MAJOR ARTICLE

Seasonality, Timing, and Climate Drivers of Influenza Activity Worldwide

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Background. Although influenza is a vaccine-preventable disease that annually causes substantial disease burden, data on virus activity in tropical countries are limited. We analyzed publicly available influenza data to better understand the global circulation of influenza viruses.

Method. We reviewed open-source, laboratory-confirmed influenza surveillance data. For each country, we abstracted data on the percentage of samples testing positive for influenza each epidemiologic week from the annual number of samples testing positive for influenza. The start of influenza season was defined as the first week when the proportion of samples that tested positive remained above the annual mean. We assessed the relationship between percentage of samples testing positive and mean monthly temperature with use of regression models.

Findings. We identified data on laboratory-confirmed influenza virus infection from 85 countries. More than one influenza epidemic period per year was more common in tropical countries (41%) than in temperate countries (15%). Year-round activity (ie, influenza virus identified each week having ≥10 specimens submitted) occurred in 3 (7%) of 43 temperate, 1 (17%) of 6 subtropical, and 11 (37%) of 30 tropical countries with available data ($P = .006$). Percentage positivity was associated with low temperature ($P = .001$).

Interpretation. Annual influenza epidemics occur in consistent temporal patterns depending on climate.

Annually, seasonal influenza is known to result in substantial morbidity and mortality in developed countries with temperate climates; however, the burden in other countries is largely unknown. In the United States, influenza epidemics of varying severity have been associated with >200 000 annual hospitalizations [1] and 3000–49 000 deaths each year [1, 2]. Ten percent to 20% of all persons each year develop clinical illness, with severe disease being most likely to occur among older persons, young children, and persons with underlying chronic illnesses, making influenza prevention an important public health goal [3]. Moreover, its economic burden is also significant. In Germany and France the estimated cost of health care related to influenza was estimated to be US $300 million, and in the United States, the direct cost of influenza was reported as US $1–3 billion per year [4].

The seasonality of influenza has been well described in high-income countries in temperate regions and where influenza activity typically coincides with winter. This distinct and predictable seasonality facilitates the timing, concentration of resources, and implementation of annual public health interventions to prevent and control influenza. These interventions include annual influenza vaccination programs, especially among high-risk groups, and risk communication messages to promote respiratory etiquette, hand-hygiene, and staying home if ill during the influenza season. Understanding the timing of influenza activity also allows for the timing of vaccination campaigns before the influenza season; these allow vaccine

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recipients to develop an immune response to influenza in advance of likely exposure to virus, but not so far in advance as to result in waning antibodies by the time of exposure. In addition, determining the timing of influenza and, therefore, the timing of annual vaccination programs guides the choice of influenza vaccine composition, making data on seasonality critical in any country interested in using vaccine.

Few data, however, are available on the timing of influenza activity in low- to middle-income tropical or subtropical countries or whether there is a relationship to seasonal climate factors that may predict such activity [5]. Data from tropical countries in Southeast Asia suggest that influenza viruses circulate year-round in these settings [6]. In Brazil, seasonal trends appear to be less distinct close to the equator, compared with more temperate regions [7]. The perception that influenza activity is mild, difficult to predict, complex, and potentially costly to prevent in the tropics may contribute to inaction and underinvestment in the prevention and control of seasonal influenza in tropical countries. Nevertheless, the timing of influenza activity in tropical countries has been difficult to describe because of lack of routine surveillance and laboratory resources to confirm influenza virus infections.

Pandemic preparedness efforts and implementation of the 2005 International Health Regulations led to strengthening of sentinel surveillance and influenza laboratory capacity in many countries, providing an opportunity to explore the timing of influenza activity [8]. These improvements include the development of surveillance protocols with standardized case definitions, sampling techniques, and laboratory methods, making it possible to obtain quality data to assess regional patterns. These efforts also encouraged the establishment of sentinel sites, enhancement of laboratory capacity, and integration of clinical and epidemiological data with virology data [9]. We used these improvements and explored laboratory-confirmed influenza data to compare the epidemic influenza activity in the tropical, subtropical, and temperate countries.

