International Journal of Infectious Diseases 163 (2026) 108278

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

# Pathogen-specific immunity debt in children after prolonged nonpharmaceutical interventions: a cross-sectional study in China

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ARTICLE INFO

*Article history:*
Received 29 September 2025
Revised 28 November 2025
Accepted 1 December 2025

ABSTRACT

*Background:* During the COVID-19 pandemic, prolonged nonpharmaceutical interventions (NPIs) reduced the circulation of respiratory pathogens. The effects of NPIs on "immunity debt" in children are unclear, especially after almost 3 years of NPIs in China.

*Methods:* Between November 2021 and October 2023, a cross-sectional study of 235 children (age 9 months-5 years) was conducted at the China–Japan Friendship Hospital, Beijing. Serum IgG antibodies against 10 respiratory pathogens, including influenza A, influenza B, respiratory syncytial virus (RSV), parainfluenza virus, adenovirus (types 7 and 55), *Mycoplasma pneumoniae*, and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants, were measured using a novel antigen-specific detection platform. Antibody levels were compared between the following three periods: during NPIs (2021-2022), after NPIs (January-June 2023), and during the *Mycoplasma pneumoniae* epidemic (July-October 2023). In parallel, hospital-based nucleic acid surveillance from 2017 to 2023 was analyzed.

*Findings:* IgG levels exhibited pathogen-specific patterns. Antibody titers against *M. pneumoniae* and influenza A declined significantly during NPIs and rebounded after the restrictions were lifted, coinciding with increased clinical detection of these two pathogens. In contrast, the antibody levels for influenza B, RSV, parainfluenza virus, and adenovirus were stable across all periods. SARS-CoV-2 antibody titers rose after December 2022, reflecting the introduction of this new pathogen.

*Interpretation:* Our results provide the first multi-pathogen serological evidence that prolonged NPIs led to pathogen-specific immunity debt in young children in China. The effects were most pronounced for pathogens with high pre-pandemic circulation or rapid antigenic drift. Sustained serological surveillance and pathogen-targeted vaccination strategies can mitigate epidemic rebounds after periods of reduced exposure.

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https://doi.org/10.1016/j.ijid.2025.108278
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Key Points

**Question**: Did the prolonged nonpharmaceutical interventions (NPIs) during COVID-19 lead to an "immunity debt" in young children, reducing antibody levels and increasing susceptibility after restrictions were lifted?
**Findings**: A cross-sectional study of 235 children (age: 9 months-5 years) in Beijing revealed that IgG antibody levels against *Mycoplasma pneumoniae* and influenza A subtypes declined significantly during NPIs and rebounded sharply after restrictions ended, paralleling pathogen resurgence.
**Meaning**: Immunity debt is pathogen-specific and most pronounced for pathogens with high pre-pandemic circulation or rapid antigenic drift. Sustained serological surveillance and targeted vaccination strategies are essential to mitigate post-NPI epidemic surges in children.

## Introduction

Nonpharmaceutical interventions (NPIs) are an essential strategy for protecting populations during pandemics of emerging respiratory infectious diseases [1,2]. During the COVID-19 pandemic, extensive NPIs were implemented. After the NPIs were lifted, infections increased, especially among children [3]. In particular, the resurgence of a wide variety of respiratory pathogens was documented in China, the United States, the United Kingdom [4], Australia [5], and France [6].

The leading explanation for the resurgence of pathogens after NPIs is "immunity debt" [7]. Immunity debt refers to reduced immune stimulation due to diminished pathogen exposure during stringent NPIs [8], This leads to an insufficient immune response to certain pathogens, creating what is termed "immunity debt" [9]. Empirical evidence supporting immunity debt is limited. Most previous studies concerning immunity debt relied on disease incidence data, which indirectly measure immunity at the population level. At present, large-scale population surveys have found that after NPI, the antibody levels of respiratory syncytial virus (RSV) and group A *Streptococcus* major antigens decrease [10]. Only a handful of studies have assessed antibody levels against pathogens in pediatric populations [5,11–13], and these studies were conducted in countries where NPIs were relatively brief or intermittent. The duration of NPI enforcement significantly affects population immunity [14,15]. Furthermore, intermittent implementation complicates the interpretation of data concerning the effects of NPIs on pathogens [16]; the observed fluctuations in immunity due to seasonal variation [17], shifts in pathogen circulation, and the direct consequences of NPIs [18] are intertwined and difficult to untangle, and determining if the changes in antibody levels are pathogen-specific or due to broader alterations in immune function is difficult [19,20]. The NPI policies were maintained for almost 3 years in China and were among the longest and most stringent NPIs worldwide [21]. The abrupt lifting of NPIs at the end of 2022 is a clearly defined intervention point, offering a unique opportunity to investigate the long-term effects of extended NPIs on immunity at the population level. Thus, a study was conducted to understand the impact of NPIs on pathogen resurgence and immunity debt using samples collected before and after the implementation of NPIs in China.

