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Neisseria meningitidis epidemiology in South Africa during a period of low endemicity

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NEISSERIA MENINGITIDIS EPIDEMIOLOGY IN SOUTH AFRICA DURING A PERIOD OF LOW ENDEMICITY

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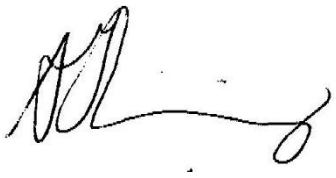
A thesis submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa in fulfilment of the requirements for the degree of Doctor of Philosophy

Johannesburg, September 2022

Declaration

I, Susan Taryn Meiring, declare that this thesis is my own work. It is being submitted for the degree of the Doctor of Philosophy at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other university.



Susan T. Meiring

7 September 2022

"It is often said that 'Epidemiology is the basic science of preventive medicine.' To prevent diseases, it is important to understand the causative agents, risk factors, and circumstances that lead to a specific disease. This is even more important for infectious disease prevention, since simple interventions may break the chain of transmission."

[*Handbook of Epidemiology.* 2014 : 2041–2119. doi: 10.1007/978-0-387-09834-0_34]

Abstract

Background

Invasive meningococcal disease (IMD) is a rare but life-threatening illness with outbreak potential. Many are aware of the meningococcal epidemics in the African meningitis belt, yet are oblivious to endemic IMD epidemiology in southern Africa. Constant changes in serogroup distribution necessitate a country-specific understanding of IMD epidemiology to drive targeted prevention efforts. There are limited country-specific data on meningococcal carriage and disease epidemiology from South Africa.

Objectives

To determine the carriage prevalence, acquisition of carriage and risk factors (including HIV-infection) for carriage of *Neisseria meningitidis* amongst first-year students entering university in South Africa; to describe the trends, serogroup distribution, sequelae and case-fatality ratio of IMD in South Africa; and to explore the association of circulating seasonal influenza virus on the incidence of IMD.

Methods

First-year university students were enrolled into a cross-sectional study to determine carriage prevalence on university registration and 6-8 weeks later. Acquisition of carriage was calculated amongst a cohort of students who participated in both studies. All students underwent HIV-testing and had an oropharyngeal swab taken for detection of meningococci.

For IMD studies, episodes were identified through a national laboratory-based surveillance programme, GERMS-SA, from January 2003 through December 2020. From 2003-2016, Poisson regression was used to calculate trends in incidence over time by serogroup and univariate and multinomial logistic regression was conducted to compare characteristics of IMD by serogroup. A temporal-spatial analysis was conducted to detect IMD serogroup clusters from 2005-2015.

From 2016-2020, additional questions were added to the GERMS-SA sentinel surveillance clinical data questionnaire to determine sequelae at discharge amongst survivors of meningococcal meningitis

and outcome two-months post-discharge. Multivariable logistic regression was used to calculate risk factors for sequelae and in-hospital death.

An ecological study was conducted using the GERMS-SA surveillance data and influenza-positive cases from a national influenza surveillance system, using time-series analyses to determine the temporal association between the peaks of the influenza and meningococcal seasons from 2003-2018.

Results

Meningococcal carriage amongst students entering university was initially low (5%), increasing to 8% after two months on campus. Carriage was diverse with representation from 6 serogroups (Y, B, W, C, X and Z). Risk factors for carriage were largely behavioural including intimate kissing and nightclub/pub attendance. In addition, HIV infection was an independent risk factor for meningococcal carriage acquisition.

From 2003-2016, 5249 incident cases of laboratory-confirmed IMD occurred in South Africa. Disease incidence peaked at 1.4 cases per 100 000 population in 2006, due to an increase in serogroup W disease, dropping to 0.2 cases per 100 000 population in 2016. The spatial-temporal analyses indicated ongoing circulation of 5 different serogroups (A, B, W, Y and C) in various districts. In-hospital case-fatality ratio (CFR) amongst persons with IMD was 17% (247/1479). HIV-infection was a risk factor for IMD - particularly due to serogroup W and Y.

From 2016 to 2020, among individuals with meningitis, in-hospital CFR was 14% (19/137) with an additional 3% (4/118) dying within two months of hospital discharge. Factors associated with poor outcome were decreased mental status on admission, presence of underlying conditions and HIV infection. Twenty percent (24/118) of survivors of meningococcal meningitis suffered major sequelae on discharge from hospital.

The ecological study demonstrated that IMD and seasonal influenza were occurring in-phase during winter with influenza leading the IMD season by five weeks and peaking in-phase with IMD.

Conclusion

In South Africa, IMD is endemic, peaking in the winter months following the peak of the influenza season. Multiple serogroups circulate concurrently, often clustering temporal-spatially in different geographic districts.

Both carriage prevalence and disease incidence were low in the later period studied, however case-fatality ratios and risk of developing sequelae amongst survivors were high. HIV infection was a risk factor for carriage acquisition, developing IMD and death following meningococcal meningitis.

The WHO “Defeating meningitis by 2030” roadmap prioritises vaccine-preventable meningitis deaths and sequelae. Currently, meningococcal vaccines are not routinely used in South Africa, due to high cost and competing health priorities. Ongoing surveillance data are important in identifying high-risk groups to be prioritised for IMD prevention, providing data for cost-effectiveness analyses of interventions and monitoring changes in disease incidence and serogroup distribution over time.

Publications contributing to this thesis

This thesis is based on the following four manuscripts:

1. **Meiring S**, Cohen C, de Gouveia L, du Plessis M, Ganesh K, Kleynhans J**,** Quan V, Tempia S, von Gottberg A. Human Immunodeficiency Virus Infection Is Associated With Increased Meningococcal Carriage Acquisition Among First-year Students in 2 South African Universities. *Clin Infect Dis*. 2021 Jul 1;73(1):e28-e38.

2. **Meiring S**, Cohen C, de Gouveia L, du Plessis M, Kularatne R, Hoosen A, Lekalakala R, Lengana S, Seetharam S, Naicker P, Quan V, Reubenson G, Tempia S, von Mollendorf C, von Gottberg A, for GERMS-SA. Declining Incidence of Invasive Meningococcal Disease in South Africa: 2003–2016. *Clin Infect Dis* 2019 August; 69(3):495-504.

3. **Meiring S,** Cohen C, Gouveia L De, Plessis M, Quan V, Kleynhans J, Menezes C, Reubenson G, Dawood H, Nchabeleng M, Said M, Mvelase N, Mahabeer P, Chomba R, Lekalakala R, Nana T, Chibabhai V, Black M, von Gottberg A, for GERMS-SA. Case-fatality and sequelae following acute bacterial meningitis in South Africa, 2016 through 2020. *Int J Infect Dis* 2022 August; 122:1056–66.

4. **Meiring S**, Tempia S, Dominic E M, de Gouveia L, McAnerney J, von Gottberg A, Cohen C Excess invasive meningococcal disease associated with seasonal influenza, South Africa, 2003-2018. *Clin Infect Dis* 2022 May; 74(10):1729-1735.

The publishers have given permission for reprinting of the published manuscripts. My role in each of the publications and co-author permission are included in Appendix A.

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Introduction

A focus on *Neisseria meningitidis*

Invasive meningococcal disease (IMD) is a devastating illness with high morbidity and mortality in both low- and high-income countries.[1] Globally, IMD incidence is declining, however, epidemics still occur in the African meningitis belt of sub-Saharan Africa.[2–7] In most other countries, IMD is endemic and cases occur sporadically, although occasionally small outbreaks/clusters arise, raising much panic in the affected communities.[8,9] Many countries recommend meningococcal vaccination as the mainstay of disease prevention, currently South Africa does not implement routine meningococcal vaccinations.[10] Available meningococcal vaccines provide serogroup-specific protection. Ideally, updated local data are necessary to inform country-specific policy with regard to IMD prevention, as meningococcal serogroup distribution can be diverse and is likely to change over time.

Pathophysiology of meningococcal disease

Invasive meningococcal disease is caused by the Gram-negative intracellular diplococcus, *Neisseria meningitidis*. The sole ecological niche of *N. meningitidis* is the mucosa of the human oropharynx.[11] Oropharyngeal carriage is asymptomatic for the individual, yet it is a necessary prerequisite for ongoing transmission and ultimately invasion of the organism leading to meningococcal bacteraemia/meningitis.[12] Transmission of *N. meningitidis* occurs through inhalation of aerosolised droplets or ingestion of droplets through close contact with asymptomatic carriers.[12] Bactericidal antibodies are produced through carriage of meningococcus and repeat occurrences of carriage are thought to be protective against transition to invasive disease.[13]

Occasionally *N. meningitidis* invades the nasal mucosa and enters the blood stream causing bacteraemia or meningitis.[12] Within 24 hours, non-specific symptoms (fever, malaise, headache and/or petechiae) can progress to multi-organ failure, and even with appropriate treatment, 10% of cases result in death, and up to 20% of survivors are left with sequelae ranging from amputations to cognitive deficits.[14–17] Due to the higher carriage rate in young adults and route of spread, outbreaks of disease are common amongst university students, miners, in military barracks and in hostels.[18] It is thought that as people come together to socialise in close contact, carriage strains are shared amongst

individuals and there is a higher chance of being exposed to a virulent strain not previously encountered that could invade the nasal mucosa and cause IMD.[19,20] Carriage prevalence in a population is useful for contextualising IMD incidence rates, i.e., in a setting of limited vaccine use and low disease incidence, carriage rates could be indicative of population susceptibility to disease and subsequent outbreak potential.[21]

The polysaccharide capsule surrounding the meningococcus is its most important virulence factor. Almost all isolates causing IMD are encapsulated, with most IMD being due to one of the following six serogroups: A, B, C, W, X and Y, whereas the majority of carriage isolates are unencapsulated.[5] Unencapsulated/ non-groupable isolates rarely cause disease, as either there is i) downregulation of the capsular gene expression, ii) phase variation in the expression of the capsule, iii) inactivation of the capsular synthesis genes or iv) an absence of the genes required for capsule production (capsule null phenotype).[22,23] The few carriage isolates that do express capsule and can be serogrouped can inform population susceptibility and outbreak potential as they are more likely to be responsible for the spread of IMD in the community.

Carriage prevalence and disease incidence globally and regionally

What is known about carriage

Carriage is influenced by the number and intimacy of social interactions, and tends to increase with age, peaking in adolescence. In industrialised countries carriage peaks at 23% in 19-24 year olds (possibly related to exposure to more densely populated spaces and close interactions with a large diversity of persons), however in the African meningitis belt, where classroom interactions may drive transmission, carriage peaks at a younger age (10-14 year olds) and at a lower rate (5%).[19,24] Besides age, other risk factors for meningococcal carriage include smoking, attendance at pubs and night clubs and intimate kissing.[19,21,25] Although carriage of *Streptococcus pneumoniae* has been shown to be higher in HIV-infected adults, it is unknown whether HIV-coinfection is a risk factor for meningococcal carriage.[26] Incidentally, meningococcal carriage is extremely high in some populations of men who have sex with men (MSM), who often have a high HIV prevalence.[27]

In Europe, Asia and North America, meningococcal carriage studies on university campuses have consistently shown high carriage rates amongst students, ranging between 12% and 34%.[25,28–30] Carriage acquisition within the first week of attending university is rapid and carriage prevalence usually plateaus after one month.[28] One study showed only 7% of students carrying meningococcus on day one of registration, increasing to 23% on day four, followed by 34% after two months.[28] More recently, carriage studies in Australian students showed a lower carriage prevalence (6.2%), similar to that seen amongst children and adolescents in the warmer climate of the African meningitis belt.[31] Non-groupable *N. meningitidis* usually accounts for the majority of carriage strains in the population, but other serogroups commonly causing carriage include serogroups B, Y, C and W.[12]

Meningococcal carriage gaps in knowledge

There have been no population-based meningococcal carriage studies performed in South Africa. Cross-sectional carriage studies representing the population are difficult to perform as they require extremely large sample sizes, and in a diverse setting such as South Africa, it is challenging ensuring representation of all population groups. This research explores carriage in university students, as they may be at increased risk of carriage and at high risk of transmitting meningococci due to their age and potential high-risk behaviours.[9,28,29,32] As in industrialised countries, clusters of IMD have previously been identified from various university residences in South Africa.[33,34] This study will identify subgroups of students at higher risk for carriage (for example people living with HIV) that may be unique to the South African setting. Should carriage be found to be high, university students are easily identifiable populations within which to consider routine meningococcal vaccination. There is an urgent need for carriage studies in South Africa as more options become available with regards to meningococcal vaccines, particularly the protein-based serogroup B vaccines and the phase III pentavalent ABCWY vaccine.[35–37]

Meningococcal disease incidence and risk factors for poor outcome

What is known about meningococcal disease

It is known that IMD is seasonal, peaking during the winter and spring months, and incidence tends to wax and wane over periods of 10-15 years.[12] Serogroup predominance differs by region and changes over time as fitter strains emerge in an area.[38] Long-term trends of IMD notifications in South Africa

were described by Kustner in the 1970's, and in the early 2000's incidence of laboratory-confirmed IMD was 0.68 cases per 100 000 population and showed serogroups A and B to be the predominant disease-causing strains in South Africa.[39,40] In 2005, serogroup W emerged in Gauteng Province and soon dominated throughout most of the country, increasing IMD incidence from 0.8 to 4 cases per 100 000 persons with a case-fatality ratio reaching 22% - possibly due to the high rate of bacteraemia caused by this new strain.[41] HIV coinfection was later associated with increased bacteraemia, and bacteraemia was associated with increased case-fatality among individuals with IMD in South Africa.[42]

In more industrialised countries, such as North and South America, Europe and Australia, serogroups B and C tend to predominate, however more recently a new serogroup W strain (ST-11 clonal complex (cc11)) has emerged in the United Kingdom, Europe and the Americas.[43–46] This serogroup W strain has spread rapidly and is different to the serogroup W cc11 Hajj strain that spread globally in the early 2000's and probably caused the wave of serogroup W in South Africa.[41,47,48] Serogroup A predominated in central and southern Asia.[43,49] Every few years serogroups A, C or W caused widespread epidemics across the meningitis belt in sub-Saharan Africa (an area spanning from The Gambia in the west to Ethiopia in the east), with disease incidence exceeding 1/1000 persons at times.[50,51] Currently, global IMD incidence is low and declined even further in most countries during the COVID-19 pandemic, possibly due to reduced social contact between individuals and use of personal protective measures when in public spaces.[36,52]

Increased risk factors for death from IMD infection have been described as increased age, HIV co-infection, bacteraemia (versus meningitis) and infection with a unique serogroup strain.[53–55] Along with the pneumococcus and *Haemophilus influenzae*, meningococcus is one of three causes of community-acquired meningitis that not only has high case-fatality rates but can cause long-term sequelae such as skin scarring, limb loss, hearing or visual impairment, or new onset seizures in survivors.[15]

Meningococcal disease gaps in knowledge

Understanding the unique situation of IMD in South Africa, a middle income country with high HIV prevalence, is important and cannot be understood through analysis of data from the African meningitis belt or from high-income countries in the Northern Hemisphere.

Since 2007, IMD epidemiology in South Africa has not been described and although IMD surveillance has been ongoing no localised epidemics or serogroup clusters have been reported.[56] South Africa was listed as having moderate endemic IMD (incidence of >2 per 100 000 population), and is thus placed in the moderate priority group for the need for vaccine intervention.[1] Although many other high-income countries with low incidence have implemented meningococcal vaccine into routine programmes, having a better understanding of high-risk groups and the morbidity and case-fatality following IMD in South Africa may be beneficial for informing vaccine recommendations in this country and using country-specific data when modelling cost effectiveness of various vaccine implementation programmes .[57–59]

Thirteen percent of the South African population is living with HIV.[60] South Africa has one of the highest numbers of people on antiretroviral (ART) therapy, yet in 2017 only 71% of people living with HIV (PLHIV) were on treatment and 86% of these had suppressed viral load.[61] In South Africa, HIV is primarily transmitted through heterosexual intercourse, while HIV-infected MSM populations and intravenous drug users are in the minority. There are many case reports and studies on meningococcal infections amongst MSM, many of whom are HIV-infected.[62–65] Meningococcal carriage is particularly high in these groups, yet it is unknown if MSM behavioural practices or HIV is the driver.[27] A study in England showed HIV-infected persons to be 4.5 times more likely to develop IMD than HIV-uninfected persons.[66] HIV prevalence in the United Kingdom is low and the population of PLHIV may be very different to that of South Africa. More population studies are needed on quantifying the relative risk of IMD amongst PLHIV, particularly in settings with high population HIV prevalence.

Meningococcal disease prevention

Chemoprophylaxis

Antibiotic chemoprophylaxis can be used to eliminate meningococcal carriage among asymptomatic individuals. Prior to availability of meningococcal vaccines, mass sulfadiazine prophylaxis was successfully used in the post-war period amongst military recruits to prevent IMD outbreaks during training camps.[67] In South Africa, chemoprophylaxis is recommended for close contacts of confirmed/probable meningococcal cases.[68] Close contacts include those who have had prolonged close contact with the case in the 7 days preceding the illness. A single dose of oral ciprofloxacin or intramuscular ceftriaxone is provided to clear carriage. Alternatively, two days of oral rifampicin may be given. Resistance to fluoroquinolones and cephalosporins may be emerging in certain countries, therefore antimicrobial susceptibility testing of meningococcal isolates should be closely monitored.[69,70]

Meningococcal vaccines

The most effective way of preventing IMD is through vaccination. Disease prevention through meningococcal vaccination can take one of three approaches. Firstly, reactive emergency mass vaccination activities can be implemented acutely to prevent subsequent spread of disease during an ongoing outbreak in a defined population.[71,72] Vaccinating the population at risk may halt transmission of virulent strains, however this approach is administratively, logistically and financially costly and the impact of such a programme is difficult to measure.[73,74] Secondly, high-risk groups can be identified and vaccines can be offered to selected individuals with increased risk of acquiring meningococcal carriage and thus development of disease. This approach may prevent disease in vulnerable individuals but is unlikely to stop the spread of IMD in the population. Thirdly, meningococcal vaccines can be incorporated into a nationwide routine vaccination programme where whole populations are targeted in order to reduce disease on a population level. Including catch up campaigns when implementing an infant vaccination programme, or targeting age-groups most at risk of carriage and thus transmission of the organism, needs to be tailored to the availability and mechanism of action of the chosen vaccine(s). This approach has been largely successful in eliminating serogroup A epidemics in the African meningitis belt and preventing serogroup C in the

United Kingdom.[24,75–78] Unfortunately when disease incidence is low, it is difficult to justify the high costs of procuring and administering vaccines (particularly from a government economic perspective) and often the second option of selectively targeting high-risk groups is adopted.[79,80]

Some of the global decline in IMD and meningococcal carriage may be due to the introduction of meningococcal vaccination programmes in Europe, the United Kingdom, United States of America, Canada, South America, New Zealand and countries in the African meningitis belt.[10,81,82] However, South Africans are not routinely vaccinated against IMD and very little vaccine has been used over the past decade– even amongst high-risk individuals. The quadrivalent polysaccharide vaccine (targeting serogroups A, C, W and Y) has been available in South Africa for more than two decades, and in 2014, a quadrivalent conjugate meningococcal vaccine (also targeting serogroups A, C, W and Y) was registered in South Africa. Use of the conjugate vaccine eliminates meningococcal carriage in individuals and thus the transmission of potentially virulent organisms. Therefore, with improved access to conjugate vaccines it is important to identify high-risk groups for both disease and carriage in order reduce meningococcal carriage and disease. The recombinant protein-based serogroup B meningococcal vaccines (Trumenba® and Bexsero®) are not yet licenced for use in South Africa. New effectiveness data on their routine use are emerging proving them a helpful addition to the conjugate vaccines for use in countries where multiple serogroups, including serogroup B are circulating.[83–86] Development of a pentavalent vaccine, combining serogroup B vaccine technology with the quadrivalent conjugate polysaccharide vaccine components offers hope for a single vaccine with broad coverage of the majority of meningococcal strains causing disease.[35,37]

National South African guidelines from 2011 recommend vaccine for four categories of patients: those with asplenia, terminal complement factor deficiency, laboratory exposure to *N. meningitidis*, and travellers to Saudi Arabia where proof of vaccination is compulsory for entry.[68] It is also recommended during vaccine-serogroup outbreaks. Quadrivalent vaccines can be bought privately with a prescription, or received free of charge through the public healthcare sector if national guideline criteria are met.

HIV infection is an independent risk factor for IMD and in the United States of America and United Kingdom, HIV-infected persons are offered meningococcal vaccination.[54,66,87] In South Africa, approximately 13% of the population are HIV infected.[60] An association between serogroup W IMD and poor outcome amongst PLHIV has been described. [42] Although guidelines by the HIV Clinicians' Society of South Africa suggest meningococcal vaccination of PLHIV, it is not an official recommendation in South Africa.[88]

Other avenues for meningococcal prevention

Routine meningococcal vaccination is rarely cost-effective when IMD incidence is low.[89–92] South Africa has many competing health priorities, therefore unless perception of disease threat increases routine meningococcal vaccination is unlikely to be implemented in South Africa. Therefore, other areas of intervention also need to be explored. Some studies have suggested that circulation of the influenza virus may influence the timing and magnitude of the winter peaks in IMD.[93–96] One ecological study in Canada showed a two times increase in IMD incidence per 100 case increase in influenza A activity.[97] Another study in the United States of America showed that two thirds of IMD during the peak of influenza seasons could be attributable to influenza, and that the height of both influenza and meningococcal seasons lagged by two weeks over nineteen out of twenty consecutive winters.[93] Observational studies of IMD outbreaks in well-defined populations, such as an army barrack, old aged home and school, used serological testing to confirm preceding outbreaks of influenza A or B within the population prior to the onset of IMD.[98–101] South Africa has a temperate climate with both influenza and IMD increasing in late autumn to winter (April through August). If a temporal correlation between IMD and influenza is identified in South Africa, preventing influenza through seasonal influenza vaccination campaigns could have the added benefit of preventing a proportion of IMD.

More recently, the usual seasonality of respiratory transmitted infections has been interrupted by various COVID-19 lock down measures – social distancing, mask wearing and general improved respiratory hygiene. This has impacted on IMD too, with very few cases reported from March 2020.[36,52,102] The phenomenon has been show in various countries for influenza, respiratory syncytial

virus, pneumococcus, and *H. influenzae* infections.[52,103,104] Although effective, behavioural measures (social distancing, mask wearing, hand-washing, improved cough-etiquette) to reduce respiratory transmitted pathogens, are difficult to sustain. Therefore, stable surveillances programmes are invaluable for monitoring trends of IMD over time.[58] Going forward, as the world reopens, respiratory transmitted disease epidemiology may change yet again, as mask wearing and social distancing eases off, global travel increases and some viruses find a new pattern of seasonality.

Public health interventions and Defeating meningitis by 2030

In South Africa, meningococcal disease is a category one notifiable medical condition and even suspected cases are to be reported through the provincial communicable diseases coordinators in order to follow up on cases and ensure adequate distribution of chemoprophylaxis to close contacts.[68] Although non-reporting of notifiable medical conditions is a criminal offence, this programme is difficult to enforce. Recently it has been relaunched using web-based applications for reporting as an alternative to paper-based forms, this has improved notifications to some extent, however the surveillance programme is more active in following up laboratory-confirmed cases and can therefore provide phenotypic/genotypic data on confirmed cases.[105] In South Africa the GERMS-SA surveillance programme on pathogens of public health importance has worked together with the notifiable medical conditions programme to get a comprehensive overview of IMD over the years.[56] Robustness of the surveillance programme should be maintained to ensure continued collection and collation of accurate data.

In 2020, the World Health Organisation launched a roadmap for defeating meningitis by 2030, with an aim to eliminate epidemics of bacterial meningitis; reduce cases and deaths from vaccine preventable causes; and reduce disability and improve the quality of life amongst survivors.[106] This initiative highlights the timeliness of my thesis in describing the epidemiology of *N. meningitidis* (one of the top three causes of vaccine preventable bacterial meningitis) in South Africa.

Providing accurate country-specific estimates of meningococcal carriage, IMD incidence, risk factors for carriage and disease, and case-fatality and sequelae from bacterial meningitis in South Africa, a

middle-income country, is important to evaluate the current situation, refine prevention strategies, provide local data for accurate cost-effectiveness analyses and monitor future progress towards the global objective of defeating meningitis over the next decade.

Problem Statement and Justification for Research

Problem statement

Invasive meningococcal disease is a rare but life-threatening illness with the potential to cause outbreaks. Many who are aware of the meningococcal epidemics in the African meningitis belt, are oblivious to the endemic IMD epidemiology in southern Africa. Constant changes in serogroup distribution necessitate a country-specific understanding of IMD epidemiology to drive targeted prevention efforts. There are limited country-specific data on meningococcal carriage and disease epidemiology from South Africa.

Justification for the research

Invasive meningococcal disease is a rare but life-threatening illness with devastating consequences for the individual and family affected. The occurrence of one case has public health ramifications which affect not only close contacts of the individual but also their immediate workplace or school and surrounding community. There has been a paucity of literature from South Africa regarding IMD since the last outbreak of serogroup W in 2006. Many countries have seen changes in serogroup prevalence over the last decade, including those with and without routine meningococcal vaccination strategies.

To gain a deeper understanding of country-specific meningococcal epidemiology one needs to look at the interaction between the causative pathogen, the host and the environment. This includes: understanding carriage of the organism and the risk factors which may influence carriage status; describing the trends in IMD incidence and serogroup distribution over time; describing the characteristics and complications of meningococcal patients in South Africa; and investigating the effect of other pathogens on the seasonality and severity of IMD.

Many studies on risk factors for IMD and carriage have been conducted in high-income countries, where disease is mostly caused by serogroup B and C and meningococcal vaccines have been part of routine immunisation strategies for many years. South Africa, however, is a middle-income country with a high burden of HIV and minimal meningococcal vaccine use, risk factors for disease and carriage may be very different. Meningococcal epidemiology from Africa is largely focused on

controlling the widespread epidemics of serogroup A, W and C occurring periodically in the African meningitis belt, which spans across sub-Saharan Africa from The Gambia in the west to Ethiopia in the east, where IMD is hyper endemic. In contrast, South Africa has a very different climate to that experienced in the meningitis belt, serogroup specific epidemics occur periodically at much lower rates than experienced in the meningitis belt but rather low to moderate endemic disease follows a seasonal pattern with increases in the winter to spring months. Understanding the unique situation of IMD in South Africa is important and cannot be understood through analysis of data from the African meningitis belt or from high-income countries in the Northern Hemisphere.

When disease occurrence is infrequent, it is important to determine whether this is driven by low pathogen circulation or natural immunity from high carriage rates. There is a need to understand *N. meningitidis* epidemiology during a period of low endemicity so that future planning can be done for dealing with potential outbreaks in high-risk groups or the general population, and for informing policy makers should vaccine funding become available.

Novel data generated by this research include a study of meningococcal carriage amongst first-year university students (with a focus on HIV as a risk factor for carriage), spatial-temporal analyses to detect ongoing serogroup-specific clusters of IMD occurring over time at district level, description of the prevalence of sequelae following meningococcal meningitis in South Africa and describing the effect of seasonal influenza on meningococcal seasonality in a Southern Hemisphere country.

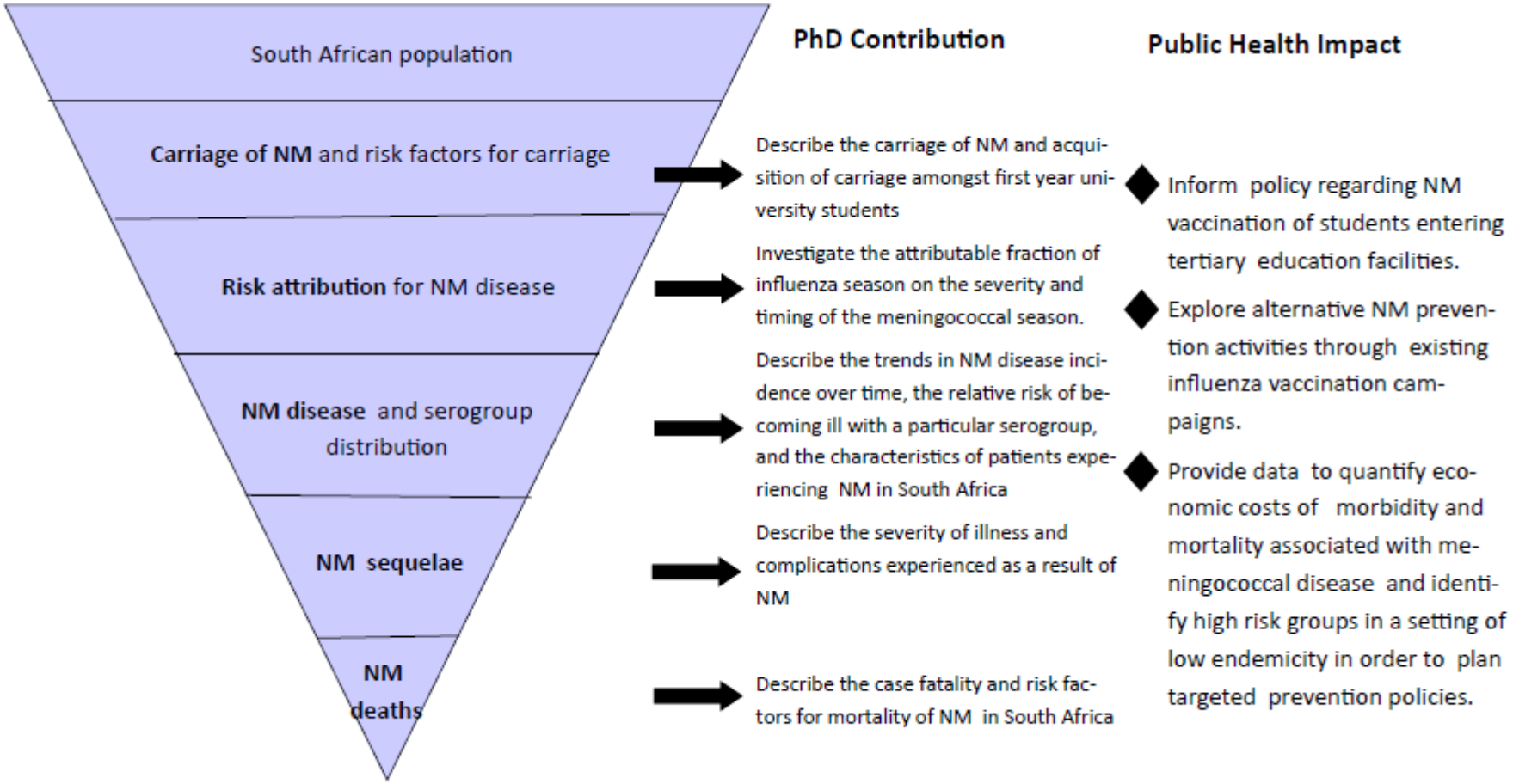
The information gained from this research (particularly the serogroup distribution and identification of high-risk groups for both carriage and disease) will be able to inform policy regarding meningococcal vaccination of high-risk populations, students entering tertiary education facilities or other defined populations. Alternative IMD prevention activities could be identified and strengthened through the existing influenza vaccination campaigns. It will provide data to quantify the economic costs of morbidity and deaths associated with IMD and identify high-risk groups for acquiring IMD in a setting of low endemicity in order to plan targeted prevention policies in South Africa.

Conceptual framework

The research was built around a framework to identify and address multiple risk factors along the pathway of becoming infected with *N. meningitidis* (carriage), developing IMD and having a poor outcome (sequelae or death). (Figure 1) All of the studies were based on data collected nationally from multiple surveillance programmes and special studies across South Africa. Gathering country-specific data detailing IMD epidemiology allows public health policy makers to make informed decisions regarding disease prevention and control.

In particular, the carriage study focusing on an at risk population of university students hopes to provide the data that can be used by the universities to promote vaccination of new students entering the facilities and will give an idea of background prevalence of meningococcal carriage in young adults as well as the country-specific risk factors for acquiring and/or maintaining carriage in a university setting. The detailed description of IMD trends and low-grade serogroup clusters, and the description of the risk factors for serogroup-specific disease, and outcomes like death or long term sequelae following IMD will all be useful for modelling studies aimed at quantifying the costs of introducing various meningococcal vaccines, as well as provide an updated baseline epidemiology in South Africa should we experience an outbreak or natural increase in disease in the near future. In addition, other preventive measures can be explored through knowledge gained in detailing the association of IMD and seasonal influenza and quantifying the meningococcal disease burden due to preceding influenza seasons.

Figure 1: Conceptual Framework: The epidemiology of *Neisseria meningitidis* in South Africa during a period of low endemicity



Aims and Objectives

Aim

To describe the epidemiology of IMD and carriage in South Africa in order to inform public health decision making regarding prevention of disease, vaccine use and outbreak response.

Objectives

1. To determine the carriage prevalence, acquisition of carriage and risk factors (including HIV infection) for carriage and carriage acquisition of *N. meningitidis* amongst first-year students entering university in South Africa

2. To determine the trends of IMD incidence over the last 14 years in South Africa, to describe the epidemiologic characteristics of IMD by serogroup, and to detect the presence of localised epidemics/clusters by serogroup distribution.

3. To identify the risk factors for death, as well as morbidity and describe the presence of sequelae following meningococcal meningitis and compare this to the sequelae following other common causes of bacterial meningitis such as *H. influenzae* and *S. pneumoniae*.

4. To determine the association between, and estimate the attributable factor of circulating seasonal influenza virus on the incidence of IMD during the winter/spring seasons in South Africa.

Methods

Study setting

The research was set in South Africa which is located at the southern tip of Africa and experiences a temperate climate. In 2019, South Africa had a population of 59 million persons, including approximately 6 million children under the age of five years.[60] Life expectancy at birth was 61 years in males and 67 years in females. The population HIV prevalence was 13.5%, and 4.3% in the youth aged 15-24 years. Fifty-one percent of the population were female and the majority were black African (81%). South Africa was classified as a middle-income country, with a Gross Domestic Product of 388 billion US Dollars in 2019 (Gross National Income per capita of 6670 US Dollars).[107]

Meningococcal vaccinations have not been included in the immunisation programme in South Africa. Currently only one meningococcal vaccine is licenced and available for use in the country (Menactra® ACWY, Sanofi Pasteur). In the public healthcare sector, which is utilised by approximately 80% of the population, conjugate meningococcal vaccine (targeting serogroups A, C, W and Y) is available for use in high-risk individuals (mainly those with anatomical/functional asplenia or complement deficiency). In the private sector, meningococcal vaccines require a doctors' prescription and are paid for out of pocket.

Data Sources

Manuscript 1 (objective 1) made use of data collected through a new study described below. Manuscripts 2, 3 and 4 were secondary data analyses that made use of routine surveillance data collected through the GERMS-SA surveillance programme for pathogens of public health importance and the Viral Watch programme for influenza surveillance.

GERMS-SA surveillance programme

GERMS-SA, coordinated by the National Institute for Communicable Diseases (NICD), is a national laboratory-based surveillance programme for IMD as well as other invasive bacteria and fungi occurring in South Africa.[56] The programme has been running since 2003. Over 200 public, private, military and mining sector microbiology laboratories participate in the programme by submitting a

laboratory report and an isolate (or specimen if no isolate is available and meningococcus was detected on polymerase chain reaction or latex agglutination) of all cases of invasive *N. meningitidis* cultured in their laboratory to the reference laboratory of the Centre for Respiratory Diseases and Meningitis (CRDM) at the NICD. All cases of laboratory-confirmed invasive infections meeting the GERMS-SA case definition from the public health sector are accounted for in the programme by conducting quarterly audits of the National Health Laboratory Service's laboratory information system.[108] Previously, audits of the private sector microbiology laboratories were not possible, but recent changes in the notifiable medical conditions regulations state that all laboratories are mandated by law to report confirmed cases of meningococcal disease and CRDM are the reference laboratory to whom these specimens are sent. The demographic details (including age, sex, district and province) of the patients as well as the results from specimen site, antimicrobial susceptibility testing and serogrouping of the isolates are recorded on an Access Database.

In addition, GERMS-SA does enhanced surveillance at 26 public hospital sites around the country where dedicated nurse surveillance officers collect additional clinical data through interview and medical record review on the cases of IMD admitted at their hospitals. Approximately 30% of the total GERMS-SA surveillance cases occur at these enhanced surveillance sites which are located across all nine provinces of South Africa. Additional clinical details collected include: clinical syndrome (meningitis, bacteraemia, other), in-hospital outcome, length of hospital stay, predisposing conditions (HIV status, diabetes, complement deficiency, asplenia, chronic lung disease, smoking and alcohol use) and Pitt bacteraemia score for severity of illness.[109]

Accessing routine surveillance data from an established surveillance platform is highly advantageous particularly in identifying trends over time and changes in serogroup distribution of pathogens. GERMS-SA routine surveillance for pathogens of public health importance has directly affected health policy in South Africa through data supporting the incorporation of vaccines and monitoring vaccine impact, monitoring antimicrobial susceptibility and identification and response to outbreaks.[110–113]

GERMS-SA surveillance data on IMD, invasive *H. influenzae*, invasive pneumococcal disease and cryptococcosis have been analysed in this thesis.

Viral Watch surveillance programme

Seasonal influenza data collected through the Viral Watch programme was used in manuscript 4 (objective 4) to estimate the attributable faction of influenza on IMD.

The Viral Watch programme was established in 1984 and is ongoing.[114,115] Nasopharyngeal samples from patients with influenza like illness are submitted by approximately 180 general practitioners from all 9 provinces of South Africa (excluding KwaZulu-Natal from 2014-2018) to the National Institute for Communicable Diseases. All nasopharyngeal samples are tested for influenza A and B using multiplex reverse transcriptase real-time polymerase chain reaction assays. The case definition used for submission of specimens includes: patients of any age presenting with an acute respiratory infection with fever $\geq$38˚C and cough with onset within the last 10 days. The proportion of positive influenza cases detected by epidemiologic week per year were included in the analysis to determine onset of the influenza seasons.

Manuscript specific methods

The research methods for each of the objectives and manuscripts are summarised in Table 1, and described in detail in the methods section of the relevant manuscripts. However specific elements from each manuscript are elaborated on below.

Table 1: Summary of methods for each manuscript in thesis: *Neisseria meningitidis* epidemiology in South Africa during a period of low endemicity

MANUSCRIPT NUMBER AND RUNNING TITLE	OBJECTIVES	DATA SOURCES	STUDY DESIGN	POPULATION/ SETTING	VARIABLES ANALYSED	METHOD OF ANALYSIS
1. Meningococcal carriage of South African students	To determine the carriage prevalence and the acquisition of carriage of *Neisseria meningitidis* amongst first-year students entering university in South Africa	A study on meningococcal carriage amongst first-year university students in South Africa	Cross-sectional study to determine prevalence; cohort study to determine acquisition of carriage	First-year university students registering at either University of Witwatersrand, Gauteng OR University of Cape Town, Western Cape; 2017	Carriage status; *N. meningitidis* serogroup; age; university; sex; home province; smoking history; passive smoking history; living arrangements; club/pub/party attendance; number of intimate kissing partners; use of online MSM dating website; pre-existing chronic conditions; HIV infection status; recent upper respiratory tract infection; recent antibiotic use; and prior meningococcal vaccine use.	Prevalence of carriage in first-year students on registration at university and 6-8 weeks following registration was calculated; Univariate and multivariable logistic regression models were used to determine significant risk factors associated with meningococcal carriage at the two time points; Acquisition, persistence and clearance of meningococcal carriage 6-8 weeks following registration was determined from the cohort returning for the second study visit; Multinomial regression was performed to determine risk factors associated with carriage acquisition and persistence using non-carriers as reference.
2. Meningococcal disease in South Africa	To determine the trends of IMD incidence over the last 14 years in South Africa, to describe the epidemiologic characteristics of IMD by serogroup, and to detect the presence of localised epidemics in South Africa by serogroup distribution.	GERMS-SA national surveillance data - laboratory and clinical data; STATS-SA mid-year population estimates	Secondary data analysis from cohort study	All laboratory-confirmed cases of IMD in South Africa from all age groups; all persons living in South Africa; 2003-2016	Meningococcal serogroup (A, B, C, W, Y, Other (including NG, X, Z)); age categories: <1, 1-4, 5-9,10-14, 15-24, 25-44, 45-64 and >64 years; length of hospital stay; in-hospital outcome; diagnosis; predisposing conditions (HIV, chronic lung disease, diabetes, asplenia, complement deficiency, smoking history, history of alcohol dependency); severity of illness (Pitt bacteraemia score); district and province	Incidence of IMD by serogroup, age-category and province were calculated for each calendar year; Trends in incidence by age-category and serogroup were calculated using Poisson regression; A multinomial logistic regression model was used to classify the clinical and epidemiologic characteristics of patients with IMD by serogroup; A space-time analysis was conducted to detect IMD serogroup clusters among all IMD cases by month and district

MANUSCRIPT NUMBER AND RUNNING TITLE	OBJECTIVES	DATA SOURCES	STUDY DESIGN	POPULATION/ SETTING	VARIABLES ANALYSED	METHOD OF ANALYSIS
3. Complications following bacterial meningitis	To identify the risk factors for death, and sequelae, and to describe the presence of sequelae following meningococcal meningitis and compare this to other common causes of bacterial meningitis such as *Haemophilus influenza*e and *Streptococcus pneumoniae*.	GERMS-SA national enhanced surveillance programme laboratory and clinical data	Secondary data analysis from cohort study	All laboratory-confirmed cases of invasive *N. meningitidis, S. pneumoniae* and *H. influenzae* meningitis in South Africa from all age groups from the GERMS-SA enhanced surveillance sites. (Approximately 30% of total GERMS-SA surveillance population); 2016-2020	Risk factors for death and sequelae analyses: in-hospital outcome; age-categories; serogroup; specimen type; days-in hospital; HIV co-infection; other comorbidities; GCS on admission; severity of illness on admission; first line antibiotics given; and antimicrobial resistance. The sequelae analysis included: presence of necrotic skin lesions; skin scarring, amputations; development of hydrocephalus; new onset of seizures; hearing loss; visual loss; or any history of neurological fallout.	Calculate the in-hospital case-fatality rate and prevalence of sequelae at discharge amongst all *N. meningitidis, H. influenzae* and *S. pneumoniae* meningitis cases; Risk factors for death and sequelae from *N. meningitidis* were explored using univariate and multivariable logistic regression modelling.
4. Excess meningococcal disease associated with influenza	To determine the association between, and estimate the attributable factor of circulating seasonal influenza virus on the incidence of IMD during the winter/spring seasons.	GERMS-SA national surveillance programme basic demographics and laboratory data and National Viral Watch Programme case counts	Ecological study. Secondary data analysis from cohort study	All laboratory-confirmed cases of IMD in South Africa from all age groups; 2003-2018	Count of invasive meningococcal cases, by week, by age category; count of influenza cases by week, by strain; total specimen count by week received through Viral Watch programme	Use of a time-series analyses to determine the temporal association between the peak of the influenza season and the peak of the meningococcal seasons for each of the 14 years; The attributable fraction of IMD associated with influenza was estimated as the proportion of IMD cases that could be averted by preventing influenza.

Manuscript 1: Meningococcal carriage among university students (objective 1)

Study design

This was a cross-sectional study to determine prevalence of meningococcal carriage among university students with a cohort study nested within it to determine the acquisition, clearance and persistence of meningococcal carriage among these same students over two time-points (at university registration and 6-8 weeks later).

Study setting and population

The study took place at the following two universities:

1. The University of the Witwatersrand (Wits), Johannesburg, Gauteng Province is a "world class African Institution" that was established as a university in 1922. In 2017, it boasted 38 380 students, 24 621 of which were undergraduates. Fifty-five percent of the student population were female and 56% were Black, 17% White, 12% Indian, 4% Coloured and 10% were International students.
2. The University of Cape Town (UCT), Western Cape, is one of Africa's leading teaching and research institutions. It is the oldest university in the country, established in 1918. In 2017 there were 28 724 students, of which 17 872 were undergraduates, 53% of which were female. Twenty-nine percent were Black, 25% White, 23% Coloured/Indian, 10% did not declare their race and 12% were International students.

The study population included first-year university students registering at the start of the 2017 academic year at either university. The intake of first-year students at each university was approximately 7000. The student population at both universities was diverse and draws from all 9 provinces of South Africa. It was thought that the initial carriage prevalence amongst first-year students entering university would give an indication of the population prevalence of meningococcal carriage amongst 18 year olds, as they enter campus from a diversity of backgrounds within South Africa. HIV prevalence amongst all university students has been previously reported as 3.4% by the Higher Education and Training HIV/AIDs programme study but may be slightly lower amongst new university recruits.[116]

The academic year in South Africa typically begins in January (mid-summer in the Southern Hemisphere), however due to various student protests causing final examination delays in the 2016 academic year, registration for 2017 only occurred from 30 January at the University of the Witwatersrand and 27 February at the University of Cape Town.[117] The second survey therefore took place in early autumn (14-17 March at the University of the Witwatersrand and 18-21 April at the University of Cape Town).

First-year students between the ages of 18-24 years registering at the respective universities for the first time were eligible to be enrolled in the carriage study. The cohort of students included those participating in both cross-sectional studies: at registration (survey 1) and 6-8 weeks later (survey 2).

Sample size calculations

Carriage of meningococcus among university students could range from as low as 6% on registration at the institution to as high as 34% once established transmission has occurred.[25,118,119]

Sample size was calculated using OpenEpi (https://www.openepi.com/SampleSize/SSCC.htm), assuming differences in the acquisition of meningococcal carriage in a cohort of students with and without HIV-coinfection. Calculations were for repeat measurements assuming an HIV prevalence of 4%, a power of 80%, 95% confidence intervals, and initial meningococcal carriage prevalence of 4% in HIV-uninfected persons and 7% in HIV-infected persons, increasing to 12% in HIV-uninfected and 28% in HIV-infected persons. We allowed for a 10% discordant proportion in both groups (i.e. 10% of study participants with meningococcal carriage in survey one may lose their carriage by survey 2). Our target was to enrol approximately 3000 students (2880 HIV-uninfected and 207 HIV-infected) to account for a potential 15% lost to follow up for survey two.

For determining differences in carriage prevalence by serogroup we assumed a meningococcal carriage prevalence of 6%, and prevalence of serogroup B of 7% of carriage isolates. This would require 226 meningococcal carriage isolates from 1 530 total students swabbed, for a power of 80% and confidence intervals of 95%.

Study procedures

Students were enrolled during registration week at the university campuses and included students living both on and off-site. The second survey was conducted on campus 6-8 weeks after registration. Participants in the first survey were invited to return for the second survey via email or sms, and scheduled appointments were made.

After providing consent to participate in the study, students were required to:

a. Answer a standardised self-administered electronic questionnaire on study provided tablets regarding risk factors for meningococcal carriage (including questions on lifestyle, living conditions and medical history).
b. Undergo pre- and post-test HIV counselling following a rapid HIV test via finger prick. A confirmatory HIV test was performed on all persons testing positive.
c. Have an oropharyngeal swab taken by trained health care workers making sure to touch the posterior pharynx and tonsillar bed.

Procedures a) and c) were repeated on all enrolled students for the second survey to obtain information regarding the acquisition and clearance of carriage. See appendix D for consent form and study questionnaire.

A unique study identification number was given to all participants to ensure confidentiality throughout the study. The unique study number was used to link the questionnaires, HIV tests and oropharyngeal carriage results.

HIV testing

HIV pre- and post-test counselling and testing was performed at survey one on all who consented to the procedure by trained nursing staff. Rapid HIV-antibody detection tests (Alere Determine™ HIV-1/2, Abbott) were used. All persons who tested positive for HIV had a second rapid HIV test performed (UniGold™ Recombingen®HIV-1/2, Trinity Biotech) to confirm the original result. Participants newly diagnosed with HIV were referred to the local student health clinic for assessment for initiation of antiretroviral therapy.

Oropharyngeal swabs

Flocked swabs (Copan Diagnostics) were used to take samples from the oropharynx of students at each visit. The swab was performed under direct observation of the posterior throat and tonsillar area. Avoiding the teeth, tongue and cheeks, the swab was inserted through the mouth touching the oropharynx, both tonsillar beds and the posterior pharyngeal wall using a figure of eight motion.