METHODS

To describe the timing of influenza activity throughout the world, we used a stepwise algorithm to identify ≥1 season of laboratory-confirmed influenza data provided by 193 countries. First, we searched FluNet, the World Health Organization (WHO) Global Influenza Surveillance Network for laboratory-confirmed influenza data [10]. If country data were not available in FluNet, we used the Google search engine, using the key words "influenza," "epidemiology," "season," "surveillance," and the country's name to identify publicly available influenza virology data from ministries of health or national influenza surveillance Web sites. If we did not find ministries of health or national influenza surveillance Web site data, we searched the US National Library of Medicine, National Institute of Health's PubMed, using the same key words. Sources that provided laboratory-confirmed seasonal influenza data presented by week or month during 1983–2008 were included in the descriptive analyses. We excluded sources with ≤6 months of data. We also excluded data from 2009 and 2010, because 2009 pandemic influenza A (H1N1) activity meant that these data would be unlikely to be representative of seasonal influenza activity.

Next, we wanted to identify epidemic activity and explore whether tropical countries had year-round, multi-phasic, or apparently random influenza activity when compared with temperate countries. We identified data from published databases, tables, and rarely histograms, regardless of whether these reported subtype data. These data were heterogeneous, having been collected using various case definitions, sampling methods, and laboratory testing methods to identify influenza virus infections. For all 85 countries in our sample, we abstracted the weekly number of samples positive for influenza A or B viruses and calculated the monthly percentage positive among all influenza positive for the year. This was done because many countries did not report data on the total number of specimens tested. We converted weekly data to monthly data by multiplying the epidemiologic week by 12 months/53 weeks and ascribing products <1 to January, 1–1.9 to February, 2–2.9 to March, and so on. For each country, we determined the annual duration, month with peak influenza proportion positivity, and the number of influenza epidemics within a year. We defined influenza epidemics as periods when the influenza proportion positivity remained above the mean proportion positivity for at least 3 weeks. The start of an influenza epidemic was defined as the first week when influenza activity exceeded and remained above the weekly mean proportion of influenza tests positive for at least 3 weeks (or 1 month when only monthly data were available). The end of an influenza epidemic was defined as the first week after an epidemic when influenza activity remained below the weekly mean influenza proportion positivity for at least 3 consecutive weeks. To explore whether greater than the mean influenza proportion positivity occurred by chance, we also determined whether peak activity during the influenza epidemic was 2 standard deviations above the mean proportion positivity.

Among countries that reported 12 months of continuous data and the number of samples submitted for testing, we assessed whether influenza virus was identified in at least 1% of samples during weeks when >10 samples were submitted for testing. We also explored whether the majority of influenza samples were type A or B during the first week of average season and the length of influenza A (H1), (H3), and B epidemic activity among this subset of countries.

To investigate associations between seasonality and environmental variables, we additionally collected data on the central latitude and longitude, mean monthly dry-bulb temperature, hours of sunlight, vapor pressure, and precipitation data from US National Oceanic and Atmospheric Administration 1961–1990 Global Climate Normal's [11]. When absolute humidity was not recorded, existing data elements (eg, relative humidity and temperature) were used and, when necessary, assumed ambient pressure of 1013.25 mars to calculate vapor pressure with the *Visalia Oyo* calculator*, 2006–2009* [12]. The climate for each country was classified as temperate if their geographical center's latitude was >|30°|, subtropical if |23.6–29°| latitude, and tropical if ≤|23.5°| (ie, in the tropics of Capricorn and Cancer). We also collected 2005 population projections and income for each included country [13, 14] and categorized countries according to World Bank classifications of high, upper-middle, lower-middle, and low income countries [15].

