PPSV23/PCV	no difference in Ig/ IgM between Caucasian and AA with either PPSV or PCV/PPSV23 only OPA varied in 2 of 3 serotypes measured gene expression IgM B cells are significantly different between ethnicities	no difference in Ig/ IgM between Caucasian and AA with either PPSV or PCV/PPSV23 only OPA varied in 2 of 3 serotypes measured gene expression IgM B cells are significantly different between ethnicities	Sex Bias Against Males
Ibarz-Pavon et al.,2018 (20)	Malawi	Combined PCV7+ PPSV23 +HVL +	RCT	18-65	436	<200	<400	on ART 40%	CD4 and HVL	2 doses of PCV7 had no effect on VL or CD4+ T-cell + ART	No difference in HVL control + placebo groups, regardless of ART No effect of PCV7 on CD4+HVL after 6months	Sex bias

		CD4 efficacy										
Jayani Pathirana et al.,2022 (16)	United States	combined PCV21 +PCV15+ PPSV23	RCT 30 Day,12 WK+8 Serotypes	18-64	300:270M	50	<50,000	On ART	ELISA+ IgG GMCs for 13 Serotypes 30-day Safety of PCV21 onsite of injection	Combined PCV21 similar response with PCV15 + PPSV23 OPA in GMT, 4-fold increase+0month PCV15 + PPSV23	IgG +GMCs+4-fold increase 30 days. PCV21 for IPD	No Bias
Kobayashi et al., 2023 (15)	United States	Combined PCV15 OR PCV20 + PPSV23	Expert review in adults CDC	>19					Guideline	PCV15 + PPSV23 in 65 years 19-64 y not received PCV before should receive single dose of PCV20 or1 PPSV23	CDC PCV15 or PCV20+PPSV23 but have not received any PCV dose. PCV7+ HSCT	Unsure
Kobayashi et al.,2022 (18)	United States	PCV13 + IPD PLWH and non-PLWH	Case-control	19-64	2440:1670M	Not reported	Not reported	Not reported	IPD in PLWH	Higher in IPD cases in non-PLWH, associated with 77-80% of IPD cases among PLWH	Serotype 19A, a PCV13-type+ serotype, causes IPD among PLWH. PCV13-type reduces disease burden in both PLWH and non-PLWH	No Bias
Lombardi F et al. 2016 (64)	Italy	Combined PCV13+ PPSV23	RCT	18-65	170:90M			on ART	ELISA IgG GMC, Diabetes, and Cardiovascular (n=5)	Same IgG GMCs at 48 months PCV13 threshold 1ug/mL and of >0.35 ug/mL	PCV13 +PPSV23 vaccination after 1 year. Decrease in IgG level for PCV and PPSV23. 2 doses of PCV13 were as safe + PPSV23	Low
Lu et al.,2012 (97)	Taiwan	Combined PCV13+ PPV23	Expert review	>18	Not Reported	Not reported	Not reported	Not reported	enhance immunogenicity in HIV-infected adult patients.	V. Efficacy 74% (95% confidence interval, 30 to 90), reduced to 85% to 25% thereafter, 1 year CD4 count <200 cells/mm3 had 7.1-fold recurrent IPD vs >500 cells/mm3. Antibody cut-off 0.35 µg/ml or 1 µg/ml.	PCV13 +PPSV23 in 8 weeks when CD4>200Cells and 19-64 y after 5y the first dose of PPSV23 with no more than 3 lifetime doses	No Bias
Lu et al.,2013 (76)	Taiwan	Combined PCV7+PPSV23 PCV7	RCT	18-64	104:100 Males	<200	50	on ART	ELISA IgG	PCV7 was not able to raise HVL; ELISA had a 2-fold rise at WK 48 to serotypes 6B and 23F.	1 dose of PCV7+Low HVL gives better serologic responses.	Sex Bias Against Males
Mohapi et al.,2022 (1)	South Africa, USA, Peru, Thailand and France	Combined PCV15 or PCV13 + PPSV23	RCT placebo + controls Day 1, Wk8	18-84	302	50	<50	On ART	OPA and MOPA serotype testing	PCV13+ ppsv23 Higher OPA (GMTs)+ IgG (GMCs) same in day 30 +WK12.te	Cover 15 serotypes+ PPSV23 8wks	Low sample size
Patricia L Hibberd, MD, PhD (84)	United States	Expert review in PLWH	Expert Review	>18	Not Reported	>200	HVL		Guideline	PCV13 vaccination is a priming dose followed by PPSV23 after 8 weeks. CD4 count should be >200 cells/ml	PCVs as a prime dose and 8 weeks with PPSV23 CD4<200+ART	No Bias
Rabian et al.,	France	Combined PCV7CR	RCT	33-57	212	159	<200	on ART	T cells and Cytokines using flow cytometry	Combining a prime PCV +PPS23 induce VS PPSV alone IgG CRM197 CD4 T cell responses.	The PCV prime-elicited memory T cell + IgG responses.	Sex Bias Against Males

2010 (59)		M197+ PPSV23								CD4 T cell responses, producing IL-2 and IFN-gamma after vaccination		
Reale et al.,2021 (63)	Italy	PCV21 (Vivomixx) + 1 dose PCV13	RCT Placebo	31-66	30	>300	<40	on ART	Human Anti-Pneumococcal CPS13 IgG ELISA Kit IgA Interleukin (IL-)10 and IL-8 ELISA assays	Anti-Pneumococcal CPS13 VivomixxÂ +PCV13 observed 0.9 vs. 0.4 ratio in placebo s ($p < 0.001$) at 4,8 WKS. Salivary IgA had a 48-fold rise ($p < 0.001$) vs the placebo group vs a 35-fold increase ($p = 0.008$). **B cells** had a 12-fold increase, and CD4+ increased in the placebo group ($p = 0.002$). **Serum Cytokine Levels** IL-8 raised in T0 received VivomixxÂ ($p = 0.009$).	VivomixxÂ vs. PCV13 immunisation, greater fold change of anti-PnCPS13 IgG. PCV13 immunisation did not affect the T cell	Sex Bias Against Males
Romaru et al.,2021 (36)	France	Combined Efficacy of PCV13 + PPSV23	Cohort study	>18	38:35 M	>200	<40	on ART	New ELISA + IgG GMC and Serotype 4, 6B, 9V, 14, 18C, 7F, 19F, and 23F) PCV13+ and PPSV23 10F and 15B MOPAGMT and Serotypes 4, 6B, 9V, 14, 18C, 7F, 19F, and 23F)	92.1% and 78.9% were globally protected at one month, and 64.7% and 55.9% were still protected at 12 months, by ELISA and MOPA A CD4/CD8 ratio of >0.8 better response for OPA (OR=6.11, p=0.02), CD4 nadir <200 ELISA (OR=0.22, p=0.04). HIV RNA viral load <40 copies/ml was significantly associated with a better global protection at M1 by ELISA and OPA (OR=21.33, p=0.025 and OR=8.40, p=0.04)	PCV13 induced protection 1month, PCV13 improved OPA in 6- 12 months OPA + using published thresholds. IgG, ELISA 4, 6B, 9V, 14, 18C, 7F, 19F, and 23F) PCV13 and PPSV23 alone (10F and 15B. MOPA (4, 6B, 9V, 14, 18C, 19F, and 23F)	Sex bias to Males+ overrepresented
SÃ¸gaard et al., 2010 (54)	Denmark	2 Dose PCV7 + CPG 7909	RCT 1b/2a:1 placebo + controls Day 0,3, 9month	>18	97:47 M:5F	<200	>50	on ART	OPA to measure IgG quality and serotype Cytokines Quantitative IgG measurements) - in the CpG 7909 group vs. the control group	Placebo+ controls had 2- 5 folds at 3 (51.1% vs 39.6%, P = .26), 4 (77.3% vs 56.3%; P = .03), and 10 months (87.8% vs 51.1%; P < .001).Non-PCV7 serotypes OPA GMT were 1.10 -1.62 for the 4 serotypes in the control. Mild systemic and injection site reactions to 7vPnC were more common placebo group (100% vs 81.3%; P = .002). 7909 did not increase non-pcv7 IgG levels after PPSV23 immunization	CPG-7909, a TLR9 to 7vPnC+ IgG antibody response at 9 months. TLR9 durable antibody in 7vPnC alone. Booster dose PPSV23 antibodies with higher functional High responses in PCVs+ CPG in males vs females 3.22(1.22-8.6) p=0.02	Sex Bias Against Males
Sadlier et al.,2016 (22)	Ireland	Combine PCV13+ PPSV23 vs the PPSV PLWH.	RCT 0,4WK prime PPSV23 WK4	18-65	104: 92M	>200	45	on ART	ELISA tested IgG in GMC serotypes OPA tested IgG GMT and serotypes	Prime does ELISA 2-fold increase in IgG GMC and a GMC >1ug/ml at week 8 (OR) 2.00, 95% (CI) 1.46- 2.74, p0.01) OPA 4-fold increase in GMT at week 8 (OR 1.71, 95% CI 1.22-2.39, p0.01) and week 28 (OR 1.6, 95% CI 1.15- 2.3, p<0.01).	PCV13+PPSV23 elicits IgG and OPA VS PPSV23 alone, CD4 count >200 cells/mm3. ELISA 2-fold increase in IgG >1ug/ml. OPA is defined as a 4-fold or greater increase in OPA titer PCV13+PPSV23 Covered SPn 1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) in WK 8 and WK28.	Sex Bias Against Males

