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Deviations in influenza seasonality: odd coincidence or obscure consequence?

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Abstract

In temperate regions, influenza typically arrives with the onset of colder weather. Seasonal waves travel over large spaces covering many climatic zones in a relatively short period of time. The precise mechanism for this striking seasonal pattern is still not well understood, and the interplay of factors that influence the spread of infection and the emergence of new strains is largely unknown. The study of influenza seasonality has been fraught with problems. One of these is the ever-shifting description of illness resulting from influenza and the use of both the historical definitions and new definitions based on actual isolation of the virus. The compilation of records describing influenza oscillations on a local and global scale is massive, but the value of these data is a function of the definitions used. In this review, we argue that observations of both seasonality and deviation from the expected pattern stem from the nature of this disease. Heterogeneity in seasonal patterns may arise from differences in the behaviour of specific strains, the emergence of a novel strain, or cross-protection from previously observed strains. Most likely, the seasonal patterns emerge from interactions of individual factors behaving as coupled resonators. We emphasize that both seasonality and deviations from it may merely be reflections of our inability to disentangle signal from noise, because of ambiguity in measurement and/or terminology. We conclude the review with suggestions for new promising and realistic directions with tangible consequences for the modelling of complex influenza dynamics in order to effectively control infection.

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Introduction

Influenza is a disease of global concern, with significant levels of morbidity and mortality, that exhibits both regular seasonal occurrence worldwide and infrequent but devastating pandemics. Research interest in elucidating factors contributing to seasonality is driven both by the desire to understand and explain normal transmission patterns, and also by the conviction that understanding of normal occurrence will provide insights into how outbreaks (local epidemic and/or globally pandemic) occur. This will then allow appropriate resource allocation and will support efforts to mitigate outbreaks. The mechanisms driving influenza seasonality are thought to be related to a number of environmental, agent-specific and host-specific factors. The exact contribution of these factors to seasonality is still largely unknown [1–6]. It is likely that an as yet undiscovered interplay among host, pathogen and environmental factors leads to increased virus transmissibility and infectivity. Great advances have been

made in the field of influenza research. Two particular examples are the use of antigenic cartography for vaccine strain selection [7,8], and the use of advanced whole genome sequence analysis to understand the diversity of the influenza viruses within and across geographically discrete outbreaks [9–11]. The above techniques, along with the ability to perform advanced mathematical modelling informed by surveillance data, provide us with an unprecedented repertoire of tools that can be used for infectious disease forecasting [4,12–14]. Despite these advances, large lacunae exist in the understanding of the processes that lead to the observed seasonal disease dynamics.

In temperate climates, influenza typically arrives with the onset of cold weather, but occasionally breaks out of its expected seasonal pattern. An unusual time of arrival of the last large-scale outbreak of 2009 and a similar occurrence for the pandemic of 1918 triggered an interest in the rules and role of deviations from the expected. A large body of literature comments that, whereas influenza exhibits strong seasonality, the timing, magnitude and individual characteristics of influenza epidemics change from year to year, place to place, and population to population [6,15–20]. To some extent, heterogeneity in influenza seasonality reflects the nature of the processes of spread, transmission and manifestation of infection. In this review, we argue that our ability to measure and characterize these processes contributes to true and perceived heterogeneity.

In measuring and characterizing influenza seasonality, methodology that is prone to substantial measurement error produces uncertainty and bias. Research publications and textbooks lack a clear and robust definition of seasonality and the methodology (ranging from determining monthly counts to results of harmonic regression) for assessing seasonality. Further complicating the analysis of seasonal factors is the failure to present findings in a uniform manner and ever-evolving terminology and case definitions for influenza. Finally, investigation into the possibility of multiple mechanisms, aiming to produce observed outcomes, has been restricted to, at most, one or two potential drivers of an admittedly highly complex system. In this review, we focus on three aspects of influenza seasonality, which are critical to any discussion of causal drivers of deviation from seasonal patterns, regardless of the mechanisms by which those seasonal patterns originally emerged: (i) systematic and normalized approaches for depicting disease incidence with existing tools and measurements; (ii) the need for a consistent and appropriate terminology related to influenza; and (iii) a framework for understanding the full complexity of seasonal oscillations in spatio-temporal dynamics. This framework will help to refine and clarify future hypothesis-driven research questions.

