Global Geographical and Temporal Patterns of Seasonal Influenza and Associated Climatic Factors

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Abstract

Understanding geographical and temporal patterns of seasonal influenza can help strengthen influenza surveillance to early detect epidemics and inform influenza prevention and control programs. This study examines variations in spatiotemporal patterns of seasonal influenza in different global regions and explores climatic factors that influence differences in influenza seasonality through a systematic review of peer-reviewed publications. The literature search was conducted to identify original studies published between January 2005 and November 2016. Studies were selected using predetermined inclusion and exclusion criteria. The primary outcome was influenza cases and additional outcomes included seasonal or temporal patterns of influenza seasonality, study regions (temperate or tropical) and associated climatic factors. Of the 2160 records identified in the selection process, 36 eligible studies were included. Results showed significant differences in influenza seasonality in terms of the time of onset, duration, number of peaks and amplitude of epidemics between temperate and tropical/subtropical regions. Different viral types, co-circulation of influenza viruses and climatic factors especially temperature and absolute humidity were found to contribute to the variations in spatiotemporal patterns of seasonal influenza. The findings of this review could inform global surveillance of seasonal influenza and influenza prevention and control measures such as vaccination recommendations for different regions.

Keywords: seasonal influenza, geographic and temporal patterns, climatic factors, influenza viral strains

Abbreviations: WHO: the World Health Organization; Influenza A H1N1: H1N1; Influenza A H3N2:

H3N2; Influenza-like illness: ILI; East and Southeast Asia: E-SE Asia; Absolute Humidity: AH

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INTRODUCTION

Influenza is a highly contagious viral infection which usually presents as an annual seasonal epidemic or occasional pandemic across the world (1). Currently there are two major types of the influenza viruses (Influenza A and Influenza B) causing human infections, with Influenza A accountable for higher mortalities than Influenza B (1, 2). The global annual incidence of influenza is significantly higher in children (20% - 30%) compared to adults (5% - 10%) (3). The epidemics of seasonal influenza are estimated to cause 3 to 5 million cases with severe illnesses and lead to 290,000 to 650,000 annual mortalities worldwide (4). These figures highlight the burden of influenza and its implications of high social and economic costs (3, 4). The World Health Organization (WHO) encourages global efforts on influenza prevention and vaccination, especially for people at a higher risk of serious complications and death (3).

In spite of being a vaccine preventable disease (5), the rapid transmission and relatively high incidence during seasonal epidemics and pandemics make influenza one of the major health concerns in the world. Furthermore, the virulent nature of some influenza viruses, the occasional zoonotic outbreaks and its ability to undergo significant genetic changes through antigenic shifts further make it challenging in predicting the next influenza epidemics and developing effective prevention measures (6, 7). The 'Global influenza activity reports' released by the World Health Organization suggest variations in the number of annual peaks and the onset of epidemics as

well as the duration of seasonal influenza transmission in northern and southern hemispheres and also various geographical locations in each hemisphere (8, 9). While there are many subtypes of Influenza A virus, the major subtypes responsible for annual seasonal influenza epidemics in humans include Influenza A H1N1 (H1N1) and Influenza A H3N2 (H3N2). The patterns of influenza transmission also vary according to the dominant viral subtype (9). Understanding geographical and temporal variations of seasonal influenza can help strengthen the existing influenza surveillance to detect early onset of epidemics, plan control measures to reduce the incidences in vulnerable populations and provide recommendations on relevant prevention strategies (such as vaccination plans) in the general population. Despite numerous empirical studies (including some population-based observational studies) available in addressing the patterns of influenza seasonality in various countries or regions of the world and covering different time periods including post 2009/2010 influenza pandemic, existing literature remains inconclusive in describing long-term patterns of seasonal influenza across different global regions, especially the transmission patterns in the tropics and subtropics (10-13). Two recent reviews examined latitudinal variations in season activity of influenza and the mechanisms explaining the different patterns of influenza seasonality across temperate and tropical regions at global level. They suggested that influenza seasonality in tropical localities and the link between different viral epidemics and climatic/ environmental factors needed to be addressed and well understood (10, 14). To date, no research has been developed to

systematically analyze the variations in the patterns of seasonal influenza around the globe in consideration of the dynamics of virus strains and possible climatic contributors. This study aims to examine the common geographical and temporal (long-term) patterns of seasonal influenza and explore variations in the patterns of seasonal influenza along with their inter-relationships with climatic factors through a systematic review of internationally published research and health reports on the relevant topics.

METHODS

Search Strategy and selection criteria

This study is a systematic review on spatial and temporal patterns of season influenza and investigates climatic factors associated with the variation of the patterns. The PubMed database was firstly used to search published literature relevant to the study topic in November 2016. As a recent published review article on exploring possible mechanisms driving global influenza seasonality covered a wide range of publications from 1960's up to 2010 (14) this present study limit the publication year to January 2005 – November 2016 to update information relevant to the topic and compare the findings with existing evidence. This duration also allowed the researchers to assess studies relating to the 2009 influenza pandemic. The searches were conducted using different combinations of key words including 'Influenza seasonality OR Seasonal Influenza' with various combinations of search terms like 'Geographical differences';

‘Geographical variations’; ‘Geographical patterns’; ‘Spatial variations’; ‘Temporal differences’; ‘Temporal variations’; ‘Temporal patterns’; ‘Changes over time’; ‘Long term trends’; ‘Climatic Factors’ and ‘Climatic Variations’. The same search strategies and key words were repeated in different databases including Google Scholar, Science Direct and Scopus in December 2016. The reference lists of the articles included in this review were manually searched for additional publications on the relevant topics.

Inclusion criteria

Original observational studies focusing on human population data and published in English within the predetermined period were included for this systematic review. In the initial article search and screening process, if the title or abstract of an article contained ‘seasonal influenza’ and either ‘geographic’ or ‘temporal’ patterns (or any interchangeable keywords as listed above), it was included for further full-text reading. Influenza activity or patterns must be included as one of the key outcomes. Many studies obtaining data from national or international surveillance systems (such as the World Health Organization’s FluNet data) in which cases of influenza-like illness (ILI) and/or acute respiratory infections (ARI) were routinely reported and monitored. In this case, confirmation of influenza cases should be established to allow a breakdown of analysis on influenza patterns. The inclusion criteria were not limited to any particular region or country of the world nor were to any particular population age group. Data and findings at both individual patient and population levels were sought in relation to the keywords of interest.