We used linear regression models to determine whether the mean proportion of samples that tested positive for influenza each month was associated with mean monthly temperature, vapor pressure, sunlight in temperate countries, and precipitations in tropical countries (eg, proportion of samples positive for influenza = $\alpha + \beta_1$ temperature in Celsius + β_2 mm of precipitation + β_3 hours of sunshine + β_4 vapor pressure + β_5 absolute value of the latitude), including 3-way interaction terms between climate parameters because we anticipated that these would be correlated. Because the unit of analysis was the country, we assumed that reported influenza activity was generally representative of the timing of influenza activity throughout the country's population.

To explore whether epidemic activity was recurrent each time of the year in seasonal patterns, we analyzed whether peak influenza percentage positivity occurred during the same 3 months each year. Data were analyzed using Stata, version 11 (StataCorp), and SAS, version 9.3 (SAS Institute). Statistical significance for categorical variables was determined using the χ^2 or Fisher's exact test, as appropriate. Two-sided *P* values are reported.

RESULTS

Countries with Available Data

We identified influenza data from 98 (51%) of 193 countries and territories. Eighty-two (84%) of the 98 countries reported data to FluNet, 9 (9%) published their data in scientific journals, and 7 (7%) in Web sites but not consistently in FluNet before 2009. Thirteen (13%) of 98 countries provided ≤6 months of total data and were excluded from the analyses, 4 (4%; ie Estonia, Kirgizstan, Oman, and Slovakia) provided 6–12 months of data, 22 (22%) had 1–3 years of data, 18 (18%) had 4–5 years of data, and 41 (42%) had ≥6 years of data (9 of which were in the tropics (Figure 1). The 85 countries used for our analyses had a cumulative population of 5.4 billion, 83% of the of the world's 6.5 billion population (Supplementary Appendix 1). These data originated from 47 (62%) of 76 temperate, 6 (40%) of 15 subtropical, and 32 (31%) of 102 tropical countries (Table 1). Similarly, the data originated from the 35 (59%) of 59 high, 22 (48%) of 46 upper-middle, 18 (33%) of 54 lower-middle, and 9 (22%) of 40 low income countries classified by the World Bank. The majority of the 85 countries (51 [60%]) in our analyses provided at least one set of 12 months of continuous data during 1983–2008, and 35 (41%) of countries only provided data during periods of influenza activity.

Identification of Annual Seasonal Influenza Epidemics by Climate Region

Although annual influenza epidemics were identifiable in most countries, temperate and subtropical countries were more likely to experience 1 influenza epidemic per year than were tropical countries (Table 1). Most (40 [85%] of 47) temperate and all 6 subtropical countries had 1 annual epidemic. Data from temperate Beijing and tropical Kowloon, S.A.R, suggest that cities in China had 2 annual influenza epidemics. Only Belarus and Kyrgyzstan did not show a seasonal pattern in influenza activity. In contrast, a smaller proportion of tropical countries (18 [56%] of 32) had 1 annual influenza epidemic; 9 (28%) had biannual epidemics, 4 (13%) had triennial epidemics, and 1 (3%) had no discernible seasonal pattern (Oman).

Characteristics of Influenza Seasons by Climate Region

Epidemic influenza lasted a mean of 4 months (range, 3–5 months), irrespective of climate region. Influenza A comprised >50% of the positive samples identified during the first week of the influenza season in 63% of the years analyzed but >50% of the positive samples identified during the last week of the influenza season in only 57% of the years analyzed. Although different strains dominated each year, epidemics where typically comprised of staggered influenza A (H1N1), A (H3N2), and/or influenza B waves, each lasting a mean of 11 weeks (range, 6–15 weeks) (Figure 1). Influenza was identified every week when at least 10 specimens were submitted for testing or recorded as positive (ie, year-round influenza activity) in 3 (7%) of 43 temperate, 1 (17%) of 6 subtropical, and 11 (37%) of 30 tropical countries with available data ($P = .006$) (Table 1). Eight (42%) of 19 Asian countries had year-round influenza activity, compared with 7 (11%) of 62 non-Asian countries.

