A parsimonious hypothesis to the cause of influenza lethality and its variations in 1918–1919 and 2009

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A R T I C L E   I N F O

S U M M A R Y

Current explanations to the high 1918–1919 mortality involve either a higher pathogenicity of the virus or bacterial super-infection in the absence of adequate therapeutic resources. However, neither of these hypotheses accounts for the age-distribution of severe cases and deaths, or for the geographic and other variations in rates and explosiveness of mortality during the Pandemic. It will be shown here that, alternatively, the epidemiology of the influenza lethality could be completely explained by a combination of two determinants: (1) acquired immune-differentiation of birth-cohorts, within populations, through developmental epigenetic adaptation (and selection) secondary to maternal or early-life episodes of influenza infection and (2) a triggering context – emergence of a new sub-type/strain, and its co-circulation (competition?) with seasonal viruses immunologically related to ones that had circulated in the past and primed particular population birth-cohorts. This article (1) presents age, geographic, and temporal variations in 1918–1919 and 2009 influenza severity, (2) presents and discusses ecologic evidence in favor of the hypothesis to influenza lethality advanced here, (3) suggests biologic mechanisms capable of explaining it, (4) retrospectively, proposes co-circulation between the Pandemic and a 1918 seasonal (H3?) influenza virus as the context for the increased lethality during the second wave of the 1918 Pandemic, and (5) predicts an increase in influenza severity in the northern hemisphere as the 2009–2010 season advances and H3 circulation increases.

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Introduction

Current explanations to the high 1918–1919 mortality involve either a higher pathogenicity of the virus [1] or bacterial super-infection in the absence of adequate therapeutic resources [2]. However, neither of these hypotheses accounts for the age-distribution of severe cases and deaths or for the geographic and other variations in rates and explosiveness of mortality during the Pandemic. According to Frost [3], epidemiologically, the overall mortality in 1918–1919 would be fully explained not by the incidence of influenza infection, but by the incidence of severe pneumonia cases. Therefore an alternative hypotheses to the severity of influenza cases will be addressed here that departs exactly from the epidemiology (time, person, and place) of the influenza mortality.

Antecedents

Azambuja [4] suggested that the high pathogenicity of the (H1) influenza virus among young adults in 1918–1919 might have re-

sulted from an immune response that went awry, in birth-cohorts originally primed by the influenza viruses emerging during the 1888–1890 Pandemic (according to sero-epidemiologic studies, possibly an H3 virus [5]). In 2009, severe cases and deaths have spared individuals born before 1957 (oldest than 60) [6–8], concentrating among those born in years of greater H3 (post-1968) and H2? (1957–1968) circulation [5].

As a general idea, it is proposed that early-life infection by contemporary circulating influenza viruses results, at the population level, in an acquired immune differentiation of successive birth-cohorts, both by adaptive epigenetic transformations capable of fitting fetal development to a new environmental condition (maternal infection and immune response), and by elimination of those genotypes unable to adapt. (For gene-environmental interactions, see Levins–Lewontin, 1996 [9], and Schmalhausen, 1949 [10]). Immune responses to different influenza sub-types would be less adaptive than to the subtype that originally primed each individual. An extensive literature exists on a phenomenon called influenza "original antigenic sin", described by Davenport [11] as follows: "It is now recognized that the major antigens of the strains of first infection of childhood permanently orient the antibody-forming mechanisms so that, on subsequent exposure to related variants of influenza virus, the cohort of the population would respond with marked reinforcement of the primary antibody" ([11],

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p. 453). Thus, it would be expected that (1) individuals originally primed by different types/sub-types of influenza viruses responded differently to ulterior influenza challenges and (2) due to the changing prevalence of influenza types/sub-types over time, individuals' priming would emerge, at the population level, as birth-cohort variation in vulnerability to influenza re-infections [12].

Birth-cohort priming, while capable of explaining the age-distribution of severe cases and deaths, does not explain the variation in the size of the outbreaks in different places or groups of people, in a same Pandemic. This paper introduces a second contributing factor to explain the epidemiology of influenza severity and mortality.

Hypothesis

It is proposed here that the levels and distribution of influenza mortality, mediated by the incidence of severe acute respiratory syndrome, would depend on levels of co-circulation (competition) between the new Pandemic virus and contemporary seasonal strains, particularly those belonging to different sub-types, and capable of reinforcing maladaptive immunologic responses in birth-cohorts initially primed by viruses similar to them.

