Seasonality of Infectious Diseases

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Key Words

periodicity, communicable diseases, disease transmission, environment

Abstract

Seasonality, a periodic surge in disease incidence corresponding to seasons or other calendar periods, characterizes many infectious diseases of public health importance. The recognition of seasonal patterns in infectious disease occurrence dates back at least as far as the Hippocratic era, but mechanisms underlying seasonality of person-to-person transmitted diseases are not well understood. Improved understanding will enhance understanding of host-pathogen interactions and will improve the accuracy of public health surveillance and forecasting systems. Insight into seasonal disease patterns may be gained through the use of autocorrelation methods or construction of periodograms, while seasonal oscillation of infectious diseases can be easily simulated using simple transmission models. Models demonstrate that small seasonal changes in host or pathogen factors may be sufficient to create large seasonal surges in disease incidence, which may be important particularly in the context of global climate change. Seasonality represents a rich area for future research.

INTRODUCTION

Seasonality, a periodic surge in disease incidence corresponding to seasons or other stereotyped calendar periods, is characteristic of many infectious diseases of public health importance (24). Occurrence of noninfectious sources of morbidity and mortality may also display seasonal fluctuations, although these fluctuations are often attributed to the presence or absence of epidemic respiratory diseases, such as influenza (28, 67). The recognition of seasonality of disease occurrence is longstanding, dating at least to the time of Hippocrates (~380 BC) (41). Nonetheless, the mechanisms underlying seasonality of infectious disease occurrence remain poorly understood. As Dowell & Ho (24) wrote in the aftermath of the 2003 outbreak of coronavirus-associated severe acute respiratory syndrome (SARS),

> Nearly every important respiratory pathogen of human beings exhibits distinct seasonal variations, yet after hundreds of years of observing and documenting this phenomenon modern science has only superficial observations and largely untested theories about the underlying causes. Is it the cold? Dry air? Crowding together of people indoors in winter? Where do pathogens such as influenza and respiratory syncytial virus (RSV) go in the summertime? Do they migrate across the equator and return the following winter, or do they remain present at low levels in human or animal populations until environmental or host conditions are suitable for re-emergence?

Here, I attempt to address several current questions and controversies related to seasonality of infectious diseases. The review begins with a discussion of the historical recognition of disease seasonality. Given the truism that "you can't change the weather," it seems appropriate to forward to current public health problems arguments related to the relevance and immediacy of problems of seasonality, weather, and other environmental factors, particularly those problems that concern emerging and reemerging infectious diseases. I present a necessarily brief review of methodological tools available for the study of seasonality and provide a review of what is known (and not known) about underlying mechanisms of seasonality and conclude by discussing the relationship of seasonality to geographic latitude and hemisphere and to major climatic events.

HISTORICAL PERSPECTIVES

Recognition of seasonality in disease occurrence dates back at least as far as the Hippocratic era (~380 BC) (41). Hippocratic medicine emphasized the interaction of individuals' constitutions with the physical environment in the development of disease in such tracts as *Airs*, *Waters*, *Places* and the first book of the Hippocratic *Epidemics*. *Epidemics* begins with a description of weather, noting that "there was much rain in Thasos about the time of the autumnal equinox. . .," and describes a subsequent season, as remarkable for a dry, windy spell followed by rains, which causes "cases of paralysis [which] became common, constituting an epidemic" (41). In later writings, such as those of the Roman physician Galen (AD 179 to ~216), disease is literally a consequence of internalization of the weather, with disease ascribed to excess heat, cold, dryness, or wetness of the liver, brain, testicles, and other organs (31).

The historical concept of miasma is closely related to the concept of weather in the genesis of disease. The late Professor Roy Porter defined miasma as "gases given off by putrefying, decomposing organic matter, flesh and vegetables," which, if inhaled, can give rise to disease (66). The notion of a corrupted environment appears in the writings of the Roman natural historian Lucretius (~55 BC), who ascribes "pestilence and plague" to "atoms" which may arise "from the earth when it has

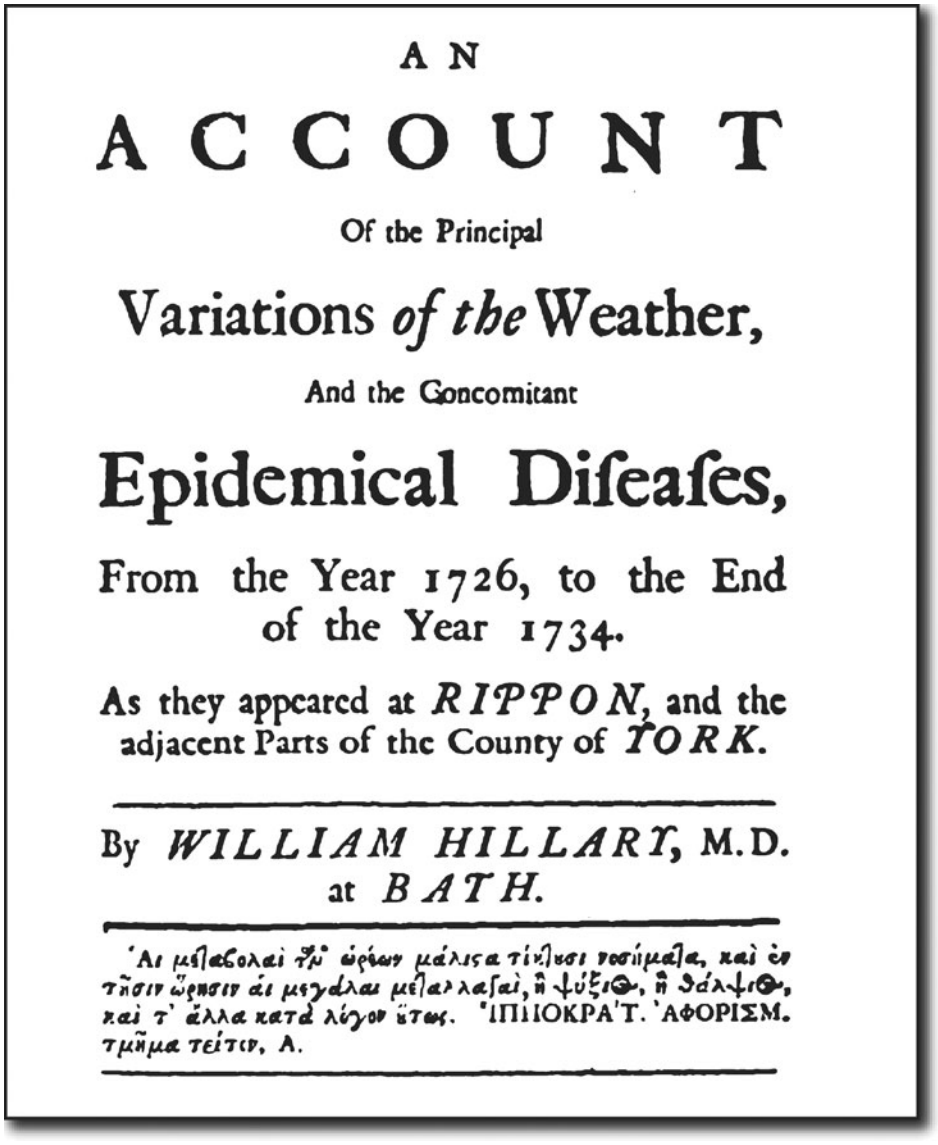
been rotted by drenching, with unseasonable rains and pelting with sunbeams" (54).

