Excess invasive meningococcal disease associated with seasonal influenza, South Africa, 2003-2018

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**Summary**

This ecological study of seasonal influenza and invasive meningococcal disease (IMD) shows a 5-week lag-time between influenza and IMD seasons, with 5% of IMD potentially attributable to influenza co-circulation. A small proportion of IMD may be prevented by seasonal influenza vaccination.
Abstract

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

Methods: This ecological study used weekly data from two nationwide surveillance programmes: Viral Watch (proportion of out-patient influenza-positive cases from throat/nasal swabs) and GERMS-SA (laboratory-confirmed cases of IMD) occurring across South Africa from 2003 through 2018 in all age-bands. A bivariate time-series analysis using wavelet transform was conducted to determine co-circulation of the diseases and the time lag between the peak seasons. We modelled excess meningococcal disease cases attributable to influenza co-circulation using univariate regression spline models. Stata and R statistical packages were used for the analysis.

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

Conclusion: A quantifiable proportion of meningococcal disease in South Africa is associated with influenza co-circulation, therefore seasonal influenza vaccination may have an effect on preventing a small portion of meningococcal disease in addition to preventing influenza.

Keywords

Influenza; meningococcus; Neisseria meningitidis; seasonal influenza; attributable fraction
**Introduction**

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

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

It has been shown that, in temperate climates, IMD peaks frequently coincide with seasonal peaks in influenza. One ecological study in Canada showed a doubling in IMD incidence per 100 case increase in influenza A activity.[4] Another study in the United States of America showed that two-thirds of meningococcal disease during the peak of influenza seasons could be attributable to influenza, and that the height of both influenza and meningococcal seasons lags by two weeks over nineteen out of twenty consecutive winters.[1] Observational studies of meningococcal disease outbreaks in well-defined populations, such as an army barracks, old-aged home and school, used serological testing to
confirm preceding outbreaks of influenza A or B within the population prior to the onset of meningococcal disease.\[8–11\] South Africa has a temperate climate with both influenza and meningococcal disease increasing in late autumn to winter (April through August). If a temporal correlation between IMD and influenza is identified in South Africa, preventing influenza through seasonal influenza vaccination campaigns could have the added benefit of preventing a proportion of IMD.

In this study, we assess the temporal association between the peaks in the timing of influenza and meningococcal activity in South Africa over a sixteen-year period; and calculate the attributable fraction of circulating seasonal influenza virus on the incidence of IMD during the winter/spring seasons in South Africa.

**Methods**

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

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

The Viral Watch programme began in 1984 and tests throat and nasal swabs taken from out-patients of all ages presenting with an acute respiratory infection: fever $\geq 38^\circ$C and cough, and onset of symptoms within the last 10 days.[14,15] The specimens are submitted by approximately 180 different general practitioners from all 9 provinces (excluding KwaZulu Natal from 2014-2018) of South Africa, to the NICD. Specimens are tested using multiplex reverse transcriptase real-time polymerase chain reaction assays for influenza A and B. The proportion of positive influenza cases detected by epidemiological week per year were included in the analysis from 1 January 2003 until 31 December 2018.

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

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

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

Where \(\beta\) was the observed number of meningococcal disease cases, \(t\) was the sequential week number of the weekly time series observations, \(\text{influenza}\) was the independent variable split into influenza type A, influenza type B and years so that for each year the count was set to 0 for all other years. We set the model to allow 64 degrees of freedom, with one degree of freedom allocated to the parametric linear time variable and the remaining distributed at 4 per year for the spline. We also allowed for a five-week lag between influenza and meningococcal cases. The lag-time was determined by the phase difference of the cross wavelet spectrum of the time-series model described above.

Excess meningococcal cases were determined by subtracting the expected weekly rate of meningococcal disease in the absence of influenza from the weekly baseline rate of meningococcal disease estimated from the spline. Annual excess meningococcal disease cases were estimated as the sum of the weekly cases per year. The attributable fraction of meningococcal disease associated with influenza was calculated as a percentage of the excess meningococcal cases over the observed number of meningococcal disease cases. We obtained the 95% confidence intervals for the estimated excess cases by using bootstrap resampling of block of calendar years from 1000 replications of the dataset. We refitted the regression model for each dataset and obtained the confidence intervals from the estimated excess cases from the 1000 resampled datasets.