Longitudinal studies using data for more than one influenza season and with clearly defined seasonality (onset, duration and peaks of epidemics) were considered. Geographic variations were refined as any differences in seasonal patterns of influenza epidemics between northern and southern hemispheres, different continents, diverse global regions (temperate, subtropical and tropical), various countries, or smaller studies including only one country/state across multiple latitudinal gradients.

Exclusion criteria

Studies focusing on non-human zoonotic influenza epidemics or viral antigenic characteristics or pathological processes of influenza were excluded from this review. Interventional studies and clinical trials examining the effects of drugs and other interventions such as vaccinations on influenza epidemics were excluded as these did not meet the objectives for the review. Studies limited to a single influenza season for one local area/city were also excluded from the review unless the topics were related to specific pandemics or large-scaled outbreaks. Studies investigating the 2009-2010 pandemic were excluded as the pandemic did not follow the usual seasonal patterns of influenza. The relevance to the review topic (spatial and/or temporal patterns of seasonal influenza) was also taken into consideration. Thus, publications without providing clear definitions on either temporal or geographic patterns of influenza seasonality were eliminated.

Study selection

Both researchers were involved in determining the keywords and process for the searches of literature and data extraction. The initial literature search was conducted by the first author.

Each keyword combination used during the search process was shared and verified with the second (corresponding) author and repeated in different database searches. All records from different data sources were retrieved and uploaded onto EndNote library. In this process, duplicated records obtained from different sources were removed.

The inclusion and exclusion criteria for eligibility screening were discussed between the researchers and determined at the title and abstract reading stages. The decision of excluding each article was made according to the criteria. The next selection process was undertaken by reading the full-text manuscripts to address all inclusion/exclusion criteria and the study aims.

The full-text articles selected to be reviewed were critically assessed for the risk of bias and the quality of information using critical appraisal tools (the PRISMA checklist and the QA tool for Quantitative studies developed by the McMaster University) (15, 16). The data of four studies were collected from influenza-like illness surveillance. However, specimens of influenza were tested in three studies to allow separate analyses on influenza patterns (17-19). Only one study used the national influenza-like illness surveillance in Vietnam data for analysis (20). Considering

the unique environmental and climatic diversity within the country and the similar patterns between influenza-like illness and influenza epidemics over time observed in other Asian countries, this study was retained for analysis. The assessment results were verified between the

authors. Any disagreements between the researchers arising during study selection and critical appraisal processes were carefully discussed to resolve any inconsistencies in making the final decision.

Data analysis

The main outcome used for this review was seasonal influenza. However, studies extended to explore large-scaled influenza outbreaks/ pandemics were also included. The majority of the studies were considered methodologically sound using appropriate study designs and rigorous data collection/analysis methods (rated 'strong' according to both tools). Overall, two studies were rated 'weak' against most of the assessment criteria and were excluded from the review. However, they were used to affirm the key findings reported in the included studies. Data extracted for this review included author, year of study, study setting, population and sample size, study design, source of data, case ascertainment, statistical analysis methods, main spatial or temporal patterns of influenza and associated climatic factors. Data were extracted from the included publications and displayed on an electronic spreadsheet (using Microsoft Excel). The outcome measure was based on confirmed cases of influenza or influenza-like illness reported by the authors of each study.

RESULTS

The total number of studies initially retrieved from the Database was 2614. After removing the duplicates from different data sources, the remaining 2160 articles were screened through title,

abstract and further full-text reading along with the application of '*inclusion and exclusion criteria*' at each step of elimination. Figure 1 illustrates the details in the process of study selection. The decisions at each step of the selection process were discussed and validated between the authors. At the end of the entire process, 36 publications were included for this systematic review.

The summary of the key extracted components of the included studies is presented in Table 1.

The year of study covered from 1915 up to 2015. The most common range of study period was from the year 2000 onward (26 articles, 72.2%). Over 40% (n=17) of the included studies involved large-scaled data from multiple countries or even across continents/ hemispheres, while 10 studies (27.8%) presenting country-based data of multiple sites such as USA, Canada, China and France. The remaining publications represented regional-level data with a relatively small scope such as Hong-Kong (China), Okinawa (Japan), Madagascar and French Guiana. The majority of the included studies used a longitudinal study design combining with time series analysis and statistical modelling. The size of study population (if stated) ranged from 900 (21) to 5.4 billion (22). Many studies (n=14) utilized international databases such as FluNet (n=10) and data from the World Health Organization (WHO)- Global Influenza Surveillance and Response Network and others used National influenza surveillance data. A small number of studies made the use of data reported by sentinel general practitioners (GP) and hospital-based data. In terms of the outcome measurement, a large proportion (80.6%, 29 out of 36) of the

included publications specified laboratory confirmed cases to ascertain the outcome. The majority of the included studies used time series, ARIMA, autoregressive models, mathematical modelling and geographic information systems (and Epi-Map) to establish or simulate spatiotemporal patterns of influenza epidemics; many performed multivariate modelling (such as linear regression, generalized linear models, logistic regression and other non-parametric approaches) and correlations (Pearson's and Spearman correlations) to determine the contributing viral strains and effects of climatic factors on influenza seasonality. The key findings of this review in relation to the study aims are organized into three major themes: 'Geographical and temporal variations in seasonal influenza', 'Influenza viral types in relation to spatiotemporal variations in influenza seasonal epidemics and co-circulation patterns of influenza viruses' and 'The role of climatic factors in influencing spatiotemporal patterns of seasonal influenza'.

Theme one: Geographical and temporal variations in seasonal influenza

Seasonal influenza epidemics show variations in the time of onset, duration, amplitude and transmission patterns. These patterns were discussed in 23 out of 36 (63.9%) studies (10, 11, 14, 17-19, 22-38). The common observations and variations in these patterns were noticed at latitudinal levels according to temperate, tropical and subtropical regions as described below and the comparisons of the common patterns in different global regions are summarized in Web Table 1.