Perceived Deviations: Heterogeneity of Seasonal Patterns

We define seasonality in disease occurrence as a temporal pattern of systematic periodic oscillation within a predetermined cycle that can be characterized by peak timing, amplitude, and duration (Fig. 1). In general, the cycle might range from months to a few years; however, for simplicity in this review, we refer to an annual cycle, the most common time period. Quantification of seasonal intensity is based on providing a magnitude of change from a nadir or pre-outbreak level to a seasonal peak. Timing of outbreaks is another important characteristic of seasonality. This concept includes the following aspects of outbreak time referencing: time of an outbreak onset, time when an outbreak reaches its maximum, time from the onset or from the peak to its end, or a return to a background or pre-outbreak level (Fig. 1). Together with the magnitude, these time-related characteristics form a unique outbreak signature. Heterogeneity in seasonality is manifested by variability in peak timing, amplitude, and duration. Seasonality can vary by location, population at risk, time period, and the type of health outcome measurement. We postulate that the seasonal oscillation in influenza occurrence is, in fact, a property of a natural process governed by various mechanisms with different manifestations in a given population.

The variability in these three characteristics is illustrated in a series of maps displaying age-adjusted weekly rates of

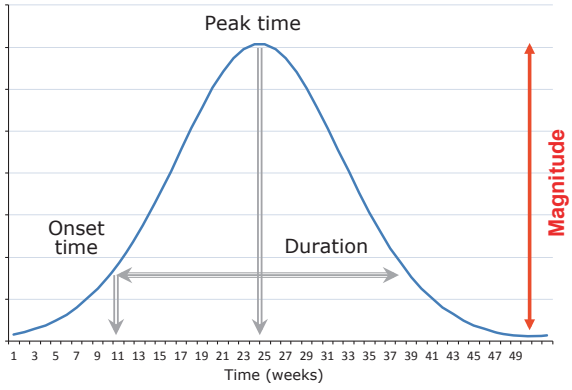

FIG. 1. Seasonal curve and seasonality characteristics. The seasonal curve depicts a temporal pattern of disease occurrence within an annual cycle. Seasonality can be characterized by peak timing, amplitude, and duration. The time when a seasonal curve reaches its maximum, and duration, defined as the time between an outbreak onset and the time when a curve returns to a background or pre-outbreak level, are shown. Seasonal intensity refers to a magnitude of change from a nadir or pre-outbreak level to a seasonal peak.

influenza-related hospitalization at the county level for four individual seasons (Video Clip S1). These dynamic maps depict the spatio-temporal distribution of hospitalizations resulting from influenza with respect to weekly averages of minimum ambient temperature; illustrate hospitalizations among patients aged 65 years and older; and demonstrate the emergence of travelling waves of influenza as the ambient temperature drops and allow the visualization of the spread or percolation of infection to adjacent areas, depending on a spatial distribution of environmental and socio-economic factors relevant to the population. For each presented season, variability was observed in the starting location, the duration, and the pattern of spread of seasonal outbreaks.

The magnitude of seasonal increase is the most commonly reported parameter of influenza seasonality. In a representative example, the rates of influenza-related hospitalization in the 1999–2000 season were substantially higher than in other years, as shown by the intensity of local clusters and global spread. However, within a single season, the magnitude may dramatically vary by age even within a seemingly homogeneous age group. For instance, among people aged 65 years and older, the oldest category exhibited the highest rate of hospitalization (Fig. S1). Considerable heterogeneity in the spread and seasonal magnitude of seasonal influenza has been documented in populations of high vulnerability (i.e. at high risk for exposure to influenza or severe health outcomes) [21,22]. Although the magnitude of the seasonal increase in influenza morbidity and mortality in a specific population might reflect the behaviour in the general population, a simple comparison of seasonal magnitudes across the various groups has to be attempted with caution. Furthermore, inferences from observed differences in the seasonal intensities have to be considered carefully, owing to potential diversity in causal underlying mechanisms. For example, the risk factors implicated in spatio-temporal patterns for children, young adults or adults with young children might have low or even no relevance to the patterns of hospitalization resulting from influenza among the elderly. The same logic applies to the comparison of seasonal peaks across regions and locations. Approaches to quantification of the seasonal magnitude also vary, ranging from providing the highest value of an outcome of interest (incidence rates, percentahe of positive test results, number of cases, etc.) observed over a time period of incidence to an estimated trough-to-peak ratio [23]. Measures of magnitude include excess mortality values [4], relative and absolute intensity [20], or their proxies.

