COVID-19 versus the 1918 influenza pandemic: different virus, different age mortality patterns

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Highlight

The influenza pandemic of 1918-19 and the SARS-CoV 2 pandemic of 2020 had markedly different age mortality patterns. Influenza in 1918 particularly killed young adults whereas the elderly are most at risk from COVID-19. Mortality depends on complex host-pathogen interactions specific to the viral and human population's history of infection.

Pandemics occur occasionally when an infectious agent wins its Darwinian gamble to successfully exploit another species such as ourselves. We are now in the midst of such a lethal pandemic with COVID-19 that has not been seen in living memory now that coronaviruses, likely of bat origin, have switched from high lethality, low transmission as in the case of SARS-CoV 1 to low lethality, high transmissionas in SARS-CoV 2; transmission being determined not only by R_0 but also by when in the clinical course cases become infectious. The likely consequences of this pandemic are unclear even as its enormous economic and human cost are only now becoming apparent. One point, however, has been fairly clear even from the earliest reports from China; COVID-19 mostly kills the elderly.[1] As the elderly are known to be a more vulnerable segment of the population, this should not come as a surprise, but it is distinctly different from the influenza pandemic of 1918-19. In the pandemic at the end of the First World War, young adults particularly those in their late 20s were those with the highest overall mortality rates for reasons that remain obscure a century later.[2] Just as coronaviruses are not the same as influenza viruses, no one would pretend that our epidemiological situation in 2020 is the same as 1918, but there are points of similarity and differences that can perhaps inform our current struggle against COVID-19 particularly in how two different age-mortality patterns resulted from these two distinct respiratory viruses.

The 1918-19 influenza pandemic remains the world's single greatest single mortality event of which we have detailed records. An estimated 50m deaths globally were not evenly spread with young adults, pregnant women and isolated populations bearing disproportional shares of the mortality. Most of those exposed to what we now know to be H1N1 influenza in 1918-19, however, did not become ill; typical attack rates were 1:5 to 1:3. Most of those who became ill had ordinary influenza-like illness and did not experience any severe symptoms.

Death was an unusual outcome (1-3%) that despite anecdotal horror stories of sudden death, more typically occurred in the second week of illness.[3] In the vast majority of cases mortality was directly due to secondary bacterial infections (e.g. pneumococcal, streptococcal) that came long after the influenza virus had completed its destruction of the respiratory epithelium.[4]

Although it is uncertain why mortality rates were particularly elevated among young adults, it is unlikely that the mortality curve which centered on age 28 years of age happened by chance. Some epidemiologists think it is more likely that the 1890 birth cohort was immunologically primed by exposure to the 1890 influenza pandemic, the last pandemic prior to that in 1918.[5] An individual's immune / infection history matters to influenza virus and has variably been referred to as "original antigenic sin" or "antigenic seniority" whose mechanism remains uncertain.[6] Children except the very young were largely spared; the elderly mortality patterns sometimes were high forming the third part of a "W" shaped curve, but that was not always seen.[7] The unique feature of the 1918 influenza pandemic was its propensity to kill young adults; the differences between subsequent pandemics in 1957, 1968 and 2009 lend credence to the proposition that variable exposure to earlier influenza viruses at least partially determines subsequent influenza mortality patterns. The pandemic of 2009 was different from seasonal influenza mortality patterns as the elderly were largely spared likely because of pre-existing immunity from infection with H1N1 viruses prior to 1957.[8]

Coronavirus mortality other than during the brief SARS-CoV 1 epidemics of 2003-04 has largely been ignored as the upper respiratory infections typical of children are rarely lethal. This changed in 2020 as the world became aware of the deadly consequences of SARS-CoV 2 among the elderly. Although it is impossible to be precise in the midst of an on-going