Statistical analysis was done using Stata version 14 (StataCorp Inc., College Station, Texas, USA) and R statistical software using the wavletComp package (Roesch and Schmidbauer (2018)) for time-series analyses.
Ethics approvals for the GERMS-SA surveillance programme have been obtained annually from the University of the Witwatersrand Human Research Ethics Committee (Medical) (Wits HREC(Medical)) (Reference M140159). Informed consent was obtained from all participants or parents/legal guardians of under-aged participants interviewed in the enhanced surveillance programme. Ethical clearance for the Viral Watch programme was obtained from Wits HREC (Medical) (M060449). Clearance for this secondary data analysis was obtained from Wits HREC(Medical) (M170951).

**Results**

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

Forty-two percent (10 421/ 24 741) of swabs tested at the NICD were positive for influenza during the study period. Median positivity for influenza by year was 44% (interquartile range 39-47%). The highest number of swabs were submitted in 2009 and 47% of them (1753/3719) were influenza positive. All influenza positive swabs were typed: 2 348/10 421 (23%) were influenza B and 8 204/10 421 (79%) were influenza A (131 episodes were caused by multiple influenza types). The mean peak for all influenza occurred at week 26 (+4 weeks) - influenza A at week 26 (+4 weeks) and B at week 30 (+4 weeks).

**Timing of the influenza and invasive meningococcal disease seasons**

The time-series analysis using the cross wavelet power spectrum indicated that meningococcus and influenza had a significant joint annual periodicity over the 16-year observation period (p<0.05). The joint cross-wavelet power levels were above 0.5 for the earlier years, but decreased in power from 2012 through 2018. Overall the joint periodicity of IMD and influenza showed high average cross-wavelet power (0.5) at time periods of 52 weeks. (Figure 2) Meningococcal disease and influenza
were circulating in-phase, peaking approximately every 52 weeks, with meningococcal disease lagging influenza. From 2003 to 2011 there was an additional low power bi-annual periodicity (every 26 weeks) with lower average cross-wavelet power of 0.12. During this low powered periodicity, meningococcal disease was leading influenza.

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

Modelling of the attributable fraction of meningococcal disease associated with influenza

Over the study period, 5.3% (95% CI 1.1-7.2%) of meningococcal disease in South Africa was attributable to influenza, with influenza A potentially contributing to 3.3% (95% CI 0.8-4.3%) of all IMD and influenza B attributable for 2% (95% CI 0.3-3.0%). The mean number of excess meningococcal cases attributable to influenza was 17 per year (95% CI 9-25). (Tables 1 and 2)

Discussion

These data from South Africa show a temporal association between influenza and meningococcal seasonality over a 16-year period, with influenza leading the meningococcal season by 5 weeks and peaking in phase with meningococcal disease during the winter months. Influenza seasonal peaks occurred prior to meningococcal peaks for 15 of the 16 years. Annually, approximately 5% of meningococcal disease can be attributable to co-circulating influenza virus infections.

The association between influenza and meningococcal disease is well established, however this is the first study from Africa showing this association.[1,2,18–20]

Although the correlation between the two diseases is small to moderate, with only 5% of IMD attributable to influenza virus circulation each year, during the peak influenza season a much higher
Variance in meningococcal disease was associated with influenza, particularly influenza A. Therefore, clinicians should be alert to increased cases of IMD following early outbreaks of influenza as well as during the peak seasons. During periods of increased influenza virus circulation, there are multiple pathways increasing one’s risk of developing IMD. Both diseases are spread via the respiratory tract and influenza symptoms of coughing and sneezing can mechanically increase meningococcal bacterial dispersion through respiratory droplets. Those persons exposed to influenza disease during the season may have disrupted nasal mucosa, nasal flora and mucosal immunity up to 2 weeks following their infection, increasing their risk of acquiring meningococcal carriage and possible invasion of the bacteria into the bloodstream. In particular, influenza A neuraminidase is known to increase adherence of meningococcus to the nasal epithelial cells, thus increasing meningococcal colonisation of the nasopharynx.[21] Although a rare occurrence, invasive meningococcal disease typically follows new onset of meningococcal carriage with a virulent strain, usually within a 10-day period of exposure to the bacteria.[22]

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

Therefore, combining the increased dispersion of meningococci through droplet spread from multiple asymptomatic meningococcal carriers during the influenza season, to the vulnerable nasal mucosa in those suffering/recovering from influenza, the five-week lag time in peaks of both diseases may account for the longer time period for acquisition of meningococci and the development of invasive meningococcal disease to occur.
Although not causal, this study reinforces the association of influenza contributing to a portion of invasive meningococcal disease cases. Quantifying the fraction of IMD attributable to influenza indicates additional potential health benefits to the influenza vaccine. Therefore, upscaling of influenza vaccination coverage could have added protection of preventing a portion of meningococcal disease. This is perhaps more impactful in countries with no routine meningococcal immunisation programmes.

