Global epidemiology of influenza A and B

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Chapter 8

General Discussion

In this thesis, we presented the results of a range of complementary investigations aimed at providing more insight into the main epidemiological characteristics of influenza B (in absolute terms, and in comparison with influenza A and its subtypes) and the spatio-temporal patterns of seasonal influenza A and B epidemics in different world regions. In this final chapter, we will summarize the results of the studies presented in the various chapters, and discuss the possible implications for the existing strategies for influenza prevention and control.

8.1 Epidemiological characteristics of influenza B

8.1.1 Summary of the main findings

We found that influenza B was responsible for a median 22.6% of all influenza cases in a season globally during 2000-2013, with considerable season-by-season variability. Influenza B was the dominant circulating virus type (i.e. accounted for ≥50% of all cases in a season) in approximately one out of seven seasons, and was generally associated with lower ILI rates (chapter 2). The above figures varied geographically: the median proportion of influenza cases caused by the B virus type was 17.8% in temperate countries of the Southern hemisphere, 21.4% in temperate countries of the Northern hemisphere, and 24.3% in countries of the inter-tropical belt. Influenza B viruses belonging to the Victoria and Yamagata lineages often co-circulated during the same season, although the former was more frequently the dominant lineage during the last fifteen years; a lineage-level vaccine mismatch was observed in approximately one fourth of seasons. In chapter 3, we found that influenza B differed from influenza A and its main circulating subtypes (pre-pandemic and 2009 pandemic AH1N1, and AH3N2) in terms of the age groups that were preferentially affected. By pooling relative illness ratios (which compare the age distribution of influenza cases infected with each virus (sub)type to that of the general

population) across countries and seasons, we found that influenza B has the highest relative frequency among older children (aged 5-17 years), and the lowest relative frequency among the adults (aged 18-64 years).

8.1.2 Discussion

We have shown that influenza B differs from influenza A and its main subtypes with regard to essential epidemiological characteristics. Other authors have reported previously that the proportion of influenza illness cases caused by the type B virus is largest among older children and adolescents [1-3]. Based on this differential age susceptibility to influenza A and B viruses, it could be predicted that the latter will cause a relatively larger share of influenza cases in countries characterised by an expansive population pyramid, i.e. with larger percentages of the population in the younger age groups. Typically, these demographic attributes characterize low-income countries, most of which are today situated at tropical and sub-tropical latitudes. Some evidence exists indeed that the proportion of influenza B out of all typed cases is higher in low-income, tropical countries [4-6] than in temperate climate, high-income countries in the Northern and Southern hemisphere [7-8]. Diversity in countries' demographics may therefore partially account for these differences; however, other authors could not detect any correlation between the country latitude and the average proportion of influenza B cases [9], and the question of whether there is a definite and consistent geographical gradient in the burden of influenza B remains therefore open. In order to be able to give a more accurate answer, it would be necessary to conduct a global comparison of the age-adjusted incidence and mortality rates of influenza B, rather than of its overall proportion over all influenza cases. However, this has been prevented so far by the lack of suitable epidemiological and virological data, even from high-income countries [7].

Our results also shed light on the question whether influenza illness severity differs across influenza virus (sub)types. Our results suggest that the comparatively higher burden of disease associated with influenza A(H3N2) may be due to the greater susceptibility to

this virus subtype of the elderly (i.e. those aged 65 years or older), as these represent the largest population at risk for severe and complicated influenza, at least in industrialized countries [10]. It has been hypothesized that the higher influenza-attributable mortality in seasons dominated by the influenza A(H3N2) virus [11-12] could be due to a much greater severity of the influenza illness caused by this virus subtype compared to patients infected with influenza A(H1N1) or B viruses. Some authors reported no or modest differences in illness severity across virus (sub)types after the patient's age was accounted for in the analysis [3, 13-14]. However, most of the studies that aimed at comparing the clinical presentation (i.e. frequency of signs and symptoms) and severity (i.e. hospitalization, admission to intensive care unit, and case-fatality ratio) of influenza illness caused by the different virus (sub)types failed to adjust by patients' age, despite this being the most important predictor of severe or complicated influenza.