## Methods

### *Study design and participants*

This cross-sectional study analyzed pediatric serum samples collected and categorized into three periods: the nonpharmaceutical intervention period ("NPI," 2021-2022), the period after NPI ("after NPI"; January-June 2023), and the period during the *Mycoplasma pneumoniae* (*M. pneumonia*) epidemic ("during MP"; July-October 2023). Blood samples were collected from 235 children aged 9 months to 5 years who were hospitalized at the China–Japan Friendship Hospital between November 2021 and October 2023. IgG antibody levels in the serum against key epitopes of 10 pathogens were measured, including influenza A (H1N1), influenza A (H3N2), influenza B, parainfluenza viruses, adenovirus subtypes 7 and 55, *M. pneumoniae*, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants, and respiratory syncytial virus (RSV). In addition, the numbers of nuclei-confirmed cases of various pathogens in the Pediatric Department of the China–Japan Friendship Hospital from the first quarter of 2017 to the fourth quarter of 2023 were analyzed.

The children included in the study had residual serum samples preserved from routine laboratory tests conducted for other research purposes, with prior approval from the hospital's Ethics Committee (2019-79-K51). All sample identifiers were replaced with anonymized codes to ensure that personal information could not be tracked to individuals.

The inclusion criteria were: (1) children hospitalized due to acute infectious diseases (respiratory, gastrointestinal, and urinary tract infections); (2) age between 9 months and 5 years; (3) retained serum samples; (4) samples from the first hospitalization if children were hospitalized multiple times during the study period; (5) complete clinical data; and (6) signed informed parental consent. The exclusion criteria were: (1) born after the end of the NPIs; (2) a history of chronic infections (e.g., hepatitis B or tuberculosis), malnutrition, craniofacial or thoracic deformities, or genetic syndromes; (3) coexisting chronic diseases involving the heart, liver, kidneys, hematopoietic system, or other chronic conditions; and (4) immunodeficiency or connective tissue diseases. The study included 235 children. Among children with multiple hospitalizations, only the sample from the first hospitalization was retained, and 148 repeat admissions were excluded accordingly. The overall study design is illustrated in Figure 1.

### *IgG antibody detection*

To assess antigen-specific immunoglobulin levels in the serum, target antigens from major respiratory-associated viruses were expressed and purified. The target antigens included the RBD protein of the wild type and XBB variant of SARS-CoV-2, the major surface adhesion protein P30 of *M. pneumoniae* (M129 NC_000912.1), the hexon proteins of adenovirus types 7 and 55 (hexon-7: QJW70255.1; hexon-55: OM714808.1), the trimeric pre-F protein of RSV, the HA proteins of the H1N1 and H3N2 influenza A viruses (A/Beijing-Chaoyang/SWL1330/2023, A/California/123/2022 OQ245336.1), the HA protein of influenza B virus (B/Beijing-Chaoyang/164/2022) with the GCN4pII sequence to stabilize the trimeric conformation, and the fusion protein of HPIV3 (I213C-G230C/Q162C-L168C/A463V/I474Y) with two pairs of disulfide bonds and two point mutations to stabilize the conformation.

The DNA sequences encoding P30, Hexon7, and Hexon55 were synthesized and cloned into the pET21a vector. *E. coli* BL21 (DE3) cells were transformed with the pET21a-P30, pET21a-Hexon7, or pET21a-Hexon55 plasmid and grown in lysogeny broth media. Protein expression was induced with 0.1 mM IPTG (Yeasen Biotech, China) at 18°C for 18 h. P30 was purified from bacterial lysates using His-tag affinity chromatography. Hexon-7 and Hexon55 were purified from bacterial inclusion bodies. The optimized coding sequences for the HA of influenza and the fusion protein of HPIV were synthesized and cloned into the pCDNA3.1 vector. The optimized coding sequences for the RBDs of SARS-CoV-2 were synthesized and cloned into the pCEP4 vector. Plasmids were tran-

