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Article *in* Clinical Infectious Diseases · October 2018

DOI: 10.1093/cid/ciy914

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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

Received 18 July 2018; editorial decision 15 October 2018; accepted 19 October 2018; published online October 23, 2018.

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Clinical Infectious Diseases® 2019;69(3):495–504

DOI: 10.1093/cid/ciy914

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 χ2-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

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

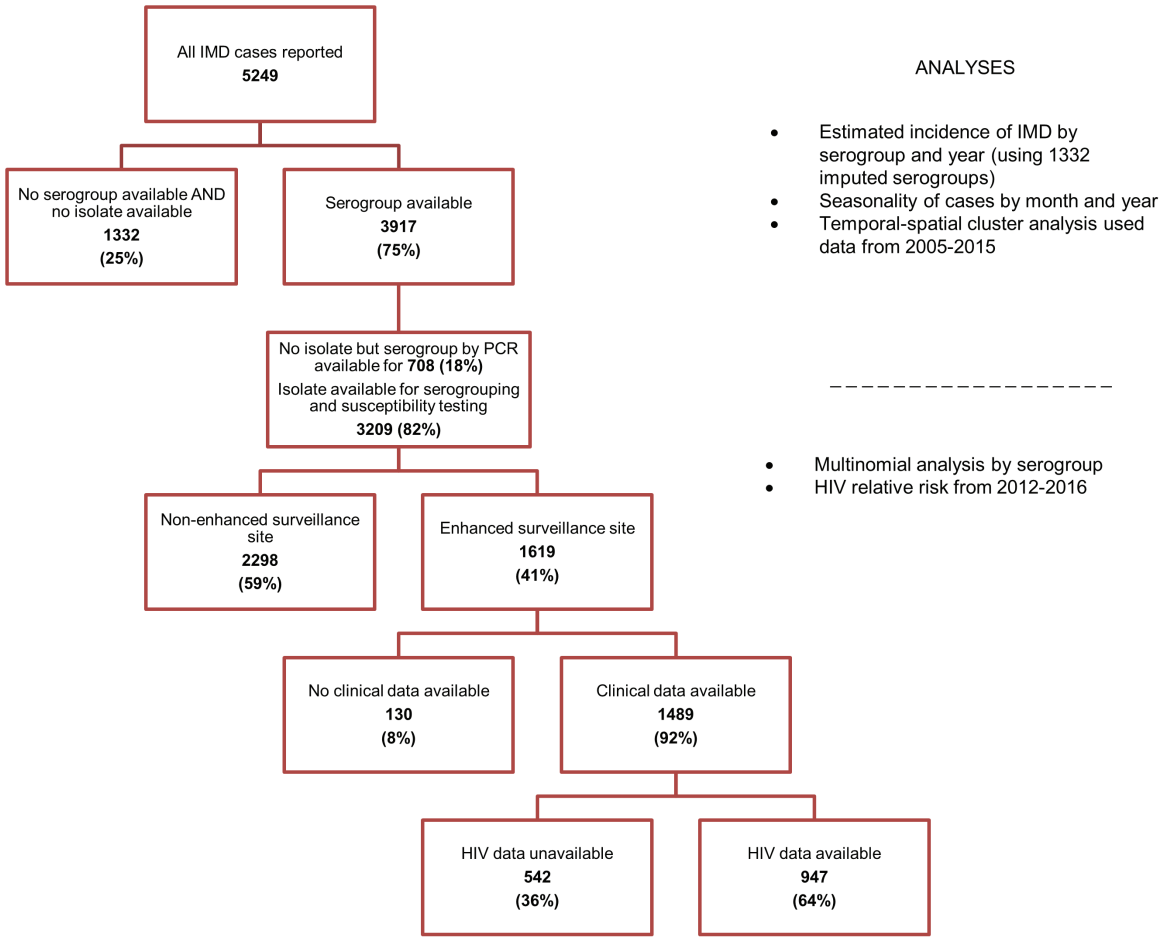

Figure 1. Flow chart of laboratory-confirmed cases of IMD reported to GERMS-SA, in South Africa, from 2003–2016 (N = 5249). Abbreviations: HIV, human immunodeficiency virus; IMD, invasive meningococcal disease; PCR, polymerase chain reaction.

