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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.

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

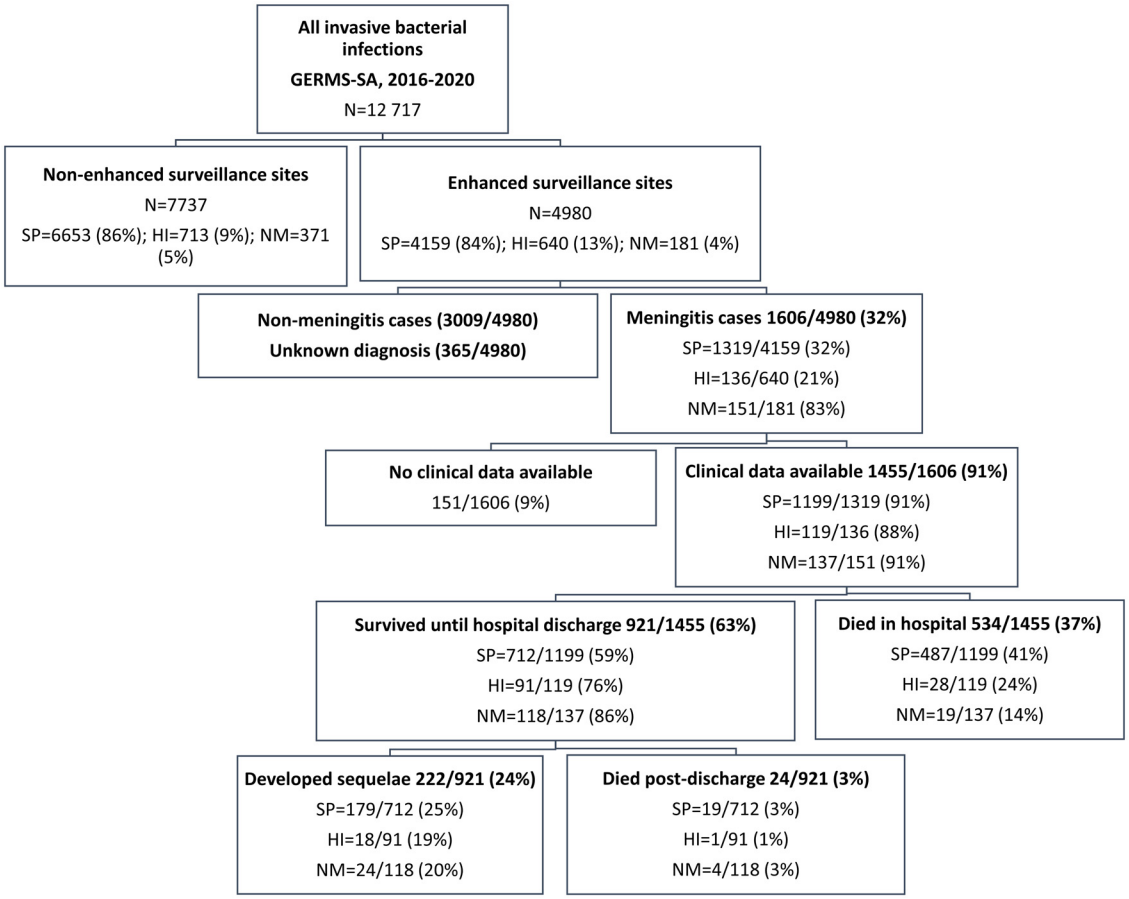

Figure 1. Flow diagram of meningitis and nonmeningitis invasive bacterial infections reported to GERMS-SA enhanced surveillance sites, South Africa, 2016-2020. Abbreviations: HI: *Haemophilus influenzae*; NM: *Neisseria meningitidis;* SP: *Streptococcus pneumoniae.*