Classic theories of pathogenesis remained central to western medicine until the seventeenth century (66). However, although that century saw the emergence of microscopy, chemistry, physiology, and anatomy as sciences that would ultimately undermine humoral notions of health and disease, medical practice was still firmly rooted in Hippocratic ideas (66). In fact, clinical innovators such as the English physician Thomas Sydenham (1624–1689) rejected emerging medical science in favor of close observation of disease in the Hippocratic tradition (66). True to his Hippocratic ideals, Sydenham emphasized weather and season in the genesis of fevers and distinguished between seasonally recurrent fevers, which he called "intercurrent fevers," and periodic epidemics, which he called "stationary fevers" (77). Current understanding of the link between climate, season, and miasma was well articulated by Benjamin Rush of Philadelphia, an eighteenth-century physician and polymath. Rush stressed that although exposure to miasma could initiate a disease process, the stimulatory effects of weather were necessary to "excite" the "dormant seeds of disease into action" and counseled that "[i]n leaving a place infected by miasmata, care should be taken not to expose the body to great cold, heat, or fatigue for eighteen or twenty days" (70). Other, lesser-known medical writers also composed treatises on the impact of weather on fevers and epidemics (**Figure 1**).

The decline of the perceived importance of the physical environment and miasma in the genesis of febrile illnesses and plagues may begin with John Snow's work during the 1854 London cholera epidemic. Snow argued for the existence of contagious particles, rather than miasma, as the cause of the cholera epidemic; according to Snow's model, such particles multiplied in an ill individual and could be transmitted over short distances by fecal-oral transmission and over longer distances through contamination of the water supply (86). Subsequent work by Robert Koch and Louis Pasteur affirmed Snow's intuitions, invalidated notions of spontaneous generation and miasma, and identified the principle of microbial specificity for individual diseases (66).

Nonetheless, awareness of the seasonal nature of infectious diseases persisted through the late nineteenth and early twentieth centuries. August Hirsch (42), in his three-volume *Handbook of Geographical and Historical Pathology* (1881), comments on the seasonality of a wide variety of infectious diseases, including erisypelas, pinta, measles, typhus, typhoid, yellow fever, cholera, and guinea-worm infection. Hirsch argued against the notion that season or weather is associated with influenza epidemics (42), as did Robert Graves, a nineteenth-century Irish physician credited with identifying "excess mortality" as a metric of influenza activity (32, 34). Perhaps wintertime influenza seasonality was less apparent to nineteenth-century physicians owing to the far larger peak of summertime infectious disease mortality, which was presumably due to typhoid and dysentery (9) (**Figure 2**).

In the early twentieth century, several attempts were made to link climatologic variables to pneumonia and influenza mortality and to all-cause mortality (4, 36, 43). In the United States, weekly surveillance for influenza and pneumonia deaths was initiated during the great influenza pandemic of 1918–1919, providing epidemiologists with a much higher degree of resolution for the study of seasonal and annual trends in the occurrence of respiratory disease, leading Selwyn Collins (17) to devise an influenza surveillance methodology that compared current deaths with seasonal expectations. This approach still provides the conceptual basis for current influenza surveillance methodologies (32). The degree to which wintertime excess all-cause mortality can be attributed to circulating influenza virus remains controversial (22, 28, 67).



AN

ACCOUNT

Of the Principal

Variations *of the* Weather,

And the Concomitant

Epidemical Diſeaſes,

From the Year 1726, to the End of the Year 1734.

As they appeared at *RIPPON*, and the adjacent Parts of the County of *YORK*.

By *WILLIAM HILLARY*, M.D. at *BATH*.

Αἱ μεταβολαὶ τῶν ὡρέων μάλιστα τίκτουσι νοσήματα, καὶ ἐν τοῖσιν ὥρεσιν αἱ μεγάλαι μεταλλαγαὶ, ἢ ψύξιος, ἢ θάλψιος, καὶ τἄλλα κατὰ λόγον ἴσως. ΙΠΠΟΚΡΑΤ. ΑΦΟΡΙΣΜ. τμῆμα τέταρτον, Α.

Figure 1

Front matter from William Hillary's *Account of the Principal Variations of the Weather and the Concomitant Epidemical Diseases* [1740] (40a). Hillary was an English physician who studied under Hermann Boerhaave in Leiden and whose *Diseases of Barbados* (1759) may have been the first English-language work on tropical medicine (13).

PUBLIC HEALTH IMPORTANCE OF SEASONALITY

Although the seasonality of infectious disease occurrence may be startling in its regularity, it is reasonable to ask what public health benefit can be expected if resources are devoted to the study of seasonality. In recent years, the emergence of novel respiratory pathogens such as the SARS-associated coronavirus (24), concern about the mechanisms that could drive pandemic influenza transmission (27), and a desire for improved tools for forecasting of infectious disease occurrence in the context of global climate change have all contributed to a resurgence in interest in the seasonality of infectious diseases (50).