Simon Belmonti, al., 2019 (79)	United States	Combined long-term PCV13 ++ PPSV23	RCT	>18	91:72 M	>200	<50	on ART 13 years	ELISA, OPA and MOPA IgG >0.35 COP + PCV13 and PPSV23	GMCs were significantly higher in PCV13+ PPV23 group (78.6%vs. 59.2%, p = 0.042). Overall serotype-specific IgG C 0.35 lg/ml, C 1 ng/ml	PCVs+PPSV23 long-term durable serologic response.	No Bias
Slayter et al., 2013 (51)	Canada	Combined PCV7 Vs PPSV23 Adverse events	RCT	18-65	80:62 M	60-500	<50	on ART 2 Months	ELISA+ IgG serotypes 4, 6B, 9V, 14, 18C, 19F and 23F) with a 22F OPA+ IgG and Serotypes14, 18C, 19F and 23F Adverse events	2-fold increase 1,6,12 months (OPA) titre 2-fold rise at 1,12 months Local reactions (redness, pain and swelling) to vaccination were common vs delayed (P = 0.05	PPSV23 or PCV7 Vaccination until the CD4 count is greater >200 cells/mm3 before vaccination.	High
Smith et al.,2013 (24)	USA	Combined PCV13+PPSV23+ Cost-E	Markov model-based cost-E	18-64	NA	NA	NA	NA	PCV13 Cost-effectiveness	A single-dose PCV13 strategy costs $70,937 per QALY compared to no vaccination. The current recommendation prevented 58 more NPP cases, 9 more IPD cases, and 9 more deaths per 100,000 immunocompromised persons over 15 years.	PCV13 is more cost-effective for immunocompromised individuals than two doses of PPSV23	small sample size
Spowart et al., 2021 (58)	South Africa, USA, Peru, Israel, France, Thailand	Combined PCV15 or PCV13 + PPSV23	RCT3 placebo + controls Day 1, Wk28	23-74	152: 120 M	>50-<200, 200-500	<50,000	On ART	Adverse events serotype-specific OPA ELISA IgG	PCV13 had efficacy of 60.7% and 71.6% following PPSV23OPA (GMTs) and IgG (GMCs), same day 30+wk12. One adverse event was 73.0% and 62.7% in the V114. Site pain 57.2%, Site swelling 19.1% Severe systemic 13.2% Solicited Fatigue 31%, Headache 20%, Myalgia 19%	Pneumococcal vaccine-naive adults: Naïve HIV compared to those on ART show that PCV15 covers 15 serotypes plus PPSV23 at 8 weeks, with good tolerance. IgG covers serotypes 3, 4, 18C,22F, and 33F.	Sex Bias Against Males
Tinggaard et al.,2023 (56)	Denmark	Combined Serology PCV13 +PPSV23	RCT		50:44 M	<200	<50	on ART for 3 Combivir	ELISA IgG and Serotypes	Serotypes 14, 18C and 19F had higher GMCs; VS serotypes 3, 4 and 6B had the lowest GMCs. Pre-vaccination GMC <100 ng/ml	PCV13+PPV23. Low pre-vaccination GMC	Sex Bias Against Males
Y.-L. Ho et al.,2013 (39)	Taiwan	PCV and PPSV23+ Efficacy PCVs alone	RCT	18-60	331:230M	>200	<400	on ART	GMC +ELISA	Combined PCV7+PPSV23 induce higher Ab serotypes 6B and 9V. A PPSV23 dose after PCV7 did not enhance immunogenicity.	Combined PPSV23+ PCV7 were safe and 4-fold rises for 6B and 9V serotypes. A PPSV23 dose after PCV7 did not enhance immunogenicity.	Small sample size

Legend: Not Shaded: Shows Selected Studies from HIC (n=28); **Light Green**: Illustrates Selected Studies Conducted in LUMIC n=2), **Light blue**: Indicates multicentred study in both HIC and LUMIC (n=2

Table 4B: Vaccination of PCVs Alone and PPSV23 alone to Prevent IPD (n=19)

