Redefining influenza seasonality at a global scale and aligning it to the influenza vaccine manufacturing cycle: A descriptive time series analysis

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S U M M A R Y

Objectives: Annual seasonal influenza vaccine manufacturing cycles align with temperate country seasonality in each hemisphere, yet influenza seasonality is poorly defined for many countries. The study introduces a novel and universal approach to defining and classifying seasonality that can be used to classify any country's influenza vaccine cycle alignment.

Methods: Countries reporting to the World Health Organization's FluNet influenza virology database in 90% of weeks during 2011 through 2017 were included. A smoothed, standardised, average proportion of influenza occurring in each week of the year was used to determine degree of seasonality based on the range of average weekly variation. The proportion of activity occurring May through October was used to align influenza activity with a hemisphere's vaccine manufacturing cycle.

Results: From 84 included countries, there were 2,239,208 positive influenza results, of which 26% were influenza type B. Degree of seasonality was moderately positively correlated with absolute value of latitude ($r = 0.69$, $p < 0.0001$). Latitude was strongly negatively correlated with the proportion of influenza occurring during May through October ($r = -0.83$, $p < 0.0001$).

Thirteen countries (12% of the included global population), mainly in tropical zones, had influenza occurrence aligned with the opposite hemisphere's influenza vaccine manufacturing cycle. In tropical zones, concordance in the degree of seasonality and vaccine cycle alignment within regions and between adjacent countries was limited. In temperate zones, on average, influenza B peaked four weeks later than A.

Conclusions: Influenza activity in many countries aligns with the vaccine manufacturing cycle of the opposite hemisphere. In tropical regions, there is limited scope for grouping countries for vaccine distribution and administration.

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Introduction

Control of morbidity and mortality due to influenza is an international priority.[1,2] The influenza virus mutates often, leading to frequent drift in seasonal virus strains and transient influenza vaccine effectiveness.[3] Thus, the World Health Organization (WHO) convenes two meetings annually, one per hemisphere, to determine the influenza virus strain composition of the influenza vaccine to be manufactured for the subsequent season in the same hemisphere.[4] The rationale is that by selecting virus strains in this way gives the greatest chance of manufacturing vaccines with strains that will closely match those circulating in the upcoming season.[5]

The annual global influenza vaccine decision-making and manufacturing cycle is based on perceived dichotomization of influenza seasonality according to hemisphere. It has been influenced heavily by seasonal patterns of influenza occurring in more developed nations located in temperate regions, where surveillance data are more readily available.[6] The northern hemisphere vaccine manufacturing cycle depends on WHO strain recommendations occurring in February for vaccines to be distributed by November of the same year. In the southern hemisphere, the late September recommendations are for vaccines to be distributed by April of the following year.[7,8]

Several studies in recent years attempted to characterise the seasonality of influenza globally. Using the WHO's FluNet database,[9] Alonso et al. used frequency analyses to estimate cyclical patterns of annual periodicity of influenza for 125 countries during 2010 through 2014. Their approach identified a single

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month of peak seasonal influenza activity for each country.[10] Azziz Baumgartner et al. analysed FluNet and other surveillance information for 85 countries, classifying for each country the month experiencing the peak proportion of virology specimens positive for influenza, and the number of influenza epidemics occurring in a year.[11]

Bloom-Feschbach et al. used FluNet and other data from 40 countries to classify the month in which peak counts of virus isolates occurred, the duration of the season, and whether countries experienced one or two seasons annually.[12] Caini et al. analysed influenza surveillance data provided by 34 countries. They averaged the proportion of influenza cases occurring in each month to characterise seasonality based on peak month and duration.[13]

Hirve et al. reported on four independent studies using FluNet and other surveillance data to examine seasonality in tropical and subtropical regions only. The included studies used different seasonality definitions, methods, time periods, and inclusion and exclusion criteria. Methods included visual inspection, considering months that explained the largest proportion of cases in at least two of five years, using historical data to develop a statistical model of seasonality, and using time series analysis to decompose influenza time series into seasonal, trend and residual components.[14] Most recently, Newman et al. used the FluNet database to analyse seasonality for 118 countries. From weekly data over a six year period, they estimated the average proportion of influenza occurring in each month of the year. Seasonality was characterised into one or two peaks each year or year-round activity.[15]

Earlier studies lacked appropriate completeness criteria. A seasonal pattern of disease requires within-year temporal variation repeated over multiple years. Thus, characterisation of seasonality requires continuous reporting of influenza results over several years. The studies variously included countries with as few as 20 influenza isolates reported over a 5 year analysis period,[10] with data for as little as one year or less,[11,12] with data for different time periods ranging from 2 to 12 seasons,[13] as few as 50 cases of influenza reported in a season,[14,15] at least 10 specimens in all weeks of the season, at least 20 weeks of the year with reported data, reporting influenza results in all months, at least 10 samples tested each month, at least 100 influenza positive cases in a year.[14] Few considered completeness of reporting during the study period.