Swabs were placed directly into a selective enrichment medium (Todd-Hewitt broth, Media Mage Products) and incubated within 6 hours at 37°C for 24 hours.[120] Following incubation, 100µL of broth was plated onto Thayer Martin, New York City and 5% blood agar (Diagnostic Media Products) and incubated in 5% CO_2 for 48 hours. An aliquot of 500µL of remaining broth was removed and stored in -70°C freezer for future polymerase chain reaction (PCR). Identification of isolates was confirmed using Matrix-assisted laser desorption/accelerated time of flight mass spectrometry (MALDI). Serogrouping of isolates was done by slide agglutination using polyclonal antibodies to the capsular polysaccharides A, C, W, X, Y and Z and monoclonal antibodies to polysaccharide B (Remel, Biotech Limited, Dartford, England). All stored broths underwent real-time PCR to detect the *sodC* gene.[121] *ctrA* and genogrouping real-time PCR (ABCEHWXYZ) was performed on all meningococcal isolates and *sodC*-positive swabs.[122,123] *ctrA* negative and genogroup PCR-negative meningococci were considered non-genogroupable. Participants were classified as meningococcal carriers if *N. meningitidis* was cultured or the *sodC* gene was detected on PCR. For simplicity, in the results/discussion section, serogroup may refer to either, serogroup classification using slide agglutination or genogroup classification using PCR.

Study definitions

Acquisition, persistence and clearance of meningococcal carriage 6-8 weeks following registration were determined from the cohort returning for the second survey. Acquisition of meningococci was defined as those who were not carriers at survey one and then were carriers at survey two. Persistence of carriage included all students carrying meningococci at survey one and survey two, regardless of serogroup. Clearance of carriage was defined as those carrying meningococci at survey one but not at survey two.

Data analysis

Data from surveys one and two (questionnaire, oropharyngeal swab and HIV test) were linked using the unique study number and entered onto a Microsoft Excel database. All statistical analyses were done using Stata version 14.0 (StataCorp Inc., College Station, Texas, USA). P-values <0.05 were considered statistically significant. Variables with p-values <0.2 in univariate analysis were evaluated in the multivariable models using manual backward elimination.

Carriage prevalence and risk factors for carriage of meningococci were determined from the cross-sectional study of first-year university students from survey one and two. Carriage prevalence was determined by day of study enrolment, and percentage changes ([rate ratio-1] x 100) in carriage were calculated to demonstrate the increase in carriage during registration at the universities and overtime from survey one to survey two. Prevalence of carriage by serogroup distribution was reported.

Acquisition, persistence and clearance of meningococcal carriage 6-8 weeks following registration were determined from the cohort returning for the second survey.

Univariate and multivariable logistic regression models were used to determine significant risk factors associated with meningococcal carriage at each of the two time points.

Further multivariable logistic regression was done to determine factors associated with carriage persistence amongst carriers in survey one versus clearance. The same variables were used as in the multivariable analysis for risk factors for carriage at survey one and two.

Multinomial regression was performed to compare those who never carried meningococci (baseline category) with the carrier acquisition and carrier persistence groups from the cohort. Multinomial regression allows modelling of outcome variables with >2 categories (levels=j) and relates the probability of being in category j to the probability of being in a baseline category. A complete set of coefficients are estimated for each of the j levels compared with the baseline and the effect of each predictor in the model is measured as the relative risk ratio (RRR).

Ethical considerations

Ethical approvals (see appendix B for clearance certificate)

The meningococcal carriage study was approved by the Wits Health Research Committee (Medical) (reference M160672) as well as that of the University of Cape Town (reference 395_2016). All participants gave written consent to participate in the study. Participation in the study was entirely voluntary and did not influence future contact with student health or other health care providers.

Risks and/or benefits to the participants

There were no direct benefits to individuals participating in this study, however knowledge gained from understanding carriage rates amongst the participants and risk factors contributing towards carriage may facilitate decisions by policy makers regarding meningococcal vaccine use amongst high-risk groups in this setting.

HIV results were made available to the participants with pre- and post-test counselling provided by trained staff. Newly diagnosed HIV-infected individuals were referred to the student health clinic for assessment and initiation of antiretroviral therapy.

The study personnel chose not to provide antibiotics to clear meningococcal carriage to persons who were found to be carrying different strains of *N. meningitidis*. This study was not being conducted in an outbreak setting and generally the majority of carriage strains have a low virulence and therefore a low propensity to invade the oropharyngeal mucosa to cause IMD. Eliminating carriage through antibiotic use may increase one's risk of acquiring a more virulent meningococcal strain, therefore putting a person at increased risk of acquiring IMD.

Manuscript 2: Meningococcal disease in South Africa (objective 2)

Study design

This was a secondary data analysis of IMD episodes as reported through the GERMS-SA national surveillance programme from 2003 through 2016.

Study setting

The study population included all individuals residing in South Africa from 2003 through 2016. All episodes of laboratory-confirmed IMD from any of the 257 public and private sector laboratories participating in the GERMS-SA surveillance programme were included.

Data collection

Basic demographic data from all IMD cases were collected (age, sex, province, specimen type). Serogroup and antimicrobial susceptibility results were available for those isolates that were received at the NICD reference laboratory (75%, 3917/5249). At 26 enhanced surveillance site hospitals, representing all 9 provinces of South Africa, we collected additional clinical data including in-hospital outcome, predisposing conditions (including HIV infection status), and severity of illness as determined by the Pitt bacteraemia score. See appendix D for GERMS-SA case report form.

The Pitt bacteraemia score was developed 30 years ago at the University of Pittsburgh and uses clinical measures to assess acute severity of illness in patients with blood stream infections.[109] Patients are scored based on temperature, systolic blood pressure reading, mental status or Glasgow Coma Scale score, need for mechanical ventilation and development of cardiac arrest. A score of $\geq$4 is indicative of critical illness due to a higher mortality risk. Its reliability to identify a patient with a life-threatening infection based on initial physical examination surpasses some of the more traditionally used systems such as the Acute Physiology and Chronic Health Evaluation II (APACHE II) systems or sepsis-related organ failure assessment (SOFA) scores.[124]

Episodes of cryptococcosis from the GERMS-SA surveillance system were used as a control group in the assessment of spatial-temporal clusters of IMD. Cryptococcosis is widespread across South Africa and its diagnosis necessitates the clinical expertise of performing a lumbar puncture on suspected patients and processing the specimen at a functioning district laboratory. Using episodes of cryptococcosis over time we could control for differences in specimen-taking practices and laboratory capacity across the different districts and provinces of South Africa.

Statistical analysis

Statistical analysis was done using STATA version 14 (StataCorp Inc., college Station, TX). Annual incidence of IMD by age category and serogroup were calculated using population estimates from Statistics South Africa.[60] Population denominators from the Thembisa 2016 model were used to calculate the average annual incidence of IMD by HIV status, as well as the relative risk of IMD amongst PLHIV and HIV-uninfected persons by age category.[125,126] Trends in incidence rates by serogroup were calculated using Poisson regression, using cases from 2003 as the reference group. A

univariate analysis of characteristics of episodes of IMD by serogroup (A, B, C, W, Y and other (X, Z and non-groupable)) was performed using Fisher's exact or the Mantel-Haenszel χ^2-test for categorical variables, followed by a multinomial regression model with serogroup B as the baseline category.

A spatial-temporal analysis, using SaTScan version 9.4.4 (http://www.satscan.org/), was conducted to detect IMD serogroup clusters among meningococcal cases with available serogroup results (3256/4261, 76%), by district and month from January 2005 through December 2015. We used a Bernoulli model to compare cases of IMD by serogroup A, B, C, W and Y to cryptococcal controls (collected through the same surveillance platform). Cryptococcal episodes were used to control for different specimen-taking-practises and laboratory-capacity in the districts. A cluster was defined as an increase in serogroup-specific IMD occurring above the expected norm in a defined geographic location and time period. Geographic location was based on districts within which the cases were hospitalised. A spatial cluster is identified using an elliptical area of search which varies in size, shape and direction. Relative risk of each serogroup-specific IMD cluster for each district was calculated by dividing the observed by the expected number of cases for each district. Maps indicating clusters were generated using ArcGIS version 9.2 (http://www.esri.com/). For each 999 replications, clusters with p-values <0.05 were considered significant.

Ethical considerations

Ethics approval for the secondary data analysis of the GERMS-SA surveillance data for this manuscript was obtained from the University of the Witwatersrand Human Research Ethics Committee (Medical) (reference: M170951). All personal identifiers from both meningococcal and cryptococcal episodes were removed prior to data analysis. See appendix B for clearance certificate.

Ethics approvals for the ongoing GERMS-SA surveillance programme were obtained annually from the University of the Witwatersrand Human Research Ethics Committee (Medical) (Wits HREC(Medical)). The first protocol was approved on 25 October 2002 with reference M021042. A revised protocol was approved on 28 October 2008 (M081117), followed by a further major revision approved on 31 January 2014 (M140159). The protocols have also been reviewed from other

provincial and university ethics committees, and where needed by the respective hospitals involved in the programme. Informed consent was obtained from all participants or parents/legal guardians of under-aged participants interviewed in the enhanced surveillance programme.

Meningococcal disease is a category one notifiable medical condition, therefore all cases should be reported to the provincial communicable diseases control offices in order to coordinate the provision of chemoprophylaxis and monitor for further disease transmission or clusters. Unfortunately, notification is rarely complete and therefore the GERMS-SA surveillance network is a great supplement to the line lists generated by the National Department of Health of notified meningococcal disease cases.

Manuscript 3: Complications following bacterial meningitis in South Africa (objective 3)

Study design

This was a secondary data analysis of GERMS-SA national surveillance data for invasive pneumococcal, *H. influenzae* and meningococcal episodes occurring in South Africa from 2016 through 2020.

Study setting

The study population included all individuals residing in South Africa from 2016 through 2020. All episodes of laboratory-confirmed invasive pneumococcal, *H. influenzae* and IMD diagnosed at 25 sentinel surveillance hospitals participating in the GERMS-SA surveillance programme located in 8 of the 9 provinces of South Africa were included (one hospital in the Northern Cape Province was not included in the enhanced surveillance programme for this time due to staff shortages).

Laboratory-confirmed meningitis included identification of *S. pneumoniae*, *H. influenzae* or *N. meningitidis* through culture or polymerase chain reaction (PCR) of cerebrospinal fluid OR any usually sterile specimen (provided a clinician diagnosis of meningitis had been made). Antimicrobial susceptibility and serotype/serogroup classification were available for viable isolates or culture-negative PCR-positive specimens sent to the NICD reference laboratory as part of the surveillance protocol.

Data collection

Demographic, clinical and antibiotic treatment data for each case of meningitis was available from the GERMS-SA data set. An additional questionnaire was added to the GERMS-SA case report form for meningitis cases to include data on the presence of sequelae at hospital discharge and two-months post-discharge in survivors.

Reported sequelae included presence of necrotic skin lesions, amputations, development of hydrocephalus, new onset of seizures, hearing loss, visual loss, or any history of neurological fallout. Sequelae were categorised as minor (neurological fallout (hypotonia), necrotic skin lesions, digit amputation or unilateral hearing loss) or major (hydrocephalus, visual impairment, seizures, neurological fallout (motor deficit), limb amputation or bilateral hearing loss) according to the Global Burden of Disease Project classification.[15]

Appropriate empiric antibiotic therapy was defined as receiving intravenous third generation cephalosporin (cefotaxime or ceftriaxone) within 24 hours of specimen collection.[127] Directed antibiotic therapy was deemed appropriate if patients received i) a third generation cephalosporin, or ii) benzyl penicillin or ampicillin provided the organism was susceptible to penicillin or ampicillin, or iii) vancomycin plus a third generation cephalosporin for pneumococcal meningitis cases if the penicillin minimum inhibitory concentration (MIC) was >0.06µg/ml. Pneumococcal and meningococcal isolates were considered resistant if penicillin MICs were >0.06µg/ml, and if *H. influenzae* isolate ampicillin MICs were >1.0µg/ml. Organisms were defined as vaccine serotype/-group if they were one of the serotypes contained in the thirteen valent pneumococcal conjugate vaccine for pneumococcus, serogroup A, C, Y or W for meningococcus or *H. influenzae* type b for *H. influenzae* meningitis.

In 2020, following the onset of the COVID-19 pandemic, there were minimal disruptions to the GERMS-SA surveillance programme despite restricted movement and stay-at-home orders. GERMS-SA was deemed a public health priority programme and thus collection of clinical data on pathogens of public health importance could continue and all hospitals and laboratories continued to provide in-patient services to those in need.

Statistical analysis

Statistical analysis was performed using STATA version 14 (StataCorp Inc., College Station, Texas, USA) and p-values <0.05 were considered significant. Medians with interquartile ranges were calculated and the Mann-Whitney rank-sum test was used for non-parametric non-categorical variables. Univariate analyses using Fisher's exact/ Mantel-Haenszel $\chi 2$-test for categorical variables were performed using death or presence of sequelae as an outcome variable for all bacterial meningitis, pneumococcal meningitis, *H. influenzae* meningitis and meningococcal meningitis cases separately. P-values <0.2 on univariate analysis were included in all multivariable logistic regression models and non-significant variables (p-value>0.05) were dropped using step-wise manual backward elimination.

Ethical considerations

In addition to the ethics approvals mentioned in manuscript 2, an amendment to the protocol was approved by the University of the Witwatersrand Health Research Ethics Committee (Medical) on 7 December 2015 (M140159) for the additional questionnaire on long-term complications following meningitis. It allowed collection of data from GERMS-SA participants with IMD, *S. pneumoniae* meningitis or *H. influenzae* meningitis at discharge and two months following their hospital admission through patient interview at the hospital or telephonically, and through medical record review.

Manuscript 4: Excess meningococcal disease due to seasonal influenza (objective 4)

Study design

This was an ecological study using surveillance data from the GERMS-SA and Viral Watch surveillance programmes in South Africa.

Study setting

The study population included all persons living in South Africa between 2003 and 2018.

All persons with IMD reported through the GERMS-SA surveillance during the study period were included. Mid-year population denominators from Statistics South Africa were used to linearly interpolate the population at risk each epidemiology week for the study period of 1 January 2003 until 31 December 2018, to calculate meningococcal weekly incidence.[60]

The proportion of positive influenza cases detected by epidemiology week through the Viral Watch surveillance programme from 1 January 2003 through 31 December 2018 were included in the analysis to determine timing of the influenza seasons each year.

Statistical analysis

Statistical analysis was done using Stata version 14 (StataCorp Inc., College Station, Texas, USA) and R statistical software (version 4.0.2) using the waveletComp package (Roesch and Schmidbauer (2018), https://rdrr.io/cran/WaveletComp/man/WaveletComppackage.html) for the time-series analyses.

A bivariate time-series analysis was used to determine the temporal association between the peaks of each season (meningococcal and influenza) each year. We used wavelet transform of the time series into a time-frequency domain. We then used the phase difference of the cross wavelet spectrum to determine the time lag between the peak of the two seasons. Position of the phase difference in either the first or last quadrant indicates that the two series are moving in-phase with x leading y or y leading x in the respective quadrants. We then looked at the cross wavelet patterns to determine if the two time-series had high common power.

We used univariate regression spline models in STATA to estimate the excess cases of IMD associated with seasonal influenza (including all influenza, influenza A and influenza B) by year, allowing for a five-week lag-time between influenza and meningococcal cases as determined by the phase difference in the cross wavelet spectrum model above. Excess cases of IMD were determined by subtracting the predicted weekly rate of IMD from the calculated basal weekly rate in the absences of influenza. The attributable fraction of IMD associated with influenza was calculated as a percentage of the excess IMD cases over the observed number of meningococcal disease cases.

Ethical considerations

Ethics approvals for the GERMS-SA surveillance programme have been obtained annually from the University of the Witwatersrand Human Research Ethics Committee (Medical) (Wits HREC(Medical) (Reference M140159). Ethical clearance for the Viral Watch programme was obtained from Wits

HREC (Medical) (M060449). Clearance for this secondary data analysis was obtained from Wits HREC(Medical) (M170951).

Table 2: Summary of main themes in results and discussion for thesis *Neisseria meningitidis* epidemiology in South Africa during a period of low endemicity

Theme	Data Gaps Filled				Implication of findings, and recommendations
	Paper 1:	Paper 2:	Paper 3:	Paper 4:	
Country-specific data	• Carriage prevalence • Risk factors for carriage • Carriage acquisition amongst high-risk groups	• Incidence of IMD • Trends over time • Presence of ongoing serogroup specific clusters over time • Risk factors for serogroup specific IMD	• Risk factors for death amongst meningococcal meningitis • Prevalence of sequelae following meningococcal meningitis	• Association of influenza seasons on IMD peaks • Quantify the effect of influenza seasons on IMD incidence	• Carriage, disease and meningococcal vaccination use is low, therefore, population immunity may be low • Monitor for increases in disease and/or changes in serogroup distribution/ emergence • Risk factors for carriage similar globally • Behavioural changes may decrease carriage and thus disease (smoking, multiple partners, crowding) • Published recommendations for meningococcal vaccination use in South Africa[128] (data generated from paper 1-3 used to inform recommendations)
HIV and meningococcus	• HIV as a risk factor for carriage acquisition	• HIV as a risk factor for serogroup W and Y disease	• HIV as a risk factor for death		• Focus on prevention efforts for PLHIV • Initiation and maintenance of antiretrovirals • Influenza vaccination • Meningococcal vaccination • Co-authored published guidelines for vaccination of HIV-infected adults[88] (data generated from paper 1-3 used to inform guidelines)
Importance of surveillance	• Platform for launching additional research studies • Carriage data are useful for interpreting surveillance findings	• Ongoing systematic collection of data • Disease fluctuation over time • Natural evolution of serogroups	• Identify high-risk groups for interventions – PLHIV, infants • Platform for launching additional research	• Robust baseline of disease in order to track changes due to various external factors (i.e. COVID-19 pandemic)	• Continue surveillance both active and passive (lab and clinical data) • Platform for launching special “nested” studies to elaborate on surveillance findings • Understand big picture - Integration of surveillance systems and data, guide prioritisation of interventions by comparing incidence to other pathogens under surveillance

Theme	Data Gaps Filled				Implication of findings, and recommendations
	Paper 1:	Paper 2:	Paper 3:	Paper 4:	
		• Detect low-grade clusters of disease • Identify high-risk groups for interventions PLHIV, infants			• Real-time data analysis and feedback important for detecting outbreaks/clusters and informing change in disease patterns • Collaborate with surveillance groups from other countries i.e. International Respiratory Infections Surveillance network
Public health relevance	• Low carriage prevalence and high rate of acquisition on entering university • Identifying country-specific and other non-reported risk factors for carriage and disease	• Recorded IMD incidence • Determined method for identifying ongoing serogroup clusters • Identifying country-specific and other non-reported risk factors for carriage and disease • Define antimicrobial resistance in South Africa	• Identify high-risk groups for death and development of complications amongst survivors	• Quantify effect of influenza on IMD in a temperate climate	• WHO Defeating meningitis by 2030 initiative • Advocate for vaccination policies in universities and amongst high-risk students • Monitor disease and serogroup evolution – natural and after certain interventions/events • Inform vaccination policies as new vaccines become available • Possible role for vaccination of populations at high-risk for severe consequences of disease. • Educate public and health-care workers on early recognition and treatment of disease • Identifying alternate indirect prevention measures for IMD • Identifying potential additional benefits from influenza vaccination • International collaborations • Co-author in paper exploring decline in IMD coinciding with COVID-19 pandemic movement restrictions • Member of the Global Meningococcal Initiative

IMD: Invasive meningococcal disease; PLHIV : People living with HIV; COVID-19: Corona Virus Disease 2019

Results and Discussion

The results are discussed under four main themes referring to specific results from the four different manuscripts as relevant. The four themes included: describing meningococcal carriage and disease in South Africa, HIV-infection and meningococcal disease, the importance of surveillance in meningococcal disease epidemiology, and the public health relevance of the study findings. A summary of the themes can be found in Table 2.

Meningococcal carriage in South Africa

Summary of the main findings

This is the first study describing meningococcal carriage in any South African population. In summary, meningococcal carriage amongst South African 18 year olds entering university was initially low (5%), increasing to 8% after two months on campus. Carriage was diverse with representation from 6 distinct serogroups (Y, B, W, C, X and Z). Risk factors for carriage were similar to that seen elsewhere and largely behavioural including intimate kissing and nightclub/pub attendance. In addition, HIV-infection was noted as an independent risk factor for meningococcal carriage acquisition.

A meningococcal carriage study was conducted at two large universities in South Africa to assess carriage and carriage acquisition on campus amongst first-year students. This age group is thought to represent the principal reservoir of meningococcal carriage and there are many reports of IMD outbreaks amongst university students, particularly amongst those residing on campus.[129,130] In total 2120 first-year students were enrolled (901 from UCT and 1219 from Wits) with 1655 students participating in both surveys. Mean age was 18 years and 59% of participants were female. Only 1% of the study participants were HIV infected. Meningococcal carriage prevalence increased from 5% (77/1655) at registration week to 8% (130/1655) after 6 weeks on campus. Carriage increased most notably during the first five days of attending campus, where a three-fold increase in carriage prevalence was observed from day one following registration (1.8% prevalence) to day five (5.9% prevalence).

Non-groupable strains were most prevalent (3.5%), followed by serogroup Y (1.5%) and B (0.9%), with few serogroup C and W (0.1% each) present. Risk factors for meningococcal carriage acquisition included attending nightclubs (adjusted relative risk ratio [aRRR] 2.1, 95% confidence interval [CI] 1.1-4.0), intimate kissing (aRRR 1.8, 95% CI 1.1-2.9) and HIV infection (aRRR 5, 95% CI 1.1-24.4). More specifically risk factors for acquiring serogroupable meningococcal carriage (versus a non-groupable organism) included: pub attendance (adjusted odds ratio [aOR] 7.9, 95% CI 1.8-35.3), intimate kissing (aOR 15.4, 95% CI 3.1-75.8) and having a recent upper respiratory tract infection (aOR 5.3, 95% CI 1.4-19.6).

As seen elsewhere, the majority of carriage isolates in our study were unencapsulated (non-groupable) with low potential for causing disease due to inactivation or absence of the capsular synthesis gene.[120,131,132] Serogroups Y, B and W occurred in varying proportions in most carriage studies, with exception of the African Meningitis Belt where serogroup B carriage and disease is extremely uncommon.[51,133] Serogroup Y carriage was the second most predominant in South Africa even though it is only the fourth most common invasive disease causing serogroup in South Africa. Although serogroup Y outbreaks are not common and invasive disease is seldom seen, increased prevalence of serogroup Y carriage should be monitored, as the United Kingdom previously noted an increase in serogroup Y carriage in university students coinciding with an increase in invasive serogroup Y IMD in a similar age group in the wider population.[29,134] In South Africa, most serogroup Y disease is seen in young adults and also in HIV-infected individuals.[135] In Australian school children serogroup Y carriage was the second most predominant however serogroup Y IMD is uncommon in Australia.[136,137] Generally, while carriage serogroups may reflect the variety of disease causing serogroups in the region, not all carriage isolates of the same serogroup belong to the same virulent disease causing strains. This study focused on risk factors for carriage and phenotypic characterisation of the organism. Genotypic characterisation through whole genome sequencing (WGS) of the organism is useful to compare carriage and invasive meningococcal isolates. This did not form part of my thesis, however there are fellow scientists at the NICD who are using the isolates from my study

and developing pipelines using WGS to compare the carriage and invasive strains detected in South Africa.

Comparison to other countries/settings

Although meningococcal carriage prevalence amongst these South African students was half that of an American university carriage study (15%) and one sixth of that reported in the United Kingdom (46%), it was similar to recent studies among adolescents in Australia (6%) and Italy (5%) and slightly higher than the peak carriage age group in population studies in the African meningitis belt (4.9%, 10 to 14 year olds).[31,138–141] Milder winters and warmer summers in the latter three regions and South Africa may partly explain the lower carriage rate as risk factors for meningococcal carriage are similar across all the university studies.[19]

Cigarette smoking and smoke exposure have been associated with meningococcal carriage and IMD.[19] In our carriage study smoking did not appear as an independent risk factor for meningococcal carriage amongst students. This could be due to the high prevalence of smoking amongst the students in our study (27% smoked and 65% were regularly exposed to cigarette smoke) and the high collinearity with smoking and nightclub/pub attendance (which were independent risk factors). Although the South African government instituted many laws restricting cigarette smoking in public and even private spaces, nationally smoking prevalence remains 18% in 2012 and many laws are not fully implemented.[142] The United Kingdom noted a decrease in IMD and carriage from 2000 to 2014, including a significant decrease in the prevalence of behaviours associated with carriage such as smoking (21% to 11%) and pub/nightclub attendance (62% to 39%).[21] This could indicate that public health policies that influence behaviour may further reduce meningococcal carriage and disease.

Implications/relevance of these findings

Carriage is the prerequisite for developing IMD, and prolonged or repeat acquisition of carriage is thought to provide protection against transition to disease.[143] Vaccination with conjugate vaccines offer protection from both carriage and invasive disease. In South Africa, a setting of limited vaccine use and low disease incidence, low carriage rates are suggestive of low immunity and possible increased susceptibility to disease with subsequent high outbreak potential should a virulent strain be

introduced into the population. Alternatively, South Africa may have unique barriers to transmission of meningococci resulting in low carriage and a low incidence of disease. This hypothesis is unlikely as risk factors for carriage explored in the university study were similar to those identified in other settings with higher carriage, and a high rate of increase in carriage was seen among students over the first few days of attending university.[21,31] Our recommendation from these findings would be to consider vaccination of all students prior to entering university, particularly those who are HIV infected.[144,145]

The low carriage prevalence detected in our study population may be influenced by age, and if carriage prevalence in the population is similar to that of the African meningitis belt, younger children might have higher rates of carriage.[141] This could be explored further in South Africa by including more age groups in future meningococcal carriage studies. Further molecular studies on the carriage isolates will be beneficial to compare the genetic population structure of the carriage isolates to disease isolates, and to assess the diversity of protein-based vaccine targets in these isolates. This molecular work is currently underway in the NICD reference laboratories with the hope that whole genome sequencing can be performed on all carriage and invasive isolates going forward.

Invasive meningococcal disease in South Africa

Summary of the main findings

Manuscripts two, three and four speak to the contribution made towards understanding the epidemiology of IMD in South Africa. In summary, manuscript two shows the typical waxing and waning of IMD in South Africa over the years, with the current incidence of IMD being very low at 0.2 cases per 100 000 population. We documented the natural evolution of the emergence and now dwindling presence of serogroup W IMD, without meningococcal vaccine implementation, as well as the low grade yet ongoing presence of multiple disease causing serogroups. Of those who develop disease, all required hospitalisation with 60% showing moderate to severe disease and 17% succumbing to the disease during their hospital stay. HIV infection was a risk factor for IMD - particularly with serogroup W and Y. Amongst those with meningococcal meningitis manuscript 3 reported an in-hospital case-fatality of 14% with an additional 3% dying within two months of

hospital discharge. Factors associated with poor outcome were decreased mental status on admission, presence of underlying conditions and HIV infection. Twenty percent of survivors of meningococcal meningitis suffered sequelae with altered mental status on presentation being a factor associated with poor outcome. In manuscript two the spatial-temporal analysis of all meningococcal cases indicated that there was ongoing, established circulation of five different serogroups across the country in multiple districts over many years indicating that all serogroups (A, B, W, Y and C) need to be accommodated in IMD prevention efforts. Manuscript 4 demonstrated that IMD and seasonal influenza were occurring in-phase over a sixteen-year period, with influenza leading the IMD season by five weeks and peaking in-phase with IMD over the winter period. We estimate that approximately five percent of meningococcal cases can be attributed to co-circulating influenza virus infections.

Manuscript 2: Meningococcal disease in South Africa

The second paper was a secondary data analysis using the GERMS-SA national laboratory-based surveillance dataset on IMD. Over 14 years, 5249 incident cases of laboratory-confirmed IMD occurred in South Africa. Invasive meningococcal disease decreased by 76% from 2003 to 2016 despite minimal meningococcal vaccination use or other preventative measures being implemented. Invasive meningococcal disease incidence peaked at 1.4 cases per 100 000 population in 2006 and has been steadily declining to 0.24 cases per 100 000 in 2016. This peak was largely due to the 10-fold increase seen in serogroup W disease between 2003 and 2006, which has previously been reported.[41] Of the 75% of IMD episodes with available serogroup data, 7 different serogroups were detected (5% A, 23% B, 9% C, 50% W, 12% Y, 0.3% X, and 0.1% Z) in addition to a few non-groupable invasive episodes (0.4% non-groupable). Serogroup W which accounted for half of all reported cases has steadily declined in recent years but is still the second most predominant serogroup occurring in South Africa after serogroup B. Prior to 2004 serogroup A was most predominant, but following the emergence of serogroup W, no cases of serogroup A have been detected in South Africa since 2010. Over the 14 years, for all serogroups, infants had the highest incidence of disease (particularly serogroups B and W with incidences of 2.4 and 3.1 episodes per 100 000 person years, respectively). A smaller peak in disease was seen in young adults in the 15-24 year and 25-44 year age groups.

The study gives detailed description of the patient demographics by meningococcal serogroup of 3917 patients with isolates available for serogrouping, as well as the clinical characteristics of 1489 patients presenting to one of 27 enhanced surveillance sites. Seventy-four percent had meningococci present in CSF and 25% had meningococcal bacteraemia. Almost two-thirds (61%) of patients presented with moderate to severe disease (as recorded by the Pitt bacteraemia score) on admission with more severe presentation occurring more commonly with serogroup W disease than B (adjusted relative risk ratio (aRRR) 2.7, 95% CI 1.1-6.3). In-hospital case-fatality was 17%, and differed by serogroup, with serogroup W having the highest case-fatality at 22%. A high proportion of patients were HIV-coinfected and incidence of IMD among PLHIV was 2.5 times higher than HIV-uninfected persons (95% CI for relative risk, 2.2-2.8), with more serogroup W and Y disease occurring amongst PLHIV.

Seventy-seven percent of the IMD episodes were reported by three of the nine South African provinces, with much of serogroup B disease occurring in the Western Cape and serogroup W in Gauteng Provinces. This could partly be explained by the higher total population and population density in these provinces, poor specimen taking practices in more rural areas and/or introduction of a virulent serogroup into the population.[41] Therefore we conducted a spatial-temporal analysis of IMD episodes from 2005-2015 using cryptococcal meningitis as a control. Cryptococcosis is widespread across the country and its diagnosis is reliant on expertise to perform a lumbar puncture and adequate laboratory capacity to detect the organism. The spatial-temporal analysis detected 8 significant clusters of IMD caused by five different serogroups (A, B, C, W and Y) occurring over the 14-year period, each lasting at least 12 months. This analysis was useful in detailing the relative risk of acquiring serogroup specific IMD if one resided inside a district in the cluster versus outside of the cluster. For example, the first serogroup B cluster occurred over Gauteng province from 2007 through 2011 with a within cluster relative risk of acquiring serogroup B disease of 2.4. The second B cluster occurred over the Western Cape from 2005-2010 with a within cluster relative risk 8.1 times that if you resided in a district outside the cluster.

Manuscript 3: Complications following bacterial meningitis in South Africa

A third paper described the case-fatality and sequelae following meningococcal meningitis cases detected between 2016 and 2020 at the 17 GERMS-SA enhanced surveillance sites. Eighty-three percent (151/181) of meningococcal infections were classified as meningitis and outcome data were available for 91% (137/151). In-hospital case-fatality was 14% (19/137) with most deaths occurring on day one following hospital admission (median one day, interquartile range 0-8 days). Of those with available data (72/118 survivors), an additional 6% of survivors (4/72) died within two months of being discharged. On univariate analysis, compared to serogroup B meningitis, in-hospital case-fatality was higher with serogroup C, W and Y combined (B 6% died vs ACWY 19% died, OR 3.7, 95% CI 1.0-14.0, p=0.057). Factors significantly associated with in-hospital death on multivariable analysis included PLHIV or unknown HIV status (PLHIV 24% died, aOR 7.4, 95% CI 1.0-54.0, p=0.048; HIV-unknown 35% died, aOR 15.8, 95% CI 1.9-131.2, p=0.011; vs HIV-uninfected 5%), having an underlying illness (55% died vs 10% without underlying illness, aOR 26.5, 95% CI 1.9-367, p=0.014) and having altered mental status on admission (27% died vs 3% with GCS 15, aOR 20.9, 95% CI 2.9-151.7, p=0.003). Receipt of directed antimicrobial therapy was protective against death (11% vs 33% with non-directed therapy, aOR 0.04, 95% CI 0.00-0.37, p=0.005). Fortuitously, the majority of *N. meningitidis* isolates were susceptible to penicillin and third generation cephalosporins, as well as to fluoroquinolones which are mainly used for post-exposure prophylaxis.

Persons surviving meningococcal meningitis spent a median of 9 days (IQR 7-12) in hospital. Twenty percent (24/118) developed sequelae, including 5% (5/118) with more than one sequelae. Necrotic skin lesions (9%), new onset seizures (8%) and neurological fallout (4%) were the most common types of sequelae following meningococcal meningitis. There were no significant differences in presence of sequelae amongst different age-categories, underlying illnesses, meningococcal serogroup or type of antimicrobial used for treatment. However, persons with meningococcal meningitis with GCS<15 were seven times more likely to develop sequelae than those who had a GCS of 15 on presentation (aOR 7.2, 95% CI 1.1-47.7, p=0.04).

Manuscript 4: Excess meningococcal disease due to seasonal influenza

Manuscript four described the association between seasonal influenza and IMD over a 16-year period. Invasive meningococcal disease and seasonal influenza circulated in-phase during the winter season with peaks in influenza leading peaks in IMD by five weeks. Overall, five percent (95% CI 1-9%) of IMD was attributable to influenza co-circulation, with both influenza A and influenza B contributing to excess IMD.

Comparison to other countries/settings

Similar to the United States of America, Finland and other countries, South Africa has seen a decline in IMD over the last decade, with similar incidence rates to many high income countries.[58,82,146] Many of these countries attribute the reduction in disease to vaccination programmes, however this cannot wholly account for the true difference as South Africa, a country with minimal meningococcal vaccine use, also showed a reduction in disease.[82,146]

The case-fatality rate for IMD is high globally with approximately one in ten persons dying even with appropriate and timeous antibiotic treatment and support. The overall case-fatality from IMD in South Africa was only slightly higher than that reported from the United States of America (17% versus 15%).[82] Whilst many countries warrant vaccination of high-risk individuals, we showed that persons with any underlying illness (excluding HIV-infection) had a case-fatality ratio of over 50%. Further north, in the African meningitis belt, where periodic epidemics of IMD occur, case-fatality ratios from meningococcal meningitis are actually much lower than experienced in South Africa (4-7% versus 14%), however in the African meningitis belt many cases are unaccounted for and the case definition of meningitis is restricted to those with positive cerebrospinal fluid cultures or PCR.[51] This difference may also be driven by the higher HIV- prevalence in South Africa where 24% of PLHIV with meningococcal meningitis died versus 5% of those who were HIV uninfected.

The presence of sequelae following bacterial meningitis was overall similar in our study to other low- to middle-income countries. However, unlike Edmond's systematic review where children were twice as likely to develop sequelae than adults, in our study, adults and children with meningococcal meningitis were equally likely to develop sequelae.[15] Since low GCS score was associated with presence of sequelae, early recognition of signs and symptoms of meningococcal meningitis by the

public and health care professionals as well as rapid access to health care services are essential for preventing poor outcome amongst persons with IMD.[147]

Antimicrobial resistance was rare amongst the isolates causing disease in South Africa, and in general this is similar globally.[69] However, there are increasing reports of reduced susceptibility to penicillin as determined by increased minimum inhibitory concentrations, which could lead to penicillin and even third generation cephalosporin resistance.[148,149] A few cases of ciprofloxacin resistant IMD have been reported from the United States of America, however of concern are reports emerging from China indicating over two-thirds of some meningococcal sequence types could be non-susceptible to ciprofloxacin.[150,151] This highlights the importance of antimicrobial resistance surveillance of meningococcal isolates to monitor for changes in antibiotic susceptibility.

We demonstrated an association between seasonal influenza and excess IMD during the winter months, other mostly northern-hemisphere countries have found similar associations with a slightly smaller lag time between influenza and meningococcal peaks.[93,152,153] Although seemingly low, the 5% attributable percentage of annual IMD cases to influenza circulation needs to be interpreted in a setting where IMD is endemic and occurs sporadically throughout the year with peaks following after the influenza season in 16 of the 17 years of data analysed. Further support of the interaction between influenza and meningococcal disease can be seen in the large reduction in meningococcal disease in 2020 following a lack of seasonal influenza and other seasonal respiratory viruses. These findings could indicate potential indirect benefits of influenza vaccination on preventing a small portion of meningococcal disease and possibly other secondary bacterial infections following influenza infection.

Implications/relevance of the findings

In South Africa (prior to the COVID-19 pandemic), despite multiple serogroups causing both carriage and disease, meningococcal carriage prevalence and disease incidence was low. Similar findings were reported from the United States, Canada, the United Kingdom and many other European countries, who have established meningococcal vaccination programmes – a few of which include both meningococcal B and ACWY vaccines given at various time points and with population catch up

campaigns, resulting in moderately high levels of immunity in the population.[21,154–157] South Africa uses minimal meningococcal vaccine, therefore low exposure to the pathogen or its antigens may indicate low immunity to meningococcal disease and a particularly susceptible population to new virulent serogroups that may be imported or be reintroduced..

Therefore, it is imperative that meningococcal surveillance continues in order to monitor and respond to changes in serogroup distribution or disease incidence. Despite lower incidence of disease globally, there have been ongoing epidemics of virulent meningococcal strains in the African meningitis belt.[51] Importation of a virulent strain into a naïve population with low natural immunity, no meningococcal vaccination protection and a high HIV burden may spark a new wave of infections in South Africa. Apart from the novel association of HIV on carriage acquisition in the university population, risk factors for carriage and carriage acquisition are similar across the globe. It has been speculated that behavioural changes (such as reduction in smokers globally) may decrease carriage and thus disease.[21] Non-pharmaceutical prevention efforts are difficult to implement and are generally not sustainable, however global COVID-19 restrictions on societal movement, social gatherings, and avoidance of crowded spaces have resulted in a reduction in many respiratory transmitted infections – including *N. meningitidis*.[52]

Data from this research have been used to justify recommendations for meningococcal quadrivalent vaccine use in South Africa as well as contribute to recommendations for vaccinating adults living with HIV.[88,128] Carriage findings have been shared with student health committees at various universities in South Africa and helped to justify recommendations for vaccination of students accommodated in the hostels.

Further information on disease incidence in South Africa was shared with the global meningococcal initiative who meet every second year to discuss global progress in IMD prevention and control.[5] Data from South Africa are particularly welcome as there is a paucity of literature from African countries outside of the meningitis belt who do not experience the large-scale epidemics of IMD but rather show seasonal endemic disease from multiple serogroups.[4,36]

Surveillance should continue, and repeat carriage studies should be done intermittently to detect novel meningococci circulating and changing meningococcal carriage prevalence in various age groups. Continuous review of country-specific meningococcal vaccine recommendations is warranted in light of the changing epidemiology of the disease both locally and globally, the continuous development of broader spectrum vaccines and the future availability of meningococcal serogroup B vaccines in South Africa. Vaccination cost-effectiveness models should be formulated to explore the cost effectiveness of various vaccination programmes in the population in both low and high incidence scenarios. Antimicrobial susceptibility patterns should be monitored as antibiotics are the main stay of treatment and prevention through prophylaxis in some settings. The findings should be shared regularly in order to make informed choices on prevention measures.

HIV and meningococcal carriage and disease

Summary of the main findings

Invasive meningococcal disease occurs infrequently and the global prevalence of HIV in adults is less than 1%, therefore, there are few reports describing the association between HIV and IMD.[158] South Africa contains over 8 million people living with HIV, making up 13% of the population.[60] My research provided a unique opportunity to explore the meningococcal/HIV association at many different levels. In this thesis we showed that although meningococcal carriage prevalence amongst first-year university students did not differ significantly by HIV-status, HIV-infection was associated with a 5 times increased risk of acquiring meningococcal carriage within 6 weeks of starting university (aRRR 5.0, 95% CI 1.1-24.4). Overall, 36% of all IMD episodes in 16 years of population level surveillance occurred in PLHIV. PLHIV were 2.5 times more likely to develop IMD (aRRR 2.5, 95% CI 2.2-2.8) than HIV-uninfected persons and this increased to 5.2 times (95% CI 4.2-6.5) if they were between 15 and 49 years of age. HIV-coinfection was twice as common with IMD due to serogroup W or Y than serogroup B (aRRR W 1.8, 95% CI 1.1-2.9; aRRR Y 1.9, 95% CI 1.0-3.4).

HIV was strongly associated with in-hospital death, amongst meningococcal meningitis cases we report an overall case-fatality of 14%, with a significant difference in deaths between HIV-uninfected persons (5% case-fatality) and PLHIV (24% case-fatality, aOR 9.4, 95% CI 1.12-78.79). In particular,

compared to HIV-uninfected persons, PLHIV with a low CD4 T-lymphocyte count <200 cells/µL had a high risk of death (OR 12.3, 95% 2.14-70.65). Notably, there was no significant difference in case-fatality between HIV-uninfected persons and PLHIV with a CD4 count ≥200cell/µL. Although we show a higher risk of death and severe disease with HIV-coinfection, PLHIV did not appear to be at increased risk of developing sequelae following meningococcal meningitis.

HIV was not independently associated with carriage of serogroupable meningococci, however the high risk of carriage acquisition, alongside the high proportion of serogroup Y carriage, makes the association of HIV and serogroup Y IMD more significant.[135] Like-wise the higher incidence of serogroup W IMD amongst PLHIV and the poorer outcome of meningococcal meningitis amongst PLHIV, along with a previous association of poorer outcomes amongst persons with serogroup W disease and HIV in a previous South African study, all highlight the importance of controlling serogroup W disease, particularly amongst PLHIV.[42]

In summary, amongst PLHIV, we show a higher acquisition of meningococcal carriage, a higher rate of IMD and a higher case-fatality rate, particularly amongst those with low CD4 T lymphocyte counts.

Few studies report on meningococcal carriage amongst PLHIV. High meningococcal carriage rates (between 26% and 75%) have been reported amongst HIV-infected men who have sex with men, however these study populations are often semi-closed groups with multiple behavioural risk factors contributing to their risk of carriage, therefore cannot be generalised to the heterosexual HIV-infected population.[27,159] A retrospective study in the United Kingdom also found higher incidence of IMD in PLHIV but did not show an increase in severity of disease.[160] Similar to our findings, a study in New York City showed PLHIV with low CD4 counts to be five times more likely to develop IMD than HIV-uninfected persons.[54] Currently, meningococcal vaccination is recommended amongst PLHIV in the United States of America and the United Kingdom.[87]

Implications/relevance of these findings

This research shows that PLHIV are more vulnerable to meningococcal carriage, disease and death than HIV-uninfected individuals and therefore focused prevention efforts should be directed to this

high-risk group, particularly in South Africa where background HIV prevalence is high. South Africa should consider following other countries and prioritise PLHIV for routine meningococcal vaccination. Serogroup coverage by the ACWY quadrivalent vaccine would alleviate the higher burden of serogroup W and Y disease amongst PLHIV, and lower the carriage rate and thus meningococcal transmission and carriage acquisition amongst this group. Findings from this research were used to develop and publish guidelines to promote meningococcal vaccination of people living with HIV for the HIV Clinicians' Society of South Africa.[88] In addition, the research was able to provide local data for a country-specific cost effectiveness analysis of meningococcal vaccination of PLHIV.[161]

Promotion of the increased uptake of seasonal influenza vaccination amongst PLHIV could prevent morbidity and deaths from not only influenza disease but also other bacterial infections temporally associated with the influenza season, such as IMD as shown in this body of research. Most importantly all persons in South Africa (and globally) should be aware of their HIV-status and ensure that appropriate antiretroviral therapy (ART) is initiated, all persons are maintained on ART, and that their HIV infection is suppressed.

This research shows associations between HIV and IMD, and does not prove causality. If possible, these associations should be confirmed in larger studies. This is the first time that meningococcal carriage acquisition has been associated with HIV and this new finding if validated in other studies and settings, may be important in emphasising the need for IMD prevention through vaccination in populations with high HIV prevalence.

Importance of meningococcal disease surveillance

Summary of the main findings

"Public health surveillance is the ongoing systematic collection, analysis, and interpretation of data, closely integrated with the timely dissemination of these data to those responsible for preventing and controlling disease and injury." (Thacker and Berkelman, 1988). Surveillance data played an important role in the understanding of meningococcal epidemiology in South Africa.

This research was a robust reflection of trends in IMD incidence over a 14-year period, detailing the fluctuation of IMD serogroups with time. We showed a disappearance of the once predominant serogroup A IMD since 2010 and more recently an absence of serogroup A carriage. We show a decreasing trend of serogroups B, Y and C overtime, yet report significant, long term geographically defined clusters of these serogroups, indicating low grade ongoing transmission of disease in certain communities. The study describes the emergence and natural evolution of serogroup W which spread across the whole country and predominated in South Africa for 11 years. Serogroup W IMD peaked in 2005 at 0.9 cases per 100 000 population and dropped to 0.06 cases per 100 000 in 2016, in a setting with minimal (if any) meningococcal vaccine use.

Multiple years of systematically collected surveillance data for a relatively rare pathogen allowed us to perform sub-analyses by serogroup and identify high-risk groups for serogroup specific disease. The GERMS-SA surveillance platform was ideal for nesting additional studies, such as the additional case report form for documenting sequelae/complications following bacterial meningitis at discharge from hospital and two months following. This research highlights the benefits of integrating various surveillance platforms and surveillance databases to study-specific questions. Here we used cryptococcal surveillance data to control for specimen taking practises and laboratory capacity for processing specimens when doing the spatial-temporal cluster analysis. We analysed *S. pneumoniae* and *H. influenzae* surveillance data alongside the meningococcal data to describe the case-fatality and sequelae following common bacterial meningitis infections in South Africa. Finally, we analysed peaks in test positivity for influenza in the community by utilising the Viral Watch surveillance data in order to assess the attribution of recent influenza infections on IMD case load.

The GERMS-SA surveillance data on IMD were extremely important in placing the meningococcal carriage findings into context. Oropharyngeal specimens are not routinely taken and tested for the presence of meningococci, therefore apart from specific population-based carriage studies, determining meningococcal carriage prevalence is difficult. We report a low carriage rate amongst mostly vaccine-naïve first-year university students on a background of low IMD incidence. This was concerning as low carriage and low disease on a background of low/no vaccine use may be indicative

of low immunity to meningococci, therefore making this population particularly vulnerable to any new/virulent meningococcal strains that could be introduced into the communities.[12] The surveillance data were also useful to interpret the relatively high serogroup Y carriage prevalence amongst the university students, as IMD surveillance data showed that serogroup Y disease at that time was the most predominant serogroup in young adults.[135]

Comparison to other settings

The GERMS-SA surveillance platform was set up to mimic that of the Centers for Disease Control and Prevention, Atlanta, United States of America's Active Bacterial Core pathogen surveillance (ABCs) system which collects isolates from various public health laboratories and links the isolate data with clinical data collected from the patients' hospital records.[162] An advantage of the GERMS-SA platform is that 80% of the population utilises public health care institutions which all use one laboratory service for testing and reporting of results. Access to this electronic laboratory information system allows GERMS-SA to complete their case count by adding patient demographic details from the laboratory form if the isolate was not sent through to the NICD for further testing and characterisation.[108] Robust surveillance systems are important and there are many surveillance programmes in Africa that focus on the clinical syndrome of meningitis, such as the Invasive Bacterial – Vaccine Preventable Diseases (IB-VPD) surveillance network (formerly Paediatric Bacterial Meningitis (PBM) network) and MenAfriNet consortium, however, these are often focusing on patients presenting to mostly tertiary institutions and often have poor reporting rates across the different sites.[163,164]

Implications/relevance of these findings

The data highlight the importance of the GERMS-SA surveillance system in monitoring disease over time. It is essential that both passive and active surveillance continues to ensure accurate reporting of disease incidence and monitor for serogroup changes. The latter is wholly reliant on clinical laboratories submitting isolates to the surveillance reference laboratory for further phenotypic and genotypic characterisation, and clinical laboratories should be encouraged in this role. Surveillance programmes should be adaptable and allow for nested studies to further explore research questions as they arise. This research demonstrated the usefulness of integrating data from various surveillance

platforms in order to understand the bigger picture of meningococcal disease epidemiology. The COVID-19 pandemic has highlighted the importance of maintaining surveillance programmes in the midst of other health priorities and having the ability to do real-time data analysis to detect uncharacteristic changes in disease incidence. Recently the GERMS-SA surveillance programme was invited to collaborate with 26 other countries doing surveillance on *S. pneumoniae*, *H. influenzae* and *N. meningitis* through the International Respiratory Infection Surveillance (IRIS) network. The IRIS network was able to demonstrate a global reduction in all the respiratory transmitted pathogens which correlated temporally with the WHO announcement of the COVID-19 pandemic and various country-specific measures instituted to prevent transmission of SARS-CoV-2 virus.[52] GERMS-SA has provided data to the Global Meningococcal Initiative over the years, most recently they reported that the incidence of IMD had fallen by over fifty percent within one year of the onset of the COVID-19 pandemic, and warn that many meningococcal vaccination programmes had been interrupted or affected by the pandemic.[36,165]

There is potential for the surveillance systems to be improved as a result of collaborations with the private and public healthcare sectors during the COVID-19 pandemic. The NICD was able to implement routine electronic reporting of all laboratory-confirmed Severe Acute Respiratory Syndrome Corona Virus-2 (SARS-CoV2) cases from all private laboratories as well as public sector cases detected through the National Health Laboratory Services. This electronic reporting system could in future be extended to include all notifiable medical conditions (including IMD), allowing for up to date line lists of laboratory-confirmed cases.