Geographic and Temporal patterns in temperate regions

Influenza activities in temperate regions commonly peak during cold winter months across the globe (10, 11, 22, 24, 27). They begin in the northern hemisphere and show a southward spread, coinciding with the winter seasons of each hemisphere (19, 22, 27). In the northern hemisphere, influenza activities increase during January-March and in the southern hemisphere, the activities peak from July-September. Influenza peak timing is associated with latitude in temperate regions of both hemispheres (10, 19). There is a lag of about 2.4 months for every 33-degree change in latitude from north to south (24). The average length of influenza season lasts for approximately 4 months in temperate regions (10, 11, 19, 22, 36, 38). The amplitude of influenza transmission increases with increasing latitudes, particularly in the northern hemisphere, but such a variation is not observed in the southern hemisphere (10, 22, 24). Most of temperate countries experience a single annual peak usually during the coldest month of the winter (22). Some temperate countries in the northern hemisphere such as Canada and parts of Europe follow a horizontal pattern of influenza transmission, with influenza cases emerging earlier in the western regions (18, 28).

Geographical and temporal patterns in tropical and subtropical regions

Many recent longitudinal studies (published in 2015 and 2016) aimed to address the knowledge gaps in understanding the patterns of influenza seasonality in tropical and subtropical regions with less well-defined but diverse seasonal patterns, complex climate conditions and relative insufficient information (under-sampled and unavailable data in many African and Central and South American and Pacific Island countries) (10, 11, 20, 23, 29, 33, 39). The classification of focused regions differed in many studies. For example, some researchers specified the regions according to specific latitudinal gradients and classified the analyzed countries into tropical and subtropical regions (22, 33); while others combined tropical and subtropical regions in their analyses (10, 11, 19, 25).

The seasonal patterns of influenza are less prominent in tropical and subtropical regions. The onset of influenza season in these regions varies between the countries from April to June, with no distinct seasonal patterns. Some countries have biannual peaks, while others have year-round activities without noticeable peaks (10, 22, 29). The duration of influenza epidemics is longer in the tropics/subtropics compared to temperate regions and lasts for an average of 6 or 7 months (11). The amplitude of the seasonal influenza epidemics decreases towards the equator, especially in the tropics (10, 24, 29). While the seasonal amplitude of the influenza activity varied with the change in latitude in the northern hemisphere, such a relationship was not found in the southern hemisphere. This variation might be due to inadequate information available or only a small number of studies addressing influenza patterns in the southern hemisphere (10, 29).

(Web Table 1). For larger countries, the temporal patterns of influenza epidemics vary between the different regions according to the latitudinal gradients (10, 11, 22-24, 29, 31, 33, 38). For example, the peak of influenza epidemics in China occurred in January- February in the Northern provinces (in temperate region), while in the southern provinces (in tropical or subtropical regions) this peak occurred during spring and early summer in April- June. The provinces located between 27.4°N- 31.3°N, had semiannual peaks, the first one during January-February and the second in June-August (38). Similar variations are also noticed in India, Brazil, Vietnam and many African countries (20, 23, 24, 29, 31).

Countries situated in subtropical regions generally experience distinct biannual influenza peaks. The first peak (usually a minor peak) generally appeared between December and March and the second one (usually the major peak) emerged later in the year around June-October (in the subtropical north); coinciding with the monsoon seasons (11, 24, 29, 33). In tropical countries across both hemispheres, influenza epidemics often exhibited a year-round influenza activity or multiple peaks without distinct seasonal patterns (low seasonality). In addition, temporal characteristics such as the onset, duration and peak timing of influenza epidemics are heterogeneous in tropical regions. The average duration of epidemics was slightly longer in the tropics (7-10 months) than that in subtropical regions (5-6 months) (10, 11, 22, 29).

Theme two: Influenza viral types in relation to spatiotemporal variations in influenza seasonal epidemics and co-circulation patterns of influenza viruses

The viral strains responsible for seasonal influenza activities in humans include influenza A H3N2, influenza A H1N1 and influenza B viruses. The global circulatory patterns of influenza epidemics in relation to these viruses differ significantly in temperate and tropical /subtropical regions. These variations were discussed in 12 out of 36 studies in terms of their time of onset, duration, co-circulation and transmission patterns (11, 18, 19, 22, 25, 27, 28, 30, 33, 38, 40, 41).

The common patterns are highlighted below.

Influenza viral strains in relation to the patterns of seasonal influenza epidemics in temperate regions

Influenza A H3N2 was the most dominant viral type in temperate regions of both hemispheres followed by influenza B and then influenza A H1N1 (27). In temperate regions, influenza A H3N2 epidemics have an earlier onset, around mid-January in the northern hemisphere and around June in the southern hemisphere. Influenza A H1N1 epidemics in the northern hemisphere begin in late January, while in the southern hemisphere, the onset is around July or August (11, 25, 27). Influenza B activities are usually observed 4 to 5 weeks later, following the activities of either type of influenza A in both hemispheres (22, 27, 28).

While the duration of influenza A H1N1 epidemics in temperate regions are limited to the typical winter months, influenza A H3N2 and influenza B show significant epidemic activities outside winter periods, extending up to March in the northern hemisphere and up to September in the southern hemisphere. There is a significant temporal overlap between influenza A (either type) and influenza B epidemics in temperate regions (11, 27). For example, a retrospective analysis of data from 30 countries over a period of 14 years suggest that the peak viral activities of influenza A and influenza B occur at the same time for about 40% of all observed epidemics in temperate regions of the northern hemisphere and for about 29% of those in the southern hemisphere (11). Another study examining the patterns of influenza seasonality in 19 temperate countries from 1997 to 2005 established a relationship between the timing of seasonal influenza epidemics and latitudinal gradients in temperate regions for influenza A. However, such a relationship was not observed for influenza B (27).

Influenza viral strains in relation to the patterns of seasonal influenza epidemics in tropical and subtropical regions

In tropical and subtropical regions, H1N1 and H3N2 epidemics are reported to have biannual activities for some regions and an all-year-round activity for others. For example, in subtropical regions such as Hong Kong, there are two peaks of influenza epidemics in late February/March and in June/July (39). Another study conducted on a subtropical island of Japan (Okinawa)

showed similar patterns: influenza A seasons often peaked in December-March, while influenza B epidemics were found to followed influenza A seasons, peaking in March-July. A further analysis of the temporal circulatory patterns of H1N1, H3N2 and Influenza B revealed that all three viral strains displayed an increased activity during March-July in subtropical regions. This period represents the time between the influenza seasons in Northern and Southern hemispheres (11, 25, 30).

