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Public Health PERSPECTIVE

The Innovation Medicine

Population immunology: Building immune barriers to confront the global challenges of respiratory pathogens

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Received: October 20, 2025; Accepted: April 29, 2026; Published Online: April 30, 2026; https://doi.org/10.59717/j.xinn-med.2026.100220

Citation: Liu J. (2026). Population immunology: Building immune barriers to confront the global challenges of respiratory pathogens. *The Innovation Medicine* **4**:100220.

The COVID-19 pandemic has profoundly reshaped the global landscape of respiratory pathogen circulation and has also fundamentally renewed our understanding of host antiviral mechanisms, particularly the population immune barrier (PIB). Understanding the dynamics mechanisms of the PIB and its interaction with the pathogen circulation, are crucial for effective pathogen control and the pandemic preparedness. Absent, low-level or decreased pathogen exposure, would create so-called immunity gap in the population, and heighten susceptibility to influenza, RSV, and other infections. Accordingly, previous infection and/or vaccination contribute a pre-existing immunity or reverse pre-existing immunity to the future emerging or re-emerging pathogen infections. The recent knowledge has put forward the initiation of Population Immunology as one of the important branches of immunology, which involves multidisciplinary collaboration across fields such as immunology, epidemiology, etc. Implementing application-orientated basic research and the strengthening the development of pathogen surveillance and intervention measures can further support a well-prepared PIB for the next pandemic.

THE FLUCTUANT GLOBAL CIRCULATION OF INFLUENZA AND OTHER RESPIRATORY DISEASES

Since the outbreak of the COVID-19 pandemic, the prevalence of influenza and other respiratory infectious diseases has shown a relatively obvious fluctuating trend in contrast to the seasonal epidemic. A sharp decline in the number of influenza cases was observed for the 2019-2020 influenza season, according to the surveillance system of different countries and regions.[1,2] However, from 2021 to 2024, a surge of influenza occurred, with levels higher than the average during the same period before 2020, followed by the high prevalence of H3N2 in the recent 2025-2026 season. Apart from influenza viruses, other respiratory pathogens like respiratory syncytial virus (RSV), human bocavirus, rhinovirus, parainfluenza viruses, and adenovirus have also atypically circulated in different periods in the past years.[3]

THE RELATED IMMUNE UNDULATION AMONG THE POPULATION

The recent rebound in common respiratory diseases across different countries and regions[2] can be attributed to the decreased population immune barrier (PIB) following a prolonged period of exposure to minimal respiratory pathogens, also referred to immune gap or immune debt. Immune gap is a concept of population associated with population immunity (or herd immunity). With the further waning of immune memory acquired from previous infections before 2020, the immune gaps increase and make population susceptible to future pathogen strains. This may potentially lead to more infection and transmission of respiratory pathogens.

Children, particularly born between 2020 and 2022, are more vulnerable in recent waves of respiratory infection, considering their developing immune system. They have minimal exposure to common pathogens like influenza and RSV for 2-3 years, limiting their natural immunity development by infection or transplacental transfer of maternal antibodies. The immune system matures through early pathogen exposure, but these infants have been only exposed to minimal pathogens in the early years. As respiratory infections surge, both the immune immaturity of the newborn and the weak immunity inherited from the mother create potential immune gap among children, making them more susceptible to common pathogen infections.

THE CONCERN ABOUT THE WANING PIB TO INFLUENZA B/YAMAGATA DUE TO ITS "EXTINCTION"

Among seasonal influenza viruses, influenza B/Yamagata shows unusual characteristics without detection in the past several years, which seems to have been driven into extinction in the last several years. Based on its sustained absence in global surveillance and biosafety concern, the World Health Organization has recommended dropping this component among many influenza vaccines.[4] However, we should be careful to distinguish with certainty between lack of detection and true extinction. According to the historical surveillance data, both the B/Victoria and A/H3N2 infections reversed after a long period of silence.[1] Rather than being eliminated, respiratory pathogens often continue to circulate, mutate, and (re)infect members of the population whose immunity wanes over time. These remind us of a resurgence of epidemics when a growing proportion of "susceptible" people in the population.