The range of definitions of seasonality behaviour that have been used, clearly point to a need for a definition of seasonality that is unconstrained by classifying the number and timing of peaks in influenza activity. This study introduces a new definition and classification of seasonality based on the range of annual average weekly variation and the proportion of influenza infections occurring during a defined period based on the influenza vaccine manufacturing cycle. A common data source and reporting period, and strict reporting completeness criteria, were used to assess the degree of seasonality and timing of influenza activity throughout the year for as many countries as possible. The aim was to determine for each country which of the two hemisphere vaccine manufacturing cycles was most appropriate. The hypotheses that latitude was associated with both the degree and timing of seasonality were assessed, and differences in seasonality between influenza types A and B were examined. Population sizes experiencing each timing of seasonality were calculated, by latitude zone.

Methods

The study period was 2011 through 2017. A country's seasonality was defined in terms of degree and timing. Degree of seasonality was a continuous measure defined by the difference between the highest and lowest weekly smoothed proportion of influenza infections in a year, on average, during the study period. That is, the range of average variation within the year

defined degree of seasonality. Timing was also a continuous measure, defined according to the hemispheric influenza vaccine manufacturing cycles. Countries were classified by the proportion of influenza activity, on average, occurring during May through October. This is the season aligned with the southern hemisphere influenza vaccine development cycle.

Data sources

The WHO FluNet database was used.[9] It systematically records weekly numbers of influenza infection test results from virology laboratories designated as National Influenza Centres in participating countries. Each participating country has up to four Centres, usually located in a main population centre. Results are reported at least by influenza type A or B but does not always include complete subtype information. Population information and geographic coordinates of capital cities were obtained from statistics published by the United Nations.[16,17] At the time of final data extraction (18 Mar 2018), data for Brazil prior to 2017 was unavailable in FluNet, so an earlier extract from pilot analyses was used for earlier years.

Study period

The study period was 2011 through 2017. The calendar year 2011 was chosen as the starting period to avoid anomalous temporal patterns of influenza associated with the emergence of the influenza A(H1N1)pdm09 pandemic influenza virus in 2009. As mentioned by Alonso et al.,[10] many countries had patchy reporting prior to 2009 and virological surveillance of influenza was boosted in many countries by the occurrence of the pandemic. At least 8 weeks prior to 1 January 2011 and post 31 December 2017 were included to permit calculation of the 13-week moving average at the extremes of the time series for each country.

Inclusion criteria

FluNet countries with influenza test results reported in at least 90% of weeks during the study period were selected. Only results for human influenza types A or B were included. For included countries, counts of influenza results in missing weeks were linearly interpolated from surrounding non-missing values.

Procedure for estimating seasonality

First, for each country, time series of 52 weekly counts of positive influenza results were prepared for each year over the study period. Second, counts of influenza cases for non-reported weeks were linearly interpolated to fill the gaps. Third, to prevent over-influencing estimates of seasonality by outliers, brief periods of unseasonal influenza activity, or periods of low counts, a 13-week (quarterly) centred moving average was applied to the time series.

Fourth, to avoid over-influence by years with greater circulation or more testing for influenza, the time series were standardised across years. This was achieved by calculating the proportion that each weekly smoothed count contributed to the total number of positive influenza specimens in the year in which that week occurred. These weekly proportions in each year became the unit of analysis for the characterisation of seasonality.

Fifth, for each country, the average proportion of annual positive influenza results in each week of the year was calculated over the seven-year study period. This provided a summary indication for each country of the seasonal pattern by estimating the proportion each week of the year contributes to annual influenza circulation, on average.

A country's degree of seasonality was estimated as the range of values of the average proportion of annual positive influenza results in each week of the year. That is, the difference, in percentage

points, between the maximum and minimum proportion across all weeks of the year. A strongly seasonal country with a single peak will have a relatively large range. Countries with less clear seasonality or with several peaks will have a reduced range. This quantity was categorised into low, moderate and high seasonality based on the distribution of the range across countries: low (<2.5 percentage points), moderate (2.5–5.0) and high (>5.0).

The proportion of influenza occurring during the May through October period, on average, was estimated by averaging across the 7 years the proportion of each year's influenza occurring in weeks with an end date during May through October. This quantity was categorised into a minority (<40% during May–October), equivocal (40–60%) or a majority (>60%).

To distinguish patterns in tropical and temperate zones and by hemisphere, countries were allocated into one of four zones based on the latitude of the capital city: northern hemisphere temperate, northern hemisphere tropical, southern hemisphere temperate, southern hemisphere tropical.

The procedure was applied to total influenza results, and separately to influenza types A and B. Pearson correlation co-efficients were estimated for the relationship between degree of seasonality and the absolute vale of latitude and for timing of seasonality and latitude. SAS Enterprise Guide version 7.12 incorporating Base SAS version 9.4 was used for the analysis, graphing and mapping.

Results

Eighty-four countries met the inclusion criteria, representing a population of 6,036 million in 2014; 83% of the global population. Table 1 summarises the data used for analysis. During 2011 through 2017, there were 2,239,208 positive influenza results included, of which 26% were influenza type B (Table 1). Countries with capital cities in the northern temperate climate zone accounted for 89% of the influenza results.

The final averaged weekly proportion time series for each country, by influenza type, are provided in the supplementary file. The supplementary video shows, week by week for each country, the estimated average proportion of influenza activity occurring in each week of the year on a world map. It is broadly consistent with expected patterns in the northern and southern temperate regions, but it clearly shows that inconsistency in the tropical regions. There is also substantial variation at this fine-grained temporal level along similar latitude bands even in temperate zones.