In 2020, during the COVID-19 pandemic, a reduction in meningococcal disease was noted in South Africa and globally.[25] Although there are multiple factors that may have impacted on this reduction (social distancing of persons, restrictions on movement, school/university closures), it is important to note that the absence of the southern hemisphere 2020 influenza season may have played a role in reducing meningococcal disease.[26]

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

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

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

Author Contributions

All authors had full access to the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Susan Meiring, Cheryl Cohen and Stefano Tempia

Acquisition, analysis or interpretation of data: Susan Meiring, Stefano Tempia, Emanuel M. Dominic, Linda de Gouveia, Jo McAnerney, Anne von Gottberg, Cheryl Cohen

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Disclaimer

The findings and conclusions in this study are those of the authors and do not necessarily represent the official position of the National Institute for Communicable Diseases, South Africa.
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Competing interests

Susan Meiring reports an investigator sponsored grant to conduct a meningococcal carriage study in university students from Sanofi Pasteur for research outside the submitted work. Anne von Gottberg and Cheryl Cohen reports 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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Tables and Figures

Figure 1: Weekly incidence of meningococcal disease and proportion of influenza episodes by week and year, 2003-2018

Figure 2: Cross wavelet power spectrum showing joint significant annual periodicity of invasive meningococcal disease and influenza, 2003 to 2018

Footnote: The direction of the arrows around period 52 indicate that meningococcal disease and influenza are in-phase with influenza leading meningococcal disease.

Figure 3: Wrapped phase in radians of invasive meningococcal and influenza seasons by year, 2003 to 2018
Table 1: Excess number, rate and percentage of meningococcal disease episodes attributable to influenza (all influenza, influenza A and influenza B) co-circulation in South Africa by year, 2003-2018

| Year | All Influenza | Influenza A | Influenza B |
|------|---------------|-------------|-------------|
|      | Number of excess meningococcal cases | Percentage of excess meningococcal cases attributable to influenza co-circulation | Number of excess meningococcal cases attributable to influenza A co-circulation | Number of excess meningococcal cases attributable to influenza B co-circulation |
|      | 95% confidence interval | 95% confidence interval | 95% confidence interval | 95% confidence interval |
| 2003 | 7 | 1.7 | 0.5 | 0.7 | 1.0 | 0.2 | 1.0 |
| 2004 | 0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| 2005 | 14 | 2.4 | 0.6 | 2.4 | 0.6 | 0.0 | 0.0 |
| 2006 | 18 | 3.0 | 1.0 | 0.0 | 0.0 | 0.0 | 1.0 |
| 2007 | 18 | 3.6 | 0.6 | 0.0 | 0.0 | 0.0 | 1.0 |
| 2008 | 28 | 6.5 | 1.5 | 2.6 | 0.6 | 0.0 | 1.0 |
| Year | ME | AN |
|------|----|----|
|      |     |     |
| 2009 | 55 | 37  |
| 2010 | 49 | 15  |
| 2011 | 23 | 8   |
| 2012 | 31 | 22  |
| 2013 | 0  | 0   |
| 2014 | 9  | 0   |
| 2015 | 1  | 0   |
| 2016 | 3  | 0   |
| 2017 | 18 | 10  |
| 2018 | 0  | 1   |

*Model assumed a five week lag between influenza and meningococcus to calculate the baseline rate of meningococcal disease (adjusted R-squared=0.79)*
Table 2: Summary table: Mean excess number, rate and percentage of meningococcal disease episodes attributable to influenza by influenza subtype from 2003 through 2018

|                        | Mean number of excess meningococcal cases [n (95% confidence interval)] | Mean rate of excess meningococcal cases (per 100,000 population) [n (95% confidence interval)] | Mean percentage of excess meningococcus cases (%) [n (95% confidence interval)] |
|------------------------|-------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------|
| All influenza           | 17 (9-25)                                                               | 0.034 (0.018-0.051)                                                                          | 5.3 (1.1-7.2)                                                                  |
| Influenza A            | 10 (6-13)                                                               | 0.019 (0.012-0.026)                                                                          | 3.3 (0.8-4.3)                                                                  |
| Influenza B            | 7 (3-12)                                                                | 0.015 (0.006-0.025)                                                                          | 2.0 (0.3-3.0)                                                                  |