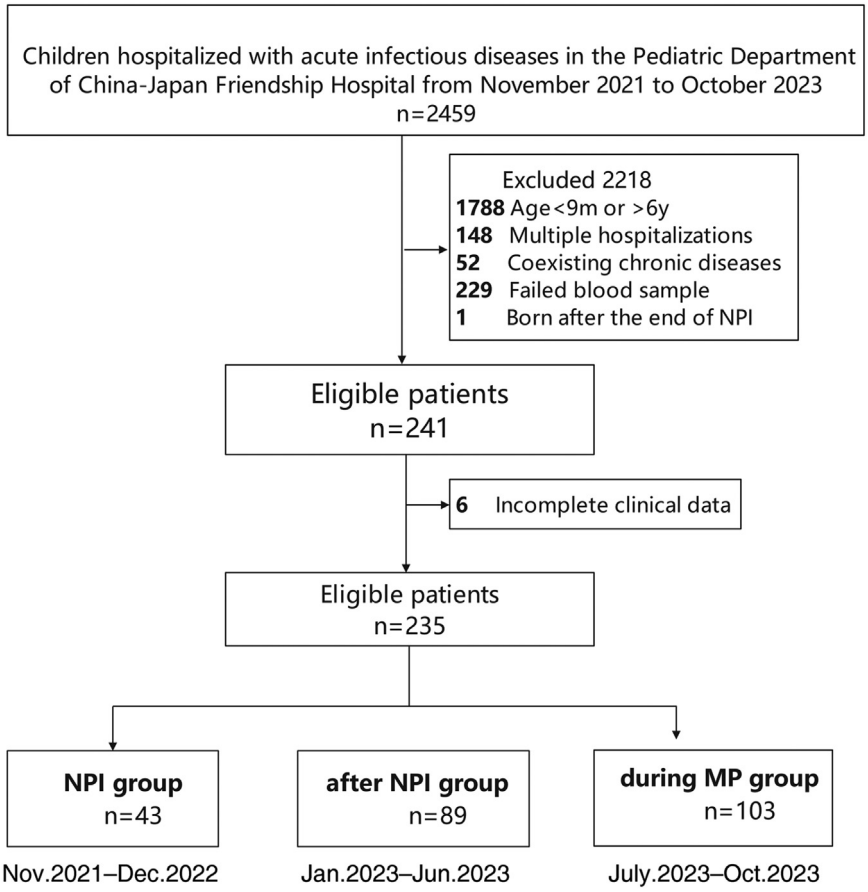


**Figure 1.** Development of the during "NPI," "after NPI," and "during *Mycoplasma pneumoniae* (MP)" groups. Among children with multiple hospitalizations, only the sample from the first hospitalization was retained, and 148 repeat admissions were excluded accordingly.

siently transfected into Expi293F cells using polyethylenimine, following the manufacturer's recommendations. Recombinant proteins were purified from the cell culture supernatants using affinity chromatography with a Ni column, followed by a Superdex200 size-exclusion column. RSV per-F protein was kindly provided by GENEVAX Biological Products Co., Ltd. The molecular size and purity of the eluted protein were confirmed by sodium dodecylsulfate polyacrylamide gel electrophoresis.

Plates (96-well, Corning) were coated with the purified proteins overnight at 4°C. Serum samples were serially diluted and added to the plates. Detection was performed using horseradish peroxidase (HRP)-conjugated anti-human IgG (H + L) (W4031, Promega, WI, USA). HRP activity was assessed using the substrate 3,3′,5,5′-tetramethylbenzidine (Sigma-Aldrich, MO, USA) by measuring the optical density at 450 nm using a microplate reader (SpectraMax, USA). The results were plotted using the A450 value of each well as the y-axis and the logarithmic value of the corresponding serum dilution as the x-axis. The area under the curve (AUC) was calculated using Y = 0 as the baseline, and the AUC was used for statistical analysis.

### *Pathogen nucleic acid detection*

Pathogen nucleic acid detection was performed using multiplex RT-PCR combined with capillary electrophoresis, T7 RNA isothermal amplification with multi-biotin signal amplification, or real-time PCR. The selection of diagnostic tests was guided by clinical judgment.

Multiplex RT-PCR and capillary electrophoresis were used to detect nucleic acids from influenza A, influenza A H1N1, influenza A H3N2, influenza B, RSV, parainfluenza virus, adenovirus, and *M. pneumoniae*. One-step RT-PCR with specific primers targeting the conserved sequences for 13 respiratory viruses was performed using the SureX 13 Respiratory Pathogen Multiplex Detection Kit (Health Gene Tech., Ningbo, China). The reaction mixture consisted of ResP premix, RT-PCR enzyme solution, and nucleic acids from the sample. PCR amplification was performed, following the manufacturer's specified cycling conditions. The products were analyzed on a 3500 Dx Series Genetic Analyzer (ABI, USA). Data analysis, including peak identification based on fragment size, shape, and signal intensity, was performed using GeneMapper 5.0 software (ThermoFisher, USA).

T7 RNA isothermal amplification with multi-biotin signal amplification was used to detect influenza A, influenza B, RSV, parainfluenza virus, adenovirus, and *M. pneumoniae* (Zhongchi Biotech, Wuhan, China). Based on the manufacturer's instructions, 2 μL of nucleic acid from the sample lysate was amplified in a reaction mixture containing 17 μL of amplification mix and 1 μL of amplification enzyme at 42°C for 1 hour. The amplified products were hybridized with specific probes in a microplate at 50°C for 1 hour, followed by incubation with a HRP-streptavidin conjugate. After the addition of the chemiluminescent substrate, signals were detected using the ADC CLIA200 automated chemiluminescence immunoassay system (Zhongchi Biotech, Wuhan, China). A sample was deemed positive if the ratio of relative light units between the test sample and the negative control exceeded 5:1.

