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An Analysis of Circulating Invasive Pneumococcal Disease Serotypes in South Africa and the Potential of New and Existing Pneumococcal Vaccines to Prevent Disease and Death, 2012–2021

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AN ANALYSIS OF CIRCULATING INVASIVE PNEUMOCOCCAL DISEASE SEROTYPES IN SOUTH AFRICA AND THE POTENTIAL OF NEW AND EXISTING PNEUMOCOCCAL VACCINES TO PREVENT DISEASE AND DEATH, 2012 - 2021.

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the Degree of Master of Medicine in Public Health Medicine.

Johannesburg, April 2024.

DECLARATION

I, Sayuri Pillay, declare that this Research Report is my own, unaided work.

It is being submitted for the Degree of Master of Medicine in Public Health Medicine at the University of the Witwatersrand, Johannesburg.

It has not been submitted before for any degree or examination at any other University.



(Signature of Candidate)

____5th_____day of____February_____20___25_____in___Johannesburg____

DEDICATION

This work is dedicated to:

My parents, Kavita and Suran Pillay, for their unwavering love, their incredible patience and for taking care of everything so I could focus on finishing my writing. I could not have done this without you, and I will be forever grateful for all you've both done for me.

My brothers, Sayen and Yuvin Pillay, for being a source of strength, inspiration, and a good number of laughs to help me balance out the writing process. Thank you so much!

My friends, too many to name, but all who played a significant role in keeping me sane and keeping me going.

PRESENTATIONS ARISING FROM THIS RESEARCH PROJECT

This work was presented in the form of a poster at the International Society of Pneumonia and Pneumococcal Diseases (ISPPD) conference, in Cape Town, from the 17th till the 20th of March 2024.

ABSTRACT

In recent years, various new pneumococcal conjugate vaccines (PCVs) (PCV10-SII, PCV15 and PCV20) containing different serotypes entered the global market to prevent invasive pneumococcal disease (IPD). This study aimed to assess the potential of these vaccines in preventing IPD within different populations in South Africa (SA) compared to current vaccines in use (PCV13 and the 23-valent pneumococcal polysaccharide vaccine (PPSV23)). A retrospective, descriptive, secondary analysis of primary data collected by GERMS-SA between 2012-2021 was performed. IPD incidence, serotype distribution and proportions of serotypes within pneumococcal vaccines were calculated. The association between case fatality rates and IPD serotypes, age group, province, HIV status, multidrug resistance and comorbidities were calculated through logistic regression.

Between 2012 and 2021, 23 789 episodes of IPD were reported to GERMS-SA across South Africa. IPD incidence followed a decreasing trend, with an average annual incidence rate of 4.22 cases per 100 000 persons. was Absolute numbers of IPD cases were highest in persons between the ages of 25-44 years old. Common serotypes noted to cause IPD across the population were serotypes 8 (11%), 19A (8%) and 12F (8%). Across the vaccines assessed, PPSV23 (68%) contained the highest percentage of serotypes causing IPD in SA, followed by PCV20 (63%), PCV15 (40%), PCV13 (37%) and lastly, PCV10-SII (26%). PCV10-SII contained the highest proportion (> 50%) of serotypes causing penicillin and ceftriaxone antimicrobial resistance in IPD cases compared to the other vaccines. The case fatality rate across IPD cases between 2012-2021 was 32%. Children less than one years old (aOR:1.074 ; 95% CI (1.015-1.137)), adults aged 45-65 years old (aOR: 1.155; 95% CI (1.095-1.219)) and those older than 65 years (aOR: 1.208; 95% CI (1.120-1.304)), as well as people living with HIV (aOR: 1.044; 95% CI (1.013-1.076)) were all noted to have a significantly higher odds of death. Interestingly, no other comorbidities were significantly associated with higher odds of mortality when controlling for age, province, the presence of other comorbidities and risk factors.

Next-generation higher-valent PCVs contain a moderate to high proportion of IPD serotypes circulating in SA and vulnerable populations including the extremes of ages, persons with comorbidities and the immunocompromised should be continuously targeted. These findings convey important implications for future pneumococcal vaccine use and policy in SA.

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LIST OF ABBREVIATIONS

ACIP –	Advisory Committee on Immunisation Practices
CDC –	Center for Disease Control and Prevention
CFR –	Case fatality rate
EC –	Eastern Cape
EPI-SA –	Expanded Programme on Immunisation in South Africa
ESS –	Enhanced surveillance sites
FDA –	Food and Drug Administration
FS –	Free State
GP –	Gauteng
HIV –	Human Immunodeficiency Virus
IPD –	Invasive pneumococcal disease
ISPPD –	International Society of Pneumonia and Pneumococcal Diseases
KZN –	KwaZulu-Natal
LMIC –	Low-and middle-income country/countries
LP –	Limpopo
MDR –	Multidrug resistant/ce
MP –	Mpumalanga
NAGI –	National Advisory Group on Immunisations
NC –	Northern Cape
NDoH –	National Department of Health
NHLS –	National Health Laboratory Service
NHRD –	National Health Research Database
NICD –	National Institute for Communicable Diseases

NVS –	Non-vaccine serotypes
NW –	North-West
PCR –	Polymerase chain reaction
PCV –	Pneumococcal conjugate vaccine
PLWH –	People living with human immunodeficiency virus
PPSV –	Pneumococcal polysaccharide vaccine
SA –	South Africa
SII –	Serum Institute of India
S. pneumoniae –	*Streptococcus pneumoniae*
Stats SA –	Statistics South Africa
USA –	United States of America
VS –	Vaccine serotypes
WC –	Western Cape
WHO –	World Health Organisation
WITS SPH –	University of Witwatersrand School of Public Health

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DEFINITIONS

GERMS-SA –	Proper noun describing a national laboratory-based surveillance program of bacterial and fungal diseases of public health importance within the National Institute for Communicable Diseases.
Head Injury –	Head injury throughout this analysis refers to a patient with a history of a head injury, head surgery, cerebrospinal fluid leak, ventricular shunt, or cochlear implants, as per the GERMS-SA case definition (1).
Higher-valent Vaccine –	A higher-valent vaccine refers to the available pneumococcal vaccines that have a higher number of serotypes contained within compared to PCV13, namely PCV15, PCV20 and PPSV23.
Lower-valent Vaccine –	A lower-valent vaccine refers to the available pneumococcal vaccine that have a lower number of serotypes contained within compared to PCV13, namely PCV10-SII.
Multidrug Resistant/ce –	Multidrug resistance in this study refers to multidrug resistant *Streptococcus pneumoniae* which is described as *Streptococcus pneumoniae* that is resistant to three or more different antibiotic drug classes (2).
Non-Vaccine Serotypes –	For the purpose of this study, non-vaccine serotypes relates to any serotypes known to cause invasive pneumococcal disease that are not serotype 6A and not included in PPSV23 as per Figure 1. A full list of the non-vaccine serotypes (NVS) can be found in Annexure 1 – Table 4.
PCV13 Additional Serotypes –	This refers to the pneumococcal serotypes included within PCV13 that are additional over and above the

	serotypes included within PCV10-SII (Figure 1), namely serotypes 3, 4 and 18C.
PCV15 Additional Serotypes –	This refers to the pneumococcal serotypes included within PCV15 that are additional over and above the serotypes included with PCV13, namely serotypes 22F and 33F.
PCV20 Additional Serotypes –	This refers to the pneumococcal serotypes included within PCV20 that are additional over and above the serotypes included within PCV15, namely 8, 10A, 11A, 12F and 15B.
PPSV23 Additional Serotypes –	This refers to the pneumococcal serotypes included within PPSV23 that are additional over and above the serotypes included within PCV20, namely 2, 9N, 17F and 20.
Vaccine Serotype –	For the purpose of this study, vaccine serotypes relates to any serotypes known to cause invasive pneumococcal disease that are included in available pneumococcal vaccines as per Figure 1, i.e., all serotypes included within PPSV23 and serotype 6A are considered vaccine serotypes.

1. INTRODUCTION

1.1. Background

Pneumococcal disease caused by *Streptococcus pneumoniae (S. pneumoniae)* is vaccine-preventable, and yet still a major contributor towards morbidity and mortality across the globe (3–11). Presenting clinically as either non-invasive or invasive pneumococcal disease (IPD) and attributable to over 100 identifiable serotypes, it is vitally important that this disease is brought under control across the population (4,6,10–12).

The first vaccine introduced to the South African population to address this issue, was the 23-valent pneumococcal polysaccharide vaccine (PPSV23) (9). According to the adult pneumococcal vaccination guideline of 1999, the vaccine contained 23 different serotypes noted to commonly cause invasive pneumococcal disease globally and covered ≥ 85% of the circulating serotypes that caused IPD within South Africa at the time (9). However, due to its inability to illicit a strong immune response in children ≤ 2 years of age, the PPSV23 vaccine was only recommended for use in persons 2-64 years old at high risk of developing pneumococcal disease (4,9,10,12–15). This worldwide predicament along with the increasingly high rates of IPD cases within young children ≤ 2 years of age led to the development of the pneumococcal conjugate vaccine (PCV) (4,10).

In 2003, the World Health Organisation (WHO) recommended that pneumococcal conjugate vaccines (PCVs) be included into the routine public immunisation programme of all nations with a substantial infant (>50 deaths per 1000 live births) and childhood (>50 000 deaths per year) mortality, as well as in countries with a high burden of children living with human immunodeficiency virus (HIV) (5,7,16).

In South Africa, between 2003 and 2008, prior to the introduction of the PCV, the incidence of IPD in South Africa was higher in children younger than one years old compared to children 1-4 years old, i.e., 87 cases per 100 000 persons and 14 cases per 100 000 persons, respectively (16). Children living with HIV across all age groups were also noted to have a higher incidence rate and relative-risk of IPD, approximately 21-fold (< 1 year old age group) and 34-fold (1-4 year old age group) higher in children with HIV compared to children without HIV (5–7,16). Similar findings were also noted in adults and were compounded by factors such as the lack of a comprehensive antiretroviral rollout, poor socioeconomic and immunocompromised statuses, and the limited use of PPSV23 throughout the population, at the time (5–7,11,16,17).

In 2009, six years after the WHO's recommendation and after an extensive nine-valent PCV trial conducted within the country, the first commercially available seven-valent PCV was included into the national expanded programme for immunisation in South Africa (EPI-SA) (Figure 1) (5–7,11,16–19). It was scheduled as a two-dose primary vaccine at 6 and 14 weeks of age, followed by a booster dose at nine months old. In 2011, PCV13, which included six additional serotypes known to commonly cause IPD, replaced the PCV7 in the EPI-SA (Figure 1) (5–7,11,16,17,20,21).

Following the inclusion of PCVs in the EPI-SA, PCV coverage was estimated to reach a peak of 86% in children receiving the full three doses in 2019 compared to 10% in 2009, however, very few adults received a pneumococcal vaccine (either PCV or PPSV23), despite their high rates of underlying illnesses, including HIV (20,22). This was partly due to there being no government endorsed adult pneumococcal vaccination schedule in the country. In 2017, the South African pneumococcal vaccination clinician guideline attempted to rectify this by incorporating both the PCV and PPSV23 into an adult vaccination schedule, recommended for use in both the private and public sector (22). This guideline was supported by research which showed that even with the introduction of pneumococcal vaccines to the paediatric population, which decreased the incidence of IPD in children and adults through direct and indirect effects, there was still significant residual IPD in adults (5–7,11,17,20,21,23). Nevertheless, these clinician-recommended adult guidelines are still not officially recognised by the National Department of Health (NDoH) (22).

After the introduction of PCVs and PPSV23 into SA, it was still noted locally and globally through investigating the serotype distribution within IPD cases, that certain serotypes not covered by PCV13 still caused a substantial amount of pneumococcal disease within the population (6,11,13,16,20,21).

In order to address this issue, two new higher-valent vaccines, namely PCV15 and PCV20, with two and seven additional serotypes compared to PCV13, respectively, were adopted into the United States of America (USA) pneumococcal vaccination guidelines determined by the advisory committee on immunisation practices (ACIP) for use in adult populations at first, followed by children (Annexure 3 – Table 6) (12–14,24–28).

Studies which evaluated the safety, tolerability and immunogenicity of these new vaccines showed that both the PCV15 and PCV20 showed a healthy immune response across all serotypes included in the vaccines (24,25,27,28). They were also noted to be acceptable for

use in both young children and adult populations due to their high safety and tolerability profiles (24,25,27,28).

Furthermore, another PCV recently entered the market, namely the PCV10-Serum Institute of India (SII), with five common and five additional serotypes compared to PCV7 and three less serotypes compared to the current 13-valent PCV in use (Figure 1) (29–32). As of 2024, South Africa confirmed that the country would be switching out PCV13 for PCV10-SII due to the cost benefits, interchangeability of the two vaccines and the coverage PCV10-SII provides against prevalent pneumococcal serotypes affecting the population (30).

This study will aim to determine the potential coverage of the new pneumococcal conjugate vaccines (PCV10-SII, PCV15 & PCV20) in preventing IPD compared to the current vaccines (PCV13 and PPSV23) used in various risk groups. This will be done through determining the incidence of IPD cases, the circulating serotypes distribution and the proportion of IPD serotypes included within each vaccine over the last ten years in SA. The case fatality rate (CFR) per serotype and associations with various IPD attributes will also be analysed before concluding remarks and recommendations are proposed.

1.2. Literature Review

Invasive Pneumococcal Disease:

Pneumococcal diseases are caused by *Streptococcus pneumoniae,* a polysaccharide encapsulated gram-positive bacterium, and most commonly affect vulnerable populations, being the extremes of ages and persons with comorbidities or an immunocompromised status (3–6,10–12,32). It is commonly spread through direct contact with respiratory droplets of infected persons or carriers and can present as either non-invasive or invasive pneumococcal disease (3–6,10–12,32). These carriers are primarily children under five years of age, who are known to be the primary source of *S. pneumoniae* with nasopharyngeal carriage rates ranging from 27%-85%, with higher rates noted amongst children from low-and-middle income countries (LMICs) (32).

Invasive pneumococcal disease, which characteristically affects multiple organs and includes a range of diseases such as meningitis, bacteraemic pneumonia and septicaemia, is of particular concern because of the severity of disease that follows (4,10,11,13,25,30,33).

According to multiple studies, there are over 100 distinct pneumococcal serotypes that have been detected across the world, with each country developing its own profile, in terms of

common serotypes and specific subsets noted in disease cases (4,6,10–12). These findings often change over time due to various factors such as patient demographics, geographical location and changes to the healthcare system or burden of disease profile (4,6,10–12).

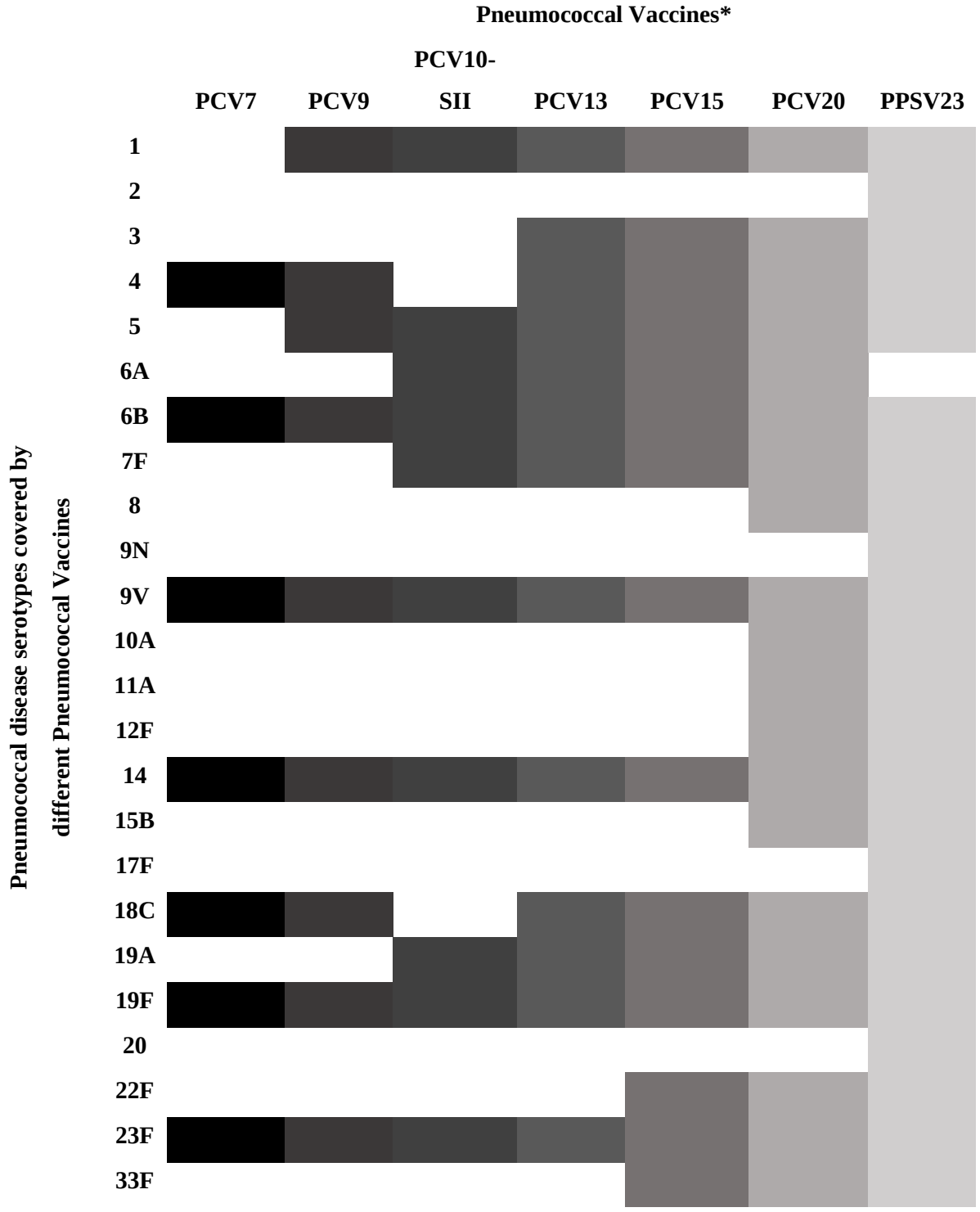
Overview of Vaccines Used Against Invasive Pneumococcal Disease:

The first vaccine designed to combat pneumococcal disease was an unconjugated polysaccharide vaccine (4,9,10,12,13,15,25). Initially, this vaccine included filtered capsular polysaccharides from 14 different serotypes that commonly caused IPD but was quickly replaced by the 23-valent unconjugated polysaccharide vaccine (PPSV23) in 1983 (10). It works through T-cell independent antigens that ultimately produce a relatively weak immune response (4,9,10,12–15). This is due to the fact that it is incapable of stimulating immune memory and is unable to prevent pneumococcal carriage or contribute to herd immunity (4,9,10,12–15). Notably, it also fails to elicit an sufficient immune response in children ≤ 2 years old, which limits its use across the population (4,9,10,12–15).

The second type of vaccine to be developed, was a pneumococcal conjugate vaccine, which is based on polysaccharides conjugated to a carrier protein and was initially developed to combat pneumococcal disease rates in the paediatric population, due to PPSV23's limitations (4,10,13,15,25). Different constitutions of the PCV were developed and underwent clinical trials, including the nine-valent PCV in South Africa, which provided substantial evidence supporting the development and use of pneumococcal conjugate vaccines to prevent IPD in children living with and without HIV (18,19).

The seven-valent PCV, however, was the first commercial conjugate vaccine to be used globally (12,13,19,24,25). Currently PCV13 is in use, with -13 referring to the number of IPD serotypes included in the vaccine itself (Figure 1) (12,13,19,24,25). This vaccine has been noted to be more effective than its predecessor (PCV7) and PPSV23 (12,13,24,25). It provides longer-lasting protection and has improved immune memory due to its composition, resulting in a strong, robust T-cell immune response (4,10,12,13,24,25). It also provides the indirect benefit of herd immunity through its ability to reduce transmission by preventing nasopharyngeal colonisation in infected individuals (4). Furthermore, it was noted that a few of the serotypes contained within the vaccine were associated with antimicrobial resistance, therefore reducing circulation of these serotypes which in turn, prevent and/or decrease antimicrobial-resistant pneumococcal disease (12,13,16,24,25).

Recently, one lower-valent (PCV10-SII) and two higher-valent PCVs (PCV15 and PCV20) have been developed. The PCV10-SII includes five serotypes (6B, 9V, 14, 19F, 23F) in common with and five additional serotypes (1, 5, 6A, 7F, 19A) compared to PCV7 and three serotypes less (3, 4, 18C) than the current PCV13 in use (29,31,32). PCV15 includes two additional serotypes (22F, 33F) compared to PCV13 and the PCV20 includes five additional serotypes (8, 10A, 11A, 12F, 15B) compared to PCV15 (Figure 1) (13,25–28).



* PCV – Pneumococcal Conjugate Vaccine; PPSV – Pneumococcal Polysaccharide Vaccine

Figure 1*:* Pneumococcal conjugate and pneumococcal polysaccharide vaccines and the serotypes included (12,13)

Invasive Pneumococcal Disease in South Africa:

In South Africa, since 2003, information on IPD has been routinely collected by GERMS-SA, which is a laboratory-based national surveillance system located at the National Institute for Communicable Diseases (NICD), an institute operating under the National Health Laboratory Service (NHLS) (16,20,23,33).

The GERMS-SA case definition for IPD is any "hospitalised individuals with laboratory confirmed *Streptococcus pneumoniae* detected from normally sterile-site specimens (e.g., cerebrospinal fluid, blood or joint fluid) detected through culture or polymerase chain reaction (PCR)." (1,20). Isolates from cases that match this definition are sent to the GERMS-SA pneumococcal reference laboratory and captured onto the database but isolates that have been repeatedly cultured within 21 days from the same person, are excluded (20). Approximately 190 laboratories across the country send pneumococcal isolates to GERMS-SA each year (20). These are serotyped using the Quellung reaction with specific antisera or through PCR serotyping with a molecular assay if isolates tested culture negative but PCR positive (20).

Between 2003 and 2008, children younger than one years old had the highest occurrence of IPD and by 2008, the incidence rates in children < 1 years old were six times higher than those of children aged 1-4 years old (16). IPD incidence in South Africa at the time was also considerably higher than in some global counterparts (32). According to the WHO, in 2006, the annual incidence of IPD in SA was 60/ 100 000 cases, compared to Europe with an annual incidence of 44.4/ 100 000 IPD cases during the same year (32). This high burden of IPD was also noted amongst adults and compounded by factors such as poverty, overcrowding, high unemployment rates and HIV disease (5–7,11,16,17).

After the introduction of the PCV7 and PCV13, cases of IPD in children younger than two years old decreased from 54.8 to 17.0 cases per 100 000 person-years by 2012 (21). Similarly, in adults between the ages of 25-44 years old, IPD caused by serotypes found in PCV7 decreased by 57%, most likely due to the indirect effects of vaccination, such as herd

immunity (21). In children without HIV, IPD incidence rates dropped by 85%, although IPD caused by non-vaccine serotypes increased by 33% (21).

There was also a large decline in the rate of IPD cases noted during the COVID-19 pandemic amongst both young children and adults (20,33). This phenomenon was possibly due to the changes the country underwent during that time including a nation-wide lockdown and curfew, restricted access and movement to various areas including public areas such as schools and the implementation of public health measures such as mask wearing, washing of hands and physical distancing (20,34).

IPD Serotypes in South Africa:

Research focusing on pneumococcal disease serotypes in South Africa, highlights the need to be observant of specific serotypes which may potentially cause severe IPD. In a study between 2012 and 2018, which focused on *Streptococcus pneumoniae* serotypes linked to death, it was found that the most common serotypes noted to cause IPD were 8, 19A, 12F and 3 (11). Two of these serotypes, 8 and 12F, are not protected by PCV13 (Figure 1) (11). They also concluded that serotype 8, 12F and 15 (15A and 15B/C) be included in future vaccines used in the country due to their distribution within IPD cases and the high case-fatality rates (CFR) associated with these serotypes (11). In data from 2019, the most common IPD serotypes in children less than five years old were 8, 12F, 19F, 7 and 14 while serotypes 8, 12F, 3, 19A and 9N were the most common IPD serotypes in children five years of age or older (23). This showcased the different patterns in serotype distribution of vaccine and non-vaccine serotypes, namely 7, 8, 9N, and 12F, which are not included in the current PCV13 (23).

Lastly, data analysed from 2012 up to and including April 2022 showed that of the serotypes included in PCV13, serotypes 3, 19A and 19F were the predominant serotypes causing IPD in children less than five years old and serotypes 3, 4 and 19A were common in persons older than five years of age (20). The GERMS-SA 2022 annual report reinforced these findings, emphasising that serotypes 3, 8, 19A and 19F consistently caused the highest number of IPD cases, with almost a third of IPD cases caused by PCV13 serotypes (33).

Even though a noticeable reduction in all serotype IPD cases was seen with the use of PCV13, there is still an evident burden of disease due to serotypes not included in PCV13, as noted above (5–7,11,16,17,21,23). It is important to remember that many of these serotypes

hold the potential to cause severe, invasive disease and that serotype subsets will constantly change according to multiple time-dependent factors (5–7,11,16,17,21,23).

