DOI:10.1111/irv.12319
www.influenzajournal.com

Original Article

Epidemiological and virological characteristics of influenza B: results of the Global Influenza B Study

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Introduction Literature on influenza focuses on influenza A, despite influenza B having a large public health impact. The Global Influenza B Study aims to collect information on global epidemiology and burden of disease of influenza B since 2000.

Methods Twenty-six countries in the Southern (n = 5) and Northern (n = 7) hemispheres and intertropical belt (n = 14) provided virological and epidemiological data. We calculated the proportion of influenza cases due to type B and Victoria and Yamagata lineages in each country and season; tested the correlation between proportion of influenza B and maximum weekly influenza-like illness (ILI) rate during the same season; determined the frequency of vaccine mismatches; and described the age distribution of cases by virus type.

Results The database included 935 673 influenza cases (2000–2013). Overall median proportion of influenza B was 22·6%, with no statistically significant differences across seasons. During seasons where influenza B was dominant or co-circulated (>20% of total detections), Victoria and Yamagata lineages predominated during 64% and 36% of seasons, respectively, and a vaccine mismatch was observed in ≈25% of seasons. Proportion of influenza B was inversely correlated with maximum ILI rate in the same season in the Northern and (with borderline significance) Southern hemispheres. Patients infected with influenza B were usually younger (5–17 years) than patients infected with influenza A.

Conclusion Influenza B is a common disease with some epidemiological differences from influenza A. This should be considered when optimizing control/prevention strategies in different regions and reducing the global burden of disease due to influenza.

Keywords Burden of disease, epidemiology, Global Influenza B Study (GIBS), influenza, vaccination, vaccine mismatch.

Please cite this paper as: Caini *et al.* (2015) Epidemiological and virological characteristics of influenza B: results of the Global Influenza B Study. Influenza and Other Respiratory Viruses 9(Suppl. 1), 3–12.

Introduction

Seasonal influenza epidemics impose a heavy burden on society, with 3–5 million cases and 250 000–500 000 deaths worldwide every year.[1] The resulting economic impact is large and includes both direct and indirect costs.[2,3] Traditionally, attention has been directed toward influenza A, which accounts for the majority of influenza cases in most seasons[4–6]; its subtypes are also responsible for influenza pandemics.[7] During interpandemic periods, however, influenza B can represent a considerable proportion of total cases.[8] Since the 1970s, influenza B viruses have belonged to two antigenically distinct lineages called the Victoria and Yamagata lineages[9]; this has been a challenge for seasonal influenza vaccines as only one influenza B strain is included in the trivalent vaccine. Studies in the United States have shown that the frequent influenza B vaccine mismatches of recent years have been associated with substantial increases in cases, hospitalizations and deaths (up to annual 970 000 cases, with 8200 hospitalizations and 485 deaths, in the USA),[10] as well as with large influenza-related medical costs, and costs associated with productivity loss.[11]

Despite the important role of influenza B, much of the published scientific literature regarding the epidemiology of influenza has focused on influenza A, and we still have a relatively poor understanding of global epidemiology and burden of disease of influenza B, especially outside Europe and the United States.[8] Several studies have reported on the burden of disease attributable to influenza B in a single season, or during consecutive seasons in a single country,[12,13] but only one study thus far has looked at the global epidemiology of influenza B.[4] In particular, it is very important to assess the epidemiology of influenza in the tropics, as this is where approximately 40% of the world's population live,[14] and influenza activity there is quite different from other world regions[15,16]: countries in the tropics may experience two annual peaks, and epidemics are not as short and intense as in the Northern and Southern hemispheres.[17–19] These differences can have important implications for effective and evidence-based decisions regarding the composition and period of administration of influenza vaccines.

The Global Influenza B Study

The Global Influenza B Study (GIBS) was launched in 2012 with the main aim of collecting information on the epidemiology and global burden of disease of influenza B during the past 10–15 years, to support future prevention policies. GIBS is a project of the Global Influenza Initiative, an expert scientific forum established to address the ongoing problems related to influenza worldwide. To achieve this objective, we contacted countries around the world during the period June 2013 to February 2014, requesting access to data from their national influenza surveillance systems. Here, we compare four important epidemiological and virological characteristics of influenza A and B in 26 countries: the proportion of influenza B over all influenza cases; the community impact of influenza B; the frequency of influenza B vaccination mismatches; and the age distribution of influenza A and B cases.

