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COMMENTARY

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The 1918 influenza and COVID-19 pandemics: The effect of age on outcomes

The 1918 'Spanish' influenza pandemic and the current coronavirus disease 2019 (COVID-19) pandemic have been caused by two distinct respiratory viruses. The similarities and differences between each pandemic are summarized in Table 1. While the exact origins of the 1918 event have not been defined, it was caused by a founder influenza A virus strain of the H1N1 subtype.[1] Early reports described transmission of this influenza virus strain in the US army camps and the American Expeditionary Forces were involved in spreading the virus to Europe via maritime routes. Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), the cause of the COVID-19 pandemic, was first associated with human disease in Wuhan, China, in late 2019 and rapidly disseminated by air travel. Both pandemics spread globally with multiple waves of infection. It is estimated that 500 million people, or almost one-third of the world's population, experienced symptomatic disease during the 1918 pandemic, with possibly 50–100 million deaths.[2] The latest figures for COVID-19 (15 June 2021) list 176 million infections or approximately 2% of the world's population and 3.8 million deaths.[3] It is important to acknowledge that infection rates based on positive swab testing may be an underestimate of COVID-19, particularly in some countries with low testing rates.

Mortality associated with infection from circulating seasonal influenza virus strains generally follows a 'U-shaped' curve with high death rates in the very young and very old. In contrast, the 1918 pandemic produced a 'W-shaped' mortality curve with a high death rate in healthy young adults, which was responsible for most of the excess influenza deaths.[1] However, the mortality associated with COVID-19 is very different, where the vast majority of deaths have occurred in people over the age of 70 years.[3] Death in young children infected with SARS-CoV-2 is very rare. Therefore, age is a major determinant of clinical disease outcome following infection with the two respiratory viruses associated with these different pandemics.

Age has a profound effect on the susceptibility of individuals to infection, but this is an area which is still not well understood.[4] Neonates are born with limited immunity, with protection provided from maternal antibodies. The innate immune response in children develops before the adaptive response. Young adults (approximately 20–40 years) have well-developed and effective immunity. In older people, the immune system becomes less effective. Immune senescence occurs with increasing age.[4,5] The ageing immune system has decreased tolerance to self-antigens, which predisposes to the development of auto-immune disease. The adaptive immune response becomes dysregulated in the elderly with changes in the number and function of T- and B-cell compartments. Macrophage and neutrophil function decreases with age. Finally, inflamm-ageing is characterized by the increased production of inflammatory mediators with age.[4,5]

The leading cause of excess mortality in healthy young adults in the 1918 pandemic was secondary bacterial pneumonia.[1] Lung autopsy specimens have demonstrated severe bronchopneumonia with epithelial necrosis, haemorrhage, oedema, thrombosis and variant pathology from which pathogenic bacteria could be cultured.[1,6] Why there was such a high death rate in healthy young adults is not understood. It is possible that an inappropriately strong immune response may have contributed to poor outcomes; however, the published data supporting this proposition are limited. Damage to the bronchial epithelium and alveolar endothelium from direct viral cytopathicity and vigorous innate immunity[7] may predispose to opportunistic pulmonary infection with pharyngeal bacteria such as *Streptococcus pneumoniae*. A 'cytokine storm' may occur in severe influenza with contributions from both innate and adaptive immune cells resulting in lung damage,[8] but there are no specific human studies published in reference to the 1918 influenza outbreak. This is because the H1N1 influenza A virus that caused the 1918 pandemic was not known to be the aetiological agent at the time, with influenza A viruses only first isolated in the 1930s. While the strain causing the 1918 pandemic has since been recovered and reconstructed,[9] the viral virulence and host response

TABLE 1 Comparison of the 1918 influenza and COVID-19 pandemics

Parameter	1918 Influenza	COVID-19
Duration	1918–1920	2019–
Number of people infected (million)	~500	176[a]
Deaths (million)	>50	3.8[a]
Multiple waves	Yes	Yes
Reproduction number (R0)	~2.0	~2.5
Age group with highest mortality (years)	20–40	>70
Bacterial pneumonia	Yes	No

Abbreviation: COVID-19, coronavirus disease 2019.
[a]As of 15 June 2021.

factors that contribute to its severe pathogenicity remain under investigation today.

A proportion of patients with COVID-19 develop lung disease, such as pneumonia or acute respiratory distress syndrome, which may result in progressive respiratory failure. Mortality overwhelmingly occurs in adults over the age of 70 years. Post-mortem findings in COVID-19 demonstrate diffuse alveolar damage including capillary congestion, pneumocyte necrosis, interstitial and alveolar oedema and widespread thrombi.[10] In contrast to the 1918 influenza virus, SARS-CoV-2 infection is not generally associated with secondary bacterial pneumonia. A cytokine storm may occur in COVID-19; whether this is an appropriate response to severe infection or contributes to lung pathology has been controversial.[11] However, mild pharmacological immune suppression with dexamethasone has been clearly demonstrated to be beneficial.[12]

Whether immune senescence or inflamm-ageing is involved in poor outcomes is currently under investigation. Young children, including those less than 2 years of age, appear to be protected against significant clinical disease with COVID-19 and surprisingly have the best outcomes of any age group. Young children typically have no or minimal symptoms with SARS-CoV-2 infection, suggesting that they control and clear the infection very early. There are likely to be a variety of mechanisms responsible for this effect,[13] although at this stage definitive studies are lacking. Airway macrophages are the immune cells that rapidly respond to viruses in the respiratory tract. It is possible that macrophages could play a key role in determining the outcome of SARS-CoV-2 infection, particularly in children, but this is an area in which there are little published data.

Age appears to be a primary factor in the outcomes of both the 1918 influenza and COVID-19 pandemics, but the mechanisms responsible remain unclear. Studies that directly compare immune responses between different age groups may provide important insights as to why this occurs and have potential implications for treatment.

KEYWORDS
COVID-19, inflammation, influenza

CONFLICT OF INTEREST

The authors have no conflict of interest in this work.

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