Heliyon 10 (2024) e32304

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

Alterations of pathogen transmission patterns and attenuated immune stimulation might be the cause of increased adult respiratory infections cases in 2023, results from a multi-center study in mainland China

Jingwen Ai [a,b,*,1], Hongyu Wang [a,1], Haocheng Zhang [a,b,1], Jieyu Song [a,1], Yi Zhang [a,1], Ke Lin [a,1], Lihong Qu [c,1], Yanliang Zhang [d,e,1], Shiliang Zhang [f,1], Qiyun Xiang [g], Jiawei Geng [h], Guangxia Jin [i], Wei Song [j], Liaoyun Zhang [k], Xiaoli Hu [l], Hongyan Liu [m], Guanmin Yuan [a], Ning Jiang [n], Yang Zhou [a,b], Yuanyuan Xu [a,b], Jun Ying [o], Jiqin Wu [b], Yajiao Xing [b], Kai Fang [b], Hui Yan [b], Feiying Chen [b], Tailin Xu [b], Sen Wang [a,b,**], Zhaohui Qian [p,q,***], Wenhong Zhang [a,b,r,****]

[a] *Department of Infectious Diseases, Shanghai Key Laboratory of Infectious Diseases and Biosafety Emergency Response, National Medical Center for Infectious Diseases, Huashan Hospital, Shanghai Medical College, Fudan University, 12 Wulumuqi Zhong Road, Shanghai, China*

[b] *Shanghai Sci-Tech InnoCenter for Infection and Immunity, Room 201, No. 6, Lane 1220, Huashan Road, Changning District, Shanghai, China*

[c] *Department of Infectious Disease, Shanghai East Hospital, Tongji University School of Medicine, No. 150, Jimo Road, Pudong New Area, Shanghai, China*

[d] *Nanjing Hospital of Chinese Medicine Affiliated to Nanjing University of Chinese Medicine, No. 157, Daming Road, Qinhuai District, Nanjing, China*

[e] *Nanjing Research Center for Infectious Diseases of Integrated Traditional Chinese and Western Medicine, Nanjing, China*

[f] *The Fifth People's Hospital of Wuxi, No. 1215, Guangrui Road, Liangxi District, Wuxi, Jiangsu, China*

[g] *The Third People's Hospital of Yichang City, No. 23, Gangyao Road, Xiling District, Yichang, Hubei, China*

[h] *Department of Infectious Diseases, The First People's Hospital of Yunnan Province, No. 157, Jinbi Road, Xishan District, Kunming, China*

[i] *Jining City Public Health Medical Center, No. 66, Chenyang Road, Rencheng District, Jining, Shandong, China*

[j] *Department of General Practice, Jinyang Community Health Service Center, No. 121, Jin Yang Road, Pudong New Area, Shanghai, China*

[k] *Department of Infectious Diseases, The First Hospital of Shanxi Medical University, No. 85, Jiefang South Road, Taiyuan, China*

[l] *Department of Infectious Disease, Heilongjiang Province Hospital, No. 82, Zhongshan Road, Xiangfang District, Harbin, Heilongjiang, China*

[m] *Liaoning Emergency Treatment and Innovation Center of Public Health Emergencies, The Sixth People's Hospital of Shenyang, No. 85, South Heping Street, Heping District, Shenyang, Liaoning, China*

* Corresponding authors. Department of Infectious Diseases, Shanghai Key Laboratory of Infectious Diseases and Biosafety Emergency Response, National Medical Center for Infectious Diseases, Huashan Hospital, Shanghai Medical College, Fudan University, Shanghai, 200040, China, 12 Wulumuqi Zhong Road, Shanghai, 200040, China.

** Corresponding author. Department of Infectious Diseases, Shanghai Key Laboratