



HAL
open science

Distribution of influenza virus types by age using case-based global surveillance data from twenty-nine countries, 1999-2014

Saverio Caini, Peter Spreuwenberg, Gabriela Kuszniertz, Juan Manuel Rudi, Rhonda Owen, Kate Pennington, Sonam Wangchuk, Sonam Gyeltshen, Walquiria Aparecida Ferreira de Almeida, Cláudio Maierovitch Pessanha Henriques, et al.

► To cite this version:

Saverio Caini, Peter Spreuwenberg, Gabriela Kuszniertz, Juan Manuel Rudi, Rhonda Owen, et al.. Distribution of influenza virus types by age using case-based global surveillance data from twenty-nine countries, 1999-2014. *BMC Infectious Diseases*, 2018, 18 (1), pp.269. 10.1186/s12879-018-3181-y . pasteur-01925131

HAL Id: pasteur-01925131

<https://riip.hal.science/pasteur-01925131>

Submitted on 16 Nov 2018

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution 4.0 International License

RESEARCH ARTICLE

Open Access



Distribution of influenza virus types by age using case-based global surveillance data from twenty-nine countries, 1999-2014

Saverio Caini^{1*}, Peter Spreeuwenberg¹, Gabriela F. Kuszniarz², Juan Manuel Rudi², Rhonda Owen³, Kate Pennington³, Sonam Wangchuk⁴, Sonam Gyeltshen⁴, Walquiria Aparecida Ferreira de Almeida⁵, Cláudio Maierovitch Pessanha Henriques⁵, Richard Njouom⁶, Marie-Astrid Vernet⁶, Rodrigo A. Fasce⁷, Winston Andrade⁷, Hongjie Yu⁸, Luzhao Feng⁸, Juan Yang⁸, Zhibin Peng⁸, Jenny Lara⁹, Alfredo Bruno¹⁰, Doménica de Mora¹⁰, Celina de Lozano¹¹, Maria Zambon¹², Richard Pebody¹³, Leticia Castillo¹⁴, Alexey W. Clara¹⁵, Maria Luisa Matute¹⁶, Herman Kosasih¹⁷, Nurhayati¹⁷, Simona Puzelli¹⁸, Caterina Rizzo¹⁹, Herve A. Kadjo²⁰, Coulibaly Daouda²¹, Lyazzat Kiyanbekova²², Akerke Ospanova²³, Joshua A. Mott^{24,25}, Gideon O. Emukule²⁴, Jean-Michel Heraud²⁶, Norosoa Harline Razanajatovo²⁶, Amal Barakat²⁷, Fatima el Falaki²⁷, Sue Q. Huang²⁸, Liza Lopez²⁸, Angel Balmaseda²⁹, Brechla Moreno³⁰, Ana Paula Rodrigues³¹, Raquel Guiomar³², Li Wei Ang³³, Vernon Jian Ming Lee³⁴, Marietjie Venter^{35,36}, Cheryl Cohen^{37,38}, Selim Badur³⁹, Meral A. Ciblak³⁹, Alla Mironenko⁴⁰, Olha Holubka⁴⁰, Joseph Bresee⁴¹, Lynnette Brammer⁴¹, Phuong Vu Mai Hoang⁴², Mai Thi Quynh Le⁴², Douglas Fleming⁴³, Clotilde El-Guerche Séblain⁴⁴, François Schellevis^{1,45}, John Paget¹ and Global Influenza B Study group

Abstract

Background: Influenza disease burden varies by age and this has important public health implications. We compared the proportional distribution of different influenza virus types within age strata using surveillance data from twenty-nine countries during 1999-2014 (N=358,796 influenza cases).

Methods: For each virus, we calculated a Relative Illness Ratio (defined as the ratio of the percentage of cases in an age group to the percentage of the country population in the same age group) for young children (0-4 years), older children (5-17 years), young adults (18-39 years), older adults (40-64 years), and the elderly (65+ years). We used random-effects meta-analysis models to obtain summary relative illness ratios (sRIRs), and conducted meta-regression and sub-group analyses to explore causes of between-estimates heterogeneity.

Results: The influenza virus with highest sRIR was A(H1N1) for young children, B for older children, A(H1N1) pdm2009 for adults, and (A(H3N2) for the elderly. As expected, considering the diverse nature of the national surveillance datasets included in our analysis, between-estimates heterogeneity was high ($I^2 > 90\%$) for most sRIRs. The variations of countries' geographic, demographic and economic characteristics and the proportion of outpatients among reported influenza cases explained only part of the heterogeneity, suggesting that multiple factors were at play.

(Continued on next page)

* Correspondence: s.caini@nivel.nl

¹Netherlands Institute for Health Services Research (NIVEL), Otterstraat 118-124, 3513, CR, Utrecht, The Netherlands

Full list of author information is available at the end of the article



(Continued from previous page)

Conclusions: These results highlight the importance of presenting burden of disease estimates by age group and virus (sub)type.

Keywords: Influenza, Age distribution, Influenza A virus, H3N2 subtype, Influenza A virus, H1N1 subtype, Influenza B virus, Meta-analysis

Background

Several studies have shown that the disease burden and costs of influenza vary considerably by age group [1, 2]. Among adults, influenza is usually a self-limiting disease and the social costs are mainly due to loss of productivity and workdays and to absenteeism due to the need to care for family members [3]. At the extremes of age there is a much higher risk of complications, hospitalization and influenza-associated death [4, 5], especially among older people with underlying conditions such as chronic heart disease or diabetes [6]. In these age groups, the costs for society are mainly related to healthcare.

The influenza burden of disease varies substantially across seasons [1]. This depends on the circulating virus strains and, where vaccination campaigns are implemented, on the vaccine uptake rate as well. Overall, the disease burden of influenza is thought to be higher in seasons dominated by A(H3N2) or A(H1N1)pdm2009 influenza viruses, and lower in seasons where pre-pandemic A(H1N1) or influenza B account for the majority of cases [7, 8].

