REIMAGINING THE 1918 PANDEMIC

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In the century that has passed since the great 1918 influenza pandemic, there have been three further influenza pandemics in 1957, 1968 and 2009, but the combined death toll from these lesser pandemics is only a small percentage of the tens of millions who died in the 1918 pandemic. More died from the 1918 pandemic than in the First World War.

Like the Great War, this disaster has gradually receded from living memory, but the public health interest has not faded. The centennial of the great 1918 pandemic provides an opportune time for risk stakeholders to look back and learn important lessons from recent research.

The past cannot be changed and is traditionally treated by risk analysts as fixed. But from a scientific perspective, history is just one realization of what might have happened, given the randomness and chaotic dynamics of Nature. Reimagining the 1918 pandemic is an exploratory exercise in counterfactual history, considering alternative possible scenarios that might have happened.

The virtues of reimagining disaster history for both natural and man-made perils have been extolled in a recent Lloyd's report[1]. Nicholas Taleb, celebrated author of 'The Black Swan'[2], has warned that intelligence without imagination is a deadly combination. The exercise of imagination in reimagining disaster history is a systematic approach to tracking Black Swans. Most disasters have either happened before, almost happened, or might have happened before.

[1] Lloyd's (2017) Reimagining history: counterfactual risk analysis. https://www.lloyds.com/news-and-insight/risk-insight/library/understanding-risk/reimagining-history.
[2] Taleb N.N. (2007) The Black Swan. Penguin books.

The two key quantitative characteristics of a pandemic influenza virus are its degree of contagion, which governs its spread along social networks from one person to another, and its case fatality rate, which is the proportion of infected persons who succumb to the disease. For both characteristics, a major source of variability exists other than what is intrinsic biologically to the influenza virus. First, the degree of contagion of a pandemic depends on mass international population movements. Secondly, the lethality rate varies by age, and depends on early individual exposure to different strains of influenza viruses. These two sources of variability are reimagined in turn.

Contagion

Consider someone who is infected with influenza. The number of secondary infections generated by this primary infection is called the basic reproductive number R_0. This depends on the chance that an infected person infects another close by, which is a characteristic of the virus, and the number of people in the social network of the infected person, which is a characteristic of the social connectivity of the person. Those at hubs of social networks can become super-spreaders of infectious disease.

Pandemics are often associated with mass fluxes of populations, such as arise during times of war, when people are mobilized on an epic international scale. The large mixture of different populations increases the contagion of infectious diseases such as influenza. Significantly for risk assessment, political conflict and disease spread are causally linked. In Yemen, ravaged by civil war since 2015, the cholera epidemic has become the largest in modern history, with a million cases by the end of 2017.

The origins of the great pandemic of a century ago remain obscure. But the mass contagion on the Western Front was greatly exacerbated by a cohort of 95,000 Chinese labourers[3] who journeyed from Northeast China via ship to Vancouver; by train across Canada to Nova Scotia; by ship to Plymouth and other English ports; by train to Folkestone in southern England; before embarkation to their destination in France and Flanders. The Chinese Labour Corps programme was eventually cancelled by the British government because of the danger of 'plague' in China. Had this programme not been cancelled, the contagion source would have continued to fuel the pandemic.

[3] Humphries M.O. (2013) Paths of infection: the first world war and the origins of the 1918 pandemic. War in History, 21, 55-81.

The labourers were despatched by the Chinese government in the forlorn hope that by providing logistical assistance to the Allies, China might be restored its beautiful seaside port city of Qingdao, a former German colony. The 1918 influenza pandemic is mistakenly called 'The Spanish Flu', because Spain was neutral during the First World War, and there was no news embargo on the death toll there. Most likely, migrant Spanish and Portuguese workers travelling by train to and from France brought the pandemic to Spain[4].

More accurately and informatively, the pandemic might be termed, 'The Qingdao Revenge'. China was never granted what was sought in sending the Chinese Labour Corps to the Western Front, but the deadly scourge of influenza was spread around the globe. Infected ships sailed from Plymouth in southern England to Brest in France, Boston in USA, and Sierra Leone. From West Africa, infected ships sailed to Brazil[5] and elsewhere in South America etc. Another consequence of China being snubbed at the post-war Treaty of Versailles, was its distrust of the western powers and its leaning towards communism.