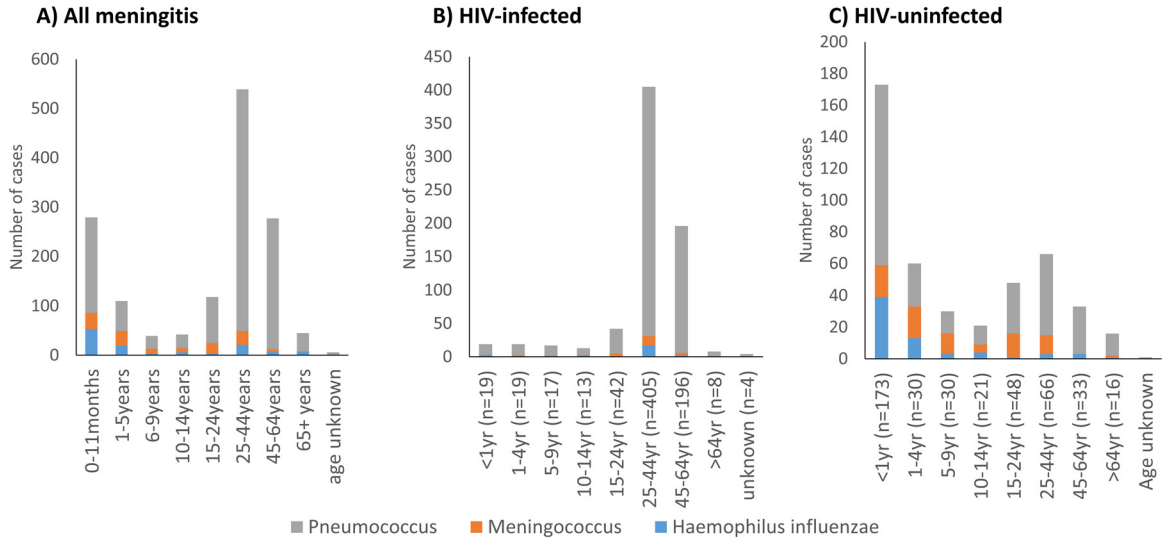

Figure 2. (a-c) Age distribution of bacterial meningitis cases reported to GERMS-SA enhanced surveillance sites, South Africa, 2016-2020 (n = 1455).

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

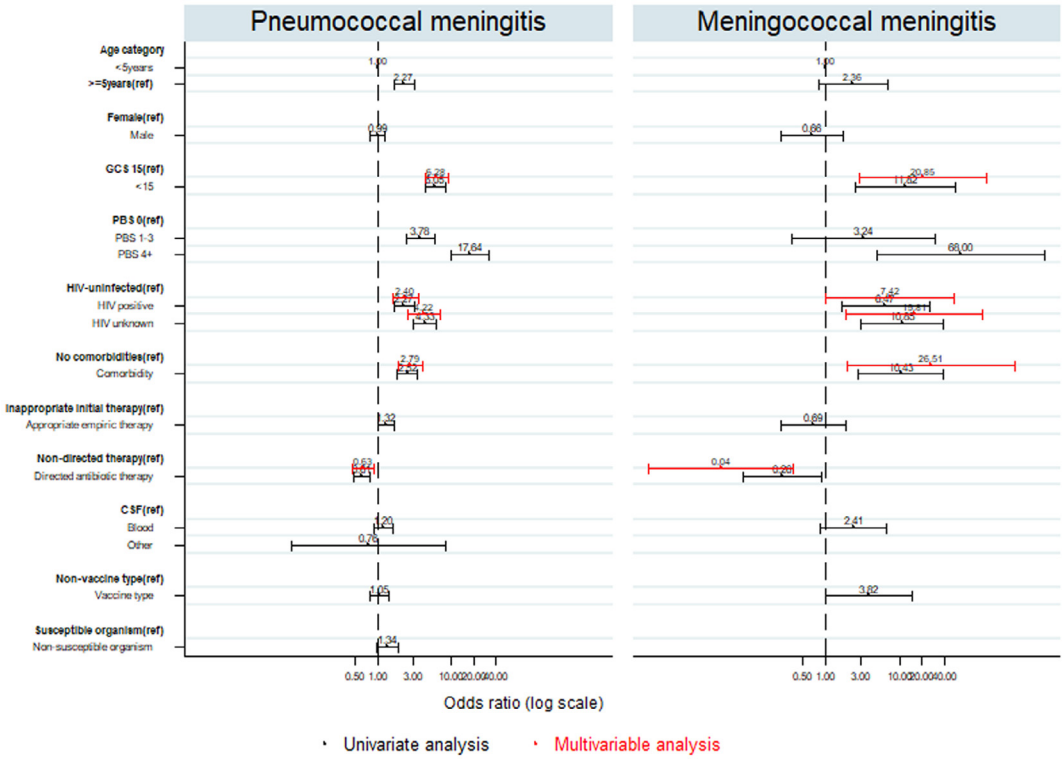

Figure 3. Forest plot: univariate and multivariable analysis of risk factors for mortality following pneumococcal and meningococcal meningitis, 2016-2020. Abbreviations: GCS: Glasgow coma score; PBS: Pitt bacteremia score for severity of illness.