Most temperate (45 [96%] of 47), subtropical (6 [100%] of 6), and tropical (30 [94%] of 32) countries had peak influenza proportion positivity that was 2 standard deviations above the annual mean. Only 7 (39%) of 18 countries with 2 or 3 annual influenza epidemics had peak influenza activity during their secondary annual influenza epidemic that was 2 standard deviations above the annual mean. None of the 4 countries

Figure 1. Mean percentage of samples positive for influenza by month in 9 tropical countries with at least 6 years of publicly available laboratory-confirmed data, 1983–2008.

Table 1. Publicly Available Data on Laboratory-Confirmed Influenza Activity, by Climate Regions, During 1983–2008

	Temperate	Subtropical	Tropical	*P* Value
Data available, n/N (%)	47/76 (62)	6/15 (40)	32/102 (32)	<.001
Modality, n/N (%)				.06
Unimodal	40/47 (85)	6/6 (100%)	18/32 (56%)	
Biannual	5/47 (11)		9/32 (28%)	
Triennial	2/47 (4)		4/32 (13%)	
No apparent seasonal pattern	2/47 (4)		1/32 (3%)	
Average length of season, months	3.9	3.9	3.5	>.1
Year-round activity n/N (%)[a]	3/43 (7)	1/6 (17)	11/30 (37)	.006
Average proportion of positive influenza samples during peak month, (%)	(17)	(13)	(16)	>.1
Annual peak activity exceeds two standard deviations about mean activity, n/N (%)	45/47 (96)	6/6 (100)	30/32 (94)	>.1
Consistent influenza peak within the same 12 weeks each year for countries with multi-year data, n/N (%)	25/33 (66)	4/5 (80)	4/20 (20)	<.001
Influenza activity occurs during or the month after the coldest month, n/N (%)	24/37 (65)	1/6 (17)	2/32 (6)	.001

Abbreviation: NS, not significant.

[a] Influenza was identified every week when at least 10 specimens were submitted for testing or recorded as positive. This analysis used total specimens for the week or month as denominator; all other analyses used total positive specimens for the year as denominator

with 3 annual influenza epidemics (ie, Côte D'Ivoire, Cuba, Dominican Republic, and Papua New Guinea) had peak influenza activity during their tertiary annual influenza epidemic that was 2 standard deviations above the annual mean influenza proportion positivity, because a smaller proportion of samples tested for influenza during peak activity in secondary and tertiary influenza epidemics (Figure 2). Although there was no association between the number of annual influenza epidemics and the number of samples submitted; the 3 countries with influenza activity that could not be defined as epidemic (ie, Belarus, Kyrgyzstan, and Oman) reported a median of 25 annual positive samples (interquartile range, 12–276), compared with a median of 143 annual positive samples (interquartile range, 55–383) among the other 82 countries.

Association of Influenza Season with Climate Parameters

Peak influenza activity occurred during the coldest month or the month after in 24 (37%) of 64 temperate, 5 (17%) of 6 subtropical, and 2 (6%) of 6 tropical countries with available data ($P < .001$) (Table 1). In a saturated multiple regression model, monthly proportion positive for influenza virus was only associated with low temperature (coefficient −0.007, $P = .001$) after adjusting for mean monthly sunshine, precipitation, absolute humidity, and latitude $R^2 = 0.09$.

Peak Influenza Activity Worldwide

Twenty-five (66%) of 33 temperate, 4 (80%) of 5 subtropical, and 4 (20%) of 20 tropical countries with weekly multi-year data annually had peak influenza activity within the same 12 weeks when each country had, on average, peak influenza activity ($P < .001$). Eleven (73%) of 15 countries with year-round influenza activity (ie, influenza positive samples every week of the year) were in the tropics, and 7 (70%) of these were in Southeast Asia. Influenza activity peaked in Southeast Asian and Oceania countries during June and July; Australia during August; Middle East, North Africa, and Mexico during December; European and North American during February and March; and South America and South Africa during May and June (Figure 3).