It is unclear why the different influenza virus (sub)types differ between one another in terms of the age groups that are preferentially affected, however a hypothesis can be formulated that is based on the distinct rate of variation by virus type. In the absence of vaccination programmes, genetically stable respiratory viruses, such as those responsible for children's exanthematous diseases, mostly infect individuals in their childhood or youth, while only a small percentage of people is spared up to adulthood. However, an outstanding characteristic of influenza A viruses is their rapidly evolving nature via antigenic drift and shift. This leads to the constant introduction of new viral variants into the community, which keeps the incidence rates at relatively high levels even among older people. This appears to be especially relevant for the A(H3N2) subtype, given its particularly accelerated mutation accumulation rate in recent years compared to the A(H1N1) subtype [15-16]. Influenza B viruses also change gradually via antigenic drift and have evolved into two distinct lineages since the 1980's. Typically, however, they do not undergo antigenic shift, which limit their variability and may explain why they are relatively less frequently responsible for infections in older ages compared to the A(H3N2) subtype.

The proportion of influenza B cases that were characterized (Victoria or Yamagata lineage) was found to be low overall (17.1% in

the GIBS database), although this varied substantially across countries. We found that influenza viruses belonging to the Victoria lineage predominated in roughly two thirds of seasons in which influenza B was circulating. The scientific literature is not unanimous on this topic: generally, there appears to be a large variability in terms of which lineage is prevailing, both geographically and over time [6-8, 17]. From a public health standpoint, however, it is critical to underline that influenza B viruses of the two lineages frequently co-circulate in the same season, and that the proportion of lineage-level mismatch of the trivalent influenza vaccine (TIV) was substantial (approximately one fourth of seasons) over the past fifteen years globally. This is in good agreement with previous reports [18-20], and emphasizes how our ability to predict which lineage will prevail next season is still unsatisfactory. The quadrivalent influenza vaccine (QIV), first marketed in 2012 and containing one influenza B virus of both lineages, might be a valuable tool to cope with the limitations of the trivalent vaccine and might further reduce the burden of disease of influenza. Available evidence suggests that switching to the QIV might be recommendable from both the public health and economic viewpoint [21]. However, more research is needed as almost all of the cost-effectiveness studies so far were conducted in industrialized countries, while the benefits of the QIV over the TIV depend on a number of factors (like demographics, attack rates of influenza, vaccine efficacy and coverage, level of cross-protection, and vaccine price) some of which vary greatly across countries and seasons.

8.2 Spatio-temporal patterns of seasonal influenza A and B epidemics in the tropics

8.2.1 Summary of the main findings

In chapter 4 and 5, we showed that the temporal patterns of influenza epidemics in tropical countries show heterogeneity on multiple levels. On one side, no seasonality of influenza activity is observable in several countries in the intertropical belt (e.g.

Madagascar, Ivory Coast, and Viet Nam), where influenza viruses circulate year-round and the timing of influenza epidemics varies substantially from year to year and is, therefore, largely unpredictable. This is evidenced by the flat distribution of epidemic peaks in the different months of the year; the low amplitude of the primary peak; and the fact that epidemics driven by different virus strains are largely independent from one another in terms of timing. On a higher level, there is also a very large heterogeneity between countries. In fact, the above picture is valid for many, but not all tropical countries, as some of them show seasonal patterns that allow issuing recommendations on the optimal time to vaccinate [4, 22]. In particular, we have shown in chapter 5 that influenza epidemics occur with a clear seasonality in several countries in Latin America, including countries in Central America and Ecuador (which also show secondary epidemic peaks) and the southernmost regions of Brazil (Southeast and South).

8.2.2 Discussion

Influenza researchers have extensively investigated the environmental and social determinants of the transmission of influenza viruses to humans, in the attempt to identify the driving factors of influenza seasonality in temperate and tropical countries. It is known that weather parameters like absolute and relative humidity, air temperature, and ventilation may affect the survival of influenza viruses in the environment and their transmissibility to humans by modulating the size and deposition of respiratory droplets and the inactivation of influenza viruses contained in aerosols or on surfaces [23-25]. Consequently, researchers have tried to figure out what climatic conditions would be most effective in triggering the onset of influenza epidemics.