Invasive Pneumococcal Disease Vaccines in South Africa:

Since PPSV23 was the first vaccine to be developed, it was the first vaccine to be introduced to the South African population for use against pneumococcal disease (9,22). The vaccine was only used in persons two years of age or older due to the poor immunogenicity of the vaccine in the paediatric population, leaving quite a large vulnerable group susceptible to disease (4,9,10,12–15). Years later, PCVs were developed to target the high incidence of pneumococcal disease in the children younger than two years of age and endorsed for use globally (4,10,12,13,25,32).

South Africa was the first country on the African continent to introduce the seven-valent PCV into its expanded immunisation programme for routine infant immunisation in April 2009 (5–7,11,16,17,20,21). This decision was aided by the reallocation of national funds towards the immunisation programme and the WHO's recommendation in 2003 to integrate the PCV into a country's public immunisation programme, especially if mortality rates in children under five were extremely high (5,7,16). Doses were given at 6, 14 and 40 weeks, with no catch-up vaccination campaign schedule for children who did not meet the age criteria (5–7,11,16,17,20,21).

The PCV7 was soon replaced in 2011 by the PCV13 which includes six additional serotypes compared to its predecessor and a catch-up campaign was held (Figure 1) (5–7,11,16,17,20,21). Children were vaccinated with one dose of PCV13 at 18 months if they had received two doses or more of PCV7 and children who were between the ages of 18-36 months received a once-off dose of PCV13 (17,20). This vaccine is currently given at 6 and 14 weeks with a booster dose given at nine months old, as stipulated by the current EPI-SA dosing schedule, which was recommended by the National Advisory Group on Immunisations (NAGI) (11,17,35).

After the introduction of these vaccines into the EPI-SA, research showed a 60% decrease in the incidence rate of IPD (all serotypes) in children less than two years of age between 2005 and 2012 and in children less than five years old, the overall IPD decline was estimated at 62% (17). This was due in part to the improvement in health services offered as well as the enhanced testing and treatment of HIV in South Africa (17). Increasing vaccine coverage over the years also contributed to the declining rates of IPD affecting the population. The

WHO estimated that between 2009 and 2020, vaccine coverage in South Africa increased from 10% to 83% (20). Thus, leaving South Africa just short of the goal of 90% vaccine coverage of PCV dose three by 2030, as set out in the global Immunisation Agenda (36).

By 2017, PPSV23 and PCVs were both included into the clinician derived pneumococcal vaccination guideline for both adults and children in South Africa (22). These recommendations were recently updated in 2022, (Annexure 2 – Table 5), but it is important to note that these clinician-derived recommendations are not endorsed by the National Department of Health (22). This could be because these guidelines have not undergone the process of validation through researching its appropriateness, the effectiveness of the recommended intervention in the South African context and the cost-effectiveness of the guidelines themselves.

Most recently, in late 2023, South Africa decided to switch from using PCV13 to the lower-valent PCV10-SII in the EPI-SA, with the changeover planned to occur in 2024 (30). This was because PCV10-SII met the minimum vaccine requirements as set out by NAGI and was thought to be more cost-effective (30). The PCV10-SII vaccine schedule will mirror the current PCV13 schedule, which requires doses to be given at 6 and 14 weeks and a booster dose at nine months, making them interchangeable (30). This changeover, however, from PCV13 to PCV10-SII needs to be carefully observed as studies have shown that switching to a lower-valent vaccine may substantially increase the number of IPD cases affecting the South African population over time, by approximately 34.7%, compared to the continued use of PCV13 (29). Similarly, mortality due to IPD would also increase when switching to PCV10-SII compared to the current vaccination strategy (29). The cost-effectiveness in the long-term also needs to be analysed as studies performed predict that PCV13 may be cost-saving in the long run compared to PCV10-SII, contradictory to government beliefs (29). The costs related to treating the increased incidence in IPD once changing to a lower-valent vaccine needs to be considered as well as the public health impact of such a decision.

<u>International Guidelines and Newly Available Pneumococcal Conjugate Vaccines:</u>

The development of vaccines is ever-changing and dependent on the commonly circulating IPD serotypes causing disease amongst the different at risk populations (11). Vaccines and specifically the PCV's are a cost-effective method of reducing morbidity and mortality (15,17,29). In light of the global trends highlighting common *Streptococcus pneumoniae* serotypes associated with IPD and the large unmet burden of pneumococcal disease still

facing many populations, there has been the introduction of one new lower-valent and two new higher-valent PCVs, namely PCV10-SII and PCV15 and PCV20 (Figure 1), into the global market (12,13,24–31).

The PCV10-SII includes three serotypes less (3, 4, 18C) than PCV13 (Figure 1), making it one of the new lower-valent PCVs that is available. PCV10-SII is a licensed, WHO pre-qualified vaccine that has a proven safety, tolerability and immunogenicity record in children and adults (31,32).

PCV15 and PCV20 have both been licensed for usage in adults and then children by the United States of America, Food and Drug Administration (FDA) and accepted into current USA guidelines by the Center for Disease Control and Prevention (CDC) through the Advisory Committee on Immunisation Practices (ACIP) as of October 2021 (updated 2023) (Annexure 3 – Table 6) (12,13,24–31). Recommendations include using the higher-valent vaccines in PCV-naïve and high-risk persons dependent on their previous vaccination status, age and comorbid status (12,13,24–31).

The ACIP is composed of many experts in the medical and public health fields and has been instrumental in providing evidence-based guidance on the use of PPSVs and PCVs in children and adults since 1997 (14,26–28). These guidelines have been used to aide and guide South African guidelines and are held in high regard globally.

Studies performed in Germany and the USA have shown that the vaccines are safe and well-tolerated by both children and adults (13,24,25). PCV15 and PCV20 have an increased coverage of serotypes causing IPD compared to PCV13 and illicit a potent immune response across all vaccine serotypes (12,13,24,25).

Therefore, newer conjugate vaccines should be considered in-depth as to whether they should be incorporated into immunisation schedules to decrease the burden of IPD cases or not and what the consequences of choosing each vaccine would be.

1.3. Problem Statement

It is well known that pneumococcal disease, more specifically IPD, causes severe disease and is a major contributor to high morbidity and mortality rates worldwide (3–11). Even after the introduction of PCV7 and PCV13 into the expanded immunisation programme in South Africa in 2009 and 2011 respectively, there is still a substantial burden of IPD facing the South African population (5–7,11,17,20,23,33).

Now, with the development of the 10-, 15- and 20-valent PCVs, the imminent switchover to PCV10-SII in South Africa and the recommendation by the ACIP to use higher-valent vaccines across the paediatric and adult populations, it is imperative that we determine which vaccines will benefit the South African population.

This study will evaluate IPD incidence, the current circulating serotypes and serotype classification of IPD in South Africa over the last ten years. Findings will be compared to the serotypes that are covered by the existing and new PCVs to determine which are more beneficial to and effective in preventing IPD and the associated mortality in different population sub-groups.

1.4. Justification

The development of healthy public policy through the use of accurate and up-to-date surveillance data is a vital step in reforming healthcare in South Africa. Country-specific surveillance data will be used to inform the use of vaccines within high-risk groups in South Africa by comparing the serotypes causing disease within these population groups to the serotypes included in the various pneumococcal vaccine formulations.

It will also provide value by laying out an overview of IPD in South Africa over the last ten years, including throughout the COVID-19 pandemic and will highlight the burden of disease affecting various sub-groups in the country. This will provide insight into the risk factors and disease patterns associated with IPD within high-risk, vulnerable population groups.

Initial pneumococcal vaccines developed included commonly circulating serotypes found in the USA and Europe (13,24,25,32). South Africa, with a high HIV burden and vastly different epidemiology of IPD compared to the West, may require a distinct vaccine compilation (5–7,11,17,20,23,33). This study will show which available vaccines cover an adequate proportion of circulating IPD serotypes in South Africa and how much invasive pneumococcal disease would have been potentially covered against if these vaccines had been in use. Thus, this study will help inform future NDoH pneumococcal vaccine guidelines surrounding the prevention of IPD and PCV vaccination schedules for various age groups and populations.

1.5. Aim

The aim of this study is to compare the potential of new and existing pneumococcal vaccines, specifically PCV10-SII, PCV13, PCV15, PCV20 and PPSV23, to prevent circulating

serotypes causing invasive pneumococcal disease and to look at the characteristics of IPD associated with increased case fatality in South Africa from 2012 – 2021.

1.6. Objectives

1. To determine the total cases of invasive pneumococcal disease in South Africa, 2012 – 2021.
2. To determine the serotype breakdown of invasive pneumococcal disease in South Africa, 2012 – 2021.
3. To compare the proportion of vaccine serotype (VS) to non-vaccine serotypes causing invasive pneumococcal disease for each new and existing pneumococcal vaccine by the following factors in South Africa, 2012 – 2021:
    a. Province
    b. Age groups
    c. Comorbidity status
    d. HIV status
    e. Antimicrobial resistant IPD
4. To describe the case fatality rate associated with the various VS and NVS causing invasive pneumococcal disease in South Africa for each of the new and existing pneumococcal vaccines, 2012 -2021.

2. METHODS

2.1. Study Design

This study was a retrospective, descriptive, cross-sectional study using data obtained from GERMS-SA, NICD in a secondary data analysis.

The dataset included all IPD cases reported to GERMS-SA from 1 January 2012 to 31 December 2021 throughout South Africa from clinical microbiology laboratories.

2.2. Study Setting

The study setting included approximately 190 clinical microbiology laboratories which reported laboratory-confirmed IPD to the GERMS-SA surveillance programme from across South Africa (20). IPD episodes were reported from both the public and private health-care sector. Basic demographic data were available for all IPD episodes. GERMS-SA has 26 enhanced surveillance sites at selected public hospitals, located throughout all nine provinces

(Annexure 4 – Table 7), whereby additional clinical information and outcome data (Annexure 5 – Table 8) were collected through medical record review and patient interview (23,33).

2.3. Study Population

The study population consisted of all laboratory-confirmed IPD cases as per the GERMS-SA case definition from 2012 to 2021 that were reported to GERMS-SA, NICD.

Participants who met the inclusion criteria as described below, were included in the study.

Inclusion criteria:

- Patients with laboratory confirmed *Streptococcus pneumoniae* from normally sterile-site specimens detected through culture or PCR.
- Laboratory-confirmed *Streptococcus pneumoniae* detected from a patient residing in or travelling through South Africa.
- Specimens taken between 01 January 2012 through to 31 December 2021 meeting the above criteria.

Exclusion criteria:

- Patients with laboratory confirmed *Streptococcus pneumoniae* from non-sterile-site specimens detected through culture or PCR.
- Patients with invasive pneumococcal disease diagnosed before 01 January 2012 or after 31 December 2021.

2.4. Study Sample

All IPD cases in the GERMS-SA database between 2012 to 2021 were reviewed for the purpose of this study and no sampling was performed.

There were 23 789 IPD cases in the GERMS-SA database between 2012 and 2021, with approximately 2 400 cases per year from 2012 to 2019 and 1 500 cases per year from 2020 to 2021. Of these, 37% (n=8 819/23 789) of the total IPD cases with additional clinical and outcome data were from the 26 enhanced surveillance sites (Annexure 4 – Table 7).

2.5. Data Extraction and Cleaning

Data Extraction:

Routinely collected surveillance data obtained by GERMS-SA through both public and private sector laboratories were used. Anonymised data on all laboratory-confirmed IPD

cases in South Africa from 01 January 2012 to 31 December 2021 were extracted (n=23 789) from the GERMS-SA database onto a Microsoft Excel spreadsheet.

Serotype data representing the circulating serotypes causing IPD in South Africa between 2012 and 2021 was determined from episodes where the isolates had been sent to the NICD (n=17 450/23 789). Serotyping was determined through the Quellung reaction for culture positive specimens or through PCR serotyping for culture negative specimens that tested PCR positive (20).

The variables that were extracted were chosen based on achieving the study aim and objectives and included: year, age, home province, final outcome status, HIV, risk factor status, comorbidities (lung, liver, renal, cardiac, diabetes mellitus, head injury, asplenia, malignancy, organ transplant), risk factors (alcohol and smoker), enhanced surveillance site, specimen site, serotype and organism antibiotic susceptibility status (penicillin, ceftriaxone, cotrimoxazole, tetracycline, erythromycin, rifampicin and chloramphenicol). The comorbidities and risk factors chosen for the analysis were based off a combination of the high-risk conditions listed by the ACIP and the South African clinician recommended guidelines as well as the variables available from the GERMS-SA database (Annexure 5 – Table 8) (26–28). The South African mid-year population estimate data were taken from Statistics SA (Stats SA) for the years 2012 – 2021 (37).

Data Cleaning:

All the extracted data underwent further data cleaning using Microsoft Excel and STATA 17.0 Basic Edition (BE) (StataCorp, Texas, USA) (38).

STATA 17.0 BE (38) was used to identify whether duplicates existed in the dataset, of which there were none (n=0). Any missing data from the extracted variables were re-assigned as "missing".

Serotype 15B/C was re-coded as serotype 15B as research showed that the inclusion of serotype 15B in PCV20 provided an adequate antibody response against IPD caused by both serotype 15B and 15C (39). All non-vaccine serotypes, which are serotypes that are not 6A or included in PPSV23 (Figure 1), were coded as "non-vaccine serotypes" (n=5 499/23 789) (Annexure 1 – Table 4).

2.6. Data Management

Data management was completed using both Microsoft Excel and STATA 17.0 BE (38).

To ensure the inclusion and exclusion criteria was met, the dataset was critically reviewed. All cases (n=23 789) were infected with *S. pneumoniae* and collected from sterile sites; therefore, all cases were kept in the dataset. Of note, 103 cases were co-infected with either *Haemophilus influenzae* (n=95/103), *Neisseria meningitidis* (n=7/103) or *Streptococcus pyogenes* (n=1/103).

Throughout the analysis, age groups were used and determined by creating a new categorical variable which stratified ages into the following groups: <1, 1-4, 5-9, 10-14, 15-24, 25-44, 45-64 and >65 years of age. Another categorical variable encoding each age group to a number 1-8, in the order stated above, was created.

The home province of the patient was used to analyse all provincial trends in this study as opposed to the province of the hospital where the patient was tested. This was because only a small proportion of patients were tested and treated for IPD in a province that differs to their home province (n=498/23 789, 2%) and a patient's home province was more likely to reflect where they initially became infected with the specific episode of IPD. A new categorical home province variable was created and encoded all nine provinces to numbers 1-9 in the following order: Eastern Cape (EC), Free State (FS), Gauteng (GP), KwaZulu-Natal (KZN), Limpopo (LP), Mpumalanga (MP), Northern Cape (NC), North-West (NW) and the Western Cape (WC).

Nominal categorical variables were created and coded (0/1) to note whether the outcome and detailed clinical variables being analysed were present or not. In all the newly created categorical variables, cases that did not have any data or were unknown, were assigned as "missing".

The binary outcome variable was coded to those who died and those who didn't, which included a combination of patients' with IPD who recovered, were discharged, or refused hospital treatment. An additional six-level nominal categorical variable was created and coded to represent the IPD serotypes (vaccine and non-vaccine serotypes) included within each pneumococcal vaccine as the exposure variable. Categories of this variable include non-vaccine serotypes, PCV10-SII serotypes (1,5,6A,6B,7F,9V,14,19A,19F,23F), PCV13 additional serotypes (3,4,18C), PCV15 additional serotypes (22F,33F), PCV20 additional serotypes (8,10,11A,12F,15B) and PPSV23 additional serotypes (2,9N,17F,20).

HIV status was coded to note people living with and without HIV disease. Adults living with HIV disease required a positive enzyme linked immunosorbent assay (ELISA) result and

children < 18 months old living with HIV, required a positive PCR result. The multidrug resistance variable was coded to note isolates which were resistant or intermediately susceptible to three or more different antibiotic drug classes as per the definition and those that were not (2).

Each comorbidity variable (lung, liver, renal, cardiac, diabetes mellitus, head injury, asplenia, malignancy and organ transplant) was coded to represent all cases who had the specific comorbidity present and those who did not. Risk factor variables (alcohol and smoking) were coded similarly to represent patients who had a history of alcohol use or smoking and those that did not.

2.7. Data Analysis

STATA 17.0 BE (38) and Microsoft Excel was used to complete the data analysis for this study. The descriptive analysis of all invasive pneumococcal disease cases reported to GERMS-SA from 2012 to 2021 was performed by determining the incidence rates, frequency summaries and proportions of IPD cases disaggregated by year, province, and age group (Annexure 6 – Table 9). The same was done to determine the serotype breakdown of all IPD cases with available serotyped data, disaggregated by year, province, and age group (Annexure 6 – Table 9).

Percentages of circulating IPD serotypes (VS and NVS) covered by new and existing pneumococcal vaccines in South Africa from 2012-2021 was calculated using frequency tables and distributions, disaggregated by age group, province, comorbidity, risk factor, HIV status and antimicrobial resistance (specifically penicillin, ceftriaxone and multidrug resistant IPD) (Annexure 6 – Table 9). Further analysis of only penicillin and ceftriaxone antibiotics was determined based off the common clinical use of these antibiotics to treat severe septic IPD episodes in the South African community (30).

The percentage of serotypes included in each vaccine for specific sub-groups was calculated by comparing the circulating IPD serotypes causing disease and the serotypes included in the pneumococcal vaccines as follows; in any particular sub-group, the number of IPD cases caused by each serotype contained within a particular vaccine was added together and then divided by the total number of serotyped IPD cases for that specific sub-group e.g., to calculate the percentage of serotypes contained within PCV10-SII in Province X = IPD cases caused by serotypes 1+5+6A+6B+7F+9V+14+19A+19F+23F/ Total serotyped IPD cases in Province X = % of vaccine serotypes included within PCV10-SII in Province X. This

percentage gives an indication of the percentage of IPD cases the specific vaccine could have hypothetically covered against, if used prior to *S. pneumoniae* infection and would help to determine which vaccine would best cover against the circulating serotypes causing IPD in South Africa over the study period.

To calculate the CFR across the serotypes, the total number of deaths was divided by the total number of IPD cases, caused by each vaccine serotype. The same method was used to calculate the CFR for each variable assessed in this study.

Univariate logistic regression models were used to analyse the association between death (independent variable) and the IPD serotypes (vaccine and non-vaccine serotypes) contained within each pneumococcal vaccine (dependent variable). Potential confounders and effect modifiers, including age, province, comorbidity, risk factor and HIV status and multidrug resistance as a potential mediator, were also assessed. Crude odd ratios (cOR), p-values and 95% confidence intervals (CI) were calculated. The dependent variable as well as all variables noted to have a significant association (p-value < 0.05) were included in a multivariate logistic regression analysis to note the strength of the associations (adjusted odds ratio (aOR), p-value and associated 95% CI) while controlling for potential confounders, effect modifiers and mediators (Annexure 6 – Table 9).

Findings were visualised in the form of relevant graphs and tables using STATA 17.0 BE and Microsoft Excel for each objective, where applicable.

3. RESULTS

The full dataset of 23 789 cases was used to complete the analysis for objective one. Objective two included individuals with serotype data available (n=17 450/23 789, 73%). Objective three used the full serotyped dataset to analyse the provincial and age group variables (n=17 450/23 789, 73%). The serotyped dataset was then restricted to IPD cases that were culture positive with antimicrobial susceptibility results in order to analyse the antimicrobial and multidrug resistance variable (n=15 119/17 450, 87%). The remaining variables including comorbidities and HIV were analysed using the serotyped dataset from enhanced surveillance sites (ESS) only (n=7 034/17 450, 40%) and risk factors were analysed by restricting the ESS dataset to those aged 18 years and older (n=5 619/7 034, 80%). Objective four used the serotyped data collected from the ESS, that contained outcome data only (n=6 476/7 034, 92%).

The dataset that was used to achieve all objectives, is outlined in Figure 2 below:

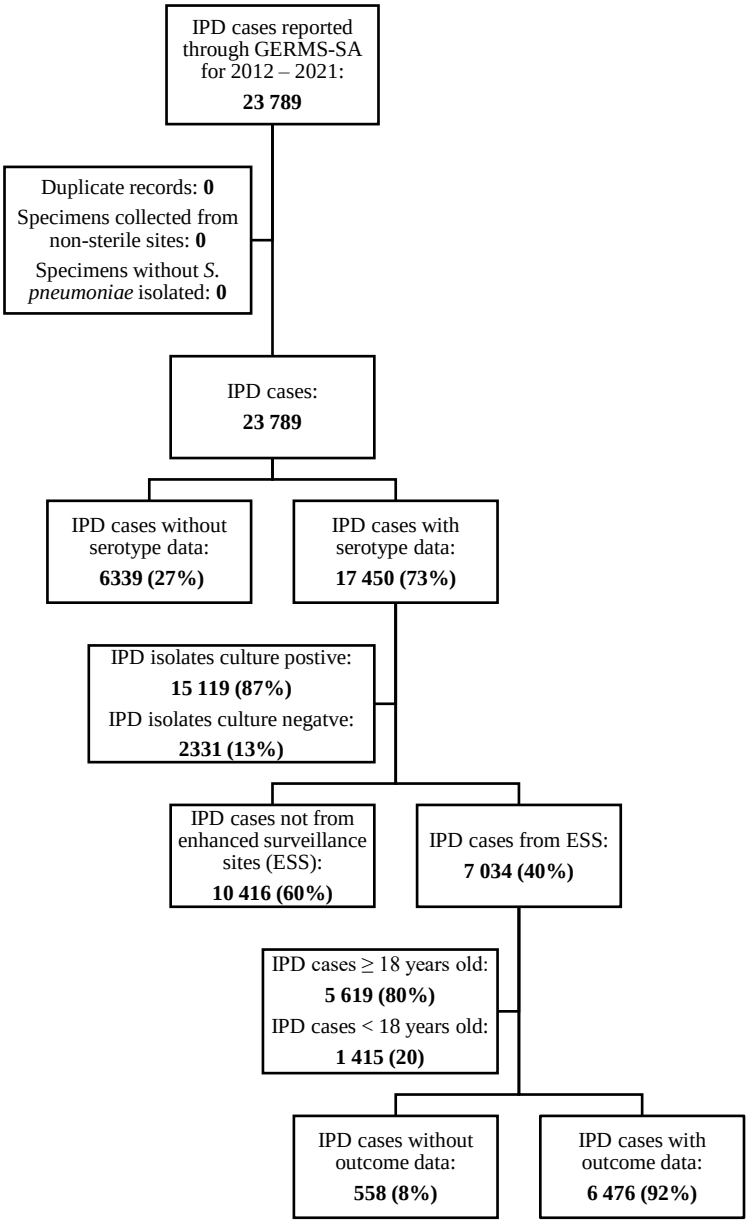


Figure 2: A flow diagram depicting each dataset used to analyse each study objective.

3.1. Overview of IPD Cases in SA, 2012-2021

A total of 23 789 IPD cases, reported to the GERMS-SA programme between 2012 and 2021, were analysed. *S. pneumoniae* was isolated in all IPD cases, with 103 cases being co-infected with either *Haemophilus influenzae* (n=95/103), *Neisseria meningitidis* (n=7/103) or *Streptococcus pyogenes* (n=1/103). Majority of the IPD cases occurred in 2012 (n=3 223/23 789, 14%) followed by a decreasing trend over the years. Cases decreased to reach a low in

2020 (n=1 242/23 789, 5%) before rising again in 2021 (n=1 550/23 789, 7%) as per Figure 3.