DISCUSSION

The publicly available data suggest that seasonal influenza is an annual public health problem worldwide. Our analyses suggest that annual influenza activity typically occurred during epidemic periods rather than randomly, even in subtropical and tropical countries. Despite previous assertions about the unpredictability of influenza activity [16], most tropical countries had 1 annual influenza epidemic. If the surveillance systems that generated these data are representative of the 5.4 billion persons living in these 84 countries (39% which were in the tropics), our findings suggest that, at predictable times each year, a proportion of the population seeking care at influenza surveillance sentinel sites had influenza.

Determining whether there is a distinct influenza season is important, because predictable activity represents an important opportunity for public health authorities to concentrate prevention and control resources (eg, influenza vaccination, respiratory and cough etiquette, and hand hygiene) during a

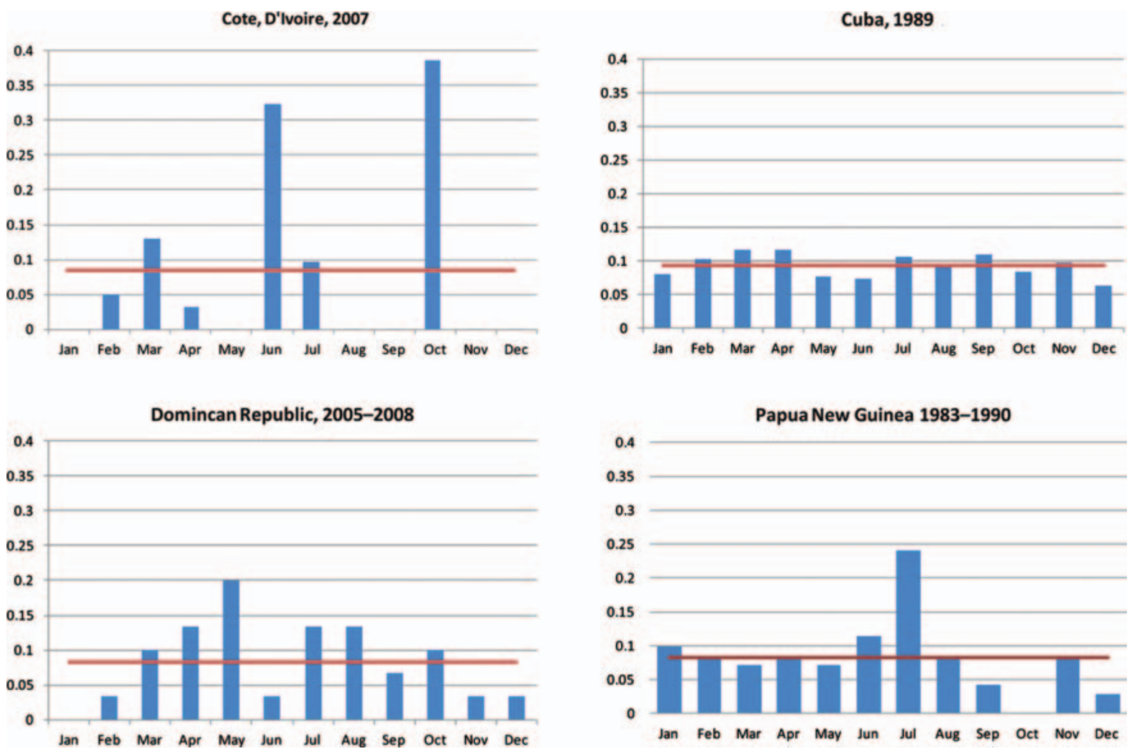

Figure 2. Four countries with 3 annual influenza epidemics.

particular time of the year [17]. Increased surveillance is likely to help to better characterize influenza activity in tropical regions, particularly among low-income countries where data are least available. The difficulty in identifying the seasonality of influenza in some countries may be the direct result of insufficient testing and reporting rather than of inherent differences in the circulation of influenza in tropical versus temperate countries. Countries that systematically collect samples from patients for 3–5 nonpandemic years using standardized surveillance protocols [17] are likely to identify the consistent seasonal influenza patterns necessary for timing influenza vaccination campaigns.

