



Original Contribution

Environmental Exposures and Invasive Meningococcal Disease: An Evaluation of Effects on Varying Time Scales

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Invasive meningococcal disease (IMD) is an important cause of meningitis and bacteremia worldwide. Seasonal variation in IMD incidence has long been recognized, but mechanisms responsible for this phenomenon remain poorly understood. The authors sought to evaluate the effect of environmental factors on IMD risk in Philadelphia, Pennsylvania, a major urban center. Associations between monthly weather patterns and IMD incidence were evaluated using multivariable Poisson regression models controlling for seasonal oscillation. Short-term weather effects were identified using a case-crossover approach. Both study designs control for seasonal factors that might otherwise confound the relation between environment and IMD. Incidence displayed significant wintertime seasonality (for oscillation, $P < 0.001$), and Poisson regression identified elevated monthly risk with increasing relative humidity (per 1% increase, incidence rate ratio = 1.04, 95% confidence interval: 1.004, 1.08). Case-crossover methods identified an inverse relation between ultraviolet B radiation index 1–4 days prior to onset and disease risk (odds ratio = 0.54, 95% confidence interval: 0.34, 0.85). Extended periods of high humidity and acute changes in ambient ultraviolet B radiation predict IMD occurrence in Philadelphia. The latter effect may be due to decreased pathogen survival or virulence and may explain the wintertime seasonality of IMD in temperate regions of North America.

case-control studies; environment; environmental exposure; meningitis; meningitis, bacterial; meteorological factors; *Neisseria meningitidis*; regression analysis

Abbreviations: CI, confidence interval; IRR, incidence rate ratio; OR, odds ratio; UVB, ultraviolet B.

Neisseria meningitidis is an important cause of bacterial meningitis and bacteremia worldwide (1). This microbe causes considerable morbidity and mortality, both in sub-Saharan Africa, where epidemics are frequent and control measures have met with limited success (2), and elsewhere in the developed and developing world (3, 4). In the United States and Canada, meningococcal disease is primarily endemic (3), and a recent downward trend in case occurrence has been noted (5). Nevertheless, *N. meningitidis* remains a leading cause of septicemia and bacterial meningitis in North American children (6); the high case-fatality rates associated with invasive infection (1) and the risk of transmission to close contacts (7) contribute to the continued public health importance of invasive meningococcal disease.

A striking feature of meningococcal epidemiology is the seasonality with which cases occur (8, 9). In the African “meningitis belt,” risk is increased during the dry season, when humidity is low and the Harmattan wind blows off the Sahara Desert (9, 10). The arrival of the wet season generally signals the end of high rates of disease (9). In North America, incidence is also seasonal, but in the United States it is highest during the late winter and early spring (1, 3). As with many other infectious diseases displaying seasonal patterns (11), the mechanisms driving the predictable seasonal periodicity of meningococcal disease are not well understood, and the specific effects of environmental factors on case occurrence remain unclear. An understanding of such causative phenomena could contribute to our understanding

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of meningococcal pathogenesis, enhance surveillance systems designed to monitor case occurrence, and provide insight into the potential effects of climate change on disease incidence (12, 13). However, the study of climatic exposures in relation to disease occurrence remains complex. Human behavior, the frequency of testing for a disease, and the occurrence of other disease are all likely to show seasonal variation, which may lead to biased inferences about causal mechanisms (12).

Traditional regression methods, such as Poisson regression analysis, are potentially useful in controlling for confounding by concurrent environmental exposures and in evaluating underlying seasonal oscillation and temporal trends (14). However, when the disease being studied is rare, the granularity of data is lost through necessary temporal aggregation of case counts and exposure measures, creating the potential for ecologic fallacy (15). Alternate approaches, such as the case-crossover design, are useful for identifying acute environmental effects when the outcome of interest is uncommon and exposures are repeated and transient (16). The latter method has been applied to evaluation of environmental effects on cardiorespiratory disease occurrence (17, 18) and to the study of infectious diseases with environmental reservoirs (19–21) but has not, to our knowledge, been applied previously to infectious diseases characterized by person-to-person transmission.

We sought to use these complementary methodological tools to evaluate the seasonality of invasive meningococcal disease in Philadelphia County, a major urban center in the United States. Our objectives were to define the environmental correlates of enhanced monthly case counts, after controlling for nonspecific seasonal oscillation, and to identify environmental effects that acutely enhance the risk of invasive meningococcal disease.

MATERIALS AND METHODS

Philadelphia County is an urban region covering 350 km² (135 square miles) in southeastern Pennsylvania. In 2000 it had a population of 1,517,550, consisting of 705,107 men and 812,443 women; the median age of residents was 34 years (22). Climate in the area is moderated by the Atlantic Ocean to the east and the Appalachian Mountains to the west. Consequently, while summers tend to be warm and winters are relatively cold, long periods of extreme temperature are rare.

Environmental exposures

We obtained meteorologic data for the period 1995–2006 from the weather station at Philadelphia International Airport, located 8 km southwest of Philadelphia's city center (23). We retrieved ultraviolet B (UVB) radiation index forecast estimates for Philadelphia during the same period from the National Weather Service's Climate Prediction Center (24). Clear-sky UVB indices represent an integral of measured UVB radiation levels weighted by the ability of the different UVB wavelengths to cause skin erythema. The issued UVB index is a similar measure which accounts for the effect of clouds on radiation transmission; because of

inconsistencies in cloud measurement during the study period, we used the clear-sky UVB index as our exposure variable.

Information pertaining to air quality in Philadelphia County during the years of interest—including concentrations of lead, ozone, particulate matter, and sulfur oxides—was obtained from the Environmental Protection Agency (25). Because daily readings were taken at various locations throughout the region, the arithmetic means of the air quality values were used as exposure variables.

Case data

Invasive meningococcal disease is a notifiable condition in the Commonwealth of Pennsylvania. As such, health-care providers or their surrogates are required to report any disease suspected to have been caused by *N. meningitidis* to the appropriate state or local authorities. Information on cases occurring in Philadelphia County is directed to the Philadelphia Department of Public Health, which identifies close contacts of cases and initiates postexposure prophylaxis if indicated. The Philadelphia Department of Public Health also classifies cases as *probable* or *confirmed*, as defined by the National Notifiable Diseases Surveillance System (26). Confirmation requires isolation of *N. meningitidis* from a normally sterile site, such as cerebrospinal fluid or blood, in addition to a clinically compatible illness. Probable cases include those with meningococcal antigens identified in the cerebrospinal fluid and those with a compatible clinical syndrome without microbiologic confirmation.

Information on cases occurring between January 1, 1995, and December 31, 2006, was obtained from the Philadelphia Department of Public Health. The available data included report date, patient's age and sex, outcome, and *N. meningitidis* serogroup (if known). The date on which symptoms began, as recorded, was considered to be the date of disease onset for study purposes.

Statistical analysis

Rates of meningococcal disease were calculated using demographic data for Philadelphia County from the 1990 and 2000 US censuses, with linear interpolation and extrapolation used as necessary to generate estimates for age and sex strata in between-census years (22). Seasonal periodicity in case occurrence was assessed through spectral decomposition, with construction of a periodogram. Such decomposition is performed by fitting multiple cosine regression models, each with a distinct frequency, to observed data; the frequency of oscillation associated with the maximum squared amplitude represents the "best fit" frequency of oscillation for the observed data (12). The observed annual periodicity of disease occurrence was incorporated into Poisson regression models, such that

$$E(Y) = \exp \{ \alpha + \beta_1(\text{year}) + \beta_2[\sin(2 \times \pi \times \text{month}/12)] + \beta_3[\cos(2 \times \pi \times \text{month}/12)] \}.$$

$E(Y)$ represents the case count expected in a given month, α is a constant, and each β term denotes a regression

coefficient for year or month (8). We used the Poisson regression model to evaluate associations between environmental exposures and monthly case counts of invasive meningococcal disease. We constructed both univariable models and multivariable models with seasonal smoothers and yearly terms.