Fig. 1 shows a map indicating the degree of seasonality estimated for the included countries (also listed in Table 2). The degree of seasonality was moderately positively correlated with the absolute value of latitude of the country's capital ($r = 0.69$, $p < 0.0001$). Of the 6 countries in the southern temperate zone, only South Africa and Uruguay had high seasonality. The remaining countries had moderate seasonality, meaning influenza activity was not solely confined to a limited period. In the northern temperate zone, 34 of 41 countries had high seasonality. The moderate seasonality countries in the northern temperate zone were Bangladesh, Bahrain, Qatar and China. The low seasonality countries were Bhutan, India and Oman. Of the 37 countries in the tropical zones, Mexico and Guadeloupe, both in the northern hemisphere, had high seasonality, and the remaining countries had a mix of moderate or low seasonality. In the tropical zones, there was no evident groupings of countries with a similar degree

Table 1
Summary statistics for FluNet data used in the study, by latitude band of country's capital, and country, 2011–2017.

Country	Number of weeks reported	Count of influenza A reported	Count of influenza B reported	Proportion of influenza B (%)	Count of total influenza reported
Total		**1,661,640**	**577,568**	**26**	**2,239,208**
Northern temperate		**1,471,663**	**515,183**	**26**	**1,986,846**
Algeria	332	1321	555	30	1876
Bahrain	335	974	223	19	1197
Bangladesh	359	3315	1708	34	5023
Belgium	346	2283	1044	31	3327
Bhutan	363	1178	550	32	1728
Bulgaria	364	1427	535	27	1962
Canada	363	171,975	48,099	22	220,074
China	365	291,273	136,171	32	427,444
Denmark	359	17,087	6771	28	23,858
Egypt	365	6831	2595	28	9426
Estonia	346	4533	1047	19	5580
Finland	333	1155	340	23	1495
Georgia	352	1354	671	33	2025
Germany	363	6752	2710	29	9462
Iceland	363	1522	446	23	1968
India	360	12,856	2809	18	15,665
Iran	365	6882	2369	26	9251
Iraq	365	1759	118	6	1877
Ireland	365	8792	3114	26	11,906
Japan	365	48,102	14,989	24	63,091
Jordan	362	1622	307	16	1929
Kazakhstan	333	3469	1029	23	4498
Lithuania	363	3093	687	18	3780
Mongolia	363	2298	893	28	3191
Netherlands	365	11,842	3304	22	15,146
Norway	365	58,295	25,407	30	83,702
Oman	329	5725	2012	26	7737
Pakistan	345	1800	503	22	2303
Poland	365	7164	1822	20	8986
Qatar	362	16,127	4797	23	20,924
Republic of Korea	365	8275	4952	37	13,227
Republic of Moldova	351	1169	461	28	1630
Romania	346	4900	2303	32	7203

Table 1 (*continued*)

Country	Number of weeks reported	Count of influenza A reported	Count of influenza B reported	Proportion of influenza B (%)	Count of total influenza reported
Russian Federation	365	103,153	28,428	22	131,581
Slovakia	361	1388	671	33	2059
Slovenia	365	11,140	4777	30	15,917
Spain	363	41,542	12,940	24	54,482
Sweden	344	42,067	13,570	24	55,637
Ukraine	343	6533	1969	23	8502
United Kingdom	365	50,516	18,811	27	69,327
United States of America	365	498,174	158,676	24	656,850
Northern tropical		**76,750**	**28,366**	**27**	**105,116**
Cambodia	365	1606	1321	45	2927
Cameroon	362	1859	1035	36	2894
Colombia	361	4315	527	11	4842
Costa Rica	364	2303	717	24	3020
Cuba	362	2314	761	25	3075
Dominican Republic	362	1125	481	30	1606
El Salvador	365	1100	434	28	1534
French Guiana	365	588	329	36	917
Ghana	363	1927	1085	36	3012
Guadeloupe	333	350	113	24	463
Guatemala	355	1138	247	18	1385
Honduras	356	691	312	31	1003
Jamaica	362	306	207	40	513
Malaysia	365	721	427	37	1148
Martinique	331	473	193	29	666
Mexico	364	28,319	6591	19	34,910
Nicaragua	365	3181	1470	32	4651
Niger	365	299	139	32	438
Nigeria	364	543	342	39	885
Panama	365	1400	345	20	1745
Philippines	359	2139	1590	43	3729
Senegal	348	3254	1709	34	4963
Singapore	363	4691	2127	31	6818
Sri Lanka	365	4869	1838	27	6707
Thailand	362	3707	2331	39	6038
Viet Nam	365	3532	1695	32	5227
Southern Tropical		**38,016**	**13,475**	**26**	**51,491**
Bolivia	364	6391	1468	19	7859
Brazil*	365	14,738	4098	22	18,836
Democratic Republic of the Congo	345	824	346	30	1170
Ecuador	364	3607	629	15	4236
Fiji	332	255	183	42	438
Indonesia	365	4195	2874	41	7069
Madagascar	363	2067	1548	43	3615
New Caledonia	364	893	364	29	1257
Peru	364	3606	1056	23	4662
United Republic of Tanzania	364	1009	435	30	1444
Zambia	364	431	474	52	905
Southern temperate		**75,211**	**20,544**	**21**	**95,755**
Argentina	365	25,884	4427	15	30,311
Australia	365	24,703	8449	25	33,152
Chile	365	13,485	3820	22	17,305
Paraguay	364	4460	1531	26	5991
South Africa	357	5919	2170	27	8089
Uruguay	334	760	147	16	907

Data source: FluNet (www.who.int/flunet), World Health Organization.

of seasonality, although almost all countries in the northern part of South America and Central America experienced moderate seasonality.