Materials and methods

Source of data

We contacted national influenza centers in 43 countries in the Northern and Southern hemispheres and the intertropical belt; countries were selected to represent all World Health Organization (WHO) influenza transmission zones.[20] All countries were asked to make available data originating from their national influenza surveillance system during recent years (ideally from 2000–2013). Spreadsheet data reporting templates were provided, along with instructions on how to report data. Each participating country was asked to provide the following:

1. Virological data: weekly number of influenza cases reported by the national surveillance system, broken down by age group (0–5, 6–35 months, 3–4, 5–17, 18–39, 40–64 and ≥65 years); virus type (A versus B); and virus subtype [A(H1N1), A(H3N2), A(H1N1)pdm2009, A (H1N2), A, unsubtyped] or lineage (B/Victoria, B/ Yamagata, B, not characterized).
2. Epidemiological data: weekly influenza-like illness (ILI)/ acute respiratory infection (ARI) rates per 100 000 population or 100 consultations (depending on what is routinely available within each national surveillance system).

For countries that extend over large areas, especially when stretched across different climate zones (such as China and Brazil), we asked for data stratified by region/province, if it were available. All countries received a National Feedback Report shortly after providing the data, so that they had the opportunity to check the data they had sent. They were also all asked to complete a short questionnaire on the main features of their national influenza surveillance system (see Table S1). The questionnaire included questions on the ILI/ ARI case definition in use; patients being sampled; representativeness of data; methods used for identification and characterization of influenza virus; and the population denominator.

Epidemiological and virological indicators

Influenza epidemics usually occur between October of a given year and April of the following year in countries in the Northern Hemisphere, and between April and October of a given year in the Southern Hemisphere, with greater variability observed for countries situated near the tropics.[17]

For the purposes of this study, we define a season as being the period between the first and last week of a given year (for the tropics and the Southern Hemisphere) or between the 27th week of a given year and the 26th week of the following year (for the Northern Hemisphere), so that each season includes the whole period of increased influenza activity in each country. For conciseness, when looking at "season 2005", we refer to 2005–2006 for countries in the Northern Hemisphere, and year 2005 for all other countries. For each country, only the seasons with at least 50 influenza reported cases and at least 20 weeks of data reporting were included in the analysis.

Analyses were conducted for all countries and then separately for countries situated in the Northern or Southern Hemisphere or in the intertropical belt (defined as the country centroid, when available, or the largest city being located north of the Tropic of Cancer and south of the Tropic of Capricorn).[21]

For each country and season, we calculated the percentage of influenza cases that were due to influenza B virus and then worked out its median value for countries in the Northern and Southern hemispheres and in the intertropical belt. Medians were compared using the Wilcoxon rank sum test.

We calculated the number of seasons that were dominated by either lineage among those where there was a significant circulation of influenza B (defined as the proportion of influenza B being ≥20% of all influenza cases reported during the season). For this analysis, we only considered seasons where the proportion of influenza B cases characterized was ≥10%.

An influenza B vaccine mismatch was defined as a mismatch between the influenza B lineage included in the vaccine and the lineage that caused the majority (>50%) of cases in a season with significant circulation of influenza B; using this definition, we calculated the proportion of seasons where a vaccine mismatch was observed. The information on vaccine composition was obtained from the WHO Website.[22] We calculated the percentage of vaccine mismatch according to three alternative scenarios: (i) all tropical countries situated north of the equator adopting the WHO recommendations for the Northern Hemisphere, and vice versa; (ii) all tropical countries using the Northern Hemisphere WHO recommendation; or (iii) all tropical countries adopting the Southern Hemisphere WHO recommendation.

Statistical analysis

To explore whether there was an association between the magnitude of the influenza season and the proportion of influenza cases due to B virus type, we obtained the country-specific Z-score of the weekly ILI/ARI rate (defined as the number of standard deviations above or below the country-specific average of the ILI/ARI rate) and calculated the Pearson's correlation coefficient between its maximum value and the proportion of influenza B cases during each season. We hypothesized that a moderate-to-mild inverse correlation would be seen between the proportion of influenza B and the maximum weekly ILI/ARI rate in the Northern and Southern hemispheres, as influenza A viruses cause most influenza cases and are responsible for short and intense epidemics—especially influenza A(H3N2)—compared with influenza B.

We calculated the percentage of influenza A and B cases in each country in each of the following age categories: 0–4, 5–17, 18–64 and ≥65 years; we tested whether the percentage of influenza A versus B cases differed in each age group using a chi-square test. When the exact age was available, we also obtained virus type-specific median age and interquartile range (IQR) and used the Wilcoxon rank sum test to detect any differences in median age of influenza A versus B cases.

All analyses were performed using Stata version 11 (StataCorp LP, College Station, TX, USA) and Microsoft Excel. All statistical tests were two-sided, and a *P*-value of <0·05 was considered significant.