In temperate countries, the onset of influenza epidemics in winter is largely determined by variations in absolute and relative humidity and average daily temperature [26-27], whose annual oscillation is mainly caused by the revolution of the earth around the sun. Once the influenza season has started, several anthropogenic factors may then modulate its rapidity of spread and overall duration,

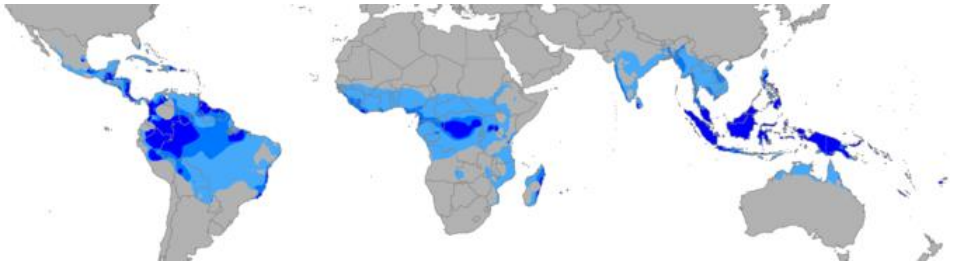
including demographic factors and social contact patterns [28], population density and mobility [29-30], school winter holidays [31], the depletion of susceptible individuals over the course of the season [32], and several others.

Annual variation of humidity and temperature may shape influenza seasonality in tropical countries as well. For instance, ILI incidence has a clear seasonal pattern in Viet Nam provinces with pronounced seasonality of absolute humidity, while no or weak regularity can be observed in provinces with weak seasonal fluctuations of absolute humidity [33]. Likewise, influenza activity was found to be negatively associated with both temperature and humidity in Kenya [34]. Moreover, the occurrence of influenza epidemics in the tropics may be linked to other climatic factors in addition to temperature and humidity, and in particular, influenza activity appears to be more likely to peak in months with intense rainfalls [35]. For instance, peaks of influenza activity in several cities in India are typically observed during the rainy monsoon season (whose exact timing varies across the country) [36], and ILI incidence was found to be associated with both humidity (negatively) and high rainfalls (positively) in French Guyana [37].

In general, the seasonality of various climatic and meteorological parameters may induce a parallel seasonality in the timing of influenza epidemics in tropical countries, although this is rarely as intense as in temperate countries. However, it is important to highlight that there is no single type of tropical climate; rather, countries of the intertropical belt differ between one another in terms of a number of weather parameters that are relevant to influenza epidemiology, like the annual and diurnal range of temperature, humidity, and rainfalls (Figure 8.1) [38-39]. This diversity may help explain the existence of seasonal patterns of influenza epidemics in some, but not all, tropical countries, and the commonly reported finding that significant differences in influenza seasonality may exist even between neighbouring countries (e.g. in countries in Latin America – see chapter 5 – and in tropical Asia [40]. In particular, many tropical countries experience no or very moderate seasonal trends in rainfalls, air temperature and humidity. Here, the environmental conditions appear to be equally favourable to the circulation of influenza viruses throughout the year, which translates,

from an epidemiological point of view, into a typical year-round influenza activity, with multiple, small-amplitude activity peaks, whose timing vary from year to year and is, therefore, largely unpredictable [41].

Figure 8.1. Types of tropical climates: tropical rainforest or equatorial (dark blue), tropical monsoon (mild blue), tropical wet and dry or savannah (light blue). Available at: http://thebritishgeographer.weebly.com/the-climate-of-tropical-regions.html [39].