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

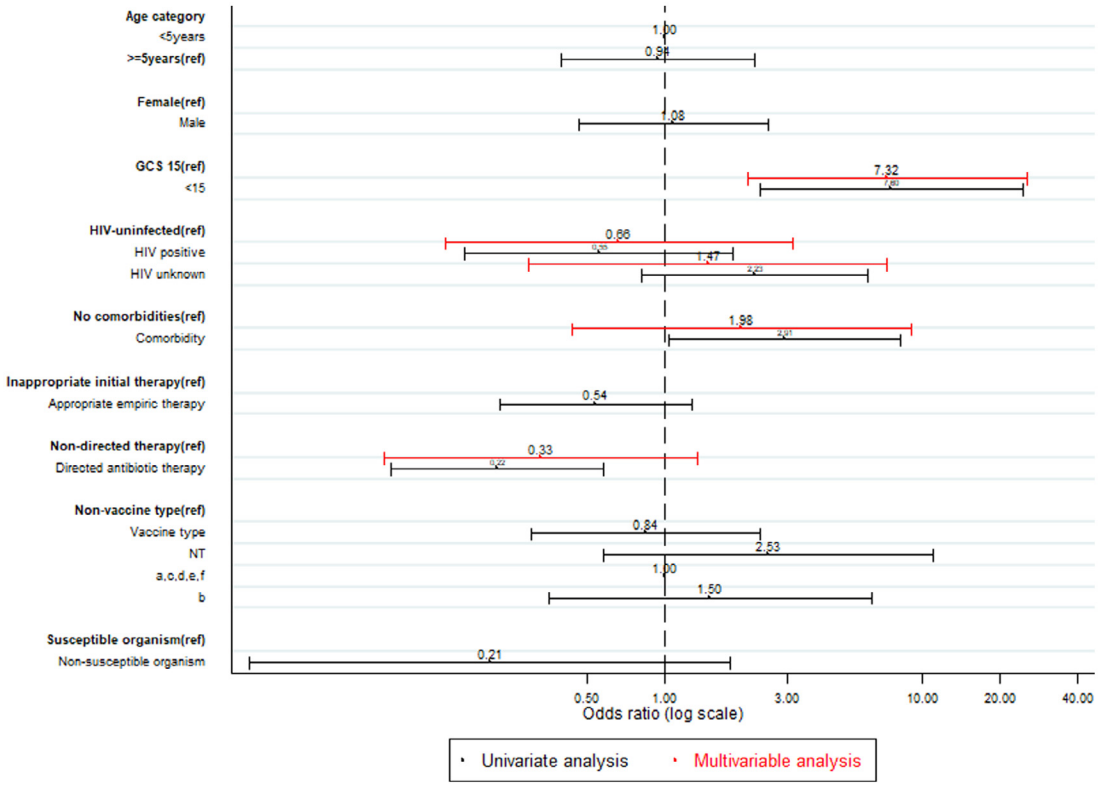

Figure 4. Forest plot: a univariate and multivariable analysis of risk factors for mortality following *Haemophilus influenzae* meningitis, 2016-2020.
Abbreviations: GCS: Glasgow coma score; PBS: Pitt bacteremia score for severity of illness.