The characterization and reporting of the peak timing in influenza are improving. Not only is the month with the highest number of cases consistently provided in the literature, but so is information on the range in timing of the regional peaks [24]. It has been shown that both the seasonal peak timing [20] and the time taken to reach the peak and baseline levels [24] can vary locally and regionally. It has been well documented that influenza A often precedes influenza B [25], indicating potential heterogeneity in seasonal peak timing associated with strain diversity. Peak timing and seasonal magnitude can be correlated: earlier outbreaks have higher intensity [20], which can be linked to antigenic drift [26]. The dynamic maps provide insights into the time elapsing from the onset to the end of a seasonal outbreak, which may take 4–7 weeks [20]. The geo-referenced sequence of seasonal peaks forms travelling waves of influenza, and allows us to characterize a global pattern of transmission [27–30].

It has been shown that there is a remarkable degree of synchronization of influenza outbreaks at a regional level [20,31–33] as well as between countries [24,34] in temperate climates. Investigators relate synchronization to globalization [35,36], social mixing patterns [37], and transportation networks [30,38]. However, it is noteworthy that synchronization in the tropics is not extensively documented, in spite of high population densities and high connectivity between regions. In larger countries such as China, Brazil, and India, a certain degree of synchronization is seen for regions that have similar climatic conditions [15,39,40].

Synchronization of influenza seasonality with environmental parameters has the potential to allow an integrated forecast of infection on a local and global scale. The link of influenza with low ambient temperature favouring survival of aerosol viruses [41] and indoor crowding [42] might be implicated in a southward trend in the occurrence of increased hospitalizations early in the season (September–October) in the Midwest and South of the USA. Another easily distinguishable wave of outbreaks from the northwest to the southeast, corresponding to decrease in temperature, was observed in Texas and Oklahoma in late October through November, with the frequent appearance of clusters at temperature gradient fronts. In both the Atlantic and Pacific coastal regions, influenza hospitalizations peaked, on average, almost 6 days later than in the central region (between -80° and -100° longitude): 4.9 weeks vs. 5.6 weeks [20]. This suggests that, in general, on a large spatial scale, travelling waves of influenza move from southwest to northeast. However, as illustrated by the dynamic maps, even within a single influenza season, it is possible to trace multiple origins contributing to the overall seasonal curve.

A seasonal pattern observed globally is not necessarily a simple sum of patterns observed locally [43]. Although annual epidemics typically begin abruptly, peak within 2–3 weeks and last from 5 to 10 weeks in the continental USA

[20], their local behavior might exhibit unusual clusters that percolate during an influenza season. In the presented example, one of the most striking observations is the presence of clusters of high influenza incidence that occurred early in the autumn of 1999, were maintained throughout the influenza season, and were among the last remaining at the end of the influenza season (Fig. S1). A potential reason for isolated percolations and for a global seasonal pattern is likely to be related to characteristics of circulating strains that were dominated in the past and were re-occurring in a given season [44].

A depiction of a typical seasonal pattern or a departure from it requires spatially explicit time-series modelling, which usually entails the selection or specification of a time period and geographical area. In locations with relatively small populations, an aggregation of data into 'meaningfully large' numbers leads to reporting of monthly or even quarterly cases of influenza that severely weakens the quality of analysis. The use of fine time units—days and weeks—allows the detection of seasonal patterns with high resolution; however, it often requires an aggregation over a large, often heterogeneous, geographical area, and may conceal an isolated pattern. A departure from what is 'typically' observed on a large geographical scale needs to be better characterized with respect to local diversity of circulating strains, and the criteria for a proper comparison should be grounded on what we can measure reliably with a sufficient degree of reproducibility, precision and accuracy for the intended purposes and goals.