The dependency of the disease burden in a given season on circulating influenza virus (sub)types may be due to two factors that are complementary to each other. On one hand, influenza viruses may differ between one another in terms of their ability to induce a severe or complicated clinical illness, for instance by favouring bacterial co-infections, worsening of underlying conditions, or other life-threatening events. This hypothesis has been questioned by studies showing that there were only negligible differences in the age-adjusted clinical presentation and severity of the illness caused by different influenza virus types and subtypes [9–12]. On the other hand, the influenza viruses may differ between one another in how frequently they affect certain age groups. For instance, school-age children are more affected during influenza seasons dominated by pre-pandemic A(H1N1) and B virus strains than during A(H3N2)-dominated season [13].

The age distribution of influenza cases is likely to be affected by several other factors beyond the mix of circulating virus (sub)types, which may vary considerably in space and time. These include the country's demographic and geographic characteristics, the implementation of vaccination campaigns against influenza, and past epidemics that affect the immunity of the different

population age groups. In addition, how the influenza surveillance system is structured, the general perception of the severity of the season (for example, during the 2009 pandemic), and health care seeking behaviour may determine how many and what influenza cases are seen in each season and country. The availability of a global database with age-specific data enables an analysis of patterns across different settings and facilitates stronger conclusions, provided there is careful examination of how the age distribution of influenza cases fluctuated across countries and seasons, and investigating the influence of potential confounding factors.

Here, we compared the proportional distribution of different influenza virus (sub)types within age strata using the database of the Global Influenza B Study (GIBS).

Methods

Sources of data and definitions

The GIBS was launched in 2012 with the aim of increasing the scientific evidence needed to optimize the influenza prevention policies worldwide [14]. Experts from over fifty countries from all continents were invited to provide data on the weekly number of influenza cases reported to their national influenza surveillance system during recent years (ideally, from 2000 onwards) (N=948,646). Importantly, and in contrast to other global surveillance databases (e.g. Flu-Net) [15], the GIBS database also includes the age (exact age or age group) of each reported influenza case. From large countries we asked to provide data stratified at a sub-national level, if available (for brevity, we will use the term “country” to refer to a whole country or to a sub-national region of it hereinafter). Experts from participating countries were also requested to describe the main characteristics of their influenza surveillance system.

Country-specific geographic, demographic and socioeconomic information necessary for the analyses was derived from the US Central Intelligence Agency World Factbook website [16]. This includes information on the population age structure, the ageing index (defined as the number of people aged 65 years or older per hundred people aged 14 years or younger), the latitude of the population centroid (when available) or of the largest city, and the per capita gross

domestic product (GDP). In terms of latitude, a country was considered as being situated in the Northern or Southern hemisphere or in the inter-tropical belt based on the latitude of its centroid/largest city.

Statistical analysis

For brevity, we will describe the outcome variable by referring to “influenza”, and the method was applied to A(H1N1), A(H1N1)pdm2009, A(H3N2), and influenza B viruses separately; influenza cases that could not be classified in an unambiguous way to any of the above (for instance, those classified as “unsubtyped influenza A”) were not included in the analysis. The statistic used to describe the age distribution of influenza cases in each season and country is the Relative Illness Ratio (RIR) [17], which is defined as the ratio of the percentage of influenza cases in a given age group to the percentage of the general population belonging to the same age group. We considered the following age groups: 0-4 years (referred to as “young children” hereinafter), 5-17 years (“older children”), 18-39 years (“young adults”), 40-64 years (“older adults”), and 65+ years (“elderly”). A RIR was calculated for each of these five age groups in each influenza season in which there were at least 100 reported influenza cases overall; 95% confidence intervals (95% CI) were calculated by using an exact method based on the Poisson distribution [18].

When calculating a RIR, the null hypothesis is that the chance of being infected with influenza is the same for all people irrespective of their age, implying an age distribution of influenza cases perfectly equal to that of the general population and the RIR equal to 1 in each age group. Therefore, a RIR equal to 3 for influenza B in the age group 5-17 years would mean that, in that season, the proportion of influenza B cases aged 5-17 years was three times the proportion of the general population of the same age group, i.e. three times higher than expected if all age groups would be equally affected by influenza.

All RIRs obtained in the different seasons and countries were pooled into a summary Relative Illness Ratio (sRIR) (separately for each age group) through random-effects meta-analysis models by using the method by DerSimonian and Laird [19]. Comparisons between pairs of sRIRs were conducted, within each age group, through meta-regression models that included an interaction term for the virus (sub)type.

We assessed the between-estimates heterogeneity by using the I^2 statistics, which can be interpreted as the percentage of total variation that is attributable to heterogeneity [20]. We expected a high degree of heterogeneity (this was an a priori consideration), as many factors combine to determine the age distribution of influenza surveillance cases in any given

country and season. In order to assess this point in detail, we fitted meta-regression models and performed sub-group analysis to explore possible correlates of between-estimates heterogeneity, using the proportion of outpatients among reported influenza cases, the percentage of all influenza cases caused by each influenza virus (sub)type in the same or in the previous season, and the country’s latitude, ageing index and per capita GDP.

All analyses were conducted using Stata version 14 (Stata Corp, College Station, TX). We used the *metan* command (with the option *random*) to pool the country- and season-specific RIR into a sRIR, obtain forest plots, and calculate the I^2 statistics [21]. The study of between-estimates heterogeneity was conducted by using the *metareg* command [21]. Maps were prepared using freely available software (<http://mapchart.net/>).

All statistical tests were two-sided, and *p*-values of less than 0.05 were considered as statistically significant.