At least four potential benefits may accrue from the study of the seasonality of infectious disease occurrence: (*a*) improved understanding of host and pathogen biology and ecology,

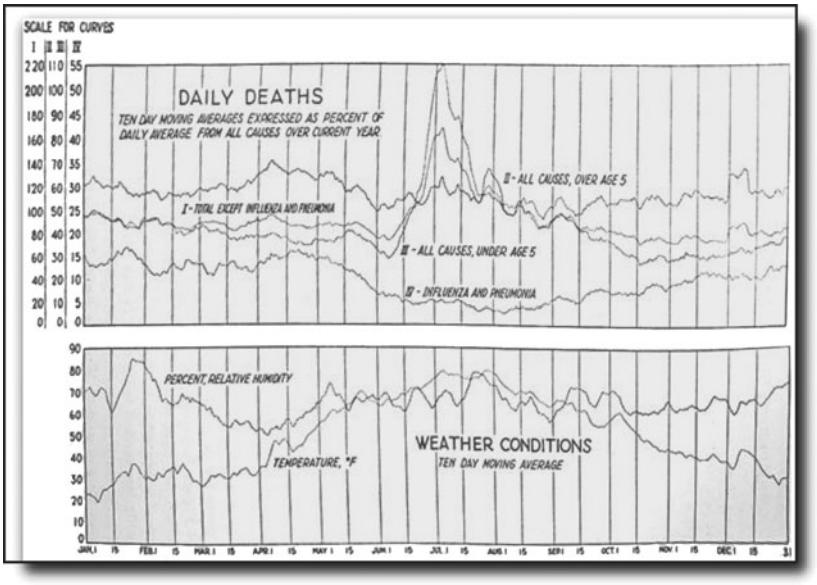


Figure 2

Temporal trends in mortality (*upper section*) and humidity and temperature (*lower section*) in New York City in 1887, as presented by Huntington (43). The lowermost mortality curve in the upper panel shows wintertime seasonality of pneumonia and influenza deaths; however, this pattern is less impressive than the summertime surge in all-cause mortality in children and adults shown in the same panel.

(*b*) enhanced accuracy of surveillance systems, (*c*) improved ability to predict epidemics and pandemics, and (*d*) better understanding of the long-term implications of global climate change for infectious disease control. The latter three benefits are discussed in this section, while understanding of host and pathogen factors is described below.

The CDC Working Group on Public Health Surveillance Systems defines public health surveillance as "the ongoing, systematic collection, analysis, interpretation, and dissemination of data about a health-related event for use in public health action to reduce morbidity and mortality and to improve health" (16) and notes that outbreak identification requires "an increase in frequency of disease above the background occurrence of the disease" (16). This model implies that one can estimate a reliable background incidence of disease (46, 56). Seasonal background rates of disease are built into such emerging surveillance tools as the INFERNO system (60), as well as more traditional tools such as the models for surveillance of pneumonia and influenza mortality described above (32). However, if improved understanding of factors underlying seasonality leads to identification of environmental factors that are predictably associated with changes in communicable disease patterns, accounting for such effects would both improve estimation of expected baseline levels of disease occurrence and enhance the specificity and predictive validity of public health surveillance systems.

Seasonal and weather-related epidemics of malaria, cholera, and influenza constitute major sources of morbidity and mortality worldwide (50), and the possible emergence of a highly virulent pandemic influenza strain is a major concern at the time of writing (62). However, surveillance functions to alert public health officials to health events occurring in communities, prediction or forecasting of epidemics, or identification of events that provide early warning of incipient epidemics would

increase the time available to public health agencies charged with providing resources and expertise to minimize the impact of epidemics. As noted in a recent World Health Organization report on climate and prediction of infectious disease epidemics, the construction of weather- and climate-based systems to provide early warning of incipient epidemics is now technologically feasible and could provide considerable population health benefit if informational, structural, and monetary barriers to implementation could be overcome (50).

The potential utility of such systems is enhanced in the face of marked and ongoing global climate change; global warming may change the reproductive capacity of pathogens and vectors, alter the survival of pathogens in the physical environment, alter patterns of water use and availability, and increase the likelihood of extreme weather events. All these factors could have a significant impact on the incidence and seasonal patterns of infectious disease occurrence (39, 50).

METHODS FOR THE STUDY OF SEASONALITY OF INFECTIOUS DISEASES

Seasonality of infectious disease occurrence is studied empirically using a variety of tools, particularly those appropriate for time-series data. Additional insights into the mechanisms underlying seasonality may be obtained through the use of mathematical models of infectious diseases. Here, I use public health surveillance data on legionellosis (1995 to 2003) and invasive pneumococcal disease (2002 to 2006) to illustrate certain concepts (C. Victor Spain, Phila. Dep. Public Health, unpublished data).

Statistical Tools

The simplest approach to the study of seasonality of infectious disease may be to aggregate cases according to predefined seasons and then use statistical methods appropriate for the comparison of counts, rates, or proportions across seasonal categories (**Figure 3**). For example, in aggregating legionellosis and pneumococcal disease incidence by season of occurrence for Philadelphia county, one finds that an increased risk of pneumococcal disease is seen in wintertime relative to other seasons [incidence rate ratio (IRR) 1.50, 95% CI 1.21 to 1.85], whereas the risk of legionellosis is increased in summer relative to other seasons (IRR 3.63, 95% CI 2.43 to 5.47).

Although such an approach is common in practice, aggregation of cases in this manner results in loss of information and may obscure patterns in disease occurrence that are not strictly seasonal (for example, the reader can see in **Figure 3** that the incidence of pneumococcal disease is almost identical in spring months as in winter months). Furthermore, aggregation across years obscures such effects as the biannual periodicity associated with measles in the era prior to vaccination (6, 29). Thus the use of time-series methods offers advantages over simple categorical analyses of communicable disease data. A complete review of time-series analysis as applied to the study of seasonality is beyond the scope of this chapter, but these methods are the subject of several complete texts (15, 20) and an excellent review of their use appeared in the *Annual Review of Public Health* in 2006 (89).

As Zeger and colleagues note, comprehension of time-series data may be enhanced by breaking series down into "smooth" and "rough" components, such that smooth components may represent seasonal or monthly periodicity or even long-term trends (89). The principal approach for the description of seasonal trends in time-series data related to infectious disease occurrence are the autocorrelogram and the periodogram (6, 89). The former tool permits graphical representation of the "autocorrelation coefficient," which is itself a measure of the degree of nonindependence between serial points in a time series. The latter tool plots the fit of cosine

regression models with varying oscillatory frequency to time-series data (89).

Autocorrelograms for invasive pneumococcal disease and legionellosis in Philadelphia county are presented in **Figure 4**. It can be seen that for both diseases, a surge in the magnitude of the autocorrelation coefficient occurs at ~12 months, consistent with an annual cycle of disease occurrence. Periodograms for the same diseases are presented in **Figure 5**). Here the spectrum (defined as the maximum squared amplitude of a cosine regression model with a given frequency) is plotted against underlying frequency. The largest peak is seen at a frequency of 1/12, which again corresponds to annual periodicity of disease occurrence. Of note, a second smaller peak is seen for legionellosis at 1/24, suggesting the possibility of biannual periodicity of legionellosis as well.

Such oscillatory frequencies may be incorporated into regression models to control directly for underlying seasonal trends; models that explicitly account for autocovariance structure may be used to achieve similar ends. Controlling for nonindependence of events or underlying trends on various time scales (e.g., season or year) may permit investigators to focus on acute changes in population behavior or environmental effects within seasons, which may in turn explain year-to-year variation in disease incidence.