Influenza: the New Tower of Babel or the source for Obscure Observation?

The paradigm of seasonality and the heterogeneity in patterns observed can originate from the process itself or from our ability to detect and measure seasonality. The lack of sound science-based definitions and reliable data, and limited methods for presenting data and assessing statistical significance in temporal oscillations, can obscure the true seasonal pattern.

Influenza is an ancient term; it lacked a firm meaning from the start, and the meaning became even more convoluted as time progressed. The term has long been in clinical and public health use, and pre-dated the discovery of the true cause of the disease in 1933. Influenza has also long been used as a blanket term to refer to and be synonymous with respiratory illness—conflation with the common cold. In both the epidemiological and medical realms, the term 'influenza' is used restrictively in some cases, referring only to the disease caused by the influenza virus as confirmed by laboratory tests. At the other end of the precision scale, influenza refers to a collection of signs and symptoms, which are themselves not clearly defined—and perhaps cannot be defined with any degree of clarity [45–49] (http://www.who.int/classifications/icd/en/). The routine use of such a wide range of case definitions undoubtedly leads to substantial noise in the observed temporal patterns, may produce false alarms, or may result in a failure to recognize an unusual departure from a seasonal curve.

On the basis of the clinical progression of the disease, we expect that mild cases will appear first in a community, with a subsequent rise in outpatient visits, an increase in hospitalizations, and then deaths, according to a pyramidal structure (Fig. 2). However, the rapid onset of influenza, high infectivity and heterogeneous herd immunity [50] might obscure this temporal pattern. Furthermore, an event attracting high media attention might distort an otherwise smooth seasonal curve by a disproportionally high sudden rise or spike in tracked records if the case definition is prone to such fluctuations. With the increase in digital tools for tracking influenza cases over the internet and social media, vague definitions of influenza are currently at the core of temporal trends [51]. These new technologies pursue the noble goal of providing an early warning for influenza arrival, and their credibility depends on the quality of tracked responses and the ability to separate signal from noise. With regard to ongoing attempts to actively use text mining in large volumes of medical records, the signal-to-noise ratio is the most important consideration in understanding the departure from an expected pattern. Until definitions and the approaches to consider various terms in data mining and text search engines are clarified, the temporal oscillations produced by massive text-mining algorithms might be severely obscured, and the similarities or differences in the detected patterns could be purely coincidental.

'Influenza-like illness' is currently recognized as the cornerstone of syndromic surveillance, and is most often used to refer to persons with signs and/or symptoms that are commonly the result of influenza virus infection. Comparisons of seasonal patterns derived from syndromic surveillance should be made with caution, as the case definition may change over time and vary from country to country and season by season, as the set of symptoms may change. A reliable surveillance system that produces systematically evaluated laboratory-confirmed cases with reasonable spatial granularity and sufficient level of detail on demographic composition and molecular characterization is key for a comprehensive depiction of influenza seasonality. Geo-referenced data that are uniformly collected and updated on a weekly