Comparing the age of influenza cases

The interpretation of sRIRs requires caution. The age distribution of patients infected with any given influenza virus in each season and country is affected by a number of socio-economic factors, including health-care seeking behaviour, influenza testing by age, and the way primary and hospital care are organized and delivered. The chance of seeking medical attention (and consequently being seen by an influenza surveillance system) once a person is infected is very probably not the same in all age groups across all participating countries. For instance, children and the elderly might be over-represented in both general practitioners- and (especially) hospital-based surveillance systems, as they seek medical attention more frequently when they are sick compared to adults. Therefore, we believe a “same virus, different age groups” approach (i.e. a comparison of sRIRs between people of different age groups infected with the same influenza virus) is not correct. In other words, it is not possible to answer the question “*Are young children more or less affected than adults (or another age group) by influenza and by how much?*” by inferring from the age distribution of cases reported to the influenza surveillance system.

Instead, there is no major obstacle in ranking the sRIRs for people of the same age group who are infected with different influenza virus (sub)types (“different viruses, same age group” approach). As mentioned, there are only minor differences in the clinical presentation of influenza illness produced by the different virus types within each age group [9–12]. This implies that the likelihood of seeking medical attention is likely to be similar for people of

any given age group in the same country who are infected with different influenza viruses. It is therefore possible to answer the question “Are young children more or less affected by influenza B compared to influenza A(H3N2)?”.

Results

The GIBS database that was used for the analysis included 358,768 influenza cases reported between 1999 and 2014 in twenty-nine countries (Table 1 and Fig. 1), of which four were in the Southern hemisphere, fifteen in

Table 1 Selected features of countries included in the study of age distribution of influenza cases. The Global Influenza B Study, 1999-2014

Country	Latitude ^(a)	Population (million)	Ageing index ^(b)	GDP per capita (USD)	% of outpatients ^(c)	No. influenza cases (seasons) included in the analysis:			
						A(H1N1)	A(H1N1)pdm2009	A(H3N2)	B
Southern hemisphere									
New Zealand	41.8 S	4.5	0.72	30,400	30%	2,274 (5)	3,763 (3)	4,840 (8)	2,763 (7)
Chile	35.8 S	16.6	0.48	19,100	5%	403 (1)	5,399 (3)	3,540 (3)	897 (2)
South Africa	29.0 S	53.0	0.22	11,500	0%	- (0)	432 (3)	421 (3)	527 (3)
Australia	25.8 S	23.4	0.84	43,000	50%	3,614 (6)	50,096 (4)	13,286 (9)	28,673 (12)
Inter-tropical belt									
Madagascar	19.4 S	21.3	0.08	1,000	100%	109 (1)	1,101 (2)	579 (4)	1,004 (4)
Brazil ^(d)	10.8 S	201.0	0.32	12,100	NA	- (0)	- (0)	- (0)	665 (4)
Ecuador	2.0 S	15.4	0.24	10,600	0%	- (0)	673 (2)	713 (3)	185 (1)
Indonesia	1.7 S	237.4	0.25	5,200	95%	720 (2)	- (0)	1,397 (4)	1,281 (4)
Kenya	0.4 S	44.4	0.07	1,800	40%	365 (2)	1,285 (3)	1,183 (5)	1,454 (5)
Singapore	1.2 N	5.4	0.63	62,400	100%	- (0)	2,634 (3)	1,436 (3)	1,483 (3)
Cameroon	5.7 N	22.5	0.07	2,400	90%	- (0)	- (0)	259 (2)	102 (1)
Ivory Coast	7.6 N	23.2	0.09	1,800	83%	- (0)	344 (2)	171 (1)	446 (2)
Panama	8.6 N	3.7	0.28	16,500	39%	- (0)	744 (1)	321 (2)	154 (1)
Costa Rica	10.0 N	4.6	0.30	12,900	27%	- (0)	4,069 (2)	1,026 (4)	387 (2)
Nicaragua	12.9 N	6.1	0.16	4,500	43%	- (0)	3,113 (3)	1,089 (4)	699 (3)
El Salvador	13.8 N	6.1	0.25	7,500	22%	- (0)	858 (2)	317 (2)	437 (3)
Honduras	14.8 N	8.2	0.11	4,800	56%	- (0)	656 (2)	277 (2)	- (0)
Guatemala	15.7 N	15.4	0.12	5,300	72%	263 (1)	1,681 (3)	169 (1)	316 (2)
Viet Nam	16.7 N	89.7	0.23	4,000	40%	1,218 (2)	1,368 (3)	2,781 (6)	2,982 (8)
Northern hemisphere									
Bhutan	27.4 N	0.7	0.22	2,600	97%	- (0)	510 (2)	130 (1)	101 (1)
China South ^(e)	31.1 N	969.4	0.56	9,800	100%	5,530 (5)	40,754 (2)	30,299 (7)	35,910 (8)
Morocco	32.0 N	33.2	0.24	5,500	70%	- (0)	2,076 (2)	354 (2)	- (0)
Turkey	39.0 N	76.7	0.26	15,300	100%	1,298 (2)	- (0)	- (0)	289 (1)
Portugal	39.3 N	10.4	1.17	22,900	97%	- (0)	648 (3)	2,085 (8)	733 (4)
China North ^(e)	39.5 N	370.9	0.56	9,800	100%	3,900 (5)	22,951 (3)	13,054 (7)	19,956 (7)
Italy	42.9 N	59.9	1.52	29,600	60%	- (0)	3,880 (2)	1,900 (2)	493 (1)
Kazakhstan	48.0 N	17.9	0.28	14,100	5%	- (0)	108 (1)	421 (3)	163 (1)
Ukraine	49.1 N	44.6	1.14	7,400	NA	- (0)	104 (1)	- (0)	- (0)
England ^(f)	52.3 N	53.0	0.91	37,300	57%	179 (1)	2,438 (3)	1,743 (6)	1,319 (3)
						19,873 (33)	151,685 (60)	83,791 (102)	103,419 (93)