For tropical countries like Singapore, influenza A epidemics occurs sporadically throughout the year without any clear seasonal patterns (36). In the tropics, influenza B activities are reported all year round (no prominent seasonality), particularly from January to August; while in subtropical regions, they are frequently observed in March through to July (11, 23, 30). Specific seasonal patterns of influenza in relation to subtypes A and B were described in the study conducted by Saha et al. in 8 Asian countries across a broad latitudinal range. Their study showed that influenza A and B epidemics coincided in regions $>30^{\circ}$ N during winter months. However, the majority of influenza A epidemics in regions 10° - 30° N were found during monsoon months; while influenza B showing a year-round pattern, with smaller peaks during the post monsoon months in areas south of 30° N(33). In tropical regions, the epidemics of influenza A and influenza B coincide less frequently than in temperate regions and usually peak at different times. Influenza B epidemics usually follow influenza A epidemics in these regions. These features would probably extend the influenza seasons in the inter-tropical belt (11, 27, 30).

The average duration of the influenza epidemics is approximately 7 months for an influenza A season alone and about 8 months for the seasons in which influenza A and influenza B co-circulate (11). Bedford et al proposed that the long lasting viral strains in tropical and subtropical regions may result in winter epidemics in temperate regions (25).

Subtype interactions between influenza A (H1N1, H3N2) and influenza B viruses

Although H3N2 dominates in most of the seasonal epidemics in both hemispheres, more than one subtypes are usually reported during each season, suggesting that viral strains co-circulate in influenza epidemics (11, 27). As described previously, influenza B is usually reported to co-circulate with either H3N2 or H1N1. Influenza A H3N2 and H1N1 provide cross immunity for each other, and therefore, these two viral subtypes rarely co-dominate in the same season (27). This was also observed during the post-pandemic period following the 2009 influenza pandemic, in a study conducted by He et al.(12). The researchers noticed a period of reduced activities for H1N1 following the pandemic in most European and East Asian countries (in 2009/10 and a single wave in 2010/11), whereas H3N2 was dominant during this ‘skip period’ (2011/12). A resurgence of H1N1 was recorded in 2012/2013 season. They also noticed that the onset of Influenza B activities always lagged following H1N1 or H3N2 seasons irrespective of the pandemic (12). This finding was consistent with the results of most studies presented in the previous section. A recent study investigating the patterns of influenza A and B epidemics pre-

and post-2009 pandemic (2007-2013) supported the finding and indicated that H1N1 pdm (Influenza A post-pandemic subtype) and H3N2 were associated with the 2009/2011 and 2012 epidemics respectively. Nevertheless, the research found that both subtypes were codominant in the studied Asian countries in 2013(33). This result contradicted the 'skip-year' theory and existing evidence (12, 27). Bedford and colleagues suggested that, unlike H1N1 and influenza B persisting across multiple seasons, H3N2 viruses seldom persisted locally over several epidemics but might be reseeded from East and Southeast (E-SE) Asia. Most importantly, H3N2 viruses were disseminated between global regions more frequently than H1N1 and influenza B. Further, global H3N2 epidemics were usually due to the introduction of new genetic variants in East and Southeast Asia, especially via overlapping epidemics of virus circulation (25). A multi-country study investigating the virological characteristics of influenza in the Western Pacific Region, WHO from 2006 to 2010 revealed that the dominant influenza strains in East and Southeast Asian countries were later detected in other countries. In this Region, the majority of viruses identified between 2006- 2009 were influenza A. However, an equal proportion of influenza A and B were reported in 2010. A dramatic increase in the number of influenza B specimens between 2009 and 2010 was noted. A detectable epidemic of influenza B epidemic (coexisting with H1N1pdm and H3N2 respectively at early and later stages of the season) was observed across four latitudinal regions in both hemispheres (19). The findings of these studies suggested that new genetic variants possibly originating in East and Southeast Asian countries,

particularly influenza A(H3N2) and its co-circulation with influenza B, could potentially lead to large-scaled epidemics.

Theme Three: The role of climatic factors in influencing spatiotemporal patterns of seasonal influenza.

Temperature, humidity and rainfall were repeatedly discussed as the major climatic and environmental factors that drive the major spatiotemporal patterns of seasonal influenza in different regions of the world, reported by 24 out of 36 studies in this review (20-22, 26-32, 34-36, 39, 40, 42-50). These climatic factors are also associated differently with the different viral strains.

The role of climatic factors in affecting the seasonal influenza patterns in temperate regions

According to Tamerius et al, (13) cold-dry climatic conditions drive the patterns of seasonal influenza in temperate regions. Low temperatures and absolute humidity are strongly associated with influenza activities in temperate regions (13, 21, 40, 48, 50). The decrease in absolute humidity (AH) increases the chances of viral survival and transmission, and thus contributing to the increase in influenza activities(48). Jaakkola et al. suggested that the decrease in temperature together with low absolute humidity was more likely to contribute to the change in influenza activities rather than the actual low temperature. According to their study, a fall in average

temperature by 1°C increased the risk of influenza activities by 11% and a decrease in absolute humidity by 0.5 g per m³ increased the risk by 58% (21). Apart from temperature and absolute humidity, solar radiation was recognized to be negatively associated with influenza seasonality in temperate regions (13, 39, 50).

Climatic factors contributing to the seasonal influenza patterns in tropical and subtropical regions

Higher influenza activities are reported with an increase in rainfall for many tropical and subtropical countries (28, 43, 45, 46). While low temperatures are strongly associated with winter onset of influenza epidemics in temperate regions, the role of temperature and humidity in tropical and subtropical regions is very unclear. Some studies suggested that increased rainfall and decreased specific humidity are believed to be the drivers for influenza seasons in the tropics and subtropical regions (13, 34, 43, 45). However, absolute humidity also shows a U-shaped effect on influenza transmission in different regions (43). In the colder climates of temperate regions, lower AH promotes viral transmission, while in the warmer climates of tropical and subtropical regions, the increase in AH increases viral transmission (43). Rainfall and precipitation are positively associated with influenza activity in countries near the equator (23, 34, 35, 45, 46). In climatically diverse countries like Kenya, influenza activities increase with both temperature and specific humidity, however, no significant association was found

between influenza activities and rainfall (26). The climatic drivers responsible for influenza A or influenza B epidemics are not well understood. Iha et al. reported that low temperature and low relative humidity were related to influenza A activity, and high relative humidity was found to be associated with influenza B epidemics in a subtropical setting (Okinawa) of Japan (30).