Lead author & Year	Country	Vaccine and Period	Study design	Age	Sample size	CD4 cells/ mm3	HVL (copies/ml	ART	Assay type	Overall Results	Key outcomes+ Summary	Any type of bias
Cheng, Aristine et al.,2016 (89)	Taiwan	Long-term effectiveness 1+2 Dose PCV7	NRCT	18	438 M	>200	<20	on ART 5 years	CD4, ELISA, OPA, Viral hepatitis	The two-dose group had persistent serological responses compared to the dose for serotypes 14, followed by 23F, 6B, and 19F.	PCV7+6B, 14, 23F and 19F	No Bias
Huang et al., 2018 (53)	China	PPSV23+ healthy elderly+ TB-cured elderly.	RCT	18-70	63M	350-970	Not reported	on ART	OPA to GMT and Serotypes Flow cytometry to measure Antibody markers	PPSV23-elicited Ab titers were highest in healthy elderly, low in TB-cured elderly +HIV. high PPSV23-Ab titers In CD19 + CD69+ cells and CD19 + CD138 + plasma cells.	Depressed CD19 + CD69+ cellular response + PPSV23-Rised OPA Ab titers healthy, TB-cured.	No Bias
Hung et al., 2010 (73)	Taiwan	Long term antibody+ serotypes 14, 19F and 23F ART	RCT	18-71	169 Men	<100	<400	on ART	ELISA measure GMC titre and Serotype	Faster loss of antibody responses was observed in HIV+, still an unknown duration Suppresses had CD4 counts >100cells/mm3 had better HVL in 5 years .	CD4 cell counts in HAART-treated patients with PPSV23 declined significantly over the 5 years in those with CD4 counts < 100 cells/mm3.	Small sample size
Irene Cavada Carranza. et al., 2022 (69)	Spain	Compliance in MSM	Cross-sectional study	>18	127:100 M	>200	<50	Not reported	Vaccination coverage and compliance	Complete vaccination coverage was observed in 11 patients (8.7%). Only)	Low adherence and compliance with Pneumococcal vaccines in PLWH	No Bias
Jensen et al.,2020 (55)	Denmark	IgG+PPSV23+ serotypes 1, 7F and 19A	RCT	42-59	47	Not reported	Not reported	on ART	Flowcytometry, Antigal3 tested, immunofluorometric assay MOPA IgG+PCV7 and PPV23.	Anti-±Gal +PPSV23 Correlates positively	Anti-±Gal +PPSV23 Correlates positively	small sample size
Johanneson et al., 2012 (31)	Denmark	B-cell+ PCV7 Naïve + not treated PLWH	RCT	41-70	97: 80M	>200	<50	on ART 3-8 years	Flow cytometry, ELISA, and OPA to measure IgG level	ART responders had isotype-switched memory B cells. ART-naive had transitional B cells and plasmablasts compared with B cells. MZ isotype-switched memory B cells and Plasmablasts increased at 3, 4, and 9 months.	Low Meb, B-cells (IgM+ plasmablasts) are not a predictor of poor PCV response. B-cell + poor vaccine response	Sex Bias Against Males

Kobayashi et al.,2022	United States	PCV13 + IPD PLWH and non-PLWH	Case-control study	19-64	2440:1670M	Not reported	Not reported	Not reported	IPD in PLWH	Higher in IPD cases in non-PLWH, associated with 77-80% of IPD cases among PLWH	Serotype 19A, a PCV13-type+ serotype, causes IPD among PLWH. PCV13-type reduces disease burden in both PLWH and non-PLWH	No Bias
Laila N.Abdulai et al., 2019 (48)	Australia	IgG2 +PPSV23, IL-7R and TFH	RCT	>18	45	>200	50	ART	, ELISA (IgGI&2)	High IgG2 antibodies to serotypes 4, 6B, 9V, and 14 vs Low IgG1+ IL-7 by cTFH cells affects the production of IgG2 antibodies to PPSV23 in PLWH	IgG2 PPSV23 may be associated with IL-7RI signalling in ICOS+ cTFH cells T-fH IgG2 causes the maturation of IgM antibodies.	No Bias
Ocampo et al.,2016 (52)	United States	PPSV23 uptake in HIV+	Cross-sectional study	>18	507:497M	>200	<50	on ART 6 years	Uptake of PPSV23	Uptake of PPV23 approached 90% in the current era, among the highest reported	PCV13 + after first PPSV23 dose 8 WKs	No Bias
RH Pedersenet al.,2011 (71)	Switzerland	PPSV23 Effectiveness Systematic Review	Systematic review	>18	16 Studies	>200	<50	on	Systematic review in adults PLWH	No differences in exposed and unexposed individuals.	Effectiveness of PPVS23 + No reduction of IPD in PLWH	No Bias
Rodriguez-Barradas et al., 2015 (82)	United States	CD4 200+PPSV23+ART	RCT Placebo+ controls 0,6,9,12 months	18-55	107: 103M	>200	<50	on ART 6 months	ELISA + IgG-GMC and Serotypes 1, 3, 4, 6B, and 23F. OPA IgG/IgM (GMT)+ serotypes 6B and 23)	ELISA Pre-vaccination had negligible to IgM,2-fold OPA titers to serotype 6B but not to 23F, no difference in IgM or IgG levels or OPA titers. Combine IgG and OPA titers to 23F but not to 6B in CD4, HVL, and IgG responses.	CD4 200 cells/mm3+ no ART OR CD4 200, delaying PPSV23 until 6 months of ART does not improve responses	overrepresented Males
Siemieniuk et al., 2011 (52)	Canada	PPSV23 +I`PD	Cohort study	18-61	1949: 1528 M:418	>200	<50	on ART	Culture Blood, peritoneum, pleura, or cerebrospinal fluid (CSF); sputum	Low IPD 30 days post PPSV23 (189 vs. 720 per 100,000 person-years, P < 0.0001) and for all serotypes CD4 counts were similar in the case group (mean: 430 cells/mm, SD: 190) and the control group (mean: 472 cells/mm3, SD: 230 Hospitalisation 64 (70%) vs 44 (80%) cases of IPD. The median stays 1-71 days.	IPD +ART and remain high post-pneumococcal vaccination At risk female, age >60, nadir CD4 <200 cells/mm3, CPD +Hepatitis C	No Bias
Tsachouridou et al., 2015 (62)	Greece	PPSV23 naïve +ART+CD4	RCT 0,4,48 WK, PPSV23 WK4 naïve vs ART	18-43	66	200	50	on ART 6Months	ELISA to quantify IgG, me B and M cells	ART +PCVs+PPSV23 from 8.25 to 8.49 vs 7.64 compared to 6.62 to 6.26 in 4 weeks and 5.92 after 48 weeks,	B cells and MeB cells are not predictors of poor PCV responses in PLWH	No Bias
Vivancos-Gallego et al., 2019 (70)	Spain	IPD case vs non-IPD controls	Case-control study	>18	254	Not reported	not reported	NA	NA	Pneumococcal vaccine PV was not associated with CPI (HR 0.65, 95% CI 0.351.32 P0.250). No evidence of protection against CPI, in 2 doses (HR 0.42 95% CI 0.151.19 P0.102).	Hazard ratio of Pneumococcal vaccination + CPI is Unable to rule out	No Bias

Winckelmann et al.,2013 (81)	United States	TLR-9+, 1mg CPG 7909+ HIV+.	RCT 1:1 placebo+ controls Day 0,3, 9 months	18-65	97:21	<200	>50	on ART 6 months	ELISA+ IgG+ T Cell MOPA	TLR9-PCVs decreased proviral load. Reductions+ rise CD8.	TLR9-PCVs decreased proviral load. Reductions+ rise CD8.	Sex Bias Against Males
X.Zou, J. He, J. Zheng et al.,2022 (94)	China	IgG level+ PPSV23 1year	Case-control study	18-60	120: 81M	318-730	<50	on ART	ELISA+ IgG (19F, 23F, 19A,6B, 14, 9 V IgG levels for 6 serotypes (19F, 23F, 19A, IgG SCR 4-fold Rise	The Effectiveness was 81.79% 4-fold rise in six serotypes studied (19F, 23F, 19A, 6B, 14 and 9 V) at 12Months. 52.17% (24/46) had 6 IgG of the six serotypes PPSV23 was well tolerated, and no adverse reaction was reported	PPSV23 can be safely administered to prevent Streptococcal pneumonia	Selection Bias