Although the true status of B/Yamagata remains uncertain, several factors warrant continued vigilance. One possibility of the "dormancy" of B/Yamagata is that the cold-chain can act as a carrier for the "silent spread" of the virus and provide a time span for virus transmission in the future. Even if the B/Yamagata does become extinct among the human, there is the potential of circulating in animals.[5] Therefore, vaccination without B/Yamagata might result in long-term immune gap and invite a later but more serious rebound of this lineage. Ongoing monitoring strategies-including sentinel surveillance and genomic sequencing are essential to detect any re-emergence promptly. It is easier to walk downhill than uphill.

PRE-EXISTING IMMUNITY AND REVERSE PRE-EXISTING IMMUNITY CONTRIBUTE TO IMMUNE BARRIER

PIB is influenced by infection, vaccination, population turnover, and pathogen evolution, etc., with pre-existing immunity from previous infection or vaccination playing a pivotal role. Due to the broadly-existing conserved T cell epitopes among different type/subtype/clade/variants of respiratory pathogens, the pre-existing T cell immunity to new virus/variant among the populations raised by previous infection/vaccination can be detected and also provide some protection. During the pandemic of SARS-CoV-2, the HLA-B15 restricted peptide $S_{919-927}$ was linked to asymptomatic infections of COVID-19 in Australia.[6] This indicates a potential role of pre-existing immunity to SARS-CoV-2 raised by previous infections of common cold coronaviruses (CCC). Up to the post COVID-19 era, most of the population worldwide have developed immunity to SARS-CoV-2 through either natural infections or vaccinations. Thus, the global spread of SARS-CoV-2 thus far has altered the baseline immune background of the population against coronaviruses, which may influence the clinical manifestations of future coronavirus infections and the efficacy of vaccination. Therefore, exploring the reverse pre-existing immunity of the population against other coronaviruses is of great significance. Our previous study on the established PIB against SARS-CoV-2 has revealed the characteristics and molecular mechanisms of the "reverse pre-existing immunity" and cross T-cell immune barrier against other human coronaviruses established by SARS-CoV-2 infection.[7] Moreover, we found non-conserved peptides play a dominant role in cross T-cell responses among the T-cell epitopes, providing new insights into SARS-CoV-2 PIB and the development of broad-spectrum peptide vaccines against coronaviruses.

In addition, the infection or vaccine can protect against unrelated infections by trained immunity and nonspecific protection through epigenetic reprogramming of innate immune cells. This "off-target" protection might explain the low influenza cases from November 2022 to January 2023 in China,[8] and also the postponement of the RSV peak during that epidemic season. As the transient innate immunity formed during the peak of respira-