Counterfactually, the Chinese Labour Corps might never have been sent. Reluctant to make any colonial concessions, the British had originally rejected the Chinese offer of labourers, as they had turned down the offer of troops[6]. The mounting attritional losses on the Western Front changed the British response, but this was a finely balanced decision. The British war cabinet did not want to give China leverage over its crown colony of Hong Kong, or its other economic interests in China. The indifferent treatment of the labourers by the British army reflects the substantial chance that the Chinese Labour Corps might never have been permitted.

The deadly virus that first appeared in China in the winter of 1917-1918 might then have spread far more slowly overland westwards through Central Asia to Europe, with a smaller effective reproductive number R_0, and less global dispersion. The worldwide toll of influenza victims might then have been significantly mitigated. To understand this, consider the Ebola crisis of 2014-2015. The virus was effectively contained within West Africa, and this greatly

[4] Trilla A., Trilla G., Daer C. (2008) The 1918 'Spanish Flu' in Spain. Clinical Infectious Diseases, 47, 668-673.
[5] Schuck-Paim C. et al. (2013) Exceptionally high mortality rate of the 1918 influenza pandemic in the Brazilian naval fleet. Influenza and Other Respiratory Viruses 7(1), 27–34.
[6] South China Morning Post (2016) The forgotten army of the first world war, http://multimedia.scmp.com/ww1-china/.

reduced the number of victims. Had there been a large inter-continental migration of many tens of thousands from West Africa, Ebola would have spread by air rapidly around the world.

Figure 1: Map of Shandong province of Northeast China, from where many of the Chinese Labour Corps were recruited. The port city of Qingdao is shown on the east coast.

In general, standards of public health today are far higher than in 1918, and we may ponder the pathways by which a pandemic disaster of 1918 proportions could re-emerge. The nexus between political conflict and a global pandemic provides one clear route to disaster. If an epidemic were to emerge in one of the numerous developing regions in a state of political unrest, civil strife or anarchy, the absence of disease surveillance and fragile public health system could well allow the contagion to become established there and then spread abroad to other continents via refugees with little constraint.

Accordingly, a major global pandemic is a systemic financial risk, being coupled with supply chain breakdowns and business disruption, potentially aggravated by the chaos and disorder of political conflict. In 2015, when a million Syrian refugees migrated to Europe, an emerging pandemic disaster

might have arisen had there been a more transmissible mutation of the Middle East Respiratory Syndrome (MERS). The previous year, the emerging Ebola crisis might not have been contained if there had been a civil war in West Africa. Counterfactually, the political situation in Sierra Leone and Liberia might have been as unstable as in the 1990s, when there were civil wars in both countries.

Case fatality rate

The lethality of an influenza pandemic is measured by the case fatality rate. The pandemics of 1957, 1968 and 2009 had low case fatality rates of 0.13%, 0.1% and 0.05%. By contrast, the 1918 pandemic had a case fatality rate of 2.5%. A most remarkable aspect of the death toll from the 1918 pandemic was its extremely large age dependence. Counter-intuitively, since immune systems weaken with age, young adults were the most at risk.

This is clearly illustrated in Figure 2, which presents the number of deaths by age recorded for September and October 1918 during the deadliest wave of the pandemic in Montreal and Toronto, Canada. (In April 1918, the Canadian surgeon-general had instructed that the remaining Chinese Labour Corps transiting through Canada have no contact with the local population)[7].

The elevated number of deaths among young adults aged 20-40 in Montreal and Toronto is a very striking and anomalous feature of these plots. The peak at age 28 corresponds to those who were less than six months old at the time of the Russian influenza pandemic (1889-1890).

Such age-dependent plots have been a puzzle to explain for decades. The immune system of the aged resembles that of the new born. Both the very young and old immune systems are similarly compromised in coping with influenza. By contrast, the human immune response is fairly flat from late-teens to mid-sixties[8]. The age-dependence of the immune system within an individual may be interpreted as reflecting the evolutionary importance of young and middle-aged adults in the procreation and survival of the human species.

[7] Humphries M.O., ibid.
[8] Simon A.K., Hollander G.A., McMichael A. (2015) Evolution of the immune system in humans from infancy to old age. Proc. R. Soc. B 282: 20143085.