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)

Table 1. *Continued*

Characteristics	All n/N (%)	B (Reference) n/N (%)	A n/N (%)	A RRR (95%CI)	A aRRR (95% CI)	C n/N (%)	C RRR (95%CI)	C aRRR (95% CI)	W n/N (%)	W RRR (95%CI)	W aRRR (95% CI)	Y n/N (%)	Y RRR (95%CI)	Y aRRR (95% CI)	Other n/N (%)	Other RRR (95%CI)	Other 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 (3.2–572)	-
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%

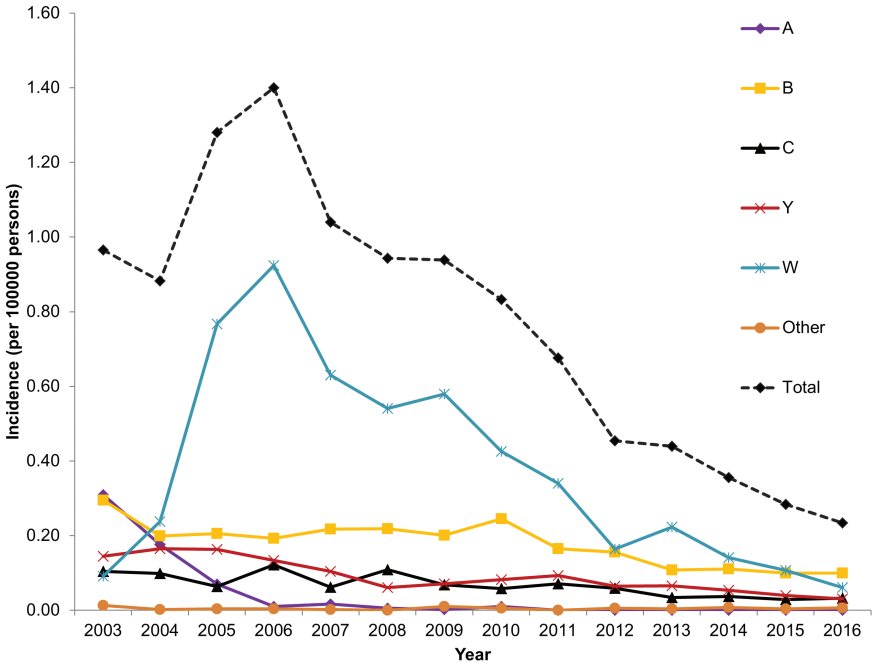

Figure 2. Estimated incidence of invasive meningococcal disease by serogroup and year, in South Africa, from 2003–2016 (N = 5249). Serogroup data were imputed for 1332 cases. The "Other" serogroups included 12 X, 4 Z, and 15 non groupable isolates. Significant increases in disease incidence were seen 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

Age Category	Invasive Meningococcal Disease Incidence, 2012–2016						Relative Risk (95% CI)	
	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.