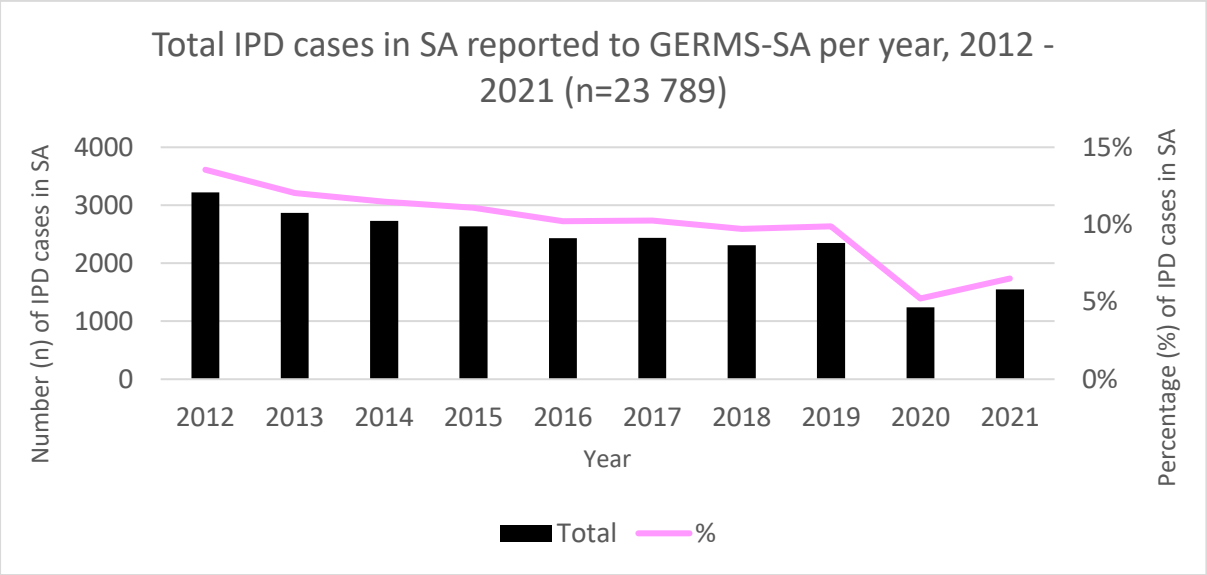
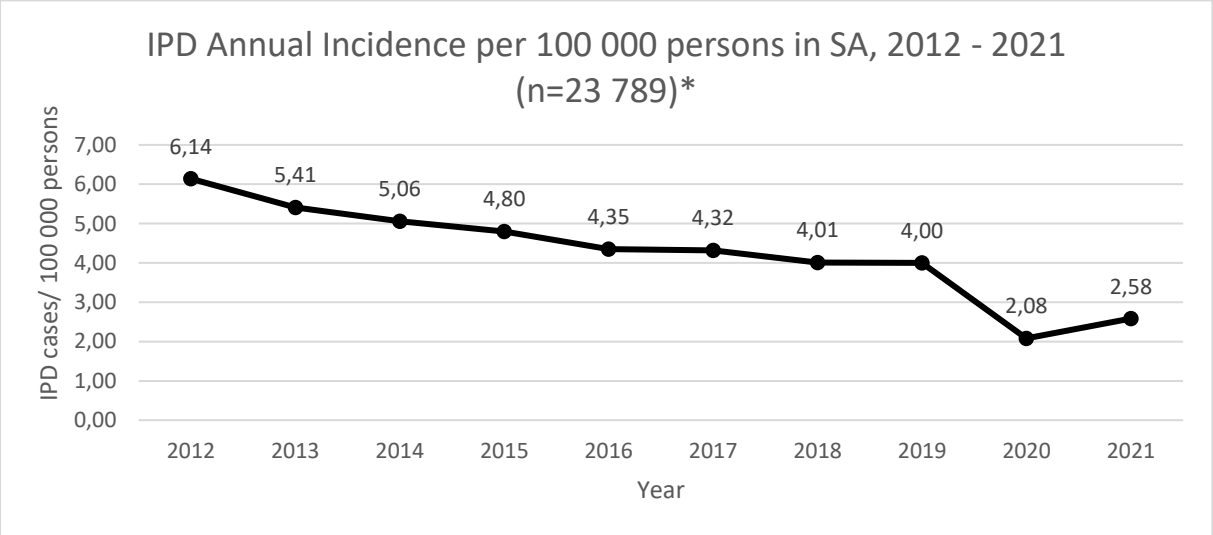


Figure 3: Total invasive pneumococcal disease cases in South Africa reported to GERMS-SA, 2012-2021.

The annual incidence rate of IPD cases declined slowly but steadily over the ten-year period until 2020, following the same pattern as seen above, with an average of 4.22 IPD cases per 100 000 persons in the population (Figure 4).



*Total IPD cases/ Mid-year population estimate per 100 000 persons used for each year from Stats SA (37).

Figure 4: Invasive pneumococcal disease annual incidence rate in South Africa, 2012-2021.

The ages of 4% (n=989/23 789) of persons with IPD was missing. Of persons with ages recorded, the median age was 36 years old (IQR: 24 – 48) with 40% (n=9 470/23 789)

between the ages of 25 and 44 years of age. This was followed by 21% (n=5 087/23 789) of all cases falling into the age group of 45-60 years of age and 10% (n=2 461/23 789) being less than 1 years of age. Provincial data for 1% (n=162/23 789) of the IPD cases was missing. Gauteng province had the highest number of IPD cases (n=7 998/23 789, 34%), followed by the Western Cape (n=5 520/23 789, 23%) and KwaZulu-Natal (n=3 192/23 789,13%), while the Northern Cape had the least number of IPD cases occurring, being 2% (n=497/23 789) as shown in Table 1 below.

Table 1: Invasive pneumococcal disease cases breakdown per year, age group and province, 2012-2021

Year	2012 n (%)	2013 n (%)	2014 n (%)	2015 n (%)	2016 n (%)	2017 n (%)	2018 n (%)	2019 n (%)	2020 n (%)	2021 n (%)	Total n (%)
Age Group											
< 1 Y	297 (9%)	308 (11%)	279 (10%)	253 (10%)	252 (10%)	247 (10%)	264 (11%)	236 (10%)	159 (13%)	166 (11%)	**2461 (10%)**
1 - 4 Y	215 (7%)	190 (7%)	184 (7%)	129 (5%)	148 (6%)	140 (6%)	122 (5%)	125 (5%)	63 (5%)	82 (5%)	**1398 (6%)**
5 - 9 Y	168 (5%)	108 (4%)	102 (4%)	68 (3%)	77 (3%)	56 (2%)	61 (3%)	51 (2%)	31 (2%)	38 (2%)	**760 (3%)**
10 - 14 Y	108 (3%)	83 (3%)	61 (2%)	61 (2%)	73 (3%)	52 (2%)	52 (2%)	61 (3%)	21 (2%)	22 (1%)	**594 (2%)**
15 - 24 Y	202 (6%)	175 (6%)	160 (6%)	152 (6%)	153 (6%)	138 (6%)	130 (6%)	116 (5%)	76 (6%)	82 (5%)	**1384 (6%)**
25 - 44 Y	1264 (39%)	1176 (41%)	1095 (40%)	1065 (40%)	962 (40%)	960 (39%)	922 (40%)	947 (40%)	486 (39%)	593 (38%)	**9470 (40%)**
45 - 64 Y	563 (17%)	531 (19%)	521 (19%)	572 (22%)	550 (23%)	617 (25%)	518 (22%)	575 (24%)	279 (22%)	361 (23%)	**5087 (21%)**
> 65 Y	158 (5%)	157 (5%)	165 (6%)	181 (7%)	177 (7%)	196 (8%)	202 (9%)	203 (9%)	97 (8%)	110 (7%)	**1646 (7%)**
Unknown	248 (8%)	138 (5%)	165 (6%)	157 (6%)	41 (2%)	34 (1%)	42 (2%)	38 (2%)	30 (2%)	96 (6%)	**989 (4%)**
Total	**3223 (14%)**	**2866 (12%)**	**2732 (11%)**	**2638 (11%)**	**2433 (10%)**	**2440 (10%)**	**2313 (10%)**	**2352 (10%)**	**1242 (5%)**	**1550 (7%)**	**23789**
Province											
Eastern Cape	311 (10%)	294 (10%)	235 (9%)	239 (9%)	208 (9%)	208 (9%)	260 (11%)	275 (12%)	137 (11%)	196 (13%)	**2363 (10%)**
Free State	220 (7%)	193 (7%)	181 (7%)	135 (5%)	146 (6%)	116 (5%)	112 (5%)	86 (4%)	61 (5%)	69 (4%)	**1319 (6%)**
Gauteng	1262 (39%)	975 (34%)	955 (35%)	912 (35%)	814 (33%)	849 (35%)	704 (30%)	733 (31%)	362 (29%)	432 (28%)	**7998 (34%)**
KZN	575 (18%)	500 (17%)	490 (18%)	349 (13%)	316 (13%)	267 (11%)	241 (10%)	242 (10%)	101 (8%)	111 (7%)	**3192 (13%)**
Limpopo	78 (2%)	61 (2%)	41 (2%)	104 (4%)	89 (4%)	70 (3%)	102 (4%)	111 (5%)	53 (4%)	49 (3%)	**758 (3%)**
Mpumalanga	171 (5%)	142 (5%)	134 (5%)	90 (3%)	108 (4%)	107 (4%)	128 (6%)	108 (5%)	45 (4%)	55 (4%)	**1088 (5%)**
Northern Cape	50 (2%)	80 (3%)	41 (2%)	32 (1%)	45 (2%)	53 (2%)	52 (2%)	91 (4%)	27 (2%)	26 (2%)	**497 (2%)**
North-West	130 (4%)	137 (5%)	117 (4%)	121 (5%)	84 (3%)	78 (3%)	76 (3%)	69 (3%)	38 (3%)	42 (3%)	**892 (4%)**
Western Cape	424 (13%)	482 (17%)	526 (19%)	627 (24%)	597 (25%)	678 (28%)	620 (27%)	628 (27%)	410 (33%)	528 (34%)	**5520 (23%)**
Unknown	2 (0%)	2 (0%)	12 (0%)	29 (1%)	26 (1%)	14 (1%)	18 (1%)	9 (0%)	8 (1%)	42 (3%)	**162 (1%)**
Total	**3223 (14%)**	**2866 (12%)**	**2732 (11%)**	**2638 (11%)**	**2433 (10%)**	**2440 (10%)**	**2313 (10%)**	**2352 (10%)**	**1242 (5%)**	**1550 (7%)**	**23789**

3.2. Serotype Breakdown of IPD Cases in SA, 2012-2021

Of the 23 789 IPD cases, 27% (n=6 339/23 789) were not available for serotyping, leaving the serotype dataset with 17 450 isolates. Of these, 68% (n=11 951/17 450) were associated with a vaccine serotype and 32% (n=5 499/17 450) were non-vaccine serotypes (Annexure 1 – Table 4).

The most common reoccurring serotype between 2012 and 2021 was serotype 8 causing 11% (n=1 846/17 450) of all reported IPD cases. This was followed by serotype 19A, causing 8% (n=1 370/17 450) and serotype 12F, causing 8% (n=1 324/17 450) of all IPD cases in South Africa between 2012 and 2021.

Table 2: Serotype breakdown of invasive pneumococcal disease cases per pneumococcal vaccine (vaccine and non-vaccine serotypes), 2012-2021.

Vaccine	Serotype	Frequency	Percent (%)	Total % of Serotypes Contained in Various Vaccines
PCV10-SII	1	749	4%	26% (4 478/ 17 450)
	5	67	0%	
	6A	370	2%	
	6B	186	1%	
	6A/ 6B	56	0%	
	7F	230	1%	
	9V	136	1%	
	14	250	1%	
	19A	1 371	8%	
	19F	710	4%	
	23F	353	2%	
PCV13 Additional	3	1 064	6%	37% (6 459/ 17 450)
	4	762	4%	
	18C	155	1%	
PCV15 Additional	22F	389	2%	40% (6 910/ 17 450)
	33F	62	0%	
PCV20 Additional	8	1 846	11%	63% (11 068/ 17 450)
	10A	414	2%	
	11A	156	1%	
	12F	1 324	8%	
	15B	418	2%	
PPSV23 Additional	2	3	0%	68% (11 951/ 17 450)
	9N	503	3%	
	17F	322	2%	
	20	55	0%	
Non-Vaccine Serotypes (NVS)	NVS	5 499	32%	
TOTAL		17 450	100%	

*Missing serotypes (n=6339, 27% of total IPD dataset)

3.2.1. Overview of Non-Vaccine Serotypes

When analysing the most common non-vaccine serotypes causing IPD in the South African population, serotype 16F (n=601/17 450) and 15A (n=554/17 450) each caused 3% of the total IPD cases that occurred over the last ten years. Serotypes 13 (n=370/17 450), 6C (n=324/17 450), 23A (n=299/17 450) and 7C (n=289/17 450) each caused 2% of the total IPD cases that occurred between 2012 and 2021. A full overview of the IPD cases caused by NVS is included in Annexure 1 – Table 4.

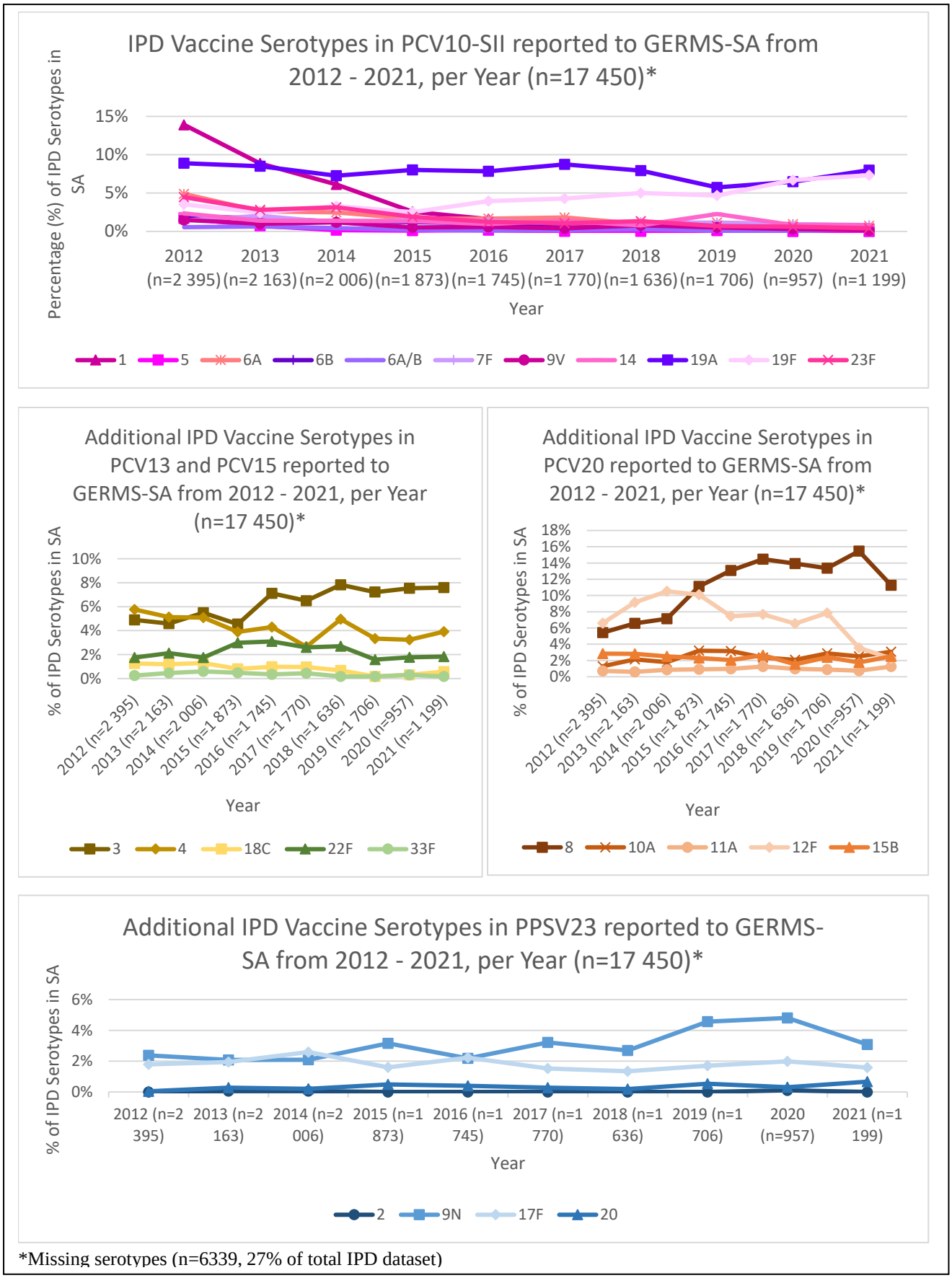
3.2.2. Vaccine Serotypes Overview per Year

To visualise the serotypes causing IPD over the years, they were analysed according to the pneumococcal vaccine in which they are contained. When focusing on serotypes included within PCV10-SII, there was a sharp decline in serotype 1 from 14% (n=333/2 395) in 2012 to 0% (n=0/ 1 199) in 2021. Serotype 19A remained fairly consistent throughout the ten-year period causing 9% (n=213/ 2 395) of IPD cases in 2012 and 8% (n=96/ 1 199) in 2021. Serotype 19F caused increasingly more IPD cases over the years, from 3% (n=47/ 1 873) in 2015 to 7% (n=88/ 1 199) in 2021. All other serotypes followed a declining trend from 2012 to 2021 except for serotype 14 which caused a brief increase in IPD cases in 2019.

When examining the additional serotypes included within PCV13 and PCV15 between 2012 and 2021, serotype 3 caused more IPD cases, from 5% (n=117/2 395) in 2012 to 8% (n=91/1 199) in 2021. Serotype 4 caused less IPD cases, from 6% (n=138/2 395) in 2012 to 4% (n=47/ 1 199) in 2021 and serotypes 18C, 22F and 33F caused the same proportion of IPD cases in 2012 as compared to 2021.

Serotype 8, found within PCV20, increased from causing 5% (n=130/2 395) of IPD cases in 2012 to 11% (n=135/1 199) in 2021. Serotype 12F caused less IPD cases over the ten years, from 7% (n=158/2 395) in 2012 to 2% (n=27/1 199) in 2021. Serotypes 10A, 11A and 15B consistently caused low numbers of IPD cases across the ten-year period.

Lastly, analysing the additional serotypes found within PPSV23, serotypes 2 and 17F caused similar proportions of IPD cases in 2012 as in 2021, 0% (n=0/2 395; n=0/1 199) and 2% (n=43/2 395; n=19/1 199), respectively. Serotypes 9N (n=57/2 395, 2%; n=37/1 199, 3%) and 20 (n=1/2 395, 0%; n=8/1 199, 1%) both saw a slight increase of 1% in IPD cases caused from 2012 to 2021. All serotype trends between 2012 and 2021 are visualised in Figure 5 below.

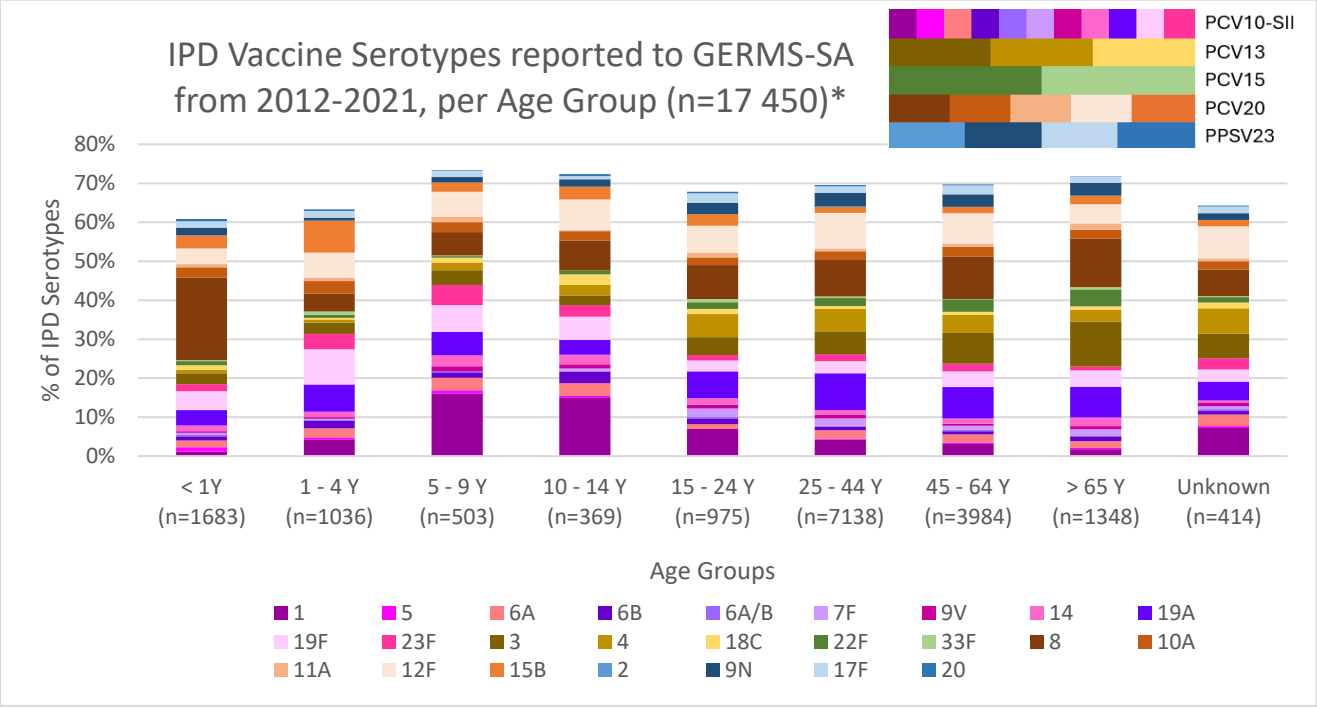


*Missing serotypes (n=6339, 27% of total IPD dataset)

Figure 5: Proportion of each serotype contributing to invasive pneumococcal disease cases per year, per pneumococcal vaccine, 2012-2021

3.2.3. Vaccine Serotype Overview per Age Group

Figure 6 focuses on dominant serotypes causing IPD amongst various age groups in South Africa. In age groups < 1 years, 15-24 years, 45-64 years and > 65 years of age, serotype 8 was the most commonly occurring serotype causing IPD at 21% (n=356/1 683), 9% (n=85/975), 11% (n=435/3 984) and 12% (n=168/1 348), respectively. In age group 1-4 years of age, serotype 19F (n=94/ 1 036, 9%) caused the most IPD cases and in age groups 5-9 years (n=81/503, 16%) and 10-14 years (n=55/369, 15%), serotype 1 caused the most IPD cases. Age group 25-44 years of age had three common serotypes causing the majority of IPD cases, including serotype 19A (n=673/ 7138, 9%), 8 (n=668/7 138, 9%) and 12F (n= 652/7 138, 9%). The majority of IPD cases within the different age groups were caused by serotypes included within PCV10-SII and PCV20 additional serotypes. In children less than one years of age and the elderly over 65 years of age, the majority of serotypes causing IPD were included within the PCV20 additional serotypes, at (n=538/1 683, 32%) and (n=317/1348, 24%), respectively. Children within the 5–9-year-old age group (n= 369/503, 73%) contained the highest percentage of vaccine serotypes causing IPD compared to children less than one years of age (n=1 024/1 680, 61%) with the lowest percentage of vaccine serotypes causing disease.



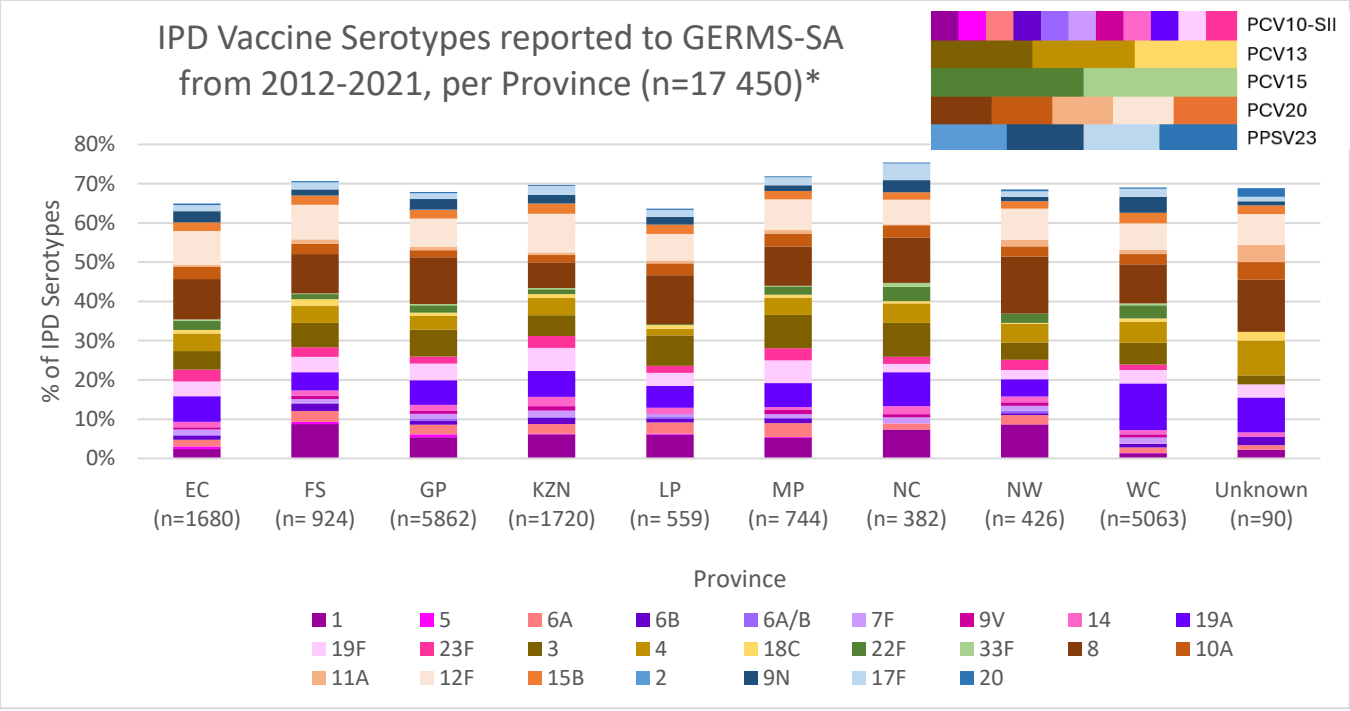
*Missing serotypes (n=6 339/23 789, 27%)

Figure 6: Serotype breakdown of invasive pneumococcal disease cases per age group, per pneumococcal vaccine, 2012-2021.