We also used a less restrictive approach to smoothing, using cubic splines (27) to account for long-term trends and seasonal variance. To avoid the pitfalls associated with both overfitting and underfitting, we used Akaike's Information Criterion to optimize the number of knots within the spline model; our optimal model incorporated knots at 4-month intervals (27). Multiple environmental exposures were incorporated into the models using a backwards-elimination algorithm, in which covariates were retained at $P \leq 0.20$ (28).

To evaluate acute (i.e., day-to-day) associations between environmental exposures and case occurrence, we used a case-crossover approach. This study design is similar to the case-control design, except that the case-crossover method utilizes self-matching rather than an external control group (16, 29). As a result, confounding by participant characteristics is reduced while the risk of selecting unrepresentative controls is essentially eliminated (16). In studies using the case-crossover method to explore environmental effects, the hazard period is constituted by person-time during which the event occurred. Person-time during which the event of interest did not occur defines the control period.

In the present study, a 2:1 matched case-crossover design was used. Hazard periods were defined according to the date of symptom onset. Beginning on January 1, 1995, person-time at risk was divided into 3-week time blocks. The 2 days within each block that could be matched to the hazard period according to day of the week were defined as control periods; thus, each analytic stratum consisted of 1 case day and 2 control days. This approach was used to produce random directionality of control period selection, since seasonal or temporal trends may introduce bias in environmental case-crossover studies when only unidirectional or bidirectional control periods are used (30). With random directionality of control selection, control periods can follow, precede, or both precede and follow the hazard period. On 3 occasions during the study period, 2 cases occurred on a single day; we tested the influence of these observations on overall results by excluding these case days in a restriction analysis.

Estimates of plausible effect periods were based on the incubation period of meningococcal disease, which is usually 3–4 days but may range from 2 days to 10 days (31). Daily measurements of environmental variables were used as exposures, as were aggregated or averaged values of the environmental variables. Exposures averaged over the 1–4 days prior to onset were defined as probably occurring during incubation. Those averaged over the 5–10 days prior to onset were considered to have probably preceded incubation, while those averaged over the 11–15 days before case onset were defined as preceding incubation.

Odds ratios for case occurrence, based on environmental exposures, were determined through construction of conditional logistic regression models, with standard errors ad-

justed for clustering by 3-week time blocks (28). Quintile ranks for exposure variables were used as indicator variables for purposes of evaluating the association between a given level of exposure and risk of a disease outcome, and were also treated as 5-level ordinal variables in regression models for the purpose of evaluating linear dose-response relations (considered to be present if P was less than 0.05 using quintile ranks and the Wald χ^2 test for trend (32)).

To explore the possibility of effect modification by patient characteristics, we created multiplicative interaction terms and incorporated them into regression models (33). We explored heterogeneity of environmental effects by serogroup and by lethality of infection (fatal vs. nonfatal) using stratum-specific analyses, with heterogeneity of effects across strata assessed through calculation of the meta-analytic Q statistic (34). SAS, version 9.1 (SAS Institute Inc., Cary, North Carolina), and Stata, version 9.1 (Stata Corporation, College Station, Texas), were used to perform all analyses.

RESULTS

Descriptive epidemiology, seasonality, and temporal trends

The Philadelphia Department of Public Health received 162 reports of meningococcal disease between January 1995 and December 2006; 153 cases were confirmed, and 9 were probable. Serogroup Y *N. meningitidis* accounted for the largest proportion of these cases (33%), while serogroups B and C accounted for 19% each. Incidence was highest in children under age 5 years (incidence rate ratio (IRR) = 2.66, 95% confidence interval (CI): 1.66, 4.09) and adolescents aged 15–19 years (IRR = 1.89, 95% CI: 1.14, 3.01). Meningococcal disease was also more common in males than in females (IRR = 2.09, 95% CI: 1.29, 3.27). There were 17 reported fatalities, for a case-fatality rate of 10.5% (95% CI: 6.2, 16.3). Table 1 presents case numbers and annualized rates by sex, age, and serogroup.