Results

Twenty-six countries joined the Global Influenza B Study (Figure 1). China provided separate data for the northern and southern parts of the country.[23] Brazil provided data stratified by its five administrative regions: north, north-east, central-west, south-east and south; however, as results of the analyses did not differ across regions, results for the whole country are shown. Participating countries are distributed in the Northern (n = 7) and Southern (n = 5) hemispheres and in the intertropical belt (n = 14), cover 16 of the 18 WHO influenza transmission zones,[20] and account for around 37% of the world's population (Table 1).

The influenza surveillance systems of the participating countries differ from each other (Table 1); in most cases, however, they cover the whole country, sample both outpatients and hospitalized patients, and send isolates to a WHO collaborating center for reference. Most countries in the Northern and Southern hemispheres had data on ILI rates (ARI rates for Singapore), with a mixture of consultation and population denominators, but many countries in the tropics had no such data.

Overall, 935 673 influenza cases were reported to the national influenza centers during 200 seasons between 2000 and 2013 (Table 2). Of these, 288 130 cases (30·8%) were reported before the emergence of the 2009 A(H1N1) pandemic influenza. Countries provided a median of seven seasons, ranging from four seasons for Argentina, Costa Rica, and Honduras, to 13 for New Zealand. The proportion of influenza A cases subtyped was 65·1%, and 17·1% of influenza B cases were characterized. The information on age was available for 47·6% and 59·1% of influenza A and B cases, respectively.

Figure 1. Countries participating in the Global Influenza B Study. April 2014.

The proportion of influenza cases due to type B virus was <20% for 90 seasons, 20–50% for 82 seasons and ≥50% for 28 seasons; the median percentage was 22·6% (IQR 8·3–37·7%). Figure 2 shows the distribution of seasons according to the proportion of influenza cases caused by type B virus, separately for countries situated in the Northern or Southern Hemisphere or in the intertropical belt. The median proportion of influenza B over all influenza seasons was 17·8% in the Southern Hemisphere (IQR 3·5–30·4%; 39 seasons), 24·3% in the intertropical belt (IQR 10·2–40·8%; 94 seasons), and 21·4% in the Northern Hemisphere (IQR 7·3–38·0%; 67 seasons). The *P*-value for the comparison of the median proportion of influenza B in the Southern Hemisphere versus the intertropical belt was borderline significant (0·07) and not significant for the other comparisons.

A measure of ILI (or ARI) rate was available for 106 seasons. The Spearman's rank correlation coefficient for the association between the proportion of influenza B during a given season and the maximum ILI rate Z-score during the same season was −0·31 in the Southern Hemisphere [95% confidence interval (CI) −0·64 to 0·12; 23 seasons], −0·09 in the intertropical belt (95% CI −0·43 to 0·26; 32 seasons), and −0·31 in the Northern Hemisphere (95% CI −0·54 to −0·04; 51 seasons) (Figure 3).

The proportion of influenza B cases that were characterized was ≥10% for 79 of the 200 seasons. If one assumes that all countries in the intertropical belt used the WHO recommendations for the hemisphere they are situated or the WHO recommendation for the Southern Hemisphere, an influenza B vaccine mismatch was seen in 19 of 79 seasons (24–25%): 11 of 36 seasons in the Northern Hemisphere (31%), six of 22 seasons in the Southern Hemisphere (27%), and two of 21 seasons in the intertropical belt (10% or 14%) (Table S2). If one assumes the WHO recommendation for the Northern Hemisphere was followed, the results are very similar: there were a total of 20 mismatches and three mismatches for the intertropical belt countries.

Influenza B accounted for 20% or more of all influenza cases during 50 of these 79 seasons: Victoria and Yamagata lineages predominated in 32 (64%) and 18 (36%) seasons, respectively. Also, the Victoria and Yamagata lineages often co-circulate in the same season: in 16 of 50 seasons, both lineages accounted for at least 20% of influenza B cases (Table S2).

Table S3 presents the age distribution of A versus B influenza cases in each country. A consistent finding across most countries is a younger age for influenza B versus A cases. In particular, there was a consistently higher proportion of influenza B cases in the 5–17 years age group, and A cases in the 18–64 years age group in Southern and Northern Hemisphere countries (except South Africa, Brazil, Turkey, and Ukraine) and in some countries of the intertropical belt (Madagascar, Indonesia, Singapore, Costa Rica, Nicaragua, Guatemala, and Vietnam). Influenza B cases were also younger than A cases in Panama, El Salvador, and Honduras, where there was a higher proportion of B cases among patients aged 0–4 years. No differences in age distribution were observed in Kenya, Cameroon, and the Ivory Coast; these were the only countries where over 50% of all influenza cases were aged ≤4 years. Finally, influenza A cases were older than B cases in South Africa, Brazil, Turkey, and Ukraine.

