The need for interdisciplinary studies of historic pandemics

1. Summary

In May 2010, biomedical and social scientists from 12 countries on 4 continents convened in Copenhagen, Denmark to discuss the epidemiological, social, and public health consequences of 5 diverse pandemics, the 1889 “Russian,” the 1918 “Spanish,” the 1957 “Asian,” the 1968 “Hong-Kong” and the 2009 pandemics. During the “Historical Influenza Pandemics: Lessons Learned” Conference, perspectives were provided by virologists, clinicians, epidemiologists, evolutionary biologists, historians, sociologists, and geographers. This diversity highlighted the advantages of a multidisciplinary approach to the study of historical pandemics.

This supplement to Vaccine includes 11 original contributions that focus on a broad range of pandemic influenza research issues, including the age-specific burden of influenza in pandemic and post-pandemic periods, transmission dynamics and mitigation strategies, co-infections, and clinical protocols [1–11]. In this editorial, we discuss the utility of these quantitative influenza studies in helping to guide public health responses to current and future pandemics in geographically diverse populations.

The 2009 H1N1 pandemic sharpened our focus on past pandemics: How can we use lessons learned from historic pandemics to better understand the epidemiology of the 2009 pandemic virus and guide the public health response to recurrent waves? Historic pandemics have repeatedly demonstrated that emerging viruses follow a pattern of returning in several recrudescent waves, in some cases with the heaviest mortality burden occurring several years after the virus first emerged. Important points that emerge from a historical perspective include:

1. Mortality impact will occur over several years, and profound geographical differences in first wave severity are not unusual; therefore, we are still in a pandemic period (2011), and deaths are currently accumulating disproportionately in younger populations;
2. The unusually young mean age of 2009 pandemic deaths will likely change as the young population gains immunity, so that a “seasonal” age pattern of mostly senior deaths is to be expected within a decade, sooner, if other influenza virus subtypes become predominant;
3. In terms of life-years lost, the 2009 pandemic will likely approach the impact of the 1968 pandemic, more severe than an average seasonal influenza epidemic. Also, to fully comprehend the societal impact of a pandemic, the burden of severe illness, intensive care, and the negative impact on the economy must be considered.

2. Convening an unusually diverse group of scientists

Influenza pandemics, though rare, directly and indirectly affect the entire world. In May 2010, 60 biomedical and social scientists from Australia, Denmark, France, Germany, Iceland, Italy, Mexico, Norway, Spain, Sweden, the United Kingdom, and the United States convened in Copenhagen to discuss research methodologies and findings from data associated with historic influenza pandemics. Participants included historians, sociologists, anthropologists, demographers, mathematicians, biostatisticians, epidemiologists, public health officials, virologists, and evolutionary biologists. Using data from diverse sources, including those from periods before influenza’s viral etiology was known, this diverse group worked to connect disparate sources of data in order to explain puzzling findings from pandemics of the past. In so doing, the group also shed light on contemporary public health questions, including the response to the 2009 A/H1N1 pandemic.

3. Archaeo-epidemiology: from anecdote to scientific inquiry

We use the term “archaeo-epidemiology” to describe the investigation of archival data for multidisciplinary influenza research. Studies of mortality patterns that occur during pandemics can reveal a great deal, even in the absence of laboratory diagnoses, but such studies require detailed historical mortality data. Specifically, mortality studies can help characterize the health burden and transmission dynamics of pandemic influenza across populations and elucidate the impact of socio-economic factors, baseline health, and access to medical and non-medical intervention measures.

Recent archaeo-epidemiology studies have identified “signature epidemiological features” of pandemic mortality during the 1889, 1918, 1957 and 1968 pandemics [12,13]. These studies rely on the availability of historical monthly (or weekly) mortality time series data stratified by age, gender, and cause of death. These are usually found in regions that have a long tradition of collecting health statistics, such as Europe and North America (114; see also [2,7,9,11] in this issue). In some cases, the hunt for such data took researchers to local archives, where they found tabulated public health records from 100 to 150 years ago; in other cases, researchers exploited the increasing availability of historic documents on the Internet [11,14]. In Iceland, innovative methods to link individuals who died in 1918 to modern genomic data from their descendants allowed an analysis of genetic risk factors for pandemic-related mortality [15], and Magnús Gottfreðsson (personal communication).
In countries where health statistics were not routinely collected, the generation of useful datasets required researchers to collate cemetery, church, or hospital records, as illustrated by the studies from Peru [3], Brazil [1], Canada [10], and Italy [8] in this issue. Some historical records of presumed influenza pandemics date as far back as the 14th century [16]; however, limited data preclude further qualitative analysis. While imperfect, such historic data from cemeteries in Latin America have already provided profound insights into the likely reasons for the unusual age pattern of the 1918 pandemic (described in detail below).