NA: not available

^(a) Latitude of centroid (when available) or largest city

^(b) Defined as the number of people aged 65 years or older per hundred people aged 14 years or younger

^(c) Proportion of outpatients among reported influenza cases

^(d) Information on subtype of influenza A cases was not available for Brazil

^(e) Ageing index and GDP per capita of China (whole country)

^(f) Ageing index and GDP per capita of United Kingdom

Table 2 Summary Relative Illness Ratio (sRIR), lower and upper 95% confidence intervals (CI), and between-estimates heterogeneity (as measured by the I^2 statistics) for A(H1N1), A(H1N1)pdm2009, A(H3N2) and B influenza virus within each age group. The Global Influenza B Study, 1999-2014

Influenza virus	sRIR	lower CI ^(a)	upper CI ^(a)	I^2
Young children (0-4 years)				
A(H1N1)	3.57	3.00	4.14	97.5%
A(H1N1)pdm2009	2.28	2.10	2.46	97.8%
A(H3N2)	3.30	2.95	3.64	98.2%
B	2.93	2.68	3.19	97.5%
Older children (5-17 years)				
A(H1N1)	1.36	1.19	1.54	95.2%
A(H1N1)pdm2009	1.23	1.02	1.45	99.5%
A(H3N2)	1.04	0.93	1.14	97.2%
B	1.69	1.53	1.85	98.4%
Young adults (18-39 years)				
A(H1N1)	0.84	0.72	0.96	97.1%
A(H1N1)pdm2009	0.94	0.87	1.01	97.5%
A(H3N2)	0.73	0.68	0.78	96.0%
B	0.65	0.59	0.71	98.1%
Older adults (40-64 years)				
A(H1N1)	0.49	0.41	0.57	95.2%
A(H1N1)pdm2009	0.62	0.55	0.69	98.7%
A(H3N2)	0.59	0.55	0.63	93.5%
B	0.41	0.37	0.45	96.6%
Elderly (65+ years)				
A(H1N1)	0.16	0.12	0.20	73.9%
A(H1N1)pdm2009	0.27	0.24	0.31	94.7%
A(H3N2)	0.74	0.66	0.83	95.2%
B	0.38	0.33	0.43	92.4%

^(a)Because of the between-estimates heterogeneity being above 50%, the reported 95% CI very likely underestimate the real uncertainty in the data, and should be considered with caution.

affected the sRIRs among older children and young adults (sRIR was highest when ageing index >0.50). Importantly, the stratified analysis indicated that the results for countries with 70% or more reported influenza cases from outpatients mirror those for the whole database, with pre-pandemic A(H1N1), B, pandemic A(H1N1)2009 and A(H3N2) being the most frequently detected virus strain among young children, older children, young adults and the elderly, respectively. For the other variables, the pattern of sRIRs across values was inconsistent across influenza virus (sub)types, making it difficult to identify a clear pattern. The between-estimates heterogeneity remained very high (>90%) for most stratified sRIRs, irrespective of the influenza virus (sub)type and age group.

Discussion

We compared the age distribution of influenza cases across different influenza viruses relative to that of the general population using the GIBS database, which encompasses case-based influenza data from twenty-nine countries during 1999-2014. We found that each influenza virus had a relatively higher frequency in a certain age group: influenza A(H1N1) appeared to be relatively more frequent among young children, B among older children, A(H1N1)pdm2009 among young and older adults, and A(H3N2) among the elderly. These results were confirmed in the analysis limited to countries with most reported influenza cases coming from the outpatient setting. In addition, the RIR was highest for young children and lowest for older adults and the elderly whatever the virus strain examined, suggesting that the young children are the age group most affected by influenza in relation to their size in the country's population. Importantly, however, because of the possible over-representation of children and elderly people in our study sample and of the large (but expected) heterogeneity, we have restrained ourselves from, and cautioned against, interpreting the point estimates in a precise way. In addition, it is very likely that the confidence intervals underestimate the real uncertainty in the data. As a result, we have limited ourselves to ranking the sRIRs for the different influenza virus (sub)types within any given age group (i.e. following a "different viruses, same age group" approach, as explained), and to drawing more cautious conclusions regarding the results.

Many factors affect the probability of being infected with influenza and of being captured by a national influenza surveillance system in each age group. The factors include epidemiological characteristics like the number of effective contacts among susceptible people, the country's population density and mobility [22, 23], the typical family composition and the average number of people living in a household [24, 25], and the pattern of contacts between people of different age groups [26-28]. Other important factors include influenza vaccine uptake and how national surveillance systems are structured (e.g. community and/or hospital based). These many factors, and the virus strains that are circulating, interact in a complex way to produce a net effect that defines the cases that are captured by the national surveillance systems. This situation may explain the large degree of heterogeneity in our data, which persisted also when conducting the stratified analysis. Because of this, we opted to (i) analyse our data by age group (to control for some of the factors listed above, e.g. the different probability by age of being tested and therefore being reported to the national surveillance system), (ii) present patterns for each influenza virus (sub)type, and (iii) draw

Table 3 Between-estimates heterogeneity (as measured by the I^2 statistics) for summary relative illness ratio calculated for each influenza virus within each age group, and variables significantly ($p < 0.05$) correlating with them. The Global Influenza B Study, 1999-2014

