

“Historical Influenza Pandemics: Lessons Learned” Meeting and Workshop

Abstracts

**May 3-7, 2010
Carlsberg Academy, Copenhagen, Denmark**



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Presenter: Lone Simonsen, PhD, George Washington University, USA

Title: Signature features of pandemic influenza

Authors: Simonsen L, Viboud C, Andreasen V, Olson D, Taylor R, Miller M.

Abstract:

Unless something dramatic happens, the 2009 H1N1 influenza pandemic may be remembered as a relatively mild pandemic. While this should be a cause for celebration, the WHO has been criticized for overdoing the public health response, including the vaccination campaign. A review of the signature features of past pandemics of 1889, 1918, 1957, and 1968, however, puts the contemporary experience in a historical perspective which justifies a rigorous public health response.

Who is at risk of pandemic mortality? A key signature of pandemic influenza is the age shift from senior deaths to younger persons. The 1918 “mother of all pandemics” and the contemporary 2009 pandemics are the most dramatic examples of this phenomenon, with respectively ~95% and ~88% of pandemic deaths occurring among persons under 65 years of age. The 1957 and 1968 pandemics featured a more moderate shift of the mortality burden away from seniors and towards younger ages, in contrast to seasonal influenza where >90% of deaths are seniors over 65 years of age.

How does one measure the severity of pandemic and seasonal influenza? Because of the age shift, the numbers of deaths is not an appropriate indicator to compare the pandemic and seasonal mortality burden. Instead, we estimated Years of Life Lost for the 2009 pandemic, as well as historic pandemics and contemporary influenza seasons. In this “apples to apples” comparison, the 2009 pandemic was perhaps as severe as the 1968 pandemic with as many as 1.7 Millions Years of Life Lost in the US.

Is the 2009 H1N1 pandemic a thing of the past? Not at all. An important historic insight is that pandemics come in multiple waves over the first several years after a novel influenza virus emerges. The first H1N1 pandemic wave in 2009 was in many ways similar to the first mild wave of the 1918 Pandemic, peaking in spring/summer in North America and Europe, followed by a second wave in early autumn. For all pandemics with reliable epidemiological data, the pandemic virus always continued to circulate and dominate in the following 2-5 winter seasons before becoming established as a “seasonal” influenza virus.

Can we be certain the worst is over? Not necessarily. The 1918 pandemic virus featured a relatively mild 1st wave several months before it went on to kill ~2% of the global population in subsequent waves during 1918-20. Likewise, the 1968-69 pandemic season was relatively mild in Europe and at least 70% of all the pandemic deaths occurred during the second season of circulation (1969-70). For the 1889 pandemic, a 3rd wave occurred 2 years after the pandemic virus first emerged and most of the cumulative pandemic mortality burden during 1889-1892 occurred during that 3rd wave in England and Copenhagen.

In this historic perspective, the numerous uncertainties about the current pandemic situation justify continued global investments in vaccines and other means of mitigation and treatment of disease for several years to come. While the reasons that subsequent waves may be more severe are not entirely clear, the fact that it happened is a good reason for real-time studies of an emerging pandemic influenza virus. The uncertainties essentially boil down to the need for maintaining vigilance and continuing efforts to protect the population with vaccination and by other means.

Presenter: Alain-Jacques Valleron, PhD, Université Pierre et Marie Curie, France

Title: The 1889 Influenza Pandemic

Authors: Valleron A, Cori A, Valtat S, Meurisse S, Carrat F, Boelle P.

Abstract:

Until now, only the 1918, 1957, and 1968 influenza pandemics have been quantitatively studied to discern spreading mechanisms and mortality, but little attention has been given to 19th century pandemics. Here, we examined the 1889 ‘Russian’ pandemic.

Clinical attack rates were retrieved for 415 geographical entities in 20 countries worldwide. Case fatality ratios were estimated from datasets of the French, British, and German armies, and morbidity and mortality records of Swiss cities. Weekly all-cause mortality was analyzed in 96 European and American cities.

The pandemic spread rapidly, taking only 4 months to circumnavigate the planet, peaking in the US 70 days after the original Saint Petersburg peak, travelling 400 km/week in continental Europe. The clinical attack rate was $51 \pm 16\%$, with a 0.1%–0.28% case fatality ratio range and excess mortality 0.16% of the total population, which is of the same order as those for the 1957 and 1968 pandemics, and 7-fold lower than 1918 pandemic values. The median basic reproduction number (R_0) was 2.1, which is comparable to the values found for the other pandemics, despite the different viruses and contact networks. There was a high city to city variability in R_0 values, only a small minority of which is within the range in which modelers' mitigation scenarios predicted effectiveness. It was also found that the 1889 and 1918 R_0 were correlated for the subset of cities for which both values were available. There are likely social and geographical factors that shape the local R_0 , which should be identified to design optimal mitigation scenarios, tailored by city.

The 1889 experience shows that worldwide spread of influenza is extremely rapid, even in the absence of air transport. Regarding mortality, it is another example of a “mild” pandemic, quite comparable to the 1957, 1968 pandemics, and—up to now—the present A/H1N1 pandemic.

Presenter: Lars Skog, MSc, ESRI S-GROUP, Sweden

Title: The Russian Influenza in Sweden in 1889-1990: an example of Geographic Information System analysis

Authors: Skog L, Hauska H, Linde A.

Abstract:

Using data from a study of the 1889-90 Russian flu in Sweden, this article describes how the application of Geographic Information System (GIS) may improve analyses and presentation of surveillance data. In 1890, immediately after the outbreak, all Swedish doctors were asked to provide information about the start of the epidemic, the peak of the epidemic and the total number of cases in their region and to fill in a questionnaire on the number, sex, and age of infected persons in the households they visited. General answers on the epidemic were received from 398 physicians and data on individual patients were available for more than 32,600 persons. These historic data were reanalysed with the use of GIS, in map documents, and in animated video sequences to depict the onset, the intensity, and the spread of the disease over time. A stack diagram with the observations grouped into one week intervals was produced to depict the spread in one figure only. To better understand how the influenza was disseminated, Thiessen polygons were created around 70 places reported on by the doctors. Having prepared GIS layers of the population (divided into parishes), estimations could be made for all the Swedish parishes on the number of infected persons for each of the 15 weeks studied. The described models may be useful in current epidemiological investigations, as well.