DISCUSSION

The findings of this review have suggested a complex dynamics of the influenza seasonal patterns and their relationships with climatic factors. Seasonality of influenza is well defined in temperate regions, but shows significant variations in the inter-tropical belt. There were some common observations such as winter epidemics in temperate regions, biannual or year-round activities in the tropics and subtropics and north to south transmission of influenza noted by many included studies. Overall, the general temporal patterns in different geographical locations identified in smaller individual studies were concordant with the results from multi-country studies using databases at global level. However, the overall mechanism and factors driving these variations in the spatiotemporal patterns observed in different regions were still not well explained. In addition, heterogeneous temporal patterns of influenza seasonality existed within large countries and between countries in the same geographical regions, especially the countries situated within similar latitudinal ranges of tropical and subtropical regions such as Southeast Asian, Central and South American and African countries (11, 20, 22, 24, 26, 29, 33). Some

global-scale longitudinal studies (using WHO FluNet surveillance data, comparisons of key finding summarized in Web Table 2) showed slightly different findings, particularly in peaks of influenza epidemics. For instance, Hirve and colleagues revealed that unlike the majority of Central and South American countries showing a single distinct influenza peak, Belize, Colombia, Costa Rica, Ecuador and Paraguay appeared to have two influenza peaks (29). However, the study by Caini et al. identified two annual peaks in Nicaragua and Honduras (11). There were also inconsistent findings with regard to the common epidemic peaks in South and Southeast Asia. Bloom-Feshbach et al. stated that semiannual epidemics were observed predominantly in E-SE Asia (10), whereas the study conducted by Hirve et al revealed that most countries in the area show a single distinct peak (exception- some countries situated in tropical/subtropical regions or near the equator). Interestingly, another study using WHO influenza surveillance and FluNet data of 85 countries found that most Asian countries showed a year-round influenza activity (22). This study also indicated that countries in subtropical regions experienced a single influenza peak of epidemics coinciding the coldest winter months each year, which was inconsistent with the common patterns observed in this review. The inconsistent findings could be due to the different coverage years of WHO surveillance data, differences in defining the secondary peak of epidemic or irregular patterns, variations in analysis methods, and diversity in the quality and availability of surveillance data contributed by small but resource-restricted countries in those specific regions. Strengthening capacity in influenza

surveillance in low-income countries is crucial to monitoring of influenza transmission patterns and timing response to potentially large outbreaks. Future studies are urged to address the above-mentioned variability in spatiotemporal patterns of influenza epidemics in those tropical and subtropical regions.

The review has suggested that while there are two distinct patterns observed according to geographical locations, a large proportion of the differences also depend upon other factors such as the dominant viral strain during a particular season, climatological conditions, and the mode of viral transmission and the ability of viral survival. The possible mechanisms are discussed below in relation to different geographic regions.

The dry-cold climate driving influenza activities in temperate regions

Considering that influenza activities in temperate regions peak during winter months in both hemispheres, it is evident from the review that low temperatures and low absolute humidity are the major drivers of seasonal influenza activities in these regions. The '*Dry-cold mechanism*' has been proposed by several researchers to explain the winter onset of influenza in temperate regions (13, 14, 21, 40, 47). According to the experimental studies conducted by Lowen et al, viral transmission for H3N2, H1N1 and Influenza B is highly efficient at temperatures around 5°C and it is almost blocked at around 30°C. They also observed that the experimental animals

shed viral particles more rapidly at low temperatures, particularly around 5°C (44, 51). Winters in temperate regions are characterized by the average temperature between 0°C to 20°C, with the minimal temperature dropping to as low as -40°C in some parts of the regions. Thus the suitable temperature range activating influenza viral transmission could partially explain the common winter epidemics in those regions.

Apart from the influence of temperature, the change in absolute humidity is considered as another key contributor to the winter-peaked influenza activities in temperate regions. Shaman et al. found in their study that 50% and 90% of variability in influenza viral survival and transmission respectively can be explained by the change in AH. They also suggest that the reduction in AH in winter is consistent with a wintertime increase in influenza viral survival and transmission in temperate regions (47). Some lived viral particles suspending in the air can be inhaled (aerosol transmission) by humans, and some can be transmitted through infected individuals (direct contact) or contaminated objects (indirect contact) (52-55). Weber et al explain that the rate and mode of transmission would depend upon the size of viral particles (56). Experimental studies conducted by the same researchers also reveal that a decrease in relative humidity by 20% makes it more likely for small droplet particles to remain airborne for a significantly longer period of time up to 24 hours, thus making the viruses easier to be spread to susceptible hosts through aerosol transmission (56). With supported evidence of these animal

experiments, the 'Dry-cold mechanism' provides a reasoning framework to explain the interactions of particular climatic conditions and viral activities to enable large-scaled transmission in cool seasons in temperate regions.

The other features of seasonal influenza in temperate regions identified in the review were periodicity and variations in annual occurrence of influenza epidemic in relation to different viral strains. Temperate regions experience a single annual peak, usually during the same months every year and the amplitude of influenza activity increases with latitude. The periodic pattern of influenza epidemic could be largely supported by the 'Dry-cold theory' (13). However, the existing literature remains inconclusive in establishing a comprehensive underlying mechanism to illustrate the geographic (latitudinal) differences of seasonal influenza in relation to different viral types.