Influenza A, influenza B, RSV, and *M. pneumoniae* were detected using real-time PCR assays, according to the manufacturer's protocols. The following kits were used: Influenza A (DAAN Gene, Guangzhou, China), Influenza B (DAAN Gene, Guangzhou, China), RSV A/B typing (Liferiver, Shanghai, China), and *M. pneumoniae*/*Chlamydia pneumoniae* (Liferiver, Shanghai, China). Reactions were conducted on the QuantStudio 5 system (ABI, USA). Daily positive and negative controls were used to ensure assay reliability.

*Statistical analysis*

Overall differences in age and AUC during the "NPI," "after NPI," and "during MP" periods were assessed for each pathogen using the Kruskal–Wallis test, using epsilon² for the effect size. Pairwise comparisons were performed using Wilcoxon rank-sum tests with Benjamini–Hochberg adjustments for multiple testing. Effect sizes were assessed using Hodges–Lehmann median differences with 95% bootstrap CIs and Cliff's delta with 95% CIs. A linear model (AUC for period + age) with heteroskedasticity-robust (HC3) standard errors was used for covariate-adjusted contrasts. A two-sided *P*-value <0.05 indicated significant differences. Data analysis and statistical computations were performed using R (version 4.3.1).

## Results

Of the 2459 pediatric patients recruited between November 2021 and October 2023, the following patients were excluded: 1788 patients outside the 9-month to 6-year age range, 148 patients readmitted within 1 month, 52 children with chronic diseases, 229 non-blood samples, 1 pediatric patient born after the end of the NPIs, and 6 children with insufficient clinical data. Thus, 235 pediatric patients were included in the experimental cohort, including 100 female patients. The patients were divided into the NPI group (n = 43, 18.30%; 2021.11-2022.12), the "after NPI" group (n = 89, 37.87%; 2023.01-2023.06), and the "during MP" group (n = 103, 43.83%; 2023.07-2023.10). The median ages in the "NPI," "after NPI," and "during MP" groups were 47 months, 44 months, and 43 months, respectively. No patients were immunocompromised.

To investigate the potential existence of immunity debt, IgG antibody levels against 10 pathogens were examined in the three groups. The age distribution did not differ significantly among the three groups (Figure S1 and Tables S1 and S2). As shown in Figure 2 and Figure S2, overall comparisons revealed pathogen-specific patterns of IgG responses. IgG levels were significantly higher in the "after NPI" and "during MP" groups compared with the "NPI" group for SARS-CoV-2 RBD-WT (overall $P < 0.05$) and XBB variant (overall $P < 0.05$). This pattern was consistent with the epidemiological dynamics observed after the emergence of new pathogens. Notably, *M. pneumoniae* exhibited a similar trend (overall $P = 0.02$). In contrast, IgG levels against influenza A(H1N1) (overall $P = 0.03$) and A(H3N2) (overall $P = 0.01$) peaked in the "during MP" group and were significantly higher than levels in the "NPI" and "after NPI" groups ($P < 0.05$). No significant group differences were observed for influenza B, adenovirus 7 and 55, RSV, or parainfluenza viruses (all $P \geq 0.05$). These findings suggest the immunity debt is pathogen-specific, particularly for *M. pneumoniae* and the influenza A viruses.

To characterize temporal changes in antibody levels, the study period was stratified into 2021, 2022, and every 2 months during 2023. As shown in Figure 3, IgG levels against SARS-CoV-2 RBD-WT, SARS-CoV-2 RBD-XBB, and *M. pneumoniae* P30 were low during 2021-2022 but rose in 2023. Similarly, IgG levels against influenza A(H1N1) and A(H3N2) increased significantly after March 2023. In contrast, antibody levels against influenza B, adenovirus, parainfluenza virus, and RSV exhibited minimal fluctuations during the study period. To assess the robustness of our findings, we performed a sensitivity analysis excluding potential outliers, which were defined as values greater than the 75th percentile plus 1.5 times the interquartile range. The results were consistent with the primary findings (Figure S3), supporting the robustness of the observed patterns.

To investigate the causes underlying the differences in antibody levels, the number of clinical submissions and the proportion of positive detections for each pathogen were analyzed (Figure 4). The detection rates for *M. pneumoniae* were low during the "NPI" period compared with the prepandemic and "after NPI" periods, accounting for the significant decline in antibody levels in the "during NPI" period. The detection rates for influenza A(H1N1) and A(H3N2) markedly increased in Q1 of 2023, consistent with the increased IgG responses. In contrast, influenza B and adenovirus detection rates were persistently low, and RSV and parainfluenza virus were detected throughout the study, providing a plausible explanation for the absence of significant antibody changes.

Collectively, these findings indicate that immunity debt is pathogen-specific, developing for *M. pneumoniae* and influenza A viruses but not the other pathogens. Antibody response levels for *M. pneumoniae* and influenza A increased substantially after reduced exposure during NPI, and the development of this immunity debt was closely linked to pathogen circulation patterns.

## Discussion

Integrating pediatric serological data with pathogen surveillance during the NPIs, after the NPIs, and during the MP outbreak revealed that "immunity debt" is pathogen-specific. Immunity debt was pronounced for *M. pneumoniae* and influenza A but negligible for influenza B, adenovirus, RSV, and parainfluenza virus.