Presenter: Mark Honigsbaum, Wellcome Trust Centre for the History of Medicine at UCL, UK
Title: The Great Dread: the 'Russian' Influenza in the United Kingdom
Authors: Honigsbaum M.

Abstract:

The 'Russian' influenza of the early 1890s has been described as the first 'truly global' pandemic of influenza. Taking advantage of the nineteenth century expansion in rail and steam communications, the virus spread rapidly between European and North American cities in a westward progression that was clearly apparent to contemporary observers. Unlike previous pandemics, the Russian flu was also closely monitored by the press with correspondents telegraphing news of the pandemic's depredations to Victorian newspaper readers well ahead of local outbreaks. The result was a widespread dread of influenza that, as with the 2009 swine flu pandemic, was far in excess of the disease's actual destructiveness.

In this paper, I will focus on the British phases of the pandemic. Tracing the three waves of infection, I will show how in London the first wave sickened a quarter of the capital's population, while in Sheffield the second wave elevated the death rate to an astonishing 70 per 1,000 of population in the spring of 1891– the highest rate ever recorded in the borough. However, it was the widespread morbidity and in particular the sickness of leading public figures at Westminster that did most to spread alarm. As MPs fled to Brighton and other coastal resorts in search of 'uncontaminated' air, there were calls for the Palace of Westminster to be fumigated. Public health officials debated making influenza a notifiable disease, isolating the sick and imposing travel restrictions, but in the end it was decided that preventative measures were pointless. Instead, doctors emphasized the importance of convalescence and after-care to guard against the dangers of relapse and lung complications.

The other significant observation was how the pandemic had taken the form of three, or possibly four, distinct waves of infection, with the second wave in the spring of 1891 being more severe than the first wave in 1890, and the third wave in the winter of 1891-2 being more severe than either. Indeed, taking into account the severe recrudescence of influenza in 1893, it is now estimated that some 125,000 Britons perished in the pandemic – a total which approaches the mortality of the better known Spanish influenza pandemic of 1918-19.

Presenter: Jim Oeppen, MA, Max Planck Institute for Demographic Research, Germany

Title: Estimating reproductive numbers by age and sex during the 1889-90 influenza pandemic in Madrid and Munich

Authors: Oeppen J, Ramiro Fariñas D, García Ferrero S.

Abstract:

Reproductive numbers for influenza are usually calculated for total populations, yet it is likely that the immune response varies by sex and age. To explore this issue, basic reproductive numbers for the 1889-90 pandemic are estimated from data for two large cities, disaggregated by sex and age. The estimates are based on the growth rate of deaths in Madrid, and of reported cases for Munich. For Madrid, we further disaggregate by marital status to speculate on the role of pregnancy in the immune response. The context of the disaggregated estimates for Munich is established by contrasting them with estimates based on aggregated mortality for this city and more than 30 others in Germany. We also compare them with estimates based on hospitalisation in Munich and on cases among working-age, adult males for 10 districts in the Bavarian hinterland of the city.

Presenter: Cécile Viboud, PhD, Fogarty International Center, USA

Title: Extreme risk of influenza-related mortality among young adults: A comparative study of the 1918-20 pandemic in 13 countries

Authors: Finkelman BS, Grenfell BT, Taubenberger, JK, Simonsen L, Bloom-Feshbach K, Richard S, Viboud C.

Abstract:

Background: The 1918-1920 influenza pandemic was marked by unusually high mortality in young adults aged 20 to 40 years, a pattern that current or future influenza pandemics may follow. Despite the broad historical significance and contemporary relevance of the 1918-1920 pandemic, this defining feature has not been fully confirmed on a global scale and remains biologically unexplained. Here we quantify the age-specific mortality patterns associated with the 1918-1920 pandemic in 13 countries in Europe, North America, and Australasia, and model biological hypotheses potentially explaining these patterns.

Methods and Findings: We use all-cause mortality data by single year of age for 1915-23 available for 11 countries from the public Human Mortality Database, and augment the dataset with digitized historical records for Japan. We estimate excess mortality associated with the influenza pandemic as mortality rates during 1918-1920 in excess of baseline years 1915-1917 and 1921-1923. For comparison purposes, we apply a similar approach to national US mortality data from all-cause and pneumonia and influenza, which are available by 5-yr age groups. Despite variations in excess mortality rates among countries, especially in infants and seniors, our study confirms a large and systematic increase in mortality risk in young adults in all 13 countries ($P < 0.05$). In addition, there is little geographic variation in the risk of death relative to baseline non-pandemic years, peaking at age 28 on average in the 13 countries (range 27 to 30 years). Modeling suggests that the observed age-mortality patterns are not explained by a single hypothesis, but are compatible with prior immunity in people over 45 years due to antigen recycling, combined with high probability of bacterial coinfection in parents of young infants who are heavy carriers of respiratory bacterial pathogens. Hypotheses involving an interaction between influenza and active tuberculosis infection, or negative antibody enhancement through shared neuraminidase antigens, do not match the observed mortality data as well.

Conclusions: This historical epidemiological study suggests that young adults aged 27-30 years experienced the most extreme risk of death during the 1918-20 influenza pandemic, relative to background mortality, and that this pattern was consistent on a global scale. Modeling suggests that coinfection with respiratory bacterial pathogens may partly explain this unusual pattern of influenza-related deaths, and further experimental work could shed light on the preferred interaction between the 1918-1920 influenza virus and respiratory bacterial pathogens. Such research is key in order to understand the unusual mortality impact and age patterns of the 1918-1920 pandemic and to help guide preparedness plans for current and future influenza pandemics.

Presenter: Viggo Andreasen, PhD, Roskilde University, Denmark

Title: Why did the Danes not die in 1918?

Authors: Andreasen V, Viboud C, Saglanmak N, Simonsen L.