The seasonality of case occurrence was confirmed through spectral decomposition, which suggested an annual periodicity to infection (Figure 1). Case counts increased in the winter (IRR = 2.85, 95% CI: 1.71, 4.74), spring (IRR = 2.30, 95% CI: 1.36, 3.89), and fall (IRR = 1.95, 95% CI: 1.14, 3.34) relative to summer. The incorporation of sine and cosine terms in Poisson models confirmed the seasonal oscillatory nature of *N. meningitidis* infection (for seasonal oscillation, $P < 0.001$) (Figure 2). A significant decrease in yearly incidence was also observed during the study period (per year, IRR = 0.95, 95% CI: 0.90, 0.99), though this effect was no longer significant after adjustment for relative humidity ($P = 0.20$).

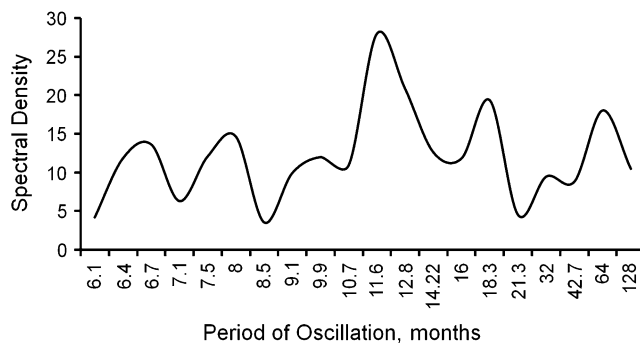
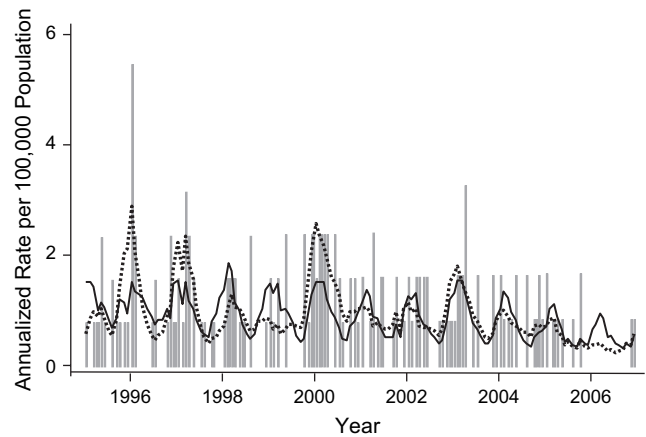
Identification of environmental effects using Poisson regression

Univariable Poisson models identified relations between numerous environmental factors and case occurrence; however, when oscillatory or cubic spline smoothers were incorporated into the models, maximum relative humidity and (in cubic spline models) mean temperature were the only

Table 1. Numbers of Cases and Incidence Rates of Invasive Meningococcal Disease ($n = 162$) in Philadelphia County, Pennsylvania, 1995–2006

Characteristic	No. of Cases	Annualized Rate per 100,000 Population
Total	162	0.89
Sex		
Male	96	1.13
Female	66	0.68
Age, years		
0–4	44	3.77
5–9	12	0.89
10–14	7	0.51
15–19	21	1.58
20–24	13	0.93
25–64	49	0.54
≥65	15	0.58
Unknown	1	
<i>Neisseria meningitidis</i> serogroup		
B	31	0.17
C	30	0.17
W-135	6	0.03
Y	54	0.30
Z	2	0.01
Other/unknown	39	

factors found to be independently associated with meningococcal disease (Table 2). There was a significant dose-response relation between quartile of relative humidity and disease risk (per quartile, IRR = 1.19, 95% CI: 1.02, 1.39) after controlling for oscillation. Models that incorporated