Table 2 shows, for each of the 84 countries, the average proportion of influenza activity that occurred during May through October across the seven years. In Fig. 2, this is categorised into majority (green), minority (blue) and equivocal (red) in which the proportion is in the range 40–60%. As expected, there was a strong and statistically significant negative correlation between latitude and the proportion of influenza occurring during May through October ($r = -0.83$, $p < 0.0001$).

Of the 84 included countries (population 6,036,075,000), 13 (population 717,267,000, 12% of the total included population), experienced the majority of their influenza aligned with the opposite hemisphere's vaccine manufacturing cycle. A further 15 countries (population 1,815,882,000, 30%) were equivocal in terms of being aligned with the northern or southern hemisphere vaccine cycle. All included countries with capitals in the southern temperate zone, were clearly aligned with the southern hemisphere vaccine cycle. All included countries with capital cities in the northern temperate zone, apart from Bangladesh, Bhutan and India, had a majority of total influenza activity outside of the May through October period. Bangladesh had 79% of influenza cases occurring May through October, setting it clearly apart from the remainder of the northern temperate zone. Bhutan and India were equivocal. Of the 37 included countries with a capital in a tropical latitude (population 1,518,605,000), 12 (439,497,000, 29% of the included tropical population) experienced the majority of influenza in the

Table 2
Degree of seasonality and average annual proportion of influenza occurring during May to October, by latitude band of country's capital, and country, 2011–2017. Countries shaded blue align with the northern hemisphere vaccine cycle, pink is equivocal, and green align with the southern hemisphere. (For interpretation of the references to colour in this figure, the reader is referred to the web version of this article.)

Latitude band of capital city	Country	Population, 2014 (,000)	Latitude of capital (degrees)	Longitude of capital (degrees)	Degree of seasonality	Proportion influenza May-Oct (%)
Northern temperate	United States of America	317,719	38.9	-77.0	High	9.3
	Canada	35,605	45.4	-75.7	High	8.1
	Iceland	328	64.1	-21.9	High	7.0
	Ireland	4,686	53.3	-6.2	High	5.5
	Spain	46,522	40.4	-3.7	High	2.1
	United Kingdom	65,016	51.5	-0.1	High	7.9
	Algeria	39,113	36.8	3.0	High	6.5
	Belgium	11,219	50.8	4.3	High	2.0
	Netherlands	16,889	52.4	4.9	High	4.8
	Norway	5,140	59.9	10.7	High	7.0
	Denmark	5,664	55.7	12.6	High	4.5
	Germany	81,490	52.5	13.4	High	4.0
	Slovenia	2,071	46.1	14.5	High	3.2
	Slovakia	5,433	48.1	17.1	High	8.6
	Sweden	9,689	59.3	18.1	High	5.2
	Poland	38,293	52.2	21.0	High	3.3
	Bulgaria	7,222	42.7	23.3	High	1.7
	Estonia	1,318	59.4	24.8	High	5.7
	Finland	5,460	60.2	24.9	High	5.9
	Lithuania	2,962	54.7	25.3	High	4.6
	Romania	19,973	44.4	26.1	High	4.4
	Republic of Moldova	4,070	47.0	28.9	High	4.7
	Ukraine	44,883	50.4	30.5	High	7.3
	Egypt	91,813	30.0	31.2	High	20.5
	Jordan	8,809	32.0	35.9	High	13.8
	Russian Federation	143,761	55.8	37.6	High	8.2
	Iraq	35,006	33.3	44.4	High	3.4
	Georgia	3,992	41.7	44.8	High	5.4
	Bahrain	1,336	26.2	50.6	Moderate	32.7
	Iran	78,411	35.7	51.4	High	10.4
	Qatar	2,374	25.3	51.5	Moderate	29.7
	Oman	3,961	23.6	58.6	Low	35.2
	Kazakhstan	17,488	51.2	71.4	High	1.5
	Pakistan	185,546	33.7	73.1	High	11.9
	India	1,293,859	28.7	77.2	Low	48.2
	Bhutan	776	27.5	89.6	Low	56.3
	Bangladesh	159,405	23.7	90.4	Moderate	79.2
	Mongolia	2,924	47.9	106.9	High	4.1
	China	1,390,110	39.9	116.4	Moderate	28.7
	Republic of Korea	50,386	37.6	127.0	High	7.2
	Japan	128,163	35.7	139.7	High	8.2
Northern tropical	Mexico	124,222	19.4	-99.1	High	10.1
	Guatemala	15,924	14.6	-90.5	Moderate	37.1
	El Salvador	6,281	13.7	-89.2	Moderate	70.5

Table 2 (*continued*)