Abstract:

Using weekly statistics on respiratory deaths in Copenhagen we have previously estimated the impact of the 1918-19 pandemic to 41 deaths per 10,000 (Andreasen et al, J Inf Dis 197: 270) and a contemporaneous report set the burden to 45 deaths per 10,000 (Annual report from the medical Officer in Copenhagen 1918). These observations appear to be at odds with the picture one gets by comparing the 1918 annual, over-all mortality in Denmark to that of the surrounding years. In contrast to most other populations, the Danes did not experience a significant increase in the over-all mortality in the pandemic year of 1918 and while the life expectancy in most European countries fell by 6-8 years in 1918, a similar phenomenon did not occur in Denmark. Using data from Copenhagen, where a detailed surveillance system was in place at the time, we find that an unusually low mortality in the spring of 1918 completely masked the impact of the pandemic. Primarily affecting the extreme age groups, the mortality reduction occurs in several causes of death and seems unrelated to the pandemic. The low 1918-mortality may be due to a combination of food-rationing and a harvesting effect arising through a high mortality in 1916 and 1917. Annual mortality data from other European countries suggests that in the early part of the 20th century, major fluctuations in the back-ground mortality of the extreme age-groups may have been common in other countries as well, emphasizing that pandemic impact should be assessed from data with high resolution in time and cause.

Presenter: Ida Kolte, PhD, NFA / University of Copenhagen, Denmark; Søren Kølholt Poder, SBK Scandinavia APS, Denmark

Title: Spatial analysis of the Spanish flu mortality in Denmark

Authors: Kolte I, Poder S.

Abstract:

Even though industrialization had accelerated during the last part of the part of the 19th century, most Danish cities were still dependent on their rural surroundings and the traditional role as central market places. However, as the infrastructure quickly developed during the same period, the old cities were soon bound close together. Furthermore, small settlements spontaneously developed along the new railways. The station became the marker of a city and consequently of a market place. Basically, this kind of urban settlements consisted of little more than just a train station, a church, and a hotel. Market towns were essential for the development of industrialized rural production units and the exchange of goods and services in the region. By 1918, this development had led to vastly increased numbers of people living in an urban settlement, and to widespread migration between towns and rural areas.

The empirical evidence suggests that the course of the 1918 epidemic was not only dominated by the size of the population in each city. To fully understand the spatial dimension of epidemics it is necessary to consider that cities are profoundly complex social systems and not merely urban pinheads in a two-dimensional landscape. Towns create dense regional interactive networks, core areas with highly complex, social, and economical interaction based on the local socioeconomic conditions and informal social conventions. The course of the Spanish flu in the individual town might very well be determined by its position in its regional network, and the extent of the interaction between other urban areas and the rural hinterland. We therefore propose a discussion of the spatial dimension of the existing incidence and mortality data on the Spanish flu. This approach is expected to yield valuable information on the geographical differences in the level of influenza mortality, and consequently which measures might be effective to combat a future epidemic.

Presenter: Gerardo Chowell, PhD, Arizona State University & Fogarty International Center, USA

Title: Unexpected mortality patterns associated with the 1918 influenza pandemic in Mexico: evidence for a spring herald wave and lack of pre-existing immunity in older populations

Authors: Chowell G, Viboud C, Simonsen L, Miller M, Acuña-Soto R.

Abstract:

Background: While the mortality burden of the devastating 1918 influenza pandemic has been carefully quantified in the US, Japan, and European countries, little is known about the pandemic experience elsewhere. Here, we compiled extensive archival records to quantify the pandemic mortality patterns in two Mexican cities, Mexico City and Toluca.

Methods: We applied seasonal excess mortality models to age-specific respiratory mortality rates for 1915-1920 and quantified the reproduction number from weekly data.

Results: We identified 3 pandemic waves in Mexico City in spring 1918, fall 1918, and winter 1920, characterized by unusual excess mortality in 25-44 years old. Toluca experienced 2-fold higher excess mortality rates than Mexico City, but did not have a substantial 3rd wave. All age groups including those over 65 years experienced increased mortality during 1918-20. Reproduction number estimates were below 2.5 assuming a 3-day generation interval.

Conclusion: Mexico experienced a herald pandemic wave with elevated young adult mortality in the spring 1918, similar to the US and Europe. In contrast to the US and Europe, there was no mortality sparing in Mexican seniors, highlighting geographical differences in pre-existing immunity to the 1918 virus. We discuss the relevance of our findings to the 2009 pandemic mortality patterns.

Presenter: Wladimir Alonso, PhD, Fogarty International Center, USA; Origem Scientifica, Brazil
Title: The pandemic wave of influenza in 1918 in Florianópolis, a Brazilian sub-tropical island
Authors: Nascimento F, Acuña-Soto R, Alonso W.

Abstract:

Few studies have addressed the impact and dynamics of the 1918 influenza pandemic in tropical and sub-tropical areas. To help cover this gap, we digitalized and analyzed all death certificates from the period from May 1916 to June 1921 in Florianópolis, a state-capital located in a sub-tropical island with a population of 41.298 inhabitants in 1920. The mean annual mortality attributed to pneumonia and influenza (after excluding the “pandemic period”, from October to December 1918) was of 8.1 deaths/year, distributed sparsely along the summer, autumn, and winter months. While temporally variable among years, average mortality was higher in the first 6 months of the year, with a peak in June (winter). In contrast, the 1918 pandemic caused 70 reported influenza and pneumonia deaths in November and 14 in December 1918 (spring months). By analyzing excess mortality, we obtain a value of 108 deaths during these two months (0.26% of the population). Contrary to observed patterns of age-shift in mortality in pandemic scenarios, seniors (60+yo) and young children were the most affected groups. Also worth noticing is a discrete peak in mortality due to renal causes in the 1918 period and the fact that pandemic influenza did not seem to affect bronchitis and bronchiolitis deaths (that in fact, seemed to present unusually higher activity the previous year). No other waves of pandemic influenza could be detected either in earlier or subsequent months.

Presenter: Nesli Saglanmak, PhD Candidate, Department of Science, Roskilde University, Denmark

Title: Gradual changes in the age distribution of deaths following the 1918 pandemic in Copenhagen: using epidemiological evidence to detect antigenic drift

Authors: Saglanmak N, Viboud C, Miller M, Andreasen V, Simonsen L.

Abstract:

Background: The 1918 influenza pandemic was associated with an unusual and yet unexplained age pattern of mortality, mostly concentrated among young adults. Here we extend the analysis of age-specific influenza mortality from the time period before and after 1918 to follow the changes in age pattern, using detailed historic surveillance data from Copenhagen.

Methods: Monthly rates of respiratory mortality and influenza morbidity were compiled by age for 1904 to 1937. Seasonal excess rates of morbidity and mortality were calculated using a spline-Serfling model baseline approach. To characterize the age-specific impact of influenza in individual seasons, we used a relative risk measure representing the ratio of excess mortality between the younger (<65) and the older population (65+).