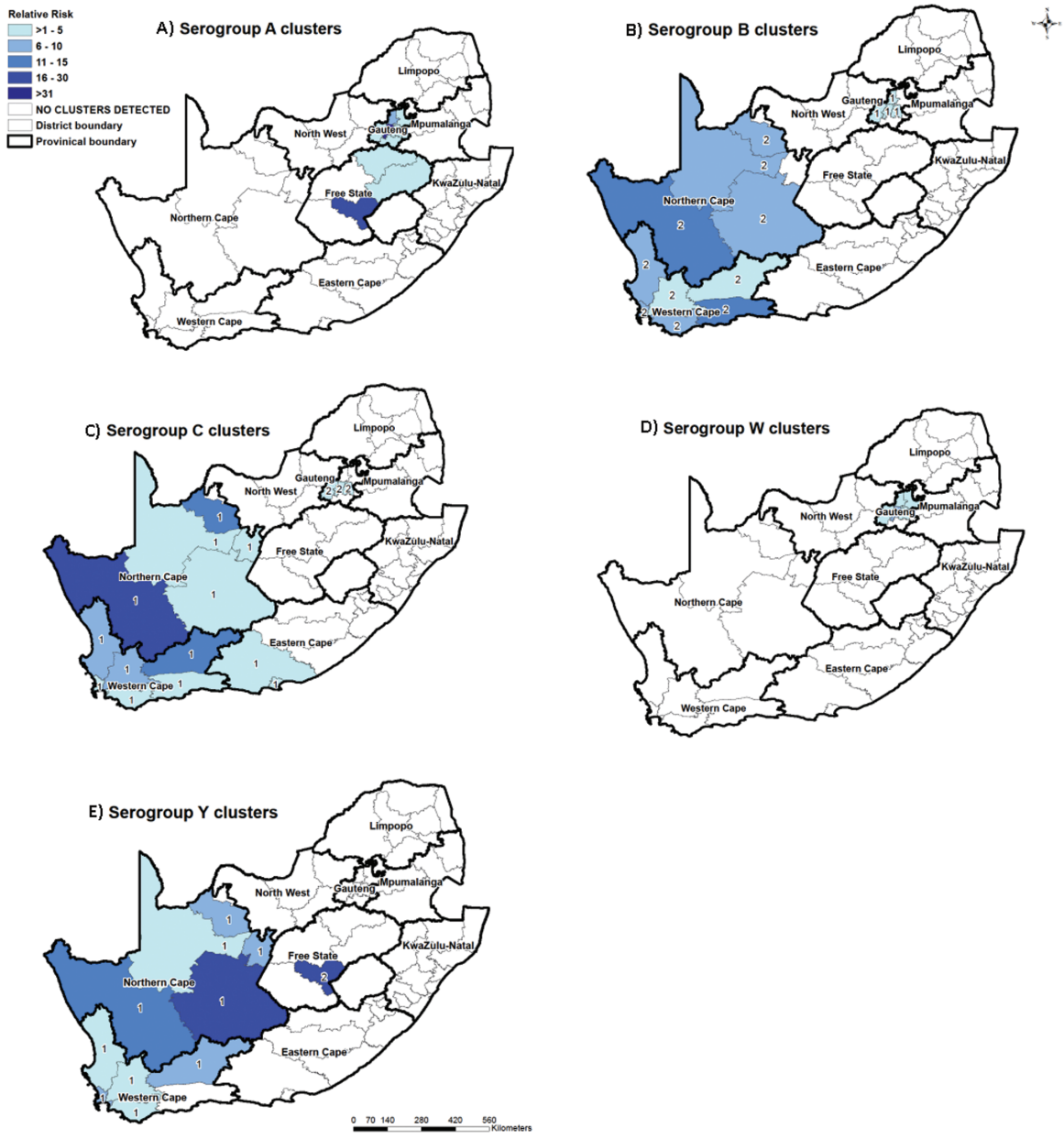

Figure 3. Invasive meningococcal disease clusters, by serogroup, by district, occurring in South Africa, from 2005–2015. (*A*) The serogroup A cluster occurred from January 2005 to September 2008 and had a within-cluster relative risk (RR) of 7.7. (*B*) There were 2 serogroup B clusters: cluster 1 occurred 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,

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.

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.