The 'Humid-rainy mechanism' driving influenza seasonal patterns in tropics and subtropics

In tropical and subtropical regions, there is no clear seasonal pattern of influenza epidemics; however, most of these regions experience high influenza activities around Monsoon (31, 39, 45, 46). It is observed a large variation in influenza seasonal patterns in these regions, with some countries having semiannual peaks in winter and spring, some showing all-year-round activities with peaks around the rainy seasons. There is a climatic diversity in these regions, with some

countries being hot and dry, others being hot and humid. Although influenza epidemics in tropical regions have been a major focus of the recent studies, existing evidence is limited in explaining the heterogeneity in the influenza seasonal patterns in these regions/countries. One of the possible explanations regarding the increased influenza activities in consistence with the monsoon seasons of different countries is the changes in the mode of viral transmission and viral survival during monsoon. The studies on climatic parameters affecting influenza seasonality suggest that ambient temperature and humidity play an important role in viral transmission and viral survival depending on the size of the viral particles (44, 56-58). Lowen et al. demonstrate in their experiments that increasing ambient temperature in a laboratory setting increases the chance of contact transmission for influenza amongst guinea pigs but prevents airborne transmission. Contact transmission of influenza viruses is most efficient at 30°C and is not affected by the change in relative humidity (51). The results of another study further indicate that wet conditions in the tropics would facilitate contact transmission by increasing the amount of viruses being deposited in fomites and by increasing viral survival in droplets (59). Considering the fact that tropical countries in E-SE Asia are densely populated, contact transmission is likely to be the main mode of transmission for influenza, particularly during rainy seasons, when people are likely to spend time indoors. However, this still does not explain the variations in the time of onset and amplitude of influenza activities according to the latitudes in tropical regions.

Furthermore, influenza viruses undergo two types of genetic change. A small rapid genetic change called 'antigenic drift' produces viral strains that are closely related to one another and are generally responsible for seasonal influenza. In contrast, a gradual major genetic change called 'antigenic shift' produces a completely new strain of virus and is more likely to cause a global pandemic (60). Several studies on global phylogenetic analysis of influenza viral strains indicate that H3N2 viruses display a higher reproduction rate and evolve more rapidly compared to H1N1 and influenza B (25, 27, 61, 62). On the other hand, H1N1 is more likely to cause global pandemics than H3N2, particularly when it undergoes a major antigenic shift as seen in the 1918 Spanish flu and the 2009 Swine flu pandemics (63). This review has also highlighted the long lasting duration of influenza B season in tropical/ subtropical regions, especially when co-circulating with influenza A subtypes, and the increasing intensity of influenza B epidemics reported in SE Asian countries. Most importantly, the dominant influenza strains in SE Asian countries were later detected in other countries (19, 33). As mentioned previously, new genetic variants of influenza are likely to originate in E-SE Asia and potentially spread to other regions of the world (25). Further, the atypical influenza seasonality (multiple peaks or year-round activities) and overlapping epidemics due to co-circulation of influenza viruses in this region may lead to further dissemination of influenza across regions or even continents. These findings warrant a long-term monitoring of influenza activity in E-SE Asian countries particularly during monsoon months in March-July to inform vaccination programs. In addition, the complex

patterns of influenza seasonality in tropical/ subtropical regions, the role of multi-strain dynamics and possible climatic drivers remain unclear (14, 27). Global efforts of influenza control and prevention and future studies can be devoted to a better understanding of global patterns of influenza epidemics in tropical/ subtropical regions and the interaction of viral circulation and contributing climatic factors. It is also important to strengthen influenza surveillance systems in low-middle income countries usually underrepresented in global studies to produce quality adequate data for timely response to potential epidemics. It is also worth exploring the effects of climate change and interactions of meteorological factors over time on potential antigenic drifts of influenza viral strains in different latitudinal regions. Other commonly identified contributors such as international travels, school/holiday periods, population immunity (such as vaccination), susceptible sub-populations should be taken into consideration in future studies.

This systematic review included a broad spectrum of longitudinal influenza studies covering billions of cases in over one hundred countries around the globe to provide a comprehensive insight of the patterns of seasonal influenza from existing evidence and possible mechanisms underpinning the complexity of the global influenza patterns. Despite the breadth and richness of population-based data included in this present review, variations in influenza surveillance systems and case reporting could potentially limit the generalizability of the research findings.

For example, many studies used data from Global Influenza Surveillance Networks such as FluNet and WHO databases others analyzed patient data from hospitalization records or reported by sentinel general practitioners. The use of country-aggregated data might have lost within-country variability in influenza spatiotemporal patterns, especially for large countries.

Limitations of this study also include the differences in the definitions of influenza season/epidemic, peaks of epidemic, case reporting required in various surveillance systems, as well as between weekly or monthly reported cases. For example, most studies analyzed weekly reported laboratory confirmed influenza cases, but some combined cases of lab-confirmed of influenza and weekly reported ILI and others used influenza mortality cases. This systematic review focuses on describing the common spatial and temporal patterns of seasonal influenza and exploring possible influencing climatic factors and mechanisms proposed by empirical studies to explain the patterns. It does not involve meta-analysis of collected data from the included studies to further establish statistical significance of the combined data. As influenza A and influenza B respond to the changes in temperature, humidity and rainfall differently, a more detailed analysis on their circulation patterns in relation to these climatic factors could help better understand the variations in influenza seasonality in temperate and tropical regions.

Future studies may draw on the major findings of this systematic review to examine the quantitative associations of climatic and environmental factors with seasonal influenza driven by different viral types.

Conclusion

In conclusion, this study has presented the common and different geographic and temporal patterns of seasonal influenza in relation to different viral strains in temperate and tropical/subtropical regions through a systematic review and synthesis of findings from existing influenza studies. It also identified the climatic factors contributing to the spatiotemporal patterns of seasonal influenza in an attempt to identify the possible mechanisms to explain the variations in influenza seasonal patterns. The results of this systematic review could inform the efforts of global surveillance of seasonal influenza and influenza prevention and control programs such as vaccination recommendations for different regions.

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Figure 1. Flow diagram of the literature search and screening results.