Public health relevance

"Public health is the science and art of preventing disease, prolonging life and promoting, protecting and improving health through the organised efforts of society." Sir Donal Acheson, Chief Medical Officer for the United Kingdom, 1988.

Summary of the public health relevance of meningococcal disease and carriage

In 2020, the WHO prioritised meningitis by initiating a global road map towards "Defeating meningitis by 2030". The primary focus of the initiative is prevention of acute bacterial meningitis

(meningococcus, pneumococcus, *H. influenzae* and Group B *Streptococcus*) which were responsible for more than 50% of the 250 000 deaths from all-cause meningitis in 2019.[106] The main objectives of the programme are to eliminate bacterial meningitis epidemics; reduce cases of vaccine-preventable bacterial meningitis and deaths; and reduce the disability and improve the quality of life for those recovering from meningitis. Therefore, my studies on meningococcal epidemiology are well timed to provide a baseline evaluation of the situation in South Africa with regard to meningococcal infection and make recommendations to assist in achieving this goal.

My research has shown that currently the incidence of IMD and carriage in South Africa is low; and in a setting of minimal meningococcal vaccination, adaptive immunity is presumably low, placing the whole population at risk of emergent strains or reintroduction of virulent strains. Currently there are numerous serogroups causing disease and carriage in South Africa, any of which may have epidemic potential. Countries in the African meningitis belt continue to experience meningococcal epidemics from serogroup C, W or X and a novel strain of serogroup W has been expanding in Europe and the America's.[51,166] Introduction of any of these hypervirulent strains could cause an upsurge of IMD in South Africa.

Invasive meningococcal disease in South Africa has devastating consequences – 17% of all meningococcal episodes end in death and one fifth of survivors are discharged from hospital with major sequelae. Therefore, even in periods of low endemic disease, there are significant economic and psychosocial consequences for the families and communities affected.

We report on specific high-risk groups for developing serogroup specific disease and death from meningococcal meningitis. Infants bear the largest burden of disease, followed by young adults. These young adults also have the highest burden of HIV in our population and we show that the relative risk of IMD is three times higher in PLHIV than in HIV-uninfected persons. In addition, immunocompromised PLHIV (CD4 T-lymphocyte count <200cells/µL) were twelve times more likely to die from meningococcal meningitis than HIV-uninfected persons or PLHIV with CD4-cell count ≥200cells/µL.

A carriage study targeting first-year university students showed massive increases in carriage prevalence within one week of attending university, and a high rate of carriage acquisition amongst PLHIV within two months of attending university. Other behavioural factors were associated with increased carriage prevalence, namely, attendance of pubs/nightclubs, and having multiple intimate kissing partners. There was also a high prevalence of smoking and cigarette smoke exposure amongst the students.

The ecological study showed an association between seasonal influenza and annual peaks in IMD and estimated that 5% of IMD could be attributable to co-circulating influenza virus amongst the population during the winter months.

The importance of monitoring disease

The data for this research were largely reliant on an established surveillance network of laboratory-confirmed episodes of IMD. Meningococcal disease epidemiology is dynamic and forever changing and it is extremely important that surveillance systems be maintained and surveillance data be analysed in order to detect changes in disease epidemiology, be it serogroup changes, increases in antimicrobial resistance, or changes in high-risk groups.[36,58] The spatial-temporal model we used to determine geographic clusters of serogroup specific disease over time is a useful tool for future identification of increasing cases of particular serogroups in the various districts or provinces of South Africa.

The COVID-19 pandemic disrupted the world in multiple ways, including affecting global IMD incidence. Multiple countries detected a decline in respiratory transmitted infections that coincided with the introduction of various measures to mitigate the spread of SARS-CoV2. Global IMD incidence declined by 42% after two months of the WHO declaring the COVID-19 pandemic, and in South Africa IMD incidence declined by 58% from 2019 to 2020 (0.19 to 0.08 cases per 100 000 population).[52,165] Data from South Africa's robust GERMS-SA surveillance programme were well placed to assist in these analyses and as societies and social movements return to normal activities, it is even more important to continue monitoring for an increase in IMD following this decline.

Surveillance must continue for other pathogens of public health importance as we know that different diseases may impact on one another. We showed how the influenza seasons were associated with peaks in IMD in the winter months, and following the lack of a 2020 or 2021 influenza season, it is essential that influenza surveillance programmes are maintained in order to detect the emergence of novel influenza subtypes, the severity of future influenza infections and seasonality, as all this may influence future IMD seasonality.[103,167]

The importance of disease prevention

Vaccination programmes and post-exposure chemoprophylaxis are the two main ways of preventing IMD. However, the last few years have shown the massive impact other indirect measures (such as social distancing, travel restrictions, mask wearing, and stay at home orders) have had on preventing transmission of bacteria/viruses in the respiratory tract and their resultant invasive diseases.[52,103]

In South Africa currently only a quadrivalent conjugate polysaccharide vaccine against meningococcal serogroups A, C, W and Y is available. Protein-based meningococcal serogroup B vaccines are currently registered in South Africa but are not yet available for purchase. Almost all IMD episodes in South Africa since 2003 were due to serogroups potentially covered by these two vaccines. At present serogroup B disease is the predominant disease causing serogroup in the population and the second most predominant carriage serogroup amongst university students. A new pentavalent vaccine aimed at covering serogroups A, B, C, W and Y is currently undergoing phase III clinical trials and would be an ideal candidate for use in South Africa.[35,36] Ideally vaccination should be implemented on a population level, and depending on the targeted group (young infants or adolescents) a catch-up campaign should accompany this.[168] In South Africa with numerous competing health interests, it is difficult to justify the large expense of introducing a new population-based immunisation programme for a disease which has been declining “naturally”. However, as meningococci are transmitted from person to person asymptomatically through respiratory droplets and the ever present potential for introduction of a hypervirulent strain from beyond our borders, an adolescent or infant meningococcal vaccination programme should always be considered by the National Advisory Group for Immunisation when contemplating new vaccination strategies.

Despite the unlikely immediate implementation of a population vaccination programme, prevention of disease in certain high-risk groups should take place. Meningococcal vaccination recommendations for South Africa were published in 2019 drawing on local data from this thesis and highlighted different risk groups for which meningococcal vaccination is a requirement, recommended or should be considered.[128] Three main groups at highest risk of disease and poor outcome which have been highlighted in these studies include the HIV-infected population, first-year university/college students prior to attending the new institution and children under one year of age. The HIV-Clinicians Society developed guidelines for vaccinating adolescents and adults living with HIV.[88] Vaccination against IMD was included in these guidelines as data from this body of work showed that PLHIV have an increased risk of acquiring meningococcal carriage, developing IMD and dying from meningococcal meningitis.[88]

Other direct ways of preventing IMD are through ensuring the provision of chemoprophylaxis to close contacts of persons with IMD.[68] Our research shows that almost all isolates causing disease in South Africa are still susceptible to all of the antibiotics recommended for prophylaxis.[68] Related to this is the importance of reporting of confirmed and clinically suspected cases through the national Notifiable Medical Conditions system in South Africa – by so doing the Provincial clinical disease coordinators can ensure that contract tracing of cases is done, the relevant people receive post exposure antibiotics and any additional epidemiologically linked cases can be identified. The GERMS-SA surveillance database on laboratory-confirmed IMD cases has been used to supplement this list as often cases are not notified to the relevant authorities. More recently, this situation has mostly been mitigated by the use of an automatic electronic reporting system once an episode has been confirmed in the clinical laboratory.

Indirect measures for IMD prevention could include advocating for increased uptake of influenza vaccination to prevent influenza disease. The ecological study showed the temporal association of the influenza seasons and IMD peaks, and more recently, the lack of an influenza season in the last two years could have contributed to a portion of the reduction in IMD cases experienced during the COVID-19 pandemic.[36,52,165] Never before has the world been restricted to such an extent with regards

to intercontinental, intercountry, interprovincial, intercity and even inter-household socialisation and movement. Humans are the sole host of *N. meningitidis* therefore restrictions on socialisation and mask-wearing when in public would have slowed the transmission of *N. meningitidis* within communities and further afield.[12] This was shown through the International Respiratory Infection Surveillance (IRIS) network, which gathered meningococcal surveillance data from numerous countries and correlated the reduction in IMD with the onset of various levels of lockdown restrictions in the different countries.[52,169]The GERMS-SA surveillance data will continue to be shared with the IRIS group as we monitor ongoing changes in disease epidemiology following the early years of the COVID-19 pandemic.

Influencing public health policy

Apart from publishing guidelines for meningococcal vaccine use in high-risk populations which were presented to the National Advisory Group for Immunisation in South Africa, these data have been shared with student health bodies at various universities in South Africa as they slowly implement compulsory meningococcal vaccination of students staying in residences.[128] We are currently working on a cost-effectiveness model for introducing meningococcal conjugate quadrivalent ACWY vaccination into a school-based programme for adolescents. Local country data such as numbers of days spent in hospital, number of days in ICU, and number of sequelae needing follow up appointments at healthcare facilities are all extremely useful to accurately reflect the costs of treating IMD in South Africa.

Data from this research can also be used for advocating and strengthening of policies regarding antiretroviral uptake and retention in HIV-care programmes. Besides HIV being an independent risk factor for acquiring meningococcal carriage and disease, immunocompromised PLHIV were particularly vulnerable. We show that meningococcal meningitis deaths were strongly associated with PLHIV with low CD4 T-cell counts and on the contrary PLHIV with CD4 counts above 200 cells/µL were as likely as HIV-uninfected persons to die.

Influenza vaccination is effective at reducing deaths from influenza and possibly secondary bacterial infections following influenza. Here we show an additional indirect benefit from preventing influenza,

and we could potentially use the same model to quantify the effect of seasonal influenza on other respiratory pathogens such as invasive pneumococcal disease and *H. influenzae*.

World meningitis day is celebrated on 14 April each year and is a perfect opportunity to educate people about meningitis, what causes it and how it presents. Our data on IMD show that most deaths occur on day one after hospitalisation and that low Glasgow coma score on presentation is associated with death or development of sequelae. Signs and symptoms of IMD are often non-specific in the early stages, however patients deteriorate rapidly with time.[170] Communities should be encouraged to recognise the early signs of IMD and insist on their loved-ones being observed/investigated should they feel symptoms are developing more rapidly than a usual mild viral infection. Early initiation of intravenous antibiotics saves lives and should be given even whilst awaiting transfer to a larger institution for definitive care or investigations.

Future work on the surveillance and carriage isolates include whole genome sequencing of all *N. meningitidis.* This will allow us to identify novel sequence types and monitor gene transfer that may confer reduced antibiotic susceptibility, increased virulence as well as determine relatedness between the various isolates.[47,69] We will also use the sequencing data to determine diversity of the serogroup B strains and evaluate the potential coverage of the serogroup B protein vaccines on IMD in South Africa.

Conclusion

Invasive meningococcal disease is a rare yet life-threatening illness. In South Africa disease incidence has declined over the years and in 2016 was 0.2 cases per 100 000 population. However, amongst those unlucky enough to be infected, 17% will die in hospital, many of them within one day of admission, and of those fortunate to survive 20% will suffer major sequelae – including deafness, loss of vision, ongoing seizures or limb weakness. Although infants have the largest disease burden, HIV-infected individuals are at increased risk of disease and acquisition of carriage (a pre-requisite for disease).

Invasive meningococcal disease epidemiology in South Africa differs from the notorious African meningitis belt countries. In South Africa IMD is endemic with mostly sporadic cases occurring all year round and peaking in the winter months. Multiple serogroups tend to circulate concurrently often clustering temporal-spatially in different geographic districts.

Through exploring IMD and carriage epidemiology in South Africa, this research has conducted the first meningococcal carriage study amongst university students in South Africa, it has highlighted the importance of having ongoing robust surveillance systems in place with multiple years of available data at hand to analyse disease trends over time and interpret changes in disease and serogroup distribution both locally and globally. Results from the study have highlighted particular high-risk groups for both carriage and disease and contributed to formulating recommendations and guidelines for meningococcal vaccination in South Africa. It has also pointed out alternate prevention measures that may impact on IMD incidence such as policies against cigarette smoking and government regulations to contain SARS-CoV-2. We also quantify the excess disease caused by preceding influenza seasons which were experienced prior to most winter peaks in IMD.

Prevention of disease is always better than cure, particularly regarding IMD where outcomes are typically poor. The World Health Association endorsed programme, Defeating meningitis by 2030, has meningococcal meningitis as well as meningococcal bacteraemia prioritised. All countries are urged to decrease cases of vaccine-preventable bacterial meningitis by 50% and deaths by 70% over the next few years.[106] Although vaccination of infants with a catch up programme extending to adolescents would be ideal, realistically, South Africa has too many competing health interests to justify introducing population level meningococcal vaccination policies targeting IMD prevention at this current time. Therefore, I propose five public health measures (apart from population group vaccination) that may work together towards Defeating meningitis (and meningococcal bacteraemia) by 2030:

1. Ensure the continuation of national laboratory-based surveillance for IMD with a particular emphasis on further characterisation of the isolates by means of serogrouping, genotyping and antimicrobial resistance testing.

2. Advocate for meningococcal vaccination of high-risk groups – particularly PLHIV
3. Advocate for early recognition and treatment of IMD through public health awareness campaigns and education of health-care workers.
4. Promote the use of influenza vaccination – particularly amongst the priority group of PLHIV
5. Encourage HIV testing for all persons seeking health-care, followed by early initiation and then maintenance of antiretroviral therapy for PLHIV.

Invasive meningococcal disease may be rare in South Africa, however, it has a tremendous impact for those unfortunate enough to experience it personally or through the loss of a family member. Population immunity is low and as the world "opens up" post the early phase of the COVID-19 pandemic, all it takes is importation of a hypervirulent strain into one of the many overcrowded neighbourhoods to spark an outbreak and subsequently an emergence of a new wave of IMD. Public health authorities should be vigilant and not afraid to act timeously with vaccine roll-out should the need arise.

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Appendices

Appendix A: Role of the student

Roles performed by the student in the four manuscripts contributing towards the PhD

Susan Meiring, student number 0717769G, performed the following roles in the research and writing of the manuscripts forming part of her thesis entitled: "*Neisseria meningitidis* epidemiology in South Africa during a period of low endemicity"

Manuscript 1:

Meiring S, Cohen C, de Gouveia L, du Plessis M, Ganesh K, Kleynhans J**,** Quan V, Tempia S, von Gottberg A. **Human Immunodeficiency Virus Infection Is Associated With Increased Meningococcal Carriage Acquisition Among First-year Students in 2 South African Universities**. *Clin Infect Dis*. 2021 Jul 1;73(1):e28-e38. doi: 10.1093/cid/ciaa521.

Student role: **Project title: Meningococcal carriage among University Students in South Africa**

Conception and design of the study, grant proposal and award of grant, oversight of study budget and finances, development of protocol, ethics application and permissions, design of case report forms and data collection tools, overall co-ordination of the study including training of study staff, oversight of field work, enrolment of study participants, initial laboratory work, data entry, data cleaning and collation, analysis and interpretation of data, drafting of the manuscript and revising drafts, corresponding author for published manuscript.

Manuscript 2:

Meiring S, Cohen C, de Gouveia L, du Plessis M, Kularatne R, Hoosen A, Lekalakala R, Lengana S, Seetharam S, Naicker P, Quan V, Reubenson G, Tempia S, von Mollendorf C, von Gottberg A, for GERMS-SA. **Declining Incidence of Invasive Meningococcal Disease in South Africa: 2003–2016**. *Clin Infect Dis* 2019 August; 69(3):495-504.

Student role: Conception and design of the study, data cleaning, analysis and interpretation of the data, drafting of the manuscript and revising the drafts, corresponding author for published manuscript

Manuscript 3:

Meiring S, Cohen C, de Gouveia L, du Plessis M, Quan V, Kleynhans J, Menezes C, Reubenson G, Dawood H, Nchabeleng M, Said M, Mvelase N, Mahabeer P, Chomba R, Lekalakala R, Nana T, Chibabhai V, Black M, von Gottberg A, for GERMS-SA. **Case-fatality and sequelae following bacterial meningitis in South Africa, 2016 through 2020.** *Int J Infect Dis* 2022 August; 122:1056–66.

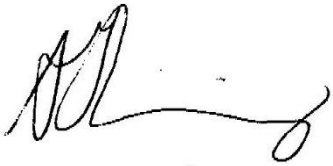
Student role: Conception and design of the study, ethics amendment application for additional data collection, creation of case report form for additional data on sequelae and long-term outcome, matching and collation of GERMS-SA data and additional data, data cleaning, analysis and interpretation of data, drafting of the manuscript and revising the drafts, corresponding author for published manuscript.

Manuscript 4:

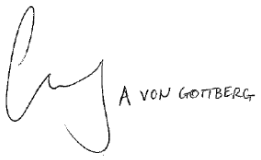
Meiring S, Tempia S, Dominic E M, de Gouveia L, McAnerney J, von Gottberg A, Cohen C **Excess invasive meningococcal disease associated with seasonal influenza, South Africa, 2003-2018** *Clin Infect Dis*, ciab702, https://doi.org/10.1093/cid/ciab702 Published: 14 August 2021

Student role: Design of the study, obtaining the influenza and invasive meningococcal disease data, data cleaning, manipulation of data format, collation of surveillance data sets, analysis and interpretation of data, drafting of manuscript and revising the drafts, corresponding author for published manuscript.

All co-authors have been informed that the manuscripts are to be used in the PhD thesis and agreed on their use within the thesis.

Student: Susan Meiring  Date: 7 September 2022

Supervisor: Cheryl Cohen  Date: 7 September 2022

Supervisor: Anne von Gottberg 

Date: 7 September 2022

Student role in the GERMS-SA surveillance programme:

Manuscripts 2-4 made use of the National Institute for Communicable Diseases' GERMS-SA surveillance data on pathogens of public health importance. Susan Meiring is employed as the clinical coordinator for this surveillance programme. Her responsibilities include updating the GERMS-SA protocol and case report forms and applying for ethics renewals on an annual basis. In addition, she manages the team of surveillance staff in various provinces and oversees database management, data analysis and feedback of data to relevant stakeholders as required.

National or international conference presentations (oral/poster) following competitive selection of abstracts:

National presentations:

University of the Witwatersrand School of Public Health Research Day 2017

> Meningococcal carriage amongst first-year students entering university: Is there a need in South Africa for meningococcal prevention strategies? (oral)

University of the Witwatersrand School of Public Health Research Day 2020

> Mortality and sequelae following invasive meningococcal disease in South Africa (oral)

PathRED conference 2019

> HIV-infection is associated with increased meningococcal carriage acquisition amongst first-year university students in South Africa (oral)

International presentations:

International Pathogenic Neisseria Conference 2018, USA

> Temporal-spatial analysis of invasive meningococcal disease in South Africa: 2005-2015 (oral presentation)

> Meningococcal carriage amongst first-year university students during a period of low invasive meningococcal disease incidence (poster)

Carriage prevalence and genotypes of *Neisseria meningitidis* amongst university students in South Africa, 2017 (poster)

Declining incidence of invasive meningococcal disease despite minimal vaccine use in South Africa from 2003 through 2016 (poster)

International Pathogenic Neisseria Conference 2020, South Africa (postponed to October 2022)

Mortality and sequelae following meningococcal meningitis in South Africa, 2016 through 2020

Other meningococcal-related peer-review publications that the student has authored or co-authored during the period of study:

1. Alderson MR, Arkwright PD, Bai X, Black S, Borrow R, Caugant DA, Dinleyici EC, Harrison LH, Lucidarme J, McNamara LA, **Meiring S**, Safadi MAP, Shao Z, Stephens DS, Taha MK, Vazquez J, Zhu B, and Collaborators of the GMI. **Surveillance and control of meningococcal disease in the COVID-19 era: A Global Meningococcal Initiative review.** J. Infect. 2021. DOI:10.1016/j.jinf.2021.11.016.
2. Brueggemann AB, Jansen van Rensburg MJ, Shaw D, et al. **Changes in the incidence of invasive disease due to *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Neisseria meningitidis* during the COVID-19 pandemic in 26 countries and territories in the Invasive Respiratory Infection Surveillance Initiative**. Lancet Digit Heal 2021; 3: e360–70.
3. Acevedo R, Bai X, Borrow R, Caugant DA, Carlos J, Ceyhan M, Christensen H, Climent Y, De Wals P, Dinleyici EC, Echaniz-Aviles G, Hakawi A, Kamiya H, Karachaliou A, Lucidarme J, **Meiring S**, Mironov K, Sáfadi MAP, Shao Z, Smith V, Steffen R, Stenmark B, Taha MK, Trotter C, Vázquez JA, Zhu B. **The Global Meningococcal Initiative meeting on prevention of meningococcal disease worldwide: Epidemiology, surveillance, hypervirulent strains, antibiotic resistance and high-risk populations.** Expert Rev Vaccines. 2019 Jan;18(1):15-30. doi: 10.1080/14760584.2019.1557520. Epub 2018 Dec 27.
4. Dlamini SK, Madhi SA, Muloiwa R, von Gottberg A, Moosa M, **Meiring S**, Wiysonge C, Hefer E, Mulaudzi, Nuttall J, Moorhouse M, Kajinga B. **Guidelines for the vaccination of HIV-infected adolescents and adults in South Africa.** S Afr J HIV Med. 2018;19(1), a839. https://doi.org/10.4102/sajhivmed.v19i1.839
5. **Meiring S**, Hussey G, Jeena P, Parker S, von Gottberg A. **Recommendations for the use of meningococcal vaccines in South Africa**. Southern African Journal of Infectious Diseases, 2017. 32:3, 82-86, DOI:10.1080/23120053.2017.1359939

6. Ganesh K, Allam M, Wolter N, Bratcher HB, Harrison OB, Lucidame J, Borrow R, de Gouveia L, **Meiring S**, Birkhead M, Maiden MCJ, von Gottberg A, du Plessis M. **Molecular characterization of invasive capsule null *Neisseria meningitidis* in South Africa.** BMC Microbiology (2017) 17:40. DOI 10.1186/s12866-017-0942-5

Appendix B: Ethical clearance certificates

R14/49 Dr S Meiring

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M170951

NAME: Dr S Meiring
(Principal Investigator)
DEPARTMENT: School of Public Health
Medical School

PROJECT TITLE: Neisseria meningitis epidemiology in South Africa during a period of low endemicity

DATE CONSIDERED: 29/09/2017

DECISION: Approved unconditionally

CONDITIONS:

SUPERVISOR: Professors A von Gottberg & C Cohen

APPROVED BY: _____
Professor PE Cleaton-Jones, Chairperson, HREC (Medical)

DATE OF APPROVAL: 14/10/2017

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on 3rd floor, Phillip V Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.
I/We fully understand the conditions under which I am/we are authorised 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 resubmit to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. in this case, the study was initially reviewed in **September** and will therefore be due in the month of **September** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

_____ 19/10/2017
Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

R14/49 Dr Susan Meiring et al

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M160672

NAME: (Principal Investigator)	Dr Susan Meiring et al
DEPARTMENT:	National Institute for Communicable Diseases University of the Witwatersrand University of Cape Town
PROJECT TITLE:	Meningococcal Carriage among University Students in South Africa
DATE CONSIDERED:	24/06/2016
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof Cheryl Cohen and Prof Anne von Gottberg
APPROVED BY:	Professor P Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	02/09/2016

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 10004, 10th floor, Senate House/3rd Floor, Phillip Tobias Building, Parktown, University of the Witwatersrand. 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 resubmit the application to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in June and will therefore be due in the month of June each year.

Principal Investigator Signature

Date 5 September 2016

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

R14/49 Dr Vanessa Quan

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M140159

NAME: (Principal Investigator) Dr Vanessa Quan

DEPARTMENT: NICD

PROJECT TITLE: GERMS-SA: Laboratory-based Surveillance for Pathogens of Public Health Importance in South Africa (previously M081117) (Protocol version 1.0)

DATE CONSIDERED: 31/01/2014

DECISION: Renewal Approved unconditionally

CONDITIONS: (Recertified 25/01/2013) (Renewal 31/01/2014)

SUPERVISOR:

APPROVED BY: Professor PE Cleaton-Jones, Chairperson, HREC (Medical)

DATE OF APPROVAL:

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Secretary in Room 10004, 10th floor, Senate House, University.

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 resubmit the application to the Committee. **I agree to submit a yearly progress report**.

Principal Investigator Signature Date 24/3/2014

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix C: Manuscripts contributing to the PhD

Manuscript I:

Meiring S, Cohen C, de Gouveia L, du Plessis M, Ganesh K, Kleynhans J, Quan V, Tempia S, von Gottberg A. Human Immunodeficiency Virus Infection Is Associated With Increased Meningococcal Carriage Acquisition Among First-year Students in 2 South African Universities. Clin Infect Dis. 2021 Jul 1;73(1):e28-e38

Clinical Infectious Diseases

MAJOR ARTICLE

Human Immunodeficiency Virus Infection Is Associated With Increased Meningococcal Carriage Acquisition Among First-year Students in 2 South African Universities

Susan Meiring,[1,2] Cheryl Cohen,[2,3] Linda de Gouveia,[3] Mignon du Plessis,[3,4] Karistha Ganesh,[3] Jackie Kleynhans,[3] Vanessa Quan,[1] Stefano Tempia,[2] and Anne von Gottberg[3,4]

[1]Division of Public Health Surveillance and Response, National Institute for Communicable Diseases, Division of the National Health Laboratory Service, Johannesburg, South Africa, [2]School of Public Health, University of the Witwatersrand, Johannesburg, South Africa, [3]Centre for Respiratory Diseases and Meningitis, National Institute for Communicable Diseases, Division of the National Health Laboratory Service, Johannesburg, South Africa, and [4]School of Pathology, University of the Witwatersrand, Johannesburg, South Africa

Background. Invasive meningococcal disease clusters occur among university students and may reflect higher carriage prevalence among this population. We aimed to measure meningococcal carriage prevalence, acquisition, and risk factors among first-year university students in South Africa.

Methods. In summer–autumn 2017, after consenting to participate, we collected oropharyngeal swabs and questionnaires on carriage risk factors and tested students for HIV at 2 universities, during registration week (survey 1) and 6–8 weeks later (survey 2). Meningococci were detected by culture and polymerase chain reaction.

Results. We enrolled 2120 students at registration. Mean age was 18.5 years, 59% (1252/2120) were female and 0.8% (16/1984) had HIV. Seventy-eight percent of students returned for survey 2 (1655/2120). Among the cohort, carriage prevalence was 4.7% (77/1655) at registration, increasing to 7.9% (130/1655) at survey 2: 5.0% (83) acquired new carriage, 2.8% (47) had persistent carriage, 1.8% (30) cleared the initial carriage, and 90.3% (1495) remained carriage free. At both surveys, nongenogroupable meningococci predominated, followed by genogroups Y, B, W, and C. On multinomial analysis, risk factors for carriage acquisition included attending nightclubs (adjusted relative risk ratio [aRRR], 2.1; 95% CI, 1.1–4.0), having intimate kissing partners (aRRR, 1.8; 95% CI, 1.1–2.9) and HIV (aRRR, 5.0; 95% CI, 1.1–24.4).

Conclusions. Meningococcal carriage among first-year university students increased after 2 months. Sociobehavioral risk factors were associated with increased carriage for all analyses. HIV was associated with carriage acquisition. Until vaccination programs become mandatory in South African universities, data suggest that students with HIV could benefit most from meningococcal vaccination.

Keywords. meningococcus; *Neisseria meningitidis*; carriage; Southern Africa; risk factors.

Neisseria meningitidis (meningococcus) is spread from human to human, the main ecological niche being the mucosa of the human oropharynx [1]. *Neisseria meningitidis* carriage is a prerequisite for ongoing transmission and invasion of the organism leading to meningococcal bacteremia or meningitis [2]. Understanding meningococcal carriage dynamics in a population is important for understanding disease epidemiology and transmission, and determining vaccination strategies for disease prevention.

The polysaccharide capsule surrounding the meningococcus is its most important virulence factor. Almost all isolates causing invasive meningococcal disease (IMD) are encapsulated, with serogroups A, B, C, W, and Y being the most frequent causes of IMD globally [3]. However, the majority of carriage isolates are nongroupable/unencapsulated and these isolates rarely cause disease, as either there is phase variation in the expression of the capsule, capsular synthesis genes have been inactivated, or there is an absence of genes required for capsule production (capsule null phenotype) [4, 5]. Carriage isolates that are sero-/genogroupable may be responsible for the spread of meningococcal disease in the community.

Invasive meningococcal disease is seasonal, peaking in May to October each year in South Africa, but it also fluctuates over periods of 10 to 15 years [2, 6]. Following the emergence of serogroup W in South Africa in 2005, IMD incidence has declined in recent years (0.2 cases per 100 000 population in 2016) [6, 7]. Human immunodeficiency virus (HIV) infection has been associated with increased risk of IMD, particularly serogroup W, which causes more severe disease and IMD in men who have

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sex with men [8–10]. Thirty-seven percent of patients with IMD in South Africa are living with HIV (in a background population HIV prevalence of 13%) [6, 11]. Recommendations for meningococcal vaccination of high-risk groups (including persons with HIV and those entering universities) have been published; however, meningococcal vaccine uptake is minimal in South Africa [12, 13]. While data on IMD incidence and risk factors are available, there are currently no published data on meningococcal carriage prevalence in any population in southern Africa or by HIV status.

Meningococcal carriage prevalence increases with age, peaking at 23% in 19- to 24-year-olds in industrialized countries [14]. However, in the African meningitis belt, an area of 26 countries in sub-Saharan Africa extending from Senegal to Ethiopia, carriage peaks at a younger age (10–14 years) and occurs at a lower rate (5%) [15, 16]. Despite this low carriage rate and huge successes with MenAfriVac controlling serogoup A IMD, periodic large-scale meningococcal epidemics still occur in this region [17, 18].

Even though carriage peaks in adolescence, carriage prevalence is often higher in young adults living in semiconfined populations such as university campuses or in army barracks [19, 20]. This may be due to mixing of diverse meningococcal strains brought in by carriers from different areas, resulting in a rapid meningococcal carriage acquisition among new students or recruits, which usually plateaus after 1 month [21]. Globally, studies on university campuses have shown varied carriage rates among students, ranging from 46% in the United Kingdom and 15% in the United States to 9% in Australia [22–24]. Spreading of new meningococcal strains is enhanced by behavioral risk factors associated with meningococcal carriage, such as smoking (active and passive), attendance at pubs/nightclubs, and intimate kissing [14, 19]. Some studies have suggested carriage of *Streptococcus pneumoniae* to be higher in adults with HIV; however, it is not known whether HIV coinfection is also a risk factor for meningococcal carriage and/or acquisition [25–27].

We aimed to describe the meningococcal carriage prevalence and risk factors for carriage among first-year university students in South Africa at 2 time points and to determine whether HIV coinfection was associated with meningococcal carriage acquisition, persistence, and clearance among students 2 months after starting university.

METHODS

We performed a cross-sectional study to determine the prevalence of meningococcal carriage among university students at 2 time points (survey 1 and survey 2), with a nested cohort study to determine the acquisition, persistence, and clearance of meningococcal carriage. The study population included first-year university students registering at the start of the 2017 academic year at 2 large universities: University of the Witwatersrand (Wits) in Gauteng Province or University of Cape Town (UCT) in Western Cape Province. The student populations are diverse and draw from all 9 provinces of South Africa. Combined, approximately 14 000 first-year students register each year at the 2 universities. The cohort of students included those participating in both cross-sectional studies: at registration (survey 1) and 6–8 weeks later (survey 2).

Sample size was calculated using OpenEpi (https://www.openepi.com/SampleSize/SSCC.htm), assuming differences in the acquisition of meningococcal carriage in a cohort of students with and without HIV coinfection. Calculations were for repeat measurements assuming an HIV prevalence of 7% and initial meningococcal carriage prevalence of 4%. Our target was to enroll 3000 students (see Supplementary Methods).

The South African university year begins in late summer. Survey 1 of the study occurred during registration week at Wits from 30 January until 3 February 2017, and at UCT from 27 February until 8 March 2017. Survey 2 occurred 6–8 weeks later for each site in the autumn: 14–17 March 2017 at Wits and 18–21 April 2017 at UCT.

Study recruitment and sample collection took place on campus at both sites. There was no random selection of the students. All students were informed of the study via e-mail and the study was introduced at student welcome lectures. Study teams were centrally situated on campus with signage inviting students to participate. Interested participants were requested to sign an informed-consent form prior to enrollment. Participants were allocated a unique study number to link the questionnaire, HIV test result, and oropharyngeal swab. Questionnaires on basic demographics and risk factors for meningococcal carriage were self-administered on tablet computers using Google forms. Risk factors evaluated included the following: sex, university, home province, active and passive smoking in the previous month, club/pub/party attendance in the preceding 2 weeks, intimate kissing partners in the preceding 2 weeks, pre-existing chronic conditions, HIV serostatus, upper respiratory tract infection in the previous month, antibiotic use in the previous month, and prior meningococcal vaccine use. Human immunodeficiency virus testing was performed at survey 1 by trained nursing staff. Rapid HIV-antibody detection tests (Alere Determine HIV-1/2; Abbott) were used on finger-prick blood samples. Persons testing positive for HIV had a second confirmatory rapid HIV test performed (UniGold Recombingen HIV-1/2; Trinity Biotech). Oropharyngeal swabs were taken using flocked swabs (Copan Diagnostics), ensuring the oropharynx, both tonsillar beds, and posterior pharyngeal wall were touched using a figure-of-8 motion and avoiding the tongue or teeth.

The oropharyngeal swabs were placed directly into Todd-Hewitt broth (Media Mage Products), a selective enrichment medium, and incubated within 6–8 hours at 37°C for 24 hours [28]. In the laboratory, a 500-µL aliquot of broth was stored at −70°C for polymerase chain reaction (PCR) later. After

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overnight incubation, 100 µL of broth was plated onto Thayer-Martin, New York City, and 5% blood agar (Diagnostic Media Products) and incubated for 48 hours in 5% CO_2. Matrix-assisted laser desorption/ionization–time-of-flight mass spectrometry was used to identify all isolates. Meningococcal isolates were serogrouped by slide agglutination using monovalent antibodies to capsular polysaccharide A, C, W, X, Y, and Z and monoclonal antibodies to polysaccharide B. All stored broths underwent real-time PCR to detect the *sodC* gene [29]. The *ctrA* and genogrouping real-time PCR (ABCEHWXYZ) was performed on all meningococcal isolates and *sodC*-positive swabs [30, 31]. *ctrA*-Negative and genogroup PCR-negative meningococci were considered nongenogroupable. Participants were classified as meningococcal carriers if *N. meningitidis* was cultured or the *sodC* gene was detected on PCR. No interventions to eliminate carriage were given to meningococcal colonized subjects in this nonoutbreak setting.

Data from surveys 1 and 2 (questionnaire, oropharyngeal swab, and HIV test) were linked using the unique study number. All statistical analyses were done using Stata version 14.0 (StataCorp). *P* values less than .05 were considered statistically significant. Variables with *P* values less than .2 in univariate analysis were evaluated in the multivariable models using manual backward elimination.

Carriage prevalence and risk factors for carriage of meningococci were determined from the cross-sectional study of first-year university students from survey 1. Carriage prevalence was determined by day of study enrolment, and percentage changes ([rate ratio − 1] × 100) in carriage were calculated to demonstrate the increase in carriage during registration at the universities and over time from survey 1 to survey 2. Prevalence of carriage by genogroup distribution was reported.

Univariate and multivariable logistic regression models were used to determine significant risk factors associated with meningococcal carriage at each of the 2 time points. Acquisition, persistence, and clearance of meningococcal carriage 6–8 weeks following registration were determined from the cohort at the second survey (see Supplementary Methods for definitions). Multinomial regression was performed to compare those who never carried meningococci (baseline category) with the carrier acquisition and carrier persistence groups (see Supplementary Methods).

The study was approved by the Wits Health Research Ethics Committee (Medical) (M160672) as well as that of the UCT (Ref395_2016). All participants gave written consent to be enrolled in the study.

RESULTS

Survey 1

In the summer of 2017, we enrolled 2137 first-year students into a cross-sectional meningococcal carriage study (survey 1). Seventeen students were excluded from the study; 6 did not consent to an oropharyngeal swab and 11 did not complete the questionnaire (Figure 1). The mean age of the students was 18.5 years (SD, 1.5 years) and the majority were female (59.1%, 1252/2120). Most students were from Gauteng (43%, 914/2120)

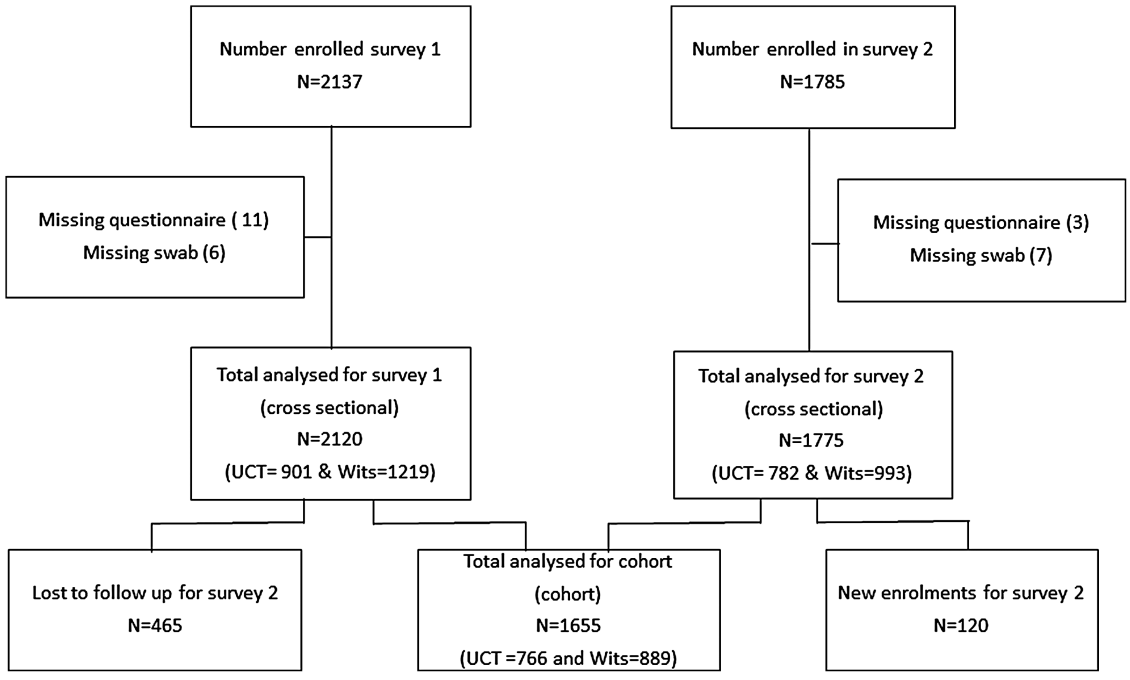

Figure 1. Flow diagram of enrollment of university students for the 2 surveys on meningococcal carriage among first-year university students: South Africa, 2017. Abbreviations: UCT, University of Cape Town; Wits, University of the Witwatersrand.

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and Western Cape Provinces (19%, 410/2120). Twenty-eight percent (600/2120) of students lived in a university residence, and 27% (581/2120) were current cigarette smokers. Of those tested for HIV at enrollment, 0.8% (16/1984) had HIV infection.

Overall meningococcal carriage was 4.6% (98/2120) and carriage prevalence increased significantly over the 5 days of enrolment (3.2-fold increase from day 1 [1.8%] to day 5 [5.9%]) (Figure 2). Meningococci were isolated from 65 of 2120 (3.1%) swabs, with the remaining meningococci (33/2120, 1.6%) identified by PCR only. No human DNA was detected on 0.6% (13/2120) of swabs. The overall meningococcal carriage prevalence by genogroup was 1.8% (38) nongroupable, 1.1% (24) MenY, 0.8% (16) MenB, 0.2% (4) MenW, and 0.1% (2) MenC of the 2120 swabs (Table 1).

On multivariable analysis, compared with Gauteng Province, students were twice as likely to carry meningococcus if their home province was KwaZulu-Natal (adjusted odds ratio [aOR], 2.1; 95% confidence interval [CI], 1.1–4.2) and 3 times as likely for the Western Cape (aOR, 2.7; 95% CI, 1.6–4.5). Carriage was more likely if they lived in a university residence (aOR, 2.0; 95% CI, 1.2–3.4) or an apartment with other students (aOR, 2.1; 95% CI, 1.2–3.9) compared with living with their family, or if they attended a nightclub (aOR, 1.8; 95% CI, 1.1–3.0) or had at least 1 intimate kissing partner (aOR, 2.8; 95% CI, 1.8–4.5) in the previous 2 weeks (Table 2).

Survey 2

In the autumn of 2017, 6–8 weeks following survey 1, we repeated the survey at the same 2 universities. Across the 2 sites, 1785 students were enrolled, but 10 were excluded due to not completing the questionnaire (n = 3) or missing the oropharyngeal swab (n = 7) (Figure 1). Overall meningococcal carriage at survey 2 was 7.5%, a 1.6-fold increase (95% CI, 1.3–2.1) from survey 1. Three percent of swabs were culture positive (3.4%, 60/1775) and an additional 4.2% (74/1775) were detected using PCR only. No human DNA was detected on 1.5% (28/1775) of swabs. The overall meningococcal carriage prevalence by genogroup was 3.5% (63) nongroupable, 1.5% (27) MenY, 0.9% (16) MenB, 0.1% (2) MenW, 0.1% (2) MenC, 0.1% (1) MenX, and 0.1% (1) MenZ of the 1775 swabs (Table 1).

Cohort Analysis

Of the 1775 students who participated in survey 2, 93% (1655/1775) had participated in survey 1. Carriage at survey 1 for this cohort was 4.7% (77/1655) and increased 1.7-fold (95% CI, 1.3–2.3) to 7.9% (130/1655) for survey 2. Factors associated with meningococcal carriage at surveys 1 and 2 were similar for the cohort and cross-sectional study (Table 2 and Supplementary Tables 1–4).

In the cohort, 90.3% (1495/1655) of students never carried meningococcus in their oropharynx, 5.0% (83) acquired meningococcus after 6–8 weeks of university life, 2.8% (47) had persistence of meningococcal carriage during the study period, and 1.8% (30) cleared their initial meningococcal carriage by the second survey. On further analysis, only 1 student in the persistent carrier group had different genogroups at the second survey (initially genogroup B then genogroup Y).

On multivariable analysis, among the 5% who acquired meningococcal carriage, risk factors for genogroupable meningococcal carriage included pub attendance (aOR, 7.9; 95% CI, 1.8–35.3), having intimate kissing partners (aOR, 15.4; 95%

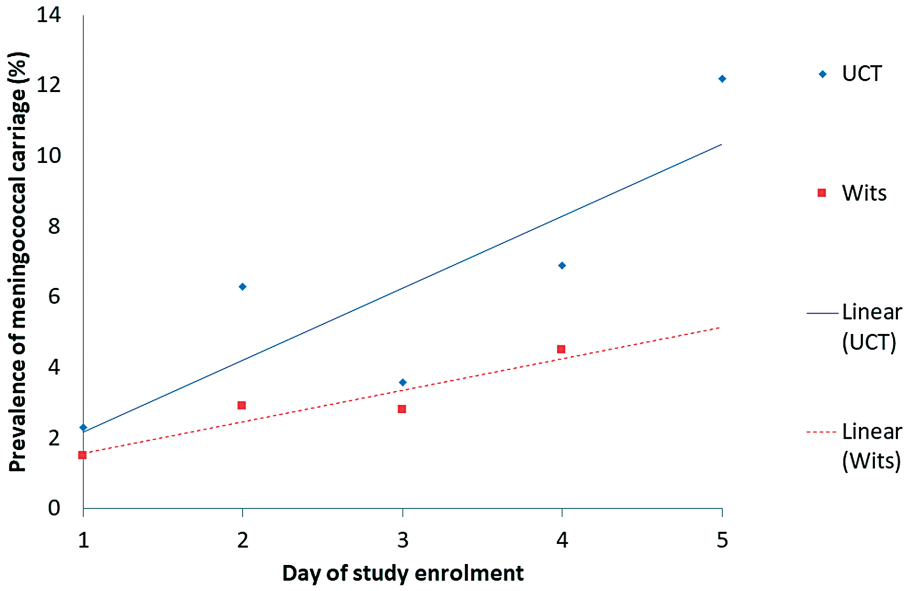

Figure 2. Trend lines depicting increasing meningococcal carriage prevalence by day of study enrollment of first-year university students during registration week: South Africa, 2017. Abbreviations: UCT, University of Cape Town; Wits, University of the Witwatersrand.

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Table 1. Carriage Prevalence by University Site, Day of Enrollment, Laboratory Testing, and Genogroup for Surveys 1 and 2: South Africa, 2017

	Survey 1		Survey 2			
	Total Enrolled	NM Carriers, n (%)	Total Enrolled, n	NM Carriers, n (%)	Percentage Change From Day 1% (95% CI)	Percentage Change From Survey 1 to 2% (95% CI)
Day of study enrollment	2120					
Day 1	217	4 (1.8)	…	…	…	…
Day 2	677	32 (4.7)	…	…	156 (−9.1 to 898)	…
Day 3	341	10 (2.9)	…	…	59 (−54 to 595)	…
Day 4	477	27 (5.7)	…	…	207 (7 to 1108)	…
Day 5	408	24 (5.9)	…	…	219 (10 to 1165)	…
Total participants	2120	98 (4.6)	1775	134 (7.5)	…	63 (25 to 114)
University of Witwatersrand	1219	34 (2.8)	993	67 (6.7)	…	142 (−58 to 277)
University of Cape Town	901	64 (7.1)	782	67 (8.6)	…	21 (−16 to 73)
Laboratory test results						
Culture positive[a]	2120	65 (3.1)	1775	60 (3.4)	…	10 (−24 to 59)
PCR positive only	2120	33 (1.6)	1775	74 (4.2)	…	168 (75 to 317)
Genogroup						
A	2120	0 (0)	1775	0 (0)	…	…
B	2120	16 (0.8)	1775	16 (0.9)	…	19 (−44 to 155)
C	2120	2 (0.1)	1775	2 (0.11)	…	19 (−91 to 1548)
W	2120	4 (0.2)	1775	2 (0.11)	…	40 (−95 to 317)
X	2120	1 (0.0)	1775	1 (0.06)	…	19 (−99 to 9276)
Y	2120	24 (1.1)	1775	27 (1.52)	…	34 (−25 to 143)
Z	2120	0 (0)	1775	1 (0.06)	…	…
Nongroupable	2120	38 (1.8)	1775	63 (3.5)	…	98 (30 to 205)
Other[b]	2120	3 (0.1)	1775	2 (0.1)	…	−20 (−93 to 595)

Abbreviations: NM, *Neisseria meningitidis*; PCR, polymerase chain reaction.

[a]All culture-positive swabs were also *sodC* PCR positive.

[b]Includes 2 E and 1 non-ABCEHWXYZ from survey 1, and 1 E and 1 non-ABCEHWXYZ from survey 2. No genogroup A was detected at either time point. Ten meningococcal positive swabs in survey 1 and 20 from survey 2 were *sodC* positive yet had inconclusive genogrouping.

CI, 3.1–75.8), and having had a recent upper respiratory tract infection (aOR, 5.3; 95% CI, 1.4–19.6) (Table 3).

On multinomial analysis, compared with those who never carried meningococci, risk factors for acquiring meningococcal carriage included attending nightclubs (adjusted relative risk ratio [aRRR], 2.1; 95% CI, 1.1–4.0), having intimate kissing partners (aRRR, 1.8; 95% CI, 1.1–2.9), and having HIV (aRRR, 5.0; 95% CI, 1.1–24.4). Persistence of meningococcal carriage across the study period was associated with being male (aRRR, 2.5; 95% CI, 1.3–4.6), studying at the UCT (aRRR, 2.1; 95% CI, 1.1–4.0), and attending pubs (aRRR, 3.0; 95% CI, 1.4–6.3) (Table 4).

DISCUSSION

Meningococcal carriage among first-year university students in South Africa was 5% upon registration, increasing by 63% to 8% after 2 months on campus. At both time points, nongroupable strains predominated, followed by Y and B genogroups. Human immunodeficiency virus infection was a risk factor for meningococcal carriage acquisition; it was not associated with baseline meningococcal carriage. Significant risk factors for meningococcal carriage included home province, male gender, intimate kissing, and nightclub attendance.