	Country					
	Honduras	8,809	14.1	-87.2	Low	60.6
	Nicaragua	6,014	12.1	-86.3	Moderate	62.6
	Costa Rica	4,758	9.9	-84.1	Moderate	42.0
	Cuba	11,440	23.1	-82.4	Low	66.9
	Panama	3,904	9.0	-79.5	Moderate	80.6
	Jamaica	2,862	18.0	-76.8	Moderate	33.3
	Colombia	47,792	4.6	-74.1	Low	54.1
	Dominican Republic	10,406	18.5	-69.9	Moderate	62.5
	Guadeloupe	451	16.0	-61.7	High	10.1
	Martinique	387	14.6	-61.1	Moderate	14.2
	French Guiana	262	4.9	-52.3	Moderate	34.4
	Senegal	14,546	14.7	-17.4	Moderate	66.3
	Ghana	26,963	5.6	-0.2	Low	57.1
	Niger	19,148	13.5	2.1	Moderate	22.1
	Nigeria	176,461	9.1	7.5	Low	43.2
	Cameroon	22,240	3.9	11.5	Moderate	51.5
	Sri Lanka	20,624	6.9	79.8	Low	45.8
	Thailand	68,417	13.7	100.5	Low	58.3
	Malaysia	30,228	3.1	101.7	Low	37.8
	Singapore	5,448	1.3	103.9	Low	52.6
	Cambodia	15,271	11.6	104.9	Moderate	67.5
	Viet Nam	92,545	21.0	105.8	Low	59.1
	Philippines	100,102	14.6	121.0	Moderate	62.6
Southern Tropical	Ecuador	15,903	-0.2	-78.5	Moderate	40.4
	Peru	30,973	-12.0	-77.0	Moderate	67.5
	Bolivia	10,562	-16.5	-68.2	Moderate	73.2
	Brazil	204,213	-15.8	-47.9	Moderate	60.8
	Democratic Republic of the Congo	73,723	-4.3	15.3	Moderate	29.9
	Zambia	15,621	-15.4	28.3	Low	57.1
	United Republic of Tanzania	52,235	-6.2	35.7	Low	37.2
	Madagascar	23,590	-18.9	47.5	Low	47.9
	Indonesia	255,131	-6.2	106.8	Moderate	31.2
	New Caledonia	265	-22.3	166.5	Moderate	65.7
	Fiji	886	-18.1	178.4	Moderate	48.6
Southern temperate	Chile	17,614	-33.5	-70.6	Moderate	86.6
	Argentina	42,982	-34.6	-58.4	Moderate	90.5
	Paraguay	6,553	-25.3	-57.6	Moderate	73.3
	Uruguay	3,420	-34.8	-56.2	High	91.2
	South Africa	54,540	-33.9	18.4	High	91.4
	Australia	23,475	-35.3	149.1	Moderate	84.2

Note: Within latitude zones, countries are sorted by longitude.

period aligned with their hemisphere's vaccine cycle, 12 (population 557,862,000, 37%) aligned with the opposite hemisphere, and the remaining 13 (population 521,246,000, 34%) were equivocal (Table 2 and Fig. 2).

Fig. 3 shows the average proportion of influenza occurring in each week, averaged across all participating countries in each latitude zone, for total influenza and by influenza type. The resulting average northern temperate seasonality spans the northern tem-

