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LETTER TO THE EDITOR

General correspondence

Origin of childhood leukaemia: COVID-19 pandemic puts the 'delayed infection' hypothesis to the test

The COVID-19 pandemic has changed human behaviour and practices. In an attempt to minimise the spread of the disease, countries worldwide have implemented various preventive measures including lockdowns, social distancing and mask mandates. While these measures proved imperative in containing the spread of the disease, their ripple effects may be detrimental to other aspects of public health.

For young children, lack of day-care and kindergarten attendance, when combined with social distancing, has not only prevented SARS-CoV-2 infections but also decreased other common childhood viral infections. For example, annual RSV and influenza infection rates in 2020 were exceptionally low.[1] As widespread COVID-19 vaccination managed to restrain the pandemic, some countries have begun lifting restrictions and returning to pre-COVID practices, reopening schools and day-cares in the process. We are now witnessing a post-restrictions surge of common childhood infections, overcrowding paediatric wards and emergency departments.

In the late 1980s, two hypotheses, the 'delayed infection' and the 'population-mixing', were suggested for the role of infections in the pathogenesis of childhood acute lymphoblastic leukaemia (ALL). There is ample evidence that the first genetic hit towards the development of childhood ALL frequently occurs *in utero*.[2] Only a small fraction of infants that are born with such aberrations will develop leukaemia.[3] The delayed infection theory claims that delayed activation of the immune system by infections results in secondary genetic changes, probably due to over-induction of lymphocyte precursors' RAG and AID enzymes, thus culminating in overt leukaemia. Both the 'population-mixing' hypothesis and the 'delayed infection' hypothesis claim that encountering an infectious agent later in life results in enhanced activation of a more mature immune system. Several epidemiologic studies, for example those that demonstrated a protective effect of day-care attendance and

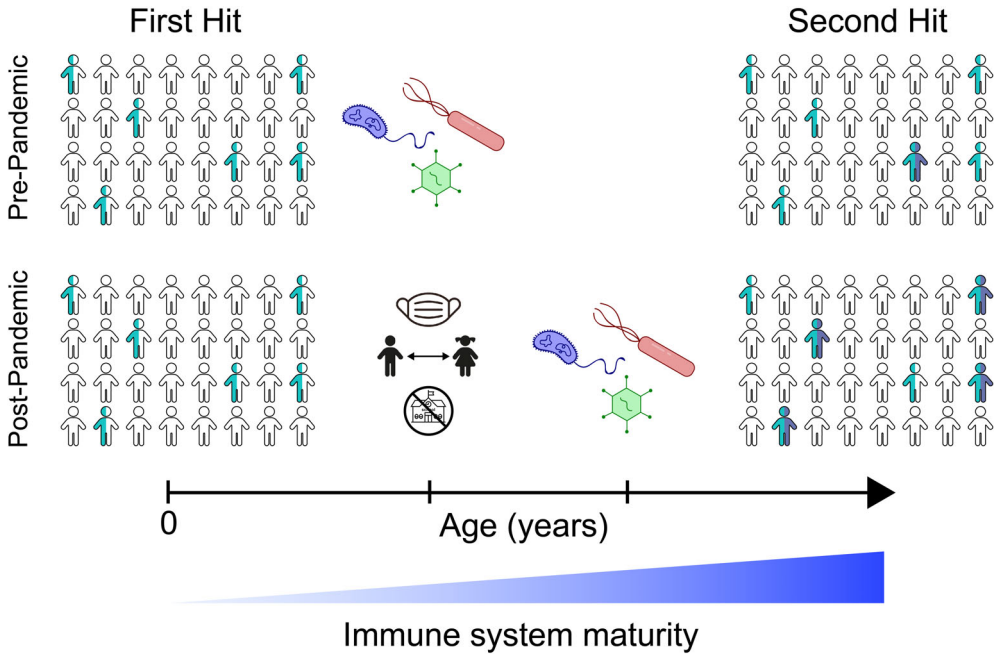

Figure 1 Schematic representation of the 'delayed infection' hypothesis applied to the COVID-19 pandemic. The first-hit leukaemogenic mutation usually occurs *in utero*. Late exposure to infections due to COVID-19 restrictions is hypothesised to increase the probability of a second-hit mutation, ultimately leading to higher acute lymphoblastic leukaemia incidence.

recently also experimental models, indeed support these theories.[4]

During the height of the COVID-19 pandemic, millions of children all over the world were shielded from common infections in early life, and are now belatedly exposed to them. Therefore, according to the 'delayed infection' hypothesis, the global response to the COVID-19 pandemic may increase the incidence of paediatric ALL in the coming years (Fig. 1). If such unfortunate occurrence is observed, it will provide a large-scale real-world setup for further substantiating the hypothesis. The proper monitoring of childhood ALL rates in various countries over the coming years, and its correlation to the restrictions put forth in these countries will further deepen our understanding of the relationship between age, type of infection and molecular characteristics of childhood ALL. This knowledge may direct future research aiming to prevent the transition from pre-leukaemic to leukaemic states. Finally, the similar, more general 'hygiene hypothesis' links decreased exposure to early life infections with a higher incidence of both autoimmune and allergic diseases.[5] Thus, a possible post-COVID restrictions surge may apply to these immune dysregulation conditions as well.

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