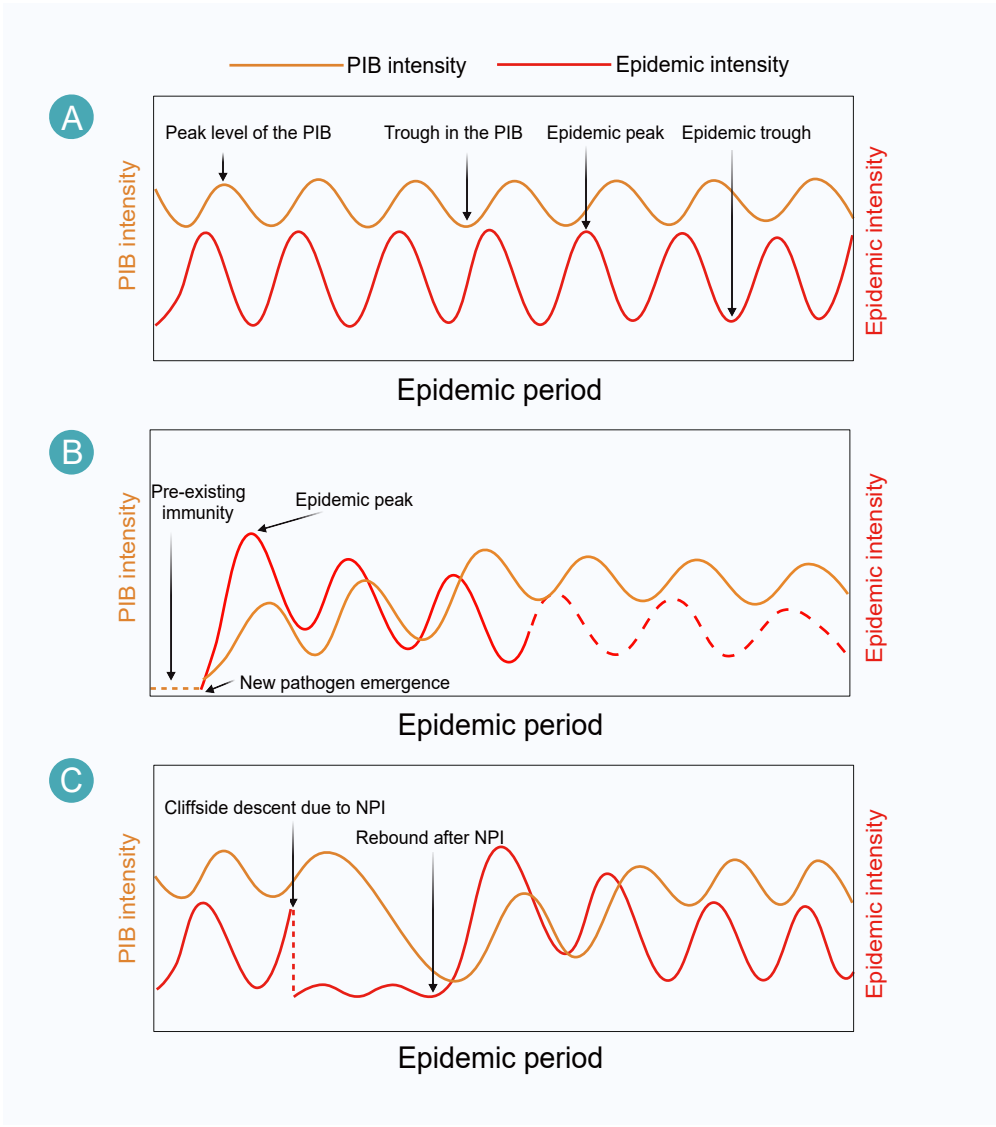

Figure 1. Herein, I propose three possible patterns of interaction between population immune barrier (PIB) and the epidemic of respiratory infectious diseases (A) The seasonal fluctuation pattern. The epidemic of the infectious disease (e.g., influenza) may be influenced by PIB, while PIB is maintained through periodic viral circulation. (B) The emerging pathogen pattern. Pre-existing PIB is absent or very weak initially, then gradually strengthens with accumulated infections and vaccinations, thereby slowing the emergence of variants. (C) The immune gap reconstruction pattern. Low-level circulation of a specific pathogen over a period of time gradually weakens PIB, leading to a rebound in the pathogen's prevalence.

tory pathogen infection waned over time, the number of influenza virus and RSV cases crept up from the spring of 2023.

THREE FORMS OF THE INTERACTION BETWEEN THE PIB AND VIRUS TRANSMISSION

For the seasonal epidemic of a pathogen, like influenza virus, the transmission might be influenced by the PIB, strengthened by the periodic epidemics (The seasonal fluctuation pattern, Figure 1A). This reflects a close interaction between the pathogen circulation and the PIB. For emerging infectious diseases, the PIB builds up and is gradually enhanced as the epidemic progresses and persists (The emergingpathogen pattern, Figure 1B), resulting in a slower emergence of potential new variants over time. For instance, our recent research based on serotype classification also revealed a similar deceleration trend of new variants in the COVID-19 epidemic. This might be related to the continuous strengthening of the PIB based on conserved epitopes. Whether the further trend of the COVID-19 epidemic will turn into a seasonal pattern like that of influenza remains to be seen. Interestingly, at the early stage of the COVID-19 outbreak, global non-pharmaceutical intervention (NPI) measures like mask-wearing and social distancing sharply reduced the prevalence of respiratory pathogens in early 2020 and remained low for a long time, leading to immune gaps in the population and weakening the PIB. With the relaxation of COVID-19 control measures, a rebound of respiratory pathogens has been observed globally, which is the process of re-establishing the PIB (The immune gapreconstruction pattern, Figure 1C). Therefore, the PIB plays a significant role in the emergence, transmission, and fluctuation of emerging and re-emerging respiratory pathogens.