3.2.4. Vaccine Serotype Overview per Province

Figure 7 below highlights that across the provinces in South Africa between 2012 and 2021, serotype 8 was the most commonly occurring serotype causing IPD in seven provinces including the Eastern Cape (n=173/1680, 10%), Free State (n=93/924, 10%), Gauteng (n=702/5862, 12%), Limpopo (n=70/559, 13%), Mpumalanga (n=75/744, 10%), Northern Cape (n=44/382, 12%) and the Northwest (n=62/426, 15%). In KwaZulu-Natal, serotype 12F (n=170/1 720, 10%) caused the most IPD and in the Western Cape, serotype 19A (n=603/5 063, 12%) caused the most IPD cases between 2012 and 2021. Across the country, the province with IPD caused by proportionately the most vaccine serotypes was the Northern Cape (n=281/382, 74%) compared to Limpopo (n=344/559, 62%) with the least number of IPD cases caused by vaccine serotypes.

Once again, across all provinces, the serotypes contained within PCV10-SII and the PCV20 additional serotypes caused the most IPD cases compared to additional serotypes contained within PCV13, PCV15 and PPSV23. In Gauteng (n=1 522/5 862, 26%), KwaZulu-Natal (n=537/1 720, 31%) and the Western Cape (n=1 213/5 063, 24%) provinces, serotypes included in PCV10-SII caused the most IPD compared to additional serotypes in each higher valent vaccine and in the Eastern Cape (n=415/1 680, 25%), Limpopo (n=142/559, 25%) and North-West (n=122/426, 29%) provinces, the additional serotypes within PCV20 caused the majority of IPD cases.



*Missing serotypes (n=6 339/23 789, 27%)

Figure 7: Proportion of serotypes causing invasive pneumococcal disease cases per province, per pneumococcal vaccine, 2012-2021 .

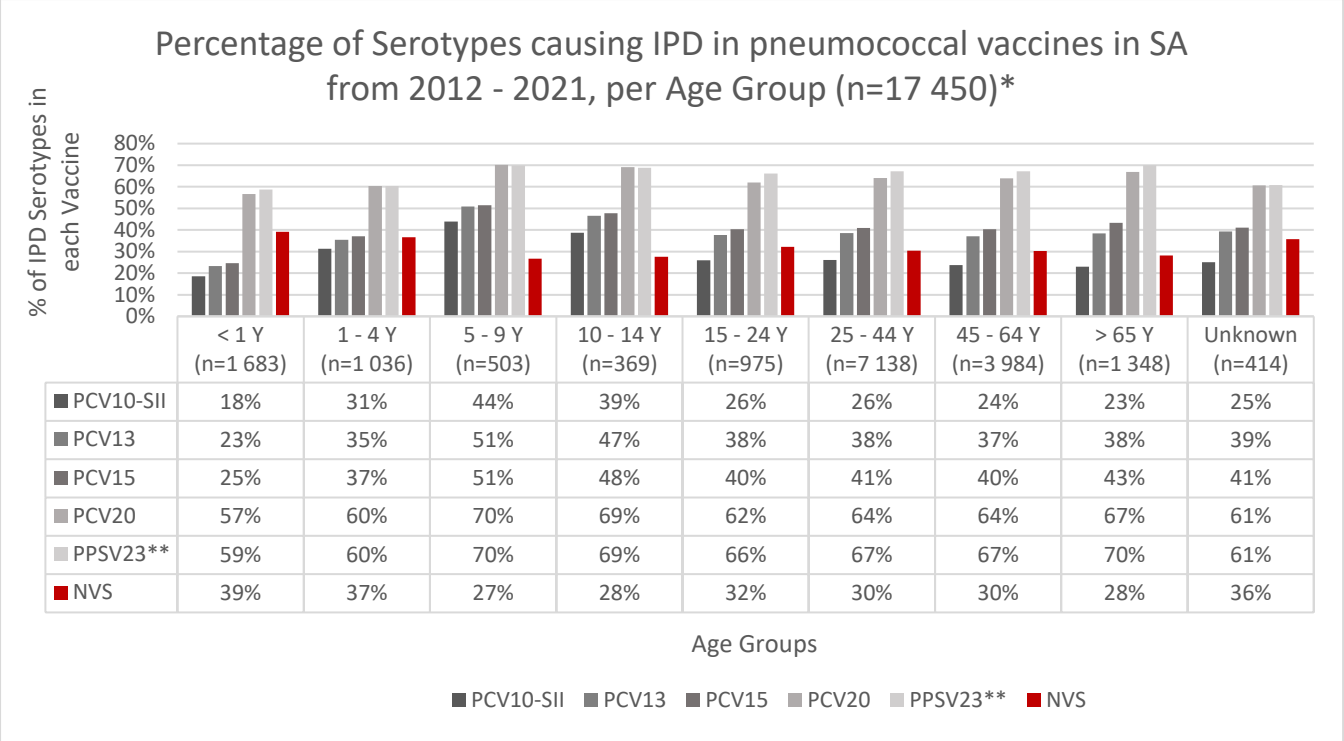
3.3. Overview of New and Existing Pneumococcal Vaccines that Protect Against IPD Cases in SA, 2012-2021

Referring to Table 2 above, PCV10-SII contained the lowest percentage (n=4 478/17 450, 26%) of IPD serotypes circulating in South Africa compared to all other PCVs and the PPSV23. PCV20 contained the highest percentage (n=11 068/17 450, 63%) of serotypes amongst all PCVs. PPSV23 contained the highest percentage of serotypes out of all the currently available vaccines against IPD (n=11 951/17 450, 68%).

This similar pattern is seen throughout the analyses and disaggregating the data down to the different sub-groups, provides the percentage of IPD cases caused by VS and NVS per sub-group. This percentage hypothetically represents the potential cover each pneumococcal vaccine would provide against IPD, if used prior to infection with *S. pneumoniae*.

3.3.1. Vaccine Overview per Age Group

Across all age groups, PCV20 (Range: 57%-70%) and PPSV23 (Range: 59%-70%) included the highest percentage and PCV10-SII the lowest percentage (Range: 18%-44%) of vaccine serotypes causing IPD, as emphasised by Figure 8 below. All pneumococcal vaccines contained the least percentage of vaccine serotypes (Range: 18%-59%) causing IPD in children aged < 1 years old. They contained the highest percentage of vaccine serotypes (Range: 44%-70%) causing IPD in children aged 5-9 years old. In the majority of the age groups, except individuals aged 5-14 years old, non-vaccine serotypes caused more IPD than the serotypes included within PCV10-SII.



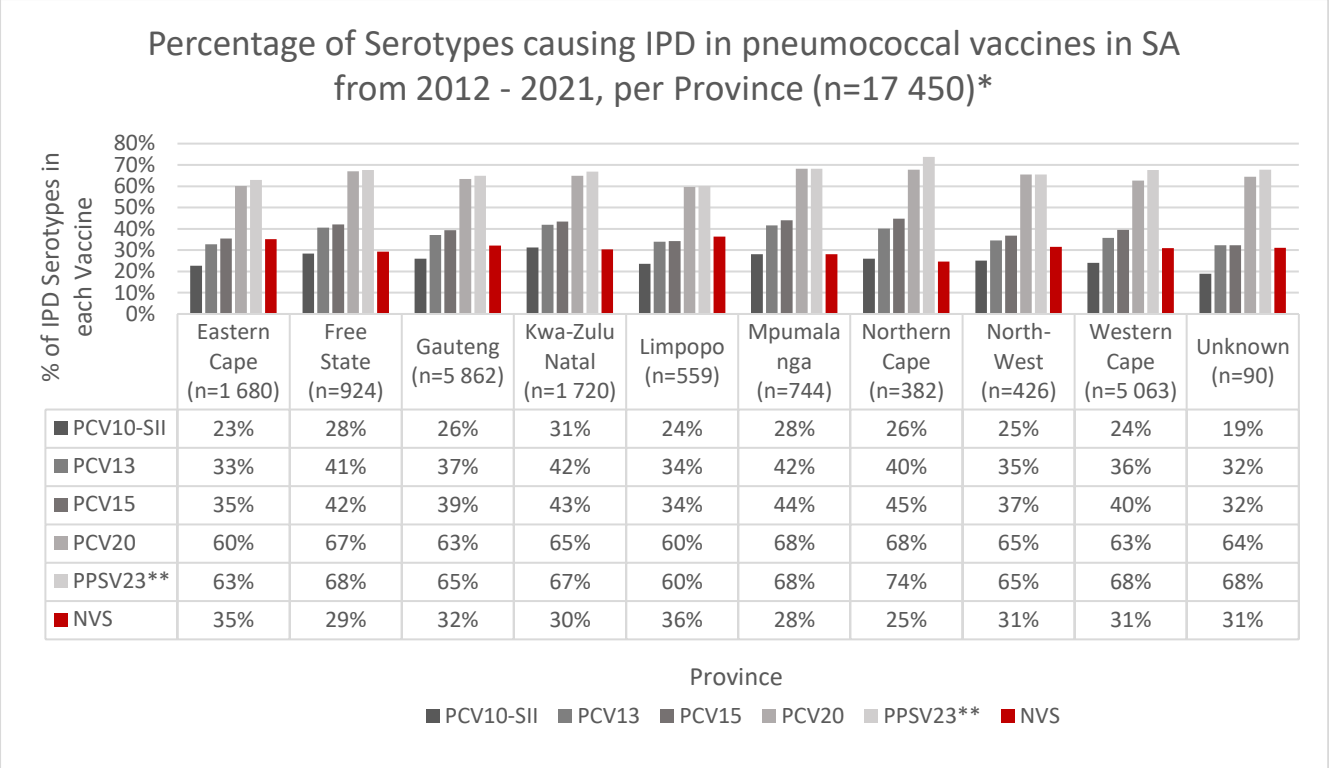
	< 1 Y (n=1 683)	1 - 4 Y (n=1 036)	5 - 9 Y (n=503)	10 - 14 Y (n=369)	15 - 24 Y (n=975)	25 - 44 Y (n=7 138)	45 - 64 Y (n=3 984)	> 65 Y (n=1 348)	Unknown (n=414)
PCV10-SII	18%	31%	44%	39%	26%	26%	24%	23%	25%
PCV13	23%	35%	51%	47%	38%	38%	37%	38%	39%
PCV15	25%	37%	51%	48%	40%	41%	40%	43%	41%
PCV20	57%	60%	70%	69%	62%	64%	64%	67%	61%
PPSV23**	59%	60%	70%	69%	66%	67%	67%	70%	61%
NVS	39%	37%	27%	28%	32%	30%	30%	28%	36%

*Missing serotypes (n=6 339/23 789, 27%)
**PPSV23 does not include serotype 6A in its constituency, therefore it is not included in its calculation.

Figure 8: Percentage of vaccine and non-vaccine serotypes in pneumococcal vaccines causing invasive pneumococcal disease in South Africa, per age group, 2012-2021.

3.3.2. Vaccine Overview per Province

Figure 9 below highlights that across all provinces throughout South Africa, PCV20 (Range: 60%-68%) and PPSV23 (Range: 60%-74%) included the highest percentage of vaccine serotypes associated with IPD cases. The least percentage of vaccine serotypes causing IPD was included in PCV10-SII (Range: 23%-31%). The Northern Cape province (Range: 26%-74%) contained the highest percentage of vaccine serotypes compared to Limpopo province (Range: 24%-60%) which included the least percentage of vaccine serotypes causing IPD across all pneumococcal vaccines. In the Eastern Cape and Limpopo provinces, non-vaccine serotypes caused more IPD cases than the serotypes included within PCV10-SII and PCV13.



	Eastern Cape (n=1 680)	Free State (n=924)	Gauteng (n=5 862)	Kwa-Zulu Natal (n=1 720)	Limpopo (n=559)	Mpumalanga (n=744)	Northern Cape (n=382)	North-West (n=426)	Western Cape (n=5 063)	Unknown (n=90)
PCV10-SII	23%	28%	26%	31%	24%	28%	26%	25%	24%	19%
PCV13	33%	41%	37%	42%	34%	42%	40%	35%	36%	32%
PCV15	35%	42%	39%	43%	34%	44%	45%	37%	40%	32%
PCV20	60%	67%	63%	65%	60%	68%	68%	65%	63%	64%
PPSV23**	63%	68%	65%	67%	60%	68%	74%	65%	68%	68%
NVS	35%	29%	32%	30%	36%	28%	25%	31%	31%	31%

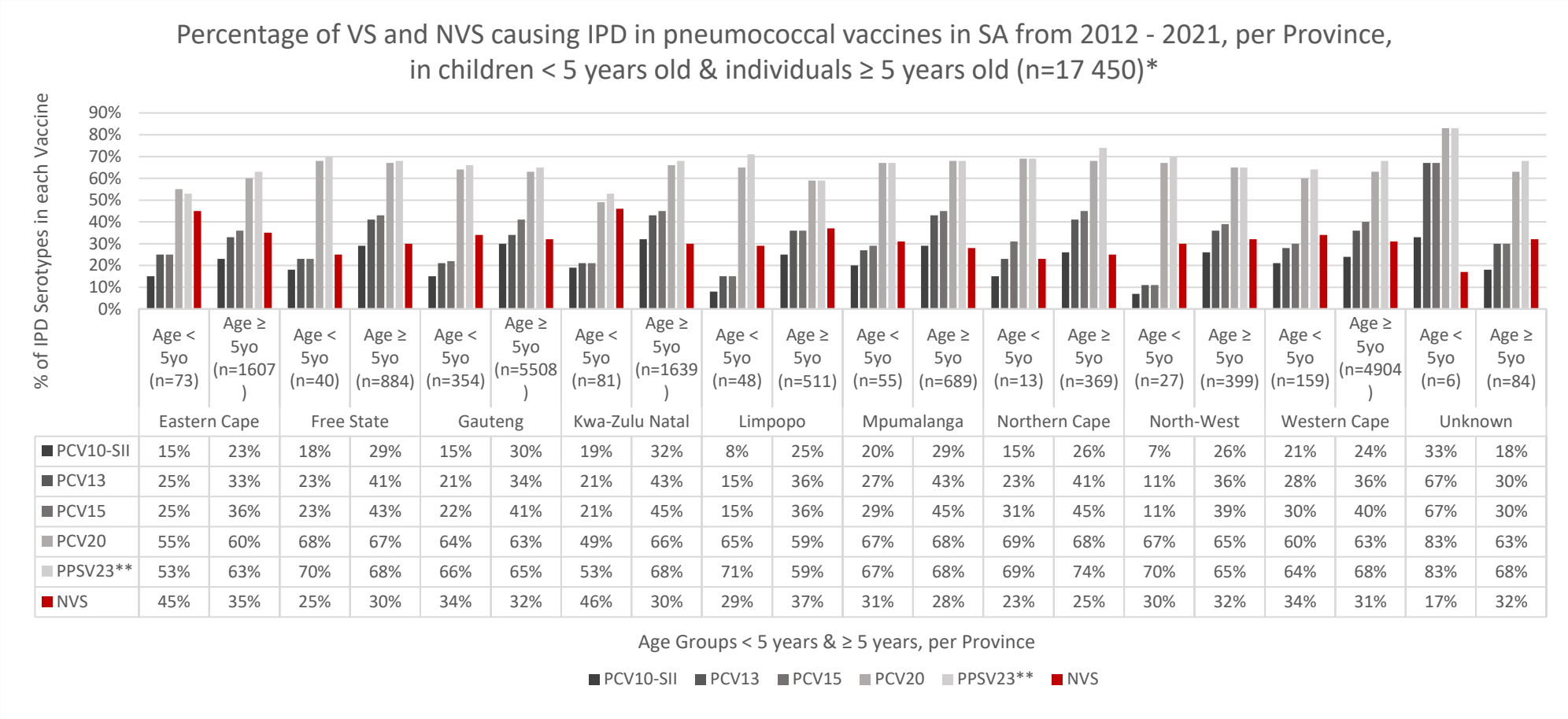
*Missing serotypes (n=6 339/23 789, 27%)

**PPSV23 does not include serotype 6A in its constituency, therefore it is not included in its calculation.

Figure 9: Percentage of vaccine and non-vaccine serotypes in pneumococcal vaccines causing invasive pneumococcal disease in South Africa, per province, 2012-2021.

3.3.3. Vaccine Overview, in Children less than five years and Individuals older than five years old, per Province

The percentage of VS and NVS causing IPD contained within pneumococcal vaccines in SA from 2012 - 2021, in children < 5 years old & individuals ≥ 5 years old, per province, is visualised in Figure 10 below. PCV10-SII, PCV13 and PCV15 contained a higher percentage of serotypes causing IPD in individuals aged five years and older compared to children less than five years across all provinces. PCV20 and PPSV23 contained a higher percentage of serotypes causing IPD in children less than five years old in Gauteng, the Free State, Limpopo, Mpumalanga, and the Northern Cape compared to individuals older than five years of age. In pneumococcal conjugate vaccines, PCV10-SII contained the least percentage of vaccine serotypes (Range: 7%-32%) compared to PCV20 (Range: 50%-71%). PPSV23 contained the most vaccine serotypes out of all available vaccines (Range: 54%-74%).



	Eastern Cape		Free State		Gauteng		Kwa-Zulu Natal		Limpopo		Mpumalanga		Northern Cape		North-West		Western Cape		Unknown	
	Age < 5yo (n=73)	Age ≥ 5yo (n=1607)	Age < 5yo (n=40)	Age ≥ 5yo (n=884)	Age < 5yo (n=354)	Age ≥ 5yo (n=5508)	Age < 5yo (n=81)	Age ≥ 5yo (n=1639)	Age < 5yo (n=48)	Age ≥ 5yo (n=511)	Age < 5yo (n=55)	Age ≥ 5yo (n=689)	Age < 5yo (n=13)	Age ≥ 5yo (n=369)	Age < 5yo (n=27)	Age ≥ 5yo (n=399)	Age < 5yo (n=159)	Age ≥ 5yo (n=4904)	Age < 5yo (n=6)	Age ≥ 5yo (n=84)
PCV10-SII	15%	23%	18%	29%	15%	30%	19%	32%	8%	25%	20%	29%	15%	26%	7%	26%	21%	24%	33%	18%
PCV13	25%	33%	23%	41%	21%	34%	21%	43%	15%	36%	27%	43%	23%	41%	11%	36%	28%	36%	67%	30%
PCV15	25%	36%	23%	43%	22%	41%	21%	45%	15%	36%	29%	45%	31%	45%	11%	39%	30%	40%	67%	30%
PCV20	55%	60%	68%	67%	64%	63%	49%	66%	65%	59%	67%	68%	69%	68%	67%	65%	60%	63%	83%	63%
PPSV23**	53%	63%	70%	68%	66%	65%	53%	68%	71%	59%	67%	68%	69%	74%	70%	65%	64%	68%	83%	68%
NVS	45%	35%	25%	30%	34%	32%	46%	30%	29%	37%	31%	28%	23%	25%	30%	32%	34%	31%	17%	32%

*Missing serotypes (n=6 339/23 789, 27%)
**PPSV23 does not include serotype 6A in its constituency, therefore it is not included in its calculation.

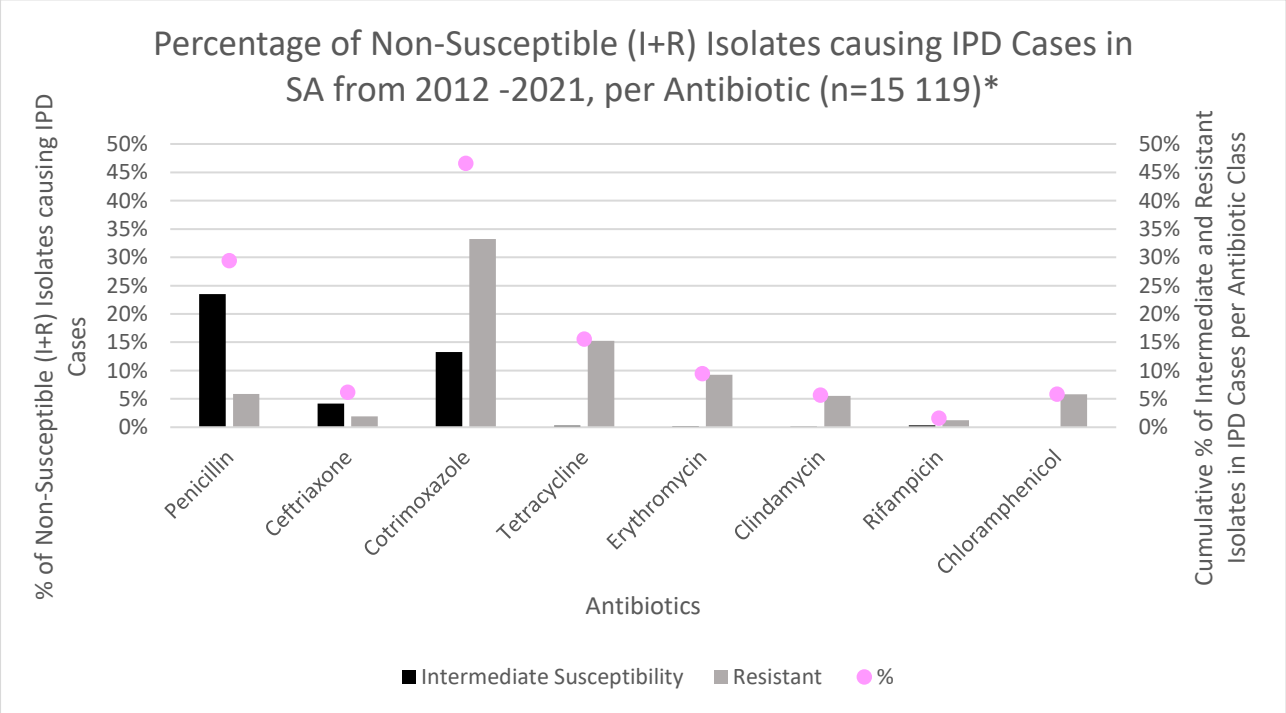
Figure 10: Percentage of vaccine and non-vaccine serotypes in pneumococcal vaccines causing invasive pneumococcal disease in South Africa, per age group, per province, 2012-2021.

3.3.4. Antimicrobial Resistance

Of the 17 450 IPD episodes with serotype data available, antimicrobial susceptibility data could only be determined for culture confirmed cases (15 119/17 450, 87%) (Figure 2). To provide an overall picture of multidrug and antimicrobial resistance in IPD cases, penicillin, ceftriaxone, cotrimoxazole, tetracycline, erythromycin, clindamycin, rifampicin, and chloramphenicol were included in the initial analysis. From these, only multidrug, penicillin and ceftriaxone's antimicrobial resistance status were analysed in-depth.

3.3.4.1. Antimicrobial Resistance Overview

Twenty-four percent of the isolates had an intermediate susceptibility to penicillin (n=3 555/15 119), 13% to cotrimoxazole (n=2 011/15 119, 13%) and 4% to ceftriaxone (n=634/15 119, 4%). In terms of resistant isolates, 33% (n=5 025/15 119) of the isolates were resistant to cotrimoxazole, 15% to tetracycline (n=2 305/15 119, 15%) and 9% to erythromycin (n=1 399/15 119), 9%). The total percentage of non-susceptible isolates (intermediate (I) + resistant (R)) highlighted that of all cases, majority of IPD cases were non-susceptible to cotrimoxazole (n=7 036/15 119, 47%), followed by penicillin (n=4 439/15 119, 29%) and lastly, tetracycline (n=2 346/15 119, 16%). Only 6% (n=928/15 119) of the isolates causing IPD were non-susceptible to ceftriaxone (Figure 11).

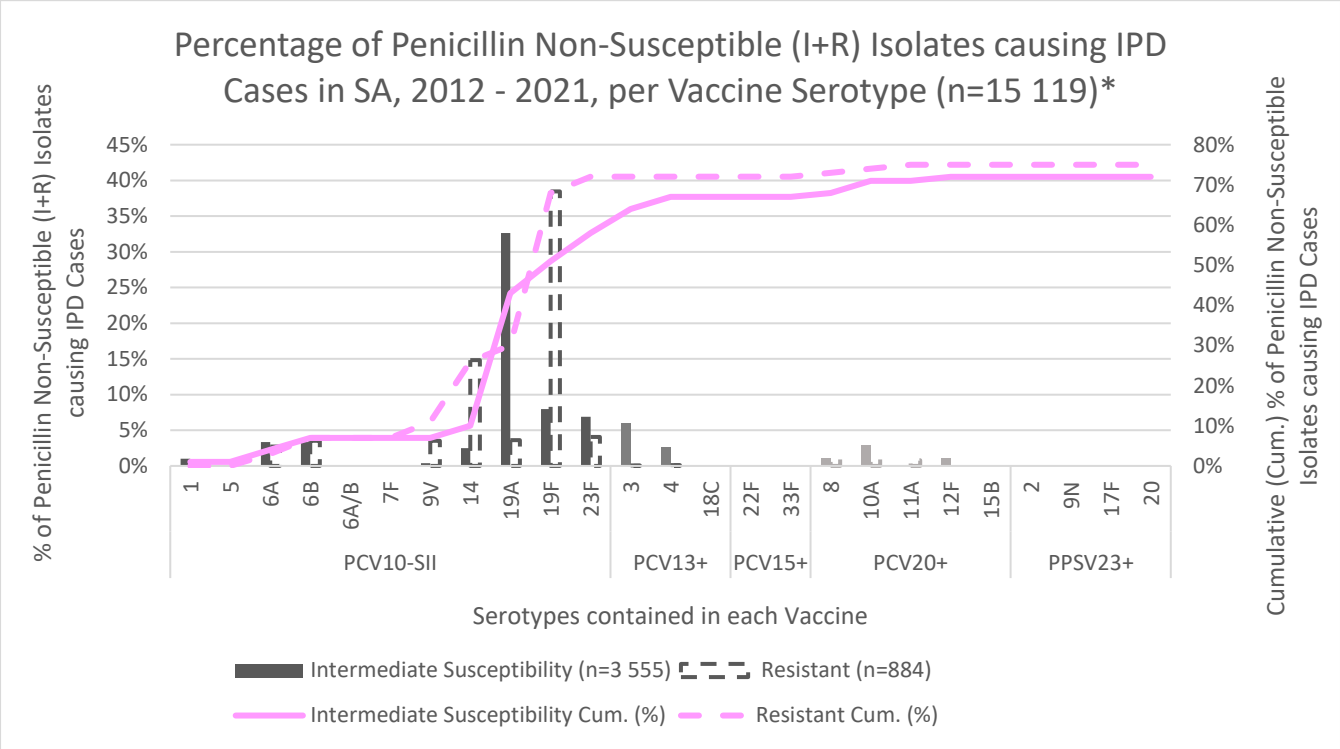


*Culture negative IPD cases with no antimicrobial susceptibility status (n=2331/17 450, 13%)

Figure 11: Percentage of non-susceptible isolates causing invasive pneumococcal disease in South Africa, per antibiotic drug, 2012-2021.

