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Caini, S.

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Chapter 2

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

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Caini S, Huang QS, Ciblak MA, Kuszniierz G, Owen R, Wangchuk S, Henriques CM, Njouom R, Fasce RA, Yu H, Feng L, Zambon M, Clara AW, Kosasih H, Puzelli S, Kadjo HA, Emukule G, Heraud JM, Ang LW, Venter M, Mironenko A, Brammer L, Mai le TQ, Schellevis F, Plotkin S, Paget J; Global Influenza B Study.

2.1 Abstract

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 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.

2.2 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].¹ The resulting economic impact is large and includes both direct and indirect costs [2-3]. Traditionally, attention has been directed towards 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 to 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.

2.2.1 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 set-up 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.

2.3 Methods

2.3.1. Source of data

We contacted national influenza centres 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, unsubtype] 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 Supplementary Table 2.1). 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.

2.3.2. 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 $\geq 20\%$ of all influenza cases reported during the season). For this analysis, we only considered seasons where the proportion of influenza B cases characterized was $\geq 10\%$.

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.

2.3.2. 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.

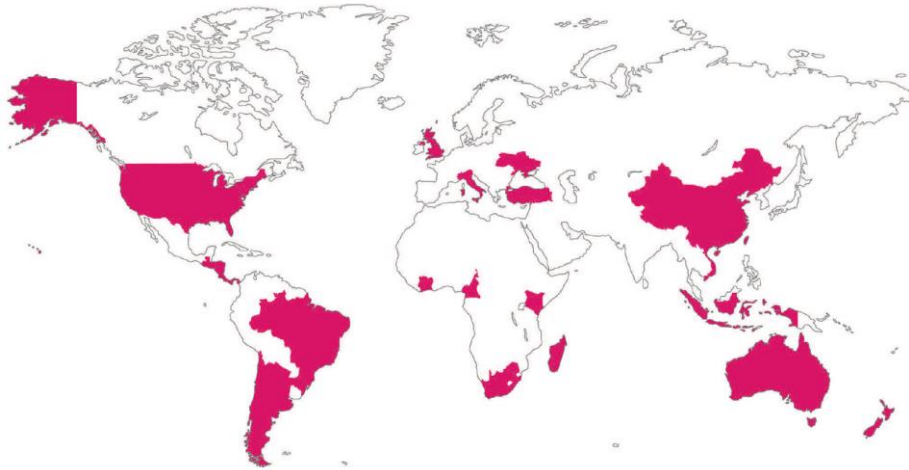
We calculated the percentage of influenza A and B cases in each country in each of the following age categories: 0–4, 5–17, 18–64 and ≥ 65 years; we tested whether the percentage of influenza A versus B cases differed in each age group using a chi-square test. When the exact age was available, we also 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.

2.4 Results

Twenty-six countries joined the Global Influenza B Study (Figure 2.1). 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.

Figure 2.1. Countries participating in the Global Influenza B Study. April 2014.



The influenza surveillance systems of the participating countries differ from each other (Table 2.1); in most cases, however, they cover the whole country, sample both outpatients and hospitalized patients, and send isolates to a WHO collaborating centre 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 centres during 200 seasons between 2000 and 2013 (Table 2.2). 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.

Table 2.1. 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) ^a	Representativeness of data	Patients sampled	Denominator	Lab methods for influenza diagnosis	Lab methods for virus characterization	Isolates 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

Country	Latitude	Population (millions) ^a	Representativeness of data	Patients sampled	Denominator	Lab methods for influenza diagnosis	Lab methods for virus characterization	Isolates to WHO for reference
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
Viet Nam	16°69' N	89.7	national	outpatients, SARI, other	ILI/consultations	PCR, culture	hemagglutination inhibition, sequencing	yes

Country	Latitude	Population (millions) ^a	Representativeness of data	Patients sampled	Denominator	Lab methods for influenza diagnosis	Lab methods for virus characterization	Isolates to WHO for reference
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
Italy	42°88' N	60.0	national	outpatients, inpatients, SARI	ILI/population	PCR	hemagglutination inhibition, sequencing	yes
USA	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

Table 2.2. 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.