Discussion

The GIBS was conceived and implemented to obtain a better understanding of the global epidemiology of influenza B, with a particular focus on the tropics, which have been

Table 1. Comparison of geography, demographics and main features of influenza surveillance systems of participating countries (from southern- to northernmost). The Global Influenza B Study

Country	Latitude	Population (millions)*	Representativeness of data	Patients sampled	Denominator	Laboratory methods for influenza diagnosis	Laboratory methods for virus characterization	Isolates sent to WHO for reference
New Zealand	41°81′S	4·5	Regional	Outpatients, inpatients, SARI	ILI/population	Sequencing	Isolates sent to WHO for reference	Yes
Chile	35°82′S	16·3	National	Outpatients, inpatients, SARI	None	PCR, culture	Hemagglutination inhibition, sequencing	Yes
Argentina (Santa Fe)	31°38′S	3·2	Regional	Outpatients, SARI	ILI/population	PCR, immunofluorescence	Isolates sent to WHO for reference	Yes
South Africa	29°05′S	53·0	Regional	SARI	None	PCR	Sequencing	Yes
Australia	25°85′S	23·4	National	Outpatients, SARI	ILI/consultations	PCR, serology, culture	Hemagglutination inhibition, sequencing	Yes
Madagascar	19°43′S	21·3	Regional (until 2008), national (afterwards)	Outpatients	ILI/consultations	PCR, culture	Hemagglutination inhibition	Yes
Brazil	10°83′S	201·0	National	Outpatients, SARI	ILI/consultations	PCR, immunofluorescence	Hemagglutination inhibition, sequencing	Yes
Indonesia	1°66′S	249·9	National	Outpatients, inpatients, SARI	None	PCR, culture	Hemagglutination inhibition, sequencing	Yes
Singapore	1°22′N	5·4	National	Outpatients	ARI/consultations	PCR	Hemagglutination inhibition, sequencing	Yes
Kenya	0°42′S	44·4	Regional	Outpatients, SARI	ILI/population	PCR	Isolates sent to WHO for reference	Yes
Cameroon	5°68′N	20·4	Regional	Outpatients, SARI	None	PCR	Hemagglutination inhibition	Yes
Ivory Coast	7°61′N	23·2	Regional	Outpatients, SARI	None	PCR, culture	Hemagglutination inhibition	Yes
Panama	8°57′N	3·7	National	Outpatients, SARI	None	PCR, culture, immunofluorescence	Isolates sent to WHO for reference	Yes
Costa Rica	10°01′N	4·6	National	Outpatients, SARI	None	PCR, culture, immunofluorescence	Isolates sent to WHO for reference	Yes
Nicaragua	12°86′N	6·1	National	Outpatients, SARI	None	PCR, culture, immunofluorescence	Isolates sent to WHO for reference	Yes
El Salvador	13°78′N	6·1	National	Outpatients, SARI	None	PCR, culture, immunofluorescence	Isolates sent to WHO for reference	Yes
Honduras	14°84′N	8·2	National	Outpatients, SARI	None	PCR, culture, immunofluorescence	Isolates sent to WHO for reference	Yes
Guatemala	15°74′N	15·4	National	Outpatients, SARI	None	PCR, culture, immunofluorescence	Isolates sent to WHO for reference	Yes
Vietnam	16°69′N	89·7	National	Outpatients, SARI, other	ILI/consultations	PCR, culture	Hemagglutination inhibition, sequencing	Yes
Bhutan	27°40′N	0·7	National	Outpatients, SARI	ILI/consultations	PCR	Isolates sent to WHO for reference	Yes
China (south)	31°12′N	769·0	National	Outpatients	ILI/consultations	PCR, culture	Hemagglutination inhibition	Yes
Turkey	39°02′N	76·7	Regional	Outpatients	None	PCR, culture	Hemagglutination inhibition	Yes
China (north)	39°54′N	563·8	National	Outpatients	ILI/consultations	PCR, culture	Hemagglutination inhibition	Yes

Table 1. (*Continued*)

Country	Latitude	Population (millions)*	Representativeness of data	Patients sampled	Denominator	Laboratory methods for influenza diagnosis	Laboratory methods for virus characterization	Isolates sent to WHO for reference
Italy	42°88′N	60·0	National	Outpatients, inpatients, SARI	ILI/population	PCR	Hemagglutination inhibition, sequencing	Yes
United States	45°62′N	317·7	National	Outpatients, inpatients, SARI	ILI/consultations	PCR, culture	Hemagglutination inhibition, sequencing	Yes
Ukraine	49°06′N	44·6	National	Outpatients, SARI	ILI/population	PCR, culture	Hemagglutination inhibition	Yes
England	52°33′N	53·0	National	Outpatients, inpatients	None	PCR, culture	Hemagglutination inhibition, sequencing	Yes