Table 1. Spatial and temporal patterns of seasonal influenza and climatic driving factors reported by the 36 included studies

First Author, Year (Reference No.)	Year of study	Study region/ continent/ country	Population	Study type	Source of data	Case ascertainment	Statistical analysis methods	Spatial or temporal patterns	Associated Climatic factors
Alonso, 2015 (23)	2002-2012	Antananarivo in Madagascar (in tropical region)	2 million in 2012	Longitudinal	National Influenza Centre, FluNet, daily climate data from the International Research Institute for Climate and Society	Weekly reported and lab confirmed influenza positive cases	Time series analysis, non-parametric hierarchical clustering approach and Spearman correlations	Irregular timing of influenza activities and temporal patterns	Precipitation
Alonso, 2007 (24)	1979-2001	27 Brazilian States		Longitudinal	National Vital Statistics Agency for Brazilian Ministry of Health	Lab confirmed influenza cases and mortality data	Detrended time series analysis	Variations in the onset, duration and amplitude of seasonal influenza in relation to latitude changes	temperature and humidity
Azziz Baumgartner, 2012 (22)	1983-2008	85 countries globally	Cumulative population of 5.4 billion (83% of the world's population)	Longitudinal	WHO ¹ Global Influenza Surveillance Network, FluNet	Lab confirmed influenza cases	Linear regression; Chi-square and Fisher's exact tests	Different temporal patterns of influenza activities in temperate and tropical regions	Low temperature
Barreca, 2012 (40)	1973-2002	359 urban US counties		Longitudinal	National Centre for Health Statistics	Influenza mortality data, climatic data	Non-linear regression and correlations	Temporal variation and cross-state	Low Temperature and low

								differences	absolute humidity
Bedford,. 2015 (25)	2000-2012	9604 samples		Longitudinal	WHO- Global Influenza Surveillance and Response Network Data	Lab confirmed cases	Epidemiological modelling (Model simulation)	Temporal circulatory patterns associated with influenza A(H3N2), (H1N1) and influenza B.	
Bloom-Feshbach, 2013 (10)	1990-2009	137 global locations		Literature review and longitudinal study	Existing literature and data from international surveillance websites	lab confirmed cases of influenza, published literature	Univariate and multivariate analyses using non parametric Wilcoxon tests and linear regression	Variations in temporal patterns of influenza activities with the change in latitude and between temperate and tropical regions	
Caini, 2016 (11)	2000-2014	30 countries	571,907 cases	Retrospective study	Global Influenza B Study Database	Weekly number of respiratory specimens tested for influenza viruses	Descriptive analyses of each study country/region; Wilcoxon rank-sum test	Different temporal patterns in temperate and tropical regions; influenza A and B circulation overlaps in temperate regions	
Charland,	2000-2005	35 cities in	63334 cases	Longitudinal	Hospitalization	A subset of	Bayesian	Timing and	Solar

2009 (42)		USA			records from 37 hospitals in the Pediatric Health Information System	ICD-9 ² coeds used to identify influenza cases (identified from records of pediatric ILI ³ in-patients),	hierarchical models	the peak of influenza activities associated with latitude	radiation
Chong, 2015 (39)	2002-2009	Hong Kong		Longitudinal	Mortality data from Hong Kong Census and Statistics Department	Deaths due to influenza		Major peak of epidemic in winter	Cold temperature, rainfall
Deyle, 2016 (43)	1996-2014	26 different countries		Longitudinal	FluNet, WHO global databases by country	Weekly Lab confirmed influenza cases	Empirical Dynamic Modeling (EDM) ⁴ ; Pearson's correlations; paired Wilcox tests; multivariate EDM approach; convergent cross-mapping	Spatial (latitudinal) variations and temporal patterns of influenza seasonality between temperate and tropical countries	Temperature and absolute humidity
Emukule, 2016 (26)	2007-2013	Kenya		Longitudinal	Data from 12 surveillance sites across Kenya	Lab confirmed cases	Logistic regression and negative binomial regression methods	Temporal patterns in different regions; multiple epidemics each year	Low Temperature and low specific humidity
Finkelman, 2007 (27)	1997-2005	19 temperate countries in northern and southern hemispheres		Longitudinal	FluNet, WHO global databases	Lab confirmed influenza surveillance data by type and subtype	Correlations; independent t-test (Student's t-test)	Varying temporal patterns in relation to different latitudes,	

								hemispheres and viral types	
He, 2013 (28)	1999-2012	Canada		Longitudinal	FluWatch surveillance programme reports	Lab confirmed influenza A cases	Generalized linear model; mathematical modelling	Spatial and temporal patterns	Low temperatures and low absolute humidity
He, 2015 (12)	2006 to 2015	138 countries		Longitudinal	Data from FluNet, WHO	Lab confirmed cases (weekly data)	Time series analysis; mathematical modelling	Global spatial-temporal patterns	
Hirve, 2016 (29)	2010-2014	70 countries	73% of the world's population	Longitudinal/ time series data analysis	FluNet, WHO	Weekly proportional positive cases	Time series analysis, binomial model	Spatial and temporal patterns in different continents and countries	
Iha, 2016 (30)	Jan 2007-Mar 2014	Okinawa, Japan	37309 influenza A infections, 7277 influenza B infections	Longitudinal	1. Data from four representative general hospitals; 2. Japanese national sentinel surveillance data	Weekly rapid antigen test results and Nation-wide Surveillance reports	Spearman's correlations	Temporal patterns with different viral strains	Low ambient temperature and relative humidity associated with influenza A epidemics; high relative humidity associated with influenza B epidemics
Jaakkola, 2014 (21)	July 2004-Dec 2005	Kajaani Garrison in northern Finland	892 military recruits	Case-cross-over study	Follow-up data of the 892 Finn military recruits	Severe influenza cases (lab confirmed)	One-way ANOVA; conditional Logistic	Temporal patterns in subarctic climatic zone	temperature and absolute humidity

							regression models; discrete logistic model		
Koul, 2014 (31)	2011-2012	New Delhi and Srinagar, India	Patients attending outpatient clinics in the study regions	Cohort study	Data of patient presenting Influenza like illnesses	Lab confirmed cases	Descriptive analyses of influenza data; correlations	Varying temporal patterns with latitude	Temperature , rainfall and humidity
Mahamat, 2013 (45)	2006 - 2010	French Guiana	1553 positive specimens	Longitudinal	Influenza surveillance data collected by sentinel GP	Positive nasal swabs confirmed by lab testing	Univariate and multivariate analyses using ARIMA ⁵ time series analysis and dynamic Regression	Seasonal circulations of pandemic influenza activities	Increased rainfall and specific humidity
N'Gattia, 2016 (46)	2007-2010	Abidjan, Cote d'Ivoire (African Tropical region)		Retrospective time series study	Data from Influenza Surveillance Network	Lab confirmed influenza cases	Box-Jenkin's method with ARIMA	All-year round activities No clear seasonality.	Rainfall and relative humidity
Oliveira, 2016 (17)	2009-2013	Salvador, Brazil	2651 patients ≥ 5 years attended emergency units in Salvador	Longitudinal	Data collected by Oswaldo Cruz Foundation as part of an enhanced surveillance study	Cases identified by blood tests and reviews of medical records	Negative binomial regression; Chi-square tests; Mann Whitney <i>U</i> test	Temporal patterns with annual peaks in between August and September	
Paget, 2007 (18)	1999-2007	Members of European Influenza Surveillance Scheme for at least 5 years		Longitudinal	Data reported by sentinel GPs and national reference laboratories	Specimens of weekly sentinel reporting ILI and ARI ⁶ cases were sent to reference	Chi-square/ Fisher exact tests and Correlations.	Temporal and spatial patterns; lengths of epidemic correlated	