The 1918–1919 and the 2009 influenza pandemics

The 1918–1919 Pandemic is usually described as a succession of three waves, the first one, mild, occurring in March–April–May in the US and reaching England in June–July [13], the second and most severe initiating in August 1918 and growing globally in September–October–November of 1918 [13,14], responsible for most of the deaths associated to the Pandemic, and a third wave early in 1919, more severe than the first but lighter than the second regarding mortality [13,14]. The main characteristic of the 1918 influenza pandemic, besides its enormous mortality toll, was the unusual age distribution of the influenza deaths. While the incidence of respiratory illness was highest in children under 10 years of age, dropping towards ages 15–24, rising to a second small peak at ages 25–40 and then declining as individuals aged, mortality from influenza and pneumonia was exceptionally concentrated in young adults [3,13,14]. Cases-fatality in 1918–1919 was higher among the military compared to the civilian population [14]. Other unexplained feature of the 1918–1919 Pandemic was the influenza-excess mortality variation across and within countries [14,15]. Among 40 US cities, Pearl [15] observed that "there [was] an extraordinary amount of difference between different cities in respect of the force with which they were struck by the epidemic ([15] p.1745)". The differences could not be accounted for by demographic factors, density of population, geographic position or recent growth of the population. The only factor that was shown to be correlated with the explosiveness of the outbreaks was the usual mortality level prevailing in the cities. Cities with relatively high normal death rates, and particularly ones associated with pulmonary tuberculosis, organic heart diseases and chronic nephritis and Bright's diseases, had also a relatively severe and explosive mortality from the influenza epidemic ([15], p. 1781).

Except for the rates of mortality, much highest in 1918–1919, there are interesting similarities between virologic, epidemiologic, and clinic descriptions of the 1918–1919 and the 2009 influenza outbreaks.

In 2009, the first confirmed cases of A/H1N1 infection in the world happened in March 2009, in the United States [16]. But the H1N1 strain responsible for the current outbreak possibly circulated among humans for several months before being identified as a new strain of flu, and possibly infected people as early as January 2009 in Mexico [17].

In Rio Grande do Sul (the southernmost Brazilian state, 10 million inhabitants), while isolated cases had occurred since May 2009, the epidemic took hold only after the Corpus Christi holiday (June 11–14, week 24), when many people traveled to the neighbor countries Argentina and Uruguay, both being then hit, as the State, by the worst winter of the last 50 years. Routine notification and testing of community cases was interrupted in week 27, when sustained local transmission of infection had been established. From then on, only severe acute respiratory syndrome cases were notified. The number of weekly notifications increased to about 1000 weekly suspected cases in weeks 30 and 31, and then rapidly declined to 136 suspected cases in week 35. Laboratory tests did not keep up with the increase in number of cases. But up until week 30, from 1466 available results, 59% were positive for the new A/H1N1 virus and 14.3%, positive for influenza A seasonal viruses, odds of 4:1. Up to week 35, the 4458 reported cases had resulted in 327 deaths. While cases concentrated around ages 20–29, deaths predominated at ages 30–59. Significant variations occurred in the geographic distribution of cases and deaths within the State, with areas heavily hit and others completely spared from severe disease and deaths [6]. Variation in mortality across different countries were also significant until September of 2009, with higher rates occurring in Mexico, Argentina, Uruguay, and Rio Grande do Sul/ Brazil than in the United States and European Countries [18].

Thus, both the 1918–1919 and the 2009 influenza pandemics (a) virologically, were shown to be associated with an H1 influenza virus, (b) epidemiologically, presented with high rates of infection among healthy young adults; were associated with unexpected severe respiratory disease among adult patients, including pregnant women [6,13], resulted in an unusual age-distribution of deaths, with low mortality rates above age 60, and showed great variation in geographic distribution of cases and deaths (c) clinically, the 2009 pneumonia cases resembled the descriptions of the 1918 hemorrhagic pneumonitis [19], with most hospitalizations occurring from 4–6 days from the first influenza manifestations (6th–8th day post-infection) and fast evolution to severe acute respiratory syndrome (Czepielewski et al., oral communication. Symposium on the A/H1N1 pandemic in the State of Rio Grande do Sul: reflections and perspectives, Universidade Federal do Rio Grande do Sul, Oct 5, 2009).

Ecologic evidence in favor of an hypothesis of association between influenza lethality and viral co-circulation

Influenza infection has a strong seasonal behavior, with marked increases in influenza-associated respiratory diseases during the winter. Co-circulation of a pandemic strain with other influenza viruses would therefore be expected to be small during the summer and highest in the winter. In 2009, the levels of circulation influenza viruses in the US in the summer was unusually high, but 99% of the identified viruses belonged to the H1N1 pandemic strain [20]. In Rio Grande do Sul, in the winter, the new H1N1 co-circulated with seasonal viruses in a proportion 4:1 [6]. Co-circulation of new and seasonal influenza viruses were also documented in Mexico. On May 15, answering a question about the possibility of a new, more pathogenic variant of the H1N1 virus to be circulating in some areas of Mexico, Celia Alpuche, head of the Instituto de Diagnóstico y Referencia Epidemiológicos (InDRE) in Mexico City told ScienceInsider: "We have seen influenza seasonal strains circulating even more than swine-origin A (H1N1) virus, in particular in areas in Mexico such as Durango, Jalisco, and Zacatecas. We started the subtyping of these strains and we are finding mostly A (H3) seasonal and also A (H1) seasonal" [21].