4. The 1889 pandemic: the earliest pandemic that has been quantitatively studied

Previous studies of influenza deaths in London during the 1889 pandemic have demonstrated that the temporal pattern of mortality can be complex; the first global wave was relatively mild, but two subsequent and more severe waves during 1890–1892 caused the majority of pandemic deaths [13,17].

Two related contributions in this supplement further characterize the 1889 influenza pandemic [5,11]. Valtat et al. describe the age-specific morbidity and mortality impact of this pandemic using a collection of surveys and city-level data collected in various European cities [11]. They find that clinical attack rates were as high as 60% in age groups ranging from 1 to 60 years, while most influenza deaths were found in older adults. Unfortunately, the lack of detailed age- and cause-specific mortality time series data from this period hinders further understanding of the age patterns of deaths associated with this pandemic. Honigsbaum offers a different perspective, describing efforts to develop a national surveillance system to monitor the spatio-temporal progression of the 1889 pandemic in England, and discusses issues arising from the government’s attempts to implement control measures [5].

5. The 1918 pandemic: extreme global mortality, geographical heterogeneity, and unusual age pattern of death

1918: global death toll, signature age pattern, and geographic variation. 1918 saw the onset of the most severe influenza pandemic in history, with an estimated global death toll of ~1–2% of the global population during 1918–1920 [18]. The unusual mortality age pattern during this pandemic—where young adults aged 20–40 were at extreme risk—has always been a frightening “signature” in our collective pandemic memory [12,18]. Recent U.S. and European studies have further elaborated on the unusual age signature of this pandemic and have demonstrated another unusual feature: adults aged 45 years and older in the US [14] and Denmark [19] were almost completely spared. This pattern is the polar opposite of that seen in seasonal epidemics, where the elderly bear most of mortality burden. The timing of deaths varied by region, however. Chowell et al. show that most pandemic deaths occurred during the 1920 recrudescence wave in Peru, demonstrating that not all countries experienced catastrophic mortality early in the pandemic period [20]. This finding highlights geographical heterogeneity and supports the use of mortality data from the entire 1918–1920 period to capture the pandemic’s full mortality impact.

Sparing of seniors did not occur everywhere. At the meeting, recent and previously unpublished studies illustrated how elderly populations were not spared in the 1918 pandemic in at least three Latin American locations—Mexico [20], Lima, Peru [3] and Florianopolis, Brazil [1]. Although these results may seem perplexing at first glance, they suggest geographical heterogeneity in age-related mortality risk and shed light on the underlying reasons for sparing of elderly in 1918 in the US and Europe. The “recycling” hypothesis states that the elderly were spared in 1918 because of their exposure to an H1-like virus in childhood, which places the time of the original exposure before 1870 [14,21]. Remote populations with limited transportation networks before 1870 would not have had the same degree of exposure to previous influenza epidemics as larger metropolitan areas, so the seniors living in these areas in 1918 would have been less likely to acquire immunity to influenza. Historical isolation also may explain the high level of mortality among adults in remote Alaskan villages in 1918 [22]. Thus, the Latin American age patterns reported in this issue and elsewhere [1,3,20] support the recycling virus hypothesis to explain the unusual 1918 pandemic age pattern.

1918 pandemic signature age pattern slowly reverted to seasonal pattern. In this issue, Saglanmak et al. quantify influenza-related mortality age patterns in Copenhagen in the decades following the 1918 pandemic [9]. They show that within two years, the 1918 pandemic age pattern began to revert to that usually seen in inter-pandemic periods: younger people were no longer at extreme risk of dying, and seniors, who were initially spared, began to fall ill and die from influenza at higher rates. By the severe epidemic of the season 1928–1929, the mortality pattern had reverted completely, so that most deaths were among people older than 65 years of age [9].

Geographical variability in 1918 pandemic mortality: the tuberculosis link. Another interesting 1918 pandemic feature was the ~40-fold difference in national mortality impact observed globally, ranging from death of 0.2%–0.4% of populations in Scandinavian countries to ~8% in some provinces in India [18]. Such geographical variations are also exemplified by comparing the Italian, Peruvian, and Danish experiences derived from detailed data and described in this issue [2,3,8] or by perusing a table of world country experiences from cruder data [18]. What accounts for this high level of variability?