3.3.4.2. Penicillin Resistance

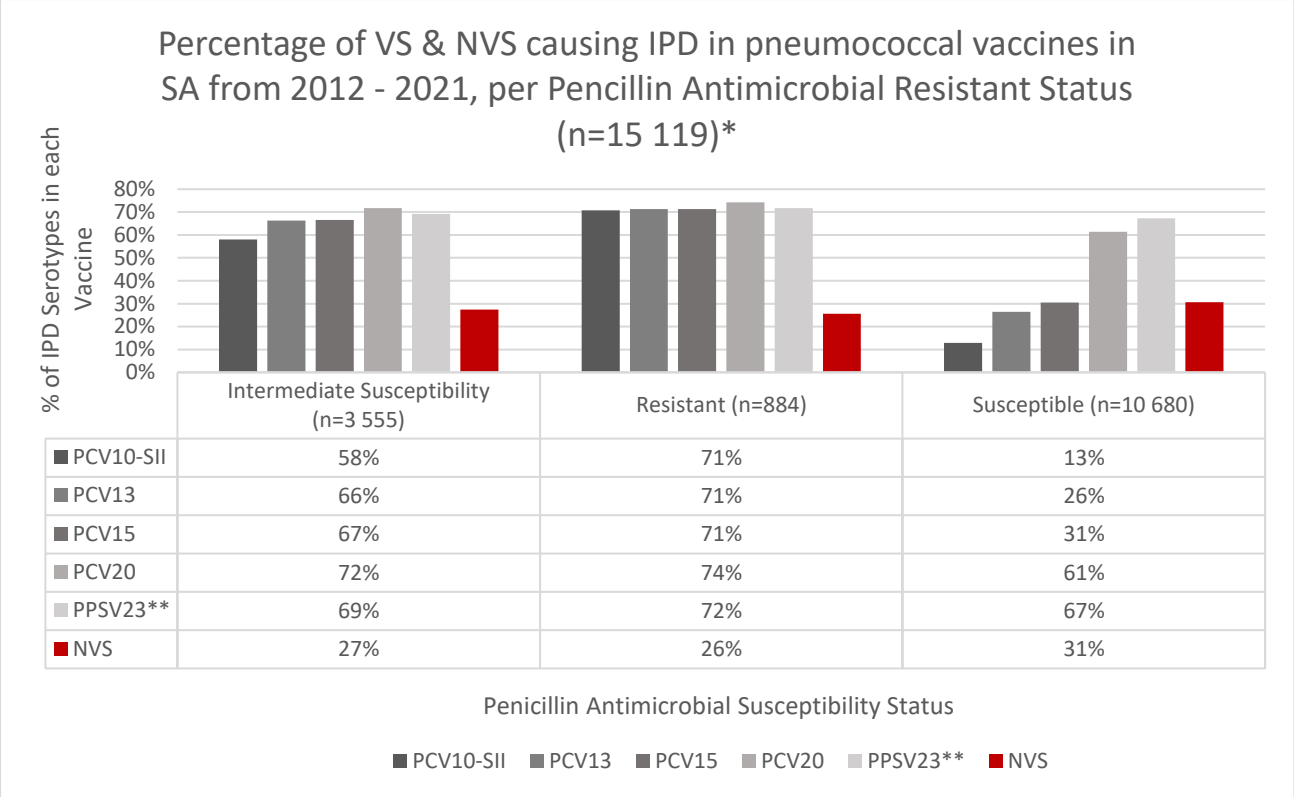
Majority of the IPD isolates were susceptible to penicillin (n=10 680/15 119, 71%), 24% of the isolates were intermediately susceptible (n=3 555/15 119) and 6% were penicillin resistant (n=884/15 119). The serotype associated with the highest percentage of intermediate susceptibility to penicillin was serotype 19A (n=1 160/3 555, 33%) followed by 19F (n=283/ 3 555, 8%) and 23F (n=245/ 3 555, 7%). The serotype with the highest percentage of resistance to penicillin was serotype 19F (n=340/ 884, 38%), followed by serotype 14 (n=131/ 884, 15%).



*Culture negative IPD cases with no antimicrobial susceptibility status (n=2331/17 450, 13%)

Figure 12: Percentage of penicillin non-susceptible isolates causing invasive pneumococcal disease cases in South Africa, per vaccine serotype, 2012-2021.

Figure 13 highlights that the majority of penicillin non-susceptible serotypes causing IPD (Range: 58%-71%) were contained within PCV10-SII. PCV20 and PPSV23 contained the highest percentage of non-susceptible serotypes causing IPD overall. However, they both only contained a minimal percentage increase (Range: 3%-14%) in the penicillin non-susceptible serotypes causing IPD compared to PCV10-SII.

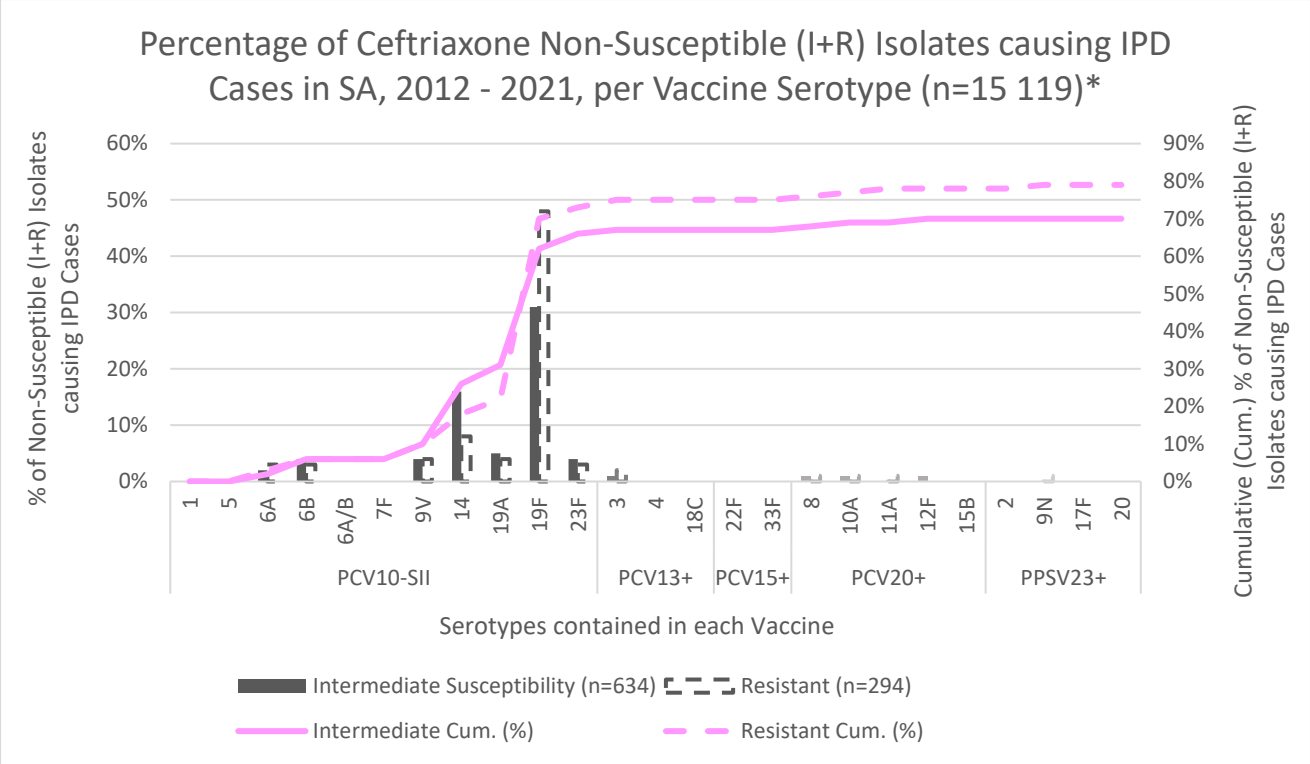


*Culture negative IPD cases with no antimicrobial susceptibility status (n=2331/17 450, 13%)
**PPSV23 does not include serotype 6A in its constituency, therefore it is not included in its calculation.

Figure 13: Percentage of vaccine and non-vaccine serotypes in pneumococcal vaccines causing invasive pneumococcal disease in South Africa, per penicillin antimicrobial resistant status, 2012-2021.

3.3.4.3. Ceftriaxone Resistance

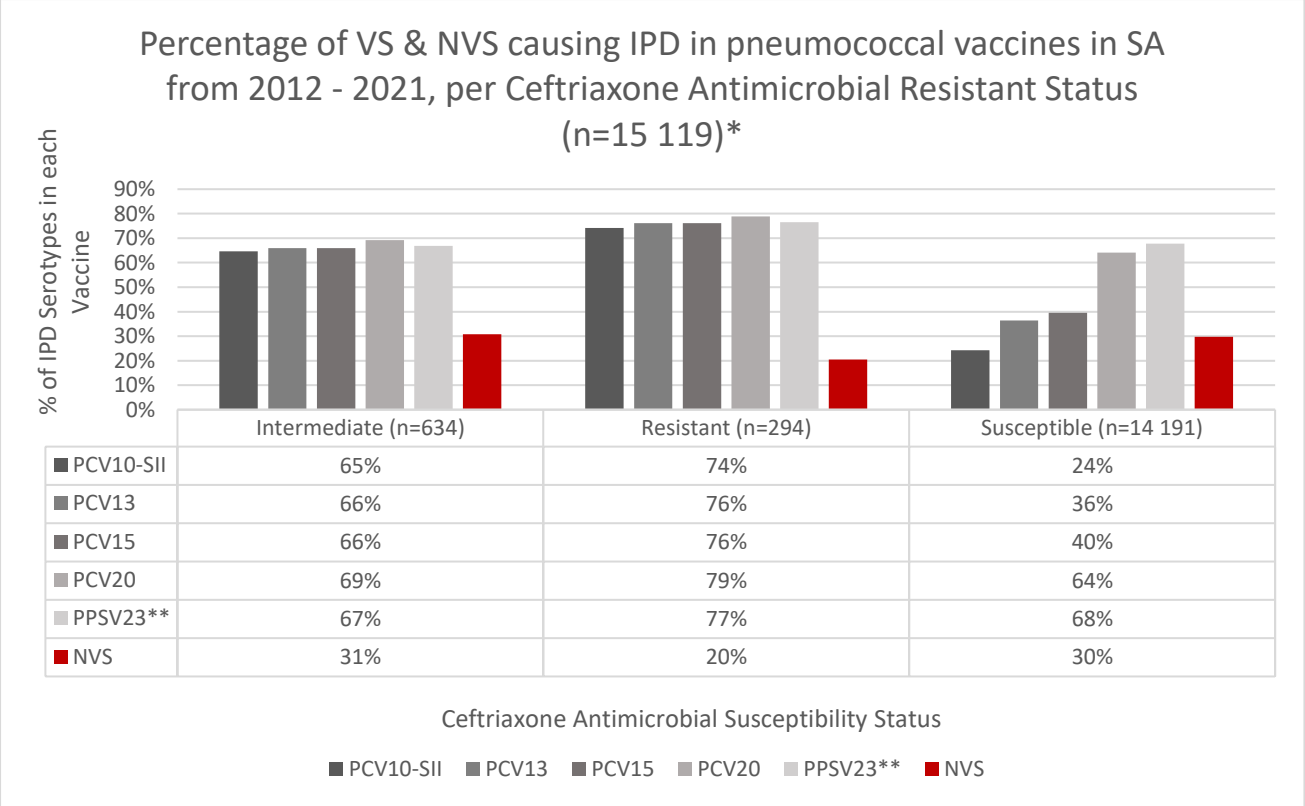
The bulk of IPD isolates were susceptible to ceftriaxone (n=14 191/15 119, 94%), 4% (n=634/15 119) had an intermediate susceptibility to ceftriaxone and 2% (n=294/15 119) were ceftriaxone resistant. Serotypes noted to have a high percentage of intermediate susceptibility to ceftriaxone included 19F (n=194/634, 31%) followed by serotype 14 (n=99/634, 16%) and serotype 19A (n=31/634, 5%). Serotypes associated with the highest percentage of resistance to ceftriaxone included serotype 19F (n=142/294, 48%) and serotype 14 (n=24/294, 8%).



*Culture negative IPD cases with no antimicrobial susceptibility status (n=2331/17 450, 13%)

Figure 14: Percentage of ceftriaxone non-susceptible isolates causing invasive pneumococcal disease cases in South Africa, per vaccine serotype, 2012-2021.

PCV10-SII included the majority of ceftriaxone non-susceptible serotypes causing IPD (Range: 65%-74%), as shown by Figure 15 below. PCV20 and PPSV23 included a minimal increase in the percentage (Range: 4%-5%) of non-susceptible serotypes covered across ceftriaxone intermediately susceptible and resistant IPD cases.



*Culture negative IPD cases with no antimicrobial susceptibility status (n=2331/17 450, 13%)
**PPSV23 does not include serotype 6A in its constituency, therefore it is not included in its calculation.

Figure 15: Percentage of vaccine and non-vaccine serotypes in pneumococcal vaccines causing invasive pneumococcal disease in South Africa, per ceftriaxone antimicrobial resistant status, 2012-2021.

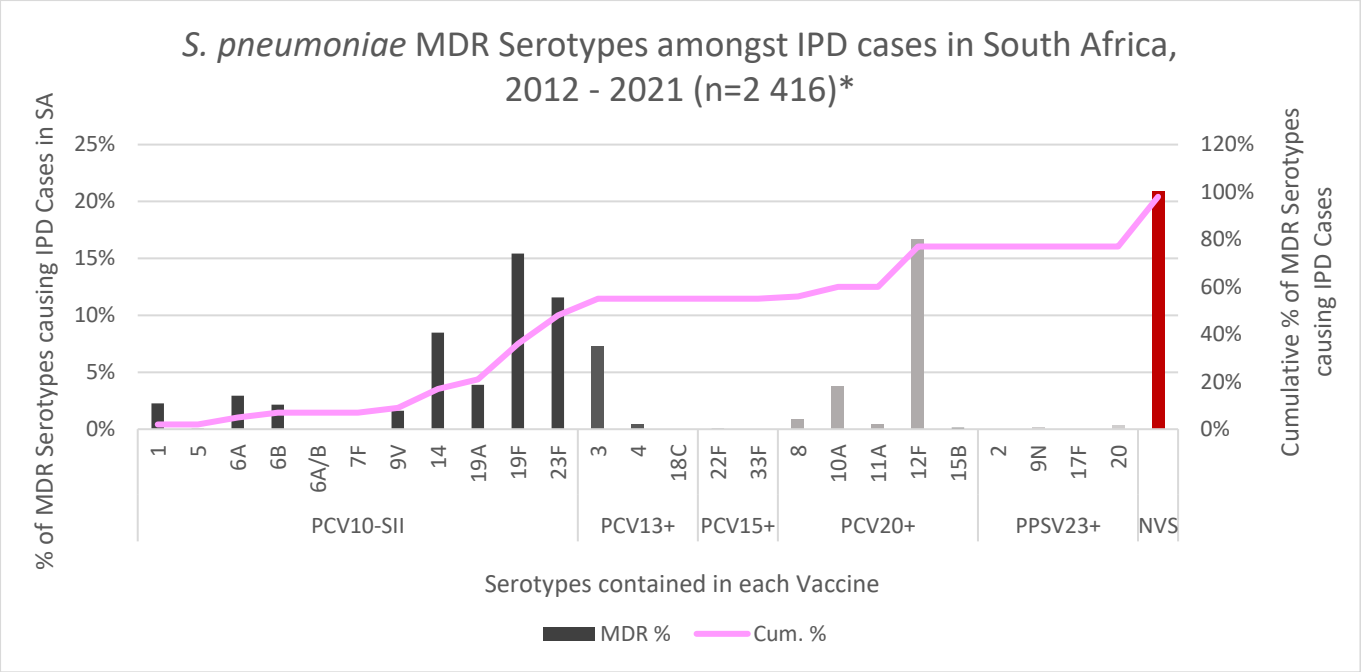
3.3.5. Multidrug Resistance

Multidrug resistance is described as IPD cases caused by *S. pneumoniae* that are resistant or intermediately susceptible to three or more different antibiotic drug classes (2). In this study, the antibiotics used to determine multidrug resistance, and their drug classes include penicillin (beta-lactam), ceftriaxone (third generation cephalosporin), cotrimoxazole (sulfonamide/ dihydrofolate reductase inhibitor), tetracycline (bacteriostatic), erythromycin (macrolide), clindamycin (lincosamide), rifampicin (rifamycin) and chloramphenicol (chloramphenicol).

Results show that out of the 15 119 IPD cases that were culture positive with antimicrobial susceptibility results available, 16% (n=2 416/15 119) of the cases met the criteria for multidrug resistance and 84% (n=12 703/15 119) of the cases did not meet the criteria.

Serotypes 12F (n=404/ 2 416, 17%), 19F (n=373/2 416, 15%), 23F (n=280/2 416, 12%), 14 (n=205/2 416, 8%) and 3 (n=176/2 416, 7%) were the serotypes most commonly associated

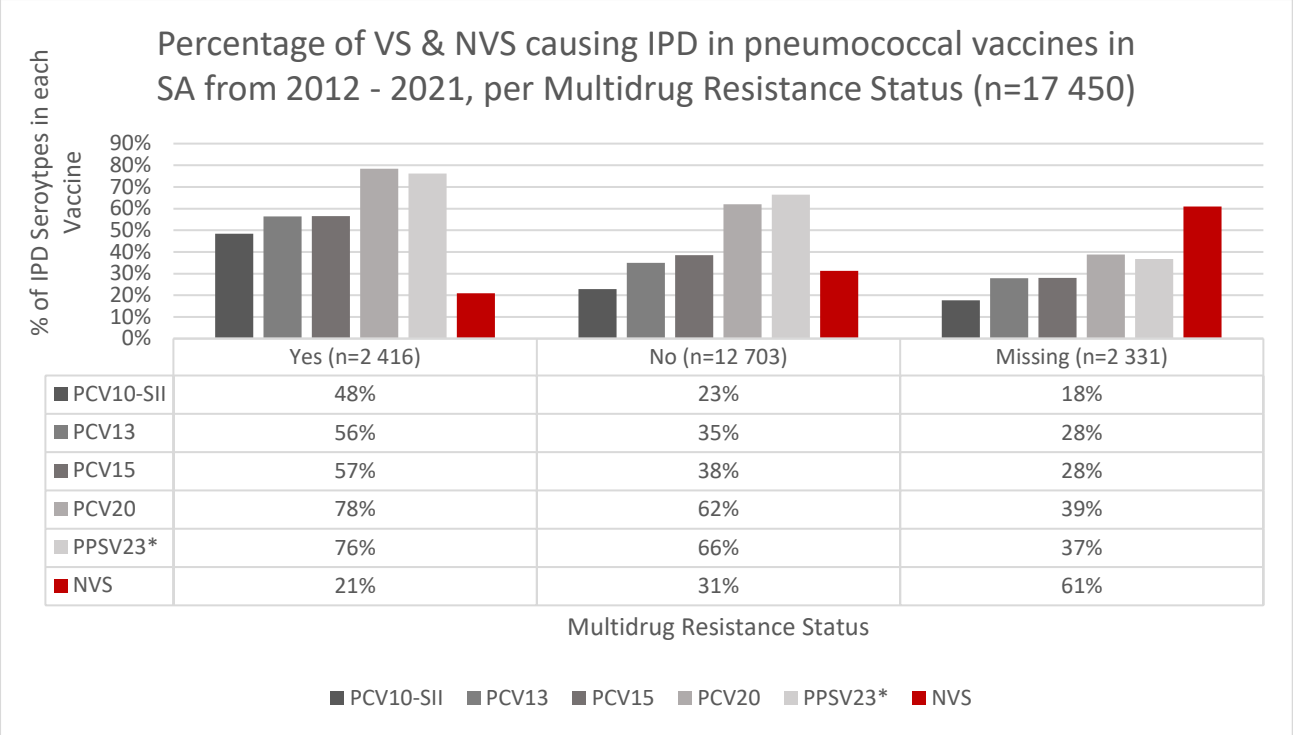
with multidrug resistance. Non-vaccine serotypes made up 21% (n=504/2 416) of the multidrug resistant serotypes causing IPD. Additional serotypes included in PCV15 (22F, 33F) and PPSV23 (2, 9N,17F, 20) were not associated with multidrug resistance.



*S. *pneumoniae* non-MDR serotypes (n=12 703/15 119, 84%)

Figure 16: Number of multidrug resistant cases in invasive pneumococcal disease cases in South Africa, per vaccine serotype, 2012-2021.

Assessing multidrug resistance serotypes causing IPD included in the different pneumococcal vaccines highlighted that PCV10-SII contained 48% (n=1 170/ 2 416) of all multidrug resistant serotypes. This increased by 30% to 78% of serotypes causing IPD contained within PCV20 (n=1 894/2 416, 78%) (Figure 17).



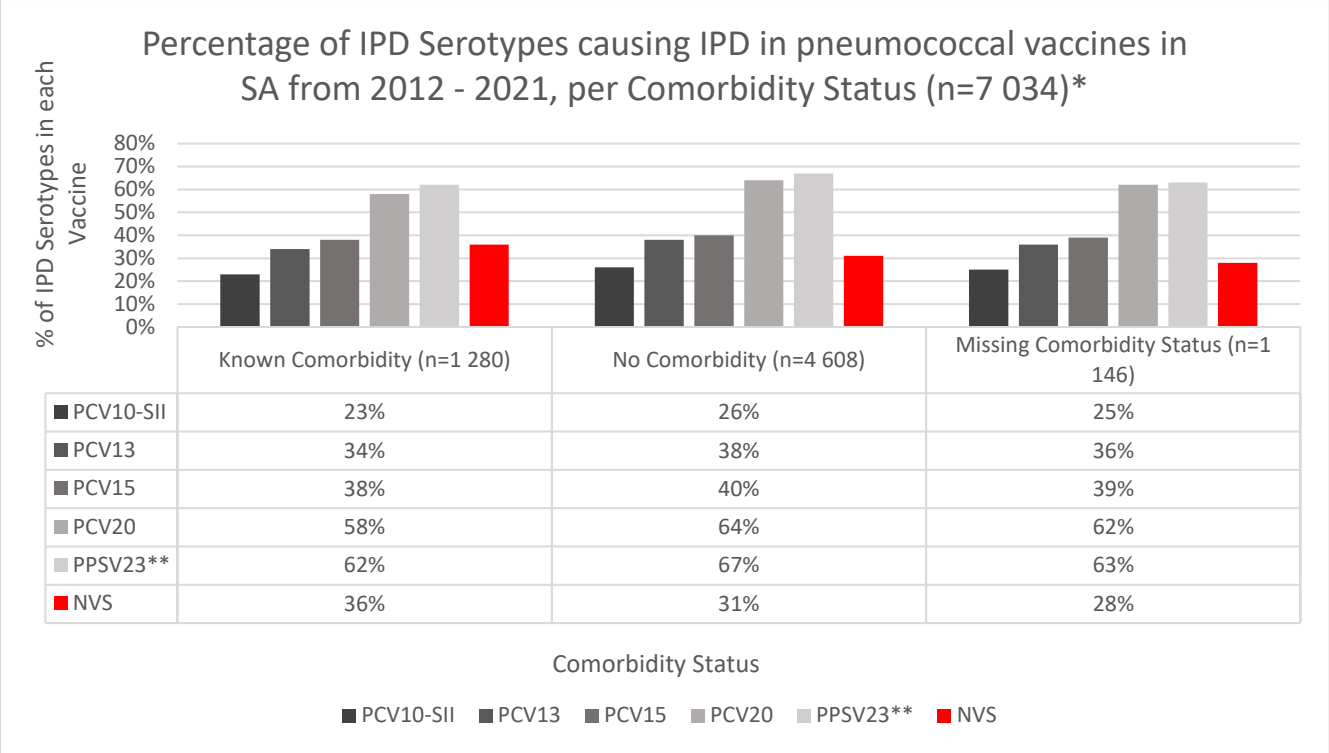
*PPSV23 does not include serotype 6A in its constituency, therefore it is not included in its calculation.

Figure 17: Percentage of vaccine and non-vaccine serotypes in pneumococcal vaccines causing invasive pneumococcal disease in South Africa, per multidrug resistant status, 2012-2021.