Legend; Not Shaded: Shows Selected Studies from HIC (n=28); **Light Green**: Illustrates Selected Studies Conducted in LUMIC n=2); **Grey**: Indicates study conducted in Healthy individuals, TB and HIV (n=1)

Table C: Selected studies observed on PPSV23 or PCV Carriage (n=8)

Lead author & Year	Country	Vaccine and Period	Study design	Age	N	CD4 cells/mm3	HVL (copies/ml	ART	Assay type	Overall Results	Key outcomes+ Summary	Any type of bias
Kobayashi et al., 2020(65)	Kenya	PCV10 + Carriage	Cross section	18-49	2028	Not reported	Not reported	Not reported	Nasopharyngeal culture and sensitivity	PCV10-type carriage decreased from 12.9% to 2.8% (HIV+) VS 11.8% to 0.7% (HIV-).	PCV10-type carriage declined in adults post-PCV10	No Bias
Johanneson et al., 2012 (82)	Denmark	B-cell+ PCV7 Naïve + not treated PLWH	RCT	41-70	97: 80 males	>200	<50	on ART 3-8 years	Flowcytometry, ELISA, and OPA to measure IgG level	ART responders had isotype-switched memory B cells. ART-naive had transitional B cells and plasmablasts compared with B cells. MZ isotype-switched memory B Cells+Plasmablasts increased at 3, 4, and 9 months.	Low Meb, B-cells (IgM+ plasmablasts) are not a predictor of poor PCV response. B-cell + poor vaccine response	Sex Bias Against Males
Lamas et al.,2017 (50)	Brazil	CAP + On ART+ no pneumococcal vaccines	Cross-sectional study	>18	2669	<200	<400	on ART 60 Days	Nasopharyngeal and sputum culture	Rise in CD4 counts (cHR 0.81, p < 0.001, per 100 cells/mm3 increase), aHR for CD4 count was 0.86, for HVL <400 copies, 2.20.	LRTI rise +ART. Higher CD4 +HVL +IPD protection	High
Dayie 2019 (60)	Ghana	Carriage + Prevalence+ Serotypes	Cross-sectional study	18-74	147: 40M:58F	Not reported	Not reported	on ART	Nasopharyngeal specimen culture, drug sensitivity	Carriage 7.3% (95% CI: 4% to 11.9%) 5-10 vs 51 years). SPn drug resistance 18.5% (5/27), Prevalent serotypes were 19A and 23F	3-fold rise carriage in adults PLWH + non-vaccine serotypes+ multidrug resistance	No Bias
Heinsbroek et al., 2015 (67)	Malawi	Carriage +ART	Cohort study	18-52	363	86-635	>10000	on ART 6 months	Culture, latex agglutination and serotyped by the Quellung reaction	High Carriage +ART Carriage of non-PCV13 serotypes.	High Carriage +ART Carriage of non-PCV13 serotypes.	No Bias
Carrim. Stefano Tempia et al., 2023 (13)	South Africa	Carriage+ PCV in HIV+	Cohort study	18-45	1684:184 M:1500F	<200	Not reported	Not reported	HIV, LytA-RT-PCR and Markov model to measure colonisation	98% SPn carriage	PLWH had a higher pneumococcal load	No Bias
Laila N.Abdulai 2019, Sonia Fernandez et al.,2019 (48)	Australia	IgG2 +PPSV23, IL-7R and TFH	RCT	>18	45	>200	50	ART	, ELISA (IgGI&2)	High IgG2 antibodies to serotypes 4, 6B, 9V, and 14 vs Low IgG1+ IL-7 by cTFH cells affects the production of IgG2 antibodies to PPSV23 in PLWH	IgG2 PPSV23 may be associated with IL-7RI signalling in ICOS+ cTFH cells T-fH IgG2 causes the maturation of IgM antibodies.	No Bias
Hung et al., 2010 (73)	Taiwan	Long term antibody+ serotypes 14, 19F and 23F ART	RCT	18-71	169 Men	<100	<400	on ART	ELISA measure GMC titre and Serotype	Faster loss of antibody responses was observed in HIV+, still an unknown duration Suppresses had CD4 counts >100cells/mm3 had better HVL in 5 years	CD4 cell counts in HAART-treated patients with PPSV23 declined significantly over the 5 years in those with CD4 counts < 100 cells/mm3.	Small sample size

Legend

Not Shaded: Shows Selected Studies or guidelines from HIC (n=3); **Light Green highlight**: Illustrates Selected Studies or guidelines Conducted in LUMIC n=5)

Table D: Selected Studies on PPSV23 or PCV Carriage (n=5)

Lead author & Year	Country	Vaccine and Period	Study design	Age	Sample Size	CD4 cells/mm3	HVL (copies/ml	ART	Assay type	Overall Results	Key outcomes+ Summary	Any type of bias
Kobayashi et al., 2020	Kenya	PCV10 + Carriage	Cross section	18-49	2028	Not reported	Not reported	Not reported	Nasopharyngeal culture and sensitivity	PCV10-type carriage decreased from 12.9% to 2.8% (HIV+) VS 11.8% to 0.7% (HIV-).	PCV10-type carriage declined in adults post-PCV10	No Bias
Lamas et al.,2017 (50)	Brazil	CAP + On ART+ no pneumococcal vaccines	Cross-sectional study	>18	2669	<200	<400	on ART 60 Days	Nasopharyngeal and sputum culture	Rise in CD4 counts (cHR 0.81, p < 0.001, per 100 cells/mm3 increase), aHR for CD4 count was 0.86, for HVL <400 copies, 2.20.	LRTI rise +ART. Higher CD4 +HVL +IPD protection	High

Dayie 2019 (60)	Ghana	Carriage + Prevalence+ Serotypes	Cross-sectional study	18-74	147: 40M:58F	Not reported	Not reported	on ART	Nasopharyngeal specimen culture, drug sensitivity	Carriage 7.3% (95% CI: 4% to 11.9%) 5-10 vs 51 years). SPn drug resistance 18.5% (5/27), Prevalent serotypes were 19A and 23F	3-fold rise carriage in adults PLWH + non-vaccine serotypes+ multidrug resistance	No Bias
Heinsbroek et al., 2015 (67)	Malawi	Carriage +ART	Cohort study	18-52	363	86-635	>10000	on ART 6 months	Culture, latex agglutination, and serotyped by the Quellung reaction	High Carriage +ART Carriage of non-PCV13 serotypes.	High Carriage +ART Carriage of non-PCV13 serotypes.	No Bias
Carrim. Stefano Tempia et al., 2023 (13)	South Africa	Carriage+ PCV in HIV+	Cohort study	18-45	1684:184 M:1500F	<200	Not reported	Not reported	HIV, LytA-RT-PCR, and Markov model to measure colonisation	98% SPn carriage	PLWH had a higher pneumococcal load	No Bias

Legend

Light Green highlight: Illustrates Selected Studies in LUMIC n=5)

Table 4E: Expert Review or Guideline, Compliance, and Perception to Pneumococcal Vaccination (n-8)