We used a Poisson regression model incorporating both seasonal and annual components to predict the monthly incidence of legionellosis in the five-county greater Philadelphia metropolitan area (GPMA) (**Figure 6**) (30). This model took the form of

$$\begin{aligned} E(Y) = \exp(&\alpha + \beta_1(\text{year}) \\ &+ \beta_2(\sin(2 \cdot \text{month}/12)) \\ &+ \beta_3(\cos(2 \cdot \text{month}/12))), \end{aligned} \qquad 1.$$

where E(Y) was the expected case count in a given month and year, α was a constant, and each β_i represented a regression coefficient for year or month.

Although the overall fit of such a model is reasonable, there is still substantial month-to-month departure from expected case numbers. If several events can be expected on a daily basis, time-series models based on a Poisson distribution may provide important insight into factors driving event occurrence. For example, Schwartz and colleagues (71, 72) used such an approach to document the close relationship between drinking water turbidity and diarrhea-related emergency room visits in Philadelphia; a similar approach taken by Aramini and colleagues (8) in Vancouver identified a similar relationship (**Figure 7**). This approach can be modified when the outcome of interest is a surge in disease activity rather than absolute case numbers, as Teklehaimot and colleagues have done in their work linking climatic conditions to acute surges in malaria cases (80, 81).

The use of temporally aggregated exposure data and aggregated case counts may make it difficult to control for confounding by coincident population or environmental effects because of a lack of granularity to exposure data. Furthermore, aggregation may introduce a type of "ecological fallacy" (48) in that average or aggregate environmental exposures may be quite different from the exposures that actually drive disease occurrence. However, it is not uncommon to aggregate communicable disease data at the weekly or monthly level, in part because many infectious diseases of public health importance are rare. Our group, and others, has identified case-crossover study design as a useful alternative to time-series methods for the study of environmental effects in communicable disease occurrence when outcome data are sparse (21, 30, 82). This design is analogous to a matched case-control study, with individuals serving as their own controls (55).

We found the case-crossover design useful in distinguishing average seasonal effects from acute environmental effects in the study of legionellosis occurrence in the GPMA. Using

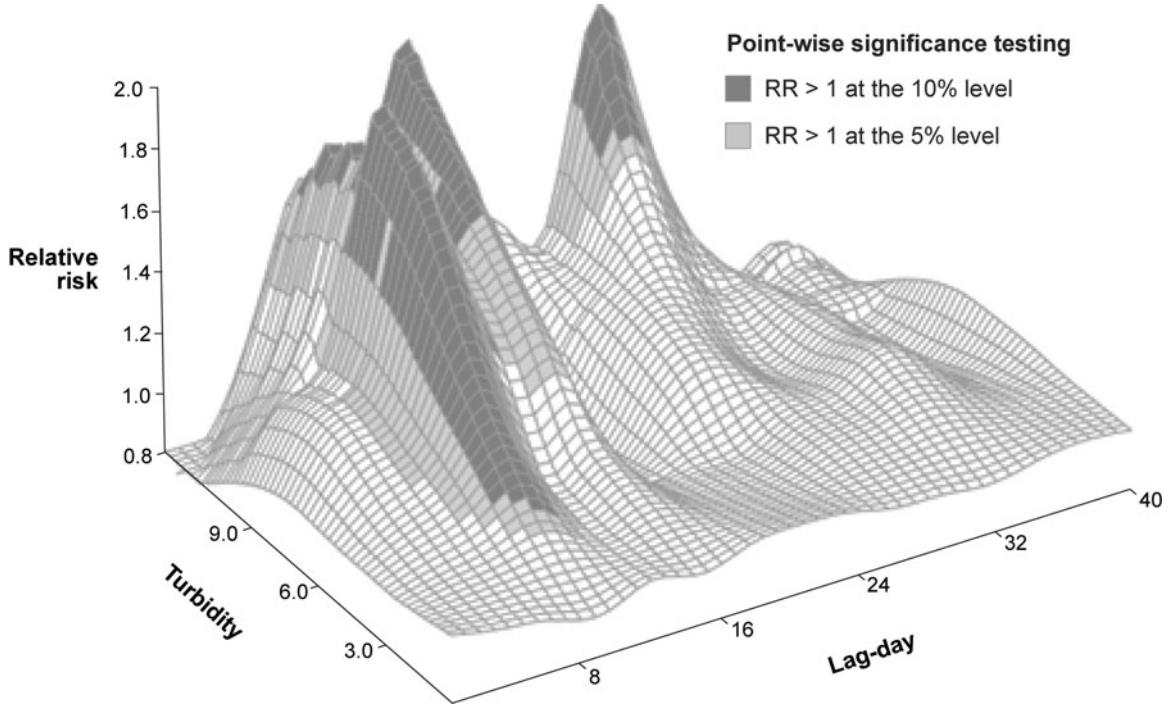


Figure 7

Impact of water turbidity on risk of diarrhea-related visits to children's hospitals in the Vancouver, Canada, area, 1996–1999, as presented in Reference 8. It can be seen that increased turbidity increases the risk at lags of ~10 days and 24 days; these different lags may represent diarrhea caused by pathogens with differing incubation periods. Source: Reference 8. Reproduced with the permission of the Minister of Public Works and Government Services Canada, 2006.

a Poisson regression approach, monthly case counts were strongly predicted by increasing average temperatures (IRR per 1°C increase in temperature 1.07, 95% CI 1.05 to 1.090), as would be expected given the summertime seasonality of legionellosis in Philadelphia. However, using a case-crossover approach, an acute increase in legionellosis risk (IRR 2.48, 95% CI 1.30–3.12) was seen 6–9 days after rainfall, an effect consistent with the waterborne ecology of this pathogen (30).

Mathematical Modeling

As with time-series methods, a comprehensive accounting of the role of mathematical modeling in the study of infectious disease seasonality is beyond the scope of this review, and the interested reader is referred to a standard reference work on this subject (6), as well as to an excellent review of mathematical modeling of seasonality that recently appeared in the ecology literature (3).

A common approach to infectious disease modeling involves the use of a compartmental model of infection, with individuals classified as susceptible to infection, infectious, or recovered from infection (and permanently or transiently immune to further infection) (27). The rate of transition between health states is defined by ordinary differential equations. Here is a model in a closed population, with transient immunity, similar to that utilized by Dushoff and colleagues in their work (27):

$$dS/dt = -\beta SI + (N - I - S)/L \text{ and} \quad 2.$$

$$dI/dt = \beta SI - I/D, \quad 3.$$

such that S, I, and N represent the number of susceptible and infectious individuals and the total population size, respectively, β represents the transmissibility of disease from infectious to susceptible individuals, and L and D represent the duration of immunity and duration of infectiousness, respectively.