pandemic, COVID-19 mortality risk factors include male gender, age >60y (particularly >80y) and chronic medical conditions including hypertension, diabetes, obesity and cardio-vascular disease.[9] Why the elderly die is still being defined; in most people SARS-CoV 2 infection is unapparent or marked by relatively mild symptoms of an upper respiratory infection. In many elderly, however, a subsequent series of events usually in the second week of illness occurs which includes pulmonary infection, respiratory compromise, multi-organ inflammatory reactions and all too often death. The role of secondary infections is unclear especially since most Intensive Care patients are treated with broad spectrum antibiotics and colonization with hospital-resident bacteria is nearly universal in such units. The contribution of the immune system to mortality is also uncertain but many patients (e.g. diabetes mellitus) seem to have a dysregulated reaction sometimes referred to as a "cytokine storm" of inflammatory events leading to respiratory compromise and death.[10] Despite the uncertainties about the mechanism, the outcomes have been frighteningly clear with large numbers of deaths among the elderly reported particularly those in aged care facilities in Europe and USA. Whether in Wuhan or New York, COVID-19 appears to be killing a disproportionate number of the elderly.

Travel restrictions have a very different impact on influenza and COVID-19. No one expects to be able to stop influenza spreading through a large urban population due to its short (1-3 day) incubation and serial interval periods. SARS CoV 2, however, is less homogenous, associated with super-spreader events and has been relatively well controlled by tight travel restrictions around epicenters. Utility of travel restrictions is therefore a key distinguishing point in the public health responses between influenza and COVID-19.[11]

What then can the very different mortality outcomes of 1918 and 2020 teach us today; where are the similarities and what are the important differences? First one should accept that mortality is an inevitable and final destination with many antecedent pathways, so no matter how much society focuses on mortality rates, they may not be very informative as to the actual mechanisms involved. Highly lethal infections, such as SARS-CoV 1, often create their own epidemiological limitations. The reason that SARS-CoV 2 is important is that it is not highly lethal, thus allowing it to infect a vastly larger population leading to many more deaths overall despite relatively low mortality rates.

All of us have some immune / infection history from previous encounters with viruses. These differences may be important as it appeared to be in the unique young adult mortality peak of 1918-19 influenza or relatively unimportant as seen in the near absence of serious infections in children infected by SARS-CoV 2 in 2020. Social isolation in 2020 certainly has played an important role in preventing at least the first wave of mortality in many Pacific countries (Australia, New Zealand, Singapore, Korea) whose deaths have been counted in hundreds compared to European countries (UK, Spain, Italy, France) where the deaths are counted in tens of thousands. This was not always true as during the influenza pandemic of 1918-19 where the worst effected populations were those that were most isolated such as Pacific islands once the virus eventually arrived often on identifiable single ships. On such small Pacific islands, greatly different mortality rates resulted in resident populations who had very different childhood infection experiences. That the determining factor of pandemic mortality on such islands had little to do with the intrinsic pathogenicity of the virus itself; the population and its respective history of previous infections was what determined lethality.[12]

Infections are the initiating factor but often not the final determining factor of mortality. In 2020 the elderly are particularly at risk because they are already approaching the time of their individual mortality with less robust immune systems that are unable to effectively deal with a completely new challenge. There is also the problem of aged immune systems being less able to turn off an immune response once it is triggered by an infection. The pulmonary immune system requires an exquisite sense of balance; enough activation to destroy an invader without an overly robust response capable of damaging the fragile gas exchange system.[13] A real sense of the history of our previous infections is written into our individual immune systems; most of the time this plays out in the host's favour but that margin becomes increasingly narrow as we age. Fewer uncommitted lymphocytes are available from older bone marrows which are often populated by cells that are not prepared to take on new pathogens. Antibodies may not always be protective and antibody-dependant enhancement of viral infection is a distinct possibility with SARS CoV 2.

What therefore can we gather from our societal history of pandemic events? Differences in viruses are important but viruses as similar as SARS-CoV 1 and SARS-CoV 2 can still have very different outcomes based on where they focus the infection, lower vs. upper respiratory infections. Differences in populations are important and log factor differences in mortality rates were observed in similar populations in both 1918-19 and 2020 where previous infections / exposures are much more likely an explanation than genetic differences. One's previous infection history is important be it advantageous to the host (elderly during the 2009 influenza pandemic) or potentially lethal (early exposure to influenza in 1890 for the 1918 pandemic). Our hopes to re-balance the mortality equation in our favour against COVID-19 may depend on an eventual vaccine but that cannot occur in a vacuum without consideration of the often elderly immune systems we are seeking to boost.

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