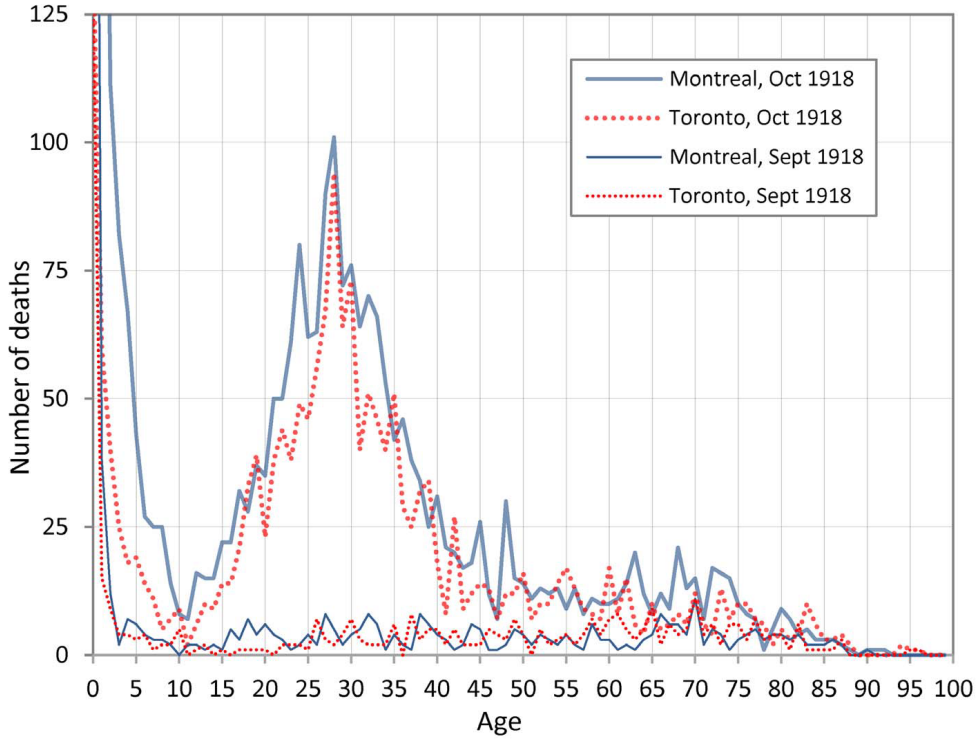

Figure 2: Age-specific mortality in Canada during the 1918 influenza pandemic[9]

There is now strong recent scientific evidence for the principle of antigenic imprinting, where the highest antibody response is against influenza virus strains from childhood[10]. The most recent pandemic in 2009 lends support to this principle[11]. This principle is a development of the concept of 'original antigenic sin'. More than sixty years ago, Thomas Francis[12] found that analysis of serum samples of influenza infections revealed minimal immunological responses against the current viral strain, but a response directed instead towards a strain previously encountered in children.

Even as someone grows older and acquires antibodies to other strains, the original antibodies are maintained at the highest levels at all times. For those people who were young around the time of the Russian influenza pandemic of the winter of 1889-1890, childhood exposure to H3N8, rather than the H1N1 strain, would have dominated their antibody response. This early exposure would explain their much higher vulnerability to the H1N1 pandemic of 1918.

[9] Gagnon A. et al. (2013) Age-specific mortality during the 1918 influenza pandemic: unravelling the mystery of high young adult mortality. PLOS ONE, 8, Issue 8, e69586.
[10] Henry C. et al. (2018) From original antigenic sin to the universal influenza virus vaccine. Trends in immunology, 39, No.1, 70-79.
[11] Reichert T. et al. (2010) Does Glycosylation as a modifier of Original Antigenic Sin explain the case age distribution and unusual toxicity in pandemic novel H1N1 influenza. BMC Infectious Diseases, 10, doi:10.1186/1471-2334-10-5.
[12] Francis T. (1953) Influenza: the new acquaintance. Ann. Intern. Med., 39, 203-221.

They would have had much lower immunity against secondary infection with a wide range of bacterial pathogens such as cause most influenza-related mortality[13].

Counterfactually, the Russian influenza pandemic might well have occurred some years earlier or later, in which case the age range of those most vulnerable to the H1N1 pandemic of 1918 would have shifted. Pandemic strains circulate as the primary seasonal flu for some years after a pandemic, so those born after a pandemic can still be exposed to the strain, as those born before.

If the Russian pandemic had struck a decade earlier, the vulnerable cohort would have been displaced to the age range 30-50 instead of 20-40. Conversely, if the Russian pandemic had struck one decade later, at the turn of the nineteenth century, the vulnerable cohort would have been aged 10-30.