Several factors may account for these differences. First, although the incidence of *M. pneumoniae* was high before the pandemic [22], the incidence decreased rapidly during the NPIs, as shown in Figure 4. This sharp reduction directly accounted for the marked fall in antibody titers. Following the cessation of NPIs, antibody levels rose rapidly and reached levels similar to the levels during the large-scale *M. pneumoniae* outbreak in late 2023 [23]. The resurgence of *M. pneumoniae* was driven by the accumulation of susceptible individuals during NPIs, seasonal transmission dynamics in winter, the increasing prevalence of macrolide resistance, and the emergence of a new dominant genotype [24,25].

Second, the rate of antigenic drift varies across pathogens. Influenza A undergoes more rapid antigenic drift [26]; after nearly 3 years of NPIs, population immunity to A-subtypes may have waned more than the immunity to influenza B [19]. Thus, infection incidence and antibody titers against influenza A increased sharply after lifting the NPIs. However, influenza B is characterized by slower drift and lower circulation, and antibody levels for influenza B did not change much after lifting the NPIs.

Third, certain pathogens, such as RSV and parainfluenza virus, continued to circulate at reduced levels during the pandemic. The persistence of these pathogens resulted in no significant differences in antibody levels across the three periods. Ongoing transmission reflects the high transmissibility, relative stability, and a large susceptible reservoir of these pathogens in the population [27].

Fourth, the SARS-CoV-2 data provided internal validation. Before lifting the NPIs, neutralizing antibody titers against the XBB variant were nearly absent because XBB had not circulated in China, but low-level titers against ancestral strains reflected prior infections in a small proportion of children. After December 2022,

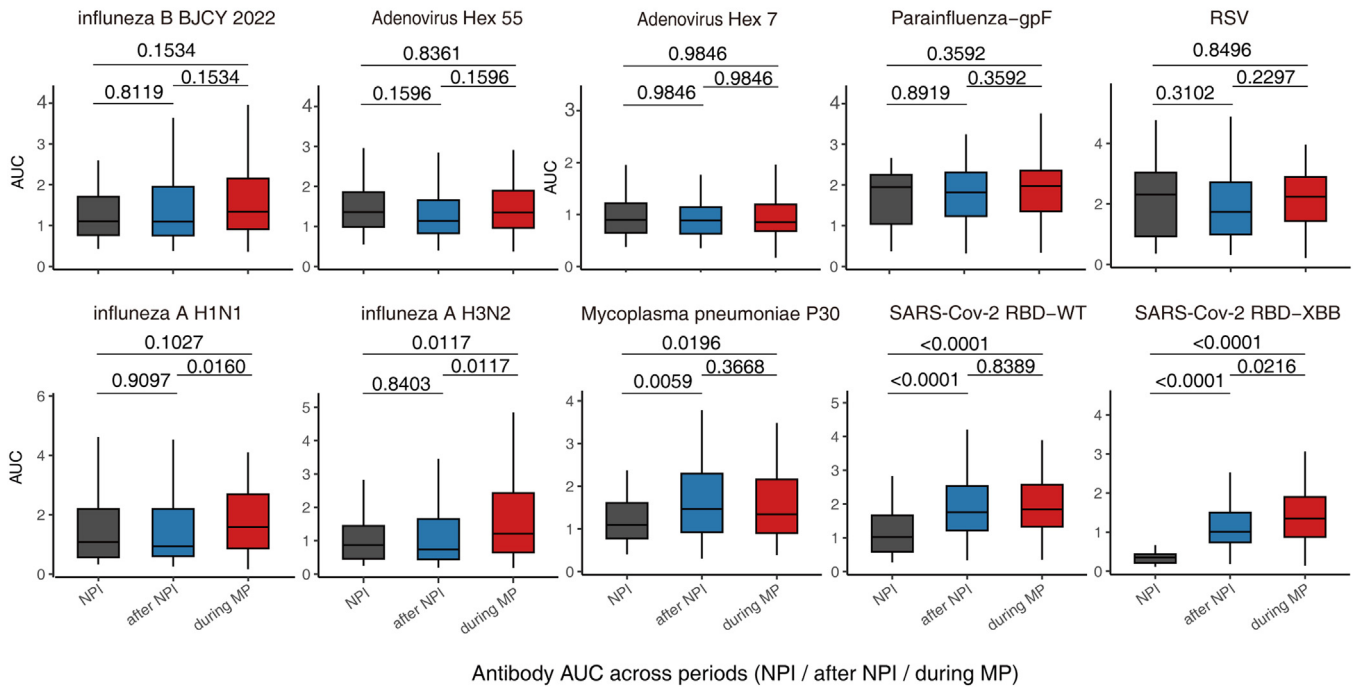


**Figure 2.** Group-wise distribution of antibody levels, measured as area under the curve (AUC), across the "NPI," "after NPI," and "during MP" periods. Boxes indicate medians and interquartile ranges; whiskers show ranges after excluding outliers. Statistical comparisons and adjusted *P* values are provided in Tables S3-S4.

antibody titers against SARS-CoV-2 rose sharply, mirroring the incidence of infection and underscoring the robust relationship between pathogen circulation and serological immunity.