ARI, acute respiratory infection; ILI, influenza-like illness; PCR, polymerase chain reaction; SARI, severe acute respiratory infection; WHO, World Health Organization.
*Most recent estimate.

relatively neglected by the research so far.[8] Our main finding was that influenza B is a common virus in the 21st century, representing roughly 20% of all cases reported to national influenza centers in 26 countries around the world during 2000–2013. Although the differences were not statistically significant, there is some evidence of geographical variability in the occurrence of influenza B around the world, with it being most common in the tropics (median 24·3%) and least common in the Southern Hemisphere (17·8%). We found that influenza B rarely represented over 50% of flu cases (once every seven seasons) and was generally associated with lower rates of ILI in the Northern and (with borderline significance) Southern hemispheres. We also found that there was frequently a vaccine mismatch when influenza B circulated in a country; this happened more often in the Northern and Southern hemispheres compared with the tropics. Finally, influenza B generally affected younger persons than influenza A, with the former mainly affecting school-aged children (aged 5–17 years) and the latter adults (aged 18–64 years).

It is not yet clear what causes the differences in influenza epidemiology (including timing, periodicity, and patterns of transmission) in the tropics compared with the Southern and Northern hemispheres.[15] The non-significant higher proportion of influenza B in the tropics may simply reflect the relatively higher proportion of children, who are the most affected age group, in most countries of this region compared to the Northern and Southern hemispheres. It would, however, be necessary to calculate age-specific incidence rates of influenza to confirm or refute this hypothesis. Future research should prioritize the study of influenza epidemiology in this very populous area of the world, to optimize prevention strategies and the composition and timing of administration of the influenza vaccine.

The divergent results of the correlation between the proportion of influenza B and peak of ILI rate mirror the differences in influenza epidemiology in temperate and tropical countries, with short epidemics and greater year-to-year fluctuations for influenza A than B in the former[4] and a year-round influenza activity and higher average proportion of B in the latter.[17] It is usually not possible to predict with reasonable accuracy the impact of the upcoming influenza season based on historical data,[24] and we have shown that Victoria and Yamagata lineages often co-circulate in the same season (Table S2). The frequency of vaccine mismatch has been high in recent years (≈24–25% in the GIBS database), but its potential consequences in terms of influenza cases, influenza-related deaths, and economic costs are difficult to estimate at the beginning of an influenza season. This has important implications for vaccination strategies, including the decision to adopt a quadrivalent influenza vaccine.[10]

Differences in the age distribution of influenza A versus B patients across countries may be explained in a variety of

Table 2. Influenza cases reported to the national influenza surveillance system of each participating country (from southern- to northernmost), and percentages of cases that were subtyped, by virus type. The Global Influenza B Study

Country	Seasons	Influenza cases (*n*)	Influenza A cases (*n*, %)		Influenza B cases (*n*, %)		Influenza A cases subtyped (*n*, %)		Influenza B cases characterized (*n*, %)	
New Zealand	2000–2012	17 629	14 664	83·2	2965	16·8	11 670	79·6	2128	71·8
Chile	2008–2012	11 162	9983	89·4	1179	10·6	9488	95·0	646	54·8
Argentina (Santa Fe)	2009–2012	683	560	82·0	123	18·0	519	92·7	123	77·2
South Africa	2009–2013	1690	1098	65·0	592	35·0	1082	98·5	316	53·4
Australia	2001–2012	179 137	150 437	84·0	28 700	16·0	67 336	44·8	924	3·2
Madagascar	2002–2013	4068	2742	67·4	1326	32·6	2511	91·6	906	68·3
Brazil	2004–2012	3282	2399	73·1	883	26·9	0	0·0	0	0·0
Indonesia	2003–2007	3653	2339	64·0	1314	36·0	2313	98·9	662	50·4
Singapore	2007–2012	12 001	9690	80·7	2311	19·3	9690	100·0	904	39·1
Kenya	2007–2012	6344	4852	76·5	1492	23·5	2933	60·4	144	9·7
Cameroon	2009–2013	733	504	68·8	229	31·2	504	100·0	0	0·0
Ivory Coast	2007–2012	1581	975	61·7	606	38·3	867	88·9	0	0·0
Panama	2008–2013	2191	1868	85·3	323	14·7	1177	63·0	0	0·0
Costa Rica	2009–2012	6083	5569	91·6	514	8·4	5569	100·0	0	0·0
Nicaragua	2007–2013	5677	4924	86·7	753	13·3	4427	89·9	0	0·0
El Salvador	2006–2013	2473	1965	79·5	508	20·5	1348	68·6	0	0·0
Honduras	2009–2012	1701	1528	89·8	173	10·2	1140	74·6	0	0·0
Guatemala	2006–2013	4360	3856	88·4	504	11·6	2441	63·3	0	0·0
Vietnam	2006–2013	8647	5636	65·2	3011	34·8	5630	99·9	0	0·0
Bhutan	2009–2013	1350	943	69·9	407	30·1	940	99·7	0	0·0
China (South)	2006–2012	122 215	86 305	70·6	35 910	29·4	76 792	89·0	14 606	40·7
Turkey	2006–2011	2155	1747	81·1	408	18·9	1597	91·4	384	94·1
China (North)	2005–2012	64 306	44 350	69·0	19 956	31·0	39 931	90·0	8040	40·3
Italy	2002–2012	23 340	21 702	93·0	1638	7·0	20 474	94·3	12	0·7
United States	2000–2012	441 547	371 050	84·0	70 497	16·0	216 990	58·5	0	0·0
Ukraine	2000–2012*	1389	1071	77·1	318	22·9	848	79·2	234	73·6
England	2003–2013	6276	4710	75·0	1566	25·0	4710	100·0	619	39·5
Total		935 673	757 467	81·0	178 206	19·0	492 926	65·1	30 648	17·1