Reimagining pandemic history still further, the Russian H3N8 pandemic might never even have happened in the 19th century. It is not so unlikely that there might instead have been another H1N1 pandemic virus. From this counterfactual perspective, the 1918 case fatality rate might be viewed as anomalously and conservatively high.

In this absence of the H3N8 pandemic, it is conceivable that the vulnerable cohort with low immunity to H1N1 would have been very small, and the average case fatality rate from the H1N1 1918 pandemic might have been much less than 2.5%, and closer to the case fatality rates observed for the three pandemics since 1918.

Lessons for pandemic risk in 2018

Traditional retrospective reviews of historical catastrophes have imagined what would happen if the event were to recur in our own time. But the fact that the lethality age-profile is dependent on childhood exposure rules out having the same age-profile as a century ago. In particular, whereas young adults were especially at risk to H1N1 in 1918 because of their childhood exposure to H3N8, this is not the case in 2018. Similarly, those in their 50s now would have been exposed to the H3N2 Hong Kong pandemic influenza in childhood. Cross-immunization within subtypes of flu, a feature of

[13] Worobey M. Han G-Z, Rambaut A. (2014) Genesis and pathogenesis of the 1918 pandemic H1N1 influenza A virus. PNAS, 111, 8107-8112.

antigenic imprinting, means that this exposure provides protection also against H7N9[14].

This review is different in reimagining what a major historical catastrophe might have been. This exercise in counterfactual risk analysis has important lessons for pandemic risk a century after the great 1918 pandemic. First, the nexus between political conflict and pandemic risk is worrying in the present unsettled global climate of international relations. According to UNHCR[15], the global population of forcibly displaced persons has grown substantially from 33.9 million in 1997 to 65.6 million in 2016 and remains at a record high.

The First World War has been the source of numerous essays in counterfactual history[16]. These are worth reading for insight into the dynamic instability of current military crises over armament, which reflects the Roman doctrine, 'If you seek peace, prepare for war'. The variability of crisis outcomes contingent on the prioritized national interests of powerful states is an obvious cause of concern in 2018. As shown by the false missile alert in Hawaii on 13 January 2018, the possibility of international conflict in Asia is taken seriously.

Secondly, recent pathogen research helps to explain the age variability of the case fatality rate and is encouraging for reducing pandemic mortality in the future. This research is improving understanding of how previous exposure to influenza strains affects antibody response. This is crucial for the future development of a universal influenza vaccine. Such a vaccine works differently from a seasonal vaccine, which has to be remade each year based on a best guess of what type of influenza is likely to be circulating. A universal vaccine would target part of the virus that does not change each year, and so should work against human, bird and swine influenza.

The recent scientific research findings are important for life insurers. Just from the age of an insured, a life insurer has knowledge of the influenza viruses against which immunity has progressively developed, most importantly possible childhood infections. For example, the cohort with childhood exposure to the H3N2 Hong Kong influenza pandemic of 1968-1969 would be more vulnerable to H1N1 or H5N1 dominated epidemics.

[14] Viboud C., Epstein S.L. (2016) First flu is forever. Science, Vol.354, 707.
[15] UNHCR (2018) Global trends: forced displacement in 2016. http://www.unhcr.org/globaltrends2016/.
[16] Ferguson N. (1998) The pity of war. Allen Lane.

A question for further research is whether antigenic imprinting can be overcome by increasing the antigen amount in a vaccine[17]. If this can be demonstrated, this would benefit those whose early childhood influenza infection was to a much different strain than is likely to occur in a future pandemic, or even epidemic.

Whilst the prospects for long-term influenza vaccine protection are bright, optimism about the current clinical trials of a universal influenza vaccine should be tempered by the increasing resistance to retroviral drugs[18], and also by the persistent threat of antimicrobial resistance (AMR). Countries, like India[19], with a particularly high consumption of antibiotics, may be especially vulnerable to an emerging pandemic.

[17] Henry C. Et al. ibid.
[18] Hussain M. et al. (2017) Drug resistance of influenza A virus: the epidemiology and management. Infection and drug resistance, 10, 121-134.
[19] Chaudhry D., Tomar P. (2017) Antimicrobial resistance: the next big pandemic. Int. J. Comm. Medicine and Public Health. 4, 2632-2636.