8.3 Spatio-temporal patterns of seasonal influenza A and B epidemics in the WHO European region

8.3.1 Summary of the main findings

Seasonal influenza epidemics in the WHO European region occur during winter months, with the peak of influenza activity taking place in February-March in most countries. Influenza A and B viruses circulate in the same period, although B epidemics tend to peak slightly after A epidemics. Typically, seasonal influenza epidemics spread along a west-to-east gradient (and, less frequently, a south-to-north gradient) across the continent, which justifies a partition of the

WHO European region into two large influenza transmission zones: "Western" and "Eastern" (chapter 6). The above is an accurate description of today's influenza epidemiology in the WHO European region; importantly, however, we found that the picture is actually evolving over time. In fact, we showed in chapter 7 that the timing of seasonal influenza epidemics has been changing over the last two decades, as influenza activity has tended to peak progressively later in Western European countries and progressively earlier in Eastern European countries. Consequently, the distance in time between the peak of influenza activity between the Western and the Eastern extremities of the WHO European region has progressively reduced during the same period.

8.3.2 Discussion

The existence of spatial trends in the peak timing of influenza epidemics in extended and densely populated world regions has been described previously for countries outside Europe, for instance in the United States (also along east-to-west and south-to-north directions) [42-43] and in a vast tropical country like Brazil (where the epidemic wave usually travels southward) [44]. In general, it is not surprising that epidemics spread to areas that have not been touched yet, that is, towards populations with a larger proportion of susceptible individuals. Much more challenging is to understand why influenza epidemics tend to arise with some regularity in well-defined areas rather than randomly over the whole territory of a continent (or large country), and to figure out what factors contribute to determine the exact timing of their start and modulate their duration in any given season.

As far as we know, ours is the first description of a long-term trend (i.e. spanning over decades) in the timing of influenza epidemics in the entire WHO European region. In one of the very few papers published so far that have focused on the same topic, an association emerged between the number of foreign travellers visiting Iceland and the increased synchrony of influenza epidemics with United States and Europe from the early 1990's [45]. Movements of people to and from their workplaces [46-47] as well as non-routine

and leisure travel [48] may affect the rapidity of spread of influenza epidemics locally and over long distances. Hence, changes in human mobility (due to increase of local commuting, international transports and trades, and tourism) might have contributed to modify the main epidemiological features of influenza epidemics in Europe, including their timing, patterns of spatial spread, and intensity. In addition, climate changes and global warming may also be suspected to be partly responsible for the observed long-term trends of influenza epidemiology in Europe. As already mentioned, influenza epidemics in temperate climates mostly occur when temperature and humidity are at minimal levels [35]. In addition to affecting virus survival and infectivity, such meteorological conditions may impair the efficiency of the mucociliary clearance, weaken the immune response because of vitamin D deficiency, and favour social and behavioural changes (like indoor crowding) that increase the frequency of contacts effective for human-to-human transmission of influenza viruses [49-51]. Overall, it is plausible to hypothesize that climate changes in recent decades may have had an impact on the epidemiology of influenza (as well as other respiratory infectious diseases). The period covered by our investigation span over only two decades (1995-2015): we are unable to make any hypothesis on when this trend has started, nor can we predict whether this will continue in the next future. However, influenza-like illness time-series extend back to the 1960s in a few European countries [52], and reliable historic weather records may be available for up to the early 1900s (at least for main variables like temperature and rainfalls). Hence, for at least a few countries in Europe it could be possible to test the hypothesis that trends in the occurrence of viral respiratory infections (in terms of timing and intensity) were caused by similar climatic changes.

Regardless of the understanding of its causes, it is critical to figure out how the evolving epidemiology of influenza epidemics (and, in particularly, their change in their timing) may affect the organization of influenza surveillance and the implementation of annual vaccination campaigns in each country in Europe. After the 2009 pandemic, the WHO defined the influenza transmission zones (ITZs) as areas encompassing “geographically related countries or territories that have similar influenza transmission patterns” [53] (and that would benefit, therefore, of a harmonization of surveillance