Demographer Andrew Noymier suggests in this issue a hypothesis linking influenza and tuberculosis co-morbidity, which may explain global heterogeneity in influenza-related mortality as an issue of heterogeneity in underlying co-morbidity patterns [7]. By considering the age and gender patterns of tuberculosis mortality in the decades before and after the 1918 pandemic in the US, Noymier argues that a disproporionately large number of people with tuberculosis died in 1918. These deaths would have occurred over the following decade had they not been harvested prematurely by the pandemic. In addition, the 1918 pandemic could have mitigated the global tuberculosis epidemic in the post-pandemic decades, by effectively removing infectious individuals from the population and thereby reducing tuberculosis transmission rates. However, data are sparse, and additional detailed mortality studies from other countries are needed to confirm this hypothesis.

An alternative explanation involving biases in the estimation of mortality burden is proposed by Andreasen et al. and could potentially explain the large reported geographical variation in 1918 pandemic mortality [2]. Annual all-cause mortality data is often the only data available from this period but remains a crude and non-specific indicator of influenza-related mortality. Using highly detailed mortality data from a historic surveillance system in Copenhagen, called “Ugeisterne,” the authors argue that use of annual data may result in over or under-estimation of excess mortality, due to high and fluctuating “background” annual mortality rates in infants and seniors stemming from measles and pertussis epidemics, as well as...
fluctuations in chronic disease mortality unrelated to influenza [2].

Mathematical models of 1918 transmissibility: relevance to public health decision making. Mathematical models play an increasing role in public health decision-making for pandemic influenza and other emerging infectious diseases. Models provide a quantitative framework to evaluate the transmission potential of novel pathogens, consider a variety of epidemic scenarios, and select appropriate public health interventions. A key parameter in such models is the reproduction number, which measures the number of secondary cases per primary infection. In this issue, mathematical modeling and statistical tools are used to analyze the transmission dynamics and impact of the 1918 influenza pandemic waves in Florence, Italy, Newfoundland, Canada, and Lima, Peru [3,8,10]. Using a mean generation interval of three days, the authors estimate the mean reproduction number in the 1918 summer and autumn waves to be around 1.0–1.5 in Florence, 1.5–3.0 in Newfoundland and 1.3–1.5 in Lima. These estimates are consistent with previous studies in the US and UK and are slightly lower than estimates for the summer 1918 wave in Copenhagen, where R was in the range 2.0–5.4 [19]. The higher R estimate in the summer wave in Copenhagen may represent a measure of the basic reproductive number R0 in a fully susceptible host population.

6. The 1957 and 1968 pandemics

Although the moderately severe 1957 A/H2N2 and the milder 1968 A/H3N2 pandemics are not the focus of any papers in this issue, they were discussed [12,13,23]. A remarkable feature of the 1968 pandemic is that mortality impact patterns in Eurasia and North America were very different. In North America, the first winter had the most pandemic deaths, while the Eurasian pattern was one of a “smoldering” impact, where most (>70%) of all deaths occurred after a full year delay, during the 1969–1970 season [13,23]. In these pandemics, a moderate age shift in mortality towards younger ages was observed, so that younger adults were at far greater risk of death than in a typical season, while the mortality risk to the elderly was not that different from a severe seasonal epidemic [12,13].

7. The 2009 H1N1 pandemic seen in a historical perspective

A 1918 pandemic-like age shift with a 1968 pandemic-like mortality burden. Seen from a historical perspective, the 2009 H1N1 pandemic has one prominent signature feature in common with the devastating 1918 H1N1 pandemic. In 1918, the mean age of mortality among Americans was 27 years [14,24,25], while in 2009, the average age of people who died with laboratory-confirmed influenza was 37 years [26]. This mean age of death is far lower than averages seen in the 1957 and 1968 pandemics, when the mean age at death was 62–65 years, and is very different from seasonal influenza epidemics, for which the mean age at death has been 76 years in recent decades [24]. Although similarity with the 1918 age-pattern was worrisome when it was initially recognized in Mexico [27], the 2009 pandemic was soon found to be relatively mild in terms of the total number of deaths as data accumulated [28].

Using Years of Life Lost (YLL) as a metric, and after age standardization to the same reference US population, the 2009 pandemic mortality impact was found to be in the range of the 1968 pandemic and likely more severe than seasonal influenza [24]. In addition, seniors were largely spared in both the 1918 and 2009 pandemics, perhaps due to previous exposure to similar viruses during childhood (1918 [14,19], 2009 [26,27]). Because the unusually “young” pattern of deaths was recognized early in the 2009 pandemic response, vaccination recommendations in the U.S and elsewhere were updated to give priority to children and young adults instead of seniors.

