COMMENTARY

Upsurge of acute respiratory infections among children post-COVID-19 pandemic

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The COVID-19 outbreak has brought about significant shifts in the epidemiology of respiratory infections across several dimensions. The advent of the COVID-19 pandemic led to a notable decrease in the circulation of typical respiratory pathogens in several countries owing to the implementation of non-pharmaceutical interventions (NPIs), such as lockdown measures, the widespread use of respiratory masks, social distance, and school closure.[1] NPIs, crucial for epidemic prevention and control, effectively slow down the spread of SARS-CoV-2. However, after the relaxation of COVID-19 restrictions, a surge was seen in respiratory infections among children. This heightened pediatric hospitalizations and medical visits. In the USA, respiratory syncytial virus (RSV) activity peaked in the spring and summer of 2021, and Australia experienced an early surge in seasonal influenza virus activity in June 2022.[1] Other pathogens, such as human metapneumovirus (hMPV) and human bocavirus (hBoV), all rebounded as pandemic NPIs were lifted.[1] The World Health Organization (WHO) reported the pandemic of *Mycoplasma pneumoniae* pneumonia in the autumn and winter of 2023 in China (https://www.who.int/news/item/22-11-2023-who-statement-on-reported-clusters-of-respiratory-illness-in-children-in-northern-china). This upsurge has garnered international attention, emerging as a focal point of research and a critical subject of inquiry. However, the factors contributing to this resurgence remain unclear.

In an article titled "Pediatric Infectious Disease Group (GPIP) position paper on the immune debt of the COVID-19 pandemic in childhood, how can we fill the immunity gap?", the French researchers were the first to introduce the concept of the immunity gap, which refers to reduced immune stimulation in the population during periods of stringent social restrictions that might heighten the vulnerability of children to infections caused by common respiratory pathogens.[2] In 2023, the WHO adopted the concept of the immunity gap, alternatively known as an immune debt, to explain the upsurge of influenza viruses, RSV, and other respiratory pathogens

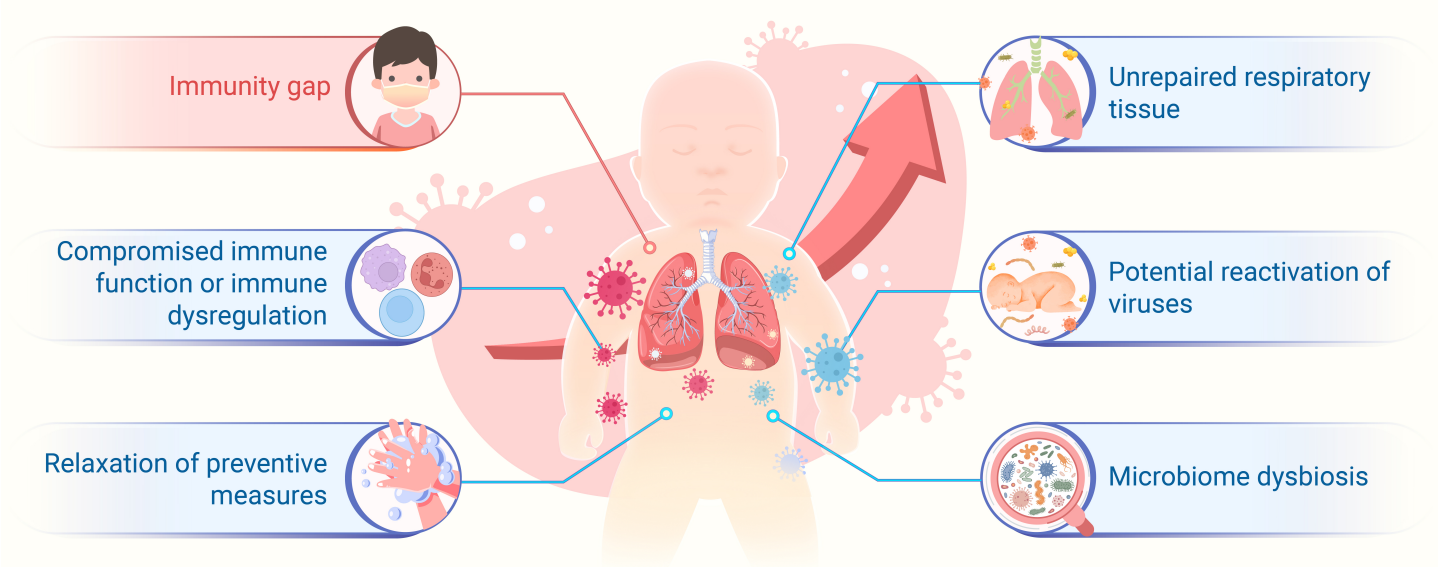

Figure 1. The possible reasons for surging of respiratory infection post- COVID-19.