perate winter, as expected. The southern temperate season is slightly broader and has a slightly less distinct low season. The tropics exhibit a markedly flatter average seasonality. Influenza B exhibits a much broader epidemic season than influenza A, peaking approximately 4 weeks later than influenza A in both the northern and southern hemispheres. The timing of the start of the average annual influenza B increase was similar to the start of the influenza A increase.
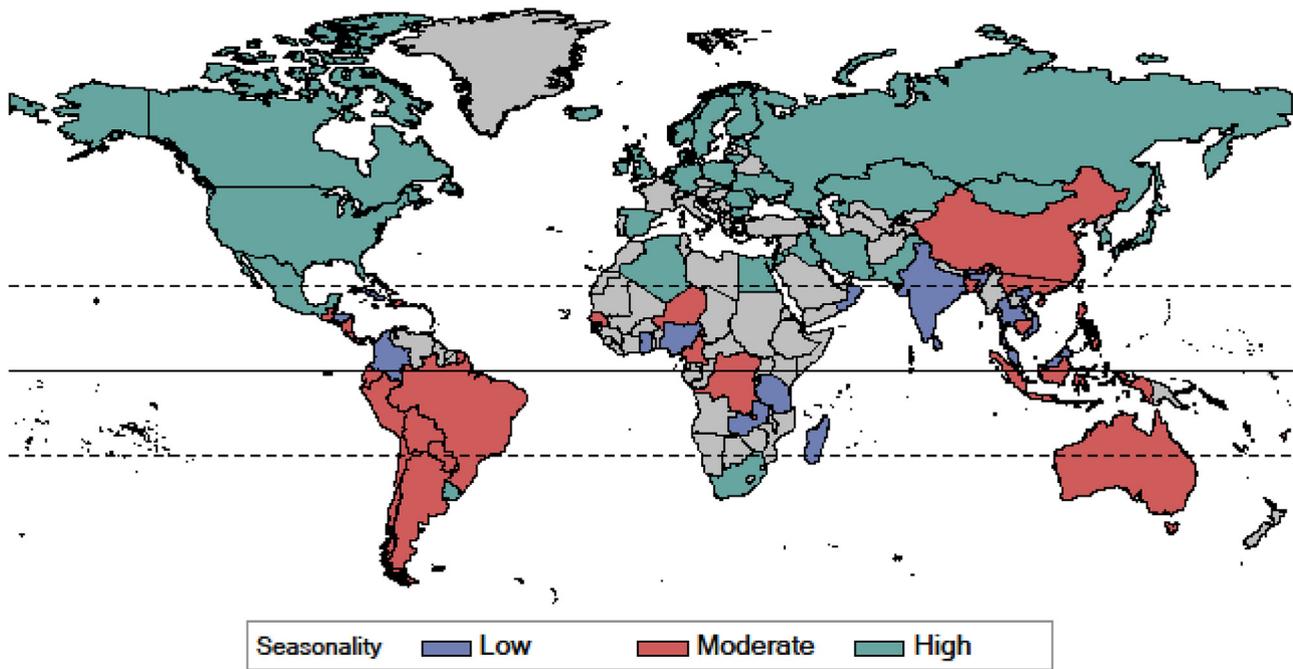
Fig. 1. World map showing the estimated degree of seasonality of each of 84 participating countries. Countries without data are shown in grey.
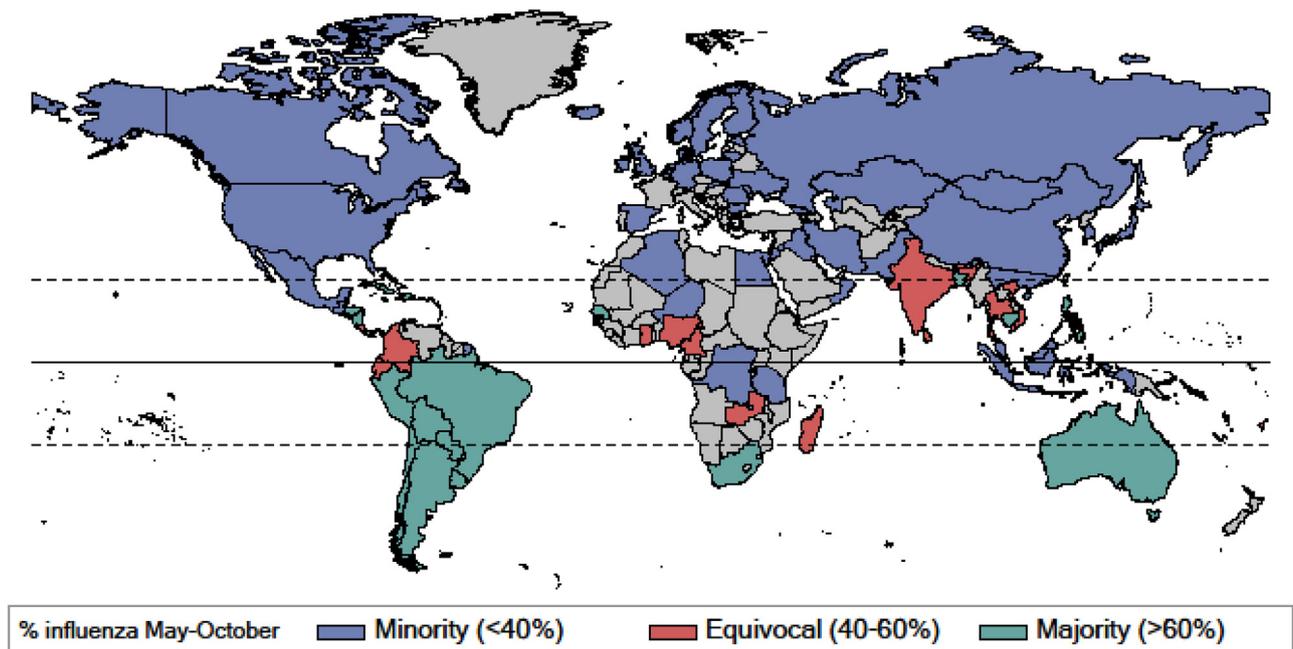
Fig. 2. World map showing the estimated proportion of influenza activity occurring during May through October in each of 84 participating countries. Countries without data are shown in grey.

Discussion

This study is the most rigorous to date on the seasonality of influenza. It links its findings to the annual global influenza vaccine production cycle, and to the size of the populations at risk. There was an identical study period for all countries, strict completeness criteria that facilitated a genuine assessment of seasonality, and a simple definition of seasonality that did not attempt to impose one or more peak timings. Despite the strict completeness criteria, 84 countries were able to be included, representing 83% of the global population.