						laboratories for influenza infections		with different viral strains	
Roussel, 2016 (32)	2003-2013; excluding 2009-2010 due to pandemic	France		Longitudinal	Weekly reports from Regional Influenza Surveillance Group Network	Clinical reports by 25 sentinels and analysis of virologic samples	Principal component analysis; autoregressive linear model	Temporal and regional variations	Temperature , absolute humidity
Saha, 2016 (33)	2007 - 2013	Nine countries in Southern and Southeast Asia	1,586,757 specimens	Longitudinal	Monthly data collected from 8 countries in the WHO Global Influenza Surveillance and Response System and data for Japan from FluNet	Patients with ILI or severe ARI were tested for influenza viruses (lab confirmed cases).	Epi-Map used to plot seasonal patterns by country/region	Temporal patterns correlated with latitudinal locations and viral strains	
Shaman, 2010 (48)	1972-2002	USA		Longitudinal study and mathematical simulations		Influenza mortality 1972-2002	Epidemiological model simulations based on previous laboratory-based findings	Spatial and temporal variations in the onset of epidemics and influenza seasonality in temperate regions	Absolute humidity
Soebiyanto, 2010 (49)	2005-2008	Hong Kong (China), Maricopa County (Arizona)		Longitudinal	Weekly influenza reports	Lab confirmed cases	ARIMA and SARIMA ⁵ (for including seasonality); correlations	Temporal patterns of influenza in tropical and sub-tropical regions	Rainfall, Relative humidity and temperature
Soebiyanto, 2014 (34)	2008-2013	Guatemala, El Salvador and Panama		Longitudinal	Influenza surveillance data (Panama); Laboratory data	Lab confirmed positive cases	Logistic regression	Temporal patterns of influenza activities	Specific humidity, temperature and rainfall

				and statistical modelling	(Guatemala and El Salvador)				
Soebiyanto, 2015 (50)	2000-2011 for Spain 2006-2011 for the other countries	Germany, Spain, Slovenia and Israel		Longitudinal and statistical modelling	Influenza sentinel surveillance data	Weekly influenza cases, lab confirmed samples,	Generalized additive model	Influenza seasonality in three temperate locations	Specific humidity, temperature and solar radiation
Soebiyanto, 2015 (35)	2008 -2013	Costa Rica, Honduras and Nicaragua		Longitudinal and statistical modelling	National Influenza Center Data (weekly samples tested positive for each influenza virus)	Lab confirmed cases	Logistic regression	Changes in influenza activity in tropical locations associated with changes in climatic factors	Specific humidity, Temperature
Suzuki, 2009 (41)	Jan 2001- March 2007	Okinawa, Japan		Longitudinal study	National Influenza Surveillance data	Lab confirmed cases	Time series analysis and phylogenetic tree analysis for viral types/subtypes	Regular winter peaks but summer peaks only in 4 out of 6 seasons. The viral circulation in Okinawa do not always coincide with the patterns in mainland Japan	
Tamerius, 2013 (13)	1975-2008	40 countries globally		Longitudinal (analysis of developed global influenza database)	Data compiled based on published influenza surveillance studies as well as regional/national surveillance	Weekly or monthly laboratory confirmed cases	Exploratory rank analyses and multivariate regression (logistic regression)	Influenza activities associated with latitudes and climatic factors	Temperature and humidity

					schemes				
Tang, 2010 (36)	2000-2007	Seven temperate/tropical locations in both hemispheres		Longitudinal	Weekly incidence data from WHO Collaborating Centers in four countries	Weekly incidence of influenza and climatic data	Time series analysis using dynamic regression modeling approach and ARIMA	Temporal patterns in relation to temperate, subtropical and tropical regions, and viral types	Temperature and humidity
Thai, 2015 (20)	1993-2010	Vietnam	26,023,574 cases	Longitudinal study	Monthly ILI surveillance aggregated data from 52 provinces of Vietnam	Monthly influenza notifications	Time series analysis and regression tree analysis	Variations in temporal pattern in northern and southern provinces of Vietnam	Absolute humidity
Weinberger, 2012 (37)	1915-2007	Iceland, North America, and Europe		Longitudinal study and time series analysis	Disease surveillance records	Mortality and morbidity data from different countries	Serfling linear regression; Pearson's correlations	Changes in influenza seasonality and timing of epidemics	
Members of Western Pacific Region Global Influenza Surveillance and Response System, 2012 (19)	2006-2010	14 countries with National Influenza Centers in Western Pacific Region	196720 specimens	Longitudinal	Influenza-like illness (ILI) and influenza virus data were obtained from the studied countries with National Influenza Centers and FluNet	Specimens processed for influenza virus testing to confirm cases	Descriptive analyses (tabulations and graphs)	Variations in timing of peak activities and temporal patterns between temperate and tropical regions, hemispheres and different latitudinal locations.	
Yu, 2013 (38)	2005-2011	China		Longitudinal	Weekly reports	Lab confirmed	Joint seasonal	Geographic	Low

				study	from sentinel hospitals in 30 provinces	Influenza A and B infections	regression; logistic regression	variations in influenza peak activities, duration and periodic patterns	temperatures and increased rainfall

WHO: World Health Organization; ICD-9: International Classification of Diseases, Ninth Revision; ILI: Influenza-like illness; EDM: Empirical Dynamic Modeling; ARIMA and SARIMA: Autoregressive integrative moving average model and Seasonal autoregressive integrative moving average model; ARI: Acute respiratory infections.