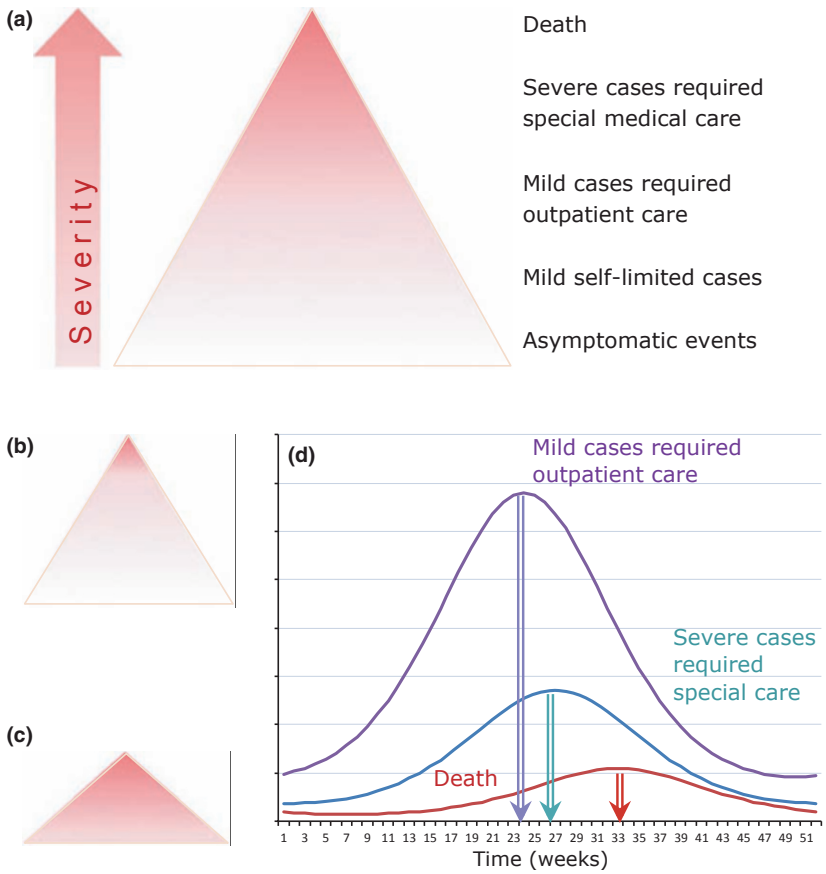

FIG. 2. Pyramidal structure of disease burden with respect to severity. As the severity of influenza infection progresses from asymptomatic to mild to severe, the number of cases decreases proportionally (a). In a population with high herd immunity, the majority of asymptomatic cases may be unnoticed (b). In vulnerable populations, the proportion of patients with severe outcomes might be very large, even though they make a relatively small contribution to the overall burden (c). On the basis of the clinical progression of influenza, we expect that outpatient visits for mild cases will peak first, severe cases requiring hospitalization and specialized medical care will peak next, and cases resulting in death will peak last (d).

basis can serve as an indicator of the level of influenza activity for the whole country. The prime example of established influenza monitoring comes from a number of national systems, where elaborate sentinel surveillance is combined with extensive laboratory characterization [33,34,52–54]. The establishment of surveillance systems in countries with tropical climates enables the depiction of seasonal trends in locations where historically data were very limited. One example of a tropical city with a good surveillance system is Hong Kong, where the burden of hospitalization can be compared with that of the USA, and a distinct pattern of seasonality exists [44,55,56]. The compilation, validation and retention of certain minimum demographic (e.g. age, gender, and location) and clinical (e.g. disease severity and outcome) information in publicly reported surveillance data are likely to increase the utilization and usefulness of monitoring efforts in the assessment of influenza seasonality.

Hospitalization and medical claims records offer a unique systematic approach to depicting seasonal patterns, which are likely to be different from those observed via surveillance, owing to a shift to a population that is likely to be more susceptible or disease-prone, such as children, the elderly, and people with underlying medical conditions (Fig. S2). Although weekly pneumonia-associated and influenza-associated hospitalizations have been used as a reliable indicator of influenza morbidity, it is likely that the seasonality, specifically the peak timing, depicted by the hospitalization claims contains substantial delays. Imprecision of clinical diagnosis may add to the noise in this seasonal pattern.

Because of the various notions associated with influenza, the attempt to be more precise has gone in the direction of adding more words to qualify the terms. The types of restriction added include geographical designations, designations related to time of year, and geography, in addition to

an assortment of other types of limit added to the central term. It is useful to disentangle various adjectival categories, and to ask whether the added words provide greater precision or merely complicate the fuzziness of the language. 'Pandemic flu' is often intended to mean a 'highly virulent' disease that leaves in its wake an excess in mortality throughout the world, whereas 'epidemic influenza' may denote a more localized viral infection, with perhaps a lower number of deaths. Some epidemics carry an adjective that identifies some aspect of the virus, such as 'swine' or 'avian' flu, based on the animal reservoir from which the strains may have originated. Are these simplifications intended for a lay audience or merely a reflection of sloppy language use? The term 'seasonal' is used in an attempt to loosely specify influenza with characteristics that are somewhat expected, or at least is not 'epidemic' or 'pandemic.' Does seasonal influenza stem from seasonal requests for testing, at least in part? Is un-seasonal flu a departure from an expected course, meaning that it should serve as an alarm? These questions need to be answered.