Results: The 15-64 age group had sharply elevated excess mortality rate in the 1918 pandemic and the season of 1919-20 compared to the average pre-pandemic excess mortality. The seniors (65+) were seemingly unaffected by the pandemic until the recrudescence (4th) pandemic wave in the winter of 1919-20, when they experienced considerable morbidity and some excess mortality. The first post-pandemic season associated with high excess mortality came in 1928-29 for this age group. The relative risk increased from <0.1 in pre-pandemic seasons to 6 in the fall wave of the pandemic, decreased below 1 the following year, and remained below 0.1 after 1925.

Conclusions: The unique increase in young adult deaths was concentrated to the first 2 years of pandemic A/H1N1 virus circulation, probably due to high attack rates and rapid build-up of population immunity in this age group. In contrast, seniors were free of elevated mortality until 1919-20, suggesting that the first post-pandemic drift of influenza viruses may have occurred in late 1919, and again more dramatically in 1928-29.

Presenter: Andrew Noymer, PhD, Department of Sociology, University of California, Irvine, USA

Title: The 1918 influenza pandemic hastened the decline of tuberculosis in the US

Authors: Noymer A.

Abstract:

This paper presents the evidence, some of which is previously-published and some of which is new, that the 1918 influenza pandemic hastened the decline of tuberculosis in the US. The evidence is clear that the 1918 flu affected the epidemiology of other diseases in the US, particularly tuberculosis. The male-female difference in life expectancy was altered for about a decade after 1918. Because this pertains to all-cause mortality, it is not subject to cause-misclassification among various diseases. After the 1918 pandemic, male life expectancy rebounded more vigorously than female life expectancy, thus altering the male-female differential. This was due to a selection effect whereby the 1918 flu killed unhealthy people. The post-flu population was therefore healthier, paving the way for longer life expectancy. In the United States, influenza mortality in 1918 was disproportionately male (this refers to deaths occurring in the United States, so is only affected by military deaths to the extent to which they occurred in American camps). The selection effect, therefore, was stronger for males and resulted in the overall effect seen in life expectancy. This selection operated most strongly through tuberculosis. A similar effect is found in Norway, which, like the US, was a high TB prevalence country in 1918. Due to some reporting differences, the Norwegian data are somewhat less clear on the matter, however. On the other hand, a similar effect is not found in Australia. Australia experienced lower death rates of TB (before and after the pandemic) and of influenza, so data from other countries (Australia and Norway) are consistent with a dose-response relationship. In sum, this paper examines the neglected topic of the impact of an influenza pandemic on the epidemiology of other, seemingly-unrelated diseases.

Presenter: Dan Weinberger, PhD, Harvard School of Public Health, USA

Title: The importance of pneumococcal serotypes in determining bacterial carriage and disease patterns: potential implications for influenza

Authors: Weinberger D.

Abstract:

Streptococcus pneumoniae, or pneumococcus, is an important cause of pneumonia, meningitis, and bacteremia. Like influenza, pneumococcal disease exhibits a strong seasonal pattern, and it has been suggested that secondary bacterial infections, such as those caused by pneumococcus, are a significant contributor to mortality during influenza outbreaks.

Pneumococcus produces a polysaccharide capsule, which forms a protective layer around the bacterium. Based on the structure and immunoreactivity of these polysaccharides, pneumococcus is classified into 92 different serotypes. A vaccine that targets 7 of the 92 serotypes has effectively reduced the burden of pneumococcal disease in areas where it is in widespread use. However, previously rare serotypes have increased in both carriage and disease and could potentially undermine the long-term effectiveness of the vaccine.

My research has sought to understand how the production of these various capsular polysaccharides influences interactions with host immune effectors and ultimately affects patterns of carriage prevalence, disease incidence, and disease severity. In particular, I have found a link between the primary chemical structure of the bacterial polysaccharides and the prevalence of the serotypes among nasopharyngeal carriage isolates. Additionally, I have found that thickly encapsulated serotypes tend to be highly prevalent among carriage isolates but proportionally are less likely to cause invasive disease. If these heavily encapsulated serotypes do invade, though, they tend to be associated with higher case-fatality ratios. Some of these data have been used to make predictions about which serotypes are likely to become more prevalent in the post-vaccine era.

Given the changes in the bacterial population following the introduction of the pneumococcal vaccine, it is important to further understand the interaction between influenza and pneumococcus. Little is known about the influence of influenza infections on the transmission, invasiveness, and disease severity patterns of specific serotypes. I plan to study how seasonal variations in influenza could influence the epidemiologic patterns of particular serotypes and would like to focus on past influenza pandemic periods.

Bibliographic citations:

Some of this work has been published in PLoS Pathogens, 2009
(<http://www.plospathogens.org/article/info:doi/10.1371/journal.ppat.1000476>)

Additional portions of this work will be presented at the International Symposium on Pneumococci and Pneumococcal Diseases, March 2010.

Presenter: Kimberly Bloom-Feshbach, BA, Fogarty International Center, USA

Title: Natality Decline and Spontaneous Abortions Associated with the 1918 Influenza Pandemic: the Scandinavian and US Experiences

Authors: Bloom-Feshbach K, Simonsen L, Viboud C, Mølbak K, Miller M, Andreasen V.

Abstract:

Background: While influenza infection causes increased mortality during pregnancy, little is known about the effect on the fetus, spontaneous abortions, or the specific impact of a pandemic viral infection. We use historical epidemiological records from the 1918 pandemic to examine the relationship between influenza and pregnancy in the US, Denmark, Sweden, and Norway.

Methods: Monthly age-specific mortality, morbidity, and birth data from national surveillance systems in place in 1911-1930 were acquired to identify trends in birth rates within 9 months of the pandemic period and in surrounding years. We developed a seasonal model to estimate baseline birth rates in the absence of any influenza activity. For each population, we identified the weeks in which the observed birth rate fell outside of the 95% confidence interval, and calculated the total rate of “missing” or “excess” births for the relevant periods.

Results: For each population, there was a reduction in birth rates in April-August 1919 by approximately 2.8 missing births per 1000 population, corresponding to a ~10-20% reduction as compared with baseline. A striking compensatory surge of excess birth occurred 7.5-10 months later, especially in the Scandinavian countries. No other sustained periods of statistically significant deviations from the expected number of births were observed throughout the 20 year study period. Further, a 1-2 months lag of pandemic activity between rural and urban Denmark coincided with a similar lag in birth rates depression. There was no increase in stillbirths in any country. Pandemic-related mortality in women of childbearing age was insufficient to explain the observed decline in birth rates.