Throughout the world, influenza activity frequently followed low seasonal temperatures, as has been suggested by other studies [18, 19]. Such findings suggest that influenza epidemics may be influenced by seasonal crowding, influenza virus survival in respiratory droplets, or vitamin D deficiency that may annually change the efficiency of transmission and host susceptibility [20]. For example, during winter, when it is often cold, dark, and dry in temperate countries, persons may crowd indoors more often to avoid inclement weather [9]. Such a hypothesis is compatible with models of dynamical resonance, in which viral dynamics can be driven by small seasonal changes in transmission patterns [21]. Although we did not find an association between influenza activity and absolute humidity, sunshine, and precipitation [22], more data are needed to assess the impact of human behavior and influenza virus transmission in different climates [9].

Our findings are consistent with the global circulation of seasonal influenza virus hypothesis [23], which suggests that annual epidemic waves may propagate from Asia where influenza activity frequently occurs year-round. Influenza viruses may travel from areas where circulation of influenza has generated sufficient herd immunity toward regions where the onset of cold inclement weather and its subsequent effects on susceptible populations (eg, through increased crowding and secondary transmission) allows for the propagation of this traveling wave. Seasonality seems to be preserved even when travelers infected with influenza viruses return to their home countries, introducing strains that did not result in community epidemics during low seasonal influenza periods [24].

This study has some important limitations. We used influenza-positive samples divided by the annual number of influenza-positive samples (rather than number of specimens tested) for most percentage positivity analyses, because approximately half of the countries in our analyses did not provide the total number of samples submitted during the entire study period. Aggregating multi-year data to determine the monthly mean of samples testing positive for influenza may have obscured existing influenza seasonal patterns or spuriously suggested multi-modal influenza activity, particularly in tropical countries that reported scant data. Although the data that we analyzed were generated