World Health Organization (WHO) unfairly criticized for 2009 pandemic response. As the relatively modest impact of the 2009 H1N1 virus became clear, the WHO was criticized for having overreacted by recommending vaccination with a monovalent vaccine and other vigorous public health measures. But given all that we know about past pandemics, a rigorous response to the 2009 pandemic was justified [24,28]. Uncertainty surrounds all emerging infectious disease events, and public health officials must make difficult policy decisions in the face of uncertainty. Early evidence from Mexico revealing a 1918 pandemic-like mortality age pattern certainly demanded a vigorous response.

Further, the 2009 pandemic has not proven to be as mild as some believe. In terms of years of life lost rather than total deaths, the 2009 pandemic toll may be similar to the 1968 pandemic and indeed far greater than that of seasonal influenza. In the US, the 2009 pandemic may have been associated with up to 1.9 million YLL, far greater than that seen in a typical inter-pandemic season [24,28]. In addition to mortality estimates, it is critical to consider hospitalizations and Intensive Care Unit (ICU) utilization associated with the 2009 pandemic; these have been included in the Danish 2009 surveillance efforts presented in this issue [6]. Even in New Zealand and Australia, where the mortality impact of the 2009 pandemic was low, many young patients required intensive care and, in some cases, extreme clinical interventions such as extracorporeal membrane oxygenation (ECMO) [29,30].

8. Not yet time to let down our guard

The 2009 H1N1 pandemic has yet to complete its course, and many uncertainties remain. Age patterns may change as population immunity increases, and seniors may lose their immune protection as the virus drifts. At the time of this writing, the UK and many other countries worldwide are experiencing a substantial 2010–2011 season, dominated in some places by the pandemic 2009 H1N1 virus, and with a “young” age pattern in morbidity and mortality reminiscent of the pandemic waves of 2009 [31].

In a study of the Danish experience with the 2009 pandemic in this issue, Mølbak et al. demonstrate a modern e-data pandemic surveillance system [6]. From this comprehensive report featuring data from many aspects of the Danish health system, the authors could report that in 2009, the pandemic impact was only modest, except for an unprecedented increase in hospital admissions of school-aged children. The modest impact of the pandemic in this setting may be an example of between-country variability, but could also be an example of a “smoldering” impact of a novel virus. Here, as was the case in most geographical settings, the pandemic burden in 2009 was likely not affected by vaccination efforts, as pandemic vaccine doses were administered late.

Estimates of the mortality burden of the 2009 pandemic in multiple countries will require the use of monthly time series data detailed by age and cause of death. We recommend adopting the use of age-standardized years of life lost (YLL), as this allows for a more realistic measure of pandemic impact and a better comparison to the impact of previous pandemics and epidemics. For countries where only annual mortality data exist, the availability of cause-specific mortality data is critical, as is careful consideration of the contribution of background deaths in the very old and the very young [2,18].

Here, we have demonstrated how multidisciplinary studies of historic influenza pandemics can help to guide pandemic public health response and provide insight into the biological
mechanisms that underlie influenza epidemiology. The WHO declaration in August 2010 that the 2009 pandemic has ended [32] should not be interpreted to mean that the entire pandemic burden has already occurred. If history is any guide, we should expect a continued excess mortality risk in younger persons, with a gradual return to normal seasonal influenza age patterns over the next few years. It is therefore critical to maintain surveillance efforts and international data sharing in the post-pandemic period so that prevention and control programs can be tailored to the changing epidemiology of post-pandemic influenza.

Acknowledgments

The “Historical Influenza Pandemics: Lessons Learned” Meeting and Workshop was held May 3–7, 2010 in Copenhagen, Denmark. We thank the Carlsberg Foundation for graciously hosting our scientific meeting at the historic Carlsberg Academy and to our colleague Kimberly Bloom-Feshbach for her tireless work organizing this conference. We also thank all Copenhagen meeting participants for their insightful discussions and a productive meeting and training workshop.

This conference was sponsored by the Fogarty International Center, NIH, USA; the Statens Serum Institute and Roskilde University, Denmark. The conference and accompanying proceedings have been organized in the context of the Fogarty International Center’s MISM Study (www.origen.info/mism), an ongoing international collaborative effort to understand the epidemiological and evolutionary patterns of influenza viruses. MISM is funded by the U.S. International Influenza Unit, U.S. Office of Global Health Affairs, U.S. Department of Health and Human Services. The Copenhagen meeting was also supported by a grant (271-07-0555) from the Danish Medical Research Council.

ES and VA wish to acknowledge support from the Danish Medical Research Council and Fogarty’s RAPID program of the Science and Technology Directorate, U.S. Department of Homeland Security. Finally, we acknowledge Robert J. Taylor of Sage Analytics for thoughtful comments and editing of earlier versions of the paper.

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10 March 2011