Influenza virus	I^2	Variables significantly ($p < 0.05$) correlating with sRIRs					
		Latitude	% of cases accounted for in the same season	% of cases accounted for in the previous season	Ageing index	GDP per capita	% of outpatients ^(a)
Young children (0-4 years)							
A(H1N1)	97.5%						
A(H1N1)pdm2009	97.8%	✓	✓				✓
A(H3N2)	98.2%			✓		✓	✓
B	97.5%			✓		✓	✓
Older children (5-17 years)							
A(H1N1)	95.2%			✓			
A(H1N1)pdm2009	99.5%	✓	✓				✓
A(H3N2)	97.2%	✓		✓			✓
B	98.4%	✓	✓	✓		✓	✓
Young adults (18-39 years)							
A(H1N1)	97.1%			✓		✓	
A(H1N1)pdm2009	97.5%	✓		✓		✓	
A(H3N2)	96.0%	✓		✓			✓
B	98.1%	✓	✓	✓		✓	
Older adults (40-64 years)							
A(H1N1)	95.2%						
A(H1N1)pdm2009	98.7%		✓				✓
A(H3N2)	93.5%			✓		✓	
B	96.6%	✓	✓	✓		✓	
Elderly (65+ years)							
A(H1N1)	73.9%						
A(H1N1)pdm2009	94.7%	✓		✓		✓	✓
A(H3N2)	95.2%	✓		✓			✓
B	92.4%	✓					✓

GDP: gross domestic product.
^(a)Proportion of outpatients among reported influenza cases

cautious conclusions and avoid giving precise effect estimates.

The main strength of our study is the wealth of data included in the GIBS database and the large diversity of countries in terms of their geographical, socio-economic and epidemiological characteristics. This allowed us to investigate simultaneously the effect of several factors on the age distribution of influenza cases relative to that of the general population, which would not have been possible by using data from a single country (or a few countries that are very similar to one another) or for a limited number of seasons. The large heterogeneity in the data prevented us from quantifying the effect of the virus (sub)type on the age distribution of influenza cases in a precise way, and therefore, to answer in a definitive way our study question. However, the adoption of a meta-analytical approach allowed us to describe the between-estimates heterogeneity both analytically and graphically, and was especially useful in exploring the many factors that contribute to determine the age distribution of influenza cases in any given country and season.

The main limitation of the paper is its reliance on data that was not purposely collected to answer the main study question. Passive influenza surveillance systems only allow inferences regarding medically-attended influenza virus infections, and are inherently unable to capture infected people who do not seek medical care. While this does not represent a limitation for the main goals of surveillance (i.e. early warning of epidemics), the data collected within a passive surveillance system may be sub-optimal for purely research purposes. In particular, influenza surveillance systems differ across countries included in GIBS in terms of the proportion of outpatients compared to all reported influenza cases, which may represent an important source of bias for the present analysis [14]. Reassuringly, our results were confirmed when limiting the analysis to countries in which over 70% of influenza cases were outpatients (i.e. originated from a community-based surveillance system). However, meta-regression and subgroup analysis are not as powerful as an analysis which takes advantage of individual-level data, which is warranted in order to confirm or refute our findings. In general, the “same virus, different age groups” interpretation of results is not possible using passive surveillance data. To allow for a more reliable comparison of influenza burden between age groups using surveillance data, each country would need to adopt a sampling protocol for virological testing that allows the probability to sample a (suspected) influenza case in each age group to be known in advance. Despite being quite expensive, active surveillance based on participatory cohorts would allow a better understanding of influenza epidemiology by providing the opportunity to

estimate key epidemiological parameters, including the age distribution of cases and the age-specific attack rate, frequency of complications and mortality [29]. A further limitation of our study is the lack of age data for countries in North America, in particular for United States; in addition, some countries contributed data for only a limited number of seasons. The proportion of influenza patients being typed and subtyped may depend on the patient’s age: this may have introduced a bias whose magnitude, however, should have been attenuated by our decision to analyse the data separately within each age group. Finally, we could not run separate analyses by influenza B virus lineage (Yamagata vs. Victoria), as this information was available in only a small percentage of influenza B cases.

Conclusions

Global surveillance data for the start of the 21st century suggest that the relative proportion of influenza cases caused by each influenza virus (sub)type may differ by age group. Our results suggest that the mix of circulating influenza viruses is one among several factors that are at play in determining the differing age distribution of influenza surveillance cases, and highlight the importance of presenting disease burden estimates by age group and virus (sub)type.

Additional files

Additional file 1: Table S1. Number of influenza cases caused by the difference influenza viruses that were included in the analysis. The Global Influenza B Study, 1999-2014. (DOCX 24 kb)

Additional file 2: Figure S1. Forest plot of the Relative Illness Ratio for patients aged 0-4 years infected with A(H1N1) influenza virus. The Global Influenza B Study, 1999-2014. **Figure S2.** Forest plot of the Relative Illness Ratio for patients aged 5-17 years infected with A(H1N1) influenza virus. The Global Influenza B Study, 1999-2014. **Figure S3.** Forest plot of the Relative Illness Ratio for patients aged 18-39 years infected with A(H1N1) influenza virus. The Global Influenza B Study, 1999-2014. **Figure S4.** Forest plot of the Relative Illness Ratio for patients aged 40-64 years infected with A(H1N1) influenza virus. The Global Influenza B Study, 1999-2014. **Figure S5.** Forest plot of the Relative Illness Ratio for patients aged 65+ years infected with A(H1N1) influenza virus. The Global Influenza B Study, 1999-2014. (DOCX 44 kb)