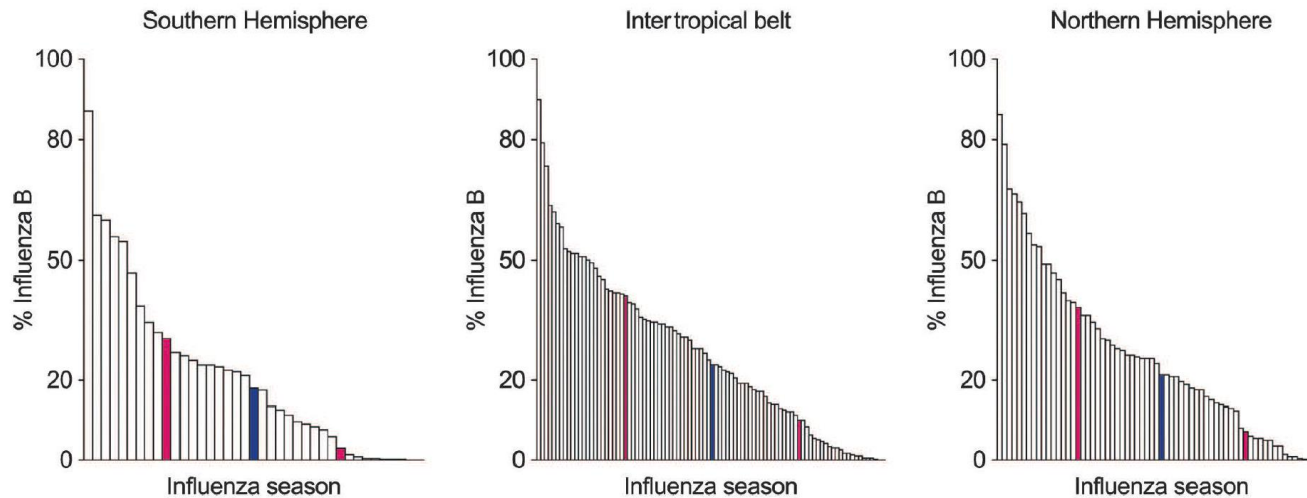
Country	Seasons	Influenza cases (n)	Influenza A cases (n, %)	Influenza B cases (n, %)	Influenza A cases subtyped (n, %)	Influenza B cases characterized (n, %)
New Zealand	2000-12	17,629	14,664 83.2	2,965 16.8	11,670 79.6	2,128 71.8
Australia	2001-12	179,137	150,437 84.0	28,700 16.0	67,336 44.8	924 3.2
Chile	2008-12	11,162	9,983 89.4	1,179 10.6	9,488 95.0	646 54.8
Argentina (Santa Fe)	2009-12	683	560 82.0	123 18.0	519 92.7	123 100.0
South Africa	2009-13	1,690	1,098 65.0	592 35.0	1,082 98.5	316 53.4
Madagascar	2002-13	4,068	2,742 67.4	1,326 32.6	2,511 91.6	906 68.3
Brazil	2004-12	3,282	2,399 73.1	883 26.9	0 0.0	0 0.0
Indonesia	2003-07	3,653	2,339 64.0	1,314 36.0	2,313 98.9	662 50.4
Kenya	2007-12	6,344	4,852 76.5	1,492 23.5	2,933 60.4	144 9.7
Singapore	2007-12	12,001	9,690 80.7	2,311 19.3	9,690 100.0	904 39.1
Cameroon	2009-13	733	504 68.8	229 31.2	504 100.0	0 0.0
Ivory Coast	2007-12	1,581	975 61.7	606 38.3	867 88.9	0 0.0
Panama	2008-13	2,191	1,868 85.3	323 14.7	1,177 63.0	0 0.0
Costa Rica	2009-12	6,083	5,569 91.6	514 8.4	5,569 100.0	0 0.0
Nicaragua	2007-13	5,677	4,924 86.7	753 13.3	4,427 89.9	0 0.0
El Salvador	2006-13	2,473	1,965 79.5	508 20.5	1,348 68.6	0 0.0
Guatemala	2006-13	4,360	3,856 88.4	504 11.6	2,441 63.3	0 0.0
Honduras	2009-12	1,701	1,528 89.8	173 10.2	1,140 74.6	0 0.0
Viet Nam	2006-13	8,647	5,636 65.2	3,011 34.8	5,630 99.9	0 0.0
Bhutan	2009-13	1,350	943 69.9	407 30.1	940 99.7	0 0.0
China (South)	2006-12	122,215	86,305 70.6	35,910 29.4	76,792 89.0	14,606 40.7
China (North)	2005-12	64,306	44,350 69.0	19,956 31.0	39,931 90.0	8,040 40.3
USA	2000-12	441,547	371,050 84.0	70,497 16.0	216,990 58.5	0 0.0
Turkey	2006-11	2,155	1,747 81.1	408 18.9	1,597 91.4	384 94.1

