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

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

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

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

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

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

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

IMD can be prevented through various meningococcal vaccination strategies and timely provision of chemoprophylaxis to close contacts of IMD cases [5]. Six IMD serogroups are responsible for the majority of disease, with serogroups B and W being the most frequently encountered disease-causing

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

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

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

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

METHODS

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

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

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

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

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

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

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

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

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

RESULTS

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

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

Timing of the Influenza and IMD Seasons

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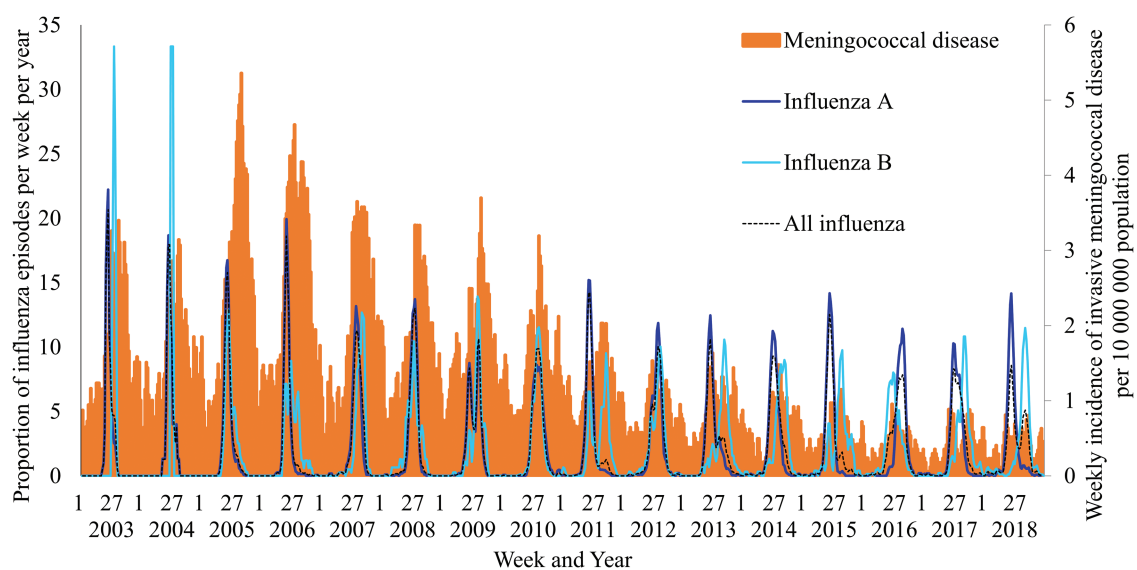

Figure 1. Weekly incidence of invasive meningococcal disease (IMD) and proportion of influenza episodes by week and year, 2003–2018.

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

Modeling the Attributable Fraction of Meningococcal Disease Associated With Influenza

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

DISCUSSION

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

Although the correlation between the 2 diseases is small to moderate, with only 5% of IMD cases attributable to influenza virus circulation each year, during the peak influenza season a much higher variance in IMD was associated with influenza, particularly influenza A. Therefore, clinicians should be alert to increased cases of IMD following
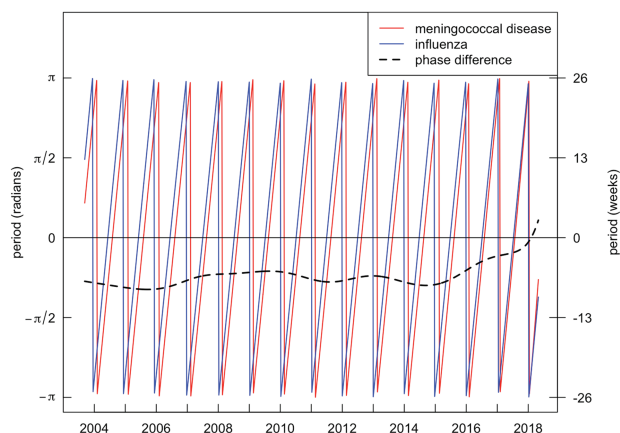

Figure 3. Wrapped phase in radians of invasive meningococcal disease (IMD) and influenza seasons by year, 2003–2018

early outbreaks of influenza, as well as during the peak seasons. During periods of increased influenza virus circulation, there are multiple pathways increasing one's risk of IMD. Both diseases are spread via the respiratory tract, and influenza symptoms of coughing and sneezing can mechanically increase meningococcal bacterial dispersion through respiratory droplets.

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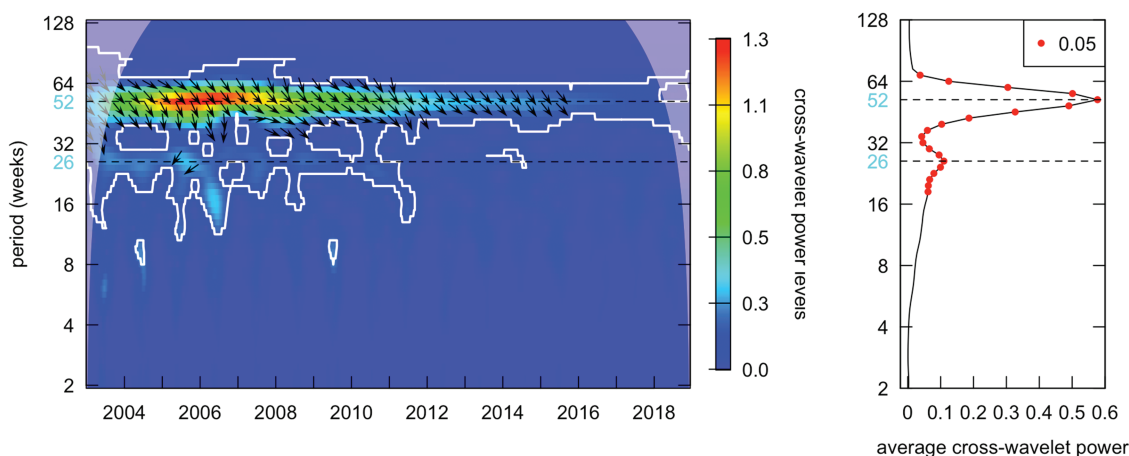

Figure 2. Cross-wavelet power spectrum showing joint significant annual periodicity of invasive meningococcal disease (IMD) and influenza, 2003–2018. The direction of the arrows around period 52 indicate that meningococcal disease and influenza are in phase, with influenza leading IMD.

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

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

Abbreviation: CI, confidence interval.

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

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

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

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

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

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

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

Abbreviation: CI, confidence interval.

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

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

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

Notes

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