**Figure 1.** Periodogram for invasive meningococcal disease in Philadelphia County, Pennsylvania, 1995–2006. The periodogram was constructed using spectral decomposition of monthly case counts, as described in the text. Spectral density may be conceptualized as a measure of goodness of fit for cosine-based regression models at various frequencies (frequency = period⁻¹). A large peak is seen at 12 months, corresponding to annual seasonality.**Figure 2.** Actual and predicted rates of invasive meningococcal disease in Philadelphia County, Pennsylvania, 1995–2006. The vertical bars depict annualized disease rates; the solid curve represents incidence predicted using a Poisson regression model incorporating year, seasonal oscillatory terms, and relative humidity; and the dashed curve represents predictions derived from a model incorporating natural cubic splines, relative humidity, and temperature terms. Incidence is seasonal, with increased risk in the winter and spring months, and it decreases over the course of the study period. Tick marks on the x-axis denote January of each year.

cubic splines showed similar effects for humidity (IRR = 1.16, 95% CI: 1.00, 1.34) and also identified a trend towards an inverse dose-response effect by quartile of temperature (per quartile, IRR = 0.86, 95% CI: 0.74, 1.00).

Exploratory analyses using linear splines revealed no threshold value beyond which the effect of humidity or temperature was significantly altered. No modification of the effect of humidity by age group or sex was detected, and no change in effect was observed when probable cases were excluded from analyses. Although humidity was associated with a significantly increased risk of serogroup C disease (IRR = 1.09, 95% CI: 1.00, 1.19) and was not associated with an increased risk of disease due to other serogroups (IRR = 1.02, 95% CI: 0.99, 1.06), there was no statistically significant heterogeneity in risk across serogroup strata (Q statistic = 1.43 (1 df), $P = 0.23$), and no difference in the effect of temperature was seen in cases with serogroup C strains as compared with non-serogroup-C strains. No significant differences were detected between fatal and non-fatal cases with respect to the effects of humidity or temperature.

Identification of acute environmental effects using the case-crossover design

Using case-crossover methods, an acute protective association was found for clear-sky UVB index during the period 1–4 days prior to case occurrence (odds ratio (OR) = 0.54, 95% CI: 0.34, 0.85). No significant relation was found between UVB index and disease risk for periods probably preceding incubation (OR = 0.89, 95% CI: 0.58, 1.37) and periods preceding incubation (OR = 0.90, 95%

Table 2. Environmental Variables Associated With the Occurrence of Invasive Meningococcal Disease in Univariable and Multivariable Poisson Regression Models, Philadelphia County, Pennsylvania, 1995–2006

Environmental Exposure	Univariable Models			Multivariable Models Including Oscillatory Seasonal Smoothers and Annual Trend			Multivariable Models Including Cubic Splines		
	IRR	95% CI	P Value	IRR	95% CI	P Value	IRR	95% CI	P Value
Wind speed, km/hour	1.14	1.06, 1.23	≤0.001						
Mean temperature, °C	0.97	0.95, 0.99	≤0.001				0.98	0.96, 1.00	0.02
Maximum relative humidity, %	1.05	1.01, 1.08	0.01	1.04	1.00, 1.08	0.03	1.04	1.00, 1.07	0.03
Snowfall, mm	1.05	1.02, 1.07	≤0.001						
Ultraviolet B index, per unit change ^a	0.92	0.86, 0.99	0.02						
Total ozone, ppm × 100	0.85	0.72, 1.01	0.06						
Carbon monoxide, ppm × 100	2.25	1.18, 4.27	0.01						
Oxides of nitrogen, ppm × 100	1.72	1.23, 2.39	0.002						
Oxides of sulfur, ppm × 100	2.52	1.34, 4.74	0.004						

Abbreviations: CI, confidence interval; IRR, incidence rate ratio; ppm, parts per million.

^a One ultraviolet B index unit is $25 \text{ mW} \times \text{m}^{-2}$.

CI: 0.58, 1.37). No change in effect was seen when the 3 case days on which 2 cases occurred simultaneously were excluded from the analysis. Figure 3 shows the relation between daily clear-sky UVB index and risk of meningococcal disease for lags of 0–15 days.