Additional file 3: Table S2. Summary Relative Illness Ratio (sRIR), 95% confidence intervals (95% CI) across age groups and influenza viruses by categories of country ageing index. The Global Influenza B Study, 1999-2014. **Table S3.** Summary Relative Illness Ratio (sRIR), 95% confidence intervals (95% CI) across age groups and influenza viruses by percentage of outpatients among cases reported to the influenza surveillance system. The Global Influenza B Study, 1999-2014. **Table S4.** Summary Relative Illness Ratio (sRIR), 95% confidence intervals (95% CI) across age groups and influenza viruses by country latitude. The Global Influenza B Study, 1999-2014. **Table S5.** Summary Relative Illness Ratio (sRIR), 95% confidence intervals (95% CI) across age groups and influenza viruses by percentage of influenza cases caused by that influenza virus in the same season. The Global Influenza B Study, 1999-2014. **Table S6.** Summary Relative Illness Ratio (sRIR), 95% confidence intervals (95% CI) across age groups and influenza viruses by percentage of influenza cases caused by that influenza virus in the previous season. The Global Influenza B Study,

1999-2014. **Table S7.** Summary Relative Illness Ratio (sRIR), 95% confidence intervals (95% CI) across age groups and influenza viruses by categories of country gross domestic product (GDP) per capita. The Global Influenza B Study, 1999-2014. (DOCX 46 kb)

Abbreviations

GIBS: Global Influenza B Study; RIR: Relative Illness Ratio; sRIR: Summary Relative Illness Ratio

Acknowledgements

The Global Influenza B Study group also includes the following members: Binay Thapa⁴, Sangay Zangmo⁴, Guy Vernet⁶, Patricia Bustos⁷, Patricio Loyola⁷, Joanna Ellis¹², Antonino Bella¹⁹, Maria Rita Castrucci¹⁸, Gulzhan Muratbayeva⁴⁵, Julia Guillebaud²⁶, Laurence Randrianasolo⁴⁶, Ausenda Machado⁴⁷, Pedro Pechirra³², Jeffery Cutter³⁴, Raymond Tzer Pin Lin³⁴.
⁴⁵ Centers for Disease Control and Prevention, Central Asia Regional Office, Almaty, Kazakhstan
⁴⁶ Epidemiology Unit, Institut Pasteur of Madagascar, Antananarivo, Madagascar
⁴⁷ National Institute of Health Doutor Ricardo Jorge, Lisbon, Portugal

Funding

The Global Influenza B Study is funded by an unrestricted research grant from Sanofi Pasteur. The study sponsor had no role in study design, data collection and analysis, and had no access to the data. The study sponsor was not involved in the writing of the paper (including the main conclusion of the study) nor in the decision to submit the paper for publication.

Availability of data and materials

The database of the Global Influenza B Study was created by collecting surveillance datasets from each of the participating countries. These national datasets are owned by the participating countries, and thus cannot be shared publicly. Researchers interested in obtaining the country-specific datasets may contact the individuals listed below for further details regarding data access.

Argentina (Santa Fe Province): Gabriela Kuszniarz (labconi@yahoo.com.ar)

Australia: Kate Pennington (kate.pennington@health.gov.au)

Bhutan: Sonam Wangchuk (swangchuk@health.gov.bt)

Brazil: Cláudio Maierovitch Pessanha Henriques (claudio.henriques@saude.gov.br)

Cameroon: Guy Vernet (vernet@pasteur-yaounde.org)

Chile: Rodrigo Fasce (rfasce@ispch.cl)

China: Feng Luzhao (fenglz@chinacdc.cn)

Costa Rica: Alexey W. Clara (wclara@cdc.gov)

Ecuador: Alfredo Bruno (alfredobruno@yahoo.es)

El Salvador: Alexey W. Clara (wclara@cdc.gov)

England: Maria Zambon (maria.zambon@phe.gov.uk)

Guatemala: Alexey W. Clara (wclara@cdc.gov)

Honduras: Alexey W. Clara (wclara@cdc.gov)

Indonesia: Herman Kosasih (hermaniasrespond@gmail.com)

Italy: Caterina Rizzo (caterina.rizzo@iss.it)

Ivory Coast: Herve A. Kadjo (hervekadjo@pasteur.ci)

Kazakhstan: Gulzhan Muratbayeva (hvn2@cdc.gov)

Kenya: Joshua Mott (zud9@cdc.gov)

Madagascar: Jean-Michel Heraud (jmheraud@pasteur.mg)

Morocco: Amal Barakat (amal.barakat@yahoo.fr)

New Zealand: Sue Huang (sue.huang@esr.cri.nz)

Nicaragua: Alexey W. Clara (wclara@cdc.gov)

Panama: Alexey W. Clara (wclara@cdc.gov)

Portugal: Ana Paula Rodrigues (ana.rodrigues@insa.min-saude.pt)

Singapore: Vernon Lee (vernonljm@hotmail.com)

South Africa: Cheryl Cohen (cherylc@nicd.ac.za)

Turkey: Meral Akcay Ciblak (ciblakm@yahoo.com)

Ukraine: Alla Mironenko (miralla@ukr.net)

Viet Nam: Le Thi Quinh Mai (lom9@hotmail.com)

Authors' contributions

SC, JP, CEGS, PS and FS conceived the study. GFK, JMR, RO, KP, SW, SG, WAFdA, CMPH, RN, MAV, RAF, WA, HY, LF, JY, ZP, JL, AB, DdM, CdL, MZ, RP, LC, AWC, MLM, HK, N, SP, CR, HAK, CD, LK, AO, JAM, GOE, JMH, NHR, AB, Fef,

SQH, LL, AB, BM, APR, RG, LWA, VJML, MV, CC, SB, MAC, AM, OH, JB, LB, PVMH, MTQL, DF and members of the Global Influenza B Study group collected the data. SC and PS performed the statistical analysis. SC, JP and CEGS interpreted the results. SC and JP wrote the first draft of the manuscript. All authors critically revised the manuscript and approved its final version.

Ethics approval and consent to participate

In all participating countries, the collection and analysis of respiratory specimens was undertaken as part of routine influenza surveillance, and no specific ethical approval was required for the statistical analysis of the resulting anonymized surveillance data according to local laws and regulations.