Coupled Resonators to Study Deviations of Seasonality

Many researchers have proposed isolated potential mechanistic drivers of seasonal/periodic fluctuations in influenza [57,58]. Such studies investigate local patterns within years independently of a broader temporal context, or focus on long-term patterns in which variation among individual years is averaged in favour of understanding emerging trends. There is, however, a different type of hypothesis with which to describe the mechanism by which 'deviations' from expected oscillations might arise: coupled resonators. Building on ideas from physics initially proposed in the 1600s, this hypothesis proposes that many different mechanisms may each contribute an oscillatory driver of influenza dynamics, but that the differences in strength, timing and the potential amplifying and damping effects that they have on each other may lead to quasi-chaotic local behaviour in an otherwise globally periodic system. (In the language of modern physics, this involves the study of coherence and resonance in loosely coupled oscillators [59]). Engineers and physicists have already developed an incredibly useful theory with which to describe the necessary and sufficient conditions for coherence and resonance behaviours in such systems, including incorporation of the impact of stochasticity and time delay, making their results not only relevant, but directly analogous to proposed drivers of disease dynamics [60]. This idea is not entirely new to the study of seasonal influenza, but has thus far been confined to studying multiple effects of single, or small sets of, mechanistic drivers of oscillation [23]. These insights have been extremely valuable, but have not yet realized their full potential as a unifying principle from which plural-mechanistic hypotheses may be considered.

Importantly, we do not mean to suggest that the correct choice of action for current research would be to compose a model of 'everything but the kitchen sink', tuning the interactions until observed patterns that include global periodicity with deviations of the observed type emerge. Although that would be possible, it would be practically meaningless. We believe that the focus of these efforts should shift away from trying to demonstrate which mechanisms may be strong enough to be primary drivers of global patterns, and instead begin to focus on how different mechanisms affect each other (starting with pairwise interactions, but then also explicitly scaling up experimentally to discover potential three-way and higher-order interactions). Only after this empirical groundwork has begun can models begin to explore at what level these interactions may be appropriate for inclusion in an all-explaining paradigm of seasonality. From this perspective, observations that are currently believed to be deviations from seasonal patterns may actually be the result of a sufficiently complex system of loosely coupled oscillators that, in fact, reveal such seeming anomalies as logical necessities in the global pattern of disease incidence.

Conclusions

In temperate climates, seasonal influenza arrives in late autumn to early winter, and dissipates in spring. In the tropics, annual fluctuations are more complex, and are linked to water content in the air, rather than to the ambient temperature cycle. On a relatively global scale, annual epidemics begin abruptly, peak within 2–3 weeks, and last for 5–10 weeks. Seasonal waves travel over large spaces, covering many climatic zones in a relatively short period of time. The precise mechanisms governing the peak timing, amplitude, shape and duration of seasonal waves are unknown. The relationships between host susceptibility, the emergence of new strains and their genetic variability, factors that influence the spread of infections and characteristics of seasonality are not well understood. This area of research is extremely promising, and is already showing substantial promise. To ensure success, we need to shape the meanings and referents of terms, and develop the models to correspond as closely as possible with what we know—and, equally important, with what we do not know. Furthermore, for monitoring

purposes and the determination of endemic levels of disease, so that we can accurately read the warning signs in nature, the use of precise terms and the development of novel creative approaches for depicting seasonal patterns and departures from the expected are critical directions of research. The development of uniformly implemented rigorous definitions will form the basis for understanding whether our observations are, in fact, measurements of a biologically fluctuating system, or actually logical necessities of a steady, but stochastic, natural state.

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Transparency Declaration

The authors declare that they have no conflicting interests in relation to this work.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Demography of residence and spatial distribution of influenza hospitalizations among older adults in the USA from 1998 to 2002.

Figure S2. Snapshots from the dynamic map of weekly influenza hospitalizations for US adults ages 65 years and older superimposed on average weekly temperature.

Video Clip S1. Script for dynamic maps.

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