Although meningococcal carriage among South African university students was lower than in studies in the United Kingdom [24, 32], it is comparable to more recent carriage studies among adolescents in Australia (6%) and Italy (5%) [22, 33]. The warmer summers and milder winters in these countries and South Africa may affect meningococcal transmission, explaining the lower prevalence as, globally, behavioral risk factors remain fairly similar [14, 19].

In our study, the risk factors associated with meningococcal carriage included being male, attending nightclubs, and having at least 1 intimate kissing partner in the previous 2 weeks. Smoking was not an independent risk factor for carriage, although the prevalence of smoking (27%) and smoke exposure (65%) was high among the students, compared with a national prevalence of 18% and 47%, respectively, among South African adults in 2012 [34]. Smoking showed collinearity with nightclub and pub attendance, which were strongly associated with carriage.

Although HIV prevalence was lower than expected, underlying HIV infection was associated with meningococcal carriage acquisition. Human immunodeficiency virus has previously been associated with increased risk of meningococcal disease and more severe disease, and some countries have included

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Table 2. Multivariable Analysis of Risk Factors for Meningococcal Carriage Among First-year University Students at Registration (Survey 1): South Africa, 2017

			Univariate Analysis		Multivariable Analysis	
Characteristics	All, N	Meningococcal Carriers, n (%)	OR (95% CI)	*P*	OR (95% CI)	*P*
Number of students	2120	98 (4.6)	…		…	
University						
Witwatersrand	1219	34 (2.8)	Ref		…	
Cape Town	901	64 (7.1)	2.7 (1.7–4.1)		…	
Home province						
Eastern Cape	117	7 (6.0)	1.9 (.8–4.5)	.125	1.9 (.8–4.5)	.178
Free State	51	3 (5.9)	1.9 (.6–6.5)	.301	1.8 (.5–6.5)	.344
Gauteng	914	29 (3.2)	Ref		Ref	
KwaZulu-Natal	179	15 (8.4)	2.8 (1.5–5.3)	.002	2.1 (1.1–4.2)	.032
Limpopo	183	1 (0.6)	0.2 (.1–1.2)	.080	0.2 (.1–1.3)	.094
Mpumalanga	90	3 (3.3)	1.1 (.3–3.5)	.934	1.1 (.3–3.6)	.951
Northern Cape	26	1 (3.9)	1.2 (.2–9.3)	.848	1.1 (.1–7.9)	.991
North West	54	0 (0)	…		…	
Western Cape	410	37 (9.0)	3.0 (1.8–5.0)	<.001	2.7 (1.6–4.5)	<.001
Outside South Africa	96	2 (2.1)	0.7 (.2–2.8)	.559	0.7 (.2–3.0)	.606
Median age, years	18.5	18.53	…	.451	…	
Sex						
Male	868	50 (5.8)	1.5 (1.1–2.3)	.039	1.5 (.9–2.3)	.067
Female	1252	48 (3.8)	Ref		Ref	
Living arrangements						
House/apartment, with family	1116	40 (3.6)	Ref		Ref	
House/apartment, with other students	404	23 (5.7)	1.6 (.9–2.8)	.071	2.1 (1.2–3.9)	.012
University residence/hostel/dormitory	600	35 (5.8)	1.7 (1.1–2.7)	.031	2.0 (1.2–3.4)	.007
Shares a room						
No	1268	65 (5.1)	Ref		…	
Yes	852	33 (3.9)	0.8 (.5–1.1)	.179	…	
Current cigarette smoker[a]						
No	1539	52 (3.4)	Ref		Ref	
Yes	581	46 (7.9)	2.5 (1.6–3.7)	<.001	1.2 (.7–1.9)	.533
Smoke exposure[a]						
No	741	20 (2.7)	Ref		Ref	
Yes	1379	78 (5.7)	2.2 (1.3–3.6)	.002	1.3 (.7–2.2)	.385
Nightclub attendance[b]						
No	1714	56 (3.3)	Ref		Ref	
Yes	406	42 (10.3)	3.4 (2.3–5.2)	<.001	1.8 (1.1–3.0)	.018
Pub/bar attendance[b]						
No	1646	58 (3.5)	Ref		…	
Yes	474	40 (8.4)	2.5 (1.7–3.8)	<.001	…	
Party attendance[b]						
No	1502	55 (3.7)	Ref		Ref	
Yes	618	43 (7.0)	2.0 (1.3–3.0)	.001	0.8 (.5–1.3)	.375
Intimate kissing[b]						
No	1260	29 (2.3)	Ref		Ref	
Yes	860	69 (8.0)	3.7 (2.4–5.8)	<.001	2.8 (1.8–4.5)	<.001
Recent upper respiratory tract infection[a]						
No	1215	61 (5.0)	Ref		…	
Yes	779	32 (4.1)	0.8 (.5–1.3)	.346	…	
Antibiotic use[a]						
No	1651	86 (5.2)	Ref		…	
Yes	359	10 (2.8)	0.5 (.3–1.1)	.055	…	
HIV						
Uninfected	1968	90 (4.6)	…		…	

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Table 2. Continued

Characteristics	All, N	Meningococcal Carriers, n (%)	Univariate Analysis OR (95% CI)	*P*	Multivariable Analysis OR (95% CI)	*P*
Infected	16	0 (0)	…	.747	…	
Received a meningococcal vaccine						
No	1492	57 (3.8)	Ref		…	
Yes	83	6 (7.2)	2.0 (.8–4.7)	.130	…	
Chronic lung disease						
No	2012	93 (4.6)	…		…	
Yes	108	5 (4.6)	1.0 (.4–2.5)	.997	…	
Diabetes						
No	1744	80 (4.6)	…		…	
Yes	9	0 (0)	…	.954	…	

N = 2120.

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio; Ref, reference.

[a]In the previous month.

[b]In the previous 2 weeks.

HIV in the criteria for meningococcal vaccination requirement [35, 36]. However, an association between HIV infection and increased risk of carriage acquisition has not been previously reported. This new finding, if validated in other studies and settings, may be important in emphasizing the need for IMD prevention through vaccination in population groups with a high HIV prevalence.

There were significant geographic differences in carriage prevalence among participants, especially in the initial survey. These differences reflect the higher incidence of meningococcal disease in the provinces with higher carriage. The provinces with higher disease are all coastal. Some provincial differences may be related to variations in lifestyle and living conditions. For example, residing in the Western Cape Province was associated with higher odds of carrying meningococcus. Other studies have shown this province to have the highest incidence of meningococcal disease, as well as the highest prevalence of smokers (37%) nationally [6, 34].

As with other carriage studies, nongroupable meningococci were the most prevalent among our participants [28, 37, 38]. Genogroup Y was the next most predominant. Serogroup Y is the fourth most predominant cause of invasive disease in South Africa and is associated with HIV coinfection, raising concern for those persons with HIV who are at higher risk of acquiring carriage [6]. Genogroup B was the third most predominant in causing carriage in this survey and the most predominant cause of invasive disease in 2016 [6]. Odds were higher for acquiring genogroupable meningococci if students attended pubs, had intimate kissing partners, or had a recent upper respiratory tract infection. Although no cases of meningococcal disease were reported among the study population during our surveys, acquisition of genogroupable meningococci is thought to drive risk of disease.

Currently, only quadrivalent conjugate meningococcal vaccines targeting serogroups A, C, W, and Y are available in South Africa. Knowing the circulating geno-/serogroups driving carriage and invasive disease in South Africa will assist policymakers to decide which meningococcal vaccine(s) to include in future vaccination campaigns should meningococcal B vaccines be registered for use in South Africa.

Limitations

Peak carriage prevalence among students in our study was 8%, much lower than university settings in the Western world [23, 24]. By only targeting first-year students, we have no reliable data for South Africa on how carriage rates change with age. Considering the lower age seen in the meningitis belt, it is possible that the observed relatively low carriage rate is a reflection of carriage peaking at a younger age in our setting [15]. Overall, 1% (41/3895) of swabs did not contain human DNA, an indicator of poor-quality specimens. These swabs may have missed meningococcus in those students. In light of previous HIV surveys at university campuses, we expected a higher HIV prevalence among our target population [39]. The prevalence of HIV in first-year students on admission to university may be lower than in the university population as a whole [39]. Even with this low HIV prevalence and not meeting our target sample size, we found a significant association between HIV and carriage acquisition.

Our study found less carriage acquisition than other university-based studies, especially among the students studying in the Western Cape Province. The delayed start of the academic year due to student protests disrupting examinations from the previous year meant that mixing of the students may have occurred prior to the official registration week—hence, the higher initial carriage rate at UCT [40]. However, we were able to show

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Table 3. Multivariable Analysis of Risk Factors for Carriage Acquisition of Nongenogroupable Versus Genogroupable Meningococci Among First-year University Students 2 Months After Registration (Survey 2 Cohort): South Africa, 2017

			Univariate Analysis		Multivariable Analysis	
Characteristics	Nongenogroupable Meningococci, n (%)	Genogroupable Meningococci, n (%)	OR (95% CI)	*P*	OR (95% CI)	*P*
Number of students	57 (69)	26 (31)	…		…	
University						
Witwatersrand	42 (89)	5 (11)	Reference		…	
Cape Town	15 (42)	21 (58)	11.8 (3.8–36.8)	<.001	…	
Sex						
Male	29 (81)	7 (19)	0.4 (.1–1.0)	.045	…	
Female	28 (60)	19 (40)	Reference		…	
Living arrangements						
House/apartment, with family	24 (75)	8 (25)	Reference		…	
House/apartment, with other students	15 (94)	1 (6)	0.2 (.02–1.8)	.147	…	
University residence/ hostel/dormitory	18 (51)	17 (49)	2.8 (1.0–8.0)	.049	…	
Shares a room						
No	35 (66)	18 (34)	Reference		…	
Yes	22 (73)	8 (27)	0.7 (.3–1.9)	.492	…	
Current cigarette smoker[a]						
No	45 (80)	11 (20)	Reference		…	
Yes	12 (44)	15 (56)	5.1 (1.9–14.0)	.001	…	
Smoke exposure[a]						
No	19 (76)	6 (24)	Reference		…	
Yes	38 (66)	20 (34)	1.7 (.6–4.8)	.347	…	
Nightclub attendance[b]						
No	45 (80)	11 (20)	Reference		…	
Yes	12 (44)	15 (56)	5.1 (1.9–14.0)	.001	…	
Pub/bar attendance[b]						
No	51 (80)	13 (20)	Reference		Reference	
Yes	6 (32)	13 (68)	8.5 (2.7–26.7)	<.001	7.9 (1.8–35.3)	.007
Party attendance[b]						
No	41 (80)	10 (20)	Reference		…	
Yes	16 (50)	16 (50)	4.1 (1.5–10.9)	.005	…	
Intimate kissing[b]						
No	36 (92)	3 (8)	Reference		Reference	
Yes	21 (48)	23 (52)	13.1 (3.5–49.1)	<.001	15.4 (3.1–75.8)	.001
Recent upper respiratory tract infection[a]						
No	37 (86)	6 (14)	Reference		Reference	
Yes	18 (49)	19 (51)	6.5 (2.2–19.1)	.001	5.3 (1.4–19.6)	.013
Antibiotic use[a]						
No	42 (67)	21 (33)	Reference		…	
Yes	12 (75)	4 (25)	0.7 (.2–2.3)	.524	…	
HIV						
Uninfected	52 (68)	25 (32)	…		…	
Infected	2 (100)	0 (0)	…	.330	…	
Received a meningococcal vaccine						
No	38 (75)	13 (25)	Reference		…	
Yes	4 (67)	2 (33)	1.5 (.2–8.9)	.681	…	
Chronic lung disease						
No	53 (69)	24 (31)	Reference		…	
Yes	4 (67)	2 (33)	1.1 (.2–6.4)	.912	…	
Diabetes						
No	57 (69)	26 (31)	…		…	
Yes	0 (0)	0 (0)	…		…	

N = 83. Genogroupable indicates any capsular genogroup. Nongenogroupable indicates cnl, NG on polymerase chain reaction, neg ACWYZYXHE.

Abbreviations: CI, confidence interval; cnl, capsular null locus; HIV, human immunodeficiency virus; neg, negative; NG, nongenogroupable; OR, odds ratio.

[a]In the previous month.

[b]In the previous 2 weeks.

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Table 4. Multinomial Analysis of Factors Associated With Meningococcal (*Neisseria meningitidis*) Carriage Status Among First-year University Students 2 Months After Registration: South Africa, 2017

		Never an NM carrier	Acquired NM Carriage			Retained NM Carriage		
Characteristics	All Students, N	Never an NM Carrier, n or n/N (%)	n or n/N (%)	RRR (95% CI)	aRRR (95% CI)	n or n/N (%)	RRR (95% CI)	aRRR (95% CI)
Number of students	1625	1495 (92.0)	83 (5.1)	…		47 (2.9)	…	
University								
Witwatersrand	881	818/881 (92.9)	47/881 (5.3)	Ref		16/881 (1.8)	Ref	
Cape Town	744	677/744 (90.8)	36/744 (4.8)	0.9 (.6–1.4)	0.8 (.5–1.3)	31/744 (4.2)	2.3 (1.3–4.3)	2.1 (1.1–4.0)
Sex								
Male	638	573/638 (89.8)	36/638 (5.6)	1.2 (.8–1.9)	1.3 (.8–2.1)	29/638 (4.6)	2.6 (1.4–4.7)	2.5 (1.3–4.6)
Female	987	922/987 (93.4)	47/987 (4.8)	Ref		18/987 (1.8)	Ref	
Living arrangements								
House/apartment, with family	647	599/647 (92.6)	32/647 (5.0)	Ref		16/647 (2.5)	Ref	
House/apartment, with other students	413	382/413 (92.5)	16/413 (3.9)	0.8 (.4–1.4)	…	15/413 (3.6)	1.5 (.7–3.0)	…
University residence/hostel/dormitory	565	514/565 (91.0)	35/565 (6.2)	1.3 (.8–2.1)	…	16/565 (2.8)	1.2 (.6–2.4)	…
Shares a room								
No	937	856/937 (91.4)	53/937 (5.7)	Ref		28/937 (3.0)	Ref	
Yes	688	639/688 (92.9)	30/688 (4.4)	0.8 (.5–1.2)	…	19/688 (2.8)	0.9 (.5–1.6)	…
Current cigarette smoker[a]								
No	1138	1056/1138 (92.8)	56/1138 (4.9)	Ref		26/1138 (2.3)	Ref	
Yes	487	439/487 (90.1)	27/487 (5.5)	1.2 (.7–1.9)	…	21/48 7 (4.3)	1.9 (1.1–3.5)	…
Smoke exposure[a]								
No	521	484/521 (92.9)	25/521 (4.8)	Ref		12/521 (2.3)	Ref	
Yes	1104	1011/1104 (91.6)	58/1104 (5.3)	1.1 (.7–1.8)	…	35/1104 (3.2)	1.4 (.7–2.7)	…
Nightclub attendance[b]								
No	1250	1165/1250 (93.2)	56/1250 (4.5)	Ref		29/1250(2.3)	Ref	
Yes	375	330/375 (88.0)	27/375 (7.2)	1.7 (1.1–2.7)	2.1 (1.1–4.0)	18/375 (4.8)	2.2 (1.2–4.0)	0.7 (.3–1.6)
Pub/bar attendance[b]								
No	1234	1148/1234 (93.0)	64/1234 (5.2)	Ref		22/1234 (1.8)	Ref	
Yes	391	347/391 (88.8)	19/391 (4.9)	0.9 (.6–1.7)	0.5 (.3–1.0)	25/391 (6.4)	3.8 (2.1–6.8)	3.0 (1.4–6.3)
Party attendance[b]								
No	1103	1026/1103 (93.0)	51/1103 (4.6)	Ref		26/1103(2.4)	Ref	
Yes	522	469/522 (89.9)	32/522 (6.1)	1.4 (.9–2.2)	…	21/522 (4.0)	1.8 (.9–3.2)	…
Intimate kissing[b]								
No	968	908/968 (93.8)	39/968 (4.0)	Ref		21/968 (2.2)	Ref	
Yes	657	587/657 (89.4)	44/657 (6.7)	1.7 (1.1–2.7)	1.8 (1.1–2.9)	26/657 (4.0)	1.9 (1.1–3.4)	1.4 (.7–2.6)
Recent upper respiratory tract infection[a]								
No	828	761/828 (91.9)	43/828 (5.2)	Ref		24/828 (2.9)	Ref	
Yes	720	662/720 (91.9)	37/720 (5.1)	0.9 (.6–1.6)	…	21/720 (2.9)	1.1 (.6–1.8)	…
Antibiotic use[a]								
No	1302	1199/1302 (92.1)	63/1302 (4.8)	Ref		40/1302 (3.1)	Ref	
Yes	238	216/238 (90.8)	16/238 (6.7)	1.4 (.8–2.5)	…	6/238 (2.5)	0.8 (.3–2.0)	…

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Table 4. Continued

Characteristics	All Students, N	Never an NM carrier	Acquired NM Carriage			Retained NM Carriage		
		Never an NM Carrier, n or n/N (%)	n or n/N (%)	RRR (95% CI)	aRRR (95% CI)	n or n/N (%)	RRR (95% CI)	aRRR (95% CI)
HIV								
Uninfected	1552	1430/1552 (92.1)	77/1552(5.0)	Ref		45/1552 (2.9)	Ref	
Infected	10	8/10 (80.0)	2/10 (20.0)	4.6 (.9–22)	5.0 (1.1–24.4)	0/10 (0.0)	…	…
Received a meningococcal vaccine								
No	1060	986/1060 (93.0)	51/1060 (4.8)	Ref		23/1060 (2.2)	Ref	
Yes	85	77/85 (90.6)	6/85 (7.1)	1.5 (.6–3.6)	…	2/85 (2.4)	1.1 (.3–4.8)	…
Chronic lung disease								
No	1531	1410/1531 (92.1)	77/1531 (5.0)	Ref		44/1531 (2.9)	Ref	
Yes	94	85/94 (90.4)	6/94 (6.4)	1.3 (.5–3.1)	…	3/94 (3.2)	1.1 (.3–3.7)	…
Diabetes								
No	1616	1486/1616 (92.0)	83/1616 (5.1)	Ref		47/1616 (2.9)	Ref	
Yes	9	9/9 (100)	0/9 (0.0)	…	…	0/9 (0.0)	…	…

Abbreviations: aRRR, adjusted relative risk ratio; CI, confidence interval; HIV, human immunodeficiency virus; NM, *Neisseria meningitidis*; Ref, reference; RRR, relative risk ratio.

[a] In the previous month.

[b] In the previous 2 weeks.

a rapid increase in carriage during the first survey at both universities, as seen in other studies conducted at registration [21]. Our swabbing techniques and detection of meningococci were standard across the sites and surveys; therefore, these factors are unlikely to be the cause for the observed difference. Persistence of carriage was not confirmed by whole-genome sequencing of the isolates; therefore, estimates of meningococcal persistence could have overestimated the actual rates.

Conclusions

Neisseria meningitidis carriage among first-year university students in South Africa was low initially, with a moderate acquisition of carriage between the 2 surveys. Nongroupable strains predominated, followed by Y, B, C, and W genogroups. Significant risk factors for meningococcal carriage at both time points included male sex, intimate kissing, and nightclub attendance. Human immunodeficiency virus is known to be associated with increased risk of IMD and more severe IMD; however, this is the first study that has shown an association between HIV infection and meningococcal carriage acquisition. These data suggest that students with HIV could benefit most from receiving meningococcal vaccination.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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HIV infection is associated with increased meningococcal carriage acquisition amongst first year students in two South African universities

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Summary:

Meningococcal carriage prevalence amongst first-year South African university students increased over time, peaking at 8%. HIV-infection was associated with carriage acquisition, whilst social-

behavioural risk factors were associated with carriage and acquisition. These data advocate for targeted meningococcal vaccination of students.

Supplementary Tables:

Table s1: Multivariable analysis of risk factors for meningococcal carriage amongst a cross section of first year university students **2 months after registration** (survey 2), South Africa, 2017 (n=1775).

Table s2: Multivariable analysis of risk factors for meningococcal carriage amongst a cohort of first year university students **at registration** (survey 1), South Africa, 2017 (n=1655).

Table s3: Multivariable analysis of risk factors for meningococcal carriage amongst a cohort of first year university students **2 months after registration** (survey 2), South Africa, 2017 (n=1655).

Table s4: Comparison of factors associated with meningococcal carriage persistence and clearance 2 months after registration amongst first year university students who were meningococcal carriers at registration, South Africa, 2017 (n=77).

Supplementary methods:

Sample size calculation for study

Sample size was calculated using OpenEpi (https://www.openepi.com/SampleSize/SSCC.htm), assuming differences in the acquisition of meningococcal carriage in a cohort of students with and without HIV-coinfection. Calculations were for repeat measurements assuming an HIV prevalence of 7%, a power of 80%, 95% confidence intervals, and initial meningococcal carriage prevalence of 4% in HIV-uninfected persons and 7% in HIV-infected persons, increasing to 12% in HIV-uninfected and 28% in HIV-infected persons. Our target was to enrol 3000 students to account for a potential 15% lost to follow up for survey two.

Enrolment procedure for survey two

For survey two, participants were informed of the study via email sent to all first-year students at the university and to individual email and WhatsApp accounts (if available) of the participants from survey one. At survey two, returning students were re-issued with a unique study number manually linked to their first study number and the questionnaire and oropharyngeal swabs were repeated. Students who did not participate in the first survey were welcome to enrol in survey two, however HIV testing was not performed on these participants.

Definitions for carriage acquisition, persistence and clearance

Acquisition, persistence and clearance of meningococcal carriage 6-8 weeks following registration were determined from the cohort returning for the second survey. Acquisition of meningococci was defined as those who were not carriers at survey one and then were carriers at survey two. Persistence of carriage included all students carrying meningococci at survey one and survey two, regardless of genogroup. Clearance of carriage was defined as those carrying meningococci at survey one but not at survey two.

Intervention for meningococcal carriers

Results for meningococcal carriage were not routinely reported back to the students and thus no interventions were given/suggested to clear carriage. Colonisation with meningococcus typically allows time for the body to build up mucosal immunity and thus control/prevent invasion of more virulent strains of meningococcus should persons be exposed to these. Chemoprophylaxis to clear meningococcal carriage is usually reserved in situations where persons have been in close contact with a person infected with a virulent strain of meningococcus causing meningococcal disease.

Multinomial regression analysis

Multinomial regression was performed to compare those who never carried meningococci (baseline category) with the carrier acquisition and carrier persistence groups from the cohort. Multinomial regression allows modelling of outcome variables with >2 categories (levels=j) and relates the

probability of being in category j to the probability of being in a baseline category. A complete set of coefficients are estimated for each of the j levels compared with the baseline and the effect of each predictor in the model is measured as the relative risk ratio (RRR).

An additional multivariable logistic regression was done to determine factors at survey two associated with carriage persistence amongst carriers in survey one versus clearance. The same variables were used as in the multivariable analysis for risk factors for carriage at survey one and two.

ADDITIONAL RESULTS

Cross-sectional study: Survey two

On multivariable analysis, the following risk factors were associated with increased odds of meningococcal carriage in survey two: residing in the Eastern Cape (aOR 2.2 (95% CI 1.1-4.4)) or KwaZulu-Natal Provinces (aOR 2.0 (95% CI 1.1-3.7)) compared to Gauteng Province; being male (aOR 1.7 (95% CI 1.2-2.4)); attending nightclubs (aOR 1.5 (95% CI 1.1-2.3)); and having at least one intimate kissing partner (aOR 1.8 (95% CI 1.2-2.5)). (Table s1)

Cohort study:

Risk factor analysis for carriage at the beginning of the academic year and two months into the academic year for the cohort of students showed similar results to the same analysis performed on the cross section of students at the two time points. (see Table 2 main body, Table s1, Table s2 and Table s3)

A multivariable analysis of risk factors associated with meningococcal carriage persistence compared to clearance two months into the academic year amongst students who were meningococcal carriers at the beginning of the academic year showed that being male was associated with persistence of meningococcal carriage (aOR 3.1 (95% CI 1.2-8.4)) across the two surveys. (Table s4)

Table s1: Multivariable analysis of risk factors for meningococcal carriage amongst a cross section of first year university students **2 months after registration** (survey 2), South Africa, 2017 (n=1775).

Characteristics	**All**	**Meningo coccal Carriers**	**Univariate analysis**		**Multivariable analysis**	
	N	n (n/N%)	Odds ratio (95% Confidence interval)	p-value	Odds ratio (95% confidence interval)	p-value
Number of students	1775	134 (7.6)				
University						
Witwatersrand	993	67 (6.8)	Ref			
Cape Town	782	67 (8.6)	1.3 (0.9-1.8)	0.150		
Home Province						
Eastern Cape	98	12 (12.2)	2.2 (1.1-4.4)	0.020	2.2 (1.1-4.4)	0.022
Free State	41	4 (9.8)	1.7 (0.6-5.1)	0.320	2.0 (0.7-5.9)	0.209
Gauteng	730	43 (5.9)	Ref		Ref	
KwaZulu-Natal	154	18 (11.7)	2.1 (1.2-3.8)	0.011	2.0 (1.1-3.7)	0.019
Limpopo	157	10 (6.4)	1.1 (0.5-2.2)	0.818	1.2 (0.6-2.5)	0.606
Mpumalanga	71	8 (11.3)	2.0 (0.9-4.5)	0.082	2.1 (0.9-4.7)	0.075
Northern Cape	24	1 (4.2)	0.7 (0.1-5.3)	0.724	0.7 (0.1-5.0)	0.685
North West	58	2 (3.5)	0.6 (0.1-2.4)	0.446	0.6 (0.1-2.6)	0.498
Western Cape	362	33 (9.1)	1.6 (1.1-2.6)	0.050	1.4 (0.9-2.3)	0.140
Outside South Africa	80	3 (3.8)	0.6 (0.2-2.1)	0.436	0.6 (0.2-2.1)	0.436
Median Age (years)	18.6	18.5		0.204		
Sex						
Male	703	68 (9.7)	1.6 (1.1-2.3)	0.007	1.7 (1.2-2.4)	0.004
Female	1072	66 (6.2)	Ref		Ref	
Living Arrangements						
House/apartment - with family	704	50 (7.1)	Ref			

House/apartment – with other students	462	32 (6.9)	0.9 (0.6-1.5)	0.909		
University Residence/Hostel/Dormitory	609	52 (8.5)	1.2 (0.8-1.8)	0.330		
Shares a room						
No	1016	82 (8.1)	Ref			
Yes	759	52 (6.9)	0.8 (0.6-1.2)	0.336		
Current cigarette smoker[a]						
No	1249	85 (6.8)	Ref			
Yes	526	49 (9.3)	1.4 (0.9-2.0)	0.069		
Smoke exposure[a]						
No	582	39 (6.7)	Ref			
Yes	1193	95 (8.0)	1.2 (0.8-1.8)	0.345		
Nightclub attendance[b]						
No	1370	88 (6.4)	Ref		Ref	
Yes	405	46 (11.4)	1.9 (1.3-2.7)	0.001	1.5 (1.1-2.3)	0.035
Pub/bar attendance[b]						
No	1352	89 (6.6)	Ref			
Yes	423	45 (10.6)	1.7 (1.2-2.5)	0.006		
Party attendance[b]						
No	1210	80 (6.6)	Ref			
Yes	565	54 (9.6)	1.5 (1.1-2.1)	0.029		
Intimate kissing[b]						
No	1058	62 (5.8)	Ref		Ref	
Yes	717	72 (10.0)	1.8 (1.3-2.6)	0.001	1.7 (1.2-2.5)	0.005
Recent Upper Respiratory tract Infection[a]						
No	911	69 (7.6)	Ref			
Yes	781	59 (7.6)	1.0 (0.7-1.4)	0.988		

Antibiotic use[a]				
No	1414	105 (7.4)	Ref	
Yes	268	24 (9.0)	1.2 (0.8-2.0)	0.389
HIV-uninfected	1656	124 (7.5)	Ref	
HIV-infected	10	2 (20.0)	3.1(0.6-14.7)	0.157
Received a meningococcal vaccine				
No	1172	77 (6.6)	Ref	
Yes	90	8 (8.9)	1.4 (0.6-3.0)	0.400
Chronic lung disease				
No	1673	125 (7.5)	Ref	
Yes	102	9 (8.8)	1.2 (0.6-2.4)	0.616
Diabetes				
No	1611	134 (7.6)	Ref	
Yes	10	0 (0)	.	0.365

Footnote: [a]in the previous month; [b]in the previous two weeks

Table s2: Multivariable analysis of risk factors for meningococcal carriage amongst a cohort of first year university students **at registration** (survey 1), South Africa, 2017 (n=1655).

Characteristics	All	Meningo coccal Carriers	Univariate analysis		Multivariable analysis	
	N	n (n/N%)	Odds ratio (95% Confidence interval)	p-value	Odds ratio (95% confidence interval)	p-value
Number of students	1655	77 (4.7)				
University						
Witwatersrand	889	24 (2.7)	Ref			
Cape Town	766	53 (6.9)	2.7 (1.6-4.4)	<0.001		
Home Province						
Eastern Cape	85	5 (5.9)	1.9 (0.7-5.2)	0.196	1.6 (0.6-4.7)	0.352
Free State	40	2 (5.0)	1.6 (0.4-7.2)	0.520	1.4 (0.3-6.6)	0.638
Gauteng	702	22 (3.1)	Ref		Ref	
Kwazulu-Natal	143	11 (7.7)	2.6 (1.2-5.4)	0.013	1.9 (0.9-4.2)	0.117
Limpopo	135	1 (0.7)	0.2 (0.1-1.7)	0.153	0.2 (0.1-1.7)	0.155
Mpumalanga	57	2 (3.5)	1.1 (0.3-4.9)	0.876	0.9 (0.2-4.3)	0.953
Northern Cape	22	1 (4.6)	1.5(0.2-11.4)	0.712	1.1 (0.1-9.1)	0.916
North West	43	0 (0.0)	.		.	
Western Cape	348	31 (8.9)	3.0 (1.7-5.3)	<0.001	2.6 (1.4-4.7)	0.001
Outside South Africa	80	2 (2.5)	0.8 (0.2-3.4)	0.628	0.7 (0.2-3.3)	0.703
Median Age (years)	18.5	18.5		0.413		
Sex						
Male	648	39 (6.0)	1.6 (1.1-2.6)	0.036	1.6 (0.9-2.5)	0.067
Female	1007	38 (3.8)	Ref		Ref	
Living Arrangements						
House/apartment - with family	849	30 (3.5)	Ref		Ref	
House/apartment – with other students	313	15 (4.8)	1.4 (0.7-2.6)	0.326	1.9 (0.9-3.9)	0.072
University Residence/Hostel/Dormitory	493	32 (6.5)	1.9 (1.1-3.2)	0.014	2.4 (1.4-4.3)	0.002
Shares a room						
No	980	49 (5.0)	Ref			
Yes	675	28 (4.2)	0.8 (0.5-1.3)	0.419		
Current cigarette smoker[a]						
No	1203	41 (3.4)	Ref			
Yes	452	36 (8.0)	2.5 (1.5-3.9)	<0.001		
Smoke exposure[a]						
No	571	17 (3.0)	Ref			
Yes	1084	60 (5.5)	1.9 (1.1-3.3)	0.021		
Nightclub attendance[b]						
No	1335	44 (3.3)	Ref		Ref	
Yes	320	33 (10.3)	3.4 (2.1-5.4)	<0.001	2.0 (1.2-3.2)	0.009
Pub/bar attendance[b]						

No	1282	45 (3.5)	Ref			
Yes	373	32 (8.6)	2.6 (1.6-4.1)	<0.001		
Party attendance[b]						
No	1150	40 (3.5)	Ref			
Yes	505	37 (7.3)	2.2 (1.4-3.5)	0.001		
Intimate kissing[b]						
No	975	23 (2.4)	Ref		Ref	
Yes	680	54 (7.9)	3.6 (2.2-5.9)	<0.001	2.8 (1.7-4.8)	<0.001
Recent Upper Respiratory tract Infection[a]						
No	934	46 (4.9)	Ref			
Yes	628	27 (4.3)	0.9 (0.5-1.4)	0.566		
Antibiotic use[a]						
No	1278	66 (5.2)	Ref			
Yes	287	10 (3.5)	0.7 (0.3-1.3)	0.235		
HIV-uninfected	1546	71 (4.6)				
HIV-infected	10	0 (0.0)	.	0.488		
Received a meningococcal vaccine						
No	1162	45 (3.9)	Ref			
Yes	66	3 (4.6)	1.2 (0.4-3.9)	0.784		
Chronic lung disease						
No	1567	73 (4.7)	Ref			
Yes	88	4 (4.6)	1.1 (0.3-2.7)	0.961		
Diabetes						
No	1365	65 (4.8)				
Yes	9	0 (0.0)	.	0.502		

Footnote: [a]in the previous month; [b]in the previous two weeks

Table s3: Multivariable analysis of risk factors for meningococcal carriage amongst a cohort of first year university students **2 months after registration** (survey 2), South Africa, 2017 (n=1655).

Characteristics	All	Meningo coccal Carriers	Univariate analysis		Multivariable analysis	
	N	N (n/N%)	Odds ratio (95% Confidence interval)	p-value	Odds ratio (95% confidence interval)	p-value
Number of students	1655	130 (7.9)				
University						
Witwatersrand	889	63 (7.1)	Ref			
Cape Town	766	67 (8.8)	1.3 (0.9-1.8)	0.211		
Home Province						
Eastern Cape	93	12 (12.9)	2.1 (1.1-4.1)	0.033		
Free State	37	4 (10.8)	2.2 (0.8-5.9)	0.117		
Gauteng	680	42 (6.2)	Ref			
KwaZulu-Natal	144	18 (12.5)	2.0 (1.1-3.6)	0.018		
Limpopo	137	9 (6.6)	1.0 (0.5-2.1)	0.983		
Mpumalanga	60	6 (10.0)	1.6 (0.6-3.8)	0.325		
Northern Cape	22	1 (4.6)	0.7 (0.1-5.1)	0.701		
North West	52	2 (3.9)	0.6 (0.1-2.4)	0.438		
Western Cape	350	33 (9.4)	1.5 (0.9-2.3)	0.108		
Outside South Africa	80	3 (3.8)	0.5 (0.2-1.8)	0.325		
Median Age (years)	18.6	18.5		0.158		
Sex						
Male	648	65 (10.0)	1.6 (1.1-2.3)	0.009	1.7 (1.2-2.4)	0.005
Female	1007	65 (6.5)	Ref			
Living Arrangements						
House/apartment - with family	656	48 (7.3)	Ref			
House/apartment – with other students	422	31 (7.4)	1.1 (0.6-1.6)	0.986		
University Residence/Hostel/Dormitory	577	51 (8.8)	1.2 (0.8-1.9)	0.327		
Shares a room						
No	953	81 (8.5)	Ref			
Yes	702	49 (7.0)	0.8 (0.6-1.2)	0.257		
Current cigarette smoker[a]						
No	1158	82 (7.1)	Ref			
Yes	497	48 (9.7)	1.4 (0.9-2.0)	0.075		
Smoke exposure[a]						
No	529	37 (7.0)	Ref			
Yes	1126	93 (8.3)	1.2 (0.8-1.8)	0.373		
Nightclub attendance[b]						
No	1270	85 (6.7)	Ref		Ref	
Yes	385	45 (11.7)	1.8 (1.3-2.7)	0.002	1.6 (1.1-2.4)	0.019
Pub/bar attendance[b]						

No	1251	86 (6.9)	Ref			
Yes	404	44 (10.9)	1.7 (1.1-2.4)	0.010		
Party attendance[b]						
No	1117	77 (6.9)	Ref			
Yes	538	53 (9.9)	1.5 (1.1-2.1)	0.037		
Intimate kissing[b]						
No	978	60 (6.1)	Ref		Ref	
Yes	677	70 (10.3)	1.8 (1.2-2.5)	0.002	1.6 (1.1-2.4)	0.009
Recent Upper Respiratory tract Infection[a]						
No	840	67 (8.0)	Ref			
Yes	738	58 (7.9)	0.9 (0.7-1.4)	0.932		
Antibiotic use[a]						
No	1323	103 (7.8)	Ref			
Yes	246	22 (8.9)	1.2 (0.7-1.9)	0.538		
HIV-uninfected	1580	122 (7.7)	Ref			
HIV-infected	10	2 (20.0)	3.0(0.6-14.2)	0.169		
Received a meningococcal vaccine						
No	1077	74 (6.9)	Ref			
Yes	85	8 (9.4)	1.4 (0.7-3.0)	0.381		
Chronic lung disease						
No	1561	121 (7.8)	Ref			
Yes	94	9 (9.6)	1.3 (0.6-2.6)	0.524		
Diabetes						
No	1646	130 (7.9)	Ref			
Yes	9	0 (0.0)	.	0.380		
Previous meningococcal carriage						
No	1578	83 (5.3)	Ref			
Yes	77	47 (61.0)	28 (17-46.9)	<0.001		

Footnote: [a]in the previous month; [b]in the previous two weeks

Table s4: Comparison of factors associated with meningococcal carriage persistence and clearance 2 months after registration amongst first year university students who were meningococcal carriers at registration, South Africa, 2017 (n=77).

Characteristics	Initial carriage	Cleared carriage	Persisted[c] in carriage	Univariate analysis		Multivariable analysis	
	N	n (n/N%)	n (n/N%)	Odds ratio (95% Confidence interval)	p-value	Odds ratio (95% confidence interval)	p-value
Number of students	77	30 (39.0)	47 (61.0)				
University							
Witwatersrand	53	22 (41.5)	31 (58.5)	0.7(0.3-1.9)	0.496		
Cape Town	24	8 (33.3)	16 (66.7)	Ref			
Median Age (years)							
Sex							
Male	39	10 (25.6)	29 (74.3)	3.2 (1.2-8.4)	0.017	3.1 (1.2-8.4)	0.024
Female	38	20 (52.6)	18 (47.4)	Ref		Ref	
Living Arrangements							
House/apartment - with family	25	9 (36.0)	16 (64.0)	Ref			
House/apartment – with other students	24	9 (37.5)	15 (62.5)	0.9 (0.3—3.0)	0.913		
University Residence / Hostel / Dormitory	28	12 (42.9)	16 (57.1)	0.8 (0.2-2.3)	0.611		
Shares a room							
No	44	16 (36.4)	28 (63.6)	Ref			
Yes	33	14 (42.4)	19 (57.6)	0.8 (0.3-2.0)	0.590		
Current cigarette smoker[a]							
No	46	20 (43.5)	26 (56.5)	Ref			
Yes	31	10 (32.3)	21 (67.7)	1.6 (0.6-4.2)	0.324		
Smoke exposure[a]							

No	20	8 (40.0)	12 (60.0)	Ref			
Yes	57	22 (38.6)	35 (61.4)	1.1 (0.4-3.0)	0.912		
Nightclub attendance[b]							
No	49	20 (40.8)	29 (59.2)	Ref			
Yes	28	10 (35.7)	18 (64.3)	1.2 (0.5-3.2)	0.659		
Pub/bar attendance[b]							
No	39	17 (43.6)	22 (56.4)	Ref		Ref	
Yes	38	13 (34.2)	25 (65.8)	2.4 (1.1-5.2)	0.030	1.1 (0.4-3.0)	0.793
Party attendance[b]							
No	40	14 (35.0)	26 (65.0)	Ref			
Yes	37	16 (43.2)	21 (56.8)	0.7 (0.3-1.8)	0.459		
Intimate kissing[b]							
No	31	10 (32.3)	21 (67.7)	Ref			
Yes	46	20 (43.5)	26 (56.5)	0.6 (0.2-1.6)	0.324		
Recent Upper Respiratory tract Infection[a]							
No	36	12 (33.3)	24 (66.7)	Ref			
Yes	39	18 (46.1)	21 (53.9)	0.6 (0.2-1.5)	0.259		
Antibiotic use[a]							
No	61	21 (34.4)	40 (65.6)	Ref			
Yes	14	8 (57.1)	6 (42.9)	0.4 (0.1-1.3)	0.123		
HIV-uninfected	73	28 (38.4)	45 (61.6)	Ref			
HIV-infected	0	0	0	.			
Received a meningococcal vaccine							
No	40	17 (42.5)	23 (57.5)	Ref			
Yes	2	0 (0.0)	2 (100.0)	.			
Chronic lung disease							

No	74	30 (40.5)	44 (59.5)	Ref
Yes	3	0 (0.0)	3 (100.0)	.
Diabetes				
No	77	30 (39.0)	47 (61.0)	Ref
Yes	0	0	0	.

Footnote: [a]in the previous month; [b] in the previous two weeks; [c]1 student who supposedly persisted in carriage may have cleared carriage and then acquired new carriage with another strain (genogroup B changing to Y).

Paper II

Meiring S, Cohen C, de Gouveia L, du Plessis M, Kularatne R, Hoosen A, Lekalakala R, Lengana S, Seetharam S, Naicker P, Quan V, Reubenson G, Tempia S, von Mollendorf C, von Gottberg A, for GERMS-SA. Declining Incidence of Invasive Meningococcal Disease in South Africa: 2003–2016. Clin Infect Dis 2019 August; 69(3):495-504

Clinical Infectious Diseases

MAJOR ARTICLE

Declining Incidence of Invasive Meningococcal Disease in South Africa: 2003–2016

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Background. Invasive meningococcal disease (IMD) is endemic to South Africa, where vaccine use is negligible. We describe the epidemiology of IMD in South Africa.

Methods. IMD cases were identified through a national, laboratory-based surveillance program, GERMS-SA, from 2003–2016. Clinical data on outcomes and human immunodeficiency virus (HIV) statuses were available from 26 sentinel hospital sites. We conducted space-time analyses to detect clusters of serogroup-specific IMD cases.

Results. Over 14 years, 5249 IMD cases were identified. The incidence was 0.97 cases per 100 000 persons in 2003, peaked at 1.4 cases per 100 000 persons in 2006, and declined to 0.23 cases per 100 000 persons in 2016. Serogroups were confirmed in 3917 (75%) cases: serogroup A was present in 4.7% of cases, B in 23.3%, C in 9.4%; W in 49.5%; Y in 12.3%, X in 0.3%; Z in 0.1% and 0.4% of cases were non-groupable. We identified 8 serogroup-specific, geo-temporal clusters of disease. Isolate susceptibility was 100% to ceftriaxone, 95% to penicillin, and 99.9% to ciprofloxacin. The in-hospital case-fatality rate was 17% (247/1479). Of those tested, 36% (337/947) of IMD cases were HIV-coinfected. The IMD incidence in HIV-infected persons was higher for all age categories, with an age-adjusted relative risk ratio (aRRR) of 2.5 (95% confidence interval [CI] 2.2–2.8; $P < .001$) from 2012–2016. No patients reported previous meningococcal vaccine exposure. Patients with serogroup W were 3 times more likely to present with severe disease than those with serogroup B (aRRR 2.7, 95% CI 1.1–6.3); HIV coinfection was twice as common with W and Y diseases (aRRR W = 1.8, 95% CI 1.1–2.9; aRRR Y = 1.9, 95% CI 1.0–3.4).

Conclusions. In the absence of significant vaccine use, IMD in South Africa decreased by 76% from 2003–2016. HIV was associated with an increased risk of IMD, especially for serogroup W and Y diseases.

Keywords. meningococcus; *Neisseria* meningitidis; epidemiology; South Africa; invasive meningococcal disease.

Invasive meningococcal disease (IMD) is a devastating illness, with high morbidity and mortality in both low- and high-income countries [1]. Its incidence is declining in many countries; however, epidemics still occur, particularly in the African meningitis belt [2–7].

Some of the global decline in IMD and meningococcal carriage, including that observed in countries in the African meningitis belt, may be due to the introduction of meningococcal vaccination programs [8, 9]. South Africans are not routinely vaccinated against IMD, with vaccine sales reaching approximately 60 000 doses in 2016. Both polysaccharide (Menomune, Sanofi Pasteur) and conjugate (Menactra, Sanofi Pasteur) quadrivalent (ACWY) meningococcal vaccines are available in South Africa.

National guidelines recommend vaccination for 4 categories of patients: those with asplenia; those with a terminal complement factor deficiency; those with laboratory exposure to *Neisseria meningitidis*; and those traveling to Saudi Arabia, where proof of vaccination is compulsory for entry [10, 11]. It is also recommended during vaccine-serogroup outbreaks. Both vaccines can be bought privately with a prescription, or the polysaccharide vaccine can be received free of charge through the public sector if national guideline criteria are met.

Human immunodeficiency virus (HIV) infection is an independent risk factor for IMD; in the United States of America and the United Kingdom, vaccination is offered to HIV-infected persons [12–14]. In South Africa, approximately 13% of the

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population are HIV-infected [15]. An association between *N. meningitidis* serogroup W (MenW) IMD and poor outcomes amongst HIV-infected persons has been described; however, only recently has vaccination been advised for HIV-infected individuals in South Africa [16, 17].

IMD is seasonal, peaking in May to October each year, but it fluctuates over periods of 10–15 years [18]. Through national surveillance programs, South Africa has reported large clusters of sporadic *N. meningitidis* serogroup A (MenA; 2001/2002) and MenW (2005/2006) diseases in Gauteng province and of serogroup B (MenB) disease in Western Cape province (1976–1986), on a background of low levels of serogroup C (MenC) and serogroup Y (MenY) IMD cases [19–21].

With minimal vaccine use, diverse serogroup circulation, and an established surveillance network, we aimed to describe the natural history of IMD trends over time and detect the presence of localized, serogroup-specific IMD epidemics. We describe the clinical and epidemiologic characteristics of MenB IMD, and compare this to MenA, C, W, and Y to assess serogroup-specific differences and, potentially, inform recommendations for meningococcal vaccine use.

METHODS

Invasive Meningococcal Disease Surveillance

IMD cases from January 2003 to December 2016 were reported through the GERMS-SA national, laboratory-based surveillance network [22]. Individuals of all ages and from all provinces in South Africa who had a laboratory-confirmed IMD diagnosis (from any of approximately 257 public and private sector laboratories) were included.

Laboratory-confirmed IMD was defined as an identification of *N. meningitidis* from any usually-sterile site (cerebrospinal fluid [CSF], blood, or joint fluid) through culture; through polymerase chain reaction (PCR); or with Gram-negative diplococcus on a Gram stain and a positive latex antigen test. Recurrent isolates from the same individual were only recounted after 21 days had elapsed. *N. meningitidis* isolates not directly reported to the surveillance network were identified through audits and included in the analysis [22].

IMD isolates were sent from clinical laboratories to the reference laboratory at the Centre for Respiratory Diseases and Meningitis, at the National Institute for Communicable Diseases. Antimicrobial susceptibility testing was interpreted using Clinical and Laboratory Standards Institute interpretive criteria [23]. Meningococcal serogroups were determined by slide agglutination, using polyclonal antibodies to capsular polysaccharides ACWXYZ and monoclonal antibodies to polysaccharide B (Remel, Biotech Limited, Dartford, United Kingdom). Serogroup results of all *N. meningitidis* isolates were confirmed by PCR [24, 25].

Demographic details for each case included: patient age, patient sex, province, and specimen type. Specimen type was hierarchically defined as (1) CSF specimen, regardless of other specimens sent; (2) blood specimen, regardless of other specimens (excluding CSF); and (3) other, such as pleural or joint fluid without a CSF or blood specimen [26]. At 26 sentinel-hospitals, representing all provinces of South Africa, we conducted enhanced surveillance to capture additional data, including in-hospital outcomes, predisposing conditions, and Pitt bacteraemia scores for severity of illness (score 0 for mild, 1–3 for moderate, 4–12 for severe illness) [22, 27].

Incidence Calculation

The annual IMD incidence per 100 000 persons was calculated by age category and serogroup using mid-year population estimates from Statistics South Africa [15]. For incidence calculations by serogroup, we imputed 1332 missing serogroups, adjusting for province and age. Population denominators from the Thembisa 2016 model were used to calculate the incidence by HIV serostatus and the relative risk of HIV coinfection for the years 2012–2016, adjusting for age and year [28, 29]. The HIV prevalence amongst persons with IMD from non–enhanced surveillance sites was assumed to be similar to age-matched persons each year at enhanced surveillance sites.

Statistical Analysis

A statistical analysis was implemented using Stata version 14 (StataCorp Inc., College Station, TX), and P values <.05 were considered significant. Trends in incidence rates by serogroup were calculated using Poisson regression, using cases from 2003 as the reference group. Univariate analyses—comparing characteristics of MenB and MenA, C, W, Y, and all other cases (MenX, MenZ, and non-groupable [MenNG]) of IMD—were performed using Fisher's exact/Mantel–Haenszel $\chi 2$-test for categorical variables. A multinomial regression model was used to assess the clinical and epidemiologic characteristics of patients with IMD by serogroup, with MenB as the baseline category. We started with all variables that were significant at a P value less than .05 in a univariate analysis, and dropped non-significant factors with a stepwise, manual, backward elimination. All 2-way interactions were evaluated.