Lead author &Year	Country	Vaccine and Period	Study design	Age	Sample Size	CD4 cells/mm^3	HVL (copies/ml)	ART	Assay type	Overall Results	Key outcomes+ Summary	Any type of bias
Kobayashi et al., 2023 (15)	United States	Combined PCV15 OR PCV20 + PPSV23	Expert review in adults CDC	>19				Not Reported	Guideline	PCV15 + PPSV23 in 65 years 19-64 y not received PCV should receive single dose of PCV20 or 1 PPSV23	CDC PCV15 or PCV20+PPSV23, but have not received any PCV dose. PCV7+ HSCT	No Bias
Lu et al.,2012 (97)	Taiwan	Combined PCV13+ PPV23	Expert review	>18	Not Reported	Not reported	Not reported	Not reported	Improve immunogenicity among HIV-infected adult patients.	V. Efficacy 74% (95% confidence interval, 30 to 90), reduced to 85% to 25% thereafter, 1 year. CD4 count <200 cells/mm3 had 7.1-fold recurrent IPD vs >500 cells/mm3. Antibody cut-off 0.35 µg/ml or 1 µg/ml.	PCV13 +PPSV23 in 8 weeks when CD4>200Cells and 19-64 y after 5y the first dose of PPSV23 with no more than 3 lifetime doses	No Bias
Grant et al.,2021 (49)	United States	Expert review US, UK, Germany, Australia, Canada, France, Italy, Japan, Spain	Expert review	>18					Recommended for 18 high-risk medical conditions	Cochlear implant, Intracranial shunts Sickle cell disease/other hemoglobinopathy Congenital or acquired asplenia or splenic dysfunction Congenital or acquired immunodeficiencies Immunocompromising therapies, HIV infection, HSCT recipient, Malignant neoplasms, including leukemia and lymphoma (e.g. Hodgkin disease), Disseminated neoplasms, Nephrotic syndrome, Solid organ or islet transplant, Chronic renal/adrenal failure, Phagocytic disorders (excluding chronic granulomatous disease) Multiple myeloma, Complement disorder, systemic steroids treatment, Chronic inflammatory diseases, Deficiency or dysfunction of myeloid cells, properdin deficiencies, neoplastic diseases; autoimmune disease	PCV use in immunocompromising conditions	No Bias
Patricia L Hibberd, MD, PhD (84)	United States	Expert review in PLWH	Expert Review	>18	Not Reported	>200	HVL		Guideline	PCV13 vaccination is a priming dose followed by PPSV23 after 8 weeks. CD4 count should be >200 cells/ml	PCVs as a prime dose and 8 weeks with PPSV23 CD4<200+ART	No Bias
Feldman et al.,2022 (19)	South Africa	Overview of pneumococcal vaccine in adults	Expert review	>18		Regardless of CD4 count	HVL <1,000 copies/ml		Recommendations	Cost of PCV13 is R912/R R46.80, and PPSV23 is 198.70/46.80. Efficacy of 0.5 ml PCV13 is>75%, while PPSV23 is 60-70% in IPD. For immunocompromised individuals with HIV, administer the PCV13 priming dose followed by PPSV23 after more than 8 weeks. An additional dose is required after 5 years.	PCV13 priming dose and PPSV23 after >8 weeks after 5 years regardless of CD4 count and HVL <1,000 copies/ml In >65 y PPSV23 effectiveness 80% versus PCV13 75% for	No Bias

											IPD PCV15/20 is licensed	
Pallotta et al.,2016 (80)	United States	N/R	Expert review	>18	Not Reported				Expert review	>PCV13 first, followed by PPSV23 8 weeks later. PPSV23 receiver can re-vaccinate with PCV13+ 1 year Immunocompromised without a spleen, CSF leaks, cochlear implants, and receive only PPSV23 < 65 years	>PCV13 first, followed by PPSV23 8 weeks later. PPSV23 receiver can re-vaccinate with PCV13+ 1 year. Immunocompromised without a spleen, CSF leaks, cochlear implants, receive only PPSV23 < 65 years	Small sample size
Mills et al.,2019 (96)	United States	Perceptions and recommendations	Cross-sectional study	>18	142			On ART	Assess perceptions and recommendations.	Both participant groups reported "family doctor" as the most trusted source,	Acceptance and completion are similar to persons without HIV	No Bias
Irene Cavada Carranza. et al., 2022 (69)	Spain	Compliance in MSM	Cross-sectional study	>18	127:100 M	>200	<50	Not reported	Vaccination coverage and compliance	Complete vaccination coverage was observed in 11 patients (8.7%). Only)	Low adherence and compliance with Pneumococcal vaccines in PLWH	No Bias

Legend: Light Green highlight: Illustrates Selected guidelines Conducted in LUMIC n=5, Studies n=3)

Annex 4: List of Supplemental Figures and Tables

Chapter One

List of Key Descriptions of Study Ideas or Terminologies

Correlate of protection (CoP)

CoPs are immune markers shown by serotype-specific IgG and T cells immunity levels or functional immune responses that protect against invasive pneumococcal disease (IPD) (1,2). The pneumococcal vaccines include a quantity of vaccine-induced antibody titers measured in geometric mean concentration ≥0.35 μg/mL is referred to as non-mechanistic CoP, and has been associated with reduced risk of IPD and nasopharyngeal carriage (2–5). Mechanistic CoP type is a functional antibody activity that reflects the ability of antibodies to promote phagocytosis and killing or clearance of bacteria (2–5).

Surrogates of Protection (SoP)

The surrogate of protection is an immune response that substitutes clinical endpoints for the true immunologic correlate of protection (1,6). They may be unknown or not easily measurable, or an indirect measure that can predict the level of protection a vaccine provides against the target disease. Pneumococcal vaccine surrogates can be described based on a measured immune response to an individual population, which is known as specific surrogates or population-based surrogates are called general surrogates (1,6). Hence, **surrogates or a non-mechanistic of protection come in** to indirectly assess vaccine efficacy and predict their ability to prevent IPD (1,6). These surrogates provide more efficient and cost-effective alternatives for vaccine evaluation, especially during the development and licensure stages.

Pneumococcal Vaccine Efficacy (VE)

VE is the proportion by which the prevalence of pneumococcal diseases is at a low level of infection rate among vaccinated individuals compared to unvaccinated individuals. OR the percentage by which the risk of an IPD or its severity is reduced in vaccinated compared to unvaccinated individuals under ideal conditions or similar exposure in

clinical randomised trials (1). Efficacy is mostly predicted by CoPs and varies by vaccine type, population and tends to wane with duration (1).

Vaccine effectiveness

Measures how well a vaccine works in the general population or real-world conditions to protect people against a disease (1). **They are evaluated in cohort and case-control studies,** expressed as a percentage of an infection reduction rate (1). A higher percentage indicates a greater protection or is not susceptible to IPD and hospitalisation, the offered by vaccination with PCV or PPSV23. Vaccine effectiveness is mostly affected by vaccination coverage, circulating strain, time of vaccination, target population and vaccine type (1).

Immunogenicity

The ability of the body to induce pneumococcal antibodies, like and/ or cell-mediated immunity, after vaccination (1,7). By measuring antibody titres, how binding and killing or clearing a specific serotype occurs, is a common method to assess immunogenicity, T-cells, and memory B-cells (1,7).