In models in which immunity is transient, and those in which immunity is permanent but in which the population is dynamic (i.e., gains and losses of susceptible individuals over time), the number of infectious individuals will oscillate at some fixed periodicity until an equilibrium prevalence of disease is reached (**Figure 8**). The period of oscillation is equivalent to

$$2\pi[DL/(1 - R_0)]^{1/2}, \qquad 4.$$

where R_0 is the "basic reproductive number" of the pathogen in question (i.e., the average number of secondary cases generated by a single infectious case introduced into a susceptible population). In models in which immunity is permanent, but oscillation occurs as a result of introduction of new susceptibles via birth, L represents average life expectancy rather than duration of immunity.

Seasonal forcing can be simulated easily in such models by adding an oscillatory component to β (**Figure 8**). Dushoff and coworkers (27) performed a series of simple stochastic simulations of influenza transmission to demonstrate that "resonance," analogous to that seen in physical systems, occurs when the period of the oscillatory factor is close to the natural period of oscillation. Such resonance leads to seasonal surges in disease incidence, even when the absolute magnitude of the seasonal forcing factor is minute (27).

Similarly, mathematical models of measles with dynamic populations show biannual surges in disease incidence when annual forcing factors are introduced, mirroring the pattern of disease that was seen in the era prior to vaccination (6, 29). Other important insights into the seasonal and periodic behavior of infectious disease processes, with relevance to public health practice, have been derived from simple mathematical models. For example, Yorke and colleagues (87) showed that variation in the size of seasonal measles outbreaks can be explained by fluctuation in the number of susceptible individuals, independent of changes in transmissibility, whereas Earn and colleagues (29) showed that the seasonal periodicity of measles is expected to be disrupted by increasing the proportion of the population vaccinated, with disease patterns becoming increasingly chaotic.

MECHANISMS UNDERLYING SEASONALITY

The obvious correlation between the rhythmic change of seasons and both environmental effects and population behaviors has led many observers to ascribe the causation of seasonality of disease to readily appreciable seasonal phenomena, including weather, pollution, and seasonal human activities. Below I briefly describe the available evidence supporting these mechanisms as drivers of infectious disease seasonality.

However, the following description carries two important caveats: First, the seasonal cooccurrence of so many different phenomena, as noted above, makes problematic the identification of causal relationships between exposures and disease occurrence. Even using a daily time scale, an apparent relationship between an environmental exposure and disease occurrence may actually be confounded by another measured or unmeasured exposure. Second, as noted by Dushoff and colleagues (27), the size of a seasonal "forcing factor" necessary to generate large-scale oscillations in disease may be only a small fraction of the annual average force of infection, and thus may be effectively unmeasurable.

Population Behaviors

Human behaviors, rituals, and activities have a seasonal rhythm that is often invoked to explain the seasonal occurrence of infectious diseases. Under such a model, seasonal

oscillation in disease transmission results from increased transmissibility of pathogens owing to increased proximity of humans to one another or to increased exposure to pathogens. For example, Anderson & May (6) note that "bringing of students together at the start of the school year [can] produce annual cycles in disease transmission efficiency." Dowell (25) notes that the mid-winter spike in invasive pneumococcal disease incidence seen in a U.S. population–based surveillance program occurs "at a time when many U.S. families gather for Christmas and New Year's holidays." Such gatherings could provide opportunities for transmission of pneumococcus from asymptomatically colonized children to older relatives at risk for invasive disease. However, despite being intuitively attractive and biologically plausible, little empiric data exist to permit quantification of the relative importance of population behavior and seasonal migration in seasonality of infectious disease occurrence.

Pathogen-Pathogen Interactions

Talbot and others proposed that the seasonality of some infectious diseases is actually driven by the seasonal occurrence of other infectious diseases. For example, the coincidence of peak incidence of invasive pneumococcal and meningococcal disease with "influenza season" in North America has led some investigators to postulate that modification of the host immune response as a result of influenza infection predisposes to infection with these pathogens (38, 78). Other examples of diseases with shared seasonality and the potential for pathogen-pathogen interaction include invasive group A streptococcal disease and varicella zoster virus infection (53), and bacterial superinfection in children with seasonal measles virus infection (26). However, the seasonal cooccurrence of infectious diseases may result from other, unmeasured seasonal factors and may not reflect any actual interaction between infections. Clearly, when two infectious diseases have similar patterns of seasonality, regression of one disease incidence on another will result in the detection of a casual correlation between the two.

Environmental Effects on Pathogens

As changes in season bring predictable changes in the physical environment, it might be postulated that seasonality of infectious disease occurrence is driven by seasonal environmental effects on pathogen abundance, survival, or virulence. For example, the abundance of such waterborne agents of human disease as *Vibrio cholerae* and *Legionella pneumophila* in source waters increases with increasing water temperature; consequently, an exposure to warmer contaminated source water will be associated with an increased inoculum of the pathogen in question (39, 75). As Harvell and colleagues (39) state, "[long-term] increases in temperature. . .allow the peak value of R_0 to increase [and] also lead to an increased annual duration of the period during which the pathogen is a problem." Changes in rainfall patterns can also result in increased breeding sites for insect vectors of disease (80) and can wash pathogens or nutrients into source waters (30, 82).

For respiratory viruses such as influenza, and gastrointestinal viruses including rotavirus and poliovirus, seasonal changes in humidity have been credited with improving the duration of viral survival in the environment, increasing opportunities for hosts to inhale aerosolized virus or to become inoculated as a result of contact with contaminated surfaces (7, 24, 40).

Finally, seasonal environmental changes could directly or indirectly influence the virulence of pathogens. Temperature and other environmental stresses influence expression of virulence factors in important pathogens including *Legionella*, *Shigella*, *Yersinia*, *Streptococcus* and *Neisseria* species, verotoxigenic *E. coli*, and other pathogens (12, 33, 45, 51, 52, 58, 59, 68, 88). The virulence of infection may also be modified indirectly via seasonal influences on route of inoculation. For example,

Currie Jacups (19) noted increased case-fatality rates with melioidosis acquired in the context of heavy rains and winds in the Northern Territory of Australia, an observation consistent with an increased risk of more virulent inhalational melioidosis in the context of monsoon weather.