Together, these results confirm a general pattern in which prolonged NPIs interrupt natural exposure, leading to declines in population-level antibody titers and the accumulation of susceptible individuals [28]. After NPIs are lifted, renewed transmission results in sharp increases in disease incidence and antibody levels. These effects are most evident for pathogens that were markedly suppressed during the NPIs. Pathogens that continued to circulate or had intrinsically low incidence did not change much. These pathogen-specific differences highlight the importance of sustained surveillance of disease incidence and antibody dynamics.

NPIs reduce the burden of respiratory infections [29], particularly in vulnerable populations. However, prolonged suppression of exposure contributes to population-level declines in antibody-mediated immunity [30]. This is similar to previous literature reports which demonstrated that the total IgG level decreased after NPI [11]. From a public health perspective, maintaining appropriate levels of immune stimulation via natural exposure and providing vaccinations for high-risk groups is crucial for sustaining population immunity and mitigating the risk of surges in low-risk groups once restrictions are lifted [31,32].

This study has several important limitations. First, the sample size was relatively modest, and all participants were recruited from a single hospital in northern China, which may limit the generalizability of the findings to other regions with different lifestyles, healthcare-seeking behaviors, and NPI patterns. Future multicenter studies spanning diverse geographical settings are needed to validate these observations. Second, the study employed a cross-sectional design, meaning that incidence, antibody relationships were inferred at the population level rather than through longitudinal follow-up. More comprehensive prospective cohort studies, including neutralizing antibody assays, mucosal immunity, and cellular immune responses, will be required to better define the dynamics of immunity debt. Third, behavioral exposure data such as travel history or attendance at public places were not collected due to patient privacy and study design constraints, however, children's activity levels and public mobility increased after COVID-19 restrictions were lifted [33,34]. introducing potential unmeasured confounding. Moreover, the antigen panel did not include pathogens with notable post-COVID resurgence, such as *Streptococcus pyogenes, Bordetella pertussis*, and *enteroviruses*, owing to technical constraints and the empirical application of antibiotics. Possible serological cross-reactivity between respiratory adenoviruses (Ad7/Ad55) and enteric adenoviruses (Ad40/41) also cannot be fully excluded. Finally, beyond pathogen-specific immunity debt, NPIs suppressed multiple respiratory pathogens simultaneously, likely altering co-infection dynamics. Synergistic interactions between viruses and bacteria—such as RSV and *Streptococcus pneumoniae*—are known to amplify epidemic waves. Changes in these ecological interactions may have contributed to the intensity of post-NPI rebounds and should be considered when interpreting immunity patterns.

Our results using serum samples from NPI and non-NPI periods and pathogen surveillance data provide new insights into the concept of immunity debt in young children. Specifically, our results demonstrate pathogen-specific patterns. *M pneumoniae* is a paradigm for prolonged NPIs causing decreased antibody levels and subsequent explosive resurgence. Our findings support the establishment of long-term, longitudinal antibody surveillance systems to mitigate epidemic rebounds.

## Research in context

### *Previous evidence*

A PubMed search for studies published in English from the inception of the database through September 1, 2025, using the terms "immune debt" or "immunity debt," identified 135 relevant articles. Most previous studies about immunity debt relied on the surveillance of disease incidence, which indirectly reflects population-level immunity. Serological studies are scarce and typically focus on only a few pathogens in settings where NPIs

