Influenza seasonality: Lifting the fog

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Seasonal variation in the incidence of communicable diseases is among the oldest observations in population biology, dating back at least to ancient Greece, yet our understanding of the mechanisms underlying this phenomenon remains hazy at best. Influenza is perhaps the seasonal disease of most profound interest, because it is responsible for much of the seasonal variation in other infectious and noninfectious causes of morbidity and mortality (1–4). Influenza virus activity displays strong seasonal cycles in temperate areas of the world and less defined seasonality in tropical regions (5), suggesting that environmental factors may drive seasonal patterns. In a recent issue of PNAS, Shaman and Kohn (6) move us a step closer to understanding influenza seasonality by clarifying the impact of environmental factors on influenza virus transmission and survival. The authors demonstrate an impressive statistical association between vapor pressure, influenza transmission, and virus survival.

Mechanisms of Seasonality

Three major classes of mechanisms have been proposed to date to explain influenza seasonality (7, 8). One class includes extrinsically driven cycles in host resistance to infection—perhaps caused by seasonal fluctuations in melatonin (1) or circulating vitamin D metabolites (7), which play a role in the immune response to infections. A second class of explanations, highlighted by Shaman and Kohn (6), is that of extrinsic variation in the survival of the virus. Explanations of this sort have typically focused on effects of ambient temperature and relative humidity, which the present study suggests are both reflections of a single causal factor, vapor pressure. A third class of explanations focuses on changing host behavior, either through more time spent indoors where contacts are closer or, more plausibly, aggregation of susceptible children in schools. School cycles play a key role in the seasonality of other epidemic diseases such as measles (9), and winter school breaks have been shown to reduce influenza transmission to children by ≈25% (10). Finally, an increase in influenza transmissibility due to one or more of these factors can lead to rapid growth of epidemics followed by natural declines due to depletion of susceptibles (9). The "natural" frequency of the disease, linked to the duration of the immune and infectious periods, may be amplified under certain circumstances by dynamic resonance with extrinsic factors and produce strongly annual epidemics (11). Unfortunately, this potpourri of possible mechanisms places us in a kind of Popperian purgatory, in which data in support of every hypothesis exist, yet none of the hypotheses has been subjected to tests that are rigorous enough to reject it (12).

Controlled influenza transmission studies conducted in mice in the 1960s were the first to suggest that transmissibility varied with temperature, relative humidity, and season (13). Experimental infections in humans further highlighted seasonal variation in disease severity and in the rate of immune seroconversion (14). Most recently, the concept that temperature and relative humidity may alter influenza transmission has been confirmed in a guinea-pig model (15, 16). These data, together with laboratory experiments testing virus survival under controlled environmental conditions (17), are carefully revisited in the new study by Shaman and Kohn (6).

Additional evidence on mechanisms of seasonality comes from population-level studies, which typically attempt to correlate fluctuation in meteorological variables with influenza epidemiological data in a specific locale (18). Results are conflicting, but some studies report an association between influenza activity and the rainy season in the tropics. Evidence for seasonal triggers of host immunity such as melatonin and vitamin D stems primarily from observational studies suggesting that respiratory infections are more frequent in individuals with known deficiencies in such factors (1, 7). Taken together, the evidence from experimental, clinical, and population studies suggest independent seasonal effects on both the host and the virus, although which is most important is unknown.

Vapor Pressure as a Mechanism

Shaman and Kohn's elegant study (6) offers a fresh perspective on seasonal variation in virus survival and is particularly novel in combining knowledge about the physics of respiratory droplets with experimental data. The authors initially reinterpret the results of influenza transmission studies in guinea pigs (15, 16) in terms of vapor pressure, a simple measure of the absolute quantity of moisture in the air. They find that transmission decreases with vapor pressure in a simple linear relationship, which is much stronger than the relationships with temperature or relative humidity. The authors proceed to test the exact mechanism by which vapor pressure may affect transmission, either via the persistence of virus-containing respiratory droplets as aerosols and/or via virus survival. Variations in droplet persistence predicted from physical laws are found to be inconsistent with the results of the guinea pig experiments, so that the aerosol-persistence mechanism is ruled out. By contrast, reinterpretation of experimental data on survival of airborne influenza virus particles (17) demonstrates that virus survival increases with low levels of vapor pressure. The authors note that vapor pressure is minimal during winter in indoor and outdoor settings in temperate regions and conclude that vapor pressure is a parsimonious mechanism of influenza seasonality, consistent with increased disease transmission in winter. Interestingly, this new study has simple practical implications and suggests that humidification of ambient air in households, schools, and work places could reduce influenza transmission by making the environment less hospitable to the virus.