3.3.6. Comorbidities

In order to conduct this stage of the analysis, only serotyped data collected from the 26 GERMS-SA enhanced surveillance sites were used (n=7 034/ 17 450) (Figure 2). This data contained details on the clinical and outcome status of each patient and therefore provided the information necessary to analyse the comorbidities, risk factors and HIV status of each IPD case against the serotypes causing IPD.

Figure 18 below highlights that all pneumococcal vaccines contained a lower percentage of vaccine serotypes causing IPD in patients with at least one known comorbidity (Range: 23%-62%), compared to patients with no known comorbidity (Range: 26%-67%). Non-vaccine serotypes caused a higher percentage of IPD in patients with a known comorbidity (n=460/1280, 36%) compared to patients without a comorbidity (n=1407/4608, 31%).



*IPD cases not from ESS (n=10 416/17 450, 60%)
**PPSV23 does not include serotype 6A in its constituency, therefore it is not included in its calculation.

Figure 18: Percentage of vaccine and non-vaccine serotypes in pneumococcal vaccines causing invasive pneumococcal disease in South Africa by presence or absence of a comorbidity, 2012-2021.

As outlined in Figure 19 and Figure 20, PCV10-SII consistently contained the lowest percentage of serotypes causing IPD in persons with and without specific comorbidities analysed, as per the ACIP guidelines (Annexure 5 – Table 8). PPSV23 contained the highest percentage of serotypes causing IPD in these patients, followed by PCV20, except in patients with confirmed diabetes mellitus.

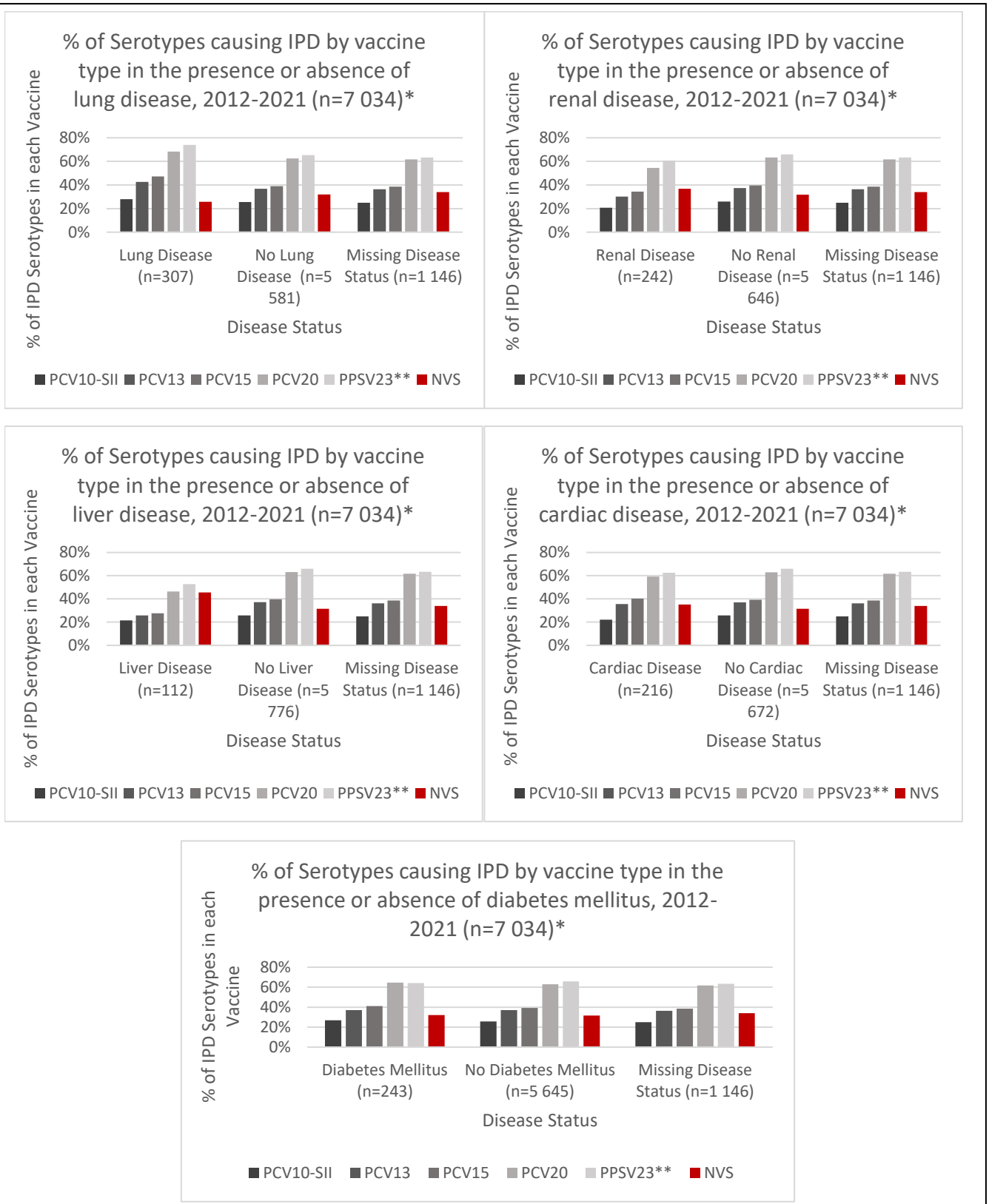
In the case of IPD patients with confirmed diabetes mellitus, PCV20 (n=157/243, 65%) contained the highest percentage of serotypes causing IPD followed by PPSV23 (n=156/243, 64%).
In patients with confirmed lung disease or a previous organ transplant, the percentage of serotypes causing IPD contained within the vaccines is notably higher than in patients without these comorbidities.

The opposite was noted in patients diagnosed with any of the other comorbidities assessed (such as chronic cardiac, renal or liver disease, asplenia, malignancy and head injury). The

percentage of serotypes causing IPD included in each pneumococcal vaccine was lower in these patients compared to patients without the comorbidity.

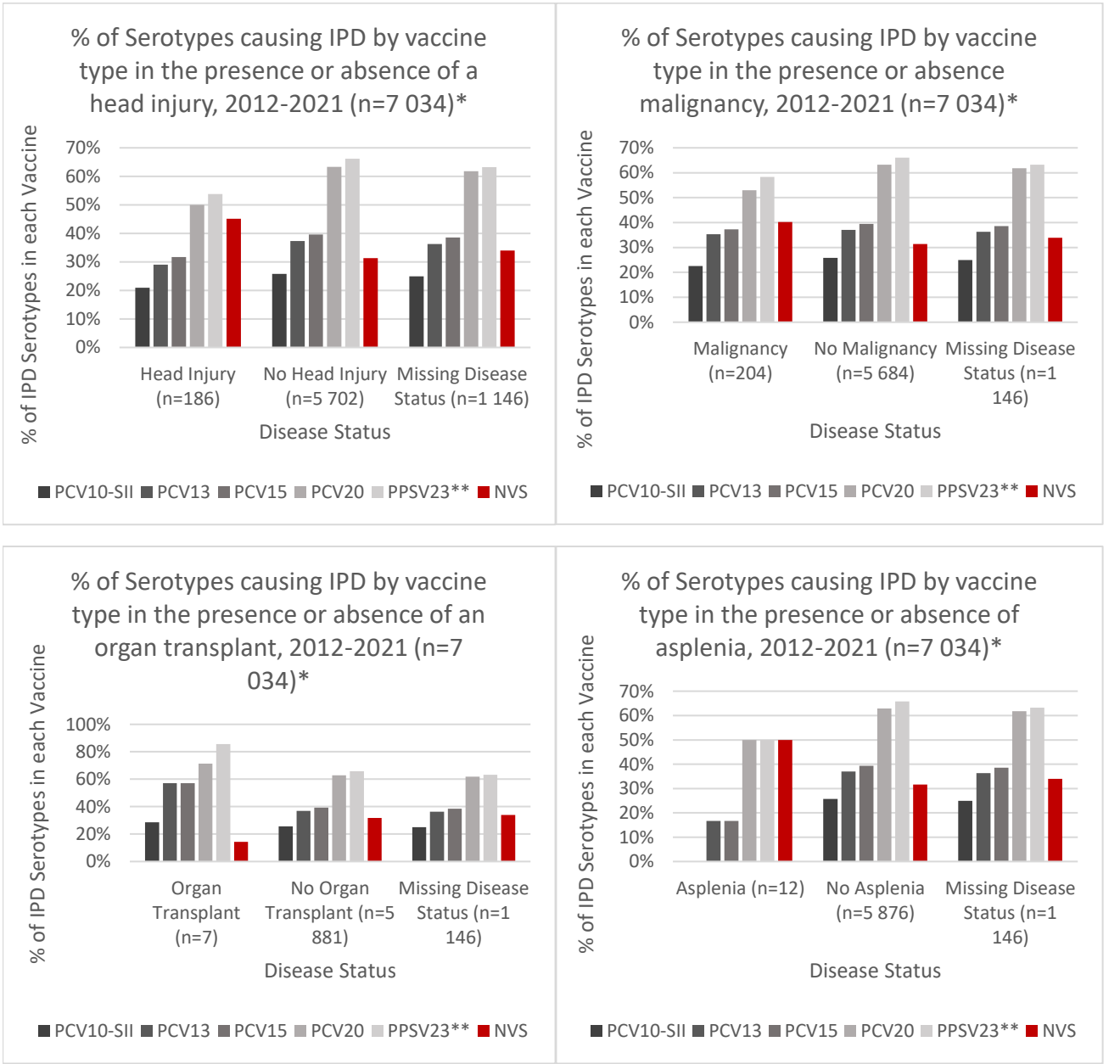
Interestingly, in cases with confirmed asplenia, PCV10-SII did not include any serotypes (n=0/12, 0%) associated with causing IPD. In these cases, PCV20 and PPSV23 only contained 50% of the serotypes causing IPD, meaning that NVS caused 50% of the IPD affecting persons with confirmed asplenia.

Similarly, patients with confirmed renal and liver disease, malignancy and head injury all had a higher percentage of IPD caused by non-vaccine serotypes than the percentage of serotypes included in PCV10-SII, PCV13 and PCV15.



*IPD cases not from ESS (n=10 416/17 450, 60%)
**PPSV23 does not include serotype 6A in its constituency, therefore it is not included in its calculation.

Figure 19: Percentage of vaccine and non-vaccine serotypes in pneumococcal vaccines causing invasive pneumococcal disease in South Africa by presence or absence of various comorbidities, 2012-2021.

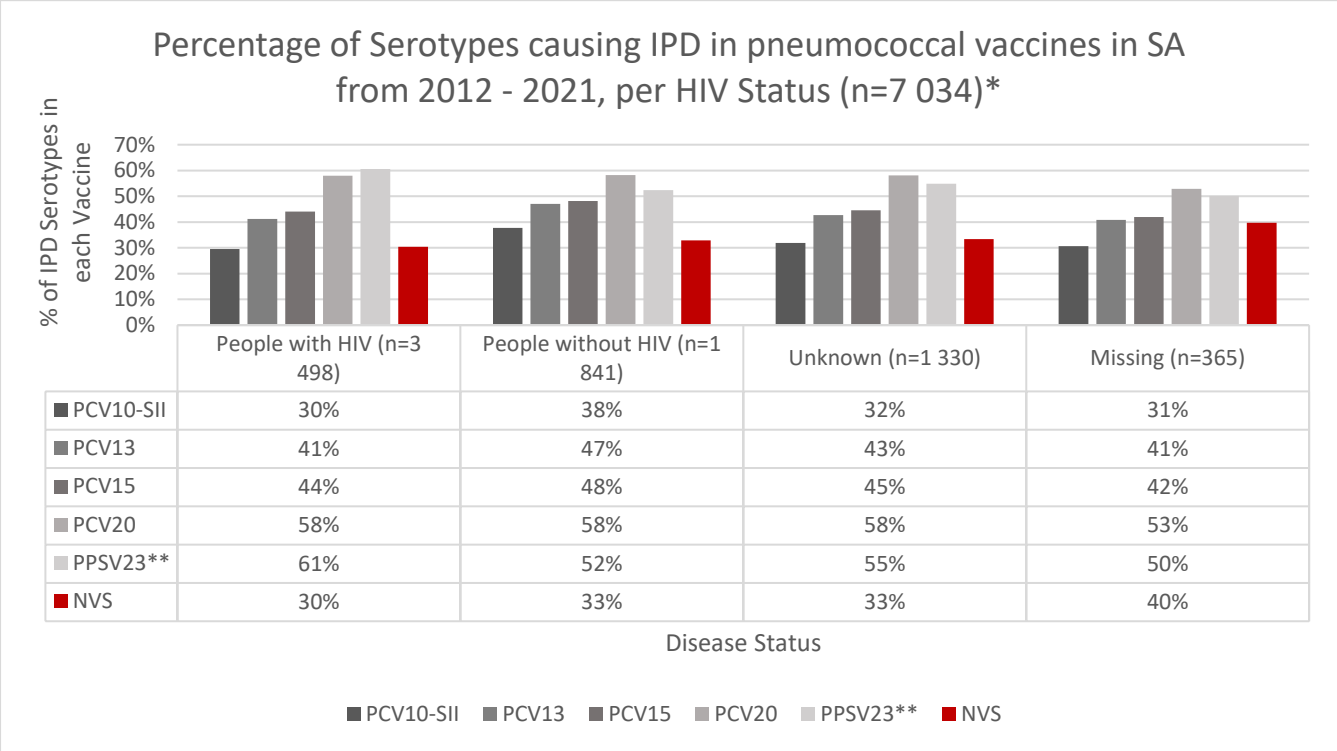


*IPD cases not from ESS (n=10 416/17 450, 60%)
**PPSV23 does not include serotype 6A in its constituency, therefore it is not included in its calculation.

Figure 20: Percentage of vaccine and non-vaccine serotypes in pneumococcal vaccines causing invasive pneumococcal disease in South Africa by presence or absence of various comorbidities, 2012-2021.

3.3.7. HIV

PCV10-SII (n=956/3 540, 27%) included the lowest proportions of vaccine serotypes causing IPD in people living with HIV disease (PLWH), and PCV20 (n=2 188/3 540, 62%) and PPSV23 (n=2 297/3 540, 65%) included the highest proportions of vaccine serotypes causing IPD in patients with comorbid HIV disease. A higher proportion of IPD serotypes were covered by PCV10-SII in people living without HIV than people living with HIV, however similar proportions of IPD was covered by PCV20 in people living with and without HIV disease.



	People with HIV (n=3 498)	People without HIV (n=1 841)	Unknown (n=1 330)	Missing (n=365)
PCV10-SII	30%	38%	32%	31%
PCV13	41%	47%	43%	41%
PCV15	44%	48%	45%	42%
PCV20	58%	58%	58%	53%
PPSV23**	61%	52%	55%	50%
NVS	30%	33%	33%	40%

*IPD cases not from ESS (n=10 416/17 450, 60%)
**PPSV23 does not include serotype 6A in its constituency, therefore it is not included in its calculation.

Figure 21: Percentage of vaccine and non-vaccine serotypes in pneumococcal vaccines causing invasive pneumococcal disease in South Africa, per HIV status, 2012-2021.

3.3.8. Risk Factors

The serotyped dataset from enhanced surveillance sites was restricted to individuals ≥ 18 years old to analyse the risk factors of alcohol use and smoking (n=5 619/7 034) (Figure 2).

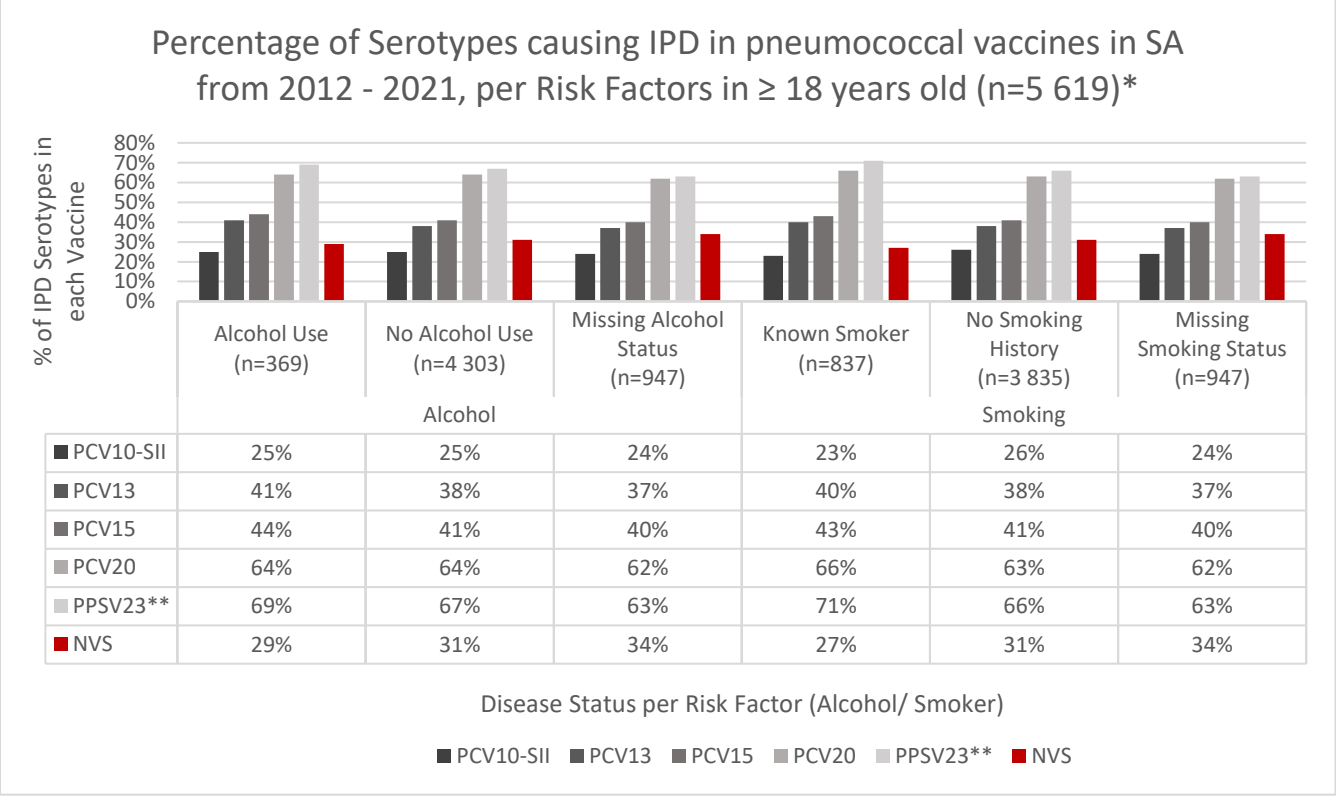
Across the risk factors analysed, in patients who confirmed alcohol use and smoking and those who did not, PCV10-SII contained the lowest percentage of serotypes causing IPD compared to PCV20 and PPSV23, which consistently contained the highest percentage, almost three times more, of serotypes causing IPD.

Alcohol Use:

The percentage of serotypes contained within pneumococcal vaccines was the same or minimally higher in patients who confirmed alcohol use (Range: 0%-3%) compared to those who did not. In patients with and without a confirmed alcohol history, non-vaccine serotypes caused a higher percentage of IPD than the percentage of serotypes included within PCV10-SII

Smoking:

Pneumococcal vaccines contained a slightly higher percentage (Range: 2%-6%) of vaccine serotypes in patients who smoked compared to patients who did not, except within PCV10-SII. Non-vaccine serotypes caused a higher percentage of IPD cases than the serotypes included within PCV10-SII, across patients who smoked and who did not.

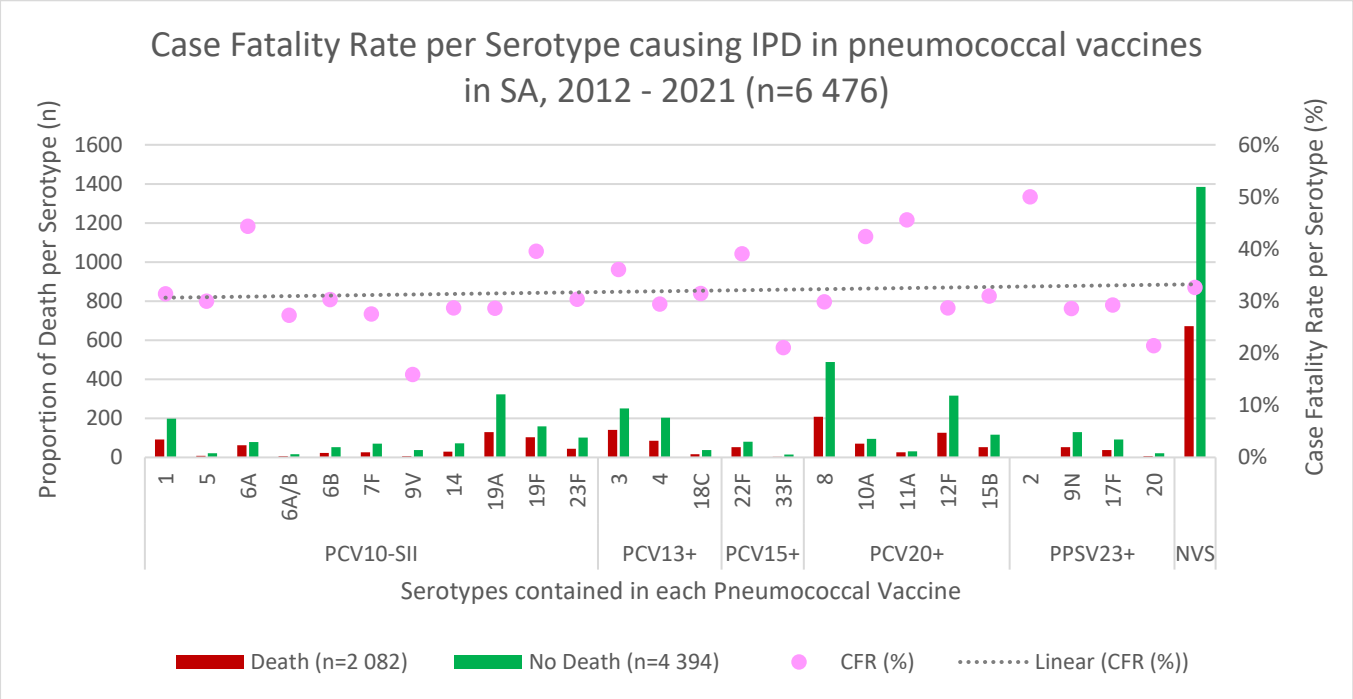


*Data of individuals < 18 years old not included in the analysis (n=1 415)
**PPSV23 does not include serotype 6A in its constituency, therefore it is not included in its calculation.

Figure 22: Percentage of vaccine and non-vaccine serotypes in pneumococcal vaccines causing invasive pneumococcal disease in South Africa, per risk factors, 2012-2021.

3.4. Case Fatality Rate (CFR) associated with IPD Serotypes Circulating in SA, 2012-2021

Overall, of all the serotyped IPD cases seen at enhanced surveillance sites with outcome data (n=6 476/7 034) (Figure 2), the case fatality rate was 32% (n=2 082/6 476). Figure 23 depicts the case fatality rate and proportion of IPD cases who died and who didn't die per IPD serotype in the various pneumococcal vaccines between 2012 and 2021. The CFR across the majority of the serotypes remained 30%-32% as seen with the trendline, which was in keeping with the overall CFR. Serotype 9V was noted to cause the lowest CFR of 16% (n=7/44). Serotypes 6A (n=63/142, 44%), 19F (n=159/263,40%), 3 (n=141/391, 36%), 10A (n=70/165, 42%), 11A (n=26/57, 46%) and 2 (n=1/2, 50%) were associated with a CFR over above the average of 32%.



*Missing outcome data (n=558/7 034, 8%)

Figure 23: Case fatality rate per serotype causing invasive pneumococcal disease in pneumococcal vaccines in South Africa, 2012 - 2021 (n=6 476).

The table below summarises the case fatality rate per variable and the results of the logistic regression analysis evaluating the association between the binary outcome variable, death, and the exposure variable being IPD serotypes (vaccine and non-vaccine serotypes) included in each pneumococcal vaccine. The effect of potential confounders and effect modifiers being age, province, HIV status and comorbidity status and multidrug resistance as a potential

mediator of this association were also analysed in the regression analysis and controlled for accordingly.

Higher case fatality rates were noted in individuals over 45 years of age, and certain provinces including the Eastern Cape (n=204/550, 37%), Limpopo (n=64/160, 40%), Mpumalanga (n=104/270, 39%) and the North-West (n=67/166, 40%).

Presence of at least one comorbidity was associated with a CFR of 32% (n=414/1274). Certain comorbidities including liver disease (n=43/112, 38%), cardiac disease (n=83/216, 38%), diabetes mellitus (n=104/242, 43%) and patients with a previous organ transplant (n=3/7, 43%) all had higher CFRs compared to the other comorbidities and risk factors analysed.

The logistic regression analysis showed that there was no significant association between the IPD serotypes (vaccine and non-vaccine serotypes) included within each pneumococcal vaccine and mortality.