The GERMS-SA membership includes Principal investigator Vanessa Quan; John Black and Vanessa Pearce, from Eastern Cape; Anwar Hoosen and Vicky Kleinhans, from Free State; Alan Karstaedt, Caroline Maluleka, Charl Verwey, Charles Feldman, David Moore, Gary Reubenson, Khine Swe Swe Han, Jeannette Wadula, Jeremy Nel, Kathy Lindeque, Maphoshane Nchabeleng, Nazlee Samodien, Nicolette du Plessis, Norma Bosman, Ranmini Kularatne, Sharona Seetharam, Teena Thomas, Theunis Avenant, Trusha Nana, and Vindana Chibabhai, from Gauteng; Adhil Maharj, Asmeeta Burra, Fathima Naby, Halima Dawood, Jade Mogamberry, Koleka Mlisana, Lisha Sookan, Praksha Ramjathan, Prasha Mahabeer, Romola Naidoo, Sumayya Haffejee, and Yacoob Coovadia, from KwaZulu Natal; Ken Hamese, Ngoaka Sibiya, and Ruth Lekalakala, from Limpopo province; Greta Hoyland and Jacob Lebudi, from Mpumalanga; Pieter Jooste, from Northern Cape; Ebrahim Variava and Erna du Plessis, from North West; Andrew Whitelaw, Kessendri Reddy, Mark Nicol, and Preneshni Naicker, from Western Cape; Adrian Brink, Elizabeth Prentice, Inge Zietsman, Maria Botha, Peter Smith, and Xoliswa Poswa, from AMPATH; Chetna Govind, Keshree Pillay, and Suzy Budavari, from LANCET; Catherine Samuel and Marthinus Senekal, from PathCare; Andries Dreyer, Khatija Ahmed, Louis Marcus, and Warren Lowman, from Vermaak and Vennote; Angeliki Messina, Dena van den Bergh, and Karin Swart, from Netcare; Cynthia Whitney, from the Centers for Disease Control and Prevention; Keith Klugman, from Emory; and Ananta Nanoo, Andries Dreyer, Anne von Gottberg, Anthony Smith, Arvinda Sooka, Cecilia Miller, Charlotte Sriruttan, Cheryl Cohen, Chikwe Ihekweazu, Claire von Mollendorf, Desiree du Plessis, Erika Britz, Frans Radebe, Genevie Ntshoe, Gillian Hunt, Hlengain Mathema, Jacqueline Weyer, Jenny Rossouw, John Frean, Karen Keddy, Kerrigan McCarthy, Linda de Gouveia, Linda Erasmus, Lucille Blumberg, Marshagne Smith, Martha Makgoba, Motshabi Modise, Nazir Ismail, Nelesh Govender, Neo Legare, Nicola Page, Ntsieni Ramalwa, Nuraan Paulse, Phumeza Vazi, Olga Perovic, Penny Crowther-Gibson, Portia Mutevedzi, Riyadh Manesen, Ruth Mpembe, Sarona Lengana, Shabir Madhi, Sibongile Walaza, Sonwabo Lindani, Sunnieboy Njikho, Susan Meiring, Thejane Motladiile, Tiisetso Lebaka, and Verushka Chetty, from the National Institute for Communicable Diseases. This work was conducted at the National Institute for Communicable Diseases, a Division of the National Health Laboratory Service, in Johannesburg, South Africa.

Acknowledgments. The authors thank all clinical and laboratory staff throughout South Africa for submitting case reports and isolates for the GERMS-SA national surveillance program, as well as all the patients who agreed to provide further clinical details. They thank Jimmy Khosa, Geographic Information Science Specialist (registration number GTc GISc1796), National Institute for Communicable Diseases, for creating the cluster maps on ArcGIS.

Disclaimer. The contents of this study are solely the responsibility of the authors and do not necessarily represent the official views of the National Institute for Communicable Diseases, a Division of the National Health Laboratory Service, or the United States Centers for Disease Control and Prevention.

Financial support. This work was supported by the National Institute for Communicable Diseases, a division of the National Health Laboratory Services, and the United States Centers for Disease Control and Prevention (cooperative agreement number 1U19GH000571-04).