The theory of the immunity gap has gained considerable traction, offering an understandable rationale for the ongoing rise in respiratory infectious diseases among children. Several factors are believed to play a role in contributing to this phenomenon. This study highlights reduced exposure to microorganisms, inadequate stimulation of the immune system, and disruptions to vaccination schedules, leading to an elevated number of susceptible individuals and a decrease in overall herd immunity. The implementation of NPIs aids in preventing COVID-19 and mitigates the risk of other respiratory pathogens. However, the decline in viral and bacterial infections during the COVID-19 lockdown, has resulted in insufficient immune stimulation within the population, further contributing to an increase in susceptibility and a decline in herd immunity. Many children who would typically have encountered RSV a year or two earlier might have their first exposure and subsequent infection with RSV after the relaxation of these interventions. The median age of the surge in RSV cases was older than that in the pre - pandemic era, which may be attributed to the expansion of the RSV - naive cohort because of strict NPIs.[3]

The disruption of immunity stimulation in children presents another potential explanation for the immunity gap. When respiratory pathogens invade, they can trigger innate and adaptive immunity. This process leads to the

development of nonspecific and specific memory immunity, enhancing the body's ability to defend against future pathogenic invasions, including macrophages, NK cells, T lymphocytes and B lymphocytes. However, the effectiveness of memory immunity decreases over time. Consequently, individuals miss out on the memory response they would have acquired if they had encountered some of these or other viruses for the first time in the preceding years. Another significant factor contributing to the immunity gap is the delay or cessation of vaccinations. Throughout the lockdown periods imposed due to COVID-19, vaccination coverage rates experienced a notable decline. Vaccines designed to combat respiratory infections play crucial roles in stimulating immune responses. However, if vaccination is delayed or halted, the protective effects decrease over time, resulting in an immunity gap rendering children more susceptible to infections. Moreover, individuals grappling with the clearance of the SARS-CoV-2 infection may experience compromised immunity, even if they have been vaccinated. Moreover, the diminishing protective effect of maternal immunity against infection emerges as a notable factor contributing to the immunity gap. Maternally derived antibodies play a crucial role in conferring immunity to newborns. The implementation of NPIs reduces maternal exposure to microorganisms, impeding the natural immune enhancement resulting from common infections. As the duration of exposure to microorganisms extends, antibody titers in mothers gradually decrease. Vaccinating mothers late in pregnancy with influenza, whooping cough, and other vaccines can elevate antibody levels in newborns, consequently reducing the risk of infection. However, when infants receive lower titers of maternal antibodies, these antibodies decline more rapidly over time. This decline prevents infants from reaching the anticipated level of immunity and widens the immunity gap. However, varying expert opinions exist, highlighting the need for further research on the immunity gap.

Furthermore, the upsurge of acute respiratory infections among children post-COVID-19 is not easily explained solely by the concept of an immunity gap, as there are still unexplained factors at play. Viruses, including SARS-CoV-2, are known to actively induce immune dysfunction. Children affected by SARS - CoV - 2 infection may undergo prolonged immune suppression or dysregulation,[4] manifesting as persistent reductions in dendritic cell numbers, exhaustion of T lymphocytes, elevated levels of activated cells and levels of IL-17, and IL-2 in patients with long COVID, and the development of autoimmune disorders. This compromised immunity can increase the susceptibility to other infections.[5] In addition, COVID-19 related physiologic and physical changes, and immunosuppression could active other viruses. Numerous intricate other factors must be considered in this context, such as changes in viral characteristics, alterations in crowd behavior, abusing and increased resistance rates of antibiotics, unrepaired respiratory tissue damage resulting from microthrombi blocking tissue perfusion, and microbiome dysbiosis (Figure 1). The high levels of dysbiosis in the respiratory microbiota of patients with COVID-19 might be a factor potentially related to infection by other pathogens. Children's susceptibility to respiratory infections is also rooted in their immature respiratory structures and the development of their immune systems.

Addressing this intricate scenario requires concerted effort involving healthcare providers, public health authorities, and families. Ongoing measures, such as health education initiatives, implementation of NPIs to combat common respiratory pathogens, pathogen surveillance, and reinforcement of vaccination programs—especially for influenza and SARS-CoV-2, should be consistently applied. These endeavors are geared towards not only limiting the transmission of pathogens, but also bolstering collective immunity, which could consequently reduce the current immunity gap. Implementing these measures could prove instrumental in mitigating or even preventing future outbreaks of respiratory infections. Sustained monitoring of respiratory pathogens and their circulation stands as a critical tool for comprehending viral seasonality and strategically planning preventive measures and healthcare resources. This surveillance contributes to understanding viral patterns and offers valuable insights for the development of preventive strategies and the efficient allocation of health resources. Concerted efforts must be made to ensure the safe and appropriate prescription of antibiotics to reduce and even prevent the development of antibiotic resistance. Essentially, recognizing and promptly responding to the evolving landscape of respiratory infections in children is vital for effectively safeguarding their health.

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