The odds of death were significantly higher in patients aged less than 1 years old (aOR:1.074 ; 95% CI (1.015-1.136)), 45-65 years old (aOR: 1.155; 95% CI (1.095-1.219)) and those older than 65 years (aOR: 1.208; 95% CI (1.120-1.304)) compared to patients 1-4 years of age (referent). The odds of death were significantly lower in IPD patients aged between 5-9 years old (aOR: 0.896; 95% CI (0.829-0.970)) compared to those aged 1-4 years old (referent).

Patients living in the Eastern Cape (aOR: 1.114, 95% CI (1.066-1.165)), Limpopo (aOR: 1.119; 95% CI (1.035-1.209)) and the North-West provinces (aOR: 1.116; 95% CI (1.038-1.200)) all had significantly higher odds of mortality compared to IPD patients in Gauteng province (referent).

With regards to comorbidities, the odds of death was significantly higher in people living with HIV (aOR: 1.044; 95% CI (1.013-1.076)) than those living without HIV (referent). Of note, in the crude analysis, patients with at least one known comorbidity and those with confirmed liver disease, cardiac disease and diabetes mellitus all had a significant increase in the odds of mortality, however, when controlling for age, province, the presence of other comorbidities and risk factors, none of these showed statistically significant associations (p-values >0.05).

Table 3: Case fatality rate (CFR) associated with the various invasive pneumococcal disease serotypes circulating in South Africa for each of the new and existing pneumococcal vaccines and other exposure variables, 2012 -2021.

Enhanced Surveillance Site Dataset = 6 476 (n)*							
	Case Fatality Rate (CFR)			Univariate Regression		Multivariate Regression	
Variable	**n**	**Died (n)**	**CFR (%)**	**cOR** (95% CI)**	**p-value**	**aOR*** (95% CI)**	**p-value**
IPD Serotypes (VS and NVS)							
PCV10-SII Serotypes (1,5,6A,6B,7F,9V,14,19A,19F,23F)	1662	532	32%	0.972 (0.846-1.116)	0.685	1.017 (0.985 - 1.050)	0.300
PCV13 Additional Serotypes (3,4,18C)	734	243	33%	1.022 (0.854-1.222)	0.816	0.992 (0.950-1.035)	0.699
PCV15 Additional Serotypes (22F,33F)	152	56	37%	1.204 (0.855-1.695)	0.288	1.051 (0.968-1.142)	0.234
PCV20 Additional Serotypes (8,10A,11A,12F,15B)	1530	483	32%	0.952 (0.826-1.097)	0.499	0.992 (0.960-1.025)	0.634
PPSV23 Additional Serotypes (2,9N,17F,20)	342	97	28%	0.817 (0.635-1.052)	0.117	0.980 (0.926-1.036)	0.472
Non-Vaccine Serotypes (Non-PPSV23/6A)	2056	671	*33%*	*ref*		*ref*	
Age Group							
<1	794	238	*30%*	**1.876 (1.411-2.495)**	**0.000**	**1.074 (1.015-1.137)**	**0.013**
1-4	436	81	19%	*ref*		*ref*	
5-9	211	23	11%	**0.536 (0.327-0.880)**	**0.014**	**0.896 (0.829-0.970)**	**0.006**
10-14	145	21	14%	0.742 (0.441-1.251)	0.263	0.964 (0.881-1.055)	0.421
15-24	417	115	28%	**1.669 (1.208-2.305)**	**0.002**	1.029 (0.964-1.098)	0.392
25-44	2644	820	31%	**1.970 (1.527-2.543)**	**0.000**	1.046 (0.995-1.100)	0.077
45-65	1393	571	41%	**3.044 (2.338-3.964)**	**0.000**	**1.155 (1.095-1.219)**	**0.000**
>65	414	197	48%	**3.979 (2.921-5.419)**	**0.000**	**1.208 (1.120-1.304)**	**0.000**
Unknown	22	16	73%				
Province							
GP	2531	767	*30%*	*ref*		*ref*	
EC	550	204	37%	**1.356 91.118-1.644)**	**0.002**	**1.114 (1.066-1.165)**	**0.000**
FS	323	99	31%	1.016 (0.791-1.307)	0.899	1.017 (0.962-1.076)	0.543
KZ	918	282	31%	1.020 (0.866-1.201)	0.815	1.005 (0.968-1.043)	0.796
LP	160	64	40%	**1.533 (1.105-2.127)**	**0.011**	**1.119 (1.035-1.209)**	**0.005**
MP	270	104	39%	**1.441 (1.111-1.868)**	**0.006**	1.058 (0.989-1.132)	0.103
NC	254	83	33%	1.116 (0.847-1.470)	0.434	1.042 (0.982-1.106)	0.176
NW	166	67	40%	**1.556 (1.129-2.147)**	**0.007**	**1.116 (1.038-1.200)**	**0.003**
WC	1264	395	31%	1.045 (0.903-1.210)	0.551	0.985 (0.950-1.020)	0.386
Unknown	40	17	43%				
HIV							
Living with HIV	3445	1002	*29%*	**1.289 (1.131-1.468)**	**0.000**	**1.044 (1.013-1.076)**	**0.005**
Living without HIV	1810	437	*24%*	*ref*		*ref*	
Missing	1221	643	*53%*				
Multidrug Resistance							
Yes	906	313	*35%*	1.108 (0.953-1.287)	0.182		
No	4660	1504	*32%*	*ref*		*ref*	
Missing	910	265	*29%*				
Comorbidities							
Comorbidity							

Yes	1274	414	*32%*	**1.261 (1.103-1.441)**	**0.001**	1.004 (0.966-1.045)	0.826
No	4556	1259	*28%*	*ref*		*ref*	
Missing	646	409	*63%*				
Lung							
Yes	306	77	*25%*	0.827 (0.635-1.078)	0.161		
No	5524	1596	*29%*	*ref*		*ref*	
Missing	646	409	*63%*				
Renal							
Yes	241	80	*33%*	1.246 (0.947-1.640)	0.115		
No	5589	1593	*29%*	*ref*		*ref*	
Missing	646	409	*63%*				
Liver							
Yes	112	43	*38%*	**1.563 (1.063-2.297)**	**0.023**	1.087 (0.985-1.199)	0.097
No	5718	1630	*29%*	*ref*		*ref*	
Missing	646	409	*63%*				
Cardiac							
Yes	216	83	*38%*	**1.579 (1.193-2.090)**	**0.001**	1.053 (0.976-1.137)	0.183
No	5614	1590	*28%*	*ref*		*ref*	
Missing	646	409	*63%*				
Diabetes							
Yes	242	104	*43%*	**1.930 (1.487-2.506)**	**0.000**	1.054 (0.979-1.135)	0.165
No	5588	1569	*28%*	*ref*		*ref*	
Missing	646	409	*63%*				
Head Injury							
Yes	183	63	*34%*	1.316 (0.965-1.795)	0.083		
No	5647	1610	*29%*	*ref*		*ref*	
Missing	646	409	*63%*				
Organ							
Yes	7	3	43%	1.865 (0.417-8.342)	0.415		
No	5823	1670	*29%*	*ref*		*ref*	
Missing	646	409	63%				
Asplenia							
Yes	12	3	25%	0.828 (0.224-3.062)	0.777		
No	5818	1670	*29%*	*ref*		*ref*	
Missing	646	409	63%				
Malignancy							
Yes	203	48	24%	0.763 (0.549-1.060)	0.106		
No	5627	1625	*29%*	*ref*		*ref*	
Missing	646	409	63%				
Risk Factors							
Alcohol							
Yes	368	118	32%	1.186 (0.945-1.488)	0.140		
No	5462	1555	*28%*	*ref*		*ref*	
Missing	646	409	63%				
Smoker							
Yes	839	220	26%	0.865 (0.733-1.021)	0.087		
No	4991	1453	*29%*	*ref*		*ref*	
Missing	646	409	63%				

*Missing outcome data (n=558/7 034, 8%)
**cOR – crude odds ratio
***aOR – adjusted odds ratio

4. DISCUSSION

High rates of invasive pneumococcal disease pose a public health threat not only globally, but specifically to countries like South Africa, where vulnerable populations such as the young, elderly and the immunocompromised are often disproportionately affected (5–7,11,16,17,21). Since 2009, vaccination strategies such as the inclusion of pneumococcal conjugate vaccines in the EPI-SA have immensely helped to mitigate the mortality and morbidity caused by IPD (5–7,11,16,17,21), however, the dynamic nature of pneumococcal serotypes and their response to vaccines required an in-depth analysis of IPD cases in South Africa. The introduction of two new higher-valent PCVs internationally and the impending change over to using PCV10-SII in South Africa has also necessitated the evaluation of IPD serotypes and available vaccines to ensure optimal protection for the South African population is maintained. The major findings of this study will be discussed throughout this section with relevant explanations and public health associations described.

This study found that 23 789 IPD cases occurred over the ten-year period in South Africa, with an average annual incidence of 4.22 IPD cases per 100 000 persons occurring between 2012-2021. Highest absolute numbers of the IPD cases occurred within Gauteng, KwaZulu-Natal and the Western Cape provinces and affected individuals between the ages of 25 to 44 years old, followed by the expected vulnerable groups, being the elderly and children less than five years of age. This highlights the changing pattern in the disease trend of IPD due to South Africa's effective immunisation programme(16). This finding correlates to Gauteng, KwaZulu-Natal and the Western Cape being the economic hubs and most densely populated provinces of the country with working class individuals between the ages of 25-44 years old partaking in a variety of social activities and travelling, increasing their risk and exposure to disease (37,40).

Over the years, South Africa saw a slow but fairly consistent decrease in the number of IPD cases occurring since the introduction of PCV13 into the EPI-SA schedule in 2011. The vaccination of children in South Africa inadvertently resulted in the decrease of adult IPD cases throughout the years due to herd immunity (5–7,11,17,20,21,23). Additionally, the effects of the COVID-19 pandemic was seen when analysing the yearly IPD trends as there was a significant decrease in IPD cases reported to GERMS-SA during 2020 and 2021. This could be due to a multitude of reasons; IPD cases may have decreased due to the public health measures in place during the pandemic such as handwashing, mask-wearing and physical distancing (20,33). Alternatively, the pandemic and the subsequent lockdowns that

occurred in an attempt to restrict movement, could have potentially resulted in the decrease of IPD transmission, particularly amongst children as schools were closed. Another reason would be increased difficulty for people to travel to seek healthcare timeously when ill (20,33).

Across age groups and provinces, serotypes 8, 19A and 12F were the top three most commonly circulating serotypes between 2012 and 2021, with serotype 19A included within all pneumococcal vaccines and serotypes 8 and 12F only included within PCV20 and PPSV23, a finding that is supported by previous studies (11,17,20,23,33). In the majority of the age groups including the marginalised (< 1, 15-24, 25-44, 45-64 and >65 years old) and across seven of South Africa's provinces (Eastern Cape, Free State, Gauteng, Limpopo, Mpumalanga, Northern Cape, and the Northwest), serotype 8 was the top circulating serotype associated with causing IPD. Overall, the additional serotypes included within PCV20 caused the majority of IPD within the vulnerable age groups in LP, NW, and EC provinces. This is important to note considering that South Africa is changing over to PCV10-SII, a vaccine with less serotypes than the current vaccine in use and which only includes serotype 19A from the list above. The percentage of IPD cases caused by serotype 8 has doubled in the last ten years, and if left unattended to, may continue on its upward trajectory, severely affecting the South African population.

In terms of serotypes causing IPD in South Africa, this study highlighted that specific non-vaccine serotypes caused a substantial number of IPD cases in the country over the ten-year period. The individual non-vaccine serotypes 16F, 15A, 13, 6C, 23A and 7C caused more cases of IPD (Range: 2%-3%) in SA between 2012 and 2021 than the following vaccine serotypes 5, 6B, 7F, 9V, 14, 18C, 33F, 11A, 2 and 20, which caused less than 2% of IPD cases each. Six of these vaccine serotypes mentioned, are contained within the current vaccine in use, PCV13. The public health implications of this is three-fold, the first being that the above showcases that PCV13 in the EPI-SA has been effective in reducing the transmission of IPD caused by the serotypes included within the vaccine. The second is that if vaccine serotypes causing disease are controlled through vaccine use, it allows for circulating non-vaccine serotypes causing IPD, that are not protected against, to increase and therefore cause disease. This is a phenomenon commonly known as serotype replacement and would need to be monitored closely, especially with the switchover to a lower-valent vaccine (PCV10-SII) occurring soon (32,41). Although this is a well-known phenomenon, one must consider that serotype replacement of vaccine serotypes is not always complete as non-

vaccine serotypes and newly circulating NVS may be less virulent than VS, resulting in lower rates of disease (42,43). The third implication being that these non-vaccine serotypes, particularly 16F and 15A, should be closely observed and considered for inclusion in future PCVs, specifically for the South African context. This finding was corroborated by previous studies which also concluded that serotype 15A should be considered for inclusion in future pneumococcal vaccines in South Africa (11).

This study analysed the circulating serotypes causing IPD in the SA population and compared these to the serotypes included in different pneumococcal vaccines, to determine which vaccine best covered the circulating serotypes found over the study period. Using serotyped data, it was found that 68% of the serotypes causing IPD were found within PPSV23, followed by 63% in PCV20, 40% in PCV15, 37% in PCV13 and lastly, only 26% of the serotypes causing IPD were found within PCV10-SII. Since only a small number of vaccination status for the different vaccines was known, it was beyond the objectives of this study and therefore not analysed. Thus, neither vaccine effectiveness nor efficacy could be reported on in its entirety.

It can be presumed, however, that IPD caused by a vaccine serotype that is included in a specific pneumococcal vaccine may have been protected against in some capacity, if the patient had been vaccinated with that pneumococcal vaccine prior to *S. pneumoniae* infection or if the vaccine has been widely used in the population for some time providing indirect immunity.

Relating this to the information above, PCV20 would potentially provide 2.4 times more protection against circulating IPD serotypes once vaccinated compared to PCV10-SII for the South African population. The current PCV13 in use, provides 1.4 times more protection against circulating IPD serotypes in vaccinated individuals compared to the proposed PCV10-SII that South Africa is switching to. The decision to use PCV10-SII in the EPI-SA was driven by its price, with PCV10-SII costing approximately R128.56 less than the current PCV13 (29,30). It was therefore deemed much more cost effective than PCV13 and other higher-valent vaccines, interchangeable and met NAGI immunisation requirements by covering prevalent serotypes causing IPD in SA (29,30). Cost-effectiveness analyses have modelled however, that use of PCV10-SII may potentially cause an increase in IPD in children younger than 2 years of age by 73.4% after ten years compared to continued use of PCV13 (29). It was also predicted that PCV13 would be cost-saving over a 5- and 10-year

period compared to PCV10-SII, which needs to be studied throughout the implementation of PCV10-SII in the EPI-SA.

Although PPSV23 would potentially cover against the highest percentage of serotypes causing IPD (68%), the vaccines inability to provoke a strong immune response and its ineffectiveness in the paediatric population prevents a direct comparison with PCVs. All of these hypotheses with regards to the potential protection offered by each vaccine would need to be investigated further in additional studies.

When this data was disaggregated down to province and age group, PPSV23 consistently contained the highest percentage of serotypes causing IPD followed by PCV20 and PCV10-SII constantly contained the lowest percentage of serotypes causing IPD in the South African population. A further in-depth analysis into the serotypes causing IPD included in each vaccine, as seen in Figure 10, emphasised that the serotypes causing IPD in children less than five years old across several provinces were not adequately covered by, PCV10-SII, PCV13 and/or PCV15. There was a significantly higher percentage, more than double of the vaccine serotypes, included within available higher-valent vaccines, such as PCV20 and PPSV23. This was likely attributable to the infant immunisation programme using PCV13 to directly prevent disease therefore resulting in far fewer vaccine serotypes in this age category, as expected. The serotype replacement due to the introduction and use of PCV13 could also explain why the prevalence of serotypes not included within PCV13 are currently on the rise (32,41).

The penicillin and ceftriaxone resistance analyses highlighted that the most common serotypes associated with penicillin and ceftriaxone resistant IPD cases were all included in PCV10-SII. The analysis of serotypes included in each available vaccine emphasized that although PCV20 would offer the greatest protection against these resistant IPD cases, PCV10-SII would offer adequate protection, covering the majority (> 50%) of the penicillin and ceftriaxone non-susceptible serotypes causing IPD.

The multidrug resistance analysis results stated that out of all the IPD cases that occurred across the country between 2012 and 2021, 13% of the cases were multidrug resistant. Serotypes 12F, 19F, 23F, 14 and 3 caused the majority of multidrug resistant IPD cases. These findings echo results from the pre-vaccine era, where the same serotypes were associated with multidrug resistant IPD (2). PCV10-SII contains almost 50% of these serotypes (19F, 23F, 14) but despite this finding, PCV20 includes a substantially higher

percentage of serotypes associated with MDR IPD cases, 30% more than PCV10-SII and 20% more than PCV13 and PCV15.

These findings accentuate that in terms of tackling resistant IPD, especially penicillin and ceftriaxone resistance, PCV10-SII would adequately protect the South African population, which bodes well for the country's future changeover to PCV10-SII from PCV13.

It is well-known that vulnerable populations are at a higher risk of contracting and developing severe IPD (5–7,11,16,17,21). The analysis of high-risk individuals with certain comorbidities, as depicted by the ACIP and South African clinician recommended guidelines, determined that regardless of whether patients suffer from these comorbidities or not, a combination of PCV15 and/or PCV20 and PPSV23 would offer the most protection against IPD compared to PCV10-SII, which consistently offered the least. According to this study, pneumococcal vaccines would potentially offer more protection against IPD in patients with confirmed lung disease (PCV20: 68%, PPSV23: 74%) and in those with a previous organ transplant (PCV20:71%, PPSV23:86%) as they include a slightly higher percentage of vaccine serotypes causing IPD compared to patients without disease (PCV20: 63%, PPSV23: 65%) or a previous transplant (PCV20: 63%, PPSV23: 66%). Therefore, provisions to prioritise these patients to receive pneumococcal vaccines should be considered. The other comorbidities analysed showed that vaccines included a similar or less percentage of serotypes causing IPD across patients with and without disease.

Of note, PCV10-SII contained 0% of the serotypes causing IPD in patients with asplenia, although only a small sample size was considered (n=12). In asplenia, renal and liver disease, malignancy, and head injury cases, NVS included more serotypes causing IPD than the serotypes contained within PCV10-SII, PCV13 and PCV15. This finding draws attention to the fact that these comorbidities with a lower percentage of vaccine serotypes causing IPD, have a wider range of serotypes causing disease. In other words, due to their chronic illnesses, they are at risk of severe IPD caused by all serotypes and not just those that are known to be highly virulent in nature. This means that only PCV20 and PPSV23 would offer optimal protection against IPD in these patients which is particularly important since South Africa will be switching over to PCV10-SII in 2024, putting children and individuals with asplenia, renal and liver disease, malignancy, and head injuries at an even higher risk of contracting and developing severe IPD, even if vaccinated. It also confirms that these individuals are indeed high-risk groups within the South African population.

Certain conjugate vaccines included a lower percentage of serotypes causing IPD in patients living with HIV (PCV10-SII: 30%, PCV13: 41% and PCV15: 44%) compared to patients living without HIV (PCV10-SII: 38%, PCV13: 47% and PCV15: 48%), offering less protection to PLWH. PCV20 and PPSV23 almost doubled the percentage of serotypes causing IPD within it compared to PCV10-SII, therefore suggesting that higher-valent vaccines would be more beneficial to this marginalised population. Alcohol and smoking habits in patients ≥ 18 years with IPD was analysed, and PCV20 and PPSV23 contained the highest percentage of serotypes causing IPD. PCV10-SII contained the lowest percentage of serotypes causing IPD in these patients, to the point where non-vaccine serotypes caused more IPD than the serotypes included in PCV10-SII.

Considering the above study findings, PCV10-SII would not provide adequate protection against IPD regardless of whether patients had the comorbidities, risk factors and HIV statuses analysed above or not, compared to other available higher-valent vaccines. The vaccines would also provide a similar level of protection against IPD regardless of whether patients suffered with disease or not in the majority of comorbidities analysed. The current PCV13 in use, hypothetically offers substantially more protection against IPD in these patients and would potentially prevent more cases of IPD from occurring than PCV10-SII. PCV20 would offer the most protection as it constantly includes the highest percentage of serotypes causing IPD in a conjugate vaccine, but as an alternative, PPSV23 should be seriously considered for inclusion in an official adult vaccination schedule, as it consistently included the highest percentage of serotypes causing IPD across South Africa.

In terms of the case fatality rate for IPD cases in South Africa between 2012 and 2021, this study found that the overall CFR was 32% based on the data collected by GERMS-SA from enhanced surveillance sites, matching the results found in previous studies calculating the CFR between 2012 and 2018 (11).

There was no significant association noted between the IPD serotypes included within each pneumococcal vaccine and mortality. The rest of the results obtained from the multivariate analysis were expected based on previous studies performed. The odds of death was significantly lower in patients aged 5-9 years old (aOR: 0.896, 95% CI (0.829-0.970)) and higher in children less than one years of age (aOR: 1.074, 95% CI (1.015-1.137)) and patients between 45-65 years (aOR: 1.155, 95% CI (1.095-1.219)) and over the age of 65 years (aOR: 1.208, 95% CI (1.120-1.304)) compared to children 1-4 years of age. This finding was

expected as the CFR in these groups were notably higher and the young and elderly are vulnerable populations that have been noted to suffer from severe disease (11). The significance of this finding stresses that these populations should continuously be targeted in future pneumococcal vaccination campaigns and that the adult population should be incorporated into official government endorsed vaccine schedules to prevent death. The Eastern Cape, Limpopo, and North-West provinces all significantly increased the odds of death by 11%, 12% and 12%, respectively, compared to the Gauteng province. This correlates to earlier findings that showed that these provinces had higher CFR's and that the majority of the IPD cases in these provinces were caused by serotypes only included in higher-valent vaccines and therefore were not protected against by the current PCV13 in use. Limited access to and availability of healthcare services such as the shortage of ambulances, exacerbated by high percentages of poverty and unemployment, in these provinces may contribute to these findings (44). Recent statistics for 2022/23 show that the Eastern Cape and Limpopo province continue to have higher pneumococcal case fatality rates than other provinces (45). The North-West and Limpopo provinces also had significantly lower immunisation rates in children less than one years old compared to other provinces, contributing to the mortality rates in these areas (45).

Patients living with HIV were also noted to have a significantly higher odds of death (aOR: 1.044, 95% CI (1.013-1.076)) compared to patients without HIV, accentuating the need to prioritise this marginalised group. With regards to other comorbidities, initially in the univariate analysis, specific comorbidities including liver and cardiac disease as well as patients with diabetes mellitus had a significantly higher odds of death compared to those without those comorbidities. The comorbidities were also singled out as having higher CFR's than other comorbidities, however, when controlling for the multiple significant variables, none of these had statistically significant associations.

5. LIMITATIONS

1. Since the data collected for the GERMS-SA database is collected through medical record review and patient interviews, there is a risk of bias introduced by the difference in the depth of details in medical records kept by clinicians in the hospitals. This could potentially affect the GERMS-SA dataset as all the comorbidities reported on need to be corroborated with clinical notes and laboratory results.

2. Using only laboratory-based surveillance data may underestimate cases due to health seeking behaviour of persons, decisions by clinicians on whether to take a specimen or just treat empirically, ability of the organism to be identified by the laboratory and lastly, ability of the laboratory to report the organism to the surveillance programme.
3. There may be an underestimation of IPD cases arising from technical errors from both the clinician (incorrect specimen collection) and diagnostic laboratory side (not submitting isolates and incorrect specimen processing) which could lead to non-reporting of cases.
4. Serotype 3 is a major vaccine serotype that is still circulating despite the wide use of pneumococcal vaccines protecting against this serotype. It appears that the conjugate vaccine may not elucidate a high enough immune response against this serotype. Therefore, by its inclusion in all the PCVs except PCV10-SII it may falsely elevate the percentage of serotypes covered by the higher valency vaccines.
5. The effectiveness and efficacy of pneumococcal vaccines was not analysed during this study due to the study design of the surveillance programme and so there are limitations attached to the protection each vaccine could have potentially offered if used prior to infection with *S. pneumoniae*.
6. There is missing data from the dataset obtained from GERMS-SA which was reported as missing data when encountered. This may diminish the accuracy of the results and reliability of the conclusions of this study.
7. Sample sizes of certain comorbidities analysed including patients with confirmed asplenia and a previous organ transplant were small in size, which may limit the generalisability of the findings within this study to the wider public.

6. ETHICS

Ethics approval was granted from the Human Research Ethics Committee (Medical) of the University of Witwatersrand (Ref No: M221167) (Appendix 2) and the Academic Affairs and Research Committee of the NHLS (Ref No: PR2232835) (Appendix 3) approved the use of the GERMS-SA collected data required for this study.

GERMS-SA received ethical clearance and approval from seven university ethics boards in the country as well as provincial approval from all provinces through the National Health Research Database (NHRD) for the surveillance of diseases of public health importance. Reference numbers for University of the Witwatersrand Health Research Ethics committee

(Human) are provided: WHREC M081117 for Protocol dated 2009-2013; WHREC M140159 for Protocol dated 2014-2018; and WHREC M1809107 for Protocol dated 2019-2023.