PERSPECTIVES AND CHALLENGES FOR POPULATION IMMUNOLOGY

Now the co-circulation of respiratory pathogens poses a serious threat to global health systems. It is a challenging undertaking to recover to a common situation as before. The covering of the immune gap takes time, but the PIB established by past infections or vaccinations gradually weakens over time. Furthermore, the immune escape is still going on, caused by frequent mutations of RNA viruses. Respiratory polymicrobial collision occasions an optimal chance for the mutation and/or reassortment events, which possibly generates novel pandemic-risk variants with high transmissibility, especially for the influenza viruses. Furthermore, PIB show substantial regional heterogeneity, particularly between high-income countries and low- and middle-income countries (LMICs), driven by differences in vaccine availability, vaccination coverage, NPI adherence, and access to diagnostics and antiviral therapies. In LMICs, lower vaccine uptake and limited healthcare resources may prolong immune gaps and increase vulnerability to the co-circulation of respiratory pathogens.

In the face of threats from co-circulation of multiple respiratory pathogens, we need the simultaneous advances of prevention, diagnosis and treatment technologies. First, Sun Tzu's art of war said that the supreme art of war is to subdue the enemy before fighting. Vaccines play a key role in bridging immunity gaps, particularly in populations with limited natural exposure or waning immunity. To maintain a resilient PIB, vaccination strategies should prioritize high-risk groups and ensure adequate coverage, including timely booster doses based on antibody waning and T-cell memory profiles. The consolidation of the PIB has put forward more requirements for enhancing the development of universal vaccines, especially based on the broad-spectrum recognizing targets by T cells. Second, integration of diagnostic and immunological data allows dynamic assessment of PIB and identification of immunity gaps. Rapid pathogen detection and identification enable timely clinical diagnosis and treatment. Therefore, adequate supply of diagnostic reagents and developing the testing capacity, particularly in multiplex testing, are necessary to tackle the outbreak. Third, timely and appropriate antibiotics and antiviral drugs use aided by accurate diagnosis is crucial to improve patient outcome and prevent antimicrobial resistance. There are limited diversity and number of available medications suitable for use, especially for susceptible populations like children. Development of broad-spectrum antiviral drugs, including monoclonal antibodies with different targets and mechanisms of action would be beneficial for prophylaxis in face of the continuous viral mutation and appearance of drug resistance. Linking drug use to real-time surveillance and immunity monitoring can further reinforce population-level protection and overall PIB resilience.

Humans are always facing the threats of diverse pathogens and their variants with emerging immune escape characteristics of mutations. The experience from COVID-19 has taught us that all individuals, specific groups, or isolated regions are all linked to each other. Guided by the concept that all of humanity is an interconnected whole, we need establish the framework of Population Immunology to study how immunological characteristics of the population, such as susceptibility, resistance, or vaccination status, influences the spread, persistence, and evolution of pathogens. Similar to the logical framework of the cold-chain-based epidemiology (CCBE) I proposed,[9] the establishment and development of Population Immunology need multi-disciplinary, multi-departmental and regional cooperation to improve the understanding from theory to practice. Firstly, multi-disciplinary cooperation is needed to establish a platform, involving immunology, epidemiology, genetics, evolutionary Biology, public health, and sociology, etc. Secondly, establishing an AI- or machine learning- based PIB monitoring and prediction platform is feasible and necessary, enabling early warning, dynamic assessment, and optimization of intervention strategies.[10] Thirdly, the disparities across countries and regions highlight the need for the cooperation between various international partners, the collaborative formulation of region-specific strategies, and the communication based on One Health concept to enhance PIB resilience in the post-pandemic era.

To address the complex and evolving pandemic preparedness, scientific popularization and strategic scientific suggestions for social governance are also essential. By integrating researches at both the pathogen (micro) and population (macro) levels, such studies will provide theoretical and applicable basis for the pandemic preparedness. Furthermore, beyond generating scientific insights, innovations can serve as collaborative platforms that strengthen international partnerships and support decision-making for future pandemic responses.

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FUNDING AND ACKNOWLEDGMENTS

I thank Professor George Fu Gao, Professor Yi Shi, Dr. Beiwei Ye, Dr. Jinmin Tian, and Ms. Jiayu Sang for their constructive suggestions and assistances. This work was supported by the Major Project of Guangzhou National Laboratory (GZNL2025C01001), the National Key Research and Development Program of China (2025YFE0206300), the National Natural Science Foundation of China (NSFC, 92269203), and NSFC Young Scientists Fund (A) (82525060). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

AUTHOR CONTRIBUTIONS

The author contributed to and approved the manuscript.

DECLARATION OF INTERESTS

Jun Liu is an Editorial Board member of The Innovation Medicine and was blinded from reviewing or making final decisions on the manuscript. Peer review was handled independently of this member and their research group.