*Seasons 2001–2002 and 2003–2004 in the Ukraine were not included as the number of reported influenza cases was <50.

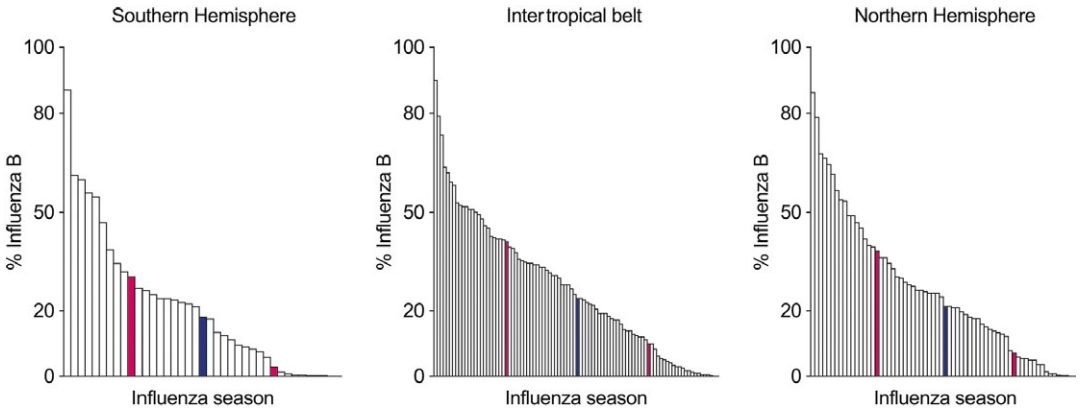

Figure 2. Distribution of influenza seasons by proportion of influenza B cases and geographical area (Southern Hemisphere, intertropical belt and Northern Hemisphere). The Global Influenza B Study. April 2014. Purple bar presents median. Pink bars indicate 25% and 75% percentiles.

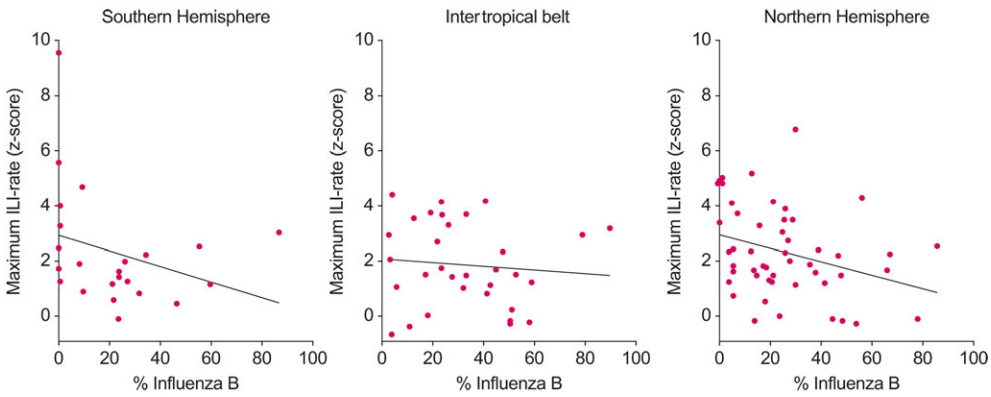

Figure 3. Proportion of influenza B and maximum influenza-like illness (ILI) rate (Z-score) during each season, by geographical area (Southern Hemisphere, intertropical belt and Northern Hemisphere). The Global Influenza B Study. April 2014.