Potential conflicts of interest. S. M. has received a grant from Sanofi Pasteur and other fees from Sanofi Pasteur and Pfizer, all outside the submitted work. M. dP. received grants from the National Health Laboratory Service, during the conduct of the study. C. C. received grants from the Centers for Disease Control and Prevention (CDC) and Sanofi Pasteur, and other fees from Parexel, during the conduct of the study. A. vG. received grants from the CDC, during the conduct of the study; other income from Pfizer and Novartis, outside the submitted work; and grants and other from Sanofi Pasteur, outside the submitted work. G. R. has received personal fees from Sanofi, Pfizer, and Aspen, 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.

References

1. Jafri RZ, Ali A, Messonnier NE, et al. Global epidemiology of invasive meningococcal disease. Popul Health Metr **2013**; 11:17–25.
2. Sidikou F, Zaneidou M, Alkassoum I, et al; MenAfriNet consortium. Emergence of epidemic Neisseria meningitidis serogroup C in Niger, 2015: an analysis of national surveillance data. Lancet Infect Dis **2016**; 16:1288–94.
3. Cohn AC, MacNeil JR, Harrison LH, et al. Changes in Neisseria meningitidis disease epidemiology in the United States, 1998–2007: implications for prevention of meningococcal disease. Clin Infect Dis **2010**; 50:184–91.
4. Borrow R, Caugant DA, Ceyhan M, et al; Global Meningococcal Initiative. Meningococcal disease in the Middle East and Africa: Findings and updates from the Global Meningococcal Initiative. J Infect **2017**; 75:1–11.
5. Borrow R, Alarcón P, Carlos J, et al; Global Meningococcal Initiative. The Global Meningococcal Initiative: global epidemiology, the impact of vaccines on meningococcal disease and the importance of herd protection. Expert Rev Vaccines **2017**; 16:313–28.
6. Passmore E, Ferson MJ, Tobin S. EpiReview: Meningococcal disease in NSW, 1991–2011: trends in relation to meningococcal C vaccination. NSW Public Health Bull **2013**; 24:119–24.
7. Abio A, Neal KR, Beck CR. An epidemiological review of changes in meningococcal biology during the last 100 years. Pathog Glob Health **2013**; 107:373–80.
8. Ali A, Jafri RZ, Messonnier N, et al. Global practices of meningococcal vaccine use and impact on invasive disease. Pathog Glob Health **2014**; 108:11–20.
9. Khatami A, Pollard AJ. The epidemiology of meningococcal disease and the impact of vaccines. Expert Rev Vaccines **2010**; 9:285–98.
10. Department of Health. Guidelines for the management, prevention and control of meningococcal disease in South Africa. Available at: https://www.medbox.org/south-africa/guidelines-for-the-management-prevention-control-of-meningococcal-disease-in-south-africa/preview?q. Accessed 10 July 2017.
11. Meiring S, Hussey G, Jeena P, Parker S, von Gottberg A. Recommendations for the use of meningococcal vaccines in South Africa. South Afr J Infect Dis **2017**; 32:82–86.
12. Miller L, Arakaki L, Ramautar A, et al. Elevated risk for invasive meningococcal disease among persons with HIV. Ann Intern Med **2014**; 160:30–7.
13. Simmons RD, Kirwan P, Beebeejaun K, et al. Risk of invasive meningococcal disease in children and adults with HIV in England: a population-based cohort study. BMC Med **2015**; 13:297–305.
14. MacNeil JR, Rubin LG, Patton M, Ortega-Sanchez IR, Martin SW. Recommendations for use of meningococcal conjugate vaccines in HIV-infected persons - advisory committee on immunization practices, 2016. MMWR Morb Mortal Wkly Rep **2016**; 65:1189–94.
15. Statistics South Africa. Mid-year population estimates, South Africa, 2016. STATS-SA, **2016**. Available at: http://www.statssa.gov.za/publications/P0302/P03022016.pdf. Accessed 1 July 2017.
16. Cohen C, Singh E, Wu HM, et al. Increased incidence of meningococcal disease in HIV-infected individuals associated with higher case-fatality ratios in South Africa. AIDS **2010**; 24:1351–60.
17. Dlamini SK, Madhi SA, Muloiwa R, et al. Guidelines for the vaccination of HIV-infected adolescents and adults in South Africa. South Afr J HIV Med **2018**; 19:1–8. doi:10.4102/sajhivmed.v19i1.839
18. Mandell GL, Bennett JE, Dolin R. Principles and practice of infectious diseases. 7th ed. Churchill Livingstone, **2010**. eBook ISBN: 9781455708727.