Assessment of Spatial-Temporal Clusters

We used SaTScan version 9.4.3 (http://www.satscan.org/) to conduct a spatial-temporal analysis, using a Bernoulli model and comparing IMD cases with controls from January 2005 to December 2015 [30]. Cases were defined as numbers of IMD episodes by serogroup occurring per district, per month. Controls were episodes of laboratory-confirmed cryptococcosis occurring per district, per month. Cryptococcosis was chosen as a control group, as this disease is widespread across South Africa and its diagnosis necessitates the clinical expertise of performing a lumbar puncture on suspected patients and processing the specimen at a functioning district laboratory; thus, we controlled for differences in specimen-taking-practices

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and laboratory capacities across the different districts of South Africa. Cases and controls were collected through the same surveillance program: GERMS-SA [22].

Spatial-temporal clusters were defined as an increase in serogroup-specific IMD cases occurring above the expected norm for a defined geographical location and time. The cryptococcal controls helped determine the expected number of IMD cases within each district. The relative risk of IMD by serogroup cluster in each district was calculated by dividing the observed number of cases by the expected number of cases. Maps indicating clusters were generated using ArcGIS version 9.2 (http://www.esri.com/). Only significant clusters, with *P* values <.05, were reported (see Supplementary Materials for a more detailed description).

Ethical Approval

Ethical approval for the secondary data analysis of the GERMS-SA surveillance data (M140159) was obtained from the University of Witwatersrand Health Research Ethics Committee (Human; M170951). All personal identifiers were removed prior to data analysis.

RESULTS

From 2003 through 2016, 5249 cases of IMD were reported through the surveillance network in South Africa, with 60% (3158/5249) occurring during winter and spring (June to October; Figure 1 and Supplementary Figure 1). The meningococcal serogroups were confirmed in 3917 (75%) cases (708 [18%] through PCR only), with 7 different serogroups identified (MenA, 183 [5%]; MenB, 912 [23%]; MenC, 369 [9%]; MenW, 1940 [50%]; MenY, 482 [12%]; MenX, 12 [0.3%]; MenZ, 4 [0.1%]; and MenNG, 15 [0.4%]; Supplementary Figure 2). Of the serotype-confirmed cases, 74% (2911/3917) were isolated from CSF, 25% (993/3917) from blood, and 0.3% (13/3917) from other sterile sites. All isolates tested were susceptible to ceftriaxone (3209/3209), 95% were susceptible to penicillin (3052/3209), and 99.9% were susceptible to ciprofloxacin (2250/2252). Of the serotype-confirmed cases, 77% occurred in 3 of the 9 South African provinces (1947/3917 [50%] in Gauteng; 736 [19%] in Western Cape; and 321 [8%] in Eastern Cape; Table 1).

The IMD incidence per 100 000 persons was 0.97 cases in 2003, peaked at 1.4 cases in 2006, and decreased to 0.23 cases in

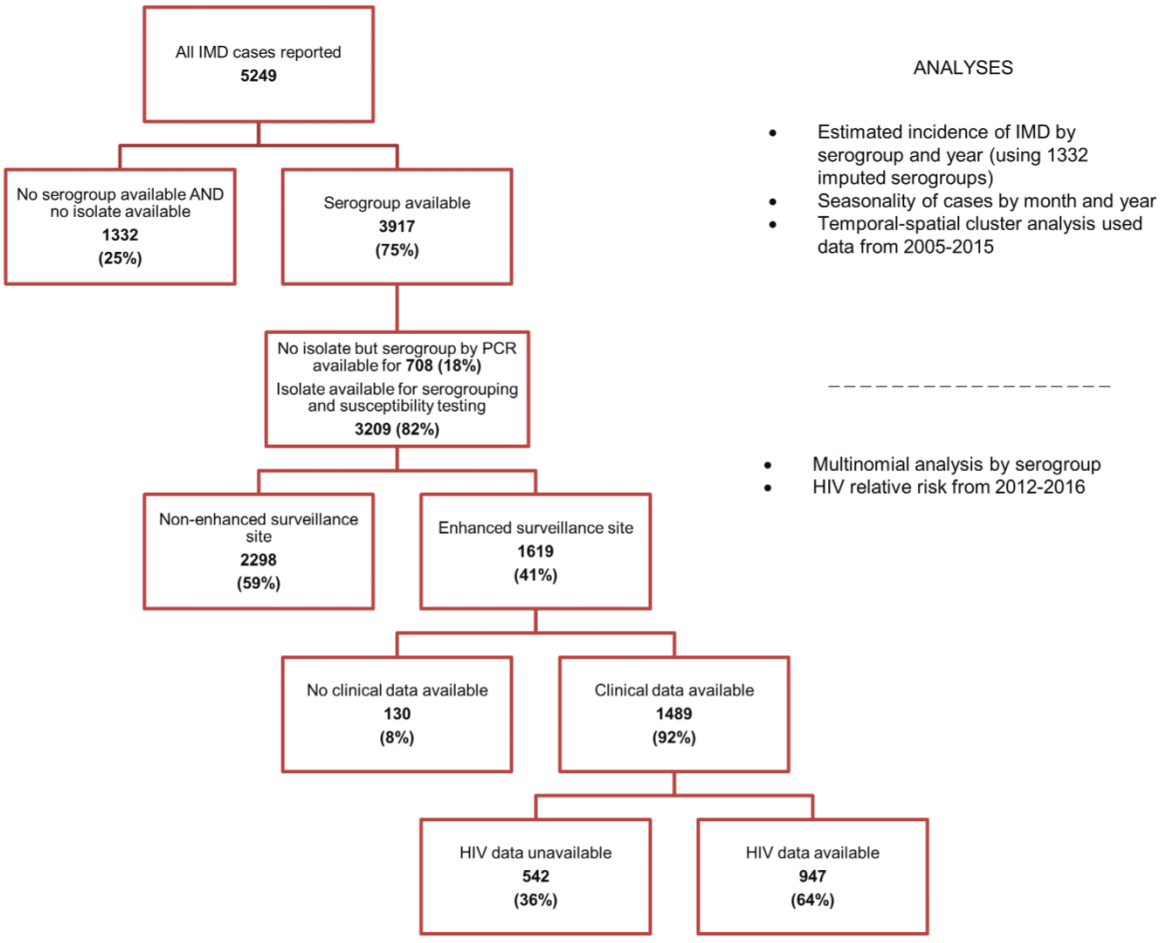

Figure 1. Flow chart of laboratory-confirmed cases of IMD reported to GERMS-SA, in South Africa, from 2003–2016 (N = 5249). Abbreviations: HIV, human immunodeficiency virus; IMD, invasive meningococcal disease; PCR, polymerase chain reaction.

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Table 1. Comparison of Clinical and Epidemiological Characteristics of Invasive Meningococcal Disease Cases, by Serogroup, Occurring in South Africa From 2003–2016 (N = 3917 With Serogroup Data Available)

	All	B (Reference)	A			C			W			Y			Other		
Characteristics	n/N (%)	n/N (%)	n/N (%)	RRR (95%CI)	aRRR (95% CI)	n/N (%)	RRR (95%CI)	aRRR (95% CI)	n/N (%)	RRR (95%CI)	aRRR (95% CI)	n/N (%)	RRR (95%CI)	aRRR (95% CI)	n/N (%)	RRR (95%CI)	aRRR (95% CI)
Number of cases	3917	912	183	-	-	369	-	-	1940	-	-	482	-	-	31	-	-
Province																	
Eastern Cape	321/3917 (8)	84/912 (9)	2/183 (1)	1.3 (0.3–6.1)	-	50/369 (14)	2.7 (1.8–4.2)	6.7 (1.4–32.8)	124/1940 (6)	3.0 (2.1–4.1)	2.2 (0.5–8.8)	57/482 (12)	2.8 (1.9–4.2)	4.3 (0.9–20.1)	4/31 (13)	2.5 (0.7–8.8)	-
Gauteng	1947/3917 (50)	298/912 (33)	154/183 (84)	27.2 (12.6–59.0)	-	132/369 (36)	2.0 (1.5–2.8)	1.8 (0.8–4.0)	1196/1940 (62)	8.0 (6.5–10.0)	4.2 (2.7–6.8)	157/482 (33)	2.2 (1.6–3.0)	1.7 (0.8–3.3)	10/31 (32)	1.8 (0.7–4.7)	0.6 (0.1–4.6)
Western Cape	736/3917 (19)	369/912 (40)	7/183 (4)	Reference	Reference	80/369 (22)	Reference	Reference	184/1940 (9)	Reference	Reference	89/482 (18)	Reference	Reference	7/31 (23)	Reference	Reference
Other[a]	913/3917 (23)	161/912 (18)	20/183 (11)	6.5 (2.7–15.8)	-	107/369 (29)	3.1 (2.2–4.3)	2.3 (1.0–5.4)	436/1940 (22)	5.4 (4.2–7.0)	2.2 (1.3–3.8)	179/482 (37)	4.6 (3.4–6.3)	3.2 (1.5–6.4)	10/31 (32)	3.3 (1.2–8.8)	3.2 (0.5–20.1)
Age category																	
<5 years	1675/3780 (44)	473/884 (54)	28/167 (17)	Reference	Reference	113/354 (32)	Reference	Reference	871/1870 (47)	Reference	Reference	183/474 (39)	Reference	Reference	7/31 (23)	Reference	Reference
≥5 years	2105/3780 (54)	411/884 (46)	139/167 (83)	5.7 (3.7–8.8)	2.6 (0.9–7.4)	241/354 (68)	2.5 (1.9–3.2)	1.6 (0.9–3.1)	999/1870 (53)	1.3 (1.1–1.5)	0.8 (0.5–1.2)	291/474 (61)	1.8 (1.5–2.3)	1.3 (0.7–2.2)	24/31 (77)	3.9 (1.7–9.3)	9.7 (1.1–84.5)
Male sex	2118/3838 (55)	510/889 (57)	126/182 (69)	1.7 (1.2–2.4)	-	216/367 (59)	1.1 (0.8–1.4)	-	992/1897 (52)	0.8 (0.7–1.0)		256/472 (54)	0.9 (0.7–1.1)		18/31 (58)	1.0 (0.5–2.1)	-
Laboratory specimen																	
Cerebrospinal fluid	2911/3917 (74)	678/912 (74)	163/183 (89)	Reference	-	295/369 (80)	Reference	-	1388/1940 (72)	Reference		363/482 (75)	Reference		24/31 (77)	-	-
Blood	993/3917 (25)	233/912 (26)	20/183 (11)	0.4 (0.2–0.6)	-	74/369 (20)	0.7 (0.5–1.0)	-	541/1940 (28)	1.1 (0.9–1.4)		119/482 (25)	1.0 (0.7–1.2)		6/31 (19)	-	-
Other[b]	13/3917 (0.3)	1/912 (0.1)	0/183 (0)	-	-	0/369 (0)	-	-	11/1940 (0.6)	5.4 (0.7–41.7)		0/482 (0)	-		1/31 (3)	-	-
Antimicrobial susceptibility																	
Ciprofloxacin susceptibility	2250/2252 (99.9)	542/543 (99.8)	12/12 (100)	-	-	204/204 (100)	-	-	1237/1238 (99.9)	-		235/235 (100)	-		20/20 (100)	-	-
Penicillin susceptibility	3052/3209 (95)	692/739 (94)	175/180 (97)	2.4 (0.9–6.1)	-	275/286 (96)	1.7 (0.9–3.3)	-	1524/1596 (95)	1.4 (1.0–2.1)		359/381 (94)	1.1 (0.7–1.9)		27/27 (100)	0	-
Ceftriaxone susceptibility	3209/3209 (100)	739/739 (100)	180/180 (100)	-	-	286/286 (100)	-	-	1596/1596 (100)	-		381/381 (100)	-		27/27 (100)	-	-
Enhanced-surveillance site cases with clinical data																	
Case fatality rate	247/1479 (17)	37/304 (12)	9/73 (12)	1.0 (0.5–2.2)	0.4 (0.1–2.2)	11/120 (9)	0.7 (0.4–1.5)	0.4 (0.1–1.4)	169/786 (22)	2.0 (1.3–2.9)	1.1 (0.5–2.0)	21/184 (11)	0.9 (0.5–1.6)	0.4 (0.2–1.2)	0/12 (0)	0	-
Severity of illness (Pitt bacteraemia score)																	
0: mild	535/1371 (39)	118/271 (44)	18/42 (43)	Reference	Reference	51/112 (46)	Reference	Reference	260/768 (34)	Reference	Reference	83/167 (50)	Reference	Reference	5/11 (45)	Reference	Reference
1–3: moderate	670/1371 (49)	133/271 (49)	21/42 (50)	1.1 (0.5–2.1)	0.7 (0.3–1.9)	51/112 (46)	0.9 (0.6–1.4)	1.1 (0.6–2.1)	395/768 (51)	1.4 (1.0–1.8)	1.2 (0.8–1.8)	67/167 (40)	0.7 (0.5–1.1)	0.8 (0.5–1.4)	3/11 (27)	0.5 (0.1–2.3)	0.7 (0.1–3.4)
4–12: severe	166/1371 (12)	20/271 (7)	3/42 (7)	1 (0.3–3.7)	2.4 (0.5–12.0)	10/112 (9)	1.2 (0.5–2.7)	2.9 (0.9–9.7)	113/768 (15)	2.6 (1.5–4.4)	2.7 (1.1–6.3)	17/167 (10)	1.2 (0.6–2.5)	2.0 (0.7–6.0)	3/11 (27)	3.6 (0.8–16.2)	11.6 (1.9–70.0)
Predisposing factors																	
HIV infected	337/947 (36)	36/159 (23)	19/42 (45)	2.8 (1.4–5.8)	1.5 (0.6–3.8)	25/70 (36)	1.9 (1.0–3.5)	1.5 (0.8–3.0)	208/550 (38)	2.1 (1.4–3.1)	1.8 (1.1–2.9)	45/116 (39)	2.2 (1.3–3.7)	1.9 (1.0–3.4)	4/10 (40)	2.3 (0.6–8.5)	1.3 (0.3–5.5)

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Table 1. *Continued*

Characteristics	All	B (Reference)	A			C			W			Y			Other		
	n/N (%)	n/N (%)	n/N (%)	RRR (95%CI)	aRRR (95% CI)	n/N (%)	RRR (95%CI)	aRRR (95% CI)	n/N (%)	RRR (95%CI)	aRRR (95% CI)	n/N (%)	RRR (95%CI)	aRRR (95% CI)	n/N (%)	RRR (95%CI)	aRRR (95% CI)
Diabetes	8/1105 (1)	0/238 (0)	0/34 (0)	-	-	0/95 (0)	-		5/595 (1)	-		2/135 (1)	-	-	1/8 (13)	-	-
Complement deficiency	10/1105 (1)	1/238 (0)	0/34 (0)	-	-	0/95 (0)	-		4/595 (1)	0.5 (0.2–2.4)		4/135 (3)	3.0 (0.7–12.8)	-	1/8 (13)	22.6 (3.2–57.2)	-
Asplenia	1/1105 (0. 1)	0/238 (0)	0/34 (0)	-	-	0/95 (0)	-		1/595 (0)	-		0/135 (0)	-	-	0/8 (0)	-	-
Chronic lung disease	15/1105 (1)	3/238 (1)	1/34 (3)	2.4 (0.2–23.5)	-	2/95 (2)	1.7 (0.3–10.2)		7/595 (1)	0.9 (0.2–3.6)		1/135 (1)	11.1 (1.0–121.5)	-	1/8 (13)	-	-
Smoking (>19 years)	32/310 (10)	5/52 (10)	2/17 (12)	1.3 (0.2–7.1)	-	5/38 (13)	1.4 (0.4–5.3)		13/161 (8)	0.8 (0.3–2.4)		6/39 (15)	1.7 (0.5–6.0)	-	1/3 (33)	4.7 (0.4–61.4)	-
Alcohol dependency[c] (>19 years)	23/310 (7)	6/52 (12)	2/17 (12)	1.0 (0.2–5.6)	-	3/38 (8)	0.7 (0.2–2.8)		10/161 (6)	0.5 (0.2–1.5)		2/39 (5)	0.4 (0.1–2.2)	-	0/3 (0)	-	-

Abbreviations: aRRR, age-adjusted relative risk ratio; CAGE, Cutting down, Annoyance by criticism, Guilty feeling, and Eye-openers; CI, confidence interval; HIV, human immunodeficiency virus; RRR, relative risk ratio.

[a]Includes Northern Cape, Free State, North West, Limpopo, Mpumalanga, and KwaZulu-Natal provinces.

[b]Includes joint fluid, pleural fluid, and vitreous fluid.

[c]Alcohol dependency was indicated using the CAGE questionnaire [31].

2016 (overall reduction of 76%; Figure 2). The incidence per 100 000 persons was highest in infants for all serogroups (MenA, 0.1; MenB, 2.4; MenC, 0.5; MenW, 3.1; MenY, 0.7; other, 0.03 [MenX, Y, and NG combined]; Supplementary Figure 3); and 55% (2118/3838) of all IMD patients were male. From 2012–2016, the relative risk of IMD amongst HIV-infected individuals was 2.5 times greater than in HIV-uninfected individuals (0.7 per 100 000 vs. 0.3 per 100 000, respectively; Table 2).

MenA was the predominant serogroup causing IMD in 2003, with an incidence of 0.3 cases per 100 000 persons. MenB disease steadily declined, from 0.3 to 0.1 cases per 100 000 persons, from 2003 to 2016 ($P < .001$). This decrease affected all age categories, except those ≥65 years of age. MenB was the second-most predominant serogroup for all years, except 2016, where it was predominant (causing 41% [47/114] of cases). Although there was an overall reduction of 90% in the incidence of MenC disease, from 0.2 cases per 100 000 persons in 2003 to 0.02 cases per 100 000 in 2016, the MenC disease incidence increased in the <1 year (0.3 to 0.4 cases per 100 000 persons), 5–9 year (0.03 to 0.08 cases per 100 000 persons), and 45–64 year (0 to 0.03 cases per 100 000 persons) age categories.

The MenW incidence increased 10-fold from 2003 to 2006 (from 0.09 to 0.9 cases per 100 000 persons, respectively; $P > 0.001$), then decreased to 0.06 cases per 100 000 persons by 2016. It caused the majority of disease in 8 of the 9 provinces. All age groups were affected by the increase in MenW IMD, but infants were particularly vulnerable, with the incidence increasing from 1.2 cases per 100 000 persons in 2003 to 7.7 cases per 100 000 persons in 2006, before declining to 0 cases in 2016. Overall, the MenY disease incidence decreased by 80%, from 0.2 cases per 100 000 persons in 2003 to 0.03 cases per 100 000 persons in 2016.

Clinical Characteristics

Clinical details were available from 92% (1489/1619) of the persons attending enhanced surveillance hospital sites (Figure 1). A total of 61% of persons were admitted with a Pitt bacteraemia score for moderate (670/1371) to severe disease (166/1371), and 17% (247/1479) died during their hospital admission. HIV coinfections were detected in 36% (337/947) of persons tested. Diabetes (8/1105), chronic lung disease (15/1105), and terminal complement deficiency (10/1105) were each present in 1% of the patients. Of those over 18 years of age, 10% (32/310) were current smokers and 7% (23/310) reported alcohol dependency (Table 1). None of the patients reported previous meningococcal vaccine exposure. There were 9 persons with recurrent IMD during the time period: 1 child, with complement deficiency, survived 3 episodes of IMD.

Invasive Meningococcal Disease Spatial-Temporal Clusters by Serogroups

We identified 8 significant IMD clusters (1 MenA, 2 MenB, 2 MenC, 1 MenW, and 2 MenY clusters), involving 45%

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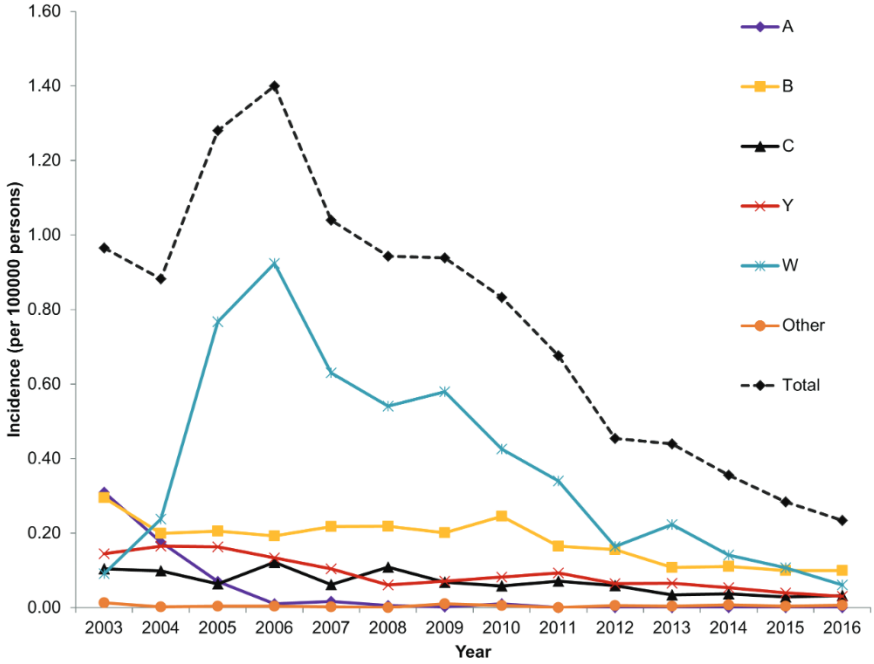

Figure 2. Estimated incidence of invasive meningococcal disease by serogroup and year, in South Africa, from 2003–2016 (N = 5249). Serogroup data were imputed for 1332 cases. The "Other" serogroups included 12 X, 4 Z, and 15 non groupable isolates. Significant increases in disease incidence were seen with serogroup W between 2003 and 2006 ($P < .001$), followed by significant decreases until 2016 ($P < .001$). All other serogroups (except Other) showed significant decreases in disease incidence over the 14 years ($P < .001$). The "Total" group includes all of South Africa.

(1450/3256) of the cases. All clusters extended over at least 12 months, with 5 clusters lasting over 5 years. Geographical-temporal overlapping occurred: 2 provinces (Gauteng in 2006–2008 and Western Cape in 2010) experienced clusters with ≥3 serogroups (Figure 3 and Supplementary Figure 1).

The MenA cluster in the Gauteng and Free State provinces (n = 33; 2005–2008) had a within-cluster relative risk of MenA disease of 7.7. The MenB clusters in Gauteng (n = 137; 2007–2011) and Western Cape (n = 174; 2005–2010) had within-cluster relative risks of MenB disease of 2.4 and 8.1 times, respectively. A MenC cluster over the Northern and Western Cape provinces persisted from mid-2006 until the end of 2011 (n = 62), with a within-cluster relative risk of 4.5; another MenC cluster occurred in Gauteng from early 2006 to September 2011 (n = 66), with a relative risk of 2.5. The largest cluster, MenW, occurred in the Gauteng province from 2005–2010 (n = 900), with a within-cluster relative risk of 6.1. We detected 2 distinct MenY clusters: 1 in Free State province (n = 16; 2005–06), with a within-cluster relative risk of 19.7, and the other in the Northern and Western Cape provinces (n = 55; 2010–2015), with a relative risk of 5.7.

Multinomial Analysis

In a multinomial analysis, compared to MenB in the Western Cape, MenC was 7 times more likely to occur in the Eastern Cape (adjusted relative risk ratio [aRRR] 6.7, 95% confidence interval [CI] 1.4–32.8) and MenW was 4 times more likely to occur in Gauteng (aRRR 4.2, 95% CI 2.7–6.8; Table 1). Collectively MenX, MenZ, and MenNG were more likely to occur in older age groups than MenB (aRRR 9.7, 95% CI 1.1–84.5). There was no significant difference between the serogroups for sex, specimen type, antimicrobial susceptibility, or case fatality. However, patients with MenW disease were 3 times more likely to present with severe disease (aRRR 2.7, 95% CI 1.1–6.3) than MenB IMD patients. HIV coinfection was twice as common amongst

Table 2. Average Annual Incidence (Per 100 000 Population) and Relative Risk of Invasive Meningococcal Disease Amongst HIV-infected and -uninfected Persons by Age Category, in South Africa, From 2012–2016

	Invasive Meningococcal Disease Incidence, 2012–2016						Relative Risk (95% CI)	
Age Category	All (95% CI)		HIV-infected (95% CI)		HIV-uninfected (95% CI)			
<15 years	0.68	0.62–0.74	2.28	1.66–3.07	0.64	0.58–0.70	3.6	2.6–4.9
15–49 years	0.23	0.20–0.25	0.65	0.56–0.75	0.13	0.11–0.15	5.2	4.2–6.5
50+ years	0.08	0.06–0.12	0.17	0.07–0.35	0.08	0.05–0.11	2.3	1.0–5.1
All ages	0.34	0.32–0.36	0.7	0.62–0.80	0.29	0.26–0.31	2.5	2.2–2.8

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus.

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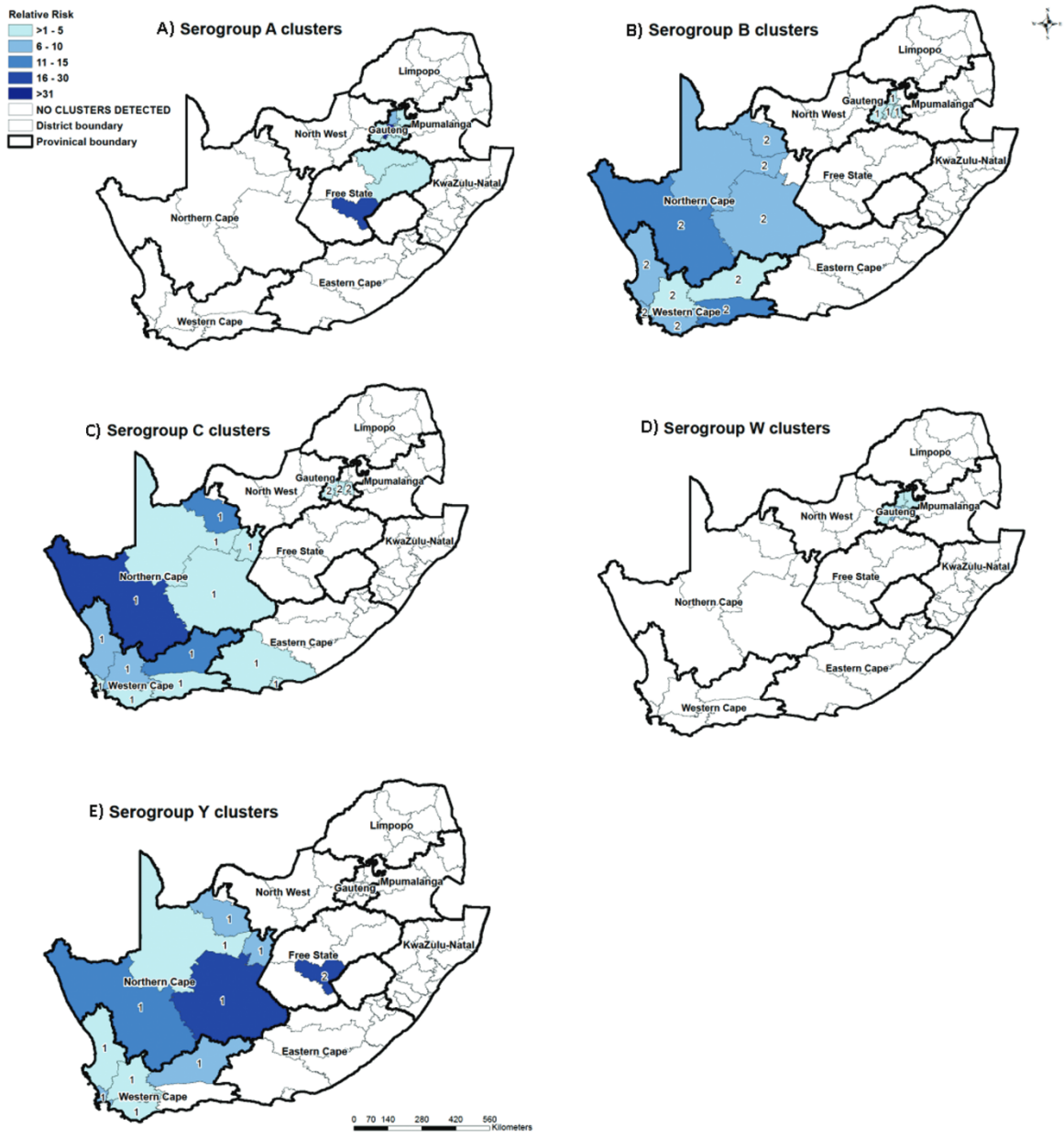

Figure 3. Invasive meningococcal disease clusters, by serogroup, by district, occurring in South Africa, from 2005–2015. (*A*) The serogroup A cluster occurred from January 2005 to September 2008 and had a within-cluster relative risk (RR) of 7.7. (*B*) There were 2 serogroup B clusters: cluster 1 occurred from June 2005 to November 2010 and had a RR of 2.4; and cluster 2 occurred from July 2007 to August 2011 and had a RR of 8.1. (*C*) There were 2 serogroup C clusters: cluster 1 occurred from July 2006 to December 2011 and had a RR of 4.5; and cluster 2 occurred from April 2006 to September 2011 and had a RR of 2.5. (*D*) The serogroup W cluster occurred from April 2005 to September 2010 and had a RR of 6.1. (*E*) There were 2 serogroup Y clusters: cluster 1 occurred from February 2010 to July 2015 and had a RR of 5.7; and cluster 2 occurred from March 2005 to November 2006 and had a RR of 19.1. The district relative risks were calculated by dividing the observed number of cases per district by the number of cases expected per district (as determined by numbers of patients in the cryptococcosis control group).

MenW and MenY cases, as compared to MenB (aRRR W = 1.8, 95% CI 1.1–2.9; aRRR Y = 1.9, 95% CI 1.0–3.4).

DISCUSSION

With trivial meningococcal vaccine use, South Africa displayed typical waxing and waning of IMD during 14 years of surveillance. Overall, IMD decreased by 76%, from a baseline of 1.0 case per 100 000 persons in 2005 to 0.2 cases per 100 000 persons in 2016, despite the 2006 peak of 1.4 cases per 100 000 persons during the height of the MenW emergence. The IMD case fatality rate was 17%; 36% of patients had an HIV coinfection; and infants had the highest incidence of disease. MenW and B caused the majority of IMD. Compared to MenB, patients with MenW disease had more severe illnesses and patients with MenW and Y were more likely to have an HIV coinfection. We identified 8 serogroup-specific,

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spatial-temporal clusters of disease over a 12-year period, indicating an established circulation of 5 different serogroups (A, B, C, W, and Y) within South Africa.

Apart from continued MenC and other IMD epidemics occurring in the meningitis belt, countries such as the United States, United Kingdom, and Finland have all reported a decline in meningococcal disease over the last decade (with similarly low IMD incidence rates to that in South Africa), and not all of this is attributable to increased meningococcal vaccine use [32, 33]. This natural decline is true for all *Neisseria meningitidis* serogroups occurring in South Africa, and particularly for MenW.

Our study demonstrates a natural waxing and waning of the MenW epidemic that peaked in 2006 [20]. Few countries have been able to show the natural evolution of MenW IMD, as many of them have introduced new vaccine campaigns aimed at targeting the emergent pathogen [34–37]. Although clustering around Gauteng province, MenW disease spread across South Africa progressively, becoming the most prominent meningococcal serogroup in all regions and across all age groups. South Africa did not implement widespread meningococcal vaccine use during the MenW emergence, but provided routine chemoprophylaxis to close contacts of cases [10]. MenW disease emerged at the tail end of a MenA epidemic, and MenA disease completely disappeared by 2010 [19]. Following the waning of MenW and all other IMD in South Africa, it remains to be seen whether MenW disease will disappear and whether any established (B, C, or Y) or emergent serogroups will replace it.

The in-hospital mortality rate from IMD (17%) was similar to that seen in the United States (15%), but higher than those in Australia and Canada (8%) [32, 38, 39]. Our study showed that, more recently, IMD occurs 2.5 times more often in HIV-infected than -uninfected individuals. Many countries are beginning to focus on HIV as a risk factor for meningococcal disease, and the United States was the first to implement a targeted vaccination program against IMD in HIV-infected persons to address this increased risk [14]. It is unknown whether meningococcal carriage is increased in HIV-infected persons or whether specific behavior practices might influence the relative risk of IMD in persons living with HIV. Persons living with HIV in South Africa have relatively good access to medical care, with approximately 4 million persons currently accessing antiretrovirals. According to new South African guidelines for vaccinating HIV-infected persons, where possible, meningococcal conjugate vaccine should be considered [17].

We showed 8 geographic clusters, each lasting 2 to 6 years. Clusters of serogroup-specific meningococcal disease that persist over prolonged periods of time warrant molecular investigation. MenA, B, and W clusters, reported in this study and occurring in Gauteng province, appear to overlap in time and location with meningococcal clonal complexes previously reported in South African molecular studies; namely, a MenA cluster of ST1 complex I/II, a MenB cluster of clonal complex ST-32/ET-5, and a MenW cluster of ST-11/ET-37 [19, 20, 40]. Even though the IMD incidence is low, there are multiple serogroups and, possibly, clonal clusters of meningococci vying to establish themselves in South Africa, opening opportunities for extensive transmission amidst an unvaccinated, immunologically-naive population.

The IMD incidence was low, based only on laboratory-confirmed cases. This underestimates the true burden of IMD, as clinically-suspected cases treated empirically and cases of people who died prior to hospitalization would not have been included. However, the surveillance program has been well established since 2005, as evidenced by pneumococcal data collected through the same program [26, 41]. Importantly, clinical specimen collection practices vary across South Africa, with the more rural provinces taking half as many specimens per capita than urban provinces [42, 43]. A study modelling the pneumococcal disease burden in South Africa showed a 170% increase in pneumococcal meningitis cases when correcting for specimen-taking practices by province [26, 42]. The knowledge of the sequelae following IMD in our setting would have been interesting, had these data been available through the surveillance program.

Applying the temporal-spatial analyses of IMD, along with genotyping of the clusters, may assist in finding associations between cases with no obvious epidemiological links in the future. Data from this study can also be used to develop models assessing the cost effectiveness of different vaccination strategies against IMD in South Africa. Other countries have used modelling techniques that show meningococcal vaccine strategies implemented outside of outbreak situations are expensive to initiate and maintain; however, due to epidemiological considerations and, in some cases, public pressure, they have been implemented [44–49]. This paper shows the cyclical nature of serogroup distribution and the seasonality of IMD in South Africa; however, it would be interesting to investigate associations of IMD with environmental conditions or other seasonal infectious diseases [50].

CONCLUSION

The South African surveillance program is well positioned to describe the natural fluctuations of IMD. Even though the IMD incidence in South Africa is low, it remains a public health priority, as over 50% of individuals with IMD have moderate to severe disease, the in-hospital case fatality rate from IMD is almost 20%, and 13% of South African citizens are at higher risk of contracting IMD, due to their underlying HIV infections. As in any country, meningococcal disease prevention is of importance: surveillance and monitoring of new cases needs to continue; the provision of chemoprophylaxis to close contacts is essential; and the meningococcal vaccination of high-risk individuals should be considered.

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Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

This study was conceived and designed by S. M., A. vG., C. C., and S. T. The data collection and laboratory processing were conducted by S. M., V. Q., L. dG., A. vG., M. dP., R. K., A. H., R. L., P. N., G. R., and S. S. The analysis and interpretation were performed by S. M., A. vG., C. C., V. Q., C. vM., and S. T. The drafting and/or critical review of the article were performed by S. M., A. vG., C. C., L. dG., M. dP., R. K., A. H., R. L., S. L., P. N., V. Q., G. R., S. S., S. T., and C. vM.

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Supplement:

Declining incidence of invasive meningococcal disease in South Africa: 2003-2016

Supplementary methods

Assessment of spatial-temporal clusters

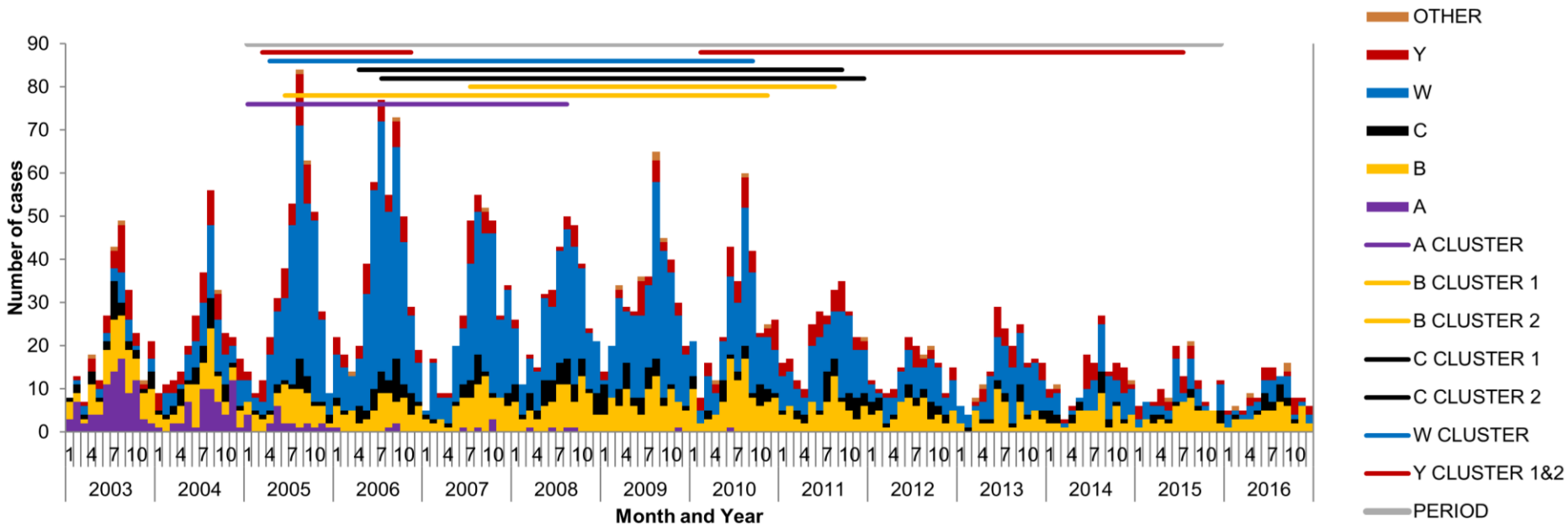
We conducted a space-time analysis to detect IMD serogroup clusters among all IMD cases with available serogroup results from 1 January 2005 to 31 December 2015 (the time period for which corresponding control data were available). We used a Bernoulli model to compare cases of IMD by serogroup A, B, C, W and Y to cryptococcal controls (collected through the same surveillance platform), in order to test whether the likely expected number of cases occurring in an area over time was exceeded.[1 2] The use of cryptococcal controls (mainly cryptococcal meningitis) was done to minimise potential biases introduced by geographic and temporal differences in specimen-taking practices (a lumbar-puncture is necessary for CSF tapping for both organisms), healthcare-seeking behaviour (patients are thought to seek healthcare more readily when suffering from meningitis), increased antiretroviral use (both conditions pose a higher risk amongst HIV-infected persons) and surveillance system improvements (minimal differences in regional clinical laboratory surveillance participation for both pathogens). Cryptococcal disease incidence has remained relatively stable over time, despite increased use of antiretroviral therapy since 2008.[3] For this analysis, numbers of IMD cases were aggregated by month and district. A cluster was defined as an increase in an IMD serogroup occurring in a specific geographic location and time period not exceeding 50%. Cluster location was based on districts within which the patient presented; the centroid of each district polygon was used as a marker of the actual geographic location of the case. A spatial cluster was identified using an elliptical area of search which varied in size, shape and direction. The space-time analysis was conducted using SaTScan version 9.4.3 (http://www.satscan.org/) and the maps were generated using ArcGIS version 9.2 (http://www.esri.com/). We calculated relative risk of IMD by serogroup cluster for each district by dividing the observed number of cases by the expected number of cases for each district. Significance was assessed at $p<0.05$ over 999 replications.

Ethical approval

The secondary data analysis was approved by the University of Witwatersrand, Health Research Ethics Committee (Human) (M170951). Permission to conduct laboratory-based and enhanced surveillance in South Africa through the GERMS-SA surveillance programme was obtained from the Health Research Ethics Committee (Human), University of Witwatersrand (M02-10-42/M081117/M140159); the National Institute for Communicable Diseases Research Committee (M060449); the South African Department of Health (Reference H2/12/8); as well as site specific health research ethics committees at enhanced surveillance sites.

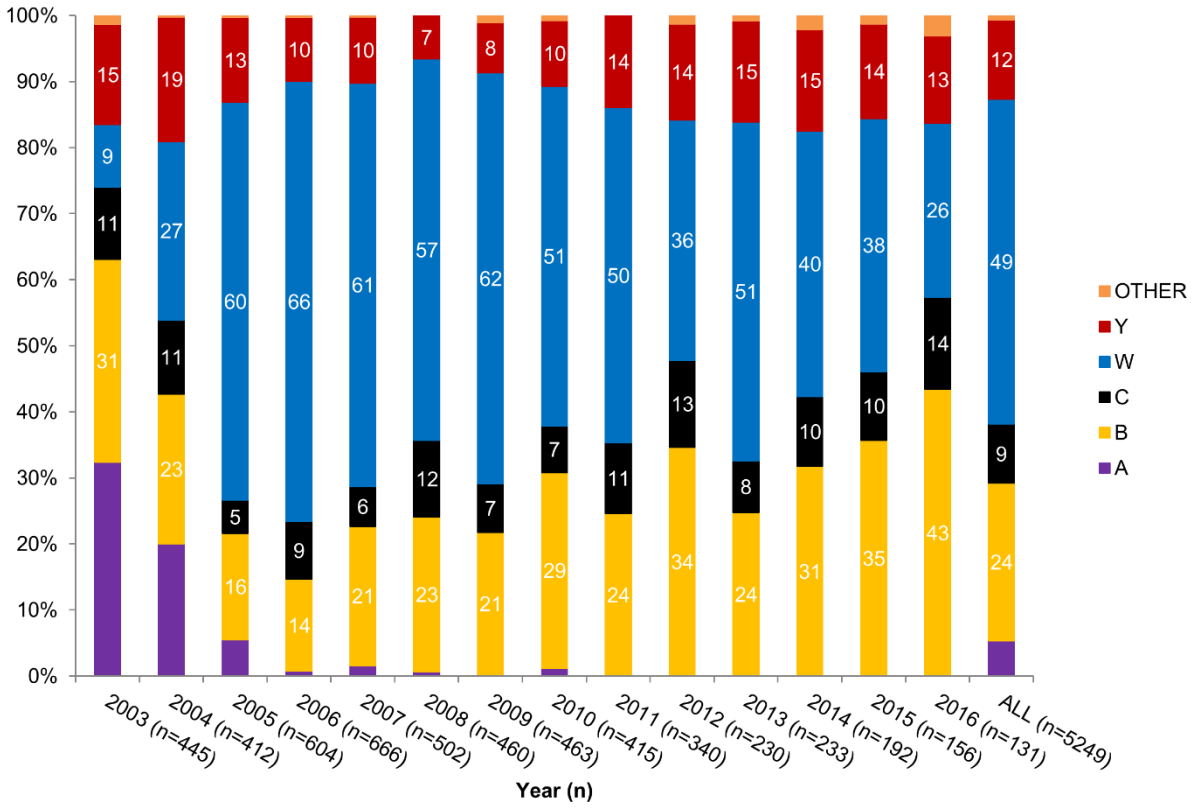
Supplementary Figures

Supplementary figure 1: Seasonality and temporal clusters of meningococcal disease by serogroup in South Africa, 2003-2016, n=3917

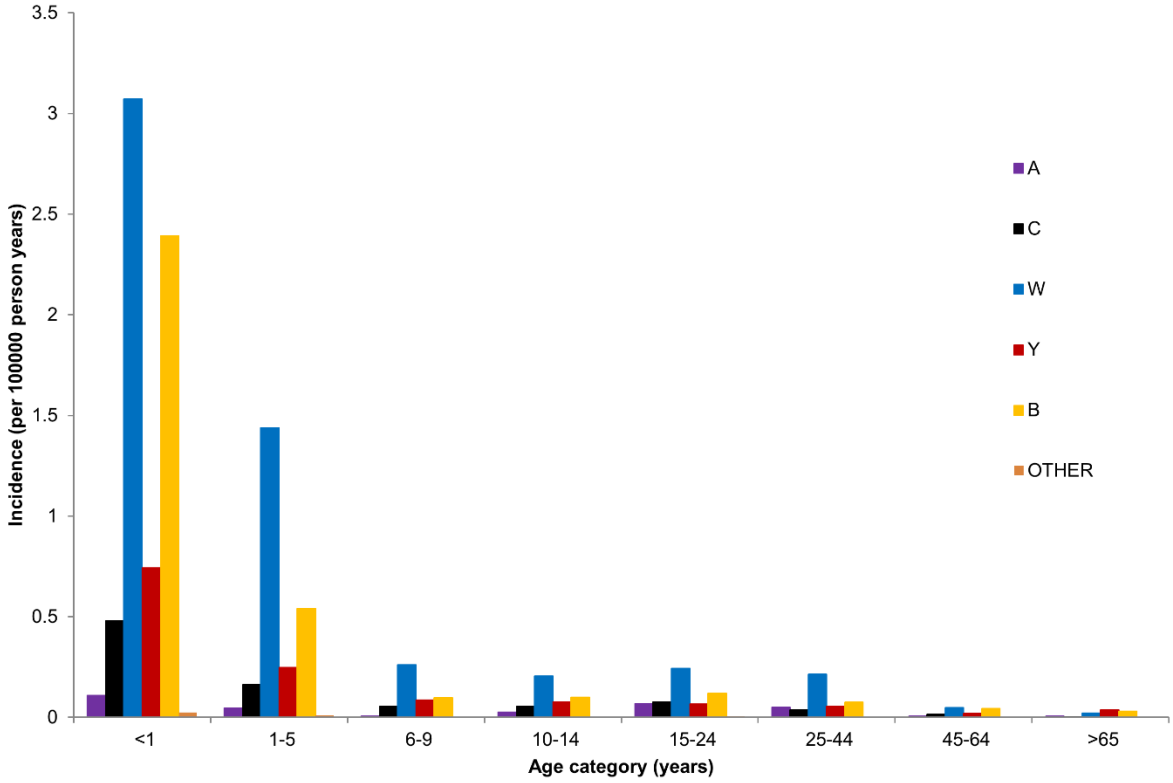


Cluster analysis done from 2005-2015 (n=3256)

Supplementary figure 2: Proportion of invasive meningococcal disease episodes by serogroup and year, South Africa, 2003-2016 (n=5249)



Supplementary figure 3: Estimated incidence of invasive meningococcal disease by serogroup and age category per 100000 person years, South Africa, 2003-2016 (n=4999, 250 with unknown age)



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Paper III

Meiring S, Cohen C, de Gouveia L, du Plessis M, Quan V, Kleynhans J, Menezes C, Reubenson G, Dawood H, Nchabeleng M, Said M, Mvelase N, Mahabeer P, Chomba R, Lekalakala R, Nana T, Chibabhai V, Black M, von Gottberg A, for GERMS-SA. Case-fatality and sequelae following bacterial meningitis in South Africa, 2016 through 2020. Int J Infect Dis 2022 August; 122:1056–66.

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Case-fatality and sequelae following acute bacterial meningitis in South Africa, 2016 through 2020

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ABSTRACT

Objectives: Providing country-specific estimates of case fatality and sequelae from bacterial meningitis (BM) is important to evaluate and monitor progress toward the World Health Organization's roadmap to "defeating meningitis by 2030".

Methods: From 2016-2020, GERMS-SA conducted enhanced surveillance at 26 hospitals across South Africa. Episodes of laboratory-confirmed BM due to *Streptococcus pneumoniae, Haemophilus influenzae*, and *Neisseria meningitidis* were included. Risk factors for in-hospital death and sequelae at hospital discharge among survivors were analyzed.

Results: Of 12,717 invasive bacterial infections reported nationally, 39% (4980) were from enhanced surveillance sites, including 4159 pneumococcal, 640 *H. influenzae*, and 181 meningococcal infections. BM accounted for 32% (1319/4159) of pneumococcal, 21% (136/640) of *H. influenzae*, and 83% (151/181) of meningococcal invasive diseases. Clinical data were available for 91% (1455/1606) of BM: 26% (376/1455)

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were aged <5 years, 50% (726/1455) were female, and 62% (723/1171) with known HIV results, were HIV-infected. In-hospital case fatality was 37% (534/1455), and 24% (222/921) of survivors had adverse sequelae. Risk factors for death included altered mental status, HIV infection, and comorbidities. Risk factors for adverse sequelae included altered mental status and antimicrobial nonsusceptibility.