Conclusions: We observed a striking dip in birth rates in spring of 1919 in Scandinavian countries and the US, 6-9 months after pandemic influenza activity peaked. The unusual natality pattern in 1919 may be due to 1st trimester abortions as a complication of maternal pandemic influenza infection in the autumn of 1918. This population-level association was strengthened by temporal synchrony of our findings in multiple geographical areas.

Presenter: Annika Linde, MD, PhD, Swedish Institute for Infectious Disease Control, Sweden

Title: Viral interference and the 2nd wave of excess “influenza and pneumonia death” in 1957-1958

Authors: Linde A, Andersson M.

Abstract:

During the autumn of 2009, it was shown that rhinovirus may interfere with the spread of pandemic influenza when climate conditions did not support the airborne spread of the pandemic influenza. On the other hand, during conditions favoring aerosolization, influenza became dominant. It may then have been likely to out-compete other viruses, thereby disturbing the ordinary patterns for the spread of viral respiratory tract infections.

From the 1957-58 pandemic period, there are several reports on a 2nd wave of prolonged “excess mortality due to influenza and pneumonia.” Virology data in the reports are scant. In Sweden, a peak of pneumonia-related mortality was observed in April 1958. A recurrence of the Asian flu, hitting almost exclusively the elderly, was assumed, despite a very low increase in the GP reports on influenza-like illness.

The assumptions may well be true, but today awareness is increasing that viral respiratory tract infections other than influenza, such as RSV and rhinoviruses, may contribute to excess mortality. Possibly a changed epidemiologic pattern for these infections as a consequence of the intense November influenza activity may have contributed to the excess deaths due to influenza and pneumonia in 1958.

In Sweden, the usual pattern for RSV epidemics is biannual, with early onset (October) and high peaks in February every 2nd year and late onset with low peak activity the other year. The season 2009 – 2010 was expected to be “early and high”. However, the increase did not start until late January 2010 and the peak with a highest number of laboratory verified RSV-diagnoses ever was reached in middle March. The reason for the unusual pattern is unknown, but influenza interference is a likely explanation. During the period of October - November, when the RSV seeding and the initial rise should have taken place, influenza peaked in children. The immune reaction against influenza may prevent replication of other viruses, postponing the spread of other viral infections, including RSV.

The absence of seasonal flu and, possibly, delayed spread of other respiratory infections in the young population affected by influenza and increased hygiene due to the pandemic threat has resulted in an exceptionally low total mortality during 2009 – 2010 in Sweden, despite an extremely cold winter. This probably has increased the number of extremely fragile people. If RSV and other delayed respiratory infections reach this population, it may result in late excess mortality, to be verified by May.

Irrespective of what happens during the spring in Sweden, it must be taken into consideration that an aberrant pattern of “influenza and pneumonia” mortality in 1958 may be related to unusually high rates of other respiratory infections than influenza. Virological proof of influenza or other viral activity from the time is desirable, as well as inclusion of the concept of viral interference in studies of present and past excess mortality periods.

Presenter: Christophe Fraser, PhD, Imperial College London, UK

Title: Insights into influenza transmission from historical and contemporary household studies

Authors: Fraser C, Cummings D, Klinkenberg D, Cauchemez S, Burke D, Ferguson N.

Abstract:

Analysis of historical data has strongly shaped our understanding of the epidemiology of pandemic influenza, and informs analysis of current and future epidemics. Here, we analyse previously unpublished documents from a large study of the 1918 H1N1 influenza pandemic, and compare these results with a smaller study of the recent 2009 H1N1 pandemic, thus obtaining a consistent and fine-scaled view of influenza transmission. For 1918, we estimated very low probability of person-to-person transmission, high probability of prior immunity, very low probability of asymptomatic infection, and moderate inter-person variability in infectiousness. Rates of transmission for the 2009 pandemic were even lower, suggesting that when desired, pandemic influenza transmission can be controlled, and highlighting the utility of large population surveys that should be considered in future pandemics.

Presenter: Magnús Gottfredsson, MD, PhD, Landspítali University Hospital, Iceland

Title: Familiality of fatal influenza in Iceland

Authors: Gottfredsson M, Halldórsson B, Berndsen MR, Sigurlásdóttir S, Gudmundsson L, Gulcher J, Stefánsson K, Jónsdóttir I.

Abstract:

Introduction: Influenza can be fatal in individuals with no predisposing conditions. This is most notable during pandemics, such as the Spanish flu in 1918. Severe influenza also frequently affects families disproportionately, suggesting that familial or genetic factors play a role. We have previously shown that increase in familial risk of death from the Spanish flu in Iceland was not significant when all potential environmental factors were corrected for. The limitations of this study were primarily the lack of statistical power due to low number of cases (n=458 fatal), and a short observation period (6 weeks in 1918). The purpose of this study was to assess familiality of fatal influenza in Iceland subsequent to 1918 and to compare this with familiality of fatal pneumonia.

Materials and methods: The Icelandic genealogy database “Book of Icelanders” was used to generate a list of weekly mortality in Iceland from 1918-1974. Weeks with excess mortality (compared to average within 5-year intervals) were identified and death certificates for individuals who died during those weeks were reviewed manually. Causes of death were registered, categorized, and classified according to ICD-10. Familiality and relative risk (RR) of death from influenza and pneumonia was calculated as described previously (1), except that geographic location was not corrected for.

Results: Death certificates of 4951 individuals who died during periods of excess mortality in 1918-1939 and 1957-1974 were reviewed. Of these, 186 died from influenza and 1117 from pneumonia. A trend towards increased risk of death from influenza for 1-2 degree relatives was noted (RR 1.98, p=0.082 for influenza vs. 1.21 for death from pneumonia, p=0.056), as well as 3-5 degree relatives (1.35, p=0.049 for influenza vs. 1.07 for death from pneumonia, p=0.076). When this cohort was combined with the 458 fatalities from the Spanish flu (N=646) the familial risk became statistically significant. RR for 1-2 degree relatives was 3.02, p<0.0001, and RR for 3-5 degree relatives was 1.47, p<0.0001. However, the RR for relatives of mates of patients with fatal influenza was also significantly increased; 2.30 for 1-2 degree relatives (p<0.0001) and 1.47 for 3-5 degree relatives (p<0.0001), but it was significantly lower than the RR of relatives of the fatal influenza cases (1.-2. degree; p=0.034, 1.-5. degree; p= 0.0056)

Discussion: This familiality study expands our previous findings by including fatal cases from endemic and pandemic years, subsequent to 1918. When the entire patient cohort was analysed increased familial aggregation of fatal influenza was observed. This contrasts with fatal pneumonia, where no significant increase was noted. The relative risk of close relatives of fatal influenza was significantly higher than the relative risk of close relatives of their mates. This suggests that despite the strong risk contributed by exposure to the influenza virus genetic factors play a role in the pathogenesis and outcome of severe influenza.

