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REVIEW

Insights from unusual aspects of the 1918 influenza pandemic

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Summary The 1918 influenza pandemic was the most lethal single event in modern history. Besides its mortality the 1918 pandemic was unusual for several reasons. It preferentially killed young adults from 20 to 40 y with a peak mortality at age 28 y. Mortality was highly variable with death rates varying by at least 10 fold within similar groups of citizens, soldiers, cities and islands. Secondary bacterial pneumonia following influenza was the overwhelming cause of death and not viral pneumonitis or acute lung injury. Clinical expressions of the 1918 pandemic were unusual with bleeding into the respiratory tree including epistaxis and dark blue cyanotic skin. The 1918 influenza virus apparently ceased circulation in the human population in the early 1920s but continued to evolve in pigs. Immunizations using viruses from 1918 and 2009 can cross-protect laboratory animals even though the human mortality outcomes were very different between the first pandemics of the 20th and 21st centuries. Unusual aspects of historical epidemics may help to reconstruct what actually occurred in 1918 and thus better prepare for the next pandemic.

1. Introduction

The 1918 influenza pandemic was the most lethal single event in recent history killing tens of millions globally, yet it is also one of the least understood major modern infectious disease outbreaks [1–4]. Several unusual or unique characteristics mark the 1918 influenza pandemic as being different from other influenza pandemics specifically and infectious disease epidemics generally [5]. The influenza virus causing the 1918 pandemic preferentially killed young adults, the healthiest segment of the population. It was also highly variable in its mortality outcome with rates varying >10 fold in apparently identical groups often those located in the same area at the same time. The final lethal event for the vast majority of patients in 1918 was a secondary bacterial pneumonia which is different from the viral pneumonitis and acute lung injury more typically seen

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in current avian influenza infections [6]. Clinically the 1918 influenza pandemic was unusual in the number of bleeding phenomenon observed including frequent epistaxis as well as a remarkably blue cyanotic skin labeled "heliotrope cyanosis" at the time. Even in the era of modern transportation it would be difficult for an influenza virus to show peak activity simultaneously on multiple continents much less when being transported in slow troopships as in 1918 [7]. For unclear reasons the lethal strain of virus disappeared in the early 1920s apparently being maintained in swine and subsequently it contributed genetic material to the virus of the 2009 pandemic [3].

These unusual aspects of the 1918 influenza pandemic beg the question of whether it was a unique event shaped by epidemiological events that will not reoccur or if it holds important unappreciated precedents for future influenza pandemics. This review will examine the extensive historical epidemiology data available as well as the admittedly sparse laboratory evidence from a time which predated the discovery of the viral cause of influenza in an attempt to answer the question of the likelihood of an event similar to the 1918 influenza pandemic reoccurring.

2. Young adult mortality

Despite most influenza infections in 1918 resulting in uncomplicated respiratory disease, young adults from 20 to 40 y died at much higher than expected rates [5]. This so-called W mortality curve where young adults died as well as the very young and very old was observed with some variation world-wide. That infants would be unable to resist a new virus is not as surprising as was the observation that many older adults survived influenza in 1918 whereas the elderly make up most modern mortality. As an example, despite the many thousands of First World War soldiers who died of influenza, no generals or admirals died unless they were particularly young for their rank due to rapid promotion [8].

More than just a band between 20 and 40 y, mortality specifically peaked in those 28 y of age in most populations where the data could be examined by single years including Canada, USA, England and New Zealand [9—11]. This means the 1890 birth cohort was particularly vulnerable to a worse outcome when infected with influenza in 1918 than those born only a few years earlier or later. Since the previous influenza pandemic began in 1890, it would appear that early life exposure to what was probably an H3N8 virus in 1890 enhanced mortality when infected by an H1N1 virus in 1918 [12]. Early life influenza infection is known to partially determine future immune reactions whereby the greatest serological reaction subsequently is still against the initial virus in a manner termed antigenic seniority or "original antigenic sin" [12]. A swine influenza model where killed virus immunization was followed by heterologous virus infection has been shown to cause a hemorrhagic pneumonitis not seen when using homologous viruses for immunization and subsequent challenge [13]. The mechanism of this enhanced disease during swine influenza is due to antibody-enhanced infection whereby non-neutralizing antibodies actually increase the virus's ability to infect respiratory epithelial cells. Epidemiological studies in three separate military populations suggest that a similar enhancement of infection was caused by previous influenza-like illness did occur in some closely followed groups in 1918 [14]. In the absence of any clinical samples from 1918 and very few remaining survivors whose first influenza infection occurred in 1918, it is unlikely one will ever be able to prove the relationship between the 1890 and 1918 pandemics, but there is sufficient data to recognize that not all influenza immunity is advantageous to the host. Further suggestions along these lines were found when Canadian seasonal influenza immunization increased illness during the 2009 influenza pandemic [15]. The sequence and timing of influenza infections partially determine subsequent disease outcomes.

3. Highly variable mortality

Just as early life influenza infection caused variation in mortality risk in 1918, entire populations appeared to have differing mortality risks despite being infected by the identical virus often in the same geographic area. In New Zealand where the Polynesian Maori population died at four times the rate of British immigrant population, this ethnically determined mortality difference was observed to decease in Maori though successive influenza pandemics [16,17]. Five percent of the Chamorro people died when the US Navy brought influenza to Guam; in spite of simultaneous high infection rates in the US sailors on Guam, only one died. Pacific islands influenza-related mortality varied by 50 fold with the most lethal epidemics occurring on the most isolated islands [18—20]. The infantry battalions with the highest and lowest mortality rates in the Australian Army fighting in Europe in 1918 were co-located in the same brigade rotating through geographic areas together [8]. Entire US cities differed by 10 fold in their influenza-related mortality with no apparent association with any particular geography despite an apparent relationship to past pneumonia rates [21,22]. Other examples could be cited but wherever accurate mortality figures could be generated, groups that would seem to have identical mortality risks actually died with at least a 10 fold difference between lowest and highest units. In 1918 this degree of mortality difference was not due to any medical or social interventions. Host factors were very important in determining the lethality of the 1918 influenza virus even if the exact mechanisms involved remain unknown.

4. Bacterial pneumonia following influenza

Influenza infects the cells of the respiratory epithelium causing an acute tracheo-bronchitis which may extend into the lung parenchyma to cause viral pneumonitis [23]. Destruction of the respiratory epithelium blocks normal resistance pathways allowing the entry of bacteria colonizing other parts of the respiratory tree to initiate bacterial pneumonia [24]. Secondary bacterial pneumonia killed approximately one in three patients in the pre-antibiotic era. The reason influenza in 1918 was so lethal was due to the increased proportion of persons with influenza who subsequently developed secondary bacterial pneumonia and not a difference in case fatality rates in