Furthermore, the fact that many severe cases in Rio Grande do Sul in 2009 occurred among travelers, truck-drivers and close to

main roads (Bercini M, Fichman A, Fagundes A, Ranieri T, Sehn L, Stima C, Paz F. Rio Grande do Sul State Health Department. Oral communication. Symposium on the A/H1N1 pandemic in the State of Rio Grande do Sul: reflections and perspectives, October 5, 2009), suggests that exposures to alien strains as well as to the ones circulating in one's own environment, within short periods of time, would increase the risk of influenza severity.

In 1918–1919, historical levels of mortality from cardiovascular, renal and respiratory diseases was the only factor associated with the differences found in the sizes of pandemic outbreaks among US cities. Elevated mortality from those chronic conditions could be taken as an indicative of high levels of influenza circulation. It is well known that influenza increases mortality associated with them [22]. Also, crowded environments, especially ones continuously receiving people from different origins, like military camps at times of induction, possibly favored high levels of co-circulation of respiratory viruses.

Biologic rational

As it is suggested to happen with Dengue, an association of disease severity with the number and order of infections by different influenza strains could be explained by cross-reactive interference of memory CD4+ T cells on the CD8+ T cell response against the secondary invader [23]. Chen and cols [24] studying immunity to lymphocytic choriomeningitis virus, murine cytomegalovirus and influenza A virus, in mouse models of respiratory viral infections, showed that "heterologous immunity induced two patterns of disease outcome dependent on the specific virus infection sequence: improved, if the acute response switched from a neutrophilic to a lymphocytic response or worsened, if it switched from a mild to a severe lymphocytic response" ([24], p. 1341), and suggested that "heterologous immunity occurs between many viruses, resulting in altered protective immunity and lung immunopathology, and that this is influenced by the specific virus infection sequence" ([24],p. 1341). Thomas and cols. [25] showed that, after a secondary challenge with a different influenza virus, hidden epitopes may emerge and switch protective immunity to an alternative antibody-mediated pathway. Oldest experimental studies also suggested immunopathology associated with influenza re-infections [26,27].

Implications

The southern hemisphere experience with the 2009 A/H1N1 influenza pandemic strongly supports the link between co-circulation of influenza sub-types (and co- or successive infections with different viruses in short period of time) and the degree of occurrence and distribution of severe influenza cases among particularly vulnerable birth-cohorts (those H2 and H3 primed, born after 1956). Severe cases were concentrated in a 2–4 weeks period during the winter, compared to a more extended period of circulation of the pandemic strain [6].

If the hypothesis presented here is correct, H3 viruses co-circulated with the 1918 pandemic virus during the second wave of the 1918 pandemic, reinforcing maladaptive responses of H3 primed birth cohorts (born around the 1888–1890 Pandemic) to the 1918 H1 pandemic virus. Serological studies done in the 1950s–1960s in the US and in Europe [11,28] found anti-H2 and anti-H3 influenza antibodies mostly among individuals born until around the turn to the 20th Century, but low levels of H3 antibodies were identified in cohorts born until about 1918 [11] and even 1936 [28], in samples collected before the 1968 Pandemic. Thus, co-circulation of different sub-types of influenza viruses, like happened after 1978, probably occurred also during the beginning of the

20th Century. The much higher level of mortality in 1918 was most likely associated with the very high level of influenza activity documented in the United States [22] and in Great Britain [13] from 1888–1890 to the mid-30s.

Based on what was discussed here, an increase in severity of influenza cases in the northern hemisphere is to be expected, as the circulation of seasonal H3 strains increases. A close observation of these trends may help us to disentangle the determinants of immunopathogenesis associated with influenza lethality.

Final remarks

We had learned a lot about influenza before the 1970s. But the decline in influenza, respiratory and infectious diseases in general, and the rise in coronary heart disease towards the second half of the 20th Century changed the research focus towards a group of diseases understood as degenerative as opposed to infection-related. The 2009 influenza pandemic represents an opportunity to re-evaluate the current research trend, to go back to unsettled issues related to infectious diseases epidemics and learning from the past the lessons we still may learn.

Conflicts of interest statement

None declared.

Acknowledgment

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