Presenter: Kirsty Bolton, PhD, Melbourne School of Population Health, University of Melbourne, Australia

Title: Alternative immune hypothesis for explaining the three mortality waves of the UK 1918-19 influenza pandemic

Authors: Bolton K, McCaw J, McVernon J, Mathews J.

Abstract:

The 1918-19 influenza pandemic was characterised by multiple waves of infection, with evidence in the United Kingdom that some individuals were infected on multiple occasions over the three waves, while others were spared entirely. These observations hint at heterogeneity in the host immune response to the pandemic influenza strain. We fit biologically motivated epidemiological models for multiple-wave influenza pandemics which incorporate various combinations of prior, partial, and temporary immunity to the mortality and reinfection data and report on progress to distinguish between the validity of different models for population immunity.

It also remains a challenge to understand the population to population variations in pandemic experience. Differences in the reported case fatality ratio between UK cities signal the possibility that the average immune response can vary even for cities in a socially connected country such as the UK. Nevertheless we expect that some aspects of the viral spread will be tied to the intrinsic viral properties and therefore common to all locations. We present preliminary work to disentangle these effects by cofitting 5 UK city data sets allowing for both global and location-dependent model parameters. Records of single wave outbreaks on military ships in 1918-19 – which were often characterised by a rapid increase in prevalence and very high morbidity rates, but with strikingly variable case fatality ratios – also reinforce the complex dependence of the pandemic scenario on the particular community and environment. We survey the difficulties in understanding these outbreaks in the context of the wider pandemic.

Our analysis highlights the complexities of the dynamic processes acting during the 1918-19 pandemic, and the pressing requirement to better understand the interaction between the immune system response to influenza, seasonal and pandemic influenza strains, age-cohort effects, and environmental influences on the transmission of influenza.

Presenter: Caterina Rizzo, MD, National Centre for Epidemiology Surveillance and Health Promotion, Istituto Superiore di Sanità, Italy

Title: Investigating the epidemiology and the transmission dynamics of the 1918-19 influenza pandemic in Florence, Italy

Authors: Rizzo C, Ajelli M, Merler S, Pugliese A, Barbetta I, Salmaso S, Manfredi P.

Abstract:

The analysis of the epidemiological patterns of past influenza pandemics is crucial to informing the best practices to adopt in preventing, containing, and mitigating the next A/H1N1v season. In this paper we investigated the 1918/19 influenza pandemic in Florence, located in the center of Italy. We collected the daily number of new hospitalizations during the 1918 influenza pandemic in the hospital of Florence (Ospedale di Santa Maria Nuova). We identified both the main and underlying causes of hospitalization (pneumonia, hemorrhagic pneumonia, influenza, and fever) in cases. As experienced by other European Countries, the Spanish flu affected Italy in several waves: the first one occurred in July 1918, the second and most severe one in October–November 1918. Then the epidemic declined until February–March 1919. The mortality rate was highest in the age group 15-44 years. In order to describe the transmission dynamics of the 1918/1919 pandemic influenza, we used a compartmental epidemic model. Model predictions showed a high level of agreement with the observed epidemic data. We estimated the basic reproductive number for the summer wave as $R_{01} = 1.04$ (95% CI: 0.95-1.46) and the reproductive number for the fall wave as $R_{02} = 1.67$ (95% CI: 1.31-3.67). The hospitalization rate for symptomatic individuals in the two waves was estimated to be 0.95 (95% CI: 0.08-2.26) and 0.62 (95% CI: 0.25-1.62), respectively. Our estimate of the reproductive number for the second wave was larger than that of the first. This is consistent with what was observed in other countries. However, the hospitalization rate was higher during the first wave. Our results for the basic reproductive number were consistent with what observed in other countries such as the United States (using mortality data range between 2 and 3), the UK (the estimate basic reproductive number was 2 for the first and 1.55 for the second wave), and in Geneva (the reproductive number varies from 1.49 to 3.75 in the first and second wave, respectively). However, the decrease of the hospitalization rates during the second wave is unexpected and might be due to several factors such as different public health policies, containment strategies, and public perceptions of hospitalizations.

Presenter: Lisa Sattenspiel, PhD, University of Missouri-Columbia, USA

Title: The spread of the 1918-19 influenza epidemic on the island of Newfoundland

Authors: Sattenspiel L.

Abstract:

The Spanish Flu pandemic reached Newfoundland and Labrador in the summer of 1918, and by the time it disappeared, over 2000 of the Dominion's 250,000 residents died. The epidemic spread in several waves, including a mild outbreak during the summer of 1918, a major, deadly outbreak in the succeeding fall and spring, and a small echo wave in 1920. Overall, the epidemic pattern appears similar to that observed in northern European countries, perhaps reflecting links between Newfoundland and these countries as a result of shipping activities.

As in most other parts of the world, the second wave was much more severe than the first wave; however, this was apparently not the case in the southwestern corner and in the Northern Peninsula of Newfoundland. Analysis of morbidity and mortality data from the island provide suggestive evidence for the possible role of immunity resulting from Wave I cases and/or indirect effects from a large 1916-17 measles epidemic in lessening the severity or limiting the extent of Wave II in the Northern Peninsula. We discuss here general patterns of spread of the epidemic on the island as well as analyses designed to determine the potential impact of these two factors in the Northern Peninsula.

Presenter: Rodolfo Acuña-Soto, MD, DSc, Facultad de Medicina/Universidad Nacional Autónoma de México, México

Title: Temporal and Spatial Distribution of the 1918 Spanish Influenza in México

Authors: Acuña-Soto R.