Conclusion: BM in South Africa has a high case fatality, and adverse sequelae frequently occur among survivors. Those with comorbidities (including HIV) are at the highest risk.

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Introduction

Despite access to antimicrobial agents and conjugate vaccines, bacterial meningitis (BM) continues to be an important disease. In 2019, an estimated 2.5 million episodes of BM occurred worldwide, resulting in approximately 236,000 deaths; among BM survivors, approximately one-fifth are estimated to suffer sequelae (Edmond *et al.*, 2010; Schiess *et al.*, 2021). The World Health Organization has launched a roadmap for defeating meningitis by 2030 to eliminate epidemics of BM, reduce cases and deaths from vaccine-preventable causes, and reduce disability and improve the quality of life among survivors (The World Health Organization, 2020). Providing accurate, country-specific estimates of mortality and sequelae from BM in low- and middle-income countries is important to evaluate the current situation and monitor progress.

Streptococcus pneumoniae and *Neisseria meningitidis* (both vaccine-preventable) are the predominant bacteria causing acute meningitis in all regions of the world (Oordt-Speets *et al.*, 2018). In Africa, pneumococcus causes 41% of BM in children and 75% in adults. In South African adults, largely because of high HIV prevalence, *Cryptococcus neoformans* and *Mycobacterium tuberculosis* are responsible for most cases of nonviral meningitis; however, *S. pneumoniae, N. meningitidis, Escherichia coli*, and *Haemophilus influenzae* remain important causes of BM (Britz *et al.*, 2016). The defeating meningitis by 2030 road map aims to target the four most common bacterial causes: *S. pneumoniae, N. meningitidis, H. influenzae*, and *S. agalactiae*. The former three will be targeted through the expansion of vaccination programs, through improved access to rapid diagnostics, and improved treatment of BM and its sequelae. *S. agalactiae* vaccines are being developed for the immunization of pregnant women to protect their infants against invasive diseases (Dangor *et al.*, 2021).

Global mortality from BM is approximately 10%; however, this varies by causative organism, age, and region (Nakamura *et al.*, 2021). Mortality from pneumococcal meningitis ranges from 20% in high-income countries to 51% in low-income countries, whereas meningococcal case-fatality ratios (CFRs) range from 3% in high- to 10% in low-income countries (Brouwer *et al.*, 2010; Van De Beek *et al.*, 2016a). Mortality from *H. influenzae* meningitis is approximately 25% among children in Africa (Ramakrishnan *et al.*, 2009).

Among BM survivors, the risk of developing at least one disabling complication is 20% (Edmond *et al.*, 2010). The risk is more than twice as high in low-income countries (25% in Africa and 22% in Asia) as in high-income countries (9% in Europe) and higher in children aged less than 5 years compared with adults (Edmond *et al.*, 2010). Sequelae are often neurological: most frequently hearing loss, cognitive or motor deficits, seizures, visual impairment, hydrocephalus, hypotonia, or behavioral/learning problems (Lucas *et al.*, 2016). Sequelae are most common after pneumococcal meningitis, with similar proportions of patients affected in high- (32%) and low-income (25%) countries (Jit, 2010; Ramakrishnan *et al.*, 2009). Risk factors for developing sequelae include altered level of consciousness at presentation and age <12 months, but few studies quantify the effect of comorbidities on the outcome (Namani *et al.*, 2013a; Zainel *et al.*, 2021). BM is ranked sixth in the causes of disability-adjusted life years for children aged less than 10 years (Abbafati *et al.*, 2020).

Data on sequelae are lacking from African countries outside the meningitis belt, including South Africa. Considering the large disparity in BM-related mortality and complication rates between low- and high-income countries, having country-specific data is important. This study aimed to describe the CFRs and risk factors for death, as well as the types of sequelae following BM in a middle-income country with high HIV prevalence. These data will potentially guide policy regarding resource allocation as we strive to defeat meningitis by 2030.

Methods

Data sources: GERMS-SA national and enhanced laboratory-based surveillance

Laboratory-confirmed invasive pneumococcal, *H. influenzae*, and meningococcal disease episodes were reported to GERMS-SA, an established prospective, national, laboratory-based surveillance program coordinated through the National Institute for Communicable Diseases (NICD), Johannesburg, South Africa (GERMS-SA, 2008)

Over 200 public and private sector laboratories submit isolates to the NICD. Within the network, 26 enhanced surveillance hospital sites situated in all nine provinces have decidated nurses onsite to collect demographic and clinical data relating to the laboratory-confirmed disease episode. They use standardized case investigation forms to collect data on age, sex, HIV status, underlying illnesses, antimicrobial therapy received, severity of illness, in-hospital outcome, presence of sequelae at discharge, type of sequelae, and outcome 2 months after discharge. In previous studies, the basic demographics of patients at GERMS-SA enhanced and nonenhanced surveillance sites with laboratory-confirmed disease have been similar (Meiring *et al.*, 2016; Müller *et al.*, 2022).

Case definition

This analysis focused on laboratory-confirmed meningitis episodes among patients of all ages, from January 2016 to December 2020, occurring at the 26 enhanced surveillance hospitals in South Africa. Laboratory-confirmed meningitis included identification of *S. pneumoniae, H. influenzae*, or *N. meningitidis* through culture or polymerase chain reaction (PCR) of cerebrospinal fluid or any usually sterile specimen (provided that a clinician diagnosis of meningitis had been made). Antimicrobial susceptibility and serotype/serogroup classification were available for viable isolates, and serotype/serogroup classification for culture-negative PCR-positive specimens sent to the NICD reference laboratory as part of the surveillance protocol.

Defining the variables

The severity of illness was determined by the Pitt bacteremia score based on systolic blood pressure, temperature, mental status, and the need for mechanical ventilation or cardiac resuscitation (Pitt bacteremia scores: 0 for mild, 1-3 moderate, or 4-12 severe illness) (Al-Hasan and Baddour, 2020). Among persons living with HIV (PLHIV), children aged less than 5 years with a cluster of differentiation 4 (CD4) T lymphocyte count of less than 15% of total lymphocyte count were analyzed in the CD4 T lymphocyte count group of <200 cells/µl, regardless of their CD4 count. Sequelae were categorized as minor (neurological fallout manifesting as hypotonia, necrotic skin lesions, digit amputation, or unilateral hearing loss) or major (hydrocephalus, visual impairment, seizures, neurological fallout manifesting as a motor deficit, limb amputation, or bilateral hearing loss) (Edmond *et al.*, 2010).

Appropriate empiric antibiotic therapy for acute meningitis was defined as receiving intravenous third-generation cephalosporin (cefotaxime or ceftriaxone) within 24 hours of specimen collection (Boyles *et al.*, 2013). Directed antibiotic therapy for acute meningitis was deemed appropriate if patients received (i) a third-generation cephalosporin or (ii) benzyl penicillin or ampicillin, provided that the organism was susceptible to penicillin or ampicillin or (iii) vancomycin plus a third-generation cephalosporin for pneumococcal meningitis if the penicillin minimum inhibitory concentration (MIC) was >0.06 µg/ml or ceftriaxone MIC was >0.5 µg/ml (Boyles *et al.*, 2013). Pneumococcal and meningococcal isolates were considered resistant if penicillin MICs were >0.06 µg/ml and if *H. influenzae* isolate ampicillin MICs were >1.0 µg/ml by broth microdilution or ETEST® (bioMérieux), as relevant and interpreted using the Clinical and Laboratory Standards Institute meningitis breakpoints (Clinical and Laboratory Standards Institute, 2020). Organisms were defined as vaccine serotype/group if they were one of the serotypes contained in the 13-valent pneumococcal conjugate vaccines, serogroup A, C, Y, or W for meningococcus or *H. influenzae* type b.

Statistical analysis

Statistical analysis was performed using STATA version 14 (StataCorp Inc., College Station, TX, USA), and *P*-values <0.05 were considered significant. Medians with interquartile ranges (IQR) were calculated, and the Mann-Whitney/rank-sum test was used for nonparametric noncategorical variables. Univariate analysis using Fisher's exact/Mantel-Haenszel/chi-squared test for categorical variables was performed using death or the presence of sequelae as an outcome variable. *P*-values <0.2 on univariate analysis were included in all multivariable logistic regression models, and non-significant variables (*P*-value >0.05) were dropped using step-wise manual backward elimination.

Human subjects review

Ethics approval for the GERMS-SA surveillance program was received from the University of the Witwatersrand Human Research Ethics Committee (Medical) (Reference M140159). Written informed consent was obtained from all participants or parents/legal guardians of underaged participants who were interviewed in the enhanced surveillance program.

Results

From 2016 through 2020, 12,717 invasive bacterial infections were reported nationally, of which 4980 (39%) were from enhanced surveillance sites (including 4159 pneumococcal, 640 *H. influenzae*, and 181 meningococcal infections) (Figure 1). A total of 32% (1606/4980) of the enhanced surveillance site cases were laboratory-confirmed meningitis episodes. Laboratory-confirmed meningitis made up 32% (1319/4159) of pneumococcal infections, 21% (136/640) of *H. influenzae* infections, and 83% (151/181) of meningococcal infections. Clinical data were available for 91% (1455/1606) of meningitis cases, of which 26% (376/1455) were children aged <5 years, 50% (726/1455) were female, and 62% (723/1171), with known HIV results, were PLHIV (Table 1 and 2, Figure 2a-c). A total of 23% (203/879) of BM organisms available for antimicrobial susceptibility testing were nonsusceptible to penicillin/ampicillin. In-hospital CFR for all BM cases was 37% (534/1455), with a median time to death of 2 days after admission (IQR 1-6 days). The median hospital stay for survivors was 13 days (IQR 9-17 days), and 24% (222/921) of survivors had sequelae at discharge. (Table 1)

Mortality and risk factors for death among BM episodes

On multivariable analysis, PLHIV (adjusted odds ratio [aOR] 2.5, 95% confidence interval [CI] 1.8-3.5, *P* <0.001) and individuals with underlying illness (aOR 3.0, 95% CI 2.1-4.2, *P* <0.001) were two to three times more likely to die than those without comorbidities. In addition, those with a Glasgow coma score (GCS) <15 were seven times more likely to die than those with a GCS of 15 (95% CI 5.0-9.5, *P* <0.001). Those receiving directed antibiotic therapy were 45% less likely to die than those not receiving directed therapy (95% CI 0.40-0.76, *P* <0.001) (Table 2, Supplementary Figure 1).

Among pneumococcal meningitis cases, in-hospital case fatality was 41%, with a median time to death of 3 days (IQR 1-6) (Table 1). On multivariable analysis of risk factors for death, PLHIV and those with unknown HIV status were more likely to die than individuals without HIV (PLHIV 42% died, aOR 2.4, 95% CI 1.6-3.5, *P* <0.001; HIV-unknown 58% died, aOR 4.2, 95% CI 2.6-6.9, *P* <0.001) (Figure 3, Supplementary Table S1). Those with an underlying illness other than HIV were almost three times more likely to die (aOR 2.8, 95% CI 1.9-4.0, *P* <0.001) than those with no underlying illness, and those with altered mental status on admission were six times more likely to die than those who were alert (aOR 6.3, 95% CI 4.4-9.0, *P* <0.001). Receiving directed antibiotic therapy was protective against death (aOR 0.63, 95% CI 0.45-0.88, *P* = 0.008). Although more adults died from pneumococcal meningitis than children, when adjusting for HIV infection, this difference was no longer significant. There was no difference in mortality by sex or by pneumococcal conjugate vaccine serotype (Figure 3, Supplementary Table S1).

The in-hospital case fatality rate from meningococcal meningitis was 14%, with most deaths occurring on day one following hospital admission (median 1 day, IQR 0-8 days) (Table 1). Factors associated with in-hospital death on multivariable analysis included PLHIV or unknown HIV status (PLHIV 24% died, aOR 7.4, 95% CI 1.0-54.0, *P* = 0.048; HIV-unknown 35% died, aOR 15.8, 95% CI 1.9-131.2, *P* = 0.011; vs HIV-uninfected 5%), having an underlying illness (55% died vs 10% without underlying illness, aOR 26.5, 95% CI 1.9-363, *P* = 0.014), and having altered mental status on admission (27% died vs 3% with GCS 15, aOR 20.9, 95% CI 2.9-151.7, *P* = 0.003) (Figure 3, Supplementary Table S2). Receipt of directed antimicrobial therapy was protective against death (11% vs 33% with nondirected therapy, aOR 0.04, 95% CI 0.00-0.37, *P* = 0.005).

Among persons with *H. influenzae* meningitis, in-hospital case fatality was 24%, with a median time to death of 2 days (IQR 1-7) (Table 1). On multivariable analysis, when controlling for HIV status, underlying medical conditions, and receiving directed antibiotic therapy: altered mental status was the only significant risk factor for death (45% with GCS <15 died vs 10% with GCS 15, aOR 7.3, 95% CI 2.1-25.5, *P* = 0.002) (Figure 4, Supplementary Table

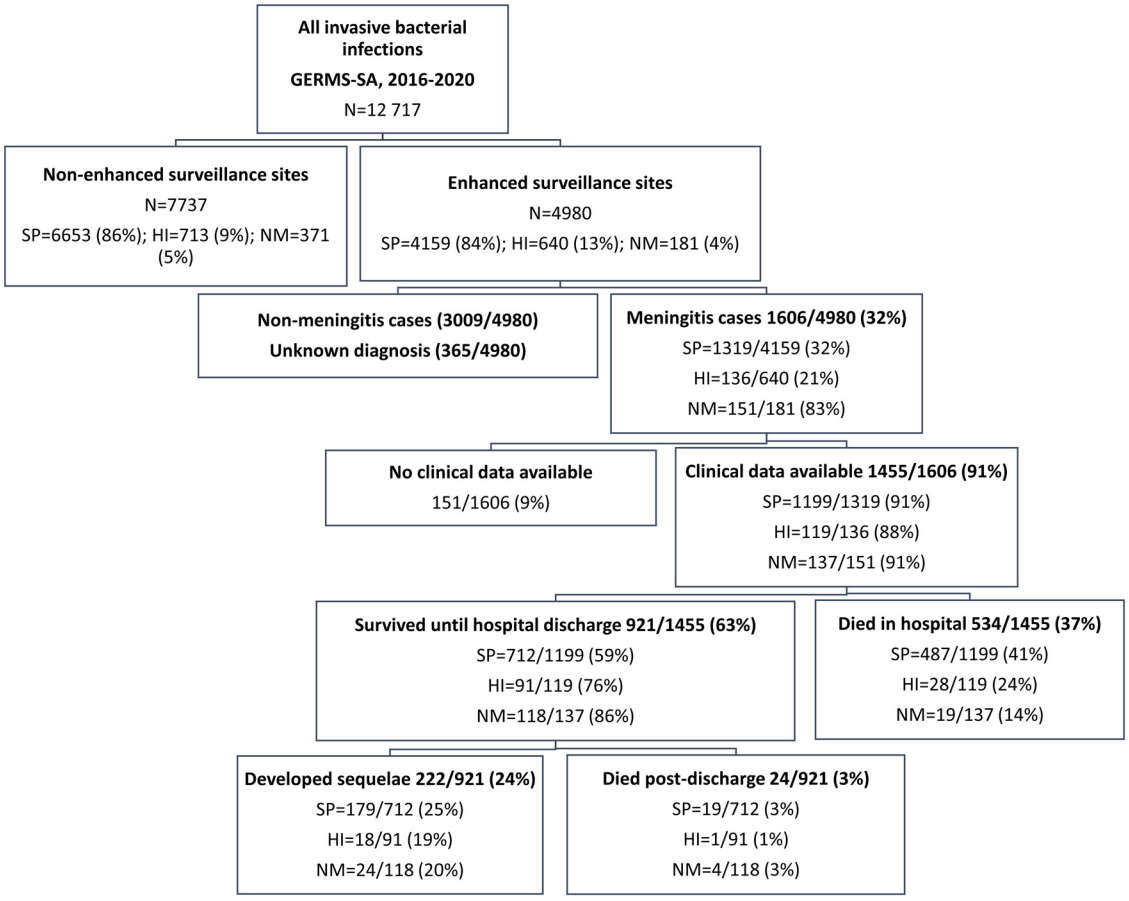

Figure 1. Flow diagram of meningitis and nonmeningitis invasive bacterial infections reported to GERMS-SA enhanced surveillance sites, South Africa, 2016-2020. Abbreviations: HI: *Haemophilus influenzae*; NM: *Neisseria meningitidis;* SP: *Streptococcus pneumoniae.*

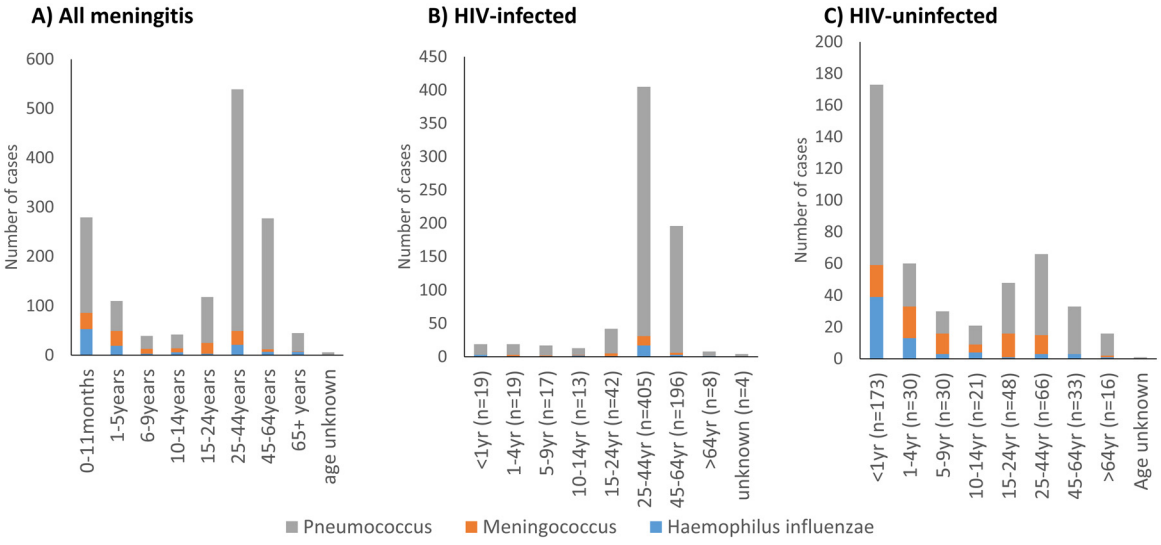

Figure 2. (a-c) Age distribution of bacterial meningitis cases reported to GERMS-SA enhanced surveillance sites, South Africa, 2016-2020 (n = 1455).

S3). There was no difference in mortality by age category, sex, or serotype.

Sequelae and risk factors for developing sequelae among survivors of BM

A total of 63% (921/1455) of individuals with BM survived their initial hospital stay, with a median admission duration of 13 days (IQR 9-17). Of these patients, 24% (222/921) were discharged with sequelae, of which 96% (222/921) were major. New-onset seizures (11/921, 11%), neurological fallout (78/921, 8%), and deafness (52/921, 6%) were the most common sequelae (Table 1). Of those with available data, a further 5% (24/518) died within 2 months of hospital discharge (19/400, 5% post pneumococcal meningitis; 1/46, 2% post *H. influenzae* meningitis; and 4/72, 6% post meningococcal meningitis) (Figure 1).

Table 1
Case fatality and sequelae following laboratory-confirmed bacterial meningitis, South Africa, 2016-2020 (n=1455).[a]

	ALL organisms		*Streptococcus pneumonaie*		*Neisseria meningitidis*		*Haemophilus influenzae*	
	n	%	n	%	n	%	n	%
	1455	**100**	**1199**	**82**	**137**	**9**	**119**	**8**
Age category								
<1 year	279/1455	19	193/1199	16	33/137	24	53/119	45
1-4 years	95/1455	7	51/1199	4	26/137	19	18/119	15
5-9 years	54/1455	4	36/1199	3	14/137	10	4/119	3
10-14 years	42/1455	3	28/1199	2	8/137	6	6/119	5
15-24 years	118/1455	8	93/1199	8	22/137	16	3/119	3
25-44 years	539/1455	37	490/1199	41	28/137	20	21/119	18
45-64 years	277/1455	19	265/1199	22	5/137	4	7/119	6
>64 years	45/1455	3	37/1199	3	1/137	1	7/119	6
Unknown	6/1455	0	6/1199	1	0/137	0	0/119	0
In-hospital case fatality	534/1455	37	487/1199	41	19/137	14	28/119	24
Median days admitted (IQR)[b] N=1454	10	3-15	10	3-15	9	6-12	11	6-18
Median days to death (IQR) N=534	2	1-6	3	1-6	1	0-8	2	1-7
Median days to discharge (IQR) N=920	13	9-17	13	10-18	9	7-12	13	10-18
Presence of sequelae at discharge	222/921	24	179/712	25	24/118	20	19/91	21
Category of sequelae								
Major	212/222	96	170/179	95	23/24	96	19/19	100
Minor	10/222	5	9/179	5	1/24	4	0/19	0
Specific types of sequelae								
Deafness	52/921	6	42/712	6	3/118	3	7/91	8
Visual loss	16/921	2	15/712	2	1/118	1	0/91	0
Neurological fallout	78/921	8	70/712	10	5/118	4	3/91	3
Necrotic skin lesions	29/921	3	18/712	3	11/118	9	0/91	0
Hydrocephalus	25/921	3	18/712	3	2/118	2	5/91	5
Seizures	98/921	11	81/712	11	10/118	8	7/91	8
Amputation	1/921	0	0/712	0	1/118	1	0/91	0
Number of sequelae								
None	699/921	76	533/712	75	94/118	80	72/91	79
One	160/921	17	124/712	17	19/118	16	17/91	19
Two	49/921	5	46/712	6	2/118	2	1/91	1
Three or more	13/921	1	9/712	1	3/118	3	1/91	1

[a] Major sequelae include: hydrocephalus, visual impairment, seizures, neurological fallout (motor deficit), limb amputation, or bilateral hearing loss; Minor sequelae include: neurological fallout (hypotonia), necrotic skin lesions, digit amputation, or unilateral hearing loss
[b] IQR in daysIQR: Interquartile range

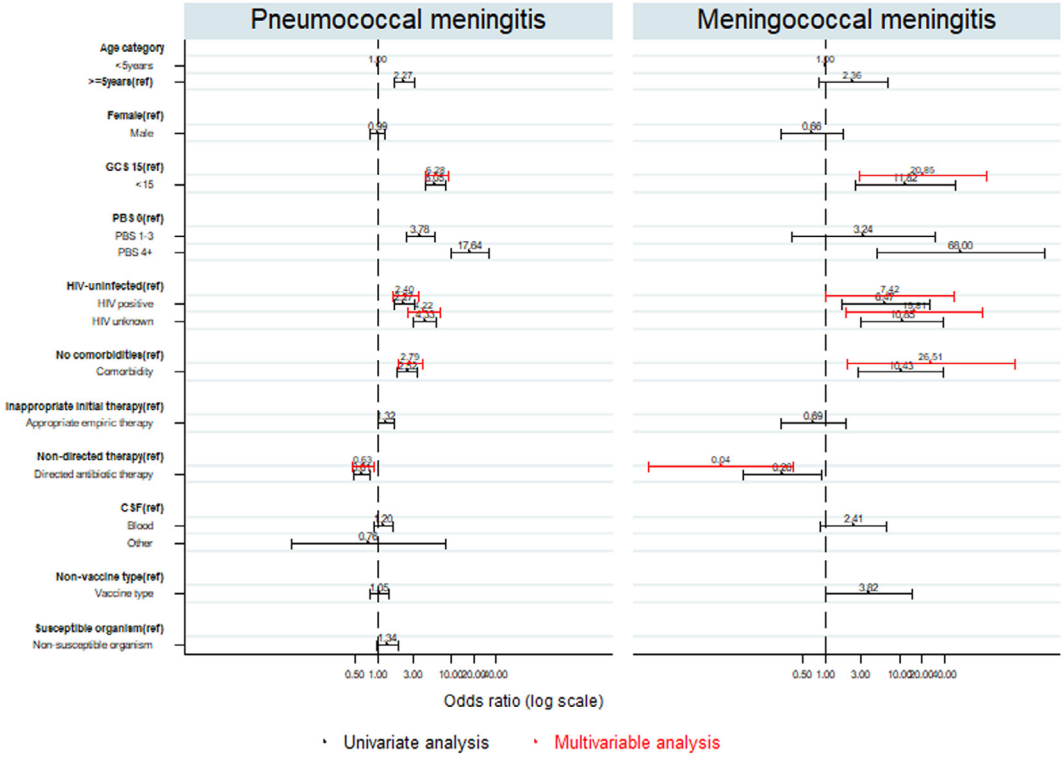

Figure 3. Forest plot: univariate and multivariable analysis of risk factors for mortality following pneumococcal and meningococcal meningitis, 2016-2020. Abbreviations: GCS: Glasgow coma score; PBS: Pitt bacteremia score for severity of illness.

Table 2
Risk factors for death following laboratory-confirmed bacterial meningitis in South Africa, 2016-2020, n = 1455.

		In-hospital outcome				Univariate analysis			Multivariable analysis		
		Alive	%	Died	%	Odds ratio	95% confidence intervals	*P*-value	Odds ratio	95% confidence intervals	*P*-value
	1455	921	63	534	37						
Sex											
Female	726/1455	457/726	63	269/726	37	Reference					
Male	729/1455	464/729	64	265/729	36	0.97	0.78-1.20	0.781			
Age category											
Less than 5 years	376/1455	290/376	77	86/376	23	Reference					
5 years and older	1079/1455	631/1079	58	448/1079	42	2.39	1.83-3.13	<0.001			
HIV											
Negative	448/1455	358/448	80	90/448	20	Reference			Reference		
Positive	723/1455	433/723	60	290/723	40	2.66	2.02-3.51	<0.001	2.49	1.77-3.51	<0.001
Not done	284/1455	130/284	46	154/284	54	4.71	3.39-6.54	<0.001	4.02	2.59-6.22	<0.001
HIV category with CD4 count value											
HIV negative	448/1033	358/448	80	90/448	20	Reference					
HIV positive CD4 ≥200 cells/µl	212/1033	154/212	73	58/212	27	1.50	1.02-2.19	0.037			
HIV positive CD4 <200 cells/µl[a]	373/1033	222/373	60	151/373	40	2.71	1.98-3.69	<0.001			
GCS category											
GCS of 15 (alert)	483/1196	422/483	87	61/483	13	Reference			Reference		
GCS <15	713/1196	356/713	50	357/713	50	6.94	5.11-9.42	<0.001	6.88	4.96-9.54	<0.001
Pitt bacteremia score on admission											
0 (mild)	247/1032	217/247	88	30/247	12	Reference					
1-3 (moderate)	667/1032	412/667	62	255/667	38	4.48	2.96-6.76	<0.001			
4-12 (severe)	118/1032	29/118	25	89/118	75	22.2	12.59-39.13	<0.001			
Underlying illness[b]											
No	1216/1455	820/1216	67	396/1216	33	Reference			Reference		
Yes	239/1455	101/239	42	138/239	58	2.83	2.13-3.76	<0.001	2.95	2.09-4.17	<0.001
Specimen type											
Cerebrospinal fluid	1147/1455	736/1147	64	411/1147	36	Reference					
Blood	304/1455	182/304	60	122/304	40	1.2	0.93-1.56	0.167			
Other	4/1455	3/4	75	1/4	25	0.6	0.06-5.76	0.655			
Organism											
Haemophilus influenzae	119/1455	91/119	76	28/119	24	Reference					
Neisseria meningitidis	137/1455	118/137	86	19/137	14	0.52	0.27-1.0	0.049			
Streptococcus pneumoniae	1199/1455	712/1199	59	487/1199	41	2.22	1.43-3.45	<0.001			
Vaccine serotype/-group[c]											
No	820/1151	511/820	62	309/820	38	Reference					
Yes	331/1151	214/331	65	117/331	35	0.9	0.69-1.18	0.458			
Resistant organism[d]											
No	676/879	413/676	61	263/676	39	Reference					
Yes	203/879	110/203	54	93/203	46	1.33	0.97-1.82	0.079			
Appropriate empiric therapy initiated within 24 hrs[e]											
No	488/1455	323/488	66	165/488	34	Reference					
Yes	967/1455	598/967	62	369/967	38	1.21	0.96-1.52	0.104			
Directed therapy initiated[f]											
No	353/1455	181/353	51	172/353	49	Reference			Reference		
Yes	1102/1455	740/1102	67	362/1102	33	0.51	0.40-0.66	<0.001	0.55	0.40-0.76	<0.001

[a] HIV-infected children aged <5 years and with CD4 T lymphocyte percentage <15% were included in the group "HIV positive CD4 <200 cells/µl" irrespective of their CD4 T lymphocyte count.
[b] Underlying illness: chronic lung, renal, heart or liver disease; previous cerebrovascular accident; previous head injury; connective tissue disease; asplenia (functional/anatomical); previous malignancy; solid organ transplant; diabetes; chromosomal abnormality; complement deficiency; or current immunosuppressive therapy.
[c] Vaccine serotype/group: pneumococcal serotype present in 13-valent pneumococcal conjugate vaccine or meningococcal serogroup present in meningococcal quadrivalent conjugate vaccine (ACWY) or *Haemophilus influenzae* type b serotype.
[d] Resistant organism: organism was not susceptible to penicillin or ampicillin.
[e] Appropriate empiric therapy initiated within 24 hours: intravenous third-generation cephalosporin.
[f] Directed antibiotic therapy initiated: antibiotics given which are appropriate to susceptibility profile of the organism.GCS: Glasgow coma scale

On multivariable analysis, when adjusting for HIV, altered mental status (aOR 3.21, 95% CI1.97-5.23, P <0.001) and having a resistant organism (aOR 1.91, 95% CI 1.12-3.26, P = 0.017) were factors contributing to increased risk of developing sequelae (Table 3, Supplementary Figure 2).

Among pneumococcal meningitis survivors discharged from the hospital, the median admission duration was 13 days (IQR 10-18), and 25% (179/712) reported at least one sequela upon discharge from the hospital (8% of survivors had between two and three new sequelae) (Table 1). New-onset seizures (11%, 81/712), neurological fallout (10%, 70/712), and deafness (6%, 42/712) were the most commonly occurring sequelae following pneumococcal meningitis. Those with altered mental status on admission (GCS <15) were three times more likely to report sequelae (aOR 2.55, 95% CI 1.52-4.26, P < 0.001) and twice as likely if their isolate was resistant to first-line antibiotics (aOR 2.06, 95% CI 1.18-3.62, P <0.011), than those with GCS of 15 and/or a susceptible organism (Figure 5, Supplementary Table S4).

Individuals surviving until hospital discharge after meningococcal meningitis spent a median of 9 days (IQR 7-12) in the hospital (Table 1). A total of 20% (24/118) were discharged with sequelae, including 5% (5/118) with more than one sequela. Necrotic skin lesions (9%, 11/118), new-onset seizures (8%, 10/118), and neurological fallout (4%, 5/118) were the most common types of sequelae after meningococcal meningitis. There were no significant differences in the presence of sequelae among different age categories, underlying illnesses, meningococcal serogroup, or type of antimicrobial used for treatment (Figure 5, Supplementary Table

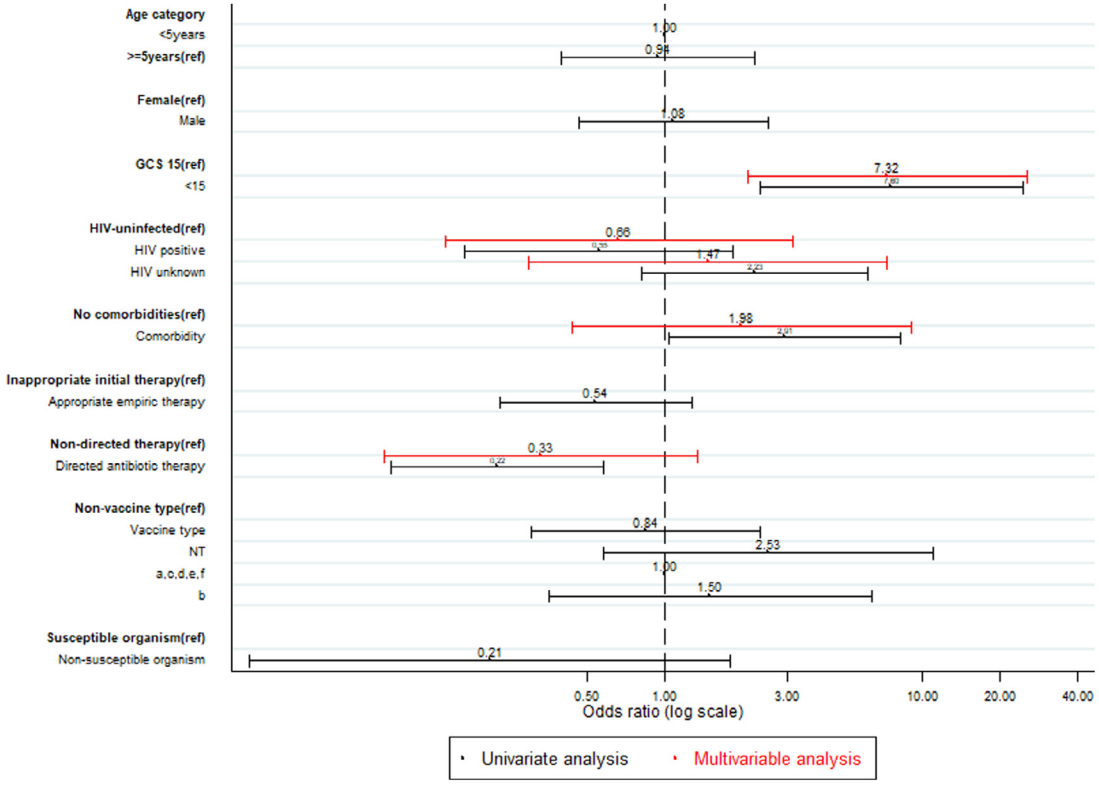

Figure 4. Forest plot: a univariate and multivariable analysis of risk factors for mortality following *Haemophilus influenzae* meningitis, 2016-2020.
Abbreviations: GCS: Glasgow coma score; PBS: Pitt bacteremia score for severity of illness.

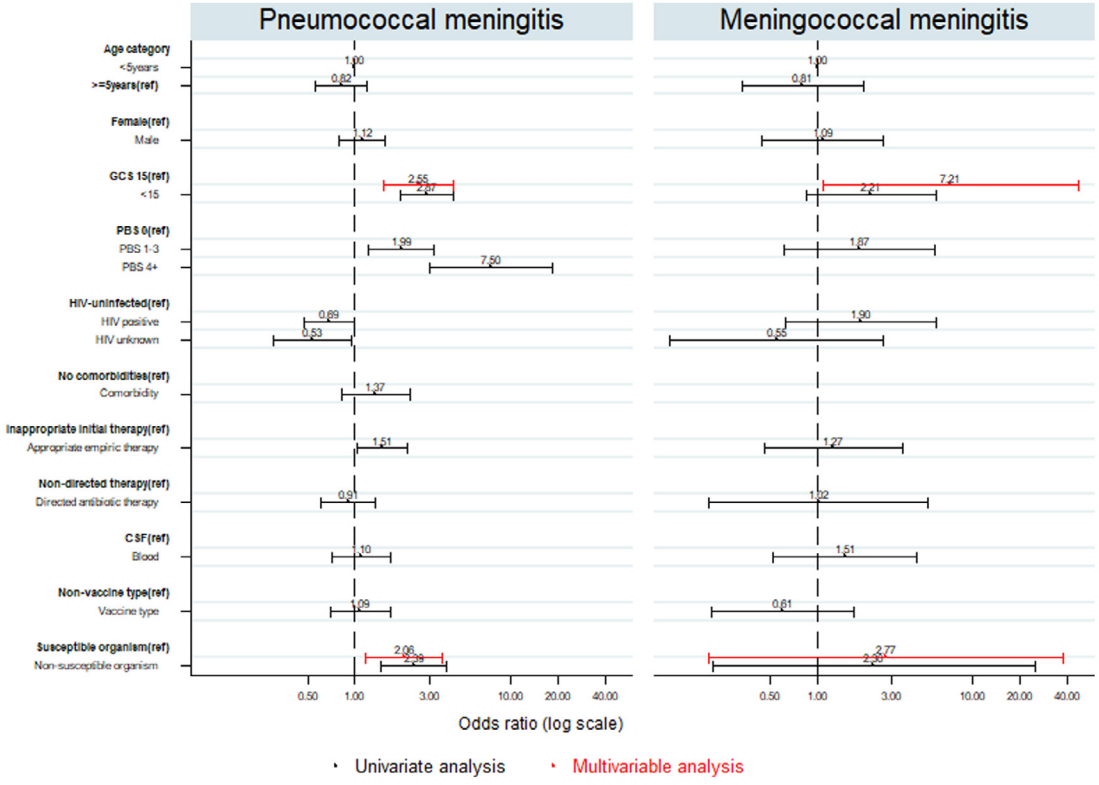

Figure 5. Forest plot: a univariate and multivariable analysis of risk factors for developing sequelae following pneumococcal and meningococcal meningitis, 2016-2020.
Abbreviations: GCS: Glasgow coma score; PBS: Pitt bacteremia score for severity of illness.

Table 3
Risk factors for sequelae following laboratory-confirmed bacterial meningitis in South Africa, 2016-2020, n = 921.

		Sequelae at discharge				Univariate analysis			Multivariable analysis		
		No	%	Yes	%	Odds ratio	95% confidence intervals	*P*-value	Odds ratio	95% confidence intervals	*P*-value
Sex											
Female	457/921	353/457	77	104/457	23	Reference					
Male	464/921	346/464	75	118/464	25	1.16	0.86-1.57	0.343			
Age category											
Less than 5 years	290/921	210/290	72	80/290	28	1.31	0.95-1.80	0.094			
5 years and older	631/921	489/631	78	142/631	23	Reference					
HIV											
Negative	358/921	259/358	72	99/358	28	Reference			Reference		
Positive	433/921	336/433	78	97/433	22	0.76	0.55-1.04	0.089	0.74	0.45-1.22	0.243
Not done	130/921	104/130	80	26/130	20	0.65	0.40-1.07	0.088	0.87	0.39-1.95	0.732
HIV category with CD4 count value											
HIV negative	358/734	259/358	72	99/358	28	Reference					
HIV positive CD4 ≥200 cells/µl	154/734	121/154	79	33/154	21	0.71	0.46-1.12	0.141			
HIV positive CD4 <200 cells/µl[a]	222/734	166/222	75	56/222	25	0.88	0.60-1.29	0.521			
GCS category											
GCS of 15 (alert)	422/778	353/422	84	69/422	16	Reference			Reference		
GCS <15	356/778	232/356	65	124/356	35	2.73	1.95-3.83	0.001	3.21	1.97-5.23	<0.001
Pitt bacteremia score on admission											
0 (mild)	217/658	179/217	82	38/217	18	Reference					
1-3 (moderate)	412/658	297/412	72	115/412	28	1.82	1.21-2.75	0.004			
4-12 (severe)	29/658	13/29	45	16/29	55	5.8	2.58-13.05	<0.001			
Underlying illness[b]											
Yes	101/921	71/101	70	30/101	30	1.38	0.88-2.18	0.165			
No	820/921	628/820	77	192/820	23	Reference					
Specimen type											
CSF	736/921	560/736	76	176/736	24	Reference					
Blood	182/921	136/182	75	46/182	25	1.08	0.74-1.57	0.701			
Other	3/921	3/3	100	0/0	0	.					
Organism											
Haemophilus influenzae	91/921	72/91	79	19/91	21	Reference					
Neisseria meningitidis	118/921	94/118	80	24/118	20	0.97	0.49-1.90	0.924			
Streptococcus pneumoniae	712/921	533/712	75	179/712	25	1.27	0.75-2.17	0.375			
Vaccine Serotype/-group[c]											
Yes	214/725	169/214	79	45/214	21	0.84	0.57-1.24	0.376			
No	511/725	388/511	76	123/511	24	Reference					
Resistant organism[d]											
Yes	110/523	72/110	65	38/110	35	2.16	1.36-3.43	0.001	1.91	1.12-3.26	0.017
No	413/523	332/413	80	81/413	20	Reference			Reference		
Appropriate empiric therapy initiated within 24 hrs[e]											
Yes	598/921	441/598	74	157/598	26	1.41	1.02-1.96	0.038			
No	323/921	258/323	80	65/323	20	Reference					
Directed therapy initiated[f]											
Yes	740/921	562/740	76	178/740	24	0.99	0.67-1.44	0.943			
No	181/921	137/181	76	44/181	24	Reference					

[a] HIV-infected children aged <5 years and with CD4 T lymphocyte percentage <15% were included in the group "HIV positive CD4 <200 cells/µl" irrespective of their CD4 T lymphocyte count.
[b] Underlying illness: chronic lung, renal, heart or liver disease; previous cerebrovascular accident; previous head injury; connective tissue disease; asplenia (functional/anatomical); previous malignancy; solid organ transplant; diabetes; chromosomal abnormality; complement deficiency; or current immunosuppressive therapy.
[c] Vaccine serotype/group: pneumococcal serotype present in 13-valent pneumococcal conjugate vaccine or meningococcal serogroup present in meningococcal quadrivalent conjugate vaccine (ACWY) or *Haemophilus influenzae* type b serotype.
[d] Resistant organism: organism was not susceptible to penicillin or ampicillin.
[e] Appropriate empiric therapy initiated within 24 hours: intravenous third-generation cephalosporin.
[f] Directed antibiotic therapy initiated: antibiotics given which are appropriate to susceptibility profile of the organism.GCS: Glasgow coma scale

S5). However, when controlling for antimicrobial resistance of the isolate, individuals with meningococcal meningitis with GCS <15 were seven times more likely to have sequelae than those who had a GCS of 15 on presentation (aOR 7.21, 95% CI 1.09-47.68, $P = 0.04$).

Survivors of *H. influenzae* meningitis were discharged after a median of 13 days (IQR 10-18), and 21% (19/91) reported sequelae on hospital discharge (Table 1). The most common sequelae on discharge were deafness (8%, 7/91), new-onset seizures (8%, 7/91), and hydrocephalus (5%, 5/91). Children aged <5 years were significantly more likely to report sequelae than individuals aged ≥5 years (17/54 [31%] vs 2/37 [5%], aOR 5.59, 95% CI 1.01-30.84, $P = 0.048$) (Figure 6, Supplementary Table S6). Individuals with *H. influenzae* serotype b meningitis were 77% less likely than those with any other serotype to report sequelae (aOR 0.23, 95% CI 0.05-1.03, $P = 0.054$).

Discussion

In this South African cohort of patients with BM due to *S. pneumoniae, H. influenzae*, and *N. meningitidis*, we found an overall in-hospital CFR of 37% with 24% of survivors reporting sequelae at discharge and a further 5% dying within 2 months of discharge. Altered mental status on admission was significantly associated with in-hospital death for all-cause meningitis, as well as underlying illness and HIV infection. Patients treated with antibiotics directed at the organisms' susceptibility profile were 45% less likely to die. Risk factors for sequelae included altered mental status on admis-

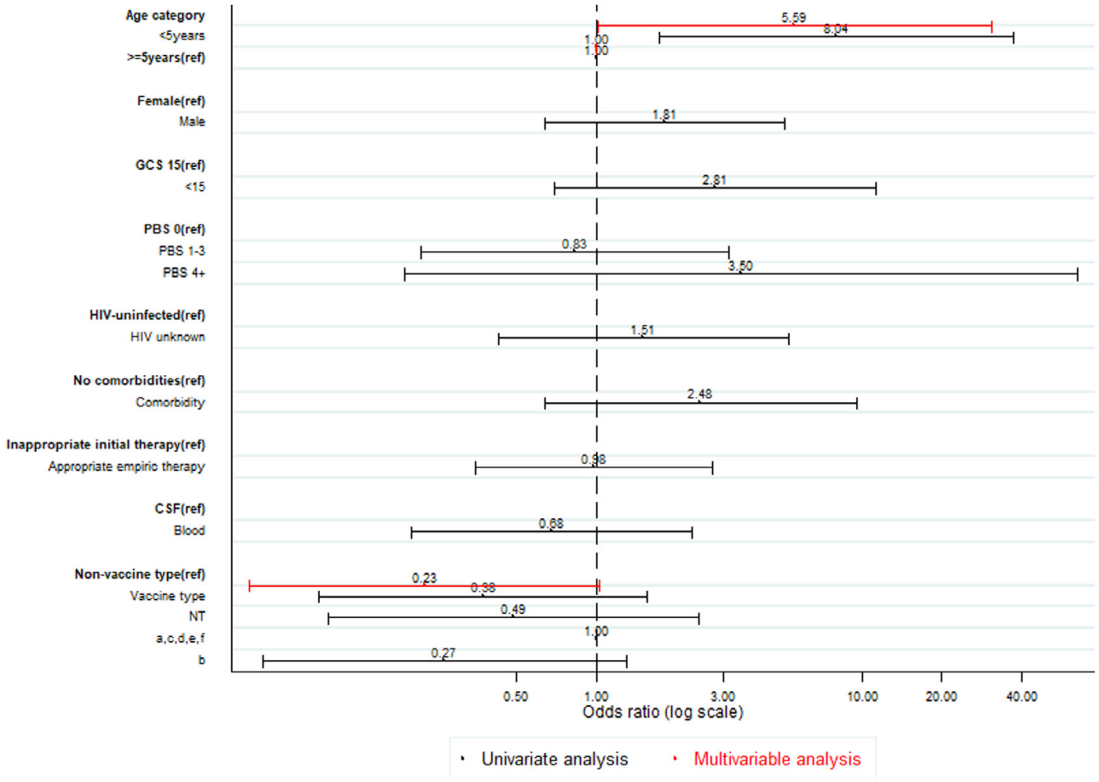

Figure 6. Forest plot: univariate and multivariable analysis of risk factors for developing sequelae following *Haemophilus influenzae* meningitis, 2016-2020 n = 91. Abbreviations: GCS: Glasgow coma score; PBS: Pitt bacteremia score for severity of illness.

sion and being infected with an organism resistant to first-line antibiotics. These results highlight the devastation caused by BM and the importance of early diagnosis, appropriate treatment, adequate follow-up, prevention through vaccination of at-risk groups, and HIV suppression through appropriate antiretroviral therapy for PLHIV.

BM case fatality ratios are higher in South Africa than in many other African countries but are similar to those reported in Botswana (a neighboring country with high HIV prevalence) (Mazamay *et al.*, 2021; Tenforde *et al.*, 2019). CFR among adults with pneumococcal meningitis was 47% in Botswana compared with 44% in our study, with over 60% of patients from both studies being HIV-infected. Further north, in the African meningitis belt where periodic epidemics of meningococcal disease occur, CFR from meningococcal meningitis was much lower than experienced in South Africa (4-7% vs 14%), possibly due to heightened awareness of BM during epidemics and under-reporting of meningitis-plus-sepsis cases (Ramakrishnan *et al.*, 2009; Van De Beek *et al.*, 2016b). This difference may also be driven by the higher HIV prevalence in South Africa, where 24% of PLHIV with meningococcal meningitis died versus 5% of those who were HIV-uninfected.

HIV infection is a recognized risk factor for poor outcomes after invasive pneumococcal and meningococcal disease due to impaired host immune response (Cohen *et al.*, 2010; Meiring *et al.*, 2016). It is also known that pneumococcal carriage and new acquisition of meningococcal carriage are higher in PLHIV (Meiring *et al.*, 2021; Nzenze *et al.*, 2015). In this study, PLHIV who are severely immunocompromised (CD4 T lymphocyte count <200 cells/μl) were three times more likely to die than individuals without HIV for all cases of BM, pneumococcal meningitis, and meningococcal meningitis. However, low CD4 counts were not associated with increased development of sequelae for any of the meningitis pathogens studied, possibly due to low numbers in each of the subanalyses or low inflammatory response in PLHIV who are severely immunocompromised. A total of 13% of the South African population are HIV-infected, including an estimated 2.7 million PLHIV who are not virologically suppressed (2020). Ensuring early initiation of antiretroviral therapy in PLHIV and continued antiretroviral therapy in those already on treatment may result in fewer deaths from BM.

The presence of sequelae following BM was overall observed to be similar in our study compared with other low- to middle-income countries (Edmond *et al.*, 2010). Unlike Edmond *et al.*'s systematic review where children were twice as likely to develop sequelae than adults, in our study, adults and children with meningococcal and pneumococcal meningitis were equally likely to develop sequelae (Edmond *et al.*, 2010). However, for *H. influenzae* meningitis, children were six times more likely than adults to develop sequelae.

The majority of sequelae reported were classified as major, with many being neurological. Seizures, neurological fallout, and deafness were most frequently seen, with similar reports elsewhere (Hoogman *et al.*, 2007; Zainel *et al.*, 2021). Altered mental state on admission and having a nonsusceptible pathogen to first-line antibiotics were associated with the presence of sequelae. However, unlike other studies where younger age was associated with sequelae, this was only true for *H. influenzae* meningitis among our cohort (Namani *et al.*, 2013b).