ways, including differences in the age structure of the population and in the national influenza surveillance systems (e.g. whether the latter is mainly outpatient or hospital based). Inequalities in access to health care by age or the presence of comorbidities (children and older patients are more likely to see a general practitioner or be taken to hospital, and therefore be sampled, compared with adults over 18 years of age) may also affect the age distribution of influenza cases. In some countries (e.g. Cameroon and Kenya), the lack of differences in age distribution may be due to the small number of influenza cases in those age categories where the differences are most frequently observed, that is, 5–17 and 18–64 years. Finally, the percentage of influenza A cases due to seasonal and pandemic A(H1N1) and A(H3N2) subtypes may differ across GIBS countries (especially as a consequence of each country providing data for different influenza seasons), so comparing B versus A as a whole may be suboptimal – virus A subtypes may preferentially affect people of different age groups.[25] A more in-depth analysis of age distribution across virus subtypes and lineages will be the topic of a future GIBS publication.

The major limitation of our study lies in the differing characteristics of the national influenza surveillance systems of participating countries. In particular, the different definitions of ILI (or ARI) that are in use and the differences in the sources of patients included in the national databases (outpatients, hospitalized patients, severe ARI patients) may reduce the comparability of data across countries. Some world regions (such as northern Africa and central Asia) are currently not represented in our database, which somewhat lessens the generalizability of our results. However, the GIBS database already includes more than 900 000 influenza cases and is still growing; in the future, therefore, it will be possible to address specific questions on subsets of cases with common characteristics. Large countries may have very different epidemiological patterns at a regional level and climatic characteristics, and in those cases, the lack of stratified data may prevent the execution of analyses with the required level of detail. For some countries, regional data are available (e.g. Brazil and China), but in other countries, for example the United States and Australia, it remains an issue.

Conclusion

This study indicates that it is important to take into consideration influenza B in the epidemiology of seasonal influenza, as it often co-circulates with influenza A and accounts for roughly 20% of total cases in all regions of the world, despite it rarely being the dominant strain. We believe that global data on the epidemiology of influenza B, as those produced by the GIBS, are needed on a continuing basis to help optimize influenza prevention policies and determine the public health value of introducing influenza vaccines containing two B lineages. In particular, we recommend that future studies exploit the potential of the GIBS database, with its age-specific data, to assess the benefits of adopting influenza vaccination in different regions of the world, and tailor the vaccination campaigns to each country's requirements.

Acknowledgements

We thank Douglas Fleming [Royal College of General Practitioners (RCGP), Birmingham, UK] for discussions regarding the age distribution of influenza A and B cases, and Peter Spreeuwenberg (NIVEL) for statistical advice. We also thank Mark Thompson, Marc-Alain Widdowson, Jazmin Duque, Stacey Spivey-Blackford, Eduardo Azziz-Baumgartner, and Alexey W. Clara from the US Centers for Disease Control and Prevention (CDC) for their support in contacting countries potentially interested in participating in the GIBS and for their valuable suggestions on data analysis. Finally, we thank Clotilde El Guerche Seblain from Sanofi Pasteur for her valuable support.

Author contributions

SC, FS, QSH, MAC, SPl, and JP participated in the design of the study. GK, RO, SW, CMPH, RN, RAF, HY, LF, MZ, AWC, HK, SPu, HAK, GE, J-MH, QSH, LWA, MV, MAC, AM, LB, and LTQM collected the data. SC and JP analyzed the data. SC, FS, QSH, MAC, SPl, and JP interpreted the data. All authors participated in article preparation and approved the final article.

Conflict of interests

Other than some of the authors being GII members, and the GIBS being supported by an unrestricted research grant from Sanofi Pasteur, the authors have no competing interests to declare.