activities and influenza vaccination schedules), and proposed a partition of the WHO European zone into five ITZs. We have shown in chapter 6 that the mix of circulating influenza viruses does not change substantially across Europe (despite the annual variability), and that a partition of the WHO European region into two ITZs ("Western" and "Eastern") based on differences in the timing of epidemics may be satisfactory. However, this picture might no longer be true in the course of a few years. If opposite trends in the timing of the peak would continue in the coming years, the gap in the timing of the peak influenza activity between the western and eastern halves of Europe would tend to shrink, and the two transmission zones in the WHO European region would become even more homogeneous than at present. Importantly, however, this hypothesis does not take into account potential simultaneous changes in the epidemiology of influenza in other world regions, either bordering the WHO European region (like North Africa, Middle East and Asia) or traditionally linked to Europe for cultural and commercial reasons (like North America). Hence, epidemiologists and health policy-makers need to reinforce constantly their awareness that the epidemiology of influenza is subject to continuous evolution under the pressure of multiple natural and anthropogenic factors, and that a continuous monitoring of all components of seasonal epidemics is essential so that our efforts to contain the disease burden of influenza are not frustrated.

8.4 Methodological considerations

In this thesis, we have resorted to a vast repertoire of methodological approaches and statistical methods, some of which were innovative or were used in an innovative way. Partly, this was made necessary by our plan to use influenza surveillance data for research purposes, while this type of data is usually not collected for this specific purpose. Indeed, influenza surveillance data possess some intrinsic features that need to be fully understood, and that require the use of appropriate analytical tools.

A most important point to be taken into account when analysing surveillance data is that the proportion of actual influenza cases that is captured by the national surveillance system is not constant; rather it, can vary considerably between countries seasons and population subgroups. First, neighbouring countries with comparable populations can report very different numbers of laboratory-confirmed influenza cases in the same season (chapters 5 and 6), which is unlikely to be due to differences in demographics or intensity of epidemics between countries. Rather, this finding can be explained by differences in the structure and representativeness of the national surveillance systems (e.g. community- or hospital-based, covering the whole country or limited to a few sites, etc.). Moreover, surveillance data may give an inaccurate picture of influenza epidemiology in large countries when most samples come from only a few sites (typically, the largest cities), which is still a common occurrence in some low-income tropical countries [54-55]. Second, reported influenza cases during the 2009 pandemic greatly outnumbered those reported in the previous and next influenza seasons in both the GIBS and the FluNet database. This does not appear to be justified by actual differences in influenza incidence rates between seasons [20], so it is likely the consequence of a much higher proportions of ILI/ARI patients being sampled during the 2009 pandemic than ever before or after. Third, individuals who are more vulnerable to influenza illness (i.e. more at risk of developing complications and have a poor outcome when infected) are also more likely to be sampled, especially when the surveillance system is mainly hospital-based. In contrast, adolescents and young adults less frequently develop symptoms requiring hospitalization or a visit to their general practitioner; therefore, their chance of being sampled (i.e. to be "seen" by the surveillance system) is probably much lower.

These features of influenza surveillance data required the use of analytical methods that were adequate to the research objective and capable of taking into account the multiple sources of variability listed above. In chapter 2, 4, 5 and 6, one important aim was to evaluate the proportion of influenza cases that were caused by the type B virus. As the 2009 pandemic strain was likely to be very much overrepresented in the data, it was not possible to pool data from different countries and seasons and calculate an *overall* proportion,

as this would have been severely biased towards low values. To overcome this limitation, we adopted a statistical approach whereby the unit of analysis was the country-season (i.e. July 1st to June 30th in Northern hemisphere countries, or January 1st to December 31st in tropical and Southern hemisphere countries), and calculated the *median* proportion of influenza cases due to the type B virus. Likewise, for the study of age distribution of influenza cases by virus type and subtype (chapter 3), we opted to resort to meta-analytical techniques in order to deal with all of the heterogeneity in the data, and explained that the interpretation of the data should be limited to the "different viruses, same age group" approach because of the differential sampling intensity by age group.