T-cell dependent

The immune response induced by all forms of PCVs in a conjugated bacterial polysaccharide to a carrier protein enhances immunogenicity (8). Following pneumococcal vaccination, dendritic cells present the polysaccharide antigens to CD4+ T helper cells, activating B-cells (8). This step gives an improved memory B-cell formation, affinity maturation, and isotype switching, resulting in high levels of IgG antibodies specific to the SPn serotypes. IgG immunological memory in prolonged protection and potentially decreases the frequency of required vaccinations (8). Their dependence on T-cells enables a more effective immune response, particularly in young children with developing immune systems.

T-cell independent

Immune response primarily occurs with protein-polysaccharide vaccines on the outer capsule of different pneumococcal serotypes. They activate B-cells directly through

extensive cross-linking of B-cell receptors, leading to a rapid production of antibodies, IgM type, but with limited class switching and memory formation. This results in a weaker and shorter-lived immune response, lacking the involvement of T helper cells. This group includes PPSV23 covering wider serotypes, despite a less effective in young children and individuals with weakened immune systems, as their T-cell function might be impaired (8–10).

Invasive Pneumococcal Disease

Invasive pneumococcal disease (IPD) is a serious infection caused by the bacterium *Streptococcus pneumoniae* when it spreads from the respiratory tract to the bloodstream, brain, or spinal cord (9). The severe forms include pneumococcal sepsis, meningitis, severe pneumonia, as well as otitis media, and joint and bone infection (9). IPD can be life-threatening, especially for young children, older adults, and people with weakened immune systems, like chronic health conditions, such as HIV, diabetes, heart disease, or lung disease

Community-acquired pneumonia (CAP)

An infection of the lungs that occurs outside the hospital or healthcare setting with complications like respiratory failure and even death (9). SPn is the most frequent bacterium that causes infection (9). CAP is a common and potentially serious illness, especially for young children, older adults, and people with weakened immune systems (9). The clinical symptoms include cough (often productive of mucus), fever, chills, shortness of breath, chest pain, fatigue, headache, and muscle aches. CAP can be prevented by vaccination against pneumococcus.

Enzyme-linked Immunosorbent Assay (ELISA)

ELISA is an enzymatic test more sensitive and specific assay to quantify specific molecules, such as proteins, pneumococcal serotype IgG, or antigens, in a serum sample. In a microplate, a detection antibody is added to bind to the captured target after the specimen is introduced (11). The enzyme reacts with a substrate, producing a coloured or

fluorescent signal (11). The intensity of the signal is measured and is proportional to the amount of the target molecule present in the sample (11).

Opsonophagocytic or Multiplex Killing Assays (OPA/MOPA)

Mechanistic CoP type, also known as the opsonophagocytic assay/multiplexed opsonophagocytic assay, is a gold standard test used to assess the in vivo functional ability of antibodies to opsonise (coat) and kill bacteria (11–13). It is primarily used in vaccine research and development to evaluate the vaccine efficacy and effectiveness against encapsulated bacteria, such as *Streptococcus pneumoniae* (pneumococcus) (11). However, multiplex can test multiple SPn serotypes in a single tube compared to OPA (11).

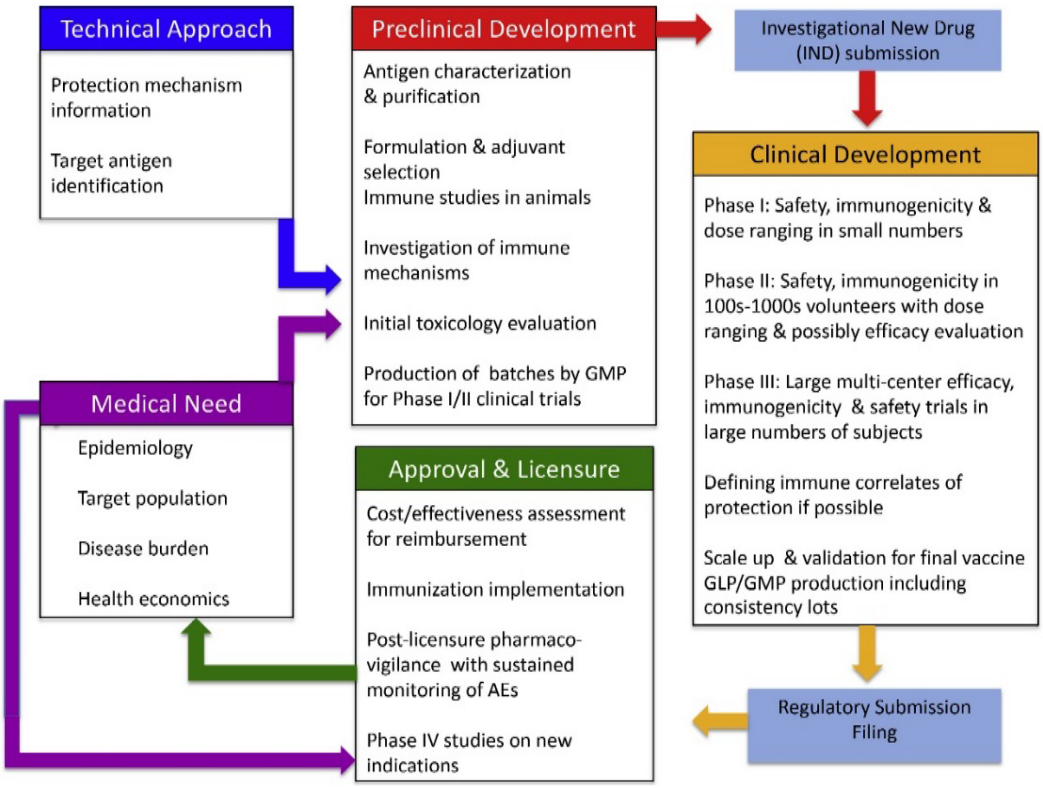
Geometric Mean Titres

The Geometric Mean titer defines a **mechanistic CoP type** to the average level of antibodies in a population that received the vaccine against specific serotypes of SPn (pneumococcus) (11). Antibody levels are measured by OPA/MOPA after vaccination to show efficacy for pneumococcal vaccines and specific serotypes. Also, it is calculated by the transformation of reading into logarithms, which helps normalise the distribution and reduces the impact of outliers (11). The geometric mean titer sis calculated by taking the anti-log of the average of the log-transformed antibody levels, shown in ug/ml or >1/8, which implies protection or opsonic index in MOPA (4,11).

Geometric Mean Concentration

Described as a non-mechanistic surrogate marker, reflects an average level of pneumococcal serotype IgG antibodies that can bind to a specific pneumococcal serotype in a population after vaccination (4,11). It helps understand the proportion of individuals with sufficient binding antibodies of IgG type against specific serotypes, mainly measured by ELISA, which typically quantifies antibody binding units per volume (e.g., 0.35µg/mL indicates protection) (4,11). Higher geometric mean concentration values indicate a stronger humoral immune response, meaning more individuals have sufficient antibodies to potentially bind to the bacteria (4,11).