References

1 World Health Organization. Influenza. Fact sheet no. 211. Available at http://www.who.int/mediacentre/factsheets/fs211/en/ (Accessed 28 March 2014).
2 Molinari NA, Ortega-Sanchez IR, Messonnier ML *et al.* The annual impact of seasonal influenza in the US: measuring disease burden and costs. Vaccine 2007; 25:5086–5096.
3 Peasah SK, Azziz-Baumgartner E, Breese J, Meltzer MI, Widdowson MA. Influenza cost and cost-effectiveness studies globally—a review. Vaccine 2013; 31:5339–5348.
4 Finkelman BS, Viboud C, Koelle K, Ferrari MJ, Bharti N, Grenfell BT. Global patterns in seasonal activity of influenza A/H3N2, A/H1N1, and B from 1997 to 2005: viral coexistence and latitudinal gradients. PLoS ONE 2007; 2:e1296.
5 Thompson WW, Shay DK, Weintraub E *et al.* Mortality associated with influenza and respiratory syncytial virus in the United States. JAMA 2003; 289:179–186.
6 Thompson WW, Shay DK, Weintraub E *et al.* Influenza-associated hospitalizations in the United States. JAMA 2004; 292:1333–1340.
7 Kilbourne ED. Influenza pandemics of the 20th century. Emerg Infect Dis 2006; 12:9–14.
8 Paul Glezen W, Schmier JK, Kuehn CM, Ryan KJ, Oxford J. The burden of influenza B: a structured literature review. Am J Public Health 2013; 103:e43–e51.
9 Biere B, Bauer B, Schweiger B. Differentiation of influenza B virus lineages Yamagata and Victoria by real-time PCR. J Clin Microbiol 2010; 48:1425–1427.
10 Reed C, Meltzer MI, Finelli L, Fiore A. Public health impact of including two lineages of influenza B in a quadrivalent seasonal influenza vaccine. Vaccine 2012; 30:1993–1998.
11 Karve S, Meier G, Davis KL, Misurski DA, Wang CC. Influenza-related health care utilization and productivity losses during seasons with and without a match between the seasonal and vaccine virus B lineage. Vaccine 2013; 31:3370–3388.
12 Grant KA, Carville K, Fielding JE *et al.* High proportion of influenza B characterises the 2008 influenza season in Victoria. Commun Dis Intell Q Rep 2009; 33:328–336.
13 Ansaldi F, D'Agaro P, Burgnich P *et al.* Three-year (1999–2002) of epidemiological and virological surveillance of influenza in north-east Italy. Eur J Epidemiol 2004; 19:885–890.
14 State of the Tropics. State of the Tropics 2014 report. Cairns, Australia: James Cook University. Available at http://www.jcu.edu.au/sottreport/ (Accessed 22 April 2014).
15 Tamerius JD, Shaman J, Alonso WJ *et al.* Environmental predictors of seasonal influenza epidemics across temperate and tropical climates. PLoS Pathog 2013; 9:e1003194.
16 Azziz Baumgartner E, Dao CN, Nasreen S *et al.* Seasonality, timing, and climate drivers of influenza activity worldwide. J Infect Dis 2012; 206:838–846.
17 Bloom-Feshbach K, Alonso WJ, Charu V *et al.* Latitudinal variations in seasonal activity of influenza and respiratory syncytial virus (RSV): a global comparative review. PLoS ONE 2013; 8:e54445.
18 Lee VJ, Yap J, Ong JB *et al.* Influenza excess mortality from 1950–2000 in tropical Singapore. PLoS ONE 2009; 4:e8096.
19 Saha S, Chadha M, Al Mamun A *et al.* Influenza seasonality and vaccination timing in tropical and subtropical areas of southern and south-eastern Asia. Bull World Health Organ 2014; 92:309–384. WHO Bulletin. 2014. Article ID:BLT.13.124412. Available at http://www.who.int/bulletin/volumes/92/5/13-124412-ab/en/ (Accessed 19 June 2014).
20 World Health Organization. Influenza transmission zones. Available at http://www.who.int/csr/disease/swineflu/transmission_zones/en/ (Accessed 29 March 2014).
21 Central Intelligence Agency. The World Factbook. Available at https://www.cia.gov/library/publications/the-world-factbook/appendix/appendix-f.html (Accessed 29 March 2014).
22 World Health Organization. Recommendations on the composition of influenza virus vaccines. Available at http://www.who.int/influenza/vaccines/virus/recommendations/en/ (Accessed 29 March 2014).
23 Yu H, Feng L, Viboud CG *et al.* Regional variation in mortality impact of the 2009 A(H1N1) influenza pandemic in China. Influenza Other Respir Viruses 2013; 7:1350–1360.
24 WHO Writing Group, Ampofo WK, Baylor N *et al.* Improving influenza vaccine virus selection: report of a WHO informal consultation held at WHO headquarters, Geneva, Switzerland, 14–16 June 2010. Influenza Other Respir Viruses 2012; 6:142–152, e1–e5.
25 Khiabanian H, Farrell GM, St George K, Rabadan R. Differences in patient age distribution between influenza A subtypes. PLoS ONE 2009; 4:e6832.

Appendix 1:

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Supporting Information

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

Table S1. Questionnaire on national influenza surveillance systems used for the Global Influenza B Study.

Table S2. Proportion of influenza B cases due to Victoria or Yamagata lineage virus, and mismatch with recommended World Health Organization (WHO) influenza vaccine. Seasons were only considered during which at least 20% of influenza cases were due to virus type B with at least 10% of these being characterized. The Global Influenza B Study.

Table S3. Proportion of influenza A versus B cases across age categories, median age and interquartile range (IQR), in countries (from southern- to northernmost) participating in the Global Influenza B Study.