Minimal changes in observed effects were seen when analyses were restricted to confirmed cases (for UVB exposure 1–4 days prior to case occurrence, OR = 0.58, 95% CI: 0.36, 0.94). The possible existence of a dose-response relation was also assessed for the 1- to 4-day effect period; a negative linear relation was found between clear-sky UVB index and disease occurrence (Table 3). The risk of meningococcal disease was not found to be acutely associated with other environmental exposures, including maximum relative humidity. We detected no significant modification of UVB effect by age or sex. In subgroup analyses, no significant differences between effects were detected by serogroup ($P = 0.87$) or case lethality ($P = 0.96$).

DISCUSSION

Seasonal variation in disease occurrence is a phenomenon that has been recognized since the Hippocratic era (35). Nevertheless, mechanisms driving the predictable periodicity of many illnesses, including invasive meningococcal disease, remain poorly elucidated (12). In this study, both Poisson regression and case-crossover methods were used to assess associations between environmental conditions and cases of invasive meningococcal disease in Philadelphia, Pennsylvania, a major US urban area. The late winter–early spring seasonality of this disease and the peaks in disease risk among young children and older adolescents observed in this study are consistent with prior observations (4). The association between perturbations in relative humidity and meningococcal disease risk is also consistent

with prior observations in numerous geographic areas (though the direction of this effect has varied) (10, 36–39).

However, our identification of a strong, acute, and independent effect of UVB radiation in reducing the risk of case occurrence is, to our knowledge, the first documentation of this relation. Our use of the case-crossover method in evaluating this relation makes it unlikely that this effect is due to confounding by other seasonal exposures (12, 16) or due to an ecologic fallacy resulting from aggregation of cases and

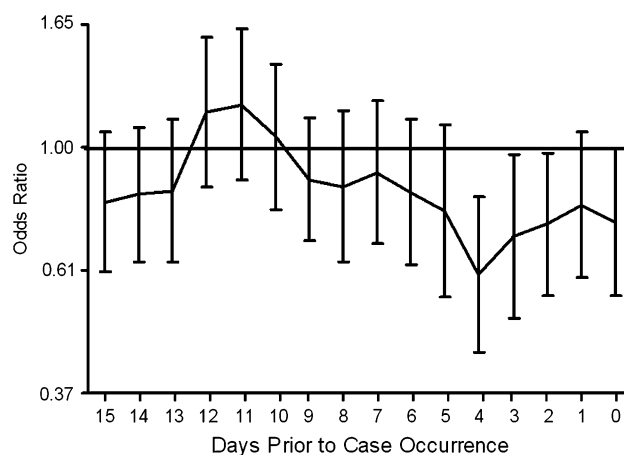


Figure 3. Association between clear-sky ultraviolet B (UVB) radiation index and risk of invasive meningococcal disease in Philadelphia County, Pennsylvania, 1995–2006. Odds ratios are plotted on a log scale on the y-axis, while lag times before case occurrence are plotted on the x-axis. A decrease in the risk of invasive meningococcal disease was seen with increasing clear-sky UVB index using a lag of 1–4 days. One UVB index unit is $25 \text{ mW} \times \text{m}^{-2}$. Bars, 95% confidence interval.

Table 3. Dose-Response Relation Between Clear-Sky Ultraviolet B Radiation Index and Risk of Meningococcal Disease for an Effect Period of 1–4 Days, Philadelphia County, Pennsylvania, 1995–2006^a

Quintile of Ultraviolet B Index	Odds Ratio	95% Confidence Interval
1 (low; referent)	1	
2	0.89	0.49, 1.67
3	1.20	0.68, 2.14
4	0.72	0.40, 1.31
5 (high)	0.59	0.34, 1.03

^a Wald χ^2 test for trend: $\chi^2 = 4.22$ (1 df); $P = 0.04$.

meteorologic exposures (15). In our analysis, the highest levels of UVB exposure, within a given 3-week time block, reduced the risk of invasive meningococcal disease by approximately 40% over the ensuing 4-day period, and a dose-response effect was seen. This lag is important, since it correlates with the usual incubation period for *N. meningitidis* (1) and suggests that the mechanism of effect of increased UVB is likely to be due to reduced transmission by colonized persons or decreased acquisition by susceptible hosts.