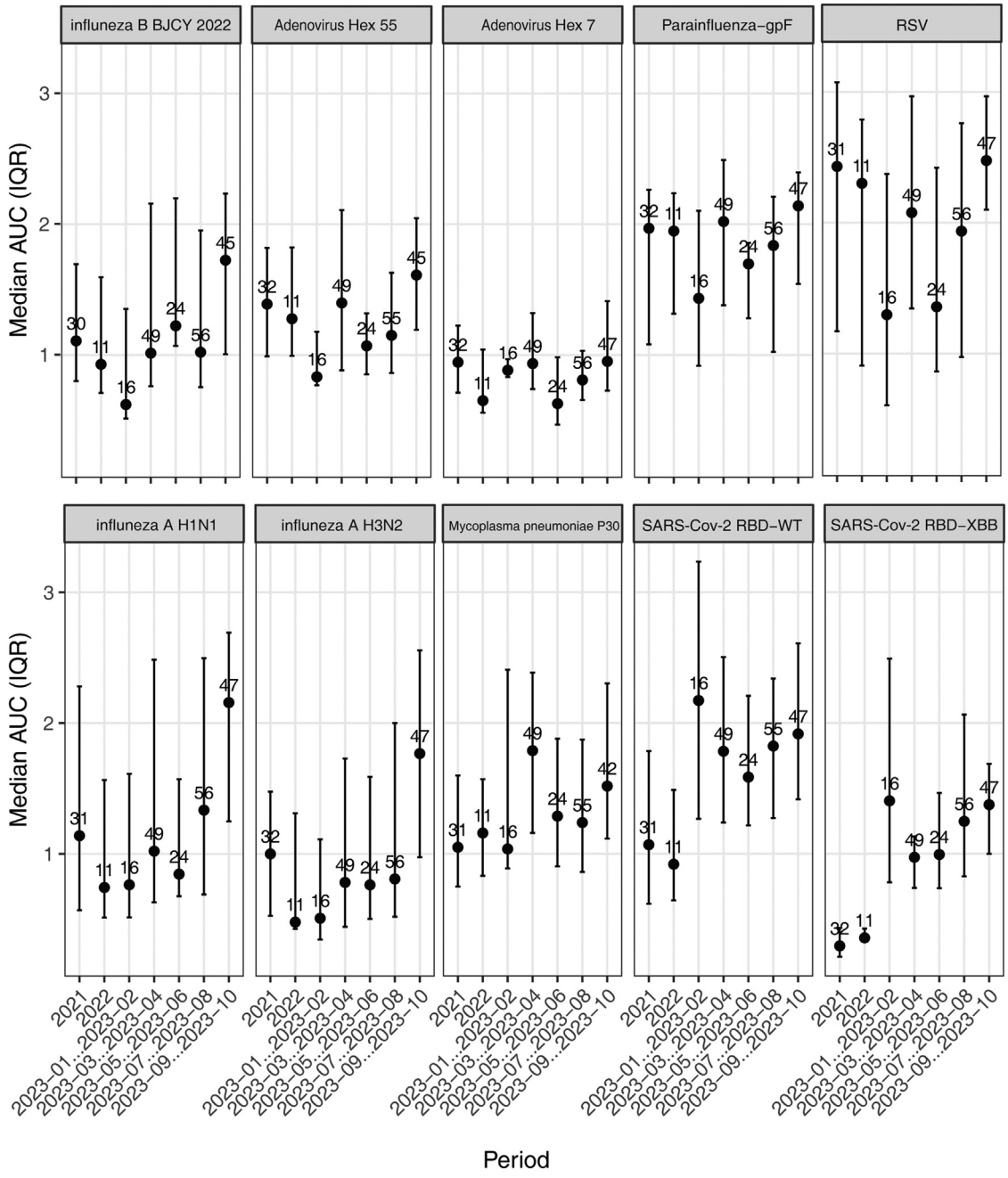


**Figure 3.** Median antibody areas under the curves (AUCs) with interquartile ranges (IQRs) across time periods according to the pathogen. Each panel corresponds to one pathogen. The x-axis shows time bins, including the entire year of 2021, the entire year of 2022, and bimonthly bins for 2023 (e.g., January-February and March-April). Points indicate the median AUCs, and error bars show the IQRs (Q1-Q3); numeric labels above the points indicate the sample size (n). Only samples that passed quality control (pathogen-specific quality control columns exist) were included.

were relatively brief or intermittent. Thus, the effects of prolonged NPIs on broad or pathogen-specific immunity in children are unclear.

*Contribution of this study*

Previous studies focused on a limited number of pathogens and the short-term effects of NPIs. In contrast, an IgG detection platform targeting the surface proteins of 10 major respiratory pathogens was established in this study. Data from this detection platform provided the first multi-pathogen serological evidence from China, where NPIs were maintained for nearly 3 years. Prolonged suppression of pathogen circulation can induce pathogen-specific immunity debt in young children. IgG antibody profiling and the hospital-based surveillance data showed that immunity debt is not universal and depends on pathogen epidemiology and antigenic drift dynamics. This serological and epidemiological approach strengthens causal inference regarding the link between reduced exposure and declines in antibody levels.

*Implications of the findings*

Our findings highlight the dual effect of NPIs. Extended NPIs are highly effective at reducing infection burden, but cause population-level declines in antibody-mediated immunity for