19. Coulson GB, von Gottberg A, du Plessis M, et al. Meningococcal disease in South Africa, 1999–2002. Emerg Infect Dis **2007**; 13:273–81. doi:10.3201/eid1302.051553
20. von Gottberg A, du Plessis M, Cohen C, et al; Group for Enteric, Respiratory and Meningeal Disease Surveillance in South Africa. Emergence of endemic serogroup W135 meningococcal disease associated with a high mortality rate in South Africa. Clin Infect Dis **2008**; 46:377–86.
21. Ryder CS, Beatty DW, Heese HD. Group B meningococcal infection in children during an epidemic in Cape Town, South Africa. Ann Trop Paediatr **1987**; 7:47–53.
22. Group for Enteric Respiratory and Meningeal Disease Surveillance in South Africa. GERMS-SA Annual Report 2007. National Institute for Communicable Diseases, **2008**. Available at: http://nicd.ac.za/?page=germs-sa&id=97. Accessed 5 June 2015.
23. Clinical and Laboratory Standards Institute. Performance standards for antimicrobial susceptibility testing. In: Wayne PA, ed. Eighteenth informational supplement. Clinical and Laboratory Standards Institute, **2008**. ISSN: 1558–6502.
24. Dolan Thomas J, Hatcher CP, Satterfield DA, et al. sodC-based real-time PCR for detection of Neisseria meningitidis. PLoS One **2011**; 6:e19361.
25. Wang X, Theodore MJ, Mair R, et al. Clinical validation of multiplex real-time PCR assays for detection of bacterial meningitis pathogens. J Clin Microbiol **2012**; 50:702–8.
26. von Gottberg A, Cohen C, de Gouveia L, et al. Epidemiology of invasive pneumococcal disease in the pre-conjugate vaccine era: South Africa, 2003–2008. Vaccine **2013**; 31:4200–8.
27. Paterson DL, Hujer KM, Hujer AM, et al; International Klebsiella Study Group. Extended-spectrum beta-lactamases in Klebsiella pneumoniae bloodstream isolates from seven countries: dominance and widespread prevalence of SHV- and CTX-M-type beta-lactamases. Antimicrob Agents Chemother **2003**; 47:3554–60.
28. Johnson LF, Rehle TM, Jooste S, Bekker LG. Rates of HIV testing and diagnosis in South Africa: successes and challenges. AIDS **2015**; 29:1401–9.
29. Johnson LF, Chiu C, Myer L, et al. Prospects for HIV control in South Africa: a model-based analysis. Glob Health Action **2016**; 9:30314–30322.
30. Kulldorff M. A spatial scan statistic. Commun Statist Theory Meth **1997**; 26:1481–96.
31. Ewing JA. Detecting alcoholism: The CAGE questionnaire. JAMA **1984**; 252:1905–7.
32. MacNeil JR, Blain AE, Wang X, Cohn AC. Current epidemiology and trends in meningococcal disease-United States, 1996–2015. Clini Infect Dis **2017**; 6:1276–81. doi: 10.1093/cid/cix993.
33. Polkowska A, Toropainen M, Ollgren J, Lyytikainen O, Nuorti JP. Bacterial meningitis in Finland, 1995–2014: a population-based observational study. BMJ Open **2017**; 7:e015080.
34. Sáfadi MA, O'Ryan M, Valenzuela Bravo MT, et al; Global Meningococcal Initiative. The current situation of meningococcal disease in Latin America and updated Global Meningococcal Initiative (GMI) recommendations. Vaccine **2015**; 33:6529–36.
35. Findlow H, Borrow R. What would be the best schedule for prevention of meningococcal disease in all ages? The UK experience. Paediatr Drugs **2016**; 18:83–7.