Degree of seasonality was high, as expected, in northern temperate countries. Major exceptions were China, which just extends into the tropical zone and had a moderate degree of seasonality, and India, which had low seasonality. China's population is most densely distributed around temperate Beijing in the east and tropical Guangzhou in the south.[18] Influenza circulating in the tropical zone may explain some of the spreading of the timing of influenza activity beyond that expected for a mainly temperate country. Just under one half of India's population resides in the tropical zone,[19] which could explain its overall indistinct seasonality.
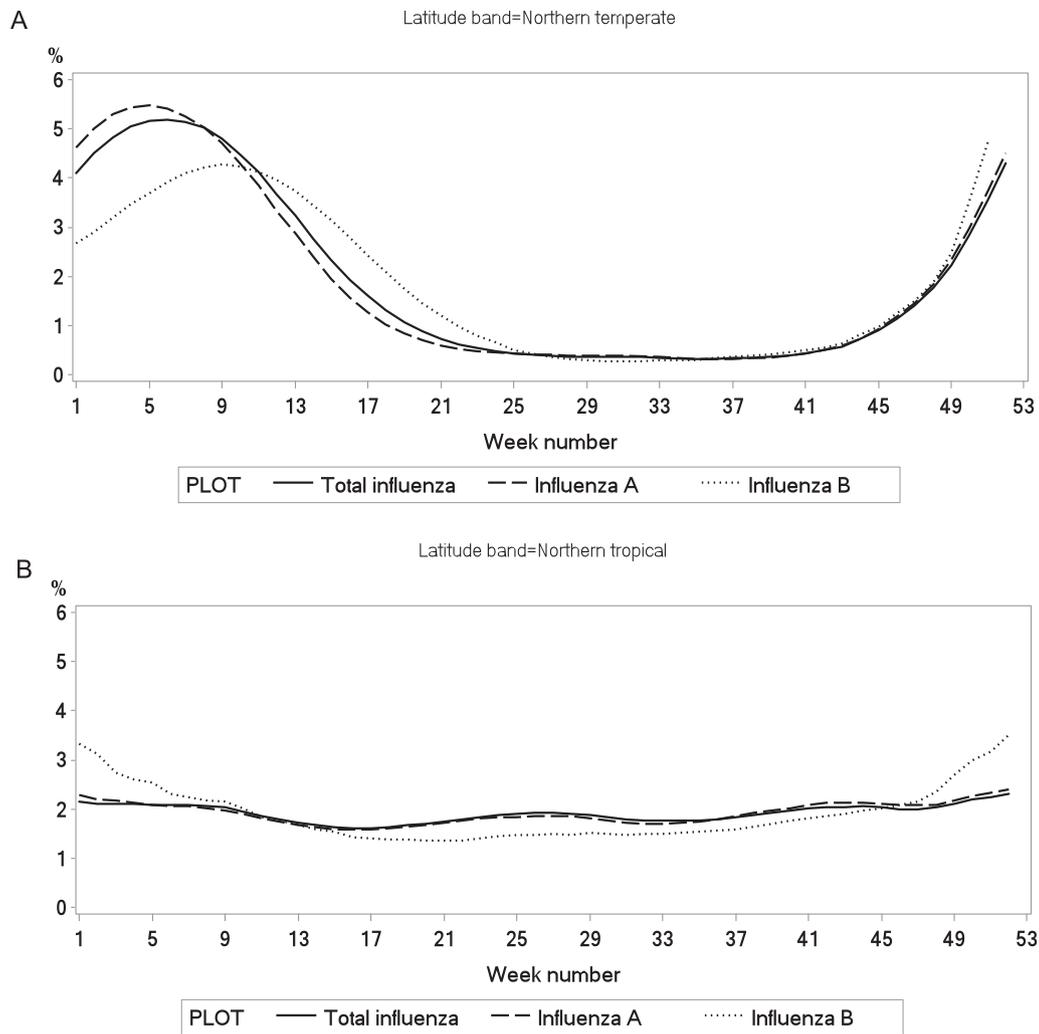
Fig. 3. Average weekly influenza activity, total and by type, averaged across latitude zones.

Somewhat surprising, is the generally more moderate degree of seasonality in the southern temperate zone. This may relate to the relative proximity of southern temperate countries to the tropical zone, compared with many northern temperate countries. Australia, Argentina and Chile extend north into the tropics. Uruguay and South Africa are wholly or almost wholly below the tropics and had a high degree of seasonality.

Consistency in the degree of seasonality was highly variable in tropical countries, and adjacent countries could experience a diverse degree of seasonality. For example, in a relatively small geographical area, Guatemala experienced moderate seasonality, while Mexico to the north experienced high seasonality and Honduras to the south-east experienced low seasonality. This presents a substantial challenge to inferring a suitable vaccination season for countries that currently do not have sufficient influenza surveillance to estimate their pattern of influenza activity.

Fifteen per cent of included countries and more than one tenth of the included global population had influenza occurrence aligned with the opposite hemisphere's influenza vaccine manufacturing cycle. Almost one in five countries and almost one third of the included global population experienced influenza at time of the year that would be addressed by either hemisphere's cycle. In tropical regions, however, almost one third of countries and more than one third of the population experienced influenza aligned with the opposite hemisphere's vaccine cycle. A minority of tropical countries experienced influenza clearly aligned with their hemisphere's cycle.

The difference in methods for classifying and reporting seasonality between this and earlier studies makes it difficult to compare findings. Where these could be compared there was substantial congruity in the findings, except for countries classified in this study as equivocal which were allocated a specific hemisphere's vaccine cycle in prior studies.[10–12,14,15] Discordances were observed between this study and Alonso and others where Cuba and Jamaica which were aligned to the opposite hemisphere.[10] By extrapolating from neighbouring countries, Hirve et al. allocated the opposite hemisphere to this study for French Guiana.[14]

Countries that were classified as equivocal in their hemisphere vaccine cycle alignment in this study could protect a substantial proportion of their population by choosing to align with either hemisphere. Including this categorisation allows flexibility in allocating a vaccination season that fits more flexibly with regional vaccine distribution logistics.