Competing interests

Clotilde El-Guerche Séblain is an employee of Sanofi Pasteur. She was involved in the debate about the interpretation of the results but had no role in study design, data collection, data analysis, decision on what results to present, and writing of the manuscript (including the main conclusion of the study). All the other authors declare they have no conflict of interests to disclose. All the other Authors declare that they have no competing interests.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Author details

¹Netherlands Institute for Health Services Research (NIVEL), Otterstraat 118-124, 3513, CR, Utrecht, The Netherlands. ²Instituto Nacional de Enfermedades Respiratorias "Dr. Emilio Coni", Santa Fe, Argentina. ³Vaccine Preventable Diseases Surveillance Section, Health Policy Protection branch, Office for Health Protection, Department of Health, Woden, Canberra, Australia. ⁴Public Health Laboratory, Department of Public Health, Ministry of Health, Thimphu, Bhutan. ⁵Ministry of Health, Brasilia, DF, Brazil. ⁶Virology Department, Centre Pasteur of Cameroon, Yaoundé, Cameroon. ⁷Sección Virus Respiratorios, Instituto de Salud Pública de Chile, Santiago, Chile. ⁸Division of Infectious Disease, Key Laboratory of Surveillance and Early-warning on Infectious Disease, Chinese Center for Disease Control and Prevention, Beijing, China. ⁹National Influenza Center, Ministry of Health, San José, Costa Rica. ¹⁰Instituto Nacional de Investigación en Salud Pública (INSPI), Centro de Referencia Nacional de Influenza y otros Virus Respiratorios, Guayaquil, Ecuador. ¹¹National Influenza Center, Ministry of Health, San Salvador, El Salvador. ¹²Respiratory Virus Unit, Public Health England, London, Colindale, UK. ¹³Respiratory Diseases Department, Public Health England, London, Colindale, UK. ¹⁴National Influenza Center, Ministry of Health, Guatemala City, Guatemala. ¹⁵US Centers for Disease Control, Central American Region, Guatemala City, Guatemala. ¹⁶National Influenza Center, Ministry of Health, Tegucigalpa, Honduras. ¹⁷US Naval Medical Research Unit No.2, Jakarta, Indonesia. ¹⁸National Influenza Center, National Institute of Health, Rome, Italy. ¹⁹National Center for Epidemiology, Surveillance and Health Promotion, National Institute of Health, Rome, Italy. ²⁰Department of Epidemic Virus, Institut Pasteur, Abidjan, Côte d'Ivoire. ²¹Service of Epidemiological Diseases Surveillance, National Institute of Public Hygiene, Abidjan, Côte d'Ivoire. ²²National Center of Expertise, Committee of Consumer Right Protection, Astana, Kazakhstan. ²³Zonal Virology Laboratory, National Center of Expertise, Committee of Consumer Right Protection, Astana, Kazakhstan. ²⁴Centers for Disease Control and Prevention - Kenya Country Office, Nairobi, Kenya. ²⁵US Public Health Service, Rockville, Maryland, USA. ²⁶National Influenza Center, Virology Unit, Institut Pasteur of Madagascar, Antananarivo, Madagascar. ²⁷National Influenza Center, Institut National d'Hygiène, Ministry of Health, Rabat, Morocco. ²⁸Institute of Environmental Science and Research, Wellington, New Zealand. ²⁹National Influenza Center, Ministry of Health, Managua, Nicaragua. ³⁰National Influenza Center, IC Gorgas, Panama City, Panama. ³¹Department of epidemiology, National Institute of Health Doutor Ricardo Jorge, Lisbon, Portugal. ³²National Influenza Reference Laboratory, National Institute of Health Doutor Ricardo Jorge, Lisbon, Portugal. ³³Epidemiology and Disease Control Division, Ministry of Health, Singapore, Singapore. ³⁴Communicable Diseases Division, Ministry of Health, Singapore, Singapore. ³⁵Global Disease Detection, US-CDC, Pretoria, South Africa. ³⁶Zoonoses Research Center, Department of Medical Virology, University of Pretoria, Pretoria, South Africa. ³⁷Centre for Respiratory

Diseases and Meningitis (CRDM), National Institute for Communicable Diseases, Johannesburg, South Africa. ³⁸School of Public Health, Faculty of Health Science, University of the Witwatersrand, Johannesburg, South Africa. ³⁹Istanbul University, Istanbul, Turkey. ⁴⁰L.V.Gromashevsky Institute of Epidemiology and Infectious Diseases National Academy of Medical Science of Ukraine, Reiv, Ukraine. ⁴¹Epidemiology and Prevention Branch, Influenza Division, Centers for Disease Control and Prevention, Atlanta, GA, USA. ⁴²National Institute of Hygiene and Epidemiology, Hanoi, Vietnam. ⁴³Independent scientist, Birmingham, UK. ⁴⁴Sanofi Pasteur, Lyon, France. ⁴⁵Department of General Practice & Elderly Care Medicine, Amsterdam Public Health Research Institute, VU University Medical Center, Amsterdam, the Netherlands.