Abstract:

The 1918 Spanish Influenza epidemic in México occurred in three waves. The first wave took place in April-May 1918, the second in October-December 1918, and the third in January-February 1920. All three waves travelled with a general North-to-South direction. However, their impact on the mortality rates varied from region to region; in general, mortality rates were higher in the cooler and drier highlands and less severe in the warmer and wetter tropical lowlands. The total mortality for México was around 500,000 persons, which represented approximately 3% of the entire population. The reconstruction of events suggests that climate was a pivotal factor since the pandemic virus started to circulate in the country with the first wave, in April-May. After this, the number of cases and deaths decreased, but the baseline was set at a higher level than that of the pre-epidemic period. This situation extended until the beginning of the drier and colder climate conditions that favored the onset of the second and largest wave of transmission in October-December. Interestingly, the advance of the seasonal cold and dry climate rather than the arrival of new waves of the pandemic virus produced the effect of North-to-South direction in the second and third waves.

The retrieval and analysis of all mortality records of the Civil Registry of México City from 1917 to 1920 allowed us to achieve the temporal and spatial distribution of the epidemic in México City. Since there was only one large cemetery for the whole city and burials were classified in different categories from the richest to the poorest, it was possible to analyze the impact of the epidemic among different socioeconomic groups. It was also possible to evaluate the frequency of unusual causes of deaths associated to influenza such as neonatal influenza, fulminant influenza, hemorrhagic influenza, influenza with acute neurological manifestations, gastroenteritis associated to influenza, etc.

Presenter: Don Olson, MPH, International Society for Disease Surveillance (ISDS), USA

Title: The Historical Epidemiology of Influenza in New York City

Authors: Olson DR.

Abstract:

In studying the epidemiology of seasonal and pandemic influenza it is important to understand the social, historical, and regional context of disease. Characterizing the epidemiology of epidemics across different locations is critical, both to replicate findings and to provide increased power of analysis. Understanding specific populations in greater detail and over longer periods of time, however, can provide an additional level of insight that can inform further data collection, analysis, and interpretation. This abstract presents preliminary work focused on the 1918 and 2009 influenza A/H1N1 pandemics. It is intended to provide a snapshot of the ongoing effort to catalog historical details and analyze disparate sources of morbidity and mortality data from New York City since 1889. This presentation focuses on: 1) the impact of the 1918 pandemic on the course of tuberculosis mortality trends from 1898-1948 in New York City; 2) the spatial pattern of epidemic mortality across the 66 neighborhood wards of New York City from 1910-1920; 3) the age-specific impact of the 2009 pandemic on excess emergency department (ED) visits in New York City; and 4) the shifting pattern of excess ED visits during the spring and fall 2009 waves across the greater New York region.

Presenter: Jens Lundgren, MD, University of Copenhagen & State University Hospital, Denmark
Title: Ongoing Global Assessment of Severity of the 2009 H1N1v Influenza A pandemic: INSIGHT (International Network for Strategic Initiatives in Global HIV Trials) FLU 002 and 003 protocols

Authors: Davey R, Dwyer D, Losso M, Lynfield R, Cozzi-Lepri A, Gey D, Herman-Lamin K, Hoppe A, Neaton J, Pett S, Standridge B, Uyeki T, Wentworth D, Lundgren J.

Abstract:

Background: Guidance on rational use of preventive and therapeutic interventions during an influenza pandemic requires detailed information on the spectrum of illness and those sections of the population at risk of severe disease. Early in the 2009 pandemic H1N1v influenza outbreak, a lack of adequate studies to address these issues was identified. INSIGHT – a global HIV trial network– received funding to launch two prospective observational studies (FLU 002/003) to address this knowledge gap.

Methods: FLU002 aims to assess risk factors for hospitalization among persons seeking care for influenza-like illness, whereas FLU003 aims to characterize risk factors for death or serious sequelae among persons hospitalized for severe and/or complicated influenza A illness. Consecutive eligible adults are being enrolled and prospectively followed (for 2 week and 2 months, respectively) at sites in 5 continents where ongoing regional community-transmission of H1N1v is documented. Specimens are collected for central virological confirmation and whole-genome sequencing. Comprehensive demographic, clinical, and laboratory data are collected real time.

Results: Funded in July 2009, both protocols were distributed to sites in August for planned implementation through an accelerated approval process in countries affected by the pandemic. However, local review processes delayed enactment at some sites until mid-Fall. Between October 2009 and February 2010, 676 outpatients (51% confirmed H1N1v+, median age 28, 52% women of whom 1% were pregnant) were enrolled in FLU002 at 37 U.S. and European sites, whereas 270 inpatients (58% confirmed H1N1v+, median age 43, 52% women of whom 12% were pregnant) were enrolled at 36 sites at these continents in FLU003. Sites in Thailand have also recently been activated, while other sites in Asia, Australia and South America await the next influenza wave.

Conclusions: Two ongoing observational studies are assessing the global severity of the 2009 H1N1v pandemic over time. The study design, implementation issues, and preliminary results from these two studies will be presented.

Presenter: Jens Nielsen, MSc PhD, Statens Serum Institut, Denmark

Title: Higher all-cause mortality in children during autumn 2009 compared with the three previous years: pooled results from nine European countries

Authors: Nielsen J, Mazick A, Mølbak K on behalf of the EuroMOMO pilot countries

Abstract:

The objective of this presentation is to describe the weekly fluctuations of all-cause mortality observed in nine European countries during the period between week 27 and 14, 2010 in comparison with three previous years. Data are derived from the weekly monitoring of mortality pilot project EuroMOMO. Results show that the mortality reported during the 2009 influenza pandemic did not reach levels normally seen during seasonal influenza epidemics. However, there was a small cumulative excess mortality in 5-14-year-olds, and possibly also among 15-64-year-olds.

This demonstrates the usefulness of timely mortality monitoring to assess the severity of the pandemic and the impact on different age groups in Europe, and underscores the added value of pooling data to detect possible deviations from baseline that may have gone unnoticed in analyses in individual small countries

Presenter: Katarina Widgren, MD, MSc, ECDC/ Statens Serum Institut, Denmark

Title: Surveillance of the 2009 influenza pandemic in Denmark: The school-children were hit the hardest

Authors: Widgren K, Skovbo Jensen K, Ethelberg S, Mølbak K.

Abstract:

Background: We estimated the burden of the disease in Denmark during the 2009 influenza pandemic using existing surveillance systems as well as setting up new ones.