CHAPTER ONE: List of Supplemental Figure 1



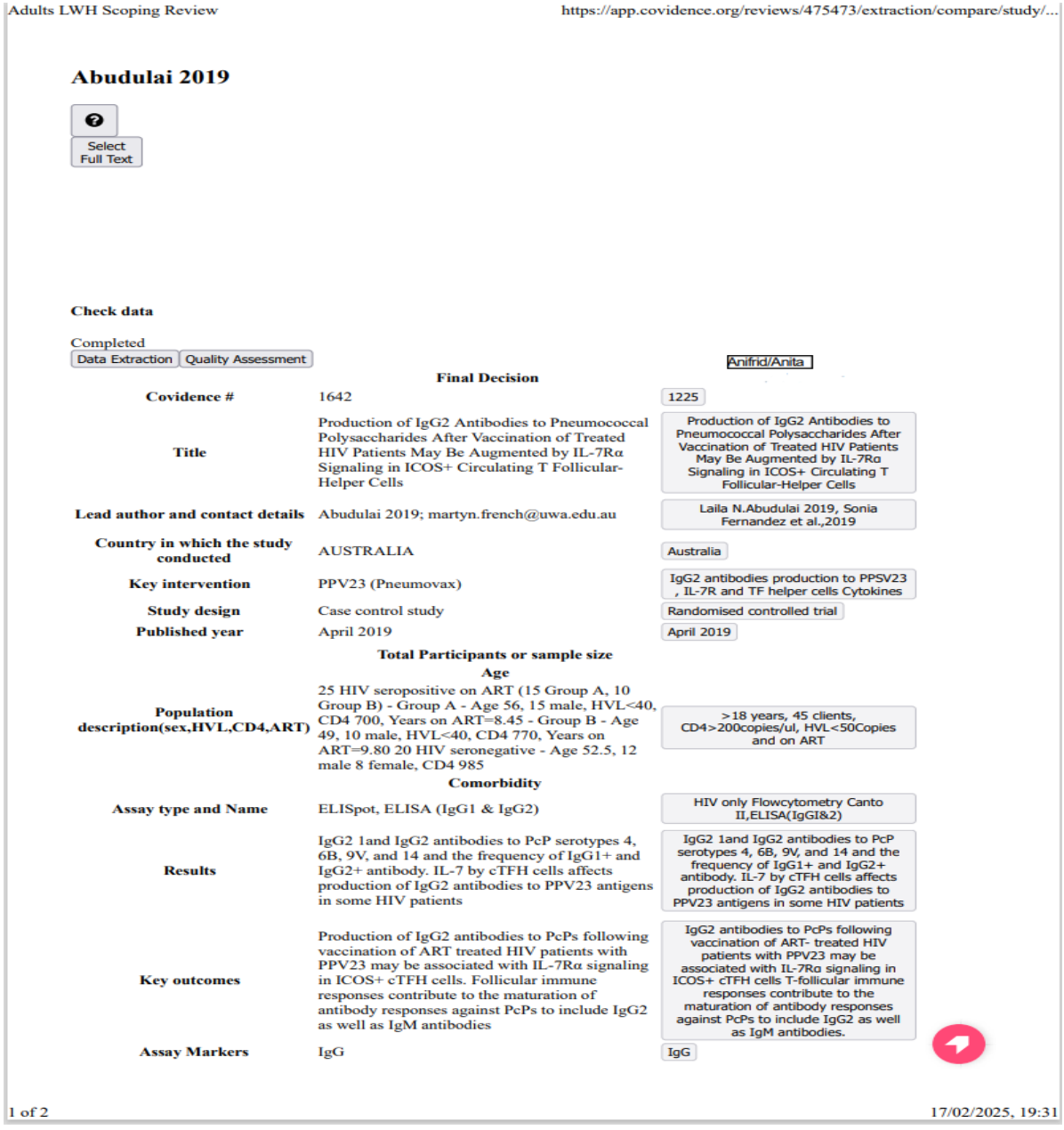
Supplemental Figure 1: Steps on the Establishment of CoP for Novel Vaccines in Adult PLWH

Source: Peter L. Stern, 2020

Supplemental Figure 1: Illustrates key steps in the preclinical, clinical, and post-licensure phases can take a considerable time (10-30 years). The process integrates the requirements to ensure safety, immunogenicity, and efficacy.

CHAPTER THREE

Supplemental Figure 2: Overview of Data Extraction Tool in Covidence Software



Adults LWH Scoping Review https://app.covidence.org/reviews/475473/extraction/compare/study/...

Abudulai 2019

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Data Extraction | Quality Assessment

	Final Decision	Anifrid/Anita
Covidence #	1642	1225
Title	Production of IgG2 Antibodies to Pneumococcal Polysaccharides After Vaccination of Treated HIV Patients May Be Augmented by IL-7Rα Signaling in ICOS+ Circulating T Follicular-Helper Cells	Production of IgG2 Antibodies to Pneumococcal Polysaccharides After Vaccination of Treated HIV Patients May Be Augmented by IL-7Rα Signaling in ICOS+ Circulating T Follicular-Helper Cells
Lead author and contact details	Abudulai 2019; martyn.french@uwa.edu.au	Laila N.Abudulai 2019, Sonia Fernandez et al.,2019
Country in which the study conducted	AUSTRALIA	Australia
Key intervention	PPV23 (Pneumovax)	IgG2 antibodies production to PPSV23 , IL-7R and TF helper cells Cytokines
Study design	Case control study	Randomised controlled trial
Published year	April 2019	April 2019
	Total Participants or sample size	
	Age	
Population description(sex,HVL,CD4,ART)	25 HIV seropositive on ART (15 Group A, 10 Group B) - Group A - Age 56, 15 male, HVL<40, CD4 700, Years on ART=8.45 - Group B - Age 49, 10 male, HVL<40, CD4 770, Years on ART=9.80 20 HIV seronegative - Age 52.5, 12 male 8 female, CD4 985	>18 years, 45 clients, CD4>200copies/ul, HVL<50Copies and on ART
	Comorbidity	
Assay type and Name	ELISpot, ELISA (IgG1 & IgG2)	HIV only Flowcytometry Canto II,ELISA(IgGI&2)
Results	IgG2 1and IgG2 antibodies to PcP serotypes 4, 6B, 9V, and 14 and the frequency of IgG1+ and IgG2+ antibody. IL-7 by cTFH cells affects production of IgG2 antibodies to PPV23 antigens in some HIV patients	IgG2 1and IgG2 antibodies to PcP serotypes 4, 6B, 9V, and 14 and the frequency of IgG1+ and IgG2+ antibody. IL-7 by cTFH cells affects production of IgG2 antibodies to PPV23 antigens in some HIV patients
Key outcomes	Production of IgG2 antibodies to PcPs following vaccination of ART treated HIV patients with PPV23 may be associated with IL-7Rα signaling in ICOS+ cTFH cells. Follicular immune responses contribute to the maturation of antibody responses against PcPs to include IgG2 as well as IgM antibodies	IgG2 antibodies to PcPs following vaccination of ART- treated HIV patients with PPV23 may be associated with IL-7Rα signaling in ICOS+ cTFH cells T-follicular immune responses contribute to the maturation of antibody responses against PcPs to include IgG2 as well as IgM antibodies.
Assay Markers	IgG	IgG

