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

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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.