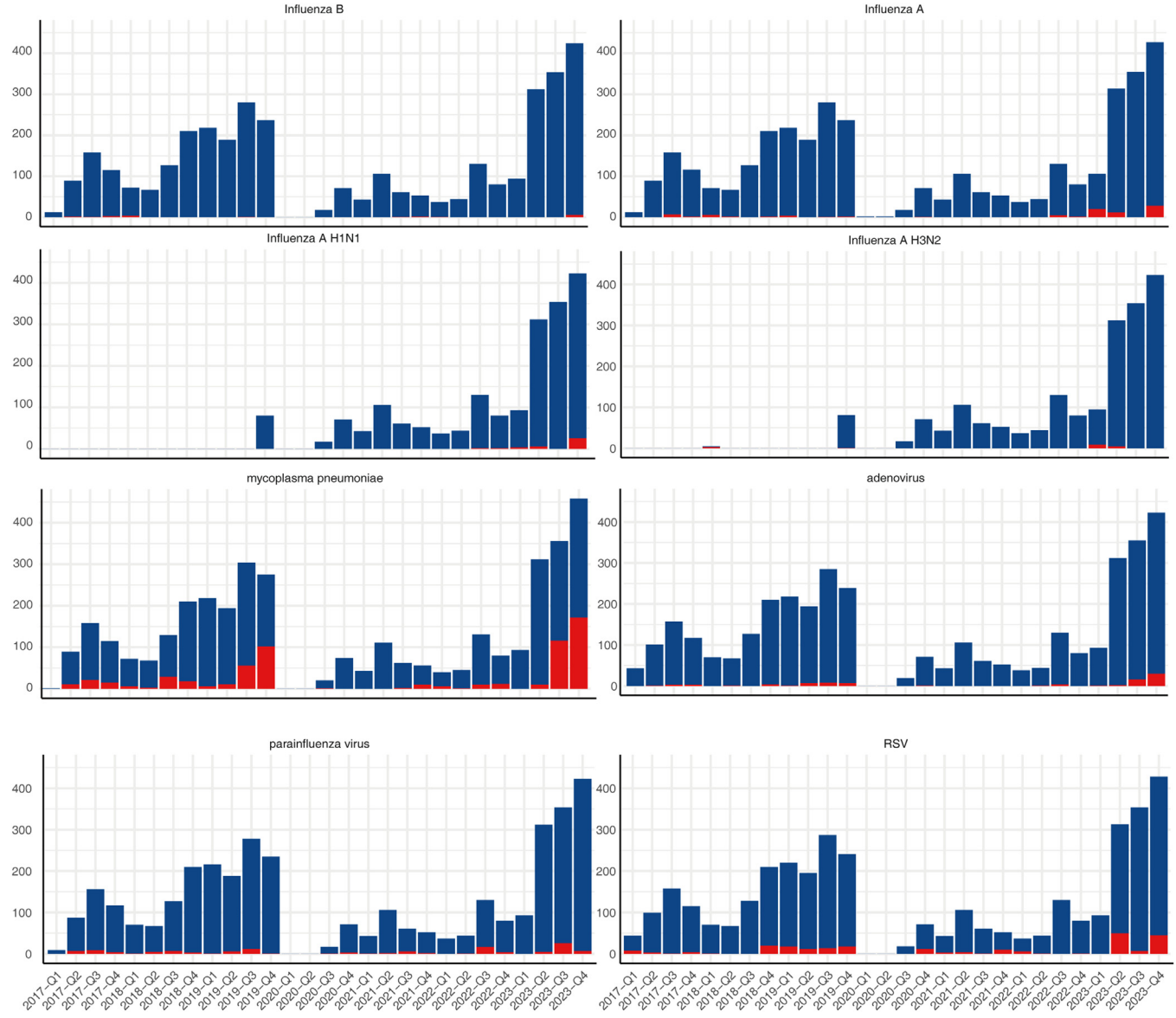


**Figure 4.** Total tests and positive counts by quarter and pathogen (stacked bars). Each panel shows one pathogen. Quarters are on the x-axis (up to 2023 Q4), and counts are on the y-axis. Each bar represents the number of tests in that quarter, and the colors indicate negative (blue) vs positive (red) counts.

certain pathogens. Public health strategies should therefore incorporate pathogen-specific monitoring and vaccination programs to maintain protective immunity, particularly in children and other vulnerable groups. Establishing long-term, multicenter serological surveillance is critical for limiting post-restriction surges in pathogenic infections and guiding immunization policies.

## Data sharing statement

Due to patient privacy concerns, the data cannot be uploaded to a public database. Interested readers may contact the corresponding author for access.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Funding

This work was supported by National High Level Hospital Clinical Research Funding (2025NHLHCRF-JBGS-B-WZ-05),Beijing Research Ward Excellence Program (BRWEP2024W114060103), National Natural Science Foundation of China (82470007. 82100009. 82530002), Chinese Academy of Medical Sciences Innovation Fund for Medical Sciences (2021-I2M-1-048), New Cornerstone Science Foundation, Chinese Academy of Medical Sciences Innovation Fund for Medical Sciences (2023-12M-2-001), State Key Laboratory Special Fund(2060204), National Key Research and Development Program of China (2021YFC2300501), and Noncommunicable Chronic Diseases-National Science and Technology Major Project (2023ZD0506200, 2023ZD0506203).

## Ethical approval

This study was approved by the Ethics Committee of the China–Japan Friendship Hospital (2024-KY-097).

## Author contributors

HBL, BDH, QZ and BC conceptualized the study. HBL, JL, CG, ZYL, QJF, GHF, BDH and BC designed methods for samples preparation and experiments. JL and ZYL are responsible for reviewing the cases and entering the information. CG and QJF did IgG antibody experiment. HBL performed data analyses and visualization. and helped with laboratory experiments. QZ, HBD and BC provided supervision. HBL and JL, CG, ZYL, QJF wrote the manuscript, which was critically revised by all the authors. HBL, JL verified the data. All authors had full access to all the data in the study and approved the final manuscript.

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2025.108278.

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