Received: 7 February 2017 Accepted: 30 May 2018

Published online: 08 June 2018

References

- Cromer D, van Hoek AJ, Jit M, Edmunds WJ, Fleming D, Miller E. The burden of influenza in England by age and clinical risk group: a statistical analysis to inform vaccine policy. *J Infect*. 2014;68(4):363–71.
- Cheng PY, Palekar R, Azziz-Baumgartner E, Iuliano D, Alencar AP, Bresee J, et al. Burden of influenza-associated deaths in the Americas, 2002–2008. *Influenza Other Respir Viruses*. 2015;(Suppl 1):13–21.
- Keech M, Beardsworth P. The impact of influenza on working days lost: a review of the literature. *Pharmacoeconomics*. 2008;26(11):911–24.
- Reed C, Chaves SS, Daily Kirley P, Emerson R, Aragon D, Hancock EB, et al. Estimating influenza disease burden from population-based surveillance data in the United States. *PLoS One*. 2015;10(3):e0118369.
- Nair H, Brooks WA, Katz M, Roca A, Berkley JA, Simmerman JM, et al. Global burden of respiratory infections due to seasonal influenza in young children: a systematic review and meta-analysis. *Lancet*. 2011;378(9807):1917–30.
- Quandelacy TM, Viboud C, Charu V, Lipsitch M, Goldstein E. Age- and sex-related risk factors for influenza-associated mortality in the United States between 1997–2007. *Am J Epidemiol*. 2014;179(2):156–67.
- Thompson WW, Shay DK, Weintraub E, Brammer L, Bridges CB, Cox NJ, et al. Influenza-associated hospitalizations in the United States. *JAMA*. 2004;292(11):1333–40.
- Chaves SS, Aragon D, Bennett N, Cooper T, D’Mello T, Farley M, et al. Patients hospitalized with laboratory-confirmed influenza during the 2010–2011 influenza season: exploring disease severity by virus type and subtype. *J Infect Dis*. 2013;208(8):1305–14.
- Mosnier A, Caini S, Daviaud I, Nauleau E, Bui TT, Debost E, et al. Clinical characteristics are similar across type A and B influenza virus infections. *PLoS One*. 2015;10(9):e0136186.
- Irving SA, Patel DC, Kieke BA, Donahue JG, Vandermause MF, Shay DK, et al. Comparison of clinical features and outcomes of medically attended influenza A and influenza B in a defined population over four seasons: 2004–2005 through 2007–2008. *Influenza Other Respir Viruses*. 2012;6(1):37–43.
- Cohen AL, Helffersce O, Pretorius M, Treurnicht F, Walaza S, Madhi S, et al. Epidemiology of influenza virus types and subtypes in South Africa, 2009–2012. *Emerg Infect Dis*. 2014;20(7):1162–9.
- Silvennoinen H, Huusko T, Vuorinen T, Heikkinen T. Comparative burden of influenza A/H1N1, A/H3N2 and B infections in children treated as outpatients. *Pediatr Infect Dis J*. 2015;34(10):1081–5.
- Turbelin C, Souty C, Pelat C, Hanslik T, Sarazin M, Blanchon T, et al. Age distribution of influenza like illness cases during post-pandemic A(H3N2): comparison with the twelve previous seasons. in France. *PLoS One*. 2013;8(6):e65919.
- Caini S, Huang QS, Ciblak MA, Kuszniarz G, Owen R, Wangchuk S, et al. Epidemiological and virological characteristics of influenza B: results of the Global Influenza B Study. *Influenza Other Respir Viruses*. 2005;9(Suppl 1):3–12.
- World Health Organization FluNet website. http://www.who.int/influenza/gisrs_laboratory/fluNet/en/. Accessed 26 Oct 2016.
- US Central Intelligence Agency World Factbook website. <https://www.cia.gov/library/publications/the-world-factbook/>. Accessed 26 Oct 2016.
- Lemaitre M, Carrat F. Comparative age distribution of influenza morbidity and mortality during seasonal influenza epidemics and the 2009 H1N1 pandemic. *BMC Infect Dis*. 2010;10:162.
- Armitage P, Berry G, Matthews JNS. Statistical methods in medical research: Blackwell Pub; 2002.
- DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7(3):177–88.
- Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*. 2002;21(11):1539–58.
- JAC S, editor. Meta-analysis In Stata: An Updated Collection From The Stata Journal. Texas: Stata Press; 2009.
- Fang LQ, Wang LP, de Vlas SJ, Liang S, Tong SL, Li YL, et al. Distribution and risk factors of 2009 pandemic influenza A (H1N1) in mainland China. *Am J Epidemiol*. 2012;175(9):890–7.
- Chandra S, Kassens-Noor E, Kuljanin G, Vertalka J. A geographic analysis of population density thresholds in the influenza pandemic of 1918–19. *Int J Health Geogr*. 2013;12:9.
- Liu F, Enanoria WT, Ray KJ, Coffee MP, Gordon A, Aragón TJ, et al. Effect of the one-child policy on influenza transmission in China: a stochastic transmission model. *PLoS One*. 2014;9(2):e84961.
- Brown CR, McCaw JM, Fairmaid EJ, Brown LE, Leder K, Sinclair M, et al. Factors associated with transmission of influenza-like illness in a cohort of households containing multiple children. *Influenza Other Respir Viruses*. 2015;9(5):247–54.
- Glasser J, Feng Z, Moylan A, Del Valle S, Castillo-Chavez C. Mixing in age-structured population models of infectious diseases. *Math Biosci*. 2012;235(1):1–7.
- Eames KT, Tilston NL, Brooks-Pollock E, Edmunds WJ. Measured dynamic social contact patterns explain the spread of H1N1v influenza. *PLoS Comput Biol*. 2012;8(3):e1002425.
- Towers S, Feng Z. Social contact patterns and control strategies for influenza in the elderly. *Math Biosci*. 2012;240(2):241–9.
- Razuri H, Romero C, Tinoco Y, Guezala MC, Ortiz E, Silva M, et al. Population-based active surveillance cohort studies for influenza: lessons from Peru. *Bull World Health Organ*. 2012;90(4):318–20.

Ready to submit your research? Choose BMC and benefit from:

- fast, convenient online submission
- thorough peer review by experienced researchers in your field
- rapid publication on acceptance
- support for research data, including large and complex data types
- gold Open Access which fosters wider collaboration and increased citations
- maximum visibility for your research: over 100M website views per year

At BMC, research is always in progress.

Learn more biomedcentral.com/submissions