The extracted data received were already de-identified and anonymised by GERMS-SA and contained no personal information to conserve patients' confidentiality and anonymity. All electronic information received is kept under password protection on the principal investigator's computer to maintain confidentiality and only the principal investigator and supervisors have access to the above-mentioned data. The principal investigator performed the data management, analysis, report writing and submission for this study with help from the supervisors, when necessary.

All data obtained will be stored by the principal investigator, electronically on their personal computer under password protection for a period of two to six years and dissemination and publication of the research will be organised by the principal investigator with the help of the NICD, WITS SPH and supervisors.

7. CONCLUSION

In conclusion, this study has shown that the IPD disease profile in South Africa is constantly shifting, and that continuous surveillance is vital to preventing the potential public health threat that IPD poses, as a third of IPD patients succumb to death from disease.

Key findings include that vaccine serotypes commonly causing IPD in South Africa are only available in PCV20 and PPSV23. PCV10-SII would sufficiently protect against antimicrobial and multidrug resistance and that IPD cases caused by non-PCV13 vaccine serotypes are on the rise, emphasising the need to critically reflect on the country's current vaccine procurement policies and vaccination strategies. Additionally, the study highlighted that pneumococcal vaccines would potentially provide more protection to patients with lung disease and a previous organ transplant than those without and that IPD disproportionately affects specific age groups, provinces and the immunocompromised, underscoring the importance of targeted public health interventions and the inclusion of adults and high-risk individuals in government approved vaccination guidelines.

In terms of vaccine coverage against serotypes causing IPD, PCV10-SII consistently included the lowest percentage of vaccine serotypes causing IPD and since South Africa is in the midst of transitioning from PCV13 to PCV10-SII in the near future, the ongoing monitoring and evaluation of IPD and serotypes is crucial to ensuring the population is optimally protected.

Overall, this study has emphasised that IPD continues to be a challenge despite the introduction of PCVs into the EPI-SA and that ongoing surveillance is imperative to provide evidence-based data which will inform the development and implementation of vaccination policies to safeguard the population of South Africa.

8. RECOMMENDATIONS

Based on the findings of the study, the following recommendations have been determined:

1. The transition from PCV13 to PCV10-SII in the EPI-SA needs to be routinely monitored and carefully observed as PCV10-SII has consistently included the lowest percentage of vaccine serotypes causing IPD compared to the current vaccine in use and other available pneumococcal vaccines.
    a. As South Africa currently only has a NDoH endorsed vaccination programme for infants (EPI-SA), it is essential that the pneumococcal vaccine used in children contains the serotypes that commonly cause IPD in children and adults alike, due to the benefits of the indirect protection provided. This underscores the need to monitor the use of PCV10-SII and the IPD incidence trends that follow, since the lower-valent vaccine only contains a fraction of the serotypes causing invasive pneumococcal disease in the population.
2. A robust vaccination guideline with different regimens, including the combined use of PCV20 and PPSV23, should be considered for use in the South African population (adults and children), especially high-risk groups, as recommended by the ACIP (Annexure 3 – Table 6).
    a. Higher-valent pneumococcal conjugate vaccines, specifically PCV20, should be considered for use throughout the South African population, including children and adults, as it consistently contained the highest percentage of serotypes causing IPD.
    b. PPSV23 will potentially cover against a high percentage of IPD cases, particularly in high-risk adult populations, but the weakness of the vaccine in terms of stimulating an immune response, its ineffectiveness in children and inability to contribute to herd immunity needs to be taken into consideration.
3. Specific populations need to be targeted during vaccine campaigns in the country; this would include the most affected, including high risk individuals between 25-44 years old. Vulnerable populations such as the young, elderly, immunocompromised and those within certain provinces would need to be prioritised during vaccination

campaigns as these are the groups highly associated with increased mortality. This also accentuates the need for an adult pneumococcal disease vaccine schedule that is approved by the National Department of Health.

   a. Patients living with HIV have a statistically significant higher odds of mortality and therefore should be prioritised in vaccination campaigns in order to prevent severe health outcomes.
   b. Patients residing within Limpopo, the North-West and Eastern Cape provinces also had a significantly higher odds of death than the other provinces and therefore should be targeted during vaccination campaigns.

4. Focusing on comorbidities analysed, the study showed that regardless of comorbidity status, higher-valent vaccines (PCV20 and PPSV23) offered the most protection against IPD by inclusion of the highest percentage of vaccine serotypes causing IPD.
   a. Patients with lung disease and possibly those with a previous organ transplant, bearing in mind the limited sample size, would benefit more from vaccination due to the slightly higher percentage of vaccine serotypes causing IPD contained within pneumococcal vaccines in these populations.
   b. Other comorbidities, especially renal and liver disease, malignancy and patients with a head injury were at a higher risk of contracting severe IPD due to the broad spectrum of serotypes causing disease compared to serotypes included in the vaccines. It is of paramount importance that these high-risk groups are prioritised and routinely vaccinated in order to maximise their protection against invasive pneumococcal disease serotypes. Patients with asplenia were also included in this category, although the small sample size analysed may limit generalisability across the population.
5. PCV20 would be the best vaccine of choice to prevent antimicrobial and multidrug resistant IPD cases, although this study found that PCV10-SII included the majority of non-susceptible serotypes causing IPD and would therefore adequately protect the population against resistant IPD.
6. In terms of non-vaccine serotypes causing IPD in South Africa, the number of IPD cases caused by NVS is on an upward trajectory and must be continuously analysed. Serotype 16F and 15A, amongst others, should be monitored and considered for inclusion in a South African specific pneumococcal vaccine.
7. Likewise, with the impending change to PCV10-SII, serotype replacement is expected to occur, with non-PCV10-SII serotypes starting to increase and cause more IPD

across the population. Some of which, may have been serotypes previously controlled for by the use of PCV13.

   a. To address this well-known phenomenon, pneumococcal vaccines that cover an extensive variety of serotypes, currently in development and clinical trial phase, should be considered for use across the population (28,46).
   b. Non-serotype dependent vaccine compositions to address the burden of IPD would be ideal for global vaccination plans going forward (46).

8. The ongoing surveillance and monitoring and evaluation of IPD, especially after the COVID-19 pandemic, is important in order to analyse the IPD trends and circulating serotypes contributing to the South African disease burden. This is crucial to combat the disease and mitigate against IPD-related morbidity and mortality.
9. Future research on the effectiveness of pneumococcal vaccines used in South Africa, including the PCV10-SII, should be conducted in order to properly ascertain the benefits of pneumococcal vaccination programmes on the population.
10. Lastly, ongoing cost-effectiveness analyses need to be done comparing the different PCV vaccines in the long run as the cost-saving on using PCV10-SII may end up being off-set by the costs of more non-PCV10-SII serotype IPD circulating in the country.

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10. ANNEXURES

Annexure 1 – Table 4: Overview of Non-Vaccine Serotypes (n=5 499/23 789)

Serotype	Freq. (n)	% causing IPD (n/17 450)
6A/B/C/D	1	0%
6AB/19BF	1	0%
6ABCD	1	0%
6C	324	2%
6C/D	52	0%
6D	5	0%
7A	4	0%
7A/F	19	0%
7B	7	0%
7C	289	2%
9A	2	0%
9A/V	10	0%
9ALVN	6	0%
9L	5	0%
10AB	9	0%
10B	6	0%
10B/F	1	0%
10F	43	0%
11A/D	18	0%
11B	12	0%
11C	8	0%
11D	1	0%
11F	4	0%
12A	1	0%
12A/B/F/44/46	164	1%
12ABF	49	0%
12B	1	0%
12B/F	1	0%
13	370	2%
15	2	0%
15A	554	3%
15A/F	20	0%
15ABCF	25	0%
15AF	44	0%
15AF/19A	1	0%
15C	9	0%
15F	22	0%
16	1	0%
16F	601	3%
17A	1	0%
18A	63	0%
18A/B/C/F	27	0%
18ABC	13	0%
18B	6	0%
18F	24	0%
19B	23	0%
19BF	16	0%
19C	7	0%
19F/21	1	0%
21	88	1%
22A	13	0%
22A/F	62	0%
23A	299	2%
23B	160	1%
24	44	0%
24/19B	1	0%
24F	6	0%
25A/38	93	1%
25AF38	4	0%
25F	55	0%
27	6	0%
28A	16	0%
28F	9	0%
29	15	0%
31	119	1%
33A	12	0%
33A/F	1	0%
33A/F/37	3	0%
33AF/37	13	0%
33B	3	0%
33D	68	0%
34	100	1%
34/16F	1	0%
35A	11	0%
35B	248	1%
35C	1	0%
35F	27	0%
36	5	0%
37	12	0%
38	8	0%
39	1	0%
45	2	0%
48	14	0%
INS	168	1%
ND	1	0%

NEG38	511	3%
NEG42	100	1%
NT	15	0%
POOL G	309	2%
POOL G/8	1	0%

Annexure 2 – Table 5: South African recommendations for vaccination against pneumococcal diseases, 2022 (22)

Age	**Recommendation**
Infants and young children are vaccinated according to the EPI-SA schedule	6 and 14 weeks and a booster at 9 months
Adults aged ≥65 years with or without comorbid conditions (PCV naïve)	A single dose of PCV13 followed by a dose of PPSV23 (≥ 1 year later)
Adults < 65 years with comorbid conditions (PCV naïve)	A single dose of PCV13 followed by a dose of PPSV23 (≥ 1 year later)
Immunocompromised and high-risk adults (PCV naïve)	A single dose of PCV13 followed by a dose of PPSV23 (≥ 8 weeks later)
PPSV23 aged ≥ 65 years (Previously vaccinated)	A single dose of PCV13 (≥ 1 year later)
PPSV23 in adults < 65 years with comorbid conditions	A single dose of PCV13 (≥ 1 year later)
PPSV23 in immunocompromised and high-risk adults < 65 years	A single dose of PCV13 (≥ 1 year later)

Annexure 3 – Table 6: The current ACIP guidelines states that the following recommendations should be adopted, 2023 (27,28)

Age Group	**Vaccination Status**	**No Underlying Condition**	**Underlying Medical Condition***	**No Specific Immunocompromising Condition**	**Specific Immunocompromised Condition**
Adults ≥ 65 years of age	PCV-naive	A single dose of PCV20 OR a single dose of PCV15 followed by PPSV23 after ≥ 1 year	A single dose of PCV20 OR a single dose of PCV15 followed by PPSV23 after ≥ 1 year	A single dose of PCV15 followed by PPSV23 after ≥ 1 year	A single dose of PCV15 followed by PPSV23 after ≥ 8 weeks
	Received PPSV23	A single dose of PCV20 after ≥ 1 year post-receiving last PPSV23 dose	-	A single dose of PCV15 after ≥ 1 year post-receiving last PPSV23 dose	
	Received PCV13	A single dose of PCV20 after ≥ 1 year post-receiving last PCV13 dose	-	A single dose of PPSV23 after ≥ 1 year post-receiving last PCV13 dose	A single dose of PPSV23 after ≥ 8 weeks post-receiving last PCV13 dose
	Received both PPSV23 and PCV13 (but no dose of PPSV23 recorded after 65 years of age)	A single dose of PCV20 after ≥ 5 year post-receiving last vaccine dose (PCV13 or PPSV23)	-	A single dose of PPSV23 after ≥ 1 year post-receiving last PCV13 dose and ≥ 5 years post-receiving PPSV23 dose	A single dose of PPSV23 after ≥ 8 weeks post-receiving last PCV13 dose and ≥ 5 years post-receiving PPSV23 dose
	Vaccination Status	**No Underlying Condition**	**Underlying Medical Condition***	**Specific Immunocompromised Condition**	
Adults 19-64 years of age	PCV-naive	None	A single dose of PCV20 OR a single dose of PCV15 followed by	A single dose of PCV20 OR a single dose of PCV15 followed by PPSV23 after ≥ 8 weeks	

			PPSV23 after ≥ 1 year	
	Received PPSV23	-	A single dose of PCV20 OR PCV15 after ≥ 1 year post-receiving last PPSV23 dose	A single dose of PCV15 OR PCV20 after ≥ 1 year post-receiving last PPSV23 dose
	Received PCV13	-	A single dose of PCV20 OR PPSV23 after ≥ 1 year post-receiving last PPSV23 dose	A single dose of PCV20 after ≥ 1 year post-receiving last PCV13 dose OR 1 dose of PPSV23 ≥ 8 weeks after PCV13 and 1 dose of PPSV23 after ≥ 5 years since last vaccination
	Received PCV13 and 1 dose of PPSV23	-	None	A single dose of PCV20 after ≥ 5 years post last PCV13 dose OR 1 dose of PPSV23 ≥ 8 weeks & after ≥ 5 years since last PPSV23 dose
	Received PCV13 and 2 doses of PPSV23	-		A single dose of PCV20 after ≥ 5 years post last PCV13/ PPSV23 dose

Age Group	**Vaccination Status**	**Recommended Guidelines (PCV15 OR PCV20)**
2-6 months	Received 0 doses	3 doses 8 weeks apart with a booster at 12-15 months
	Received 1 dose	2 doses 8 weeks apart with a booster at 12-15 months
	Received 2 doses	1 doses 8 weeks after last dose with a booster at 12-15 months
7-11 months	Received 0 doses	2 doses 8 weeks apart with a booster at 12-15 months
	Received 1 or 2 doses before 7 months	1 dose at 7-11 months, 2nd dose after ≥ 8 weeks at 12-15 months
12-23 months	Received 0 doses	2 doses ≥ 8 weeks apart
	Received 1 dose before 12 months	2 doses ≥ 8 weeks apart
	Received 1 dose after 12 months	1 dose ≥ 8 weeks after last dose
	Received 2 or 3 doses before 12 months	1 dose ≥ 8 weeks after last dose
24-59 months and healthy	Incomplete schedule	1 dose ≥ 8 weeks after last dose
	Incomplete schedule ≤ 2 doses	2 doses, 1 dose ≥ 8 weeks after last dose and 2nd dose ≥ 8 weeks later

24-71 months with high-risk conditions	3 doses < 12 months	1 dose ≥ 8 weeks after last dose
6-18 years with high-risk conditions	Received 0 doses	1 dose

Annexure 4 – Table 7: 26 GERMS-SA enhanced surveillance sites (23,33)

Province	**Number of Sites**	**Site Description**
Eastern Cape	3	Livingstone Hospital, Dora Nginza Hospital and Port Elizabeth Provincial Hospital
Free State	2	Universitas Academic Hospital and Pelonomi Academic Hospital
Gauteng	6	Johannesburg - Chris Hani Baragwanath Academic Hospital, Charlotte Maxeke Johannesburg Academic Hospital, Helen Joseph Hospital and Rahima Moosa Mother and Child Hospital;
		Pretoria – Steve Biko Academic Hospital and Dr George Mukhari Academic Hospital
Kwa-Zulu Natal	6	Durban - RK Khan Hospital, King Edward Hospital VIII and Inkosi Albert Luthuli Central Hospital
		Pietermaritzburg – Northdale Hospital, Greys Hospital and Edendale Hospital
Limpopo	2	Polokwane-Mankweng Hospital Complex* (Polokwane Provincial Hospital and Mankweng Hospital) and Seshego Hospital
Mpumalanga	2	Rob Ferreira Hospital and Themba Hospital
Northwest	1	Klerksdorp-Tshepong Hospital Complex* (Klerksdorp Hospital and Tshepong Hospital)
Northern Cape	1	Kimberley Hospital
Western Cape	3	Groote Schuur Hospital, Red Cross Hospital and Tygerberg Hospital

* Hospital complexes as noted above, share a laboratory which collects information for the GERMS-SA surveillance programme.

Annexure 5 – Table 8: Data Variables from GERMS-SA

Enhanced Surveillance Site	IPD Case	Site of Specimen collection	Patient Demographics	Co-morbidity/ Risk Factor Status	HIV Status	Antibiotic Resistance Status	Final Outcome

• Yes
• No
	• Year
	• Serotype classification
		• CSF
		• Joint fluid
		• Blood culture
		• Other
			• Age
			• Home province
				• Risk Factor Status
				  ○ Yes
				  ○ No
				• Alcohol dependency
				• Current smoker
				• Chronic lung conditions
				• Chronic liver disease
				• Chronic renal disease
				• Cardiac conditions
				• Metabolic Disease (Diabetes Mellitus)
				• Head Injury*
				• Asplenia
				• Malignancy
				• Organ transplant
					• HIV	• Penicillin
						• Ceftriaxone
						• Cotrimoxazole
						• Tetracycline
						• Erythromycin
						• Clindamycin
						• Rifampicin
						• Chloramphenicol
							• Death
							• Recovered
							• Discharged
							• Refused hospital treatment

*Head injury refers to a patient with a history of a head injury; head surgery; cerebrospinal fluid leak; ventricular shunt or cochlear implants (1).

Annexure 6 – Table 9: Data Analysis Outcomes

Objective	Data Source	Variables	Data Analysis Outcome

To determine the total cases of circulating invasive pneumococcal disease in South Africa, 2012 – 2021.	• NHLS, NICD GERMS-SA
	• Stats SA
		• IPD case
		  Age
		  Province
		  Year
			• Total IPD cases reported to GERMS-SA in South Africa from 2012 – 2021 (per year/ cumulative).
			• Total IPD cases 2012 – 2021/ Midyear population 2012 – 2021 per 100 000 population.
			• Incidence rate per age group, province, year.
			• Frequency table, graphs.

To determine the serotype breakdown of circulating invasive pneumococcal disease in South Africa, 2012 – 2021.	• NHLS, NICD GERMS-SA (Only cases with isolate/specimen received by GERMS-Sa had serotype data available)	• IPD case
		• Serotype classification:
		  Age
		  Province
		  Year
			• Serotype breakdown of all IPD cases reported to GERMS-SA in South Africa from 2012-2021 to note commonly occurring serotypes within specific population groups.
			• Absolute number of specific serotypes identified, and relative frequency noted in frequency table.
			• Number of IPD caused by specific serotype/ Total IPD cases.
			• Incidence rate per age group, province, year.
			• Frequency tables, graphs.

To compare the potential of new and existing pneumococcal vaccines to cover against circulating invasive	• NHLS, NICD GERMS-SA	• Vaccine serotype dataset (Figure 1) • IPD Cases • Serotype classification	• Proportion of circulating IPD serotypes (VS and NVS) covered by new and existing pneumococcal vaccines in South Africa from 2012-2021 dependent on serotypes included in different available vaccines.

pneumococcal disease serotypes in South Africa, 2012 – 2021. • Disaggregated by the following sub-groups: a. Province b. Age groups c. Comorbidity status d. HIV status e. Antimicrobial resistant IPD		• Disaggregated by: Province Age Comorbidity HIV status Antimicrobial resistant IPD ○ Penicillin ○ Ceftriaxone Multidrug Resistant (MDR) IPD	○ Circulating serotypes (VS and NVS) noted within PCV10-SII/ Total IPD cases (%) ○ Circulating serotypes (VS and NVS) noted within PCV13/ Total IPD cases (%) ○ Circulating serotypes (VS and NVS) noted within PCV15/ Total IPD cases (%) ○ Circulating serotypes (VS and NVS) noted within PCV20/ Total IPD cases (%) ○ Disaggregated per: ▪ Province ▪ Age groups in years: <1, 1-4, 5-9, 10-14, 15-24, 25-44, 45-64, >65 ▪ Comorbidity status (Grouped according to variables in Table 8) ▪ HIV status ▪ Antimicrobial resistant IPD category • Penicillin • Ceftriaxone ▪ MDR ○ Frequency tables, graphs
To describe the case fatality rate associated with the various VS and NVS causing invasive	• NHLS, NICD GERMS-SA	• Vaccine serotype dataset (Figure 1) • IPD Cases	• The CFR will be calculated by dividing those who died in each variable by the total number of patients in that sub-group.

pneumococcal disease in South Africa for each of the new and existing pneumococcal vaccines, 2012 -2021.		• Serotype classification • Case fatality rates	• Patients who died or didn't die (outcome variable) associated with IPD vaccine and non-vaccine serotypes within each pneumococcal vaccine (exposure variable) will be analysed using logistic regression, while controlling for the potential confounders and effect modifiers such as age, province, comorbidity, HIV status and multidrug resistant IPD as a potential mediator.

11. APPENDICES

Appendix 1: Plagiarism Declaration

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

FACULTY OF HEALTH SCIENCES

PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS

SENATE PLAGIARISM POLICY: APPENDIX ONE

I SAYURI PILLAY (Student number: 442827) am a student registered for the degree of MASTER OF MEDICINE – PUBLIC HEALTH MEDICINE in the academic year 2025

I hereby declare the following:

- I am aware that plagiarism (the use of someone else's work without their permission and/or without acknowledging the original source) is wrong.
- I confirm that the work submitted for assessment for the above degree is my own unaided work except where I have explicitly indicated otherwise.
- I have followed the required conventions in referencing the thoughts and ideas of others.
- I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my own unaided work or that I have failed to acknowledge the source of the ideas or words in my writing.
- I have included as an appendix a report from "Turnitin" (or other approved plagiarism detection) software indicating the level of plagiarism in my research document.

Signature:  Date: 5 FEBRUARY 2025

1

Appendix 2: Human Research Ethics Committee (Medical) of the University of Witwatersrand Ethics Approval (Ref No: M221167)

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R49 Dr S Pillay

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M221167

NAME: (Principal Investigator)	Dr S Pillay
DEPARTMENT:	School of Public Health Department of Community Health Medical School University
PROJECT TITLE:	*An analysis of circulating invasive pneumococcal disease stereotypes in South Africa and the potential of new and existing pneumococcal vaccines to prevent disease and death, 2012-2021*
DATE CONSIDERED:	2022/11/25
DECISION:	Approved unconditionally
CONDITIONS:	
NOTE:	If contact information regarding student study participants is required, please contact the Registrar's office - <Nicoleen.Potgieter@wits.ac.za>
SUPERVISOR:	Drs S Meiring, V Quan and H Somaroo
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	2023/04/14

This Clearance Certificate is valid for 5 years from the date of approval. An extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office secretariat on the 3rd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to submit details to the Committee. **I agree to submit a yearly progress report**. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in **November** and therefore reports and re-certification will be due in the month of **November** each year. Unreported changes to the study may invalidate the clearance given by the HREC (Medical).

Sayuri Pillay — Signature of Principal Investigator

16 April 2023 — Date

Appendix 3: Academic Affairs and Research Committee of the NHLS Ethics Approval (Ref No: PR2232835)

Academic Affairs and Research
1 Modderfontein Road, Sandringham, 2031
Tel: +27 (0)11 555 0367/0406
Email: babatyi.kgokong@nhls.ac.za
academic.research@nhls.ac.za
Web: www.nhls.ac.za

25 January 2023

Applicant: Sayuri Pillay
Institution: University of the Witwatersrand
E-mail Address: sayuri.pillay@wits.ac.za
Cell: 083 633 0721

CC: Susan Meiring, Vanessa Quan, Harsha SOmaroo

Project Title: A descriptive analysis of the potential of new and existing pneumococcal vaccines to prevent invasive pneumococcal disease serotypes circulating in South Africa, 2012 – 2021
Reference Number: PR2232835

Research Application Type(s):
1. Request for Data

RE: APPROVAL LETTER: REQUEST TO ACCESS NHLS RESOURCES FOR RESEARCH PURPOSES

This letter serves to advise that the application requesting permission to conduct the above-mentioned research using the listed NHLS resources has been reviewed and **"Approved"**. Please note that the approval is granted on the condition that you comply with the NHLS Research Material and Data Access Policy and requirements stated below.

1. All material and data requested shall be used as per the research protocol submitted to the NHLS and as approved by the relevant Health Research Ethics Committee (HREC) in South Africa.
2. Access to the NHLS material and/or data shall be limited to the minimum required for successful completion of the approved study and shall be made available ***without patient names and other patient identifiers (including, but not limited to, national identity numbers, hospital/clinic file numbers, addresses and telephone numbers)***.
3. Confidentiality shall be maintained at the participant and institutional level and there shall be no disclosure of personal information or confidential information.
4. Data and/or material shall not be shared with other parties unless approved by the NHLS
5. The material and/or data obtained from the NHLS shall be anonymised and not, for any reason, be used to track or recruit patients as no pre-approval/consent is obtained from patients.
6. Processes shall be discussed with the relevant NHLS departments (i.e. Corporate Data Warehouse (CDW), NHLS Laboratory Management, Operations Office, etc.) and agreed upon.
7. Any amendments to the study requirements, including the use of the material and/or data for purposes not initially disclosed to the NHLS) shall be cleared by an approved HREC and submitted to the NHLS for approval via the AARMS system – https://aarms.nhls.ac.za.
8. The NHLS shall be acknowledged as a source of material and/or data in any output, such as abstracts and journal articles, emanating from the project.
9. A final report of the research study and any published output resulting from this study shall be submitted to the NHLS via AARMS

Please note that this letter constitutes approval by the NHLS Academic Affairs and Research Office. The NHLS entities tasked with providing the material and/data may have additional requirements for access. Data related queries may be directed to NHLS CDW, email: zarina.sabat@nhls.ac.za; contact number: 011 386 6074 and sample related queries (if applicable) shall be directed to the relevant business manager.

01 Feb 2023

Dr Babatyi Malope-Kgokong
National Manager: Academic Affairs and Research

Appendix 4: Turnitin Report Declaration



I, _____hereby declare that I have checked and approved the Turnitin Report for this Mmed Research Report submission.

_____ _____

Signature of Supervisor Date

Sayuri Pillay Mmed 2024 - Turnitin.docx

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