In chapters 5 and 6, we used the software EPIPOI to investigate the temporal characteristics of seasonal influenza epidemics [56]. EPIPOI decomposes time-series into annual, semi-annual and quarterly sinusoids by means of Fourier decomposition, and extracts "typical" values of the timing and amplitude of primary and secondary peaks. In tropical countries, this approach is especially advantageous in that it allows to assess whether influenza epidemics show any seasonality, how strong this is (i.e. what percentage of annual influenza cases occur during the main epidemic waves), and whether this varies geographically (for instance, whether there is a given latitude beyond which seasonality disappears). The identification of a typical timing of influenza epidemics has considerable importance from a public health standpoint as it allows making inferences on the optimal time for the implementation of national immunization campaigns, and helps understand whether different areas within large countries may benefit of different vaccination schedules (e.g. southern- and northernmost regions of Brazil, see chapter 5).

The extraction of "typical" parameters of seasonal influenza epidemics is important fro public health purposes, however it implicitly assumes that the data are stationary, i.e. that the timing of the primary epidemic peak in each season oscillates around an "average" value that is assumed to be stable over time [56]. We challenged this assumption in chapter 6, where time trends in the timing of the epidemic peak in each season were analysed against time for countries in the WHO European region. This approach led to

the identification of a long-term temporal trend in the timing of the peak, which had never been reported previously for such an extended world area.

The choice of a cluster analysis approach for the identification of influenza transmission zones in the WHO European region was mainly driven by their definition. In fact, a clustering algorithms typically produces a partition of countries into groups that are internally (i.e. within group) homogeneous, and externally (i.e. between groups) heterogeneous, in terms of influenza transmission patterns. In addition, each single clustering algorithm identifies subgroups of countries that are mutually exclusive and collectively exhaustive, which is consistent with the definition of ITZ given by the WHO. However, clustering is a largely exploratory technique whose output depends on the specific algorithm and the set of parameters inputted in the model. As there was no clear guidance or *a priori* reason to choose any specific algorithm, we opted to fit several different models and present averaged results. Although the results that were obtained were sensible and reasonably in line with what was known earlier (i.e. differences in timing between Eastern and Western Europe, with no differences in terms of circulating viruses), this innovative approach needs to be implemented in other world regions in order to better clarify its advantages and limitations.

8.5 Implications for the strategies of influenza prevention and control

8.5.1 Implications for influenza vaccination campaigns

Our findings on the main epidemiological characteristics of influenza B have important implications for the implementation of influenza vaccination campaigns worldwide. In particular, the implications concern both the type of influenza vaccine to be used, and the optimal timing for its administration.

We observed a lineage-level mismatch between the influenza B virus contained in the vaccine and the dominating B virus in

approximately 25% of seasons globally. A recent review found that switching from the trivalent (TIV) to the quadrivalent (QIV) influenza vaccine would be a valuable intervention from both the public health and economic viewpoint [21]. The authors pointed out that several factors affect the cost-benefits balance of adopting the QIV, including epidemiological parameters like the distribution of incidence between influenza A and influenza B, the level of match of TIV with the circulating B lineage, and the risk of influenza-associated death by virus type. Some of these parameters may vary across countries and, in particular, may differ substantially between temperate- and tropical-climate countries, which implies that findings from studies conducted in the former cannot be extrapolated easily to the latter. For instance, we have shown in chapter 2 that the proportion of influenza cases caused by the B virus type is higher in countries in the intertropical belt (median 24.3%) than in the Northern (median 21.4%) and Southern (median 17.8%) hemispheres. However, based on our findings in chapter 2 and 3, this excess in influenza B cases in low-income countries occur mainly among adolescents and young adults, who develop complications (including influenza-associated hospitalization and death) quite rarely and are unlikely to be vaccinated where resources are limited. Critically, the authors of the review emphasised that most evidence to date originates from studies carried out in high-income countries, while much fewer studies were conducted in low-income countries. Recently, some evidence has emerged that QIV may be a cost-effective tool in tropical countries of Latin America [57], although the quantitative estimates were not precise due to lack of local data. Overall, however, the evidence in favour of, or against, the adoption of QIV in low-income countries is still insufficient, and cost-effectiveness studies conducted in these countries are warranted.