Such an effect is biologically plausible, since this pathogen needs to be transmitted through the environment in large respiratory droplets in order to infect new hosts (1). The ability of UVB radiation to cause accumulation of harmful genetic mutations in bacteria, via creation of pyrimidine dimers, is well-documented (40, 41). In piliated Gram-negative species, UVB irradiation causes depolymerization of pili with concomitant diminution in pathogen-epithelium binding (42). It is therefore conceivable that exposure to UVB radiation could either kill bacteria on surfaces or impair the ability of *N. meningitidis* to adhere to the mucosa, which is an important step in its pathogenesis.

Note that the UVB effects reported here are distinct from the casual correlation between decreased environmental UVB radiation during wintertime in temperate areas and increased occurrence of respiratory disease (43). While season-long decreases in UVB exposure may contribute to wintertime surges in respiratory illness, the effect we report here is an *acute* reduction in risk associated with increases in UVB radiation within a 3-week time block (i.e., the self-matching characteristic of the case-crossover design) (16). Further, while the mechanism of the effect of diminished UVB radiation on increased respiratory disease has been suggested to be decreased host production of 1,25-dihydroxyvitamin D (43), the results presented here occurred on too short a time scale to be consistent with acute enhancement of vitamin D levels.

Other environmental exposures identified in this study as being linked to increases in *N. meningitidis* case counts were relative humidity and temperature. The association with humidity is well-described, although, as noted above, the direction of this association has varied geographically: Increased humidity is associated with increased incidence in Israel (36), New Zealand (37), and England (39) and with

decreased incidence in the African “meningitis belt” (10) and Italy (38). The reason for altered ambient humidity’s increasing the risk of invasive meningococcal disease is unclear; 1 theory holds that changes in humidity alter the susceptibility of the nasopharynx to colonization by bacteria (44). The apparent disparity in findings between regions suggests that effects related to humidity may be region-specific. Identification of weather effects as important drivers of meningococcal infection, independent of season-level behavioral patterns (e.g., indoor crowding or school attendance), is of particular interest given the rapid changes in global climate documented by the Intergovernmental Panel on Climate Change (13). Drying and perturbation of Harmattan winds in the face of a warming climate could increase the magnitude of meningitis epidemics in the sub-Saharan meningitis belt; the implications of such linkages for disease control activities are described elsewhere (10, 13, 45). The potential implications of our findings for meningococcal disease in North America are less clear: Projections of warmer, wetter winters might suggest an increased risk of meningococcal disease based on the association between relative humidity and disease risk described here (13). However, although UVB radiation exposure in the Northern Hemisphere is projected to increase in coming decades (which could theoretically diminish meningococcal risk), the magnitude of this increase is uncertain and projections vary widely (46).

This study had several limitations. The first is the possible incompleteness of public health surveillance data. It is thought that many notifiable infectious diseases are under-reported despite state and local laws (47), possibly because of a lack of understanding as to how to report cases or the belief that another person will assume the responsibility for doing so (48). Therefore, there may have been cases of invasive meningococcal disease in Philadelphia County during the study period that were not included in our analyses. However, this would have biased our results only if environmental effects were somehow correlated with the likelihood of disease reporting. Another limitation is that misclassification of exposures may have occurred, which is an inherent issue in any study using environmental data. Because this misclassification is likely to have been random or nondifferential rather than differential, our results may have been underestimates and are probably biased towards the null (49).

In summary, the seasonal nature of meningococcal disease in Philadelphia County was confirmed, and environmental factors that might contribute to the observed seasonality were evaluated. While traditional Poisson regression analysis identified maximum relative humidity and temperature as significant predictors of monthly disease incidence, case-crossover methods found acute increases in clear-sky UVB index to be protective—a finding that may be important in explaining the wintertime seasonality of other droplet-borne respiratory pathogens as well. These results provide insight into host and pathogen factors that affect disease risk and the importance of environmental conditions in infectious disease occurrence. In future studies, investigators might seek to establish whether this effect is observable in other geographic locales.

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