36. Martin NV, Ong KS, Howden BP, et al. Rise in invasive serogroup W meningococcal disease in Australia 2013–2015. Commun Dis Intell Q Rep **2016**; 40:E454–e59.
37. Campbell H, Ladhani S. The importance of surveillance: Group W meningococcal disease outbreak response and control in England. Int Health **2016**; 8:369–71.
38. Archer BN, Chiu CK, Jayasinghe SH, et al. Epidemiology of invasive meningococcal B disease in Australia, 1999–2015: priority populations for vaccination. Med J Aust **2017**; 207:382–87.
39. Sadarangani M, Scheifele DW, Halperin SA, et al. Outcomes of invasive meningococcal disease in adults and children in Canada between 2002 and 2011: a prospective cohort study. Clin Infect Dis **2015**; 60:e27–35.
40. du Plessis M, Moodley C, Mothibeli KM, et al. Population snapshot of invasive serogroup B meningococci in South Africa from 2005 to 2008. J Clin Microbiol **2012**; 50:2577–84.
41. von Gottberg A, de Gouveia L, Tempia S, et al; GERMS-SA Investigators. Effects of vaccination on invasive pneumococcal disease in South Africa. N Engl J Med **2014**; 371:1889–99.
42. von Mollendorf C, Tempia S, von Gottberg A, et al. Estimated severe pneumococcal disease cases and deaths before and after pneumococcal conjugate vaccine introduction in children younger than 5 years of age in South Africa. PLoS One **2017**; 12:e0179905.
43. Cheyip M, Cohen C, von Gottberg A, Govender N, Keddy K, for GERMS-SA. Collection rates for blood culture and cerebrospinal fluid specimens and estimated burden of disease due to invasive respiratory, meningeal and enteric bacterial pathogens in South Africa. **2007**.
44. Kuznik A, Iliyasu G, Lamorde M, et al. Cost-effectiveness of expanding childhood routine immunization against Neisseria meningitidis serogroups C, W and Y with a quadrivalent conjugate vaccine in the African meningitis belt. PLoS One **2017**; 12:e0188595.
45. Updated recommendations for use of meningococcal conjugate vaccines --- Advisory Committee on Immunization Practices (ACIP), 2010. MMWR Morb Mortal Wkly Rep **2011**; 60:72–6.
46. Delea TE, Weycker D, Atwood M, et al. Cost-effectiveness of alternate strategies for childhood immunization against meningococcal disease with monovalent and quadrivalent conjugate vaccines in Canada. PloS One **2017**; 12:e0175721.
47. De Wals P, Zhou Z. Cost-effectiveness comparison of monovalent C versus quadrivalent ACWY meningococcal conjugate vaccination in Canada. Pediatr Infect Dis J **2017**; 36:e203–e07.
48. Izquierdo G, Torres JP, Santolaya ME, Valenzuela MT, Vega J, Chomali M. Cost-effectiveness analysis of a multicomponent meningococcal serogroup B vaccine in hypothetic epidemic situation in a middle-income country. Hum Vaccin Immunother **2015**; 11:875–83.
49. Christensen H, Trotter CL. Modelling the cost-effectiveness of catch-up 'MenB' (Bexsero) vaccination in England. Vaccine **2017**; 35:208–11.
50. Cohen AL, McMorrow M, Walaza S, et al. Potential impact of co-infections and co-morbidities prevalent in Africa on influenza severity and frequency: A systematic review. PloS One **2015**; 10:e0128580.