Other factors that need to take into consideration in cost-effectiveness studies are the level of cross-protection of TIV against the mismatched B lineage, and the difference in price per dose of QIV compared to QIV [21]. In particular, the relatively higher price of QIV can be a barrier against its adoption in low-income countries. Recently, other authors have proposed an optimized strategy for the composition of the TIV, whereby the influenza B lineage to be included each year is determined by the number of years since

vaccination with either lineage, whether there has been antigenic drift in either lineage in recent years, and by the serological assessment of residual protections in the population (if available) [58]. The authors showed that this strategy would be more effective than the current practice for the composition of the TIV, and might be an economically affordable option for low-income countries.

Our findings have also implications for the determination of the optimal timing to administer the vaccine. We revealed that the timing of seasonal influenza epidemics has been changing in countries of the WHO European region. The annual change in the timing of the epidemic peak is nearly irrelevant in practical terms (slightly more than 2 days per year for countries situated at more extreme longitudes); however, the time displacement accumulated in the course of 20 years (≈3 weeks, assuming that the trend remains constant over time) is large enough to require a check that the timing of annual vaccination campaigns is still optimal in relation to the time to develop immunity. Public health implications of our findings are even larger for tropical countries in Latin America, Africa and Asia. The considerable variability of seasonal patterns of influenza epidemics in those world areas (even between neighbouring countries, see chapters 4 and 5) requires that recommendations on the optimal time to vaccinate must be issued separately for each country based on local epidemiological data. In particular, attention must be paid to large tropical and subtropical countries, whose provinces may frequently differ in terms of influenza seasonality (e.g. in India [36, 59], China [60], Mexico [61]; see also our findings for Brazil in chapter 5) and require therefore distinct recommendations.

8.5.2 Implications for influenza surveillance systems

In this thesis, we took advantage of existing influenza surveillance data and aimed to produce scientific evidence that would help optimize the strategies for influenza prevention and control globally. In doing so, we came across a number of important gaps in data availability and quality, which can be interpreted as shortcomings of the surveillance systems that generated those data.

Filling those gaps can lead to a further enhancement of the possibility to use surveillance data for research purposes.

The global capacity for sentinel and laboratory surveillance of influenza has improved greatly in recent years, and the WHO's Global Influenza Surveillance and Response System (GISRS) currently includes over 152 institutions in 113 countries worldwide [62-63]. In particular, the global network of influenza surveillance has extended to areas that were virtually lacking it until recently [54-55]. However, the number of respiratory specimens collected, and of laboratory-confirmed influenza cases reported each year, is still very low (in comparison with the total population) in several countries, suggesting that the surveillance system is probably not covering yet the whole country territory (rather, it is limited to a small number of sentinel sites and hospitals in the country). This was observed for several low-income countries in the tropics (chapters 2 and 4) and for some areas within the WHO European region as well, like the Balkan peninsula and Central Asia (chapter 6 and 7). As mentioned in the previous paragraph, this is a particularly severe limitation for large countries extending over several climatic zones. Global representativeness of influenza surveillance is key to a clear understanding of influenza epidemiology and an effective influenza preparedness and response; therefore, the further expansion and strengthening of the GISRS network is an important public health priority for next years.

According to the WHO recommendations, human influenza surveillance should comprise two components: influenza-like illness (ILI) surveillance, and severe acute respiratory infections (SARI) surveillance. An important limitation in data availability that we faced in our research project was the lack of information on ILI incidence rates, both in the FluNet database and for several countries participating to the GIBS (chapter 2). In addition, it is worth noting how the influenza surveillance system appears to be severely unbalanced towards SARI surveillance for some countries in the GIBS database, with the large majority (up to ≥ 90%) of respiratory specimens being collected in hospital-based settings (chapter 3). Critically, information on ILI incidence rates is of primary importance in studies that aim at estimating the burden of disease of influenza and at quantifying the health and economic impact of alternative interventions strategies. It is therefore recommended that this

information is collected systematically and made freely available to researchers, as is currently the case for virological surveillance data through the FluNet database. In addition, it would be desirable to include information on the surveillance system and on the sampling strategy that is adopted (e.g. whether or not all ILI/ARI patients have the same chance of being sampled regardless of their age, vaccination status, clinical severity, and presence of underlying conditions), as this information would be important for the correct interpretation of the data.

