Global epidemiology of influenza A and B

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Chapter 9

Summary

The primary objectives of influenza surveillance are to issue early warnings that enable health systems, governments and supranational organizations to respond to epidemics in the most timely and appropriate manner; and to perform a continuous monitoring of circulating viruses, in order to promptly detect novel strains and update the vaccine composition accordingly. The global capacity for influenza surveillance has been strengthened and extended to an increasing number of countries in recent years, in particular following the 2009 pandemic. This greatly enhanced surveillance activity has produced a growing mass of epidemiological and virological data, unprecedented in terms of quantity, quality and geographic coverage.

In this thesis, we took advantage of the growing availability of influenza surveillance data and explored different aspects of global epidemiology of influenza. The overall aim of this thesis was to produce knowledge that may help optimize the strategies of prevention and control of influenza (in particular, vaccination campaigns) where they are already in place, and support their implementation in countries where they are still lacking or inadequate. The main research questions were the study of the epidemiological characteristics of influenza A and B; the description of spatiotemporal patterns of seasonal influenza A and B epidemics in different world regions; and the study of the link between the results of the above investigations and the strategies for influenza prevention and control.

We used two data sources to answer the research questions addressed in this thesis: the WHO FluNet database and Global Influenza B Study (GIBS). The WHO FluNet database contains virological surveillance data from the majority of world countries, entered by National Influenza Centres and other influenza reference laboratories that participate in the Global Influenza Surveillance and Response System (GISRS). The GISRS network was established in 1952 and is the oldest existing global surveillance network; the FluNet tool has been in operation for the last 20 years. The GIBS database encompasses influenza surveillance data from thirty countries (accounting for over one third of world’s population) for the period 2000-2015, and includes influenza-like illness incidence rates, the weekly number of processed respiratory specimens, and the weekly number of influenza-positive specimens by patient's age and by virus type, subtype, and lineage. In addition, information is available on characteristics of the influenza surveillance system from which the provided data originated.

Up until a few years ago, most research on influenza targeted type A viruses, while type B influenza was comparatively neglected. Therefore, a main goal of this thesis was to better characterize the epidemiology of influenza B, in particular by comparing its metrics with those of influenza A and its subtypes. In chapter 2, we showed that influenza B was responsible for a median 22.6% of all influenza cases in a season globally (higher in countries of the inter-tropical belt, and lower in temperate climate countries of the Northern and Southern hemispheres), and was the dominant circulating virus type in approximately one out of seven seasons. The percentage of influenza B cases that were characterized (Victoria or Yamagata lineage) was found to be low (<20%) overall, although this varied substantially across countries. Influenza B viruses belonging to the Victoria and Yamagata lineages often co-circulated during the same season, and a lineage-level vaccine mismatch was observed in approximately one fourth of seasons (chapter 2). In chapter 3, we showed that influenza B differed from influenza A and its main circulating subtypes in terms of the age groups that were preferentially affected, as it had the highest relative frequency among older children (5-17 years), and the lowest relative frequency among the adults.

Another focus of the thesis is the analysis of seasonality, which is especially important for the timing of prevention and control measures. The recent rise in the availability of influenza surveillance data allows studying the spatiotemporal patterns of influenza epidemics in nearly all world areas, which has important implications for the determination of the optimal timing to vaccinate in different regions. In this thesis, we aimed to study the spatiotemporal patterns of influenza epidemics globally and discuss implications for influenza vaccination campaigns, and focused in particular on tropical countries and Europe.

We found that no seasonality of influenza activity is observable in several countries in the tropics (chapter 4 and 5): influenza viruses circulate year-round and the timing of influenza epidemics varies substantially from year to year and is, therefore, largely unpredictable. However, some other tropical countries show seasonal patterns that allow issuing recommendations on the optimal time to vaccinate. Influenza researchers have demonstrated since long that weather parameters like humidity, temperature, and rainfalls may affect the survival of influenza viruses in the environment and their transmissibility to humans and contribute to determine the timing of influenza epidemics. Importantly, however, there is no single type of tropical climate; rather, tropical countries differ largely between one another in terms of weather parameters that are relevant to influenza epidemiology. 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. The considerable variability of seasonal patterns of influenza epidemics in the tropics 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 and require therefore distinct recommendations.

Influenza epidemiology in Europe has been the subject of extensive research, yet the availability of high-quality surveillance data from a growing number of countries makes it possible to conduct, much more than in the past, in-depth investigations of how influenza viruses spread across Europe. Also, influenza time-series are today available for up to twenty consecutive years for several European countries, which allowed assessing whether changes have occurred over time in the main characteristics of influenza epidemics in Europe. In this thesis, we aimed to describe the temporal patterns of spread and geographic diversity (chapter 6), and changes over time of influenza epidemics (chapter 7) in Europe. We found that the typical timing of the peak of influenza activity is in February-March in most countries, and that 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 Europe into two large influenza transmission zones: “Western” and “Eastern”. The above is an accurate description of today’s influenza epidemiology in Europe; importantly, however, we found that the picture is evolving over time. In fact, we found that the timing of seasonal influenza epidemics has been changing over the last two decades, with influenza activity tending 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 Europe has progressively shortened during the same period. Climate changes and increased human mobility may contribute to explaining the existence of spatial trends in the peak timing of influenza epidemics in Europe and changes in the timing of epidemics in recent decades. Regardless of the understanding of its causes, however, it is critical to figure out how the evolving epidemiology of influenza epidemics may affect the organization of influenza surveillance and the implementation of annual vaccination campaigns in each country in Europe. The annual change in the timing of the epidemic peak is nearly irrelevant in practical terms; however, the time displacement accumulated in the course of 20 years (≈3 weeks) 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. In general terms, 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.

The global capacity for sentinel and laboratory surveillance of influenza has improved greatly in recent years, yet in the course of our investigations we found that a number of important gaps in data availability and quality still persist. 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, including low-income countries in the tropics and some areas within the WHO European region, like the Balkan peninsula and Central Asia. 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 influenza surveillance global network is an important public health priority for next years. An additional important limitation in data availability that we faced in our research project was the lack of information on influenza-like illness incidence rates in most countries we included in our studies. This information should be collected systematically and made freely available to researchers, as it is of primary importance for the estimation of the burden of disease of influenza and for the quantification of the health and economic impact of alternative interventions strategies.

The investigations we conducted on the global epidemiology of influenza generated additional hypotheses that would 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. A global study comparing the differences between the influenza B Victoria and Yamagata lineages in terms of age susceptibility, geographic distribution and seasonality patterns is still lacking. Our finding of a long-term temporal trend in the timing of the influenza epidemic peak in Europe is novel, and we believe it important to scrutinize what might be its underlying causes, in order to advance our knowledge of the biological interactions between influenza viruses, the environment, and human populations. Moreover, the model of scientific collaboration that has led to the establishment of the Global Influenza B Study could 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 and it would be important to establish a new global network (similar to GIBS) which looks at all respiratory viruses, including RSV. The current 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.

In conclusion, we found that influenza B causes a substantial proportion of influenza cases globally each year, and that influenza A and B differ in terms of important epidemiological characteristics. With regard to the timing of influenza epidemics, we found that several countries in the tropics show clear seasonality that permits to issue recommendations for the implementation of vaccination campaigns, and that the timing of influenza epidemics in Europe has been changing over the last twenty years. Our findings have considerable implications for influenza surveillance and prevention policies globally.