The presence of neurological complications soon after hospital admission identifies BM patients at the highest risk for death or disability. More aggressive supportive care for such patients could possibly help mitigate this risk. However, there are many public sector facilities in South Africa with limited intensive care resources. A total of 60% of patients were admitted with reduced GCS and the median time to death was 2 days from admission, indicating advanced disease at presentation and rapid disease evolution. It is unknown the extent to which late presentation for care

could have influenced this outcome. South Africa has free primary healthcare for all; however, transport challenges and long waiting times at clinics/hospitals may delay early diagnosis and initiation of appropriate empiric antibiotics. Improved rapid diagnostic tests at clinics may also shorten the time taken to confirm BM and initiate treatment; this is an area of focus for the defeating meningitis roadmap, particularly for Africa (Poplin *et al.*, 2020; The World Health Organization, 2020).

Almost 30% of BM episodes in this study were potentially vaccine-preventable (serotypes/groups covered by currently available 13-valent pneumococcal, meningococcal quadrivalent conjugate vaccine (ACWY), and *H. influenzae* type b vaccines in South Africa). This is markedly less than the three-quarters estimated 10 years ago in low-income countries (Davis *et al.*, 2013). South Africa has provided routine infant vaccination with a 13-valent pneumococcal vaccine since 2011 and *H. influenzae* type b-conjugate vaccine since 2000, both contributing to significant declines in invasive disease (von Gottberg *et al.*, 2014, von Gottberg et al., 2012). Currently, serogroup B accounts for most meningococcal disease in South Africa; however, although recently licensed, meningococcal serogroup B vaccines are not available in South Africa, and quadrivalent vaccine is infrequently administered. Improving routine vaccination coverage subsequent to the COVID-19 pandemic and extending vaccine recommendations to adults with HIV and other comorbidities could further reduce BM in South Africa.

This study did not collect data on corticosteroid use; therefore, we were unable to assess the effect of this intervention. Routine adjunctive corticosteroids are not routinely recommended in South Africa due to delayed presentation of BM and the high HIV prevalence (Boyles *et al.*, 2013). Study sites were mostly academic hospitals in urban centers; therefore, patient outcomes may not reflect the overall South African situation, potentially underestimating poor outcomes in settings with fewer resources. The study likely underestimates the burden of BM in South Africa because it includes only laboratory-confirmed cases and not clinically suspected or culture-negative/PCR-negative cases. Other limitations affecting reporting on sequelae included (i) not controlling for baseline rates of neurological disorders in the population (which may only have been detected at this meningitis admission), (ii) not using a standardized assessment tool for neurological impairment, and (iii) subtle deficits that may have long-term effects on behavior, education, and/or employment potential may not have been appreciated at hospital discharge and therefore would not have been accounted for. For further studies, evaluation of sequelae after 6 months and preferably up to 5 years should be considered as well as an evaluation of the economic cost to families of patients and communities, bearing in mind the high ranking of meningitis as a contributor to disability-adjusted life years worldwide (Abbafati *et al.*, 2020).

BM in South Africa has high mortality and frequent adverse sequelae, with adults and those with comorbidities (including HIV) being at the highest risk. Sequelae after meningitis often involve neurological fallout with consequent long-standing effects increasing the education, employment, and economic costs among those with disabilities. These data should be used to advocate for change to prevent and treat disabilities and deaths relating to BM in South Africa as we strive toward defeating meningitis by 2030.

Author contributions

All authors had full access to the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: SM, CC, AvG; acquisition, analysis, or interpretation of data: SM, CC, LdG, MdP, VQ, JK, CM, GR, HD, MN, MS, NM, PM, RC, RL, TN, VC, MB, AvG; drafting of the manuscript: SM wrote the full draft and CC, LdG, MdP, VQ, JK, CM, GR, HD, MN, MS, NM, PM, RC, RL, TN, VC, MB, AvG contributed to subsequent versions; critical revision of the manuscript for important intellectual content: SM, CC, LdG, MdP, VQ, JK, CM, GR, HD, MN, MS, NM, PM, RC, RL, TN, VC, MB, AvG.

Disclaimer

The findings and conclusion in this study are those of the authors and do not necessarily represent the official position of the NICD, South Africa.

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Ethical approval

Ethical approval for the GERMS-SA surveillance program was received from the University of the Witwatersrand Human Research Ethics Committee (Medical) (Reference M140159).

Declaration of Competing interest

Susan Meiring reports a grant from Sanofi Pasteur for research outside the submitted work. Anne von Gottberg and Cheryl Cohen report grants from US CDC, PATH, Wellcome Trust, Sanofi, and from South African MRC, outside the submitted work. All other authors declare that they have no commercial or other associations that may pose a conflict of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2022.07.068.

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Supplementary material

Case-fatality and sequelae following bacterial meningitis in South Africa, 2016 through 2020

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Table S1: Risk factors for death following pneumococcal meningitis in South Africa, 2016-2020, n=1199

		In hospital Outcome				Univariate analysis			Multivariable analysis		
		ALIVE	%	DIED	%	Odds Ratio	95% confidence intervals	p-value	Odds Ratio	95% confidence intervals	p-value
	1199	712	59	487	41						
Sex											
female	602/1199	357/602	59	245/602	41	Reference					
male	597/1199	355/597	59	242/597	41	0.99	0.79-1.25	0.955			
Age category											
less than 5 years	246/1199	182/246	74	64/246	26	Reference					
5 years and older	953/1199	530/953	56	423/953	44	2.27	1.66-3.10	<0.001			
HIV											
negative	295/1199	224/295	76	71/295	24	Reference			Reference		
positive	669/1199	389/669	58	280/669	42	2.27	1.67-3.09	<0.001	2.40	1.64-3.50	<0.001
not done	235/1199	99/235	42	136/235	58	4.33	2.99-6.29	<0.001	4.22	2.59-6.88	<0.001
HIV category with CD4 count value											
HIV negative	295/835	224/295	76	71/295	24	Reference					
HIV positive CD4 ≥200cells/µL	190/835	133/190	70	57/190	30	1.35	0.90-2.04	0.149			
HIV positive CD4 <200cells/µL*	350/835	204/350	58	146/350	42	2.24	1.61-3.18	<0.001			
GCS category											
GCS of 15 (alert)	344/992	292/344	85	52/344	15	Reference					
GCS <15	648/992	312/648	48	336/648	52	6.05	4.34-8.44	<0.001	6.28	4.41-8.95	<0.001
Pitt Bacteraemia Score on admission											
0 (mild)	185/878	156/185	84	29/185	16	Reference					
1-3 (moderate)	586/878	344/586	59	242/586	41	3.78	2.46-5.81	<0.001			
4-12 (severe)	107/878	25/107	23	82/107	77	17.64	9.70-32.09	<0.001			
Underlying illness											
no	990/1199	627/990	63	363/990	37	Reference			Reference		

yes	209/1199	85/209	41	124/209	59	2.52	1.86-3.42	<0.001	2.79	1.94-4.02	<0.001
Specimen type											
Cerebrospinal fluid	954/1199	575/954	60	379/954	40	Reference					
Blood	242/1199	135/242	56	107/242	44	1.2	0.90-1.60	0.205			
Other	3/1199	2/3	67	1/3	33	0.76	0.07-8.40	0.822			
Serotype category											
PCV7	113/1197	69/113	61	44/113	39	Reference					
PCV13 add	118/1197	64/118	54	54/118	46	1.32	0.78-2.23	0.295			
non PCV	718/1197	423/718	59	295/718	41	1.09	0.73-1.64	0.666			
Not-typed	248/1197	154/248	62	94/248	38	0.96	0.61-1.51	0.851			
Vaccine serotype											
no	719/951	424/719	59	295/719	41	Reference					
yes	232/951	134/232	58	98/232	42	1.05	0.78-1.42	0.744			
Resistant organism											
no	577/762	332/577	58	245/577	42	Reference					
yes	185/762	93/185	50	92/185	50	1.34	0.96-1.87	0.084			
Appropriate empiric therapy initiated within 24hrs											
no	393/1199	251/393	64	142/393	36	Reference					
yes	806/1199	461/806	57	345/806	43	1.32	1.03-1.70	0.027			
Directed therapy initiated											
no	313/1199	158/313	50	155/313	50	Reference			Reference		
yes	886/1199	554/886	63	332/886	37	0.61	0.47-0.79	<0.001	0.63	0.45-0.88	0.008

*HIV-infected children <5 years of age and with CD4 T lymphocyte percentage <15% were included in the group "HIV positive CD4 <200cells/µL" irrespective of their CD4 T lymphocyte count. GCS: Glasgow Coma Scale. Underlying illness: chronic lung, renal, heart or liver disease; previous cerebrovascular accident; previous head injury; connective tissue disease; asplenia (functional/anatomical); previous malignancy; solid organ transplant; diabetes; chromosomal abnormality; complement deficiency; or current immunosuppressive therapy. Serotype category: PCV pneumococcal conjugate vaccine, PCV7 – 4, 6B, 9V, 14, 18C, 19F and 23F, PCV13 additional – 1, 3, 5, 6A, 7F and 19A, non PCV – serotypes not in the 13-valent PCV, Not-typed – episodes where the pneumococcus was not serotyped. Vaccine serotype: pneumococcal serotype present in 13-valent PCV. Resistant organism: organism was not susceptible to penicillin (minimum inhibitory concentration >0.6µg/ml). Appropriate empiric therapy initiated within 24hours: intravenous third generation cephalosporin. Directed antibiotic therapy initiated: antibiotics given which are appropriate to susceptibility profile of the organism.

Table S2: Risk factors for death following meningococcal meningitis in South Africa, 2016-2020, n=137

		In hospital Outcome				Univariate analysis			Multivariable analysis		
		ALIVE	%	DIED	%	Odds Ratio	95% confidence intervals	p-value	Odds Ratio	95% confidence intervals	p-value
	137	118	86	19	14						
Sex											
female	67/137	56/67	84	11/67	16	Reference					
male	70/137	62/70	89	8/70	11	0.66	0.25-1.75	0.401			
Age category											
less than 5 years	59/137	54/59	92	5/59	8	Reference					
5 years and older	78/137	64/78	82	14/78	18	2.36	0.80-6.98	0.12			
HIV											
negative	86/137	82/86	95	4/86	5	Reference			Reference		
positive	25/137	19/25	76	6/25	24	6.47	1.66-25.22	0.007	7.42	1.02-54.02	0.048
not done	26/137	17/26	65	9/26	35	10.85	2.99-39.36	<0.001	15.81	1.91-131.17	0.011
HIV category with CD4 count value											
HIV negative	86/105	82/86	95	4/86	5	Reference					
HIV positive CD4 ≥200cells/µL	11/105	10/11	91	1/11	9	2.05	0.21-20.19	0.539			
HIV positive CD4 <200cells/µL*	8/105	5/8	63	3/8	38	12.30	2.14-70.65	0.005			
GCS category											
GCS of 15 (alert)	67/112	65/67	97	2/67	3	Reference			Reference		
GCS <15	45/112	33/45	73	12/45	27	11.82	2.50-55.93	0.002	20.85	2.87-151.65	0.003
Pitt Bacteraemia Score on admission											
0 (mild)	35/87	34/35	97	1/35	3	Reference					
1-3 (moderate)	46/87	42/46	91	4/46	9	3.24	0.35-30.34	0.303			
4-12 (severe)	6/87	2/6	33	4/6	67	68	4.98-928.89	0.002			
Underlying illness											
no	126/137	113/126	90	13/126	10	Reference			Reference		

yes	11/137	5/11	45	6/11	55	10.43	2.79-38.98	<0.001	26.51	1.94-362.96	0.014
Specimen type											
Cerebrospinal fluid	107/137	95/107	89	12/107	11	Reference					
Blood	30/137	23/30	77	7/30	23	2.41	0.85-6.80	0.097			
Serogroup category											
B	51/111	48/51	94	3/51	6	Reference					
ACWY	59/111	48/59	81	11/59	19	3.67	0.96-13.97	0.057			
other	1/111	1/1	100	0/1	0	.					
Vaccine serogroup											
no	53/112	50/53	94	3/53	6	Reference					
yes	59/112	48/59	81	11/59	19	3.82	1.00-14.54	0.049			
Resistant organism											
no	57/62	51/57	89	6/57	11	Reference					
yes	5/62	5/5	100	0/5	0	.					
Appropriate empiric therapy initiated within 24hrs											
no	41/137	34/41	83	7/41	16	Reference					
yes	96/137	84/96	88	12/96	13	0.69	0.25-1.91	0.480			
Directed therapy initiated											
no	15/137	10/15	67	5/15	33	Reference			Reference		
yes	122/137	108/122	89	14/122	11	0.26	0.08-0.89	0.029	0.04	0.00-0.37	0.005

*HIV-infected children <5 years of age and with CD4 T lymphocyte percentage <15% were included in the group "HIV positive CD4 <200cells/µL" irrespective of their CD4 T lymphocyte count.

GCS: Glasgow Coma Scale. Underlying illness: chronic lung, renal, heart or liver disease; previous cerebrovascular accident; previous head injury; connective tissue disease; asplenia (functional/anatomical); previous malignancy; solid organ transplant; diabetes; chromosomal abnormality; complement deficiency; or current immunosuppressive therapy. Vaccine serogroup: meningococcal serogroup present in quadrivalent meningococcal conjugate vaccine (A, C, W or Y). Resistant organism: organism was not susceptible to penicillin. Appropriate empiric therapy initiated within 24hours: intravenous third generation cephalosporin. Directed antibiotic therapy initiated: antibiotics given which are appropriate to susceptibility profile of the organism.

Table S3: Risk factors for death following *Haemophilus influenzae* meningitis in South Africa, 2016-2020, n=119

		In hospital Outcome				Univariate analysis			Multivariable analysis		
		ALIVE	%	DIED	%	Odds Ratio	95% confidence intervals	p-value	Odds Ratio	95% confidence intervals	p-value
	119	91	76	28	24						
Sex											
female	57/119	44/57	77	13/57	23	Reference					
male	62/119	47/62	76	15/62	24	1.08	0.46-2.52	0.859			
Age category											
less than 5 years	71/119	54/71	76	17/71	24	Reference					
5 years and older	48/119	37/48	77	11/48	23	0.94	0.40-2.25	0.897			
HIV											
negative	67/119	52/67	78	15/67	22	Reference			Reference		
positive	29/119	25/29	86	4/29	14	0.55	0.17-1.84	0.336	0.66	0.14-3.13	0.603
not done	23/119	14/23	61	9/23	39	2.23	0.81-6.15	0.122	1.47	0.29-7.29	0.64
HIV category with CD4 count values											
HIV negative	67/93	52/67	78	15/67	22	Reference					
HIV positive CD4 ≥200cells/µL	11/93	11/11	100	0/11	0	.					
HIV positive CD4 <200cells/µL*	15/93	13/15	87	2/15	13	0.53	0.11-2.63	0.440			
GCS category											
GCS of 15 (alert)	72/92	65/72	90	7/72	10	Reference			Reference		
GCS <15	20/92	11/20	55	9/20	45	7.6	2.34-24.64	0.001	7.32	2.10-25.53	0.002
Pitt Bacteraemia Score on admission											
0 (mild)	27/67	27/27	100	0/27	0	.					
1-3 (moderate)	35/67	26/35	74	9/25	26	Reference					
4-12 (severe)	5/67	2/5	40	3/5	60	4.33	0.62-30.25	0.139			
Underlying illness											
no	100/119	80/100	80	20/100	20	Reference			Reference		

yes	19/119	11/19	58	8/19	42	2.91	1.03-8.18	0.043	1.98	0.43-9.05	0.377
Specimen type											
Cerebrospinal fluid	86/119	66/86	77	20/86	23	Reference					
Blood	32/119	24/32	75	8/32	25	1.1	0.43-2.83	0.843			
Other	1/119	1/1	100	0/1	0	1	.				
Serotype category											
Non-typeable	27/88	19/27	70	8/27	30	2.53	0.58-11.05	0.218			
a,c,d,e,f	21/88	18/21	86	3/21	14	Reference					
b	40/88	32/40	80	8/40	20	1.5	0.35-6.38	0.583			
Vaccine serotype											
no	48/88	37/48	77	11/48	23	Reference					
yes	40/88	32/40	80	8/40	20	0.84	0.30-2.35	0.741			
Resistant organism											
no	42/55	30/42	71	12/42	29	Reference					
yes	13/55	12/13	92	1/13	8	0.21	0.02-1.78	0.152			
Appropriate empiric therapy initiated within 24hrs											
no	54/119	38/54	70	16/54	30	Reference					
yes	65/119	53/65	82	12/65	18	0.54	0.23-1.27	0.156			
Directed therapy initiated											
no	25/119	13/25	52	12/25	48	Reference			Reference		
yes	94/119	78/94	83	16/94	17	0.22	0.09-0.56	0.002	0.33	0.08-1.34	0.122

*HIV-infected children <5 years of age and with CD4 T lymphocyte percentage <15% were included in the group "HIV positive CD4 <200cells/µL" irrespective of their CD4 T lymphocyte count.

GCS: Glasgow Coma Scale. Underlying illness: chronic lung, renal, heart or liver disease; previous cerebrovascular accident; previous head injury; connective tissue disease; asplenia (functional/anatomical); previous malignancy; solid organ transplant; diabetes; chromosomal abnormality; complement deficiency; or current immunosuppressive therapy. Vaccine serotype: *Haemophilus influenzae* type b serotype. Resistant organism: organism was not susceptible to ampicillin. Appropriate empiric therapy initiated within 24hours: intravenous third generation cephalosporin. Directed antibiotic therapy initiated: antibiotics given which are appropriate to susceptibility profile of the organism.

Table S4: Risk factors for sequelae amongst survivors of pneumococcal meningitis in South Africa, 2016-2020, n=712

		SEQUELAE at DISCHARGE				Univariate analysis			Multivariable analysis		
		NO	%	YES	%	Odds Ratio	95% confidence intervals	p-value	Odds Ratio	95% confidence intervals	p-value
Sex											
female	357/712	271/357	76	86/357	24	Reference					
male	355/712	262/355	74	93/355	26	1.12	0.80-1.57	0.517			
Age category											
less than 5 years	182/712	131/182	72	51/182	28	1.22	0.84-1.79	0.299			
5 years and older	530/712	402/530	76	128/530	24	Reference					
HIV											
negative	224/712	155/224	69	69/224	31	Reference					
positive	389/712	298/389	77	91/389	23	0.69	0.47-0.99	0.045			
not done	99/712	80/99	81	19/99	19	0.53	0.30-0.95	0.032			
HIV category with CD4 count values											
HIV negative	224/561	155/224	69	69/224	31	Reference					
HIV positive CD4 ≥200cells/µL	133/561	104/133	78	29/133	22	0.63	0.38-1.03	0.067			
HIV positive CD4 <200cells/µL*	204/561	149/204	73	55/204	27	0.83	0.55-1.26	0.382			
GCS category											
GCS of 15 (alert)	292/604	246/292	84	46/292	16	Reference			Reference		
GCS <15	312/604	203/312	65	109/312	35	2.87	1.94-4.25	<0.001	2.55	1.52-4.26	<0.001
Pitt Bacteraemia Score on admission											
0 (mild)	156/525	130/156	83	26/156	17	Reference					
1-3 (moderate)	344/525	246/344	72	98/344	28	1.99	1.23-3.22	0.005			
4-12 (severe)	25/525	10/25	40	15/25	60	7.5	3.04-18.5	<0.001			
Underlying illness											
yes	85/712	59/85	69	26/85	31	1.37	0.83-2.24	0.219			
no	627/712	474/627	76	153/627	24	Reference					

Specimen type											
CSF	575/712	432/575	75	143/575	25	Reference					
Blood	135/712	99/135	73	36/135	27	1.1	0.72-1.68	0.665			
Other	2/712	2/2	100	0/2	0	.					
Serotype category											
PCV7	69/710	48/69	70	21/69	30	Reference					
PCV13 add	64/710	50/64	78	14/64	22	0.64	0.29-1.40	0.264			
non PCV	423/710	320/423	76	103/423	24	0.74	0.42-1.29	0.282			
Not-typed	154/710	114/154	74	40/154	26	0.8	0.43-1.50	0.49			
Vaccine serotype											
yes	134/558	99/134	74	35/134	26	1.09	0.70-1.70	0.711			
no	424/558	320/424	75	104/424	25	Reference					
Resistant organism											
yes	93/425	56/93	60	37/93	40	2.39	1.46-3.90	0.001	2.06	1.18-3.62	0.011
no	332/425	260/332	78	72/332	22	Reference			Reference		
Appropriate empiric therapy initiated within 24hrs											
yes	461/712	333/461	72	128/461	28	1.51	1.04-2.18	0.029			
no	251/712	200/251	80	51/251	20	Reference					
Directed therapy initiated											
yes	554/712	417/5545	75	137/554	25	0.91	0.61-1.36	0.636			
no	158/712	116/158	73	42/158	27	Reference					

*HIV-infected children <5 years of age and with CD4 T lymphocyte percentage <15% were included in the group "HIV positive CD4 <200cells/µL" irrespective of their CD4 T lymphocyte count. GCS: Glasgow Coma Scale. Underlying illness: chronic lung, renal, heart or liver disease; previous cerebrovascular accident; previous head injury; connective tissue disease; asplenia (functional/anatomical); previous malignancy; solid organ transplant; diabetes; chromosomal abnormality; complement deficiency; or current immunosuppressive therapy. Serotype category: PCV pneumococcal conjugate vaccine, PCV7 – 4, 6B, 9V, 14, 18C, 19F and 23F, PCV13 additional – 1, 3, 5, 6A, 7F and 19A, non PCV – serotypes not in the 13-valent PCV, Not-typed – episodes where the pneumococcus was not serotyped. Vaccine serotype: pneumococcal serotype present in 13-valent PCV. Resistant organism: organism was not susceptible to penicillin (minimum inhibitory concentration >0.6µg/ml). Appropriate empiric therapy initiated within 24hours: intravenous third generation cephalosporin. Directed antibiotic therapy initiated: antibiotics given which are appropriate to susceptibility profile of the organism.

Table S5: Risk factors for sequelae amongst survivors of meningococcal meningitis in South Africa, 2016-2020, n=118

		SEQUELAE at DISCHARGE				Univariate analysis			Multivariable analysis		
		NO	%	YES	%	Odds Ratio	95% confidence intervals	p-value	Odds Ratio	95% confidence intervals	p-value
Sex											
female	56/118	45/56	80	11/56	20	Reference					
male	62/118	49/62	79	13/62	21	1.09	0.44-2.67	0.858			
Age category											
less than 5 years	54/118	42/54	78	12/54	22	1.24	0.50-3.04	0.641			
5 years and older	64/118	52/64	81	12/64	19	Reference					
HIV											
negative	82/118	66/82	80	16/82	20	Reference					
positive	19/118	13/19	68	6/19	32	1.9	0.63-5.78	0.256			
not done	17/118	15/17	88	2/17	12	0.55	0.11-2.65	0.456			
HIV category with CD4 count values											
HIV negative	82/97	66/82	80	16/82	20						
HIV positive CD4 ≥200cells/µL	10/97	6/10	60	4/10	40						
HIV positive CD4 <200cells/µL*	5/97	4/5	80	1/5	20						
GCS category											
GCS of 15 (alert)	65/98	53/65	82	12/65	18	Reference			Reference		
GCS <15	33/98	22/33	67	11/33	33	2.21	0.85-5.75	0.105	7.21	1.09-47.68	0.04
Pitt Bacteraemia Score on admission											
0 (mild)	34/78	28/34	82	6/34	18	Reference					
1-3 (moderate)	42/78	30/42	71	12/42	29	1.87	0.62-5.65	0.269			
4-12 (severe)	2/78	2/2	100	0/2	0	1					
Underlying illness											
yes	5/118	5/5	100	0/5	0	1					
no	113/118	89/113	79	24/113	21	Reference					

Specimen type												
Cerebrospinal fluid	95/118	77/95	81	18/95	19	Reference						
Blood	23/118	17/23	74	6/23	26	1.51	0.52-4.37	0.447				
Other						1						
Serogroup category												
B	48/97	38/48	79	10/48	21	Reference						
ACWY	48/97	41/48	85	7/48	15	0.65	0.22-1.88	0.425				
other	1/97	1/1	100	0/1	0	1						
Vaccine serogroup												
yes	48/98	41/48	85	7/48	15	0.61	0.21-1.72	0.346				
no	50/98	39/50	78	11/50	22	Reference						
Resistant organism												
yes	5/56	4/5	80	1/5	20	2.3	0.21-24.80	0.492	2.77	0.20-37.96	0.445	
no	51/56	46/51	90	5/51	10	Reference			Reference			
Appropriate empiric therapy initiated within 24hrs												
yes	84/118	66/84	79	18/84	21	1.27	0.46-3.54	0.644				
no	34/118	28/34	82	6/34	18	Reference						
Directed therapy initiated												
yes	108/118	86/108	80	22/108	20	1.02	0.20-5.16	0.978				
no	10/118	8/10	80	2/10	20	Reference						

*HIV-infected children <5 years of age and with CD4 T lymphocyte percentage <15% were included in the group "HIV positive CD4 <200cells/µL" irrespective of their CD4 T lymphocyte count.

GCS: Glasgow Coma Scale. Underlying illness: chronic lung, renal, heart or liver disease; previous cerebrovascular accident; previous head injury; connective tissue disease; asplenia (functional/anatomical); previous malignancy; solid organ transplant; diabetes; chromosomal abnormality; complement deficiency; or current immunosuppressive therapy. Vaccine serogroup: meningococcal serogroup present in quadrivalent meningococcal conjugate vaccine (A, C, W or Y). Resistant organism: organism was not susceptible to penicillin. Appropriate empiric therapy initiated within 24hours: intravenous third generation cephalosporin. Directed antibiotic therapy initiated: antibiotics given which are appropriate to susceptibility profile of the organism.

Table S6: Risk factors for sequelae amongst survivors of *Haemophilus influenzae* meningitis in South Africa, 2016-2020, n=91

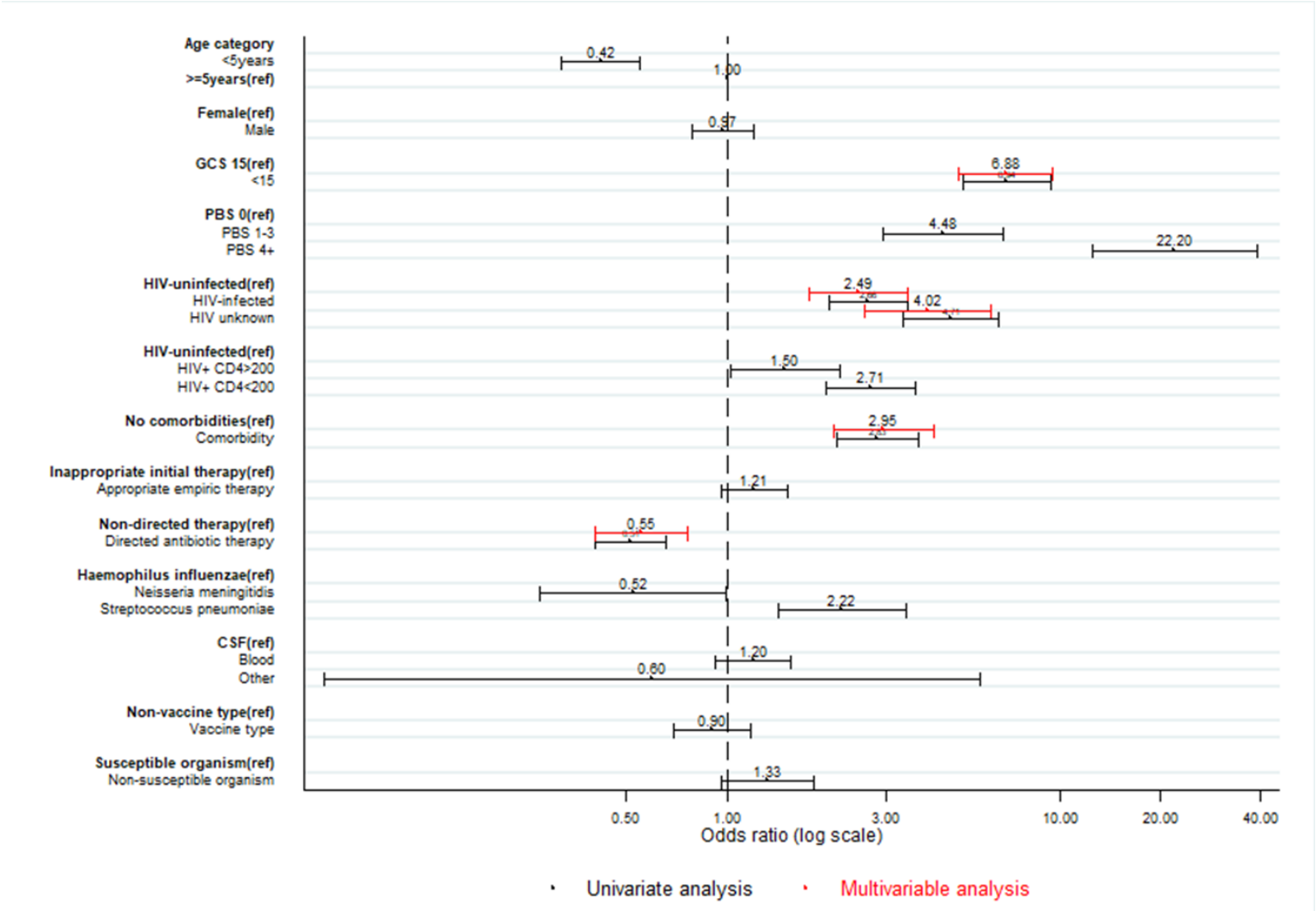
		SEQUELAE at DISCHARGE				Univariate analysis			Multivariable analysis		
		NO	%	YES	%	Odds Ratio	95% confidence intervals	p-value	Odds Ratio	95% confidence intervals	p-value
Sex											
female	44/91	37/44	84	7/44	16	Reference					
male	47/91	35/47	74	12/47	26	1.81	0.64-5.13	0.263			
Age category											
less than 5 years	54/91	37/54	69	17/54	31	8.04	1.73-37.36	0.008	5.59	1.01-30.84	0.048
5 years and older	37/91	35/37	95	2/37	5	Reference			Reference		
HIV											
negative	52/91	38/52	73	14/52	27	Reference					
positive	25/91	25/25	100	0/25	0	1					
not done	14/91	9/14	64	5/14	36	1.51	0.43-5.28	0.521			
HIV category with CD4 count values											
HIV negative	52/76	38/52	73	14/52	27	Reference					
HIV positive CD4 ≥200cells/µL	11/76	11/11	100	0/11	0	1					
HIV positive CD4 <200cells/µL*	13/76	13/13	100	0/13	0	1					
GCS category											
GCS of 15 (alert)	65/76	54/65	83	11/65	17	Reference					
GCS <15	11/76	7/11	64	4/11	36	2.81	0.70-11.25	0.146			
Pitt Bacteraemia Score on admission											
0 (mild)	27/55	21/27	78	6/27	22	Reference					
1-3 (moderate)	26/55	21/26	81	5/26	19	0.83	0.22-3.16	0.788			
4-12 (severe)	2/55	1/2	50	1/2	50	3.5	0.19-64.67	0.4			
Underlying illness											
yes	11/91	7/11	64	4/11	36	2.48	0.64-9.56	0.188			
no	80/91	65/80	81	15/80	19	Reference					

Specimen type												
Cerebrospinal fluid	66/91	51/66	77	15/66	23	Reference						
Blood	24/91	20/24	83	4/24	17	0.68	0.20-2.30	0.535				
Other	1/91	1/1	100	0/1	0	1						
Serotype category												
NT	19/69	16/19	84	3/19	16	Reference						
a,c,d,e,f	18/69	13/18	72	5/18	28	2.05	0.41-10.24	0.381				
b	32/69	29/32	91	3/32	9	0.55	0.10-3.06	0.496				
Vaccine serotype												
yes	32/69	29/32	91	3/32	9	0.38	0.09-1.56	0.177	0.23	0.05-1.03	0.054	
no	37/69	29/37	78	8/37	22	Reference			Reference			
Resistant organism												
yes	12/42	12/12	100	0/12	0	1						
no	30/42	26/30	87	4/30	13	Reference						
Appropriate empiric therapy initiated within 24hrs												
yes	53/91	42/53	79	11/53	21	0.98	0.35-2.74	0.972				
no	38/91	30/38	79	8/38	21	Reference						
Directed therapy initiated												
yes	78/91	59/78	76	19/78	24	1						
						Reference						
no	13/91	13/13	100	0/13	0							

*HIV-infected children <5 years of age and with CD4 T lymphocyte percentage <15% were included in the group "HIV positive CD4 <200cells/µL" irrespective of their CD4 T lymphocyte count.

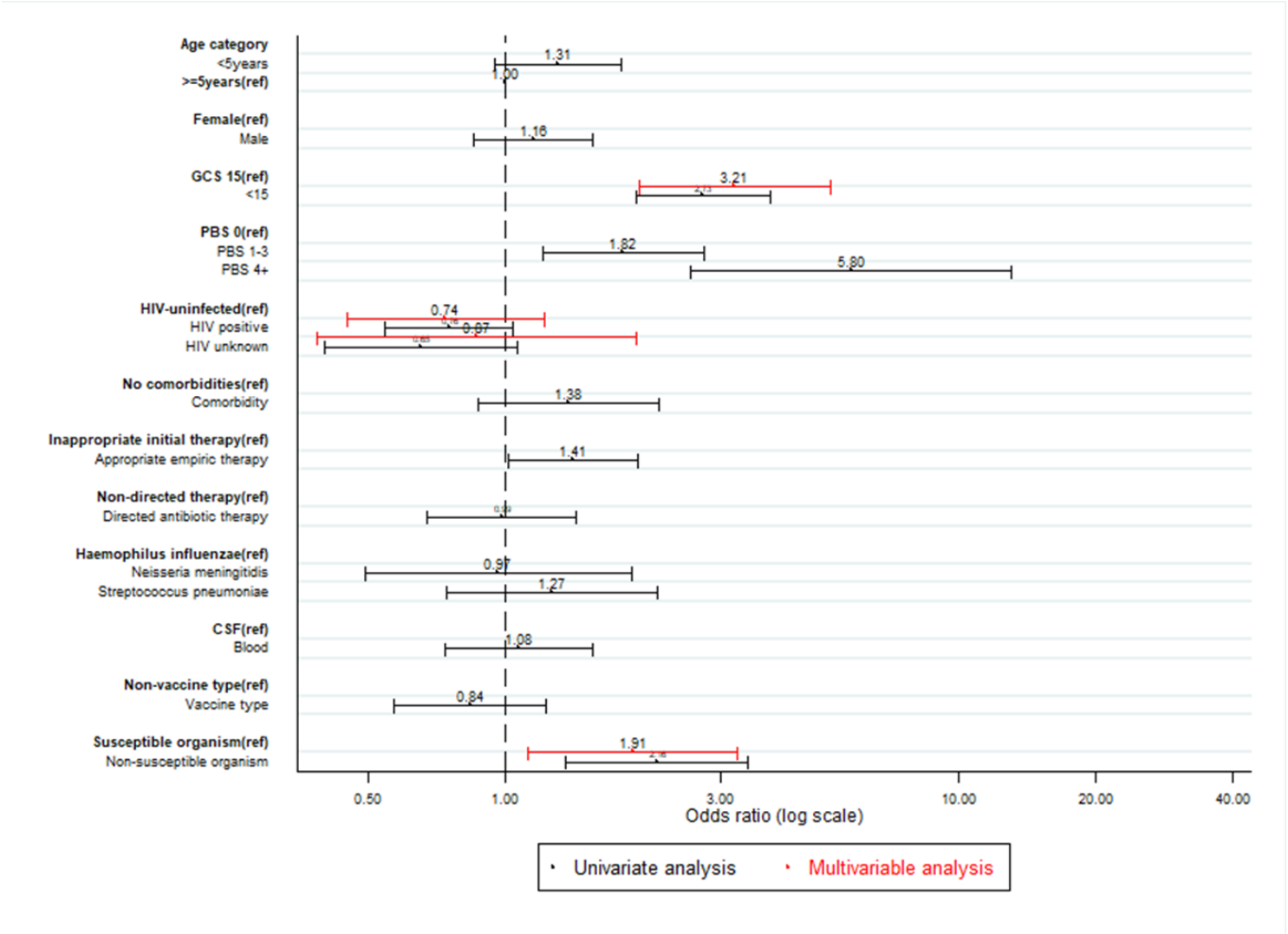
GCS: Glasgow Coma Scale. Underlying illness: chronic lung, renal, heart or liver disease; previous cerebrovascular accident; previous head injury; connective tissue disease; asplenia (functional/anatomical); previous malignancy; solid organ transplant; diabetes; chromosomal abnormality; complement deficiency; or current immunosuppressive therapy. Vaccine serotype: *Haemophilus influenzae* type b serotype. Resistant organism: organism was not susceptible to ampicillin. Appropriate empiric therapy initiated within 24hours: intravenous third generation cephalosporin. Directed antibiotic therapy initiated: antibiotics given which are appropriate to susceptibility profile of the organism.

Supplementary figure 1: Forest plot: univariate and multivariable analysis of risk factors for mortality following bacterial meningitis, 2016-2020



Footnote: GCS: Glasgow coma score; PBS: Pitt Bacteraemia Score for severity of illness

Supplementary figure 2: Forest plot: univariate and multivariable analysis of risk factors for developing sequelae following bacterial meningitis, 2016-2020



Footnote: GCS: Glasgow coma score; PBS: Pitt Bacteraemia Score for severity of illness

Paper IV

Meiring S, Tempia S, Dominic E M, de Gouveia L, McAnerney J, von Gottberg A, Cohen C Excess invasive meningococcal disease associated with seasonal influenza, South Africa, 2003-2018 Clin Infect Dis, ciab702, https://doi.org/10.1093/cid/ciab702 Published: 14 August 2021 (online ahead of print)

Clinical Infectious Diseases

MAJOR ARTICLE

Excess Invasive Meningococcal Disease Associated With Seasonal Influenza, South Africa, 2003–2018

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Background. Invasive meningococcal disease (IMD) is a devastating illness with high mortality rates. Like influenza, endemic IMD is seasonal, peaking in winter. Studies suggest that circulation of influenza virus may influence the timing and magnitude of IMD winter peaks.

Methods. This ecological study used weekly data from 2 nationwide surveillance programs: Viral Watch (proportion of outpatient influenza-positive cases from throat or nasal swab samples) and GERMS-SA (laboratory-confirmed cases of IMD), occurring across South Africa from 2003 through 2018 in all age bands. A bivariate time series analysis using wavelet transform was conducted to determine cocirculation of the diseases and the time lag between the peak seasons. We modeled excess meningococcal disease cases attributable to influenza cocirculation, using univariate regression spline models. Stata and R statistical software packages were used for the analysis.

Results. A total of 5256 laboratory-confirmed IMD cases were reported, with an average annual incidence of 0.23 episodes per 100 000 population and a mean seasonal peak during week 32 (±3 weeks). Forty-two percent of swab samples (10 421 of 24 741) were positive for influenza during the study period. The mean peak for all influenza occurred at week 26 (±4 weeks). There was an average lag time of 5 weeks between annual influenza and IMD seasons. Overall, 5% (1%–9%) of IMD cases can be attributable to influenza cocirculation, with, on average, 17 excess IMD cases per year attributable to influenza.

Conclusions. A quantifiable proportion of IMD in South Africa is associated with influenza cocirculation; therefore, seasonal influenza vaccination may have an effect on preventing a small portion of IMD in addition to preventing influenza.

Keywords. influenza; meningococcus; *Neisseria meningitidis*; seasonal influenza; attributable fraction.

Invasive meningococcal disease (IMD) is a devastating illness with high mortality and morbidity rates. Disease onset is sudden, affecting both healthy and immunocompromised individuals. Like influenza, endemic meningococcal disease is seasonal, with peaks in the winter months. Studies suggest that circulation of the influenza virus may influence the timing and magnitude of IMD winter peaks [1–4].

IMD can be prevented through various meningococcal vaccination strategies and timely provision of chemoprophylaxis to close contacts of IMD cases [5]. Six IMD serogroups are responsible for the majority of disease, with serogroups B and W being the most frequently encountered disease-causing serogroups in South Africa [6]. Guidelines for meningococcal vaccine use among high-risk groups in South Africa are available, however vaccine uptake is extremely low, and there is no publicly funded IMD vaccination program [7]. Meningococcal vaccines target specific serogroups; thus, 2 different vaccines would be necessary to address the 2 most predominant serogroups circulating in South Africa. The recombinant serogroup B meningococcal vaccines (Trumenba and Bexsero) are not yet licensed for use in South Africa, although the quadrivalent conjugate meningococcal vaccine targeting serogroups A, C, W, and Y is available for selected patients in the public health sector or can be accessed privately with a doctor's prescription. IMD is currently occurring at a low rate (0.2 cases per 100 000 population in 2016); therefore, unless perception of the disease threat increases, routine meningococcal vaccination is unlikely to be implemented in South Africa, and other areas of IMD prevention need to be investigated [6].

It has been shown that, in temperate climates, IMD peaks frequently coincide with seasonal peaks in influenza. One ecological study in Canada showed a doubling in IMD incidence per 100-case increase in influenza A activity [4]. Another study in the United States showed that two-thirds of IMD cases during the peak of influenza seasons could be attributable to influenza, and

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that the height of both influenza and IMD seasons lagged by 2 weeks over 19 of 20 consecutive winters [1]. Observational studies of IMD outbreaks in well-defined populations—as in an army barrack, old-aged home, or school—used serological testing to confirm preceding outbreaks of influenza A or B within the population prior to the onset of IMD [8–11].

South Africa has a temperate climate, with both influenza and meningococcal disease increasing in late autumn to winter (April through August). If a temporal correlation between IMD and influenza is identified in South Africa, preventing influenza through seasonal influenza vaccination campaigns could have the added benefit of preventing a proportion of IMD case. In the current study, we assessed the temporal association between the peaks in the timing of influenza and meningococcal disease activity in South Africa over a 16-year period and calculated the fraction of IMD cases attributable to circulating seasonal influenza virus during the winter and spring seasons in South Africa.

METHODS

This is an ecological study using data from the GERMS-SA and Viral Watch surveillance programs coordinated by the National Institute for Communicable Diseases (NICD) in South Africa. The study population contains all persons living in South Africa from 2003 until 2018. For meningococcus incidence calculation, midyear population denominators from Statistics South Africa were used to linearly interpolate the population at risk each week for the study period, 1 January 2003 through 31 December 2018 [12].

GERMS-SA is a national laboratory-based surveillance program for IMD as well as other invasive bacteria and fungi occurring in South Africa [13]. On average, 215 public, private, military, and mining sector microbiology laboratories participate in the program by submitting reports of IMD cases identified in the laboratory to the reference laboratory of the Centre for Respiratory Diseases and Meningitis at the NICD. This program is representative of all laboratory-confirmed cases of IMD in South Africa. Patients' demographic details (including age, sex, district, and province) and laboratory test results (ie, serogroup) are recorded. Laboratory-confirmed IMD cases from 1 January 2003 until 31 December 2018 were included in the analysis and categorized according to epidemiological week and year. Annual (per 100 000 population) and weekly (per 10 000 000) incidence rates for IMD were calculated, and percentage change in disease over the years was calculated, using Poisson regression with 2006 as the reference year.

The Viral Watch program began in 1984, and tests throat and nasal swab samples were obtained from outpatients of all ages presenting with an acute respiratory infection, defined as fever >38°C, cough, and onset of symptoms within the last 10 days [14, 15]. The specimens are submitted to the NICD by approximately 180 general practitioners from all 9 provinces (excluding KwaZulu Natal in 2014–2018) of South Africa. Specimens are tested using multiplex reverse transcriptase real-time polymerase chain reaction assays for influenza A and B. The proportions of positive influenza cases detected by epidemiological week per year were included in the analysis from 1 January 2003 until 31 December 2018.

The timing of seasonality of laboratory-confirmed *Neisseria meningitidis* disease each year was determined using weekly data from the GERMS-SA program, from 2003 until 2018. The timing of influenza seasonality was retrieved from the Viral Watch program, which indicates proportions of laboratory-confirmed influenza cases detected, by epidemiological week, for the corresponding 16 years. A bivariate time series analyses was performed to determine the temporal association between the peak of the influenza season and the peak of the meningococcal disease seasons for each of the 16 years. We used wavelet transform to decompose a time series into a time-frequency domain, and we used the phase difference of the cross-wavelet spectrum to quantify the time lag between the peak of the seasons. A phase difference located in either the first or fourth quadrant indicates that the 2 series are moving in phase, with x leading y or y leading x in the respective quadrants. Cross-wavelet power indicates regions where 2 time series have high common power.

We used univariate regression spline models to estimate the excess cases of IMD associated with seasonal influenza viruses (all influenza, influenza A, and influenza B) by year [15–17]. Separate models for all influenza, influenza A, and influenza B were fit for the expected meningococcal disease dependent variable. The models included a parametric independent variable indicating the weekly proportion of influenza cases (all influenza, influenza A, or influenza B) per year. A smoothing spline of time (represented by consecutive week number) was used to control for variance arising from time-varying and seasonal IMD. The spline model equation was as follows:

$$\text{Expected (meningococcal disease)} = \beta_0 + \beta_1 t + \sum_{y=2003}^{2018} \beta_{2,y}(\text{influenza}) + \text{spline}(t),$$

where β represents the observed number of IMD cases; *t,* the sequential week number of the weekly time series observations; and "influenza" was the independent variable, split into influenza type A, influenza type B, and years, such that for each year the count was set to 0 for all other years. We set the model to allow 64 degrees of freedom, with 1 degree of freedom allocated to the parametric linear time variable and the remaining distributed at 4 per year for the spline. We also allowed for a 5-week lag between influenza and IMD cases. The lag time was determined by the phase difference of the cross-wavelet spectrum of the time series model described above.

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Excess IMD cases were determined by subtracting the expected weekly rate of IMD in the absence of influenza from the weekly baseline rate of IMD estimated from the spline. Annual excess IMD cases were estimated as the sum of the weekly cases per year. The attributable fraction of IMD associated with influenza was calculated as a percentage of the excess IMD cases over the observed number of IMD cases. We obtained the 95% confidence intervals (CIs) for the estimated excess cases by using bootstrap resampling of block of calendar years from 1000 replications of the data set. We refitted the regression model for each data set and obtained the confidence intervals from the estimated excess cases from the 1000 resampled data sets. Statistical analysis was done using Stata software (version 14; StataCorp) and R statistical software (version 4.0.2), using the WaveletComp package (Roesch and Schmidbauer; 2018, https://rdrr.io/cran/WaveletComp/man/WaveletComp-package.html) for time series analyses.

Ethics approvals for the GERMS-SA surveillance program have been obtained annually from the University of the Witwatersrand Human Research Ethics Committee (Medical) (Wits HREC [Medical]) (reference M140159). Informed consent was obtained from all participants or parents/legal guardians of underaged participants interviewed in the enhanced surveillance program. Ethical clearance for the Viral Watch program was obtained from Wits HREC (Medical) (reference M060449). Clearance for this secondary data analysis was obtained from Wits HREC (Medical) (reference M170951).

RESULTS

Over 16 years there were 5256 laboratory-confirmed IMD cases reported through the national surveillance program, with an average annual incidence of 0.23 episodes per 100 000 population and a mean seasonal peak during week 32 (+3 weeks). IMD incidence was highest in 2006 (1.3 per 100 000 population) and has decreased by 15% each year, to 0.21 episodes per 100 000 in 2018 (Figure 1).

Forty-two of swab samples tested at the NICD percent (10 421 of 24 741) were positive for influenza during the study period. The median positivity for influenza by year was 44% (interquartile range, 39%–47%). The highest number of swab samples was submitted in 2009, and 47% of them (1753 of 3719) were influenza positive. All influenza-positive swab samples were typed: 2348 of 10 421 (23%) were influenza B, and 8204 of 10 421 (79%) were influenza A (131 episodes were caused by multiple influenza types). The mean peak for all influenza occurred at week 26 (+4 weeks), the mean peak for influenza A at week 26 (+4 weeks), and the mean peak for influenza B at week 30 (+4 weeks).

Timing of the Influenza and IMD Seasons

The time series analysis using the cross-wavelet power spectrum indicated that meningococcal disease and influenza had a significant joint annual periodicity over the 16-year observation period ($P < .05$). The joint cross-wavelet power levels were > 0.5 for the earlier years, but they decreased from 2012 through 2018. Overall, the joint periodicity of IMD and influenza showed high average cross-wavelet power (0.5) at time periods of 52 weeks (Figure 2). IMD and influenza were circulating in phase, peaking approximately every 52 weeks, with IMD lagging influenza. From 2003 to 2011, there was an additional low-power biannual periodicity (every 26 weeks), with lower average cross-wavelet power of 0.12. During this low-powered periodicity, IMD was leading influenza.