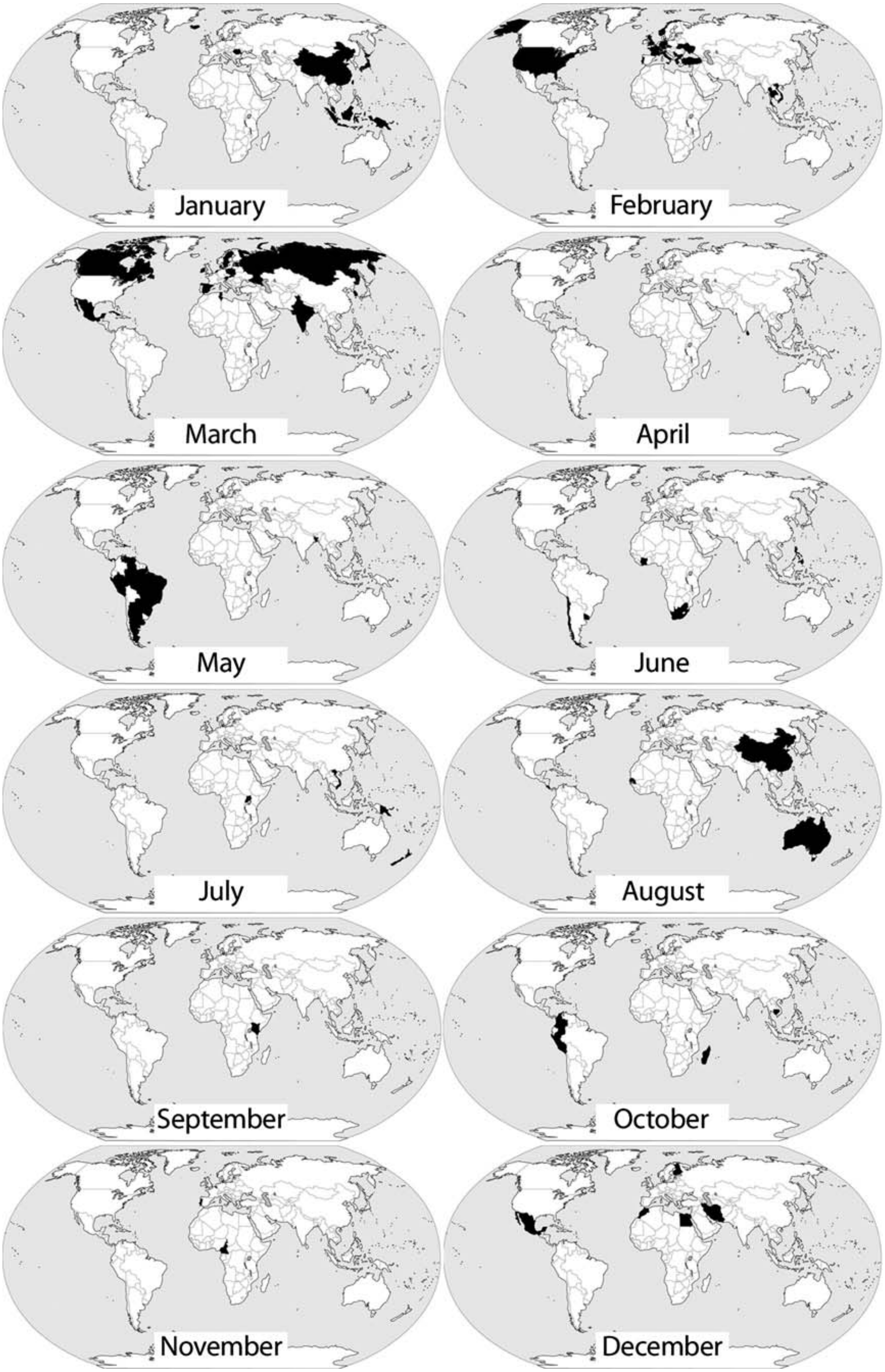

Figure 3. Peak influenza activity among 85 countries with laboratory-confirmed seasonal influenza data, 1983–2008.

by countries with the majority of the world's population, it is difficult to ascertain how representative the data are of each country's population, particularly among populous and geographically large countries. We also analyzed data from disparate influenza surveillance sources where countries used a variety of case identification, influenza testing methods, and in 40% of the cases, reported <12 months of annual data. The recent efforts to expand and standardize influenza surveillance worldwide may facilitate regional and global data analyses, particularly if the Global Influenza Surveillance Network requests that countries provide information about the source of the data in FluNet (eg, random or convenience sampling, case definitions used, and the population denominator if available). In addition, although we used robust multi-year climate data from weather stations in the NOAA dataset, these data were not necessarily representative of indoor environments or concurrent with influenza surveillance data. To better understand determinants of influenza seasonality, it will be important to examine influenza virus strain data, indoor environment, household crowding, and vitamin D levels among populations during multiple years in a variety of countries.

Conclusion

Publicly available data suggest that seasonal influenza is an annual public health problem throughout the world, including temperate, subtropical, and tropical countries. Scant data are available from Africa and the Middle East, however, suggesting the importance of expanding standardized influenza surveillance and reporting among these underrepresented regions. In the countries with available data, influenza viruses typically caused 1 or 2 predictable annual epidemics. These epidemics suggest annual influenza activity that may represent an opportunity for public health authorities to concentrate limited resources and annually time risk communication campaigns (eg, vaccination campaigns, hand washing and respiratory hygiene campaigns, stay at home while-sick policies, and instructions on when to seek care), select appropriate vaccine formulations, and deploy vaccines and antivirals when these will have the greatest impact.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online (http://jid.oxfordjournals.org/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Supplementary Appendix 1 conveys countries with more than one or more years of publicly available data on laboratory-confirmed influenza published during 1983–2008 and their central latitude [9, 25–34].

Notes

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