Methods: To assess the dimension of disease burden, we collaborated with the Danish Broadcasting Corporation (DR) with an online survey during the peak of the pandemic, from which we attained age-specific proportions of people in society who consult their general practitioner (GP) when experiencing influenza-like illness (ILI). These proportions were combined with age-specific weekly ILI-counts from the existing surveillance of ILI reported by sentinel GPs. In order to correct for non-influenza ILI, we used week-specific percentages of positive samples out of all influenza samples sent to the SSI laboratory. To assess severity of disease, we compared the number of influenza-related hospitalisations in this season to the previous five seasons with a new registry-based surveillance system.

Results: The model gave an overall number of approximately 300,000 cases of pandemic influenza in Denmark between week 20 of 2009 and week 2 of 2010, which corresponds to approximately 5.5% of the population. The majority of cases (50-60%) were seen in the 15-64 years age group. The highest incidence of 15,800 influenza cases per 100,000 inhabitants was seen in the age group 5-14 years. The influenza-related hospitalisations showed the highest incidence in the elderly and children below 5 years. The relative burden compared to previous seasons was 2.0 in the age group 5-14 years and 1.1 in the elderly.

Conclusion: The surveillance of influenza in Denmark during the 2009 pandemic showed the highest incidence and a disproportionately high burden of influenza-related hospitalisations among school-children. These findings of a large disease burden in the young along with sparing of the elderly are consistent with the features of the first waves of the 20th century pandemics. Decision-making for public health actions in the future of the current pandemic could be backed using this consistency. With about 5.5% of the population affected by disease plus at least 6% of the population vaccinated plus the assumed immunity among the 16% of the population who are above 65 years of age, we believe it is unlikely that another wave of the pandemic influenza will affect Denmark before the winter of 2010/2011.

Presenter: Douglas Gill, Retroscreen Virology Ltd., UK.

Title: Harvard & the Great Pandemic

Authors: Gill D.

Abstract:

Two articles published in the year 1917 reported on an outbreak of ‘purulent bronchitis’ occurring during the preceding winter. In both articles, and particularly in relation to an outbreak at Etaples, in northern France, the word ‘epidemic’ was employed.

The question has arisen: Were these outbreaks in any way connected with the subsequent Pandemic?

To date, no certain answer can be given to this question. Our programme of research, though, addresses two subordinate enquiries:

1. Is it possible to confirm that an epidemic of a respiratory disease did pass through northern France in the winter of 1916-1917?
2. If such an epidemic did occur, by what mechanism could the underlying pathogen have spread throughout the Western world?

Our analysis of deaths at Etaples (and at other hospitals in France) does indeed point to the passage of an epidemic wave during the winter of 1916-1917. And no group of men and women were closer to the epidemic than were those graduates of the Harvard Medical School, who, together with nurses from Boston, Massachusetts, had volunteered for service at Etaples. They played a major part in dealing with the sick, they themselves fell sick, and, throughout 1916 and 1917, they were crossing and re-crossing the Atlantic and travelling through Western Europe on a scale which was scarcely matched by any other group.

The inference is clear. If the pathogen underlying the ‘purulent bronchitis’ was in fact an early form of the virus which caused the Great Pandemic, then these Harvard graduates and nurses may well have contributed to its ‘seeding’ throughout the Western world.

Presenter: Sverre-Erik Mamelund, PhD, Norwegian Institute of Public Health, Norway

Title: The impact of influenza on mental health in Norway 1872-1929

Authors: Mamelund S.

Abstract:

Previous research has studied whether influenza infection may have long-term effects. Studies have linked long-term effects of pandemics to indicators of mental health, intelligence, functional limitations, socioeconomic status, and mortality. Despite the clear impact of the Russian Influenza of 1889-90 and Spanish influenza of 1918-20 on mental health, as indicated by a large body of anecdotes from contemporary observers, there are very few empirical studies on the long-term historical association between influenza and mental health. First, a flow-chart model showing the effects the two pandemics had on mental health is given here. Second, annual correlates of first-time asylum hospitalizations of individuals with mental disease linked to influenza and the corresponding influenza mortality in the non-institutionalized Norwegian population 1872-1929 will be analyzed.

Results show that the number of first time hospitalized patients with mental diseases caused by influenza, compared to normal situations (respectively 1872-1889 and 1901-1917), increased by an average annual factor of 2.6 in the 5 years following the Russian influenza 1890-1894 in 1889 and by an average annual factor of 7.2 in the 6 years following the Spanish influenza 1918-1924. The analysis cannot determine the part played by social isolation, individual pain and depression of illness from influenza, fear and discomfort, or the interactions of these factors in explaining the excess hospitalizations. However, the analysis also shows that inter-pandemic seasonal influenza has an effect on the hospitalization rates, although much smaller compared to pandemics. The mental-health effect of seasonal influenza should mainly be a product of individual experience of influenza illness.

Presenter: Gearóid Ó Cuinn, MSC, LLM, University of Nottingham, UK
Title: The evolving relationship between influenza and the law in Britain
Authors: Ó Cuinn G.

Abstract:

Only a handful of governments took precautionary measures to mitigate the impact of the Spanish flu pandemic of 1918-19. Britain, a pioneer in public health, was no exception as the central authorities failed to take preventative action and tackle the disease. Most scholars blame World War I as necessitating a detached 'carry on' attitude in public health policy. Using discourse analysis of primary archival, medical, legal and media sources this paper follows the particular actors, including public health laws and the influenza microbe, to reveal how relevant networks coalesced, strengthen or failed during the Spanish flu pandemic.

Owing to prior experience of many of the actors involved with tackling the Spanish flu, it was the Russian flu pandemic (1889-92), as it is known in the West, which pre-determined how influenza was to be dealt with. In 1889 the medical profession, eager to maintain professional autonomy, was reluctant to take on public health legal obligations to tackle the disease. Their successful resistance of these measures shaped a reactive rather than proactive policy towards influenza which persisted until the arrival of Spanish flu. This paper also suggests that it was a constitutional crisis that promoted the predominance of legality and formal accountability within the civil service. This burdened the public health service and reduced its capacity to anticipate and prepared for emergencies. Furthermore the shift in understanding of the influenza microbe from being a bacterium to a virus resulted in the production of new legal actors to accommodate these changes. These laws became associated to the microbe forming a hybrid actor that influenced public health actors, bacteriologists and the medical profession. This sheds new light on the failure of public health authorities to assume leadership during the both pandemics.