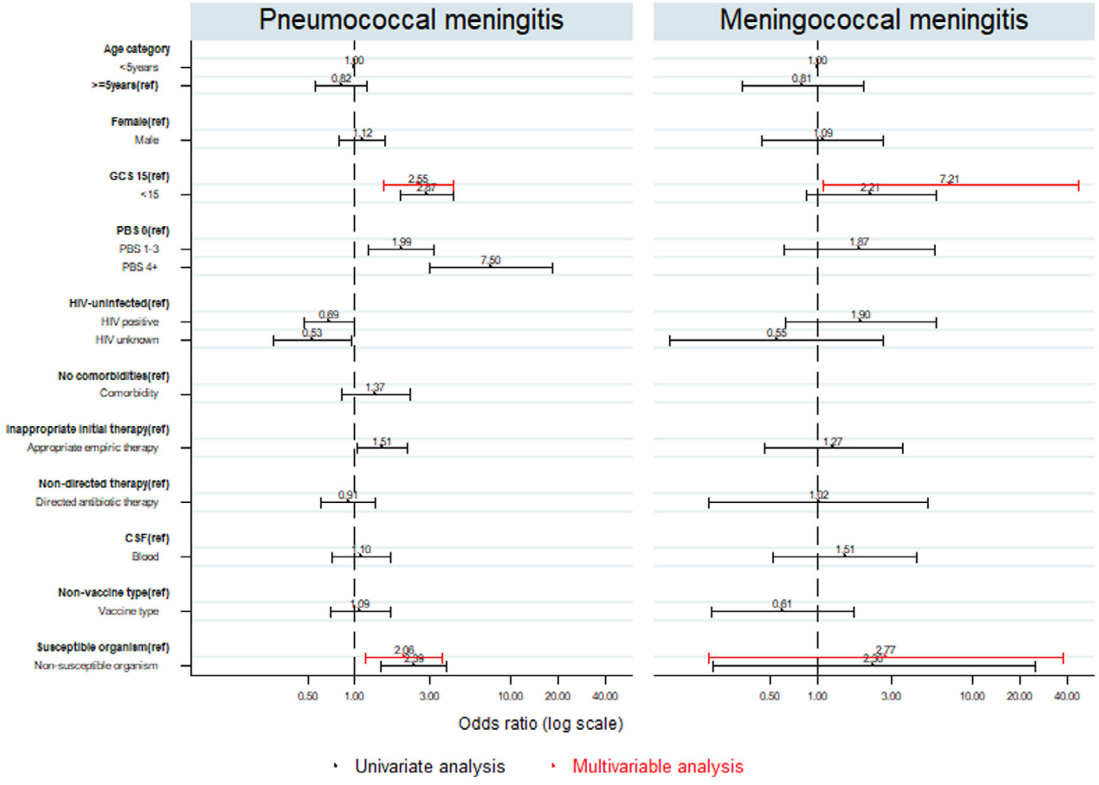

Figure 5. Forest plot: a univariate and multivariable analysis of risk factors for developing sequelae following pneumococcal and meningococcal meningitis, 2016-2020.
Abbreviations: GCS: Glasgow coma score; PBS: Pitt bacteremia score for severity of illness.

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-

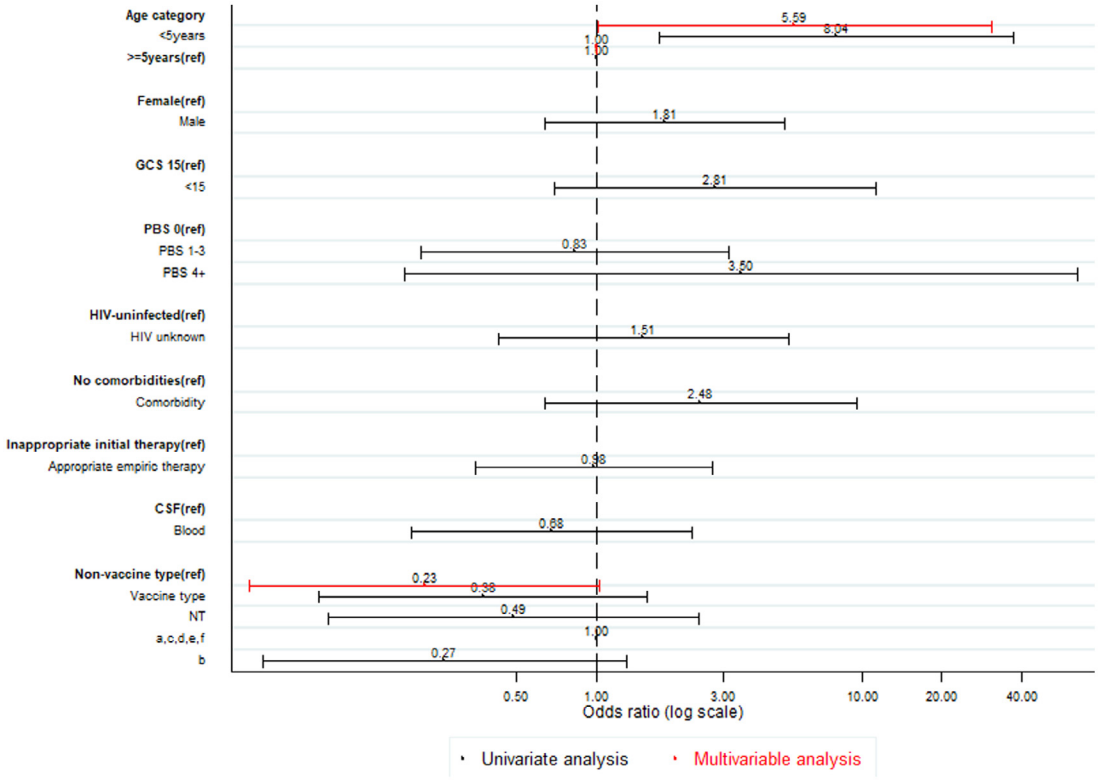

Figure 6. Forest plot: univariate and multivariable analysis of risk factors for developing sequelae following *Haemophilus influenzae* meningitis, 2016-2020 n = 91. Abbreviations: GCS: Glasgow coma score; PBS: Pitt bacteremia score for severity of illness.

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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