Finally, we recommend that the laboratories' capacity to determine the lineage of influenza B-positive samples be enhanced globally. In fact, the proportion of influenza B positive specimens that were characterized was low (17% in the GIBS database, chapter 2; and 12% in the FluNet database for countries in the WHO European region, chapter 6) and, in particular, much lower than the proportion of influenza A cases being subtyped (65% and 72% in the GIBS and the FluNet database, respectively). This limited the generalizability of the findings regarding the circulation of the two lineages and the frequency of lineage-level mismatch for the trivalent influenza vaccine (chapter 2), and impeded to extend the study of the age distribution to the comparison of Victoria vs. Yamagata influenza patients (chapter 3).

8.6 Future directions for research

Typically, research starts with questions and ends with questions, and this thesis was no exception. In addition to produce findings immediately translatable into public health recommendations, the investigations we conducted on the global epidemiology of influenza also highlighted some important knowledge gaps, and generated additional hypotheses that deserve to be addressed through dedicated studies.

An important goal to be pursued in the coming years is a better quantification of the burden of disease of influenza B, overall and in comparison to influenza A and its main subtypes. We now have a detailed knowledge of the proportion of influenza cases that are

caused by influenza B, and how this varies geographically and over time (see chapters 2, 5 and 6, and reports by other authors [9]). With the exception of paediatric populations, however, we still have very limited information on influenza B-associated GP visits, work and school absenteeism, use of antibiotics and antivirals, and hospitalization and mortality rates, which all contribute to determine the burden of disease and societal costs of influenza B [7, 64]. Studies aimed at estimating those health and economic indexes, and combining them into more precise of influenza B disease burden are warranted, in order to feed more accurate cost-effectiveness studies and increase the value-for-money of public health interventions.

We described how influenza A and B differ in terms of important epidemiological characteristics, but we were relatively unable to conduct similar investigations to compare Victoria and Yamagata lineages. As mentioned above, this was mainly due to the very low proportion of influenza B cases being characterized in the database we used. Some authors have reported differences in age susceptibility, geographic distribution and seasonality patterns between the two lineages in single countries [65-68], however a global study is still lacking.

Our finding of a long-term temporal trend in the timing of the influenza epidemic peak in the WHO European region is novel, and claims for a number of follow-up investigations, which we have already briefly examined in the Discussion of chapter 7. We suggest that two major research lines deserve to be pursued. On one hand, it is important to keep monitoring the observed trend, explore whether (and how) other world areas are affected (e.g. subtropical and tropical areas of America, Africa and Asia), and assess whether other public health-relevant features of influenza epidemics (e.g. their timing of onset and duration) have also been changing in recent decades. On the other hand, we believe it indispensable to scrutinize what might be the underlying causes of the observed phenomena: in addition to help make predictions and contribute to improve the prevention of influenza, these investigations might greatly advance our knowledge of the biological interactions between the influenza viruses, the environment, and human populations.

Finally, we would like to propose that the model of scientific collaboration that has led to the establishment of the Global Influenza

B Study be replicated in future years to address new research topics. In fact, with the exception of influenza and the respiratory syncytial virus, we still have very limited knowledge of the global epidemiology and burden of disease of most other viral agents of respiratory infections, like parainfluenza viruses, coronaviruses, and human metapneumovirus [69-70]. This scarcity of data represents a decisive impediment to the development and implementation of public health interventions aimed at reducing further the mortality from acute respiratory infections, which is especially high among children and in developing countries [69-70].

8.7 Conclusions

In summary, we found that influenza B accounts for a substantial proportion of influenza cases globally, and that influenza A and B differ in terms of important epidemiological characteristics. We also found that several countries in the tropics show clear seasonality in the timing of influenza epidemics, which permits to issue recommendations for the organization of vaccination campaigns, and that that the timing of influenza epidemics has been changing in the WHO European region over the last twenty years. While more research is needed, our findings have immediate, important implications for influenza surveillance and prevention policies globally.

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