The longer duration, but similar start of the influenza B season compared with influenza A in temperate zones is a previously unknown finding. This is consistent with a lower epidemic reproduction rate of influenza B than A that has been previously hypothesised. This may in turn be related to slower antigenic drift and lower age of susceptibility in influenza B.[20] Consistent with

C
Latitude band=Southern Tropical

D
Latitude band=Southern temperate
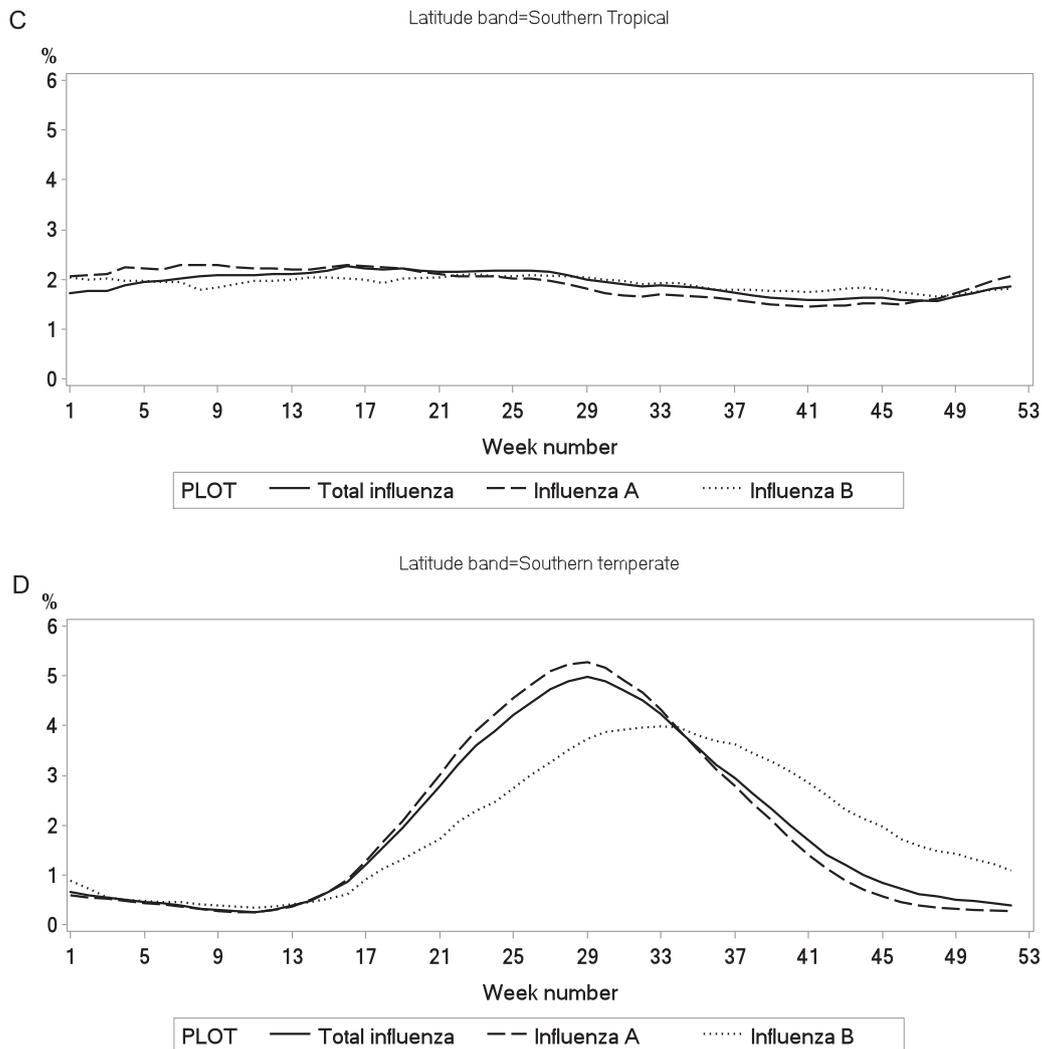
Fig. 3. Continued

this study, Caini et al. found that seasons with influenza B co-circulating with A tend to be longer than those dominated by A.[13]

Limitations of this study include the possible limited representativeness of overall influenza activity in each country provided by the relatively few National Influenza Centres participating in FluNet. This may be more acute in countries that traverse both temperate and tropical zones such as Brazil, India and China. On the other hand, the Centres are often in major population centres. Changes in seasonal patterns by virus subtypes or in relation to viral evolution or local climate were unable to be related to seasonality. A large proportion of African countries did not have sufficient completeness of influenza data to meet the inclusion criteria. Influenza surveillance in Africa remains an important area for development.

Conclusion

Degree and timing of seasonality are clearly associated with latitude, yet there are many exceptions in countries that either are in, or extend into, tropical regions. The study provides supporting evidence for different population dynamics of influenza B compared with A. These findings highlight the challenge of optimising influenza vaccine recommendations that best serve all countries. Vaccine manufacturing, supply and distribution that aligns with one country's needs may not be suitable for the adjacent country.

This complicates the logistics of the annual vaccine manufacturing and distribution cycle. Until a universal influenza vaccine can be developed,[5] decisions on the best period for vaccinating against influenza should be based on sound evidence.

Conflict of interest

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Supplementary material

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jinf.2018.10.006.

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