1 of 2 17/02/2025, 19:31

Supplemental Table 1: Search Strategy in Five Databases

Searched Library via WITS library https://libguides.wits.ac.za/whsl-eresources	
Database	Searched Link
1. Cochrane Library	https://www.cochranelibrary.com/advanced-search/search-manager
2. Scopus	https://www.scopus.com/results/results.uri?sort=plf-f&src=s&sid=7c0b52aec08be1d9b6242f004de78735&sot=a&sdt=b&cluster=scosubjabbr%2C%22MEDI%22%2Ct%2C%22IMMU%22%2Ct%2C%22PHAR%22%2Ct&sl=197&s=ALL%28adults+OR+hiv%2B+OR+pregnant+OR+mothers+AND+pneumococcal+OR+vaccines+OR+pcv7+OR+pcv10+OR+pcv13+OR+pcv15+OR+pcv20+OR+pcv21+OR+ppsv23+AND+correlates+OR+protections+OR+efficacy+OR+effectiveness+OR+immunogenicity+AND+pneumococcal+OR+carriages+AND+opsonophagocytic+OR+killing+OR+assays+OR+multiplex+OR+opsonophagocytic+OR+killing+OR+assays+OR+anti-pneumococcal+OR+immunoglobulins+OR+antibodies+AND+comorbidities%29&origin=searchbasic&editSaveSearch=&txGid=eabd4e5b887b66130de213d238b67551&sessionSearchId=7c0b52aec08be1d9b6242f004de78735&limit=200&yearFrom=2010&yearTo=2024
3. PubMed	https://pubmed.ncbi.nlm.nih.gov/?term=%28%28%28%28%28%28%28%28%28%28%28%28%28%28Adults%29+OR+%28%3E8+years%29%29+AND+%28HIV%29%29+AND+%28Pregnant+Mothers%29%29+AND+%28Pneumococcal+vaccines%29%29+AND+%28PCV7%29+OR+%28PCV10%29%29+OR+%28PCV13%29%29+OR+%28PCV15%29%29+OR+%28PCV20%29+OR+%28PCV21%29%29+OR+%28PCV24%29%29+OR+%28PCV31%29%29+OR+%28PPSV23%29%29+OR+%28PPV23%29%29+OR+%28Correlates+of+Protections%29%29+OR+%28Efficacy%29%29%29+OR+%28Effectiveness%29%29+OR+%28Immunogenicity%29%29+AND+%28Pneumococcal+carriages%29%29+OR+%28Anti-pneumococcal%29%29+OR+%28Opsonophagocytic+killing+assays%29%29+OR+%28Multiplexed+Opsonophagocytic+Assays%29%29+OR+%28Commorbidities%29%29&filter=dates.2010%2F1%2F1-2024%2F2%2F1&filter=hum_ani.humans&filter=sex.female&filter=sex.male&size=580
4. Global health library	https://0-web-p-ebscohost-com.innopac.wits.ac.za/ehost/results?vid=28&sid=26f2f78e-622d-4c5b-b629-2b2ab017a7b5%40redis
5. Science Direct/Embase	https://0-www-sciencedirect-com.innopac.wits.ac.za/search?date=2010-2024&qs=pneumococcal%20vaccines%20correlates%20of%20protection%20efficacy%20immunogenicity%20and%20adult%20with%20hiv
6. Science Direct/Embase	https://0-www-sciencedirect-com.innopac.wits.ac.za/search?date=2010-2024&qs=pneumococcal%20vaccines%20correlates%20of%20protection%20efficacy%20immunogenicity%20and%20adult%20with%20hiv

Supplemental Table 2: Gnat Chart Indicates Study Timeline

Task Name	Duration	Start	End
Literature review and Study title approval	20 days	30 June 23	27 July 2023
Protocol development			
Prepare Draft 1	15 days	28 July 2023	17 August 2023
Submit Draft 1 to the supervisor	0 day	17 August 2023	17 August 2023
Update protocol draft 1	16 days	18 August 2023	08 September 2023
Submit draft 2	0 day	08 September 2023	08 September 2023
Update draft 2	6 days	08 September 2023	15 September 2023
Internal Submission to WITS-ALIVE	0 day	15 September 2023	15 September 2023
Review by WITS-ALIVE	7 days	15 September 2023	25 September 2023
Protocol Presentation to WITS-ALIVE	2 days	26 September 2023	27 September 2023
Update protocol with comments from WITS_ALIVE	6 days	28 September 2023	05 October 2023
Post-grad committee review			
Submit to the Postgraduate (PG)committee	0 day	04 October 2023	04 October 2023
PG committee review	15 days	06 October 2023	26 October 2023
PG committee meeting	1 day	29 November 2023	29 November 2023
Updated protocol submitted to PG for comments	110 days	30 November 2023	22 March 2024
Final approval received from the PG office	0 day	17 April 2024	17 April 2024
Ethics			
Preparation of the Health Research Ethics Committee (HREC) application	16 days	18 April 2024	04 May 2024
Submission to HREC	0 day	05 May 2024	05 May 2024
HREC review	60 days	06 May 2024	29 May 2024
Responses received from HREC	0 day	22 May 2024	22 May 2024
Preparation of response to HREC	3 days	22 May 2024	25 July 2024
Submission of responses to HREC	0 day	25 May 2024	25 May 2024
Review by HREC	3 days	28 May 2024	28 May 2024
Final HREC approval date	0 day	29 May 2024	29 May 2024
Report preparation			
Literature review	30 days	15 January 2024	23 February 2024
Submission of Lit review draft 1 to the supervisor	0 day	23 February 2024	23 February 2024
A literature review by supervisors	17 days	23 February 2024	18 March 2024
Methods section	60 days	23 February 2024	22 April /2024
Submit revised lit review & methods to supervisor	0 day	22 April 2024	22 April 2024
Shell table planning	42 days	23 April 2024	17 June 2024
Submit shell tables to the supervisor	0 day	17 June 2024	17 June 2024
Analysis	39 days	18 June 2024	25 July 2024
Results section	20 days	26 July 2024	16 Aug 2024
Submit draft results to supervisor	0 day	16 Aug 2024	16 Aug 2024
Supervisor review	7 days	17 Aug 2024	25Aug 2024
Results revision, discussion	15 days	26 Aug 2024	11 Sept 2024
Project Report Presentation	1 day	19 Aug 2024	19 Aug 2024
Update comments from the Presentation	7 days	20 Aug 2024	27 Aug 2024
Submit a complete draft to the supervisor	0 day	26 Sept 2024	26 Sept 2024
Supervisor review	100 days	27 Sept 2024	15 Jan 2025
Revise draft	30 days	16 Jan 2025	15 Feb 2025
Submit the final draft to the supervisors	0 day	18 Feb 2025	18 Feb 2025
Supervisor review	20 days	18 Feb 2025	16 March 2025
Revision and Resubmission	13 days	17 March 2025	30 March 2025
Final report submitted to the Faculty of Health Sciences	0 day	31 Feb 2025	31 March 2025

(PG)			
Feedback from the Faculty of Health Sciences (PG)	0 day	07 Oct 2025	07 Oct 2025
Work on the examiner's comments	21 days	08 October 2025	29 October 2025
Submit the examiner's responses to the supervisors	0 day	29 October 2025	29 October 2025
Revision and Resubmission	4 Days	09 November 2025	13 November 2025
Final report submitted to the Faculty of Health Sciences (PG)	0 day	14 November 2025	14 November 2025

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