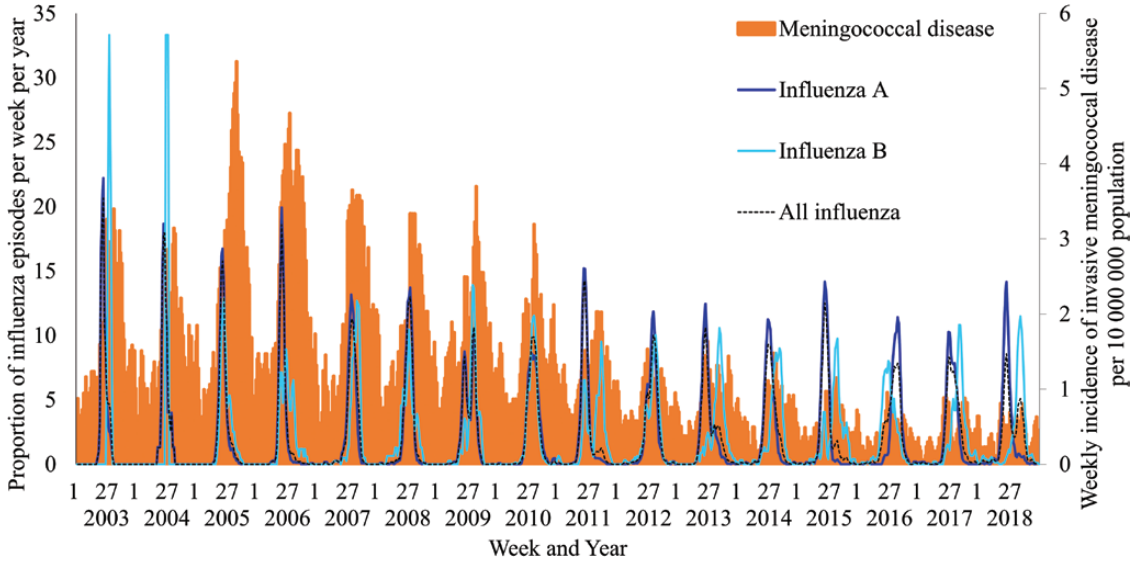

Figure 1. Weekly incidence of invasive meningococcal disease (IMD) and proportion of influenza episodes by week and year, 2003–2018.

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Figure 3 shows the wrapped phase (time) difference between IMD and influenza time series. The 2 series are shown to be in phase, with IMD lagging behind influenza by a period of approximately 5 weeks. Influenza seasons peaked before IMD seasons for 15 of the 16 years, with a reduction in the phase difference between the series from 2016 through 2018.

Modeling the Attributable Fraction of Meningococcal Disease Associated With Influenza

Over the study period, 5.3% (95% CI, 1.1%–7.2%) of IMD cases in South Africa were attributable to influenza, with influenza A potentially contributing to 3.3% (.8%–4.3%) of all IMD cases, and influenza B to 2% (.3%–3.0%). The mean number of excess IMD cases attributable to influenza was 17 per year (95% CI, 9–25) (Tables 1 and 2).

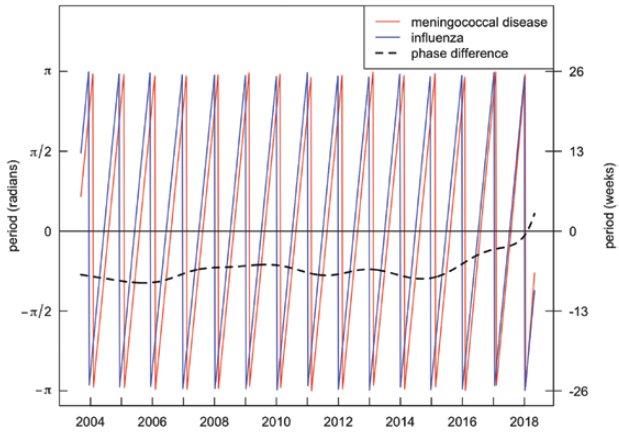

Figure 3. Wrapped phase in radians of invasive meningococcal disease (IMD) and influenza seasons by year, 2003–2018

DISCUSSION

These data from South Africa show a temporal association between influenza and meningococcal disease seasonality over a 16-year period, with influenza leading the meningococcal disease season by 5 weeks and peaking in phase with meningococcal disease during the winter months. Influenza seasonal peaks occurred before meningococcal disease peaks for 15 of the 16 years. Annually, approximately 5% of meningococcal disease cases can be attributable to cocirculating influenza virus infections. The association between influenza and meningococcal disease is well established, but this is the first study from Africa showing this association [1, 2, 18–20].

Although the correlation between the 2 diseases is small to moderate, with only 5% of IMD cases attributable to influenza virus circulation each year, during the peak influenza season a much higher variance in IMD was associated with influenza, particularly influenza A. Therefore, clinicians should be alert to increased cases of IMD following early outbreaks of influenza, as well as during the peak seasons. During periods of increased influenza virus circulation, there are multiple pathways increasing one's risk of IMD. Both diseases are spread via the respiratory tract, and influenza symptoms of coughing and sneezing can mechanically increase meningococcal bacterial dispersion through respiratory droplets.

Persons exposed to influenza disease during the season may have disrupted nasal mucosa, nasal flora, and mucosal immunity up to 2 weeks after their infection, increasing their risk of acquiring meningococcal carriage and possible invasion of the bacteria into the blood stream. In particular, influenza A neuraminidase is known to increase adherence of meningococcus to the nasal epithelial cells, thus increasing meningococcal colonization of the nasopharynx [21]. Although a rare occurrence, IMD typically follows new onset of meningococcal carriage with a virulent strain, usually within a 10-day period of exposure to the bacteria [22].

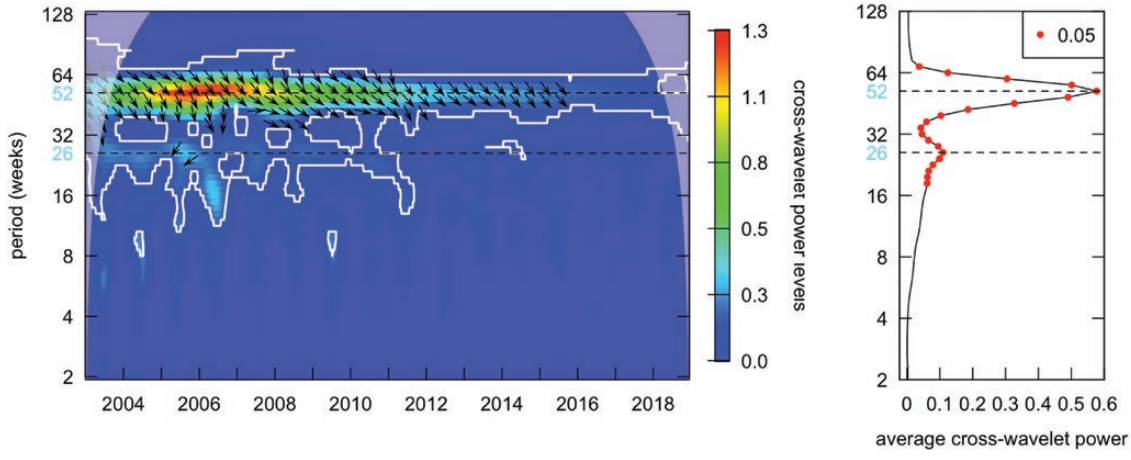

Figure 2. Cross-wavelet power spectrum showing joint significant annual periodicity of invasive meningococcal disease (IMD) and influenza, 2003–2018. The direction of the arrows around period 52 indicate that meningococcal disease and influenza are in phase, with influenza leading IMD.

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Table 1. Excess Invasive Meningococcal Disease Cases Attributable to Influenza (All Influenza, Influenza A, and Influenza B) Cocirculation in South Africa by Year, 2003–2018[a]

	Excess Invasive Meningococcal Disease Cases Attributable to Influenza Circulation					
	All Influenza		Influenza A		Influenza B	
Year	No. of Cases (95% CI)	% of Cases (95% CI)	No. of Cases (95% CI)	% of Cases (95% CI)	No. of Cases (95% CI)	% of Cases (95% CI)
2003	7 (5–7)	1.7 (.5–1.7)	3 (3–4)	.7 (.2–.7)	4 (2–4)	1.0 (.2–1.0)
2004	.0 (.0–.0)	.0 (.0–.0)	.0 (.0–.0)	.0 (.0–.0)	.0 (.0–.0)	.0 (.0–.0)
2005	14 (6–40)	2.4 (.6–5.9)	14 (6–40)	2.4 (.6–5.9)	.0 (.0–.0)	.0 (.0–.0)
2006	18 (17–23)	3.0 (1–3.6)	.0 (.0–.0)	.0 (.0–.0)	18 (17–23)	3.0 (1.0–3.6)
2007	18 (7–23)	3.6 (.6–4.3)	.0 (.0–.0)	.0 (.0–.0)	18 (7–23)	3.6 (.6–4.3)
2008	28 (16–36)	6.5 (1.5–8.4)	11 (7–13)	2.6 (.6–3.0)	17 (9–23)	3.9 (1.0–5.3)
2009	55 (37–61)	11.8 (3.3–12.4)	55 (37–61)	11.8 (3.3–12.4)	.0 (.0–.0)	.0 (.0–.0)
2010	49 (15–103)	12.7 (1.6–24.7)	.0 (.0–.0)	.0 (.0–.0)	49 (15–103)	12.7 (1.6–24.7)
2011	23 (8–24)	7.6 (1.5–7.6)	23 (8–24)	7.6 (1.5–7.6)	.0 (.0–.0)	.0 (.0–.0)
2012	31 (22–40)	14.0 (3.9–18)	31 (22–40)	14.0 (3.9–18.0)	.0 (.0–1)	.0 (.0–.5)
2013	.0 (.0–.0)	.0 (.0–.0)	.0 (.0–.0)	.0 (.0–.0)	.0 (.0–.0)	.0 (.0–.0)
2014	9 (.0–15)	5.0 (.0–5.6)	.0 (.0–.0)	.0 (.0–.0)	9 (.0–15)	5.0 (.0–5.6)
2015	1 (.0–3)	0.7 (.0–2.0)	1 (.0–3)	.7 (.0–2.0)	.0 (.0–.0)	.0 (.0–.0)
2016	3 (.0–7)	2.5 (.0–5.8)	.0 (.0–5)	.0 (.0–4.1)	3 (.0–3)	2.5 (.0–2.5)
2017	18 (10–21)	13.3 (3.0–14.8)	18 (10–21)	13.3 (3.0–14.8)	.0 (.0–.0)	.0 (.0–.0)
2018	.0 (.0–1)	.0 (.0–.8)	.0 (.0–1)	.0 (.0–.8)	.0 (.0–.0)	.0 (.0–.0)
Mean (2003–2018)	17 (9–25)	5.3 (1.1–7.2)	10 (6–13)	3.3 (.8–4.3)	7 (3–12)	2.0 (.3–3.0)

Abbreviation: CI, confidence interval.

[a]Model assumed a 5-week lag between influenza and invasive meningococcal disease to calculate the baseline rate of invasive meningococcal disease (adjusted R^2 = 0.79)

Our study showed a 5-week lag time between the peak of influenza and IMD seasons, which is longer than the 1–2-week lag reported from other, similar ecological studies [1, 18, 20]. It must be noted that even with the extended lag time, the standard deviation around the average peak week of IMD, all influenza and both influenza subtypes overlapped by at least 2 weeks. In addition, influenza seasons often extend for a mean period of 10 weeks [14]. A likely explanation for the increased time lag may be that outpatient-based influenza surveillance programs (in which influenza disease is typically milder) show a slightly earlier peak (approximately 2 weeks earlier) than hospital-based influenza surveillance of more severe disease, which may account for some of the time difference in the studies [1, 23, 24].

Therefore, combining the increased dispersion of meningococci through droplet spread from multiple asymptomatic meningococcal carriers during the influenza season, together with the vulnerable nasal mucosa in those with or recovering from influenza, the 5-week lag time in peaks of both diseases may account for the longer time period for the acquisition of meningococci and the development of IMD.

Although not causal, this study reinforces the association of influenza contributing to a portion of IMD cases. Quantifying the fraction of IMD cases attributable to influenza indicates additional potential health benefits of the influenza vaccine. Therefore, upscaling of influenza vaccination coverage could have the added protection of preventing a portion of IMD. This might have more impact in countries with no routine meningococcal immunization programs.

In 2020, during the coronavirus disease 2019 pandemic, a reduction in meningococcal disease was noted in South Africa and globally [25]. Although multiple factors may have affected this reduction (eg, social distancing of persons, restrictions on movement, and school/university closures), it is important to note that the absence of the southern hemisphere 2020 influenza season may have played a role in reducing IMD [26].

Table 2. Mean Excess Number, Rate, and Percentage of Invasive Meningococcal Disease Cases Attributable to Influenza by Influenza Subtype, 2003–2018

	Excess Invasive Meningococcal Disease Cases, Mean (95% CI)		
Influenza Subtype	No. of Cases	No. per 100 000 Population)	% of Cases
All influenza	17 (9–25)	0.034 (.018–.051)	5.3 (1.1–7.2)
Influenza A	10 (6–13)	0.019 (.012–.026)	3.3 (.8–4.3)
Influenza B	7 (3–12)	0.015 (.006–.025)	2.0 (.3–3.0)

Abbreviation: CI, confidence interval.

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The long time series of both influenza and IMD in South Africa added strength to the model and allowed for control of seasonal factors of both diseases. The Viral Watch program, used to determine influenza seasonality, was established in 1984, and this long time series is a robust system for determining the timing of the influenza season [14]. Even though the high percentage positive for influenza testing may indicate low testing rates outside the influenza seasons, the timing of these seasons correlates well with more systematically collected data from inpatient influenza surveillance programs conducted at sentinel hospitals in South Africa from 2009 [23]. The various analyses undertaken complemented the modeled results for attributable fraction determination, the time difference in the calculated mean peak of influenza and IMD, and the phase difference using the cross-wavelet spectrum.

The study looked only at the interaction between influenza and IMD and did not incorporate any other climatic factors (such as humidity or rainfall) that could influence seasonality for either disease. South Africa is a vast country with a mixed Mediterranean and subtropical temperate climate, with the southwestern parts experiencing cold, wet winters (average winter humidity of 83%) and the rest of the country experiencing cool, dry winters (average winter humidity of 47%). A study from 4 diverse countries (Australia, Canada, France, and United States) did not show a generalizable effect of humidity on IMD seasonality, even when considering specific humidity in different jurisdictions [20]. No causal relationship between the diseases is inferred. Unfortunately, owing to the low incidence of IMD, we were unable to report on other factors that might have had an effect on the models, such as age, comorbid conditions, and meningococcal serogroup. On preliminary analysis using meningococcal serogroup B and other analyses using IMD in children <5 or ≥5 years of age (results not shown), models were weak and there were many years when no effect was seen owing to the low numbers of cases per week entered into the models.

In South Africa, as in northern hemisphere countries, meningococcal disease and influenza have a temporal association, with influenza leading IMD peaks by a period of 5 weeks. A small, but not negligible, proportion of IMD cases each year can be attributable to influenza circulation. The current study highlights an additional benefit of seasonal influenza vaccination (particularly in countries with no routine meningococcal vaccination), because preventing influenza may have an additional effect on preventing a small portion of IMD cases.

Notes

Author contributions. All authors had full access to the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: S. M., S. T., and C. C. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: S. M. Critical revision of the manuscript for important intellectual content: All authors.

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Disclaimer. The findings and conclusions in this study are those of the authors and do not necessarily represent the official position of the NICD, South Africa.

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Potential conflicts of interest. S. M. reports an investigator-sponsored grant from Sanofi Pasteur, to conduct a meningococcal carriage study in university students for research, outside the submitted work. A. v. G. and C. C. report grants from the US Centers for Disease Control and Prevention, PATH, Wellcome Trust, Sanofi, and the South African Medical Research Council, outside the submitted work. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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Appendix D: Study materials

Meningococcal carriage among university students

Consent Form

Centre for Respiratory Diseases and Meningitis (CRDM)
TEL: 011 386 6410 or 011 386 6434
FAX: 0113866850

As a first-year university student we are inviting you to participate in a study looking at the risk factors among university students for carriage of meningococcus (bacteria that can cause meningitis) in the back of the throat.

1. **Who are we?**
   We are from the National Institute for Communicable Diseases which is a division of the National Health Laboratory Services. We do surveillance and research at a national level on respiratory diseases and meningitis.

2. **Why is this study being done?**
   Neisseria meningitidis (sometimes known as the meningococcus) is a bacteria that grows in the throats of approximately 1 out of 10 people but may be more common in adolescents. Having these bacteria in your throat does not cause any symptoms and is known as meningococcal carriage. Occasionally the meningococcus can get into your blood stream and cause a meningitis or severe sepsis. If this happens, about 10% of affected people will die, even with appropriate antibiotic treatment. In some countries there have been outbreaks of meningococcal meningitis amongst university students, these can be controlled and prevented by vaccinating teenagers/adolescents with the meningococcal vaccine. We are doing this study to see:
   a. how many first-year university students in South Africa carry meningococcus in their throat,
   b. what the risk factors are for meningococcal carriage, and
   c. whether HIV infection is a risk factor for carriage?

   If you are a first-year university student and are at least 18 years old, we would like you to participate in this survey.

2. **How many people will take part in the pilot study?**
   We want to enrol 3 000 first-year university students at 2 different universities: University of the Witwatersrand, Gauteng and University of Cape Town, Western Cape Province. We will enrol students during February/March and then do a follow up visit after one month. Thereafter the study will be finished.

3. **What will happen if you decide to take part in the study?**
   If you agree to take part in the study there are 3 things which we would require of you.

   a. We will ask you to complete a **brief questionnaire** regarding your risk factors for carrying *Neisseria meningitidis* in your throat.
   b. We will **prick your finger** to get a drop of blood which we will use to perform an HIV test at our laboratories
   c. We will **swab the back of your throat**. This entails touching the back of your throat with a long handled cotton bud and rubbing the tonsil area for a few seconds.

   In one month's time we will contact you via sms or email to ask you to meet us on campus to repeat the questionnaire and throat swab.

4. **What are the risks and discomforts of this study?**
   There are no risks to you for participating in this study, however there may be some pain and discomfort from the needle prick to get a drop of blood from your finger and brief discomfort (a feeling of gagging) whilst taking the throat swab.

5. **Are there any benefits to you for being in the study?**
   There are no direct benefits to you for being part of the study. However the information collected from you will be useful for informing public health policy makers on whether or not to encourage meningococcal vaccine use prior to attending university.

6. **Will your test results be shared with you?**
   A rapid HIV test will be done after pre-HIV test counselling, and the results will be available to you immediately, followed by post-HIV test counselling. If you are found to be HIV-infected and you are not currently receiving care for this condition we will refer you to the local campus health clinic for follow up. Individual results from the throat swab will not be shared directly with you. If *Neisseria meningitidis* is grown from your swab, we will not be contacting you or providing eradication treatment as it is known that eliminating carriage through antibiotic use may increase one's risk of acquiring a more dangerous strain of meningococcus, therefore putting you at increased risk of acquiring meningococcal meningitis or sepsis.

7. **Will the results of the research be shared with you?**
   The results of the research will be shared in peer-reviewed medical journals and possibly at an international conference. Individual results will not be shared.

8. **Will any of your blood, tissue or other samples be stored and used for research in the future?**
   None of your body cells will be stored or kept for future work, however any meningococci isolated will be kept for future molecular work.

9. **Will you receive any reward (money or food vouchers) for taking part in this study?**
   At the one month follow up visit you will receive R100 to compensate you for your time and transport costs.

10. **Who will see the information which is collected about you during the study?**
    We will keep your information confidential, unless we are compelled by law to reveal any of your details. All the forms will be kept in locked cabinets or offices and on secure databases. Your information is being collected under a special number (study identification number) and not your name, therefore no-one will know which questionnaire/ HIV result/ throat swab belongs to you. A log of your study identification number and your name and contact details will be kept on a separate database by the principal investigators in order to contact you for the follow up visit at one month.

11. **Who do I speak to (or contact) if I have any questions about the study?**
    If you have any questions about the study, about your rights while taking part in the study or about any injury that may have happened because of the study you may contact one of the study investigators listed below:

Dr Susan Meiring	021 404 5302	susan.meiring@nhls.ac.za
Prof Cheryl Cohen	011 386 6593	cherylc@nicd.ac.za

    In addition, if you are a student from a Cape Town university, the UCT's Faculty of Health Sciences Human Research Ethics Committee can be contacted on 021 406 6338 in case you have any ethical concerns or questions about your rights or welfare as a participant on this research study.

    Students from Gauteng universities may contact, the University of the Witwatersrand's Committee for Research on Human Subjects (Medical), 011 717 1234.

NATIONAL HEALTH LABORATORY SERVICE
NATIONAL INSTITUTE FOR COMMUNICABLE DISEASES

Meningococcal carriage among university students

Consent Form

Centre for Respiratory Diseases and Meningitis (CRDM)
TEL: 011 386 6410 or 011 386 6434
FAX: 0113866850

Subject declaration section

I, _____ (*name of participant*), acknowledge that the study questionnaire, the HIV test and the throat swab have all been explained to me and that I agree to participate in the following study procedures:

☐ Y ☐ N I agree to answer the questions from the study questionnaire.

☐ Y ☐ N I agree to be tested for HIV for the purpose of this study.

☐ Y ☐ N I agree to have my throat swabbed for the purpose of this study.

The signature of the participant below means that the study questionnaire, the HIV test and the oropharyngeal swab have been explained to the participant and that he/ she agrees to participate only in the study procedures marked "Y" above.

I also agree to be contacted in one month to arrange an appointment for these procedures to be repeated to assess acquisition of meningococcal carriage.

☐ Yes ☐ No

Name and Surname of participant: _____

Date of consent taking: _____

Signature of participant: _____

Participant study identification number: _____

Name of staff member taking consent: _____

STUDY

NATIONAL HEALTH LABORATORY SERVICE
NATIONAL INSTITUTE FOR COMMUNICABLE DISEASES

Meningococcal carriage among university students

Case Investigation Form (CIF)

Centre for Respiratory Diseases and Meningitis (CRDM)
TEL: 011 386 6410 or 011 386 6434
FAX: 0113866850

1	*SURVEY 1* ☐ *SURVEY 2* ☐	*Date of completion:*
2	*Wits* ☐ *UCT* ☐	*Study Identification Number:*
	QUESTIONS/INSTRUCTIONS	RESPONSES
3	How old are you?	____years D D M M Y Y Y Y DOB:
4	Sex?	☐ Male ☐ Female
5	Are you currently registered as a first-year student?	☐ Yes ☐ No
6	What is your home province?(Province where you were staying prior to registration)	☐ EC ☐ FS ☐ GA ☐ KZ ☐ LP ☐ MP ☐ NC ☐ NW ☐ WC ☐ Outside South Africa
7	What are your current living arrangements?	☐ In dormitory/hostel ☐ In apartment/house with other students ☐ In apartment/house with family ☐ In apartment/house alone
8	Do you have any roommates? (i.e.do you share a bedroom with anyone)	☐ Yes ☐ No ☐ N/A If yes, how many people share the room (including yourself)? _____
9	In the last month, did you smoke tobacco (cigarettes, hookah, cigars) or marijuana?	☐ Yes, every day ☐ Yes, some days ☐ No, not at all
10	In the last month, were you exposed to second-hand smoke indoors?	☐ Yes, every day ☐ Yes, some days ☐ No, not at all
11	In the last 2 weeks, how often have you visited a night-club?	☐ Never ☐ Once per week ☐ 2-3 times per week ☐ 4 or more times per week
12	In the last 2 weeks, how often have you visited a pub/bar?	☐ Never ☐ Once per week ☐ 2-3 times per week ☐ 4 or more times per week
13	In the last 2 weeks, how often have you attended a party? (organised gathering of 10 or more persons)	☐ Never ☐ Once per week ☐ 2-3 times per week ☐ 4 or more times per week

14	In the last 2 weeks, have you attended any pubs/bars/clubs associated with the MSM community? (men who have sex with men)	☐ Yes ☐ No ☐ Unknown
15	If you are male, have you used the app "Grindr" in the last month?	☐ N/A I'm female ☐ Yes ☐ No ☐ Unknown
15	In the last 2 weeks, how many "French kissing"* partners have you had? (*open mouth kissing with tongue contact)	☐ None ☐ One ☐ Two ☐ Three or more
16	In the past month, have you taken any antibiotics? (Amoxil, Augmentin, Orolox, Ciprobay, Zithromax, etc.)	☐ Yes ☐ No ☐ Unknown
17	In the past month, have you had any upper respiratory infections? (symptoms of cough, runny nose, or sore throat)	☐ Yes ☐ No ☐ Unknown
18	What is your HIV status?	☐ HIV positive ☐ HIV negative ☐ Unknown
19	Please mark if you have any of the chronic medical conditions listed?	Diabetes ☐Yes ☐No ☐Unk Chronic lung disease ☐Yes ☐No ☐Unk Asplenia (no spleen) ☐Yes ☐ No ☐ Unk Complement deficiency ☐Yes ☐ No ☐Unk
20	Have you ever received a meningococcal vaccine? (Menactra, Menomune)	☐ No, never ☐ Yes, in the last 2 years ☐ Yes, more than 2 years ago ☐ Unknown
Thank you for completing this questionnaire regarding risk factors for carriage of *Neisseria meningitidis*		

For study staff use only:

Swab taken: ☐ Yes ☐ No	Exudate present: ☐ Yes ☐ No	Swabber/plater initials:
HIV test done: ☐ Yes ☐ No HIV rapid test result: ☐ Pos ☐ Neg ☐ Unk	2nd HIV test done: ☐ Yes ☐ No Confirmatory result: ☐ Pos ☐ Neg ☐ Unk	Phlebotomist initials:

NATIONAL INSTITUTE FOR COMMUNICABLE DISEASES
Division of the National Health Laboratory Service

GERMS-SA – Laboratory Enhanced Surveillance

Case Report Form 2016 and 2017

TEL: 011 555 0412 OR 011 386 6234
FAX: 011 386 6221

CRF start date: ☐☐/☐☐/☐☐☐☐ (dd/mm/yyyy) | **CRF finalised date:** ☐☐/☐☐/☐☐☐☐ (dd/mm/yyyy)

CRF completed by Surveillance Officer name: **Signature:** | **CRF checked by Surveillance Officer name:**

Sources of data: Patient/ Guardian ☐ Clinician ☐ Medical Records ☐ No record found ☐ Not admitted ☐ Informed consent refused ☐

Was a telephonic interview done: Yes ☐ No ☐ Who was the telephonic interview with? Patient ☐ Next of kin ☐

Lab specimen No: **Laboratory name:**

Hospital Name: **Hospital Number:** **Ward:** _____ Adult ward ☐ Paed ward ☐

Gender: Male ☐ Female ☐ Unk ☐ **Race:** Asian ☐ Black ☐ Coloured ☐ White ☐ Unk ☐

Date of Birth: ☐☐/☐☐/☐☐☐☐ (dd/mm/yyyy) DOB Unk ☐ **Age:**_____ Days ☐ Months ☐ Years ☐ Age Unk ☐

Identity No: ☐☐☐☐☐☐☐☐☐☐☐☐☐ Identity No Unk ☐

Patient surname: **Patient first names:**

Address: **Town/ City:** **Province:**

Telephone No: (H) (Work) (Cell) (Neigbour)

Has patient stayed in SA for the last month? Yes ☐ No ☐ Unk ☐ If no, which country has patient come from?

Was the patient referred from a hospital or chronic-care facility? Yes ☐ No ☐ Unk ☐ If yes, specify:

Number of days in above facility before transfer to acute hospital: N/A ☐ 0-2 days ☐ 3-4 days ☐ >4 days ☐ Unk ☐

Date of admission to acute hospital: ☐☐/☐☐/☐☐☐☐ Date Unk ☐

Was patient transferred to another hospital? Yes ☐ No ☐ Unk ☐ **If yes, name of other hospital:**

Date of transfer: ☐☐/☐☐/☐☐☐☐

Final outcome of patient: Discharged ☐ Died ☐ RHT/ Absconded ☐ Unk ☐ **Outcome date:** ☐☐/☐☐/☐☐☐☐

If discharged, patient discharged to: Home ☐ TB Hosp/ Chronic care facility ☐ Other ☐ Specify: Unk ☐

Diagnosis related to the organism isolated: Meningitis ☐ LRTI ☐ Fungaemia/ Bacteraemia without focus ☐ Other ☐ Specify:

Organism isolated:

S. pneumoniae ☐ *Haemophilus* sp. ☐ *N. meningitidis* ☐

Cryptococcus sp. ☐ *Candida* sp. ☐ *Salmonella* Typhi ☐

Date of specimen collection: ☐☐/☐☐/☐☐☐☐

Site of specimen collection:

CSF ☐ Blood ☐ Joint Fluid ☐ Other ☐ Specify:

Severity of illness (on the day positive specimen was taken):

Temp: ºC Unk ☐ **BP** / Unk ☐ **Mechanical ventilation** Yes ☐ No ☐ Unk ☐ **Cardiac Arrest:** Yes ☐ No ☐ Unk ☐

GCS: /15 Unk ☐ **Mental status:** Alert ☐ Responds to verbal commands (Disoriented) ☐ Responds to painful stimuli (Stuporous) ☐

Unresponsive/unconscious (Comatose) ☐ Sedated/Post ictal ☐ Unk ☐

Previous admissions in the last 12 months: Yes ☐ No ☐ Unk ☐ Number of admissions: ☐

Cotrimoxazole prophylaxis (not current treatment): Yes ☐ No ☐ Unk ☐ **Dosage:** **Frequency:**

Date initiated: ☐☐/☐☐/☐☐☐☐ Date unk ☐ **Compliant in last month:** Yes ☐ No ☐ Unk ☐

TB treatment (from the last 3 months and current): Yes ☐ No ☐ Unk ☐ **If Yes, is it**: Pulmonary ☐ Meningeal ☐ Other ☐ Unk ☐

TB Drugs :	1.	3.	**Date initiated:** ☐☐/☐☐/☐☐☐☐
	2.	4.	**Date stopped:** ☐☐/☐☐/☐☐☐☐

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GERMS-SA – Laboratory Enhanced Surveillance

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Laboratory Specimen Number: ☐☐☐☐☐☐☐☐☐☐

Conditions predisposing patient to infections: Yes ☐ No ☐ Unknown ☐ (**if yes**, please specify)

Pregnancy ☐	Prematurity ☐ Age at birth: _____	Chromosomal conditions incl Down Syndrome ☐	Protein Energy Malnution (PEM) ☐	
Chronic lung disease incl Asthma/ COPD/ Cystic Fibrosis ☐	Chronic renal disease incl nephrotic syndrome/ Fanconi Anaemia ☐	CVA/ Stroke neuromuscular diseases/ cerebral palsy ☐	Chronic liver conditions incl cirrhosis/ liver failure ☐	Head injury/ CSF leak/ head surgery/ ventricular shunt/ cochlear implants ☐
Connective tissue diseases incl SLE ☐	Metabolic diseases incl diabetes mellitus ☐	Functional/ anatomic asplenia incl sickle cell disease ☐	Primary Immuno-deficiency conditions ☐	Immunosuppressive Rx (steroids, chemoRx) ☐
Aplastic anaemia ☐	Complement deficiency ☐	Burns ☐	Gastric acid suppression ☐	Pancreatitis ☐
Current smoker ☐	Alcohol dependency ☐	Abdominal surgery ☐	Non-abdominal surgery ☐ _____	
Cardiac conditions incl valvular disease, heart failure ☐ Specify:		Malignancy ☐ Specify:	Organ transplant ☐ Specify:	Other ☐ Specify:

Information regarding HIV status

HIV status on presentation: Positive ☐ Negative ☐ Unk ☐ If positive when was diagnosis made? ☐☐/☐☐/☐☐☐☐ Unk ☐

Source of HIV status: Verbal ☐ Med rec ☐ RTHC ☐ Other ☐ Specify……..

If negative, when was the last test done? ☐☐/☐☐/☐☐☐☐ Unk ☐

If HIV unknown or tested negative >6 months ago, patient needs to be tested

HIV status now (after testing): Positive ☐ Negative ☐ Not done ☐ Unk ☐ Date of recent HIV test ☐☐/☐☐/☐☐☐☐

For children <18 months: was HIV PCR done? N/A ☐ Yes ☐ No ☐ Unk ☐ Date of PCR ☐☐/☐☐/☐☐☐☐ Unk ☐

HIV EXPOSURE: If child is <5 years, what was the **mother's** HIV status during pregnancy? N/A ☐ Positive ☐ Negative ☐ Unk ☐

Date of mother's HIV test ☐☐/☐☐/☐☐☐☐ Unk ☐

Source of mother's HIV status: Verbal ☐ Med rec ☐ RTHC ☐ Other ☐ Specify……..

If mother was HIV positive during pregnancy, which ARVs were given: HAART ☐ AZT only ☐ None ☐ Unk ☐ Other ☐ Specify……..

Date mother was started on ARV therapy: ☐☐/☐☐/☐☐☐☐ Unk ☐

Mother's CD4 count in pregnancy: Absolute: _____ Unk ☐ Date of CD4 count during pregnancy ☐☐/☐☐/☐☐ Unk ☐

Most recent CD4 count: N/A or not done ☐ Absolute: _____ Percentage _____% Date ☐☐/☐☐/☐☐☐☐

Most recent viral load: N/A or not done ☐ <400 ☐ 400-10 000 ☐ >10 000 ☐ Date ☐☐/☐☐/☐☐☐☐

Any antiretroviral use? N/A ☐ Yes ☐ No ☐ Unk ☐ **If yes, is it:** Current ☐ Previous ☐ Perinatal ☐ Unk ☐

If current, what was the date of initiation of HAART? ☐☐/☐☐/☐☐☐☐ Date unk ☐

Clinical markers for HIV N/A ☐ Yes ☐ No ☐ Unk ☐ If yes , tick all that apply:

Diarrhoea >10 days ☐ HIV wasting ☐ Oral candidiasis ☐ Cryptococcosis ☐

Suspected PCP ☐ Kaposis sarcoma ☐ Other, specify ☐ WHO staging 1 ☐ 2 ☐ 3 ☐ 4 ☐ Unk ☐

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PLEASE COMPLETE RELEVANT SECTIONS FOR SPECIFIED ORGANISMS

For N. meningitidis ONLY

Do you attend school or college (as a learner or a teacher)?	Yes ☐	No ☐	Unk ☐
If yes, what kind of institution? University ☐	College ☐	School ☐	Other ☐
Do you live in a communal home?	Yes ☐	No ☐	Unk ☐
If yes, mark type of home:	school/university hostel ☐	Care institution ☐	
Prison ☐	Barracks ☐	Other, specify	
Have you ever had meningococcal vaccine?	Yes ☐	No ☐	Unk ☐

PLEASE COMPLETE RELEVANT SECTIONS FOR SPECIFIED ORGANISMS

Laboratory specimen Number: ☐☐☐☐☐☐☐☐☐☐☐

***Haemophilus* spp, *S. pneumoniae*, *N. meningitidis* ONLY**

For children <5 yrs of age:

During the first 4 months of life, how was the child fed? Breastfed exclusively ☐ No breast milk ☐ Breast milk plus other feeds ☐ Unk ☐

Did the child attend a crèche (outside the home) in the last 3 months Yes ☐ No ☐ Unk ☐

What was the birth weight? ☐☐☐☐ grams Unk ☐ | What is the current weight? ☐☐☐☐☐ grams Unk ☐

What was the gestational age at birth? ☐☐ weeks Unk ☐

Is oedema present? Yes ☐ No ☐ Unk ☐ If yes, what is the cause? Malnutrition ☐ Renal ☐ Sepsis ☐ Other ☐ Specify……..

For all ages: **Number of children <18 years, living with patient :** None ☐ Number ☐ Place of safety ☐ Unk ☐

Have any of these children been hospitalised in the last 3 months? N/A ☐ Yes ☐ No ☐ Unk ☐

Antibiotic use prior to this specimen collection date:

ABX in 24hr before specimen: Yes ☐ No ☐ Unk ☐ **Date initiated:** ☐☐/☐☐/☐☐☐☐

Name of antibiotic: 1. 2. 3. 4.

Other ABX in last 2 months (excluding last 24hrs): Yes ☐ No ☐ Unk ☐ | **In last 30 days** Yes ☐ No ☐ Unk ☐

Name of antibiotic : 1. 2. | **In last 30 to 60 days:** Yes ☐ No ☐ Unk ☐

Antibiotic use in hospital during this admission (excluding TB therapy and cotrimoxazole prophylaxis) **Weight:** ☐☐☐.☐ kg Unk ☐ | Antimicrobial therapy unknown: ☐ | Antimicrobial therapy not prescribed ☐

Name of antimicrobial	Dose	Route			Freq	Date initiated	Total doses given	No of days
		PO	IVI	IMI				
1.						☐☐/☐☐/☐☐☐☐		
2.						☐☐/☐☐/☐☐☐☐		
3.						☐☐/☐☐/☐☐☐☐		
4.						☐☐/☐☐/☐☐☐☐		
5.						☐☐/☐☐/☐☐☐☐		

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***ANSWER FOR Haemophilus* spp, *S. pneumoniae*, *N. meningitidis* MENINGITIS and *N. meningitidis* BACTERAEMIA ONLY**

SEQUELAE: by the end of the hospital admission did the patient develop or experience any of the following complications?

Necrotic skin lesions	Yes ☐	No ☐	Unk ☐	
Amputation	Yes ☐	No ☐	Unk ☐	If yes, specify
Hydrocephalus	Yes ☐	No ☐	Unk ☐	
New onset seizures	Yes ☐	No ☐	Unk ☐	
Hearing loss	Yes ☐	No ☐	Unk ☐	If yes, was it documented by an audiologist ? Yes ☐ No ☐ Unk ☐
If yes to hearing loss, was it unilateral or bilateral ?	Unilateral ☐	Bilateral ☐	Unsure ☐	
Loss of vision (new onset) ?	Yes ☐	No ☐	Unk ☐	If yes is it: Unilateral ☐ Bilateral ☐ Unsure ☐
Neurological fall out (ie weakness of limbs, limp, cognitive slowness)?	Yes ☐	No ☐	Unk ☐	If yes, specify

***ANSWER FOR Haemophilus* spp, *S. pneumoniae*, *N. meningitidis* MENINGITIS and *N. meningitidis* BACTERAEMIA ONLY**

Additional outcome follow up at 2 months post admission date Best contact number:

Date of follow up: ☐☐/☐☐/☐☐☐☐

What was the follow up outcome? Alive ☐ Died ☐ Unk (not possible to determine) ☐ If died, date of death: ☐☐/☐☐/☐☐☐☐

If alive are there sequelae: Yes ☐ No ☐ Unk ☐

If yes to sequelae please mark if yes to the following :

Skin scarring	Yes ☐	No ☐	Unk ☐	If yes does patient attend plastic surgery OPD? Yes ☐ No ☐ Unk ☐
Amputations	Yes ☐	No ☐	Unk ☐	If yes, specify: If yes does patient attend orthopaedic clinic? Yes ☐ No ☐ Unk ☐
Hydrocephalus	Yes ☐	No ☐	Unk ☐	
New onset seizures	Yes ☐	No ☐	Unk ☐	
Neurological fallout::	Yes ☐	No ☐	Unk ☐	If yes, specify: If yes does patient attend physiotherapy? Yes ☐ No ☐ Unk ☐
Hearing loss:	Yes ☐	No ☐	Unk ☐	If yes to hearing loss, was it unilateral or bilateral ? Unilateral ☐ Bilateral ☐ Unsure ☐

If yes to hearing loss, was it documented by an audiologist ? Yes ☐ No ☐ Unk ☐

Does patient have a hearing aid or need surgery to improve hearing? Yes ☐ No ☐ Unk ☐

Visual Loss: Yes ☐ No ☐ Unk ☐ If yes to visual loss is it Unilateral ☐ Bilateral ☐

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PLEASE COMPLETE RELEVANT SECTIONS FOR SPECIFIED ORGANISMS

For *Haemophilus* spp, *S. pneumoniae* : If child is <15 yrs please complete the details on the following vaccines

Vaccine	Dose	Dose given	Batch number of dose given (recorded on RTHC)	If yes, date given (dd/mm/yyyy)
PCV	Dose 1 (*6 weeks*)	Yes No N/A	Unk	____ / ____ / _____ Unk
	Dose 2 (*14 weeks*)	Yes No N/A	Unk	____ / ____ / _____ Unk
	Dose 3 (*9 months*)	Yes No N/A	Unk	____ / ____ / _____ Unk
	Catch-up dose	Yes No N/A	Unk	____ / ____ / _____ Unk
Rotavirus	Dose 1 (*6 weeks*)	Yes No N/A	Unk	____ / ____ / _____ Unk
	Dose 2 (*14 weeks*)	Yes No N/A	Unk	____ / ____ / _____ Unk
BCG	Birth dose	Yes No		____ / ____ / _____ Unk
Measles	Dose 1 (*9 months*)	Yes No		____ / ____ / _____ Unk
	Dose 2 (*18 months*)	Yes No		____ / ____ / _____ Unk
	Campaign dose	Yes No		____ / ____ / _____ Unk
DTP+HIB	Dose 1 (*6 weeks*)	Yes No		____ / ____ / _____ Unk
(or Pentaxim)	Dose 2 (*10 weeks*)	Yes No		____ / ____ / _____ Unk
	Dose 3 (*14 weeks*)	Yes No		____ / ____ / _____ Unk
	Dose 4 *(18 months)*	Yes No		____ / ____ / _____ Unk
OPV/IPV	Birth dose	Yes No		____ / ____ / _____ Unk
	Dose 1 (*6 weeks*)	Yes No		____ / ____ / _____ Unk
	Dose 2 (*10 weeks*)	Yes No		____ / ____ / _____ Unk
	Dose 3 (*14 weeks*)	Yes No		____ / ____ / _____ Unk
	Dose 4 (*18 months*)	Yes No		____ / ____ / _____ Unk
Hep B	Dose 1 (*6 weeks*)	Yes No		____ / ____ / _____ Unk
	Dose 2 (*10 weeks*)	Yes No		____ / ____ / _____ Unk
	Dose 3 (*14 weeks*)	Yes No		____ / ____ / _____ Unk

Source of vaccine status information:

Road to health card seen by S. officer ☐ Verbal report from caregiver/ patient ☐ Notes in medical record from RTHC ☐

Notes in medical record ☐ Directly from the clinic ☐ Other ☐ Specify:

Name of clinic(s) where the child was vaccinated:

Clinic 1: Name Location: Telephone number

Clinic 2: Name Location: Telephone number

Clinic 3: Name Location: Telephone number

Has the **patient (all ages)** received the 23 valent polysaccharide pneumococcal vaccine? N/A ☐ Yes ☐ No ☐ Unk ☐

If yes, give date most recently given: ☐☐/☐☐/☐☐☐☐

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Laboratory Specimen Number: ☐☐☐☐☐☐☐☐☐☐

***Candida* spp. ONLY**

Did this patient have a prior episode of candidaemia? Yes ☐ No ☐ Unk ☐ **If yes, date of specimen collection:** ☐☐/☐☐/☐☐☐☐

Did patient require hospitalisation in the 90 days before the first positive culture for *Candida* was drawn? Yes ☐ No ☐ Unk ☐

Was patient ever in an ICU during this hospital admission? Yes ☐ No ☐ Unk ☐

Did the patient have a central venous catheter (CVC) before or while the first positive culture was drawn? Yes ☐ No ☐ Unk ☐

Were CVCs removed or changed after the date of candidaemia? N/A ☐ Yes ☐ No ☐ Unk ☐

Did the patient receive any of the following in the 14 days before initial culture date?
Systemic antibacterials: Yes ☐ No ☐ Unk ☐ Total parenteral nutrition (TPN): Yes ☐ No ☐ Unk ☐

Did the patient receive systemic antifungal medication in the 14 days before the date the first positive culture was drawn? Yes ☐ No ☐ Unk ☐

If yes, please specify antifungals:

Antifungal drug can't be specified – unk ☐ Amphotericin B, any formulation ☐ Itraconazole (Sporanox) ☐ Caspofungin (Cancidas) ☐
Posaconazole (Noxafil) ☐ Fluconazole (Diflucan) ☐ Voriconazole (Vfend) ☐ Other:

Was systemic antifungal therapy given to treat candidaemia during this admission? Yes ☐ No ☐ Unk ☐

If yes, please specify antifungals: Antifungal drug can't be specified – unk ☐ **Weight:** ☐☐.☐kg Unk ☐

Name of antimicrobial	Dose	Route			Freq	Date initiated	Date stopped
		PO	IVI	Other			
Amphotericin B, any formulation						☐☐/☐☐/☐☐☐☐	☐☐/☐☐/☐☐☐☐
Fluconazole (Diflucan)						☐☐/☐☐/☐☐☐☐	☐☐/☐☐/☐☐☐☐
Caspofungin (Cancidas)						☐☐/☐☐/☐☐☐☐	☐☐/☐☐/☐☐☐☐
Voriconazole (Vfend)						☐☐/☐☐/☐☐☐☐	☐☐/☐☐/☐☐☐☐
						☐☐/☐☐/☐☐☐☐	☐☐/☐☐/☐☐☐☐
						☐☐/☐☐/☐☐☐☐	☐☐/☐☐/☐☐☐☐

Has *Candida* disseminated to the deep organs? Yes ☐ No ☐ Unk ☐

If yes, specify: CNS ☐ Cardiac ☐ Osteoarticular ☐ Hepatosplenic ☐ Renal ☐ Ocular ☐

Is this specimen thought by the clinicians to be causing a true infection? Yes ☐ No ☐ (thought to be a contaminant)

Is patient ≤90 days of age at the time of candidaemia? Yes ☐ No ☐ Unk ☐ **If no or unknown, questionnaire is complete**

Infant and neonatal candidaemia (≤90 days)

Is patient ≤30 days of age at the time of candidaemia? Yes ☐ No ☐ Unk ☐

What kind of delivery did the patient have? Vaginal delivery ☐ Caesarean section ☐ Unk ☐

What was the 5-minute Apgar score? ☐☐ Unk ☐ **What was the birth weight?** ☐☐☐☐ grams Unk ☐

What was the gestational age at birth? ☐☐ weeks Unk ☐ **What is the current weight?** ☐☐☐☐ grams Unk ☐

Were H2 blockers used before the date of the first positive culture? Yes ☐ No ☐ Unk ☐

How was the baby fed before the date of the first positive blood culture? Breastfeeding ☐ Formula ☐ Mixed ☐ Unk ☐
N/A (TPN only) ☐

At what age were the feeds introduced? ☐☐ days Unk ☐ N/A (TPN only) ☐

Underlying conditions prior to candidaemia (check all that apply): None ☐ Unk ☐

Abdominal pathology (e.g. gastroschisis or exomphalos) ☐ Congenital malformation ☐ Surgery ☐
Postnatal steroid exposure ☐ Hyperglycaemia ☐

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***Cryptococcus* spp. ONLY**

Antifungals prior to this admission:

Fluconazole: Yes ☐ No ☐ Unk ☐ If yes, date initiated: ☐☐/☐☐/☐☐☐☐ **Dose:** Daily ☐ BD ☐

Amphotericin B: Yes ☐ No ☐ Unk ☐ If yes, date initiated: ☐☐/☐☐/☐☐☐☐ **Dose:**

Is this the first episode of cryptococcosis? Yes ☐ No ☐ Unk ☐ **Weight:** ☐☐☐.☐ kg Unk ☐

Did the patient have symptoms/ signs of meningitis at this admission? Yes ☐ No ☐ Unk ☐ **If yes to symptoms, specify: Headache** ☐ **Confusion** ☐ **Other** ☐ Specify:

If no symptoms, was blood CrAg test performed? Yes ☐ No ☐ Unk ☐ **If yes to blood CrAg test, specify date of test:** ☐☐/☐☐/☐☐☐☐

Management during this admission: Antifungal therapy unknown ☐ Antifungal therapy not prescribed ☐

	Dose	Route		Frequency		Date initiated	Total number of doses/ number of days
Fluconazole		PO ☐	IVI ☐	Daily ☐	BD ☐	☐☐/☐☐/☐☐☐☐	
Amphotericin B			IVI ☐	Daily ☐	BD ☐	☐☐/☐☐/☐☐☐☐	

Rifampicin Yes ☐ No ☐ Unk ☐

Was opening intracranial pressure documented at any time? Yes ☐ No ☐ Unk ☐ **If yes, what was the recorded opening pressure?** _____ cm H_20 Unk ☐

On discharge, was patient given fluconazole? Yes ☐ No ☐ Unk ☐ Died ☐