Perspective

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

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Submitted 5 May 2020; Revised 21 May 2020; Accepted 25 May 2020

Key words: Influenza, SARS CoV 2, epidemiology, historical, age mortality rates

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 transmission as in SARS-CoV 2, transmission being determined not only by R₀ 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 50 m 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 > 60
years (particularly >80 years) and chronic medical conditions including hypertension, diabetes, obesity and cardio-vascular disease. 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. 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.

What then 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 favor 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.

### Acknowledgements

The author thanks Dr John Brundage and Prof John Aaskov for their long-term collaboration and comments on an earlier version of this manuscript.

### Funding

G.D.S. is an employee of the Australian Defence Force; no specific funding was given for this epidemiological study.

### Conflicts of interest

The author does not claim any conflict of interest.

### Contributors

G.D.S. is responsible for the entire perspective.
Disclaimer

The opinions expressed are those of the author and do not necessarily reflect those of the Australian Defence Force.

References

1. Verity R, Okell LC, Dorigatti I et al. Estimates of the severity of coronavirus disease 2019: a model-based analysis. Lancet Infect Dis 2020; 20:669–77.
2. Morens DM, Fauci AS. The 1918 influenza pandemic: insights for the 21st century. J Infect Dis 2007; 195:1018–28.
3. Shanks GD, Brundage JF. Pathogenic responses among young adults during the 1918 influenza pandemic. Emerg Infect Dis 2012; 18:201–7.
4. Morens DM, Taubenberger JK, Fauci AS. Predominant role of bacterial pneumonia as a cause of death in pandemic influenza; implications for pandemic influenza preparedness. J Infect Dis 2008; 198:962–70.
5. Gagnon A, Miller MS, Hallman SA et al. Age-specific mortality during the 1918 influenza pandemic: unravelling the mystery of high young adult mortality. PLoS One 2013; 8:e69586.
6. Gagnon A, Acosta JE, Madrenas J, Miller MS. Is antigenic sin always "original?" re-examining the evidence regarding circulation of a human H1 influenza virus immediately prior to the 1918 Spanish flu. PLoS Pathog 2015; 11:e1004615.
7. Chowell G, Viboud C, Simonsen L, Miller MA, Acuna-Soto R. 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. J Infect Dis 2010; 202:567–75.
8. Viboud C, Simonsen L. Global mortality of 2009 pandemic influenza a H1N1. Lancet Infect Dis 2012; 12:651–3.
9. Zhou F, Yu T, Du R et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020; 395:1054–62.
10. Li H, Liu L, Zhang D et al. SARS-CoV-2 and viral sepsis: observations and hypotheses. Lancet 2020; 395:1517–20.
11. Browne A, Ahmad SS, Beck CR, Nguyen-Van-Tam JS. The roles of transportation and transportation hubs in the propagation of influenza and coronaviruses: a systematic review. J Travel Med 2016; 23.
12. Shanks GD, Wilson N, Kippen R, Brundage JF. The unusually diverse mortality patterns in the Pacific region during the 1918–21 influenza pandemic: reflections at the pandemic’s centenary. Lancet Infect Dis 2018; 18:e323–32.
13. Goulding J, Snelgrove R, Saldana J et al. Respiratory infections: do we ever recover? Proc Am Thorac Soc 2007; 4:618–25.