A key contribution of the new study (6) is to turn what was a noisy, hence essentially qualitative relationship between environmental variables and influenza virus transmission into a stronger and more parsimonious relationship. Quantification of such relationships is the first step toward a more mechanistic approach to incorporating seasonal variation in environmental variables into models of influenza transmission. Shaman and Kohn suggest the way forward by modeling the connection between vapor pressure and survival of respiratory particles. Ideally, one would want a multilevel approach that connects environmental variables to the sur-

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vival of virus respiratory droplets and the viability of the viruses within them, then to transmission intensity by various routes, and ultimately to dynamic patterns of disease incidence.

Assessing Mechanisms of Seasonality

Like previous studies, Shaman and Kohn's study (6) focuses on one particular mechanism of influenza seasonality (seasonal effects on the virus), which suggests there is now a need for a rigorous inferential framework in which different mechanisms can be simultaneously evaluated. First, the candidate mechanism should be consistent with the results of previous studies of virus survival and transmission in mice, guinea pigs, and humans—the starting point of Shaman and Kohn's study. Second, quantitative research needs to demonstrate that the amplitude and timing of seasonal variation in the proposed environmental variable (vapor pressure, vitamin D, melatonin) are large enough to affect virus survival or host susceptibility, and make a significant impact on disease patterns. Third, any proposed mechanism of seasonality should explain the diversity of influenza seasonal patterns reported globally, in particular, the intriguing biannual epidemic cycles of influenza in subtropical Southeast Asia (19, 20) and lack of seasonality in some equatorial regions (5). It is most important to include data from multiple locations in such analyses, especially from the tropics; otherwise, the danger of spurious correlations with environmental factors is high. Indeed, simple application of the hypothesis that influenza transmission requires wintry conditions—low vapor pressure, short days, low temperature, and/or limited sun exposure—predicts that influenza should be extremely rare in most tropical and subtropical regions—a prediction that is at odds with the limited data available from such regions (5, 20). This simple argument represents an important challenge for nearly any proposed mechanism.

Separate validation should come from intervention studies in humans when they are feasible, to test, for instance, whether supplementation with vitamin D or melatonin, or indoor humidification, can effectively reduce disease burden. In this respect, it may be important to disentangle mechanisms that are predicted to affect the probability of infection from those that affect severity of symptoms, as severity could be confounded by the interaction with other pathogens, for instance, bacterial infections (2, 3). Finally, one cannot rule out that a combination of factors may synergistically contribute to seasonal variation in influenza transmission. Indeed, if further studies confirm the relatively high burden of influenza in the tropics, it seems unlikely that simple fluctuation in the level of a single factor could explain influenza seasonal patterns globally. Instead, it may be necessary to invoke some additional mechanism—perhaps geographical differences in host immunity (11) or virus evolutionary patterns (19) to explain why the infection persists in tropical regions under conditions associated with the near absence of influenza at high latitudes (15, 16).

Several kinds of data are critical to test proposed mechanisms. Most important is a comprehensive description of the global patterns of influenza seasonal activity. Global surveillance efforts have been substantially strengthened in recent years, but laboratory capacity and disease data are still scarce in many tropical countries of Latin America and Africa. Further, simple indicators of influenza activity such as the proportion of people infected each season are imprecisely known, and a basic understanding of fluctuations in population immunity is lacking. Quantitative comparison of disease burden between tropical and temperate locations is especially important but is hampered by lack of laboratory diagnostics and poorly specific clinical indicators, and may be biased by health disparities. Large prospective cohort studies would be needed to explore these questions.

Understanding why infections, and influenza in particular, have strong seasonal cycles has obvious interest for basic science. Such an understanding would also provide very practical benefits for public health, as it may help mitigate the burden of interpandemic influenza and improve preparedness plans for future pandemics. The ability to predict how seasonality operates would change our expectations for the timing and duration of a future pandemic. This in turn would affect estimates of the required duration and intensity of control measures and our expectations of whether a seasonal pause in the pandemic might help to extend the time available to manufacture vaccines. Finally, some of the proposed mechanisms to explain seasonality might be modifiable, such that influenza (and maybe other infections) could be mitigated, perhaps by nutritional interventions to improve host resistance (1, 7) or environmental measures to decrease virus survival (6). With such exciting advancements in basic and applied research ahead, we hope that the ancient mystery of influenza seasonality will stimulate interest in fields as diverse as immunology, virology, epidemiology, and physics.

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