Environmental Effects: Hosts

Seasonal environmental factors could also influence host susceptibility to infection, either as a result of seasonal changes in host immune function or as a result of direct environmental effects on host defenses. Dowell (23) reviewed the seasonal fluctuations in seasonality of mammalian susceptibility to infection and human immune function (including changes in humoral and cellular immune function), and he concluded that changes in human susceptibility, driven perhaps by seasonal changes in photoperiod, could serve as a key driver of infectious disease seasonality. A recent hypothesis suggests that seasonal changes in vitamin D metabolism may be an important driver of wintertime susceptibility to infectious diseases. As recently described by Cannell and coauthors (16a), diminished exposure to B-spectrum ultraviolet radiation in wintertime leads to diminished conversion of 7-dehydrocholesterol in the skin to vitamin D, with resulting seasonal 1,25-dihydroxyvitamin D deficiency. Vitamin D appears to play an important role in phagocyte function regulation and is associated with the elaboration of antiviral and antibacterial peptides by immune cells, such that seasonal intracellular vitamin D deficiency could be an important driver of impaired wintertime host immune function (16a).

Other seasonally varying environmental influences could directly disrupt host defenses. For example, the rainy season predominance of "tropical pyoderma," due to group A beta-hemolytic streptococcus, could relate to the effects of chronic moisture on host skin (35). Seasonal variation in the incidence of respiratory infections could be due to the effects of atmospheric pollutants on host mucociliary action (2, 83). Ozone, a seasonally varying component of cigarette smoke and ambient air pollution, appears to enhance susceptibility to respiratory infection in mice (37). Dry air and changes in temperature may also alter mucociliary function (5, 10), although the association between dry home environments and respiratory infection risk remains controversial (10, 69, 73).

REGIONAL AND HEMISPHERIC VARIATION IN SEASONALITY

If seasonally varying environmental effects are responsible for seasonal variation in infectious disease incidence, one could expect that the peak incidence of seasonal diseases would vary by six months, on average, between the northern and southern hemispheres, with seasonality of occurrence absent in equatorial areas. In general, inversion of seasonality does exist for such infectious diseases of global range as cholera and influenza (79, 84), with influenza epidemics occurring in winter months and cholera displaying summertime seasonality.

However, although influenza occurs with similar seasonality in northern and southern hemispheres, the notion of global oscillation of influenza transmission is likely overly simplistic. In a study of influenza season onset in the United States, France, and Australia, researchers noted that the intercontinental timing of northern hemisphere influenza epidemics is synchronized, but their temporal relationship to Australian epidemics is unpredictable (i.e., they may proceed or follow Australian epidemics, with variable lags) (84).

Similarly, although cholera displays general summertime seasonality in northern and southern hemispheres, there is substantial variability in the onset of cholera epidemics within regions. For example, as noted by Tauxe, attempts to link the onset of "cholera season" to monsoon rains have been unsuccessful, and the observation that epidemics caused by classical and El Tor strains of cholera have differing seasonality in

ENSO: El Niño Southern Oscillation

Bangladesh suggests that drivers of seasonality may be more complicated than simply increased ambient temperature (79).

Loss of seasonality with increasing proximity to the equator, or increasing temporal lags in epidemic onset with increased distance from the equator, may also suggest that seasonal environmental factors have an important role in the genesis of seasonality. For example, wintertime seasonality of rotavirus infections has been reported in North America, Japan, Australia, and Europe (14, 49, 57, 90) [although a review of all studies published as of 1990 identified several reports of spring and autumn seasonality in temperate locales (18)], with less distinct seasonality in tropical areas. Koopmans & Brown (49) have suggested a generally northerly march of rotavirus disease occurrence in Europe as winter months progress. Similar peak months of rotavirus disease activity have been reported in South America as in North America, despite inversion of seasons in the southern hemisphere (63).

Conversely, the enteroviruses, such as poliovirus, exhibit summertime seasonality in temperate climates. Dowell (23) notes the loss of summertime seasonality of polio epidemics with decreasing distance from the equator (**Figure 9**). The behavior of respiratory virus–related epidemics with respect to distance from the equator has been noted to be inconsistent; for example, respiratory syncitial virus appears to circulate year round in tropical locales, but between-region variation has been noted in the timing of peak incidence (74).

Several attempts have been made to link variability in regional and temporal onset of infectious disease epidemics to intermittent large-scale weather phenomena. Disease caused by *Neisseria meningitidis* (principally meningococcal meningitis) occurs with predictable wintertime seasonality in North America and western Europe, and large-scale epidemics due to serogroup A strains occur in the sub-Saharan African "meningitis belt" during the local dry season (44, 76). Sultan and colleagues (76) investigated the impact of dry seasonal Harmattan winds and found a linear relationship between the timing of onset of peak Harmattan winds and onset of local meningitis epidemics in Mali (**Figure 10**).

Another major climatic event that appears to influence communicable disease occurrence is the El Niño Southern Oscillation (ENSO), a periodic change in the character of thermal gradients in the Pacific Ocean that accompanies a change in the intensity of the east-to-west trade winds. ENSO is associated with changing rainfall patterns in Asia, Australia, and South America, as well as changes in aquatic nutrient composition. Pascual and colleagues have identified ENSO events, along with ocean temperatures and the immune status of local populations, as important predictors of cholera risk due to El Tor strains in Bangladesh (47, 65). A number of other infectious diseases have been postulated to be influenced by ENSO including influenza, malaria, and arboviral infectious diseases (1, 61, 85).

CONCLUSION AND FUTURE DIRECTIONS

Seasonality of infectious diseases is a long-recognized but poorly understood phenomenon that likely represents a final common expression of environmental and population factors that support oscillatory disease transmission patterns. The apparent ubiquity of seasonal patterns of disease occurrence suggests that this phenomenon represents a rich vein that might be mined to produce improved understanding of communicable disease transmission and improve preventive health interventions.

The intent of this review has been to raise, rather than answer, questions related to seasonality, and basic questions clearly still exist: How is seasonality best defined? What are the preferred methodological tools and modeling approaches for the further study of seasonality? Are the mechanisms of seasonality of

individual pathogens similar in different regions and different climates? Is it possible to distinguish acute environmental effects from the underlying season of occurrence, from one another, and from the behavioral patterns that they produce? For example, can the direct biological effects of cold weather be distinguished from the tendency of populations to crowd indoors when it is cold outside?

The multifactorial nature of the questions raised by the study of seasonality should also create rich opportunities for cross-disciplinary collaboration by epidemiologists, microbiologists, ecologists, statisticians, climate scientists, and public health planners. Although differences in perspective, skills, and even vocabulary between these groups stand as potential hurdles to collaboration, successful cross-disciplinary efforts have the potential to produce not only excellent science, but also the means to apply new knowledge for the improvement of population health.

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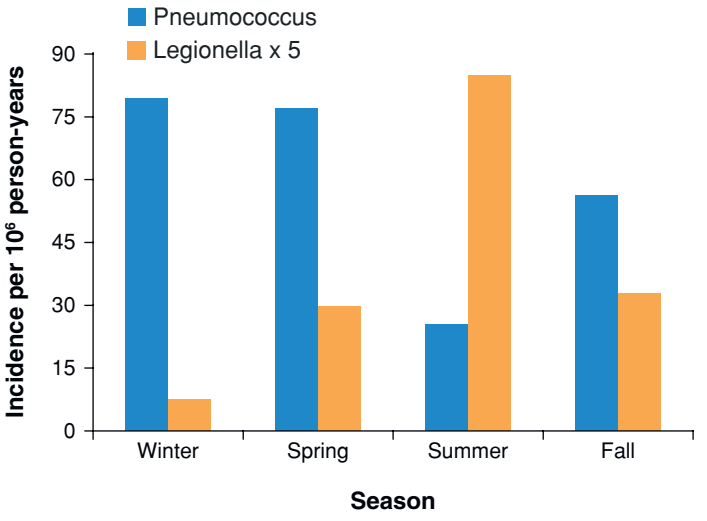

Figure 3

Annualized incidence of invasive pneumococcal disease and legionellosis (multiplied by 5), by season, Philadelphia county. Pneumococcal disease incidence is highest in winter and spring months, whereas legionellosis incidence peaks in summer. Legionellosis incidence is multiplied by a factor of 5 for comparability of scales. Data courtesy of C.V. Spain, Philadelphia county department of public health.

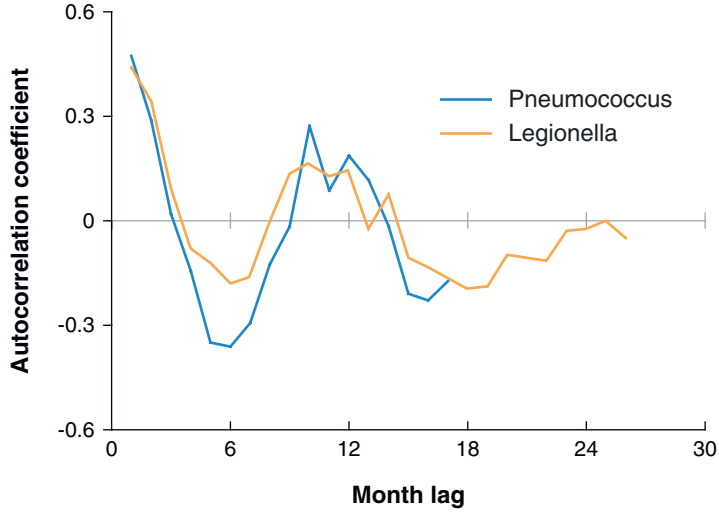

Figure 4

Autocorrelogram for invasive pneumococcal disease and legionellosis, Philadelphia county. Both diseases show positive autocorrelation coefficients with lags of 12 months, denoting annual periodicity of occurrence. Data courtesy of C.V. Spain, Philadelphia county department of public health.

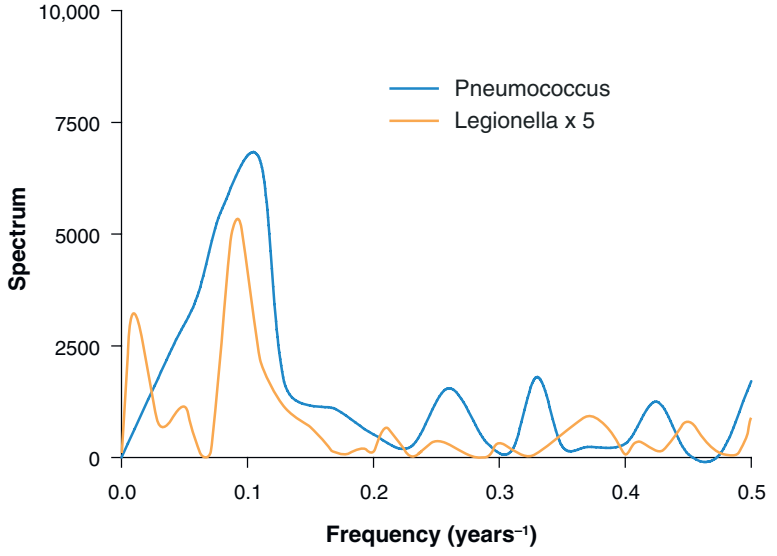

Figure 5

Periodogram for invasive pneumococcal disease and legionellosis, Philadelphia county. Both diseases show maximal spectra with a frequency of 1/12, corresponding to annual seasonality. A second biannual peak may be present for legionellosis. Spectrum of legionella is multiplied by a factor of 5 for comparability of scales. Data courtesy of C.V. Spain, Philadelphia county department of public health.

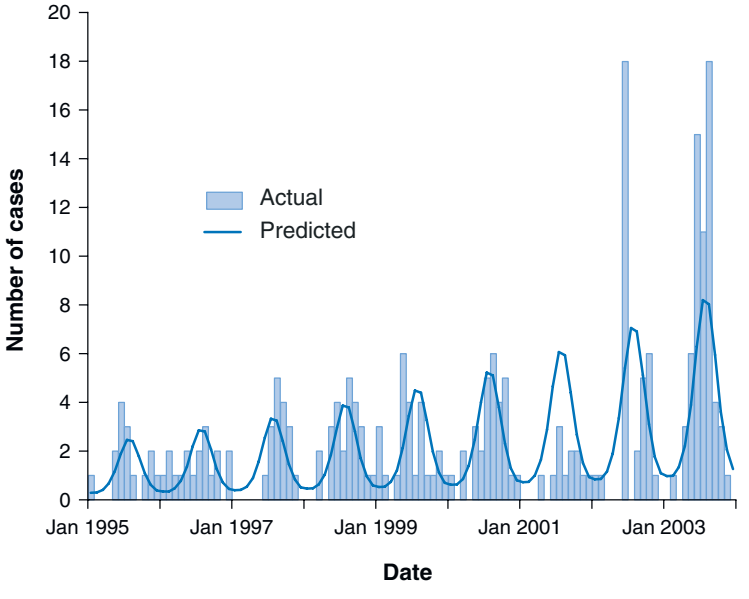

Figure 6

Temporal trends in legionellosis cases occurrence in the greater Philadelphia metropolitan area, 1995–2003, as presented in Reference 30. Bars represent case counts, whereas the superimposed curve represents expected cases based on Poisson regression. Disease occurs with summertime seasonality, and incidence increased during the period under observation. Reproduced from the *Journal of Infectious Diseases* with permission from the publisher.

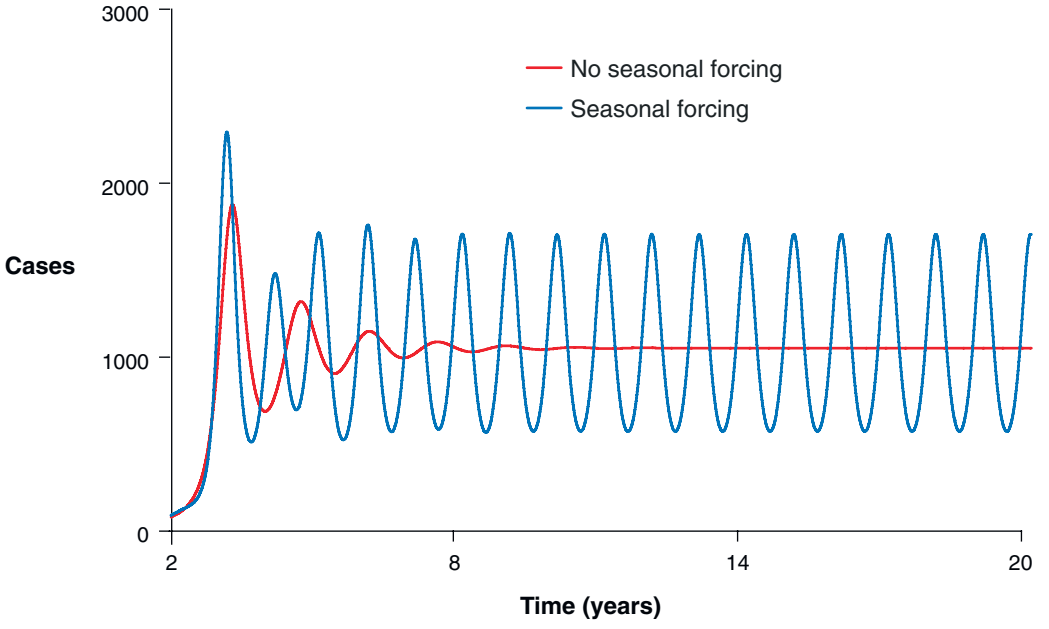

Figure 8

Output of a simple transmission model of an infectious disease with transient immunity, with (*blue curve*) and without (*red curve*) seasonal forcing, similar to the model created by Dushoff and colleagues (27). Without seasonal forcing, it can be seen that initial oscillations in incidence become damped over time. With a small seasonal forcing factor, "resonance" results in maintenance of seasonal oscillation in incidence.

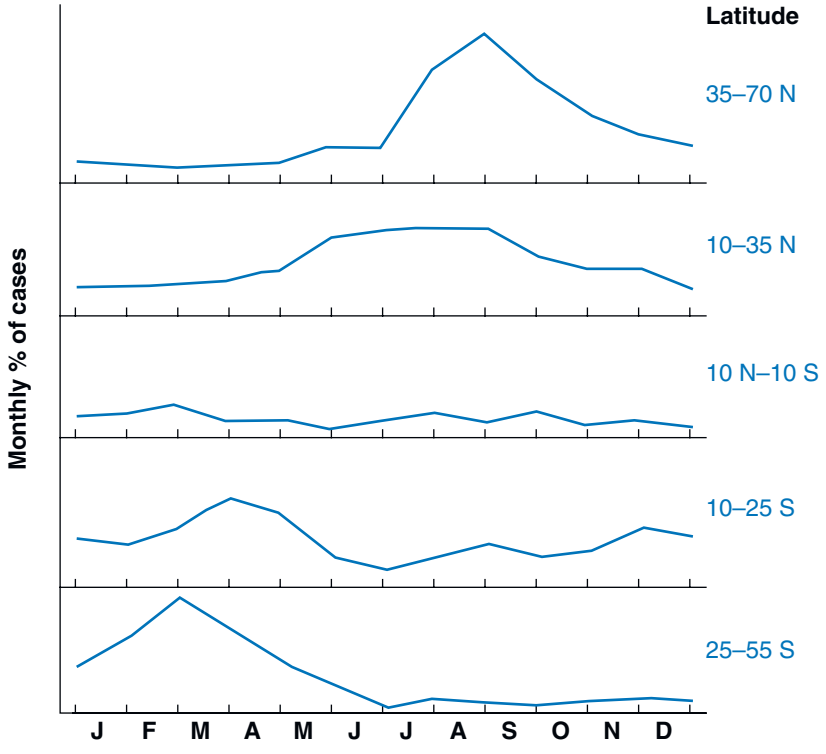

Figure 9

Seasonality of poliomyelitis, according to distance in degrees from the equator, 1956–1957. Month of year is presented on the X-axis. The top graph shows polio incidence peaking in September in the northern hemisphere, whereas the bottom graph shows a peak in March in the southern hemisphere. The middle graphs show attenuated seasonality with increased proximity to the equator. Figure constructed by Dowell (23) from data in Reference 64; reproduced from *Emerging Infectious Diseases* with permission from the publisher.

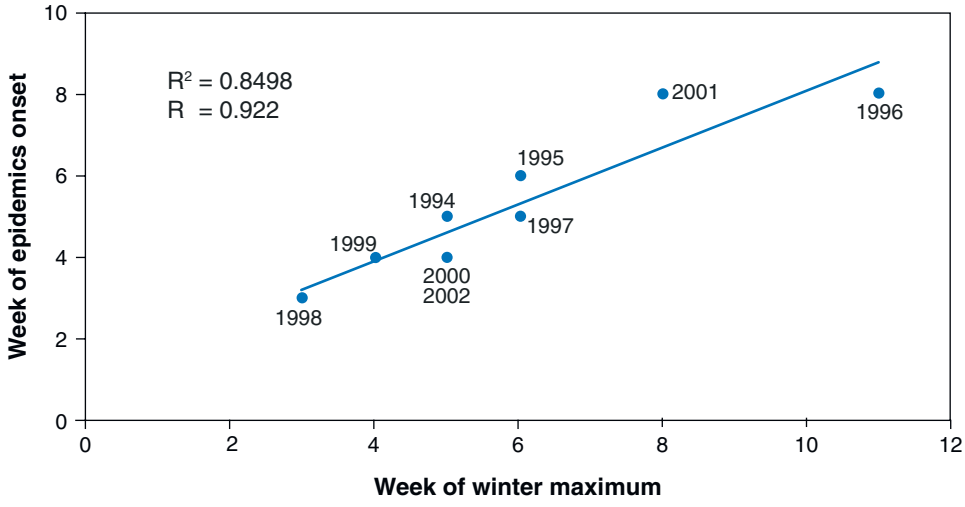

Figure 10

Sultan and colleagues demonstrated that the week of onset of epidemic meningococcal disease in Mali shows a linear relationship with the timing of maximum Harmattan winds. Reproduced from *Public Library of Science Medicine* (76) under terms of the Creative Commons Attribution License.

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