Country	Seasons	Influenza B cases (n)	Influenza A cases (n, %)	Influenza B cases (n, %)	Influenza A cases subtyped (n, %)	Influenza B cases characterized (n, %)
Italy	2002-12	23,340	21,702 93.0	1,638 7.0	20,474 94.3	12 0.7
Ukraine ^(a)	2000-12	1,389	1,071 77.1	318 22.9	848 79.2	234 73.6
England	2003-13	6,276	4,710 75.0	1,566 25.0	4,710 100.0	619 39.5
Total		935,673	757,467 81.0	178,206 19.0	492,926 65.1	30,648 17.2

(a) Seasons 2001-2002 and 2003-2004 in Ukraine were not included as the number of reports influenza cases was <50

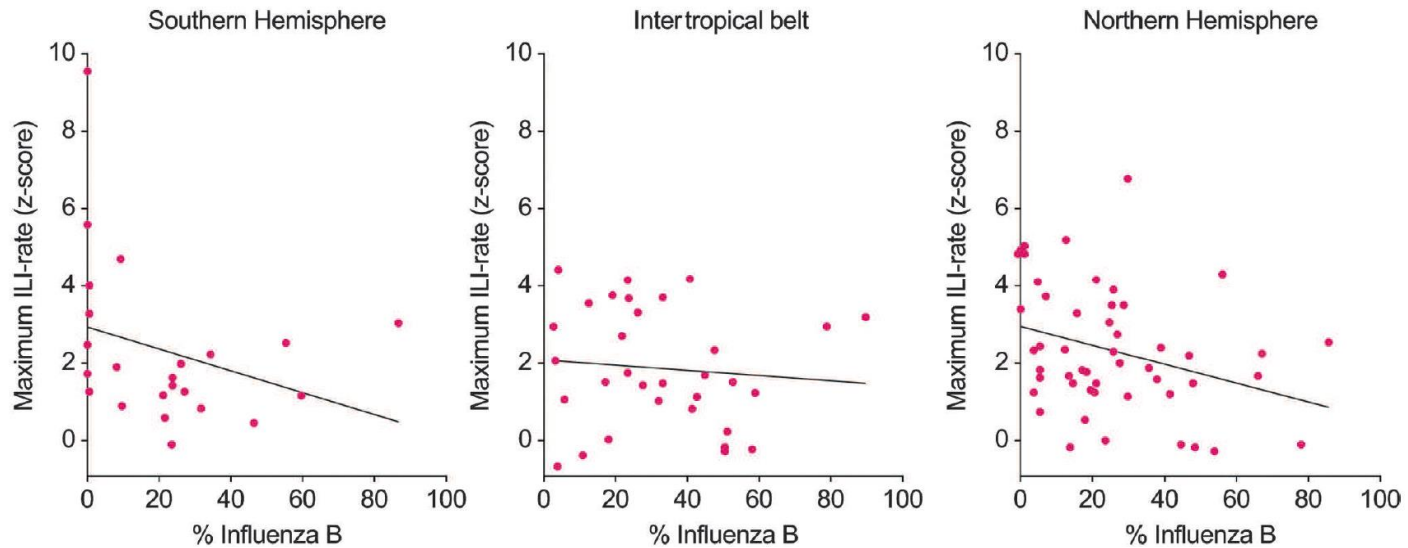
The proportion of influenza cases due to type B virus was <20% for 90 seasons, 20-50% for 82 seasons and ≥50% for 28 seasons; the median percentage was 22.6% (IQR 8.3-37.7%). Figure 2.2 shows the distribution of seasons according to the proportion of influenza cases caused by type B virus, separately 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.

Figure 2.2. 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.



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 2.3).

Figure 2.3. 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.



The proportion of influenza B cases that were characterized as $\geq 10\%$ 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%) (Supplementary Table 2.2). 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 (Supplementary Table 2.2).

Supplementary Table 2.3 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.

2.5 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 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 centres 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 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 (Supplementary Table 2.2). The frequency of vaccine mismatch has been high in recent years ($\approx 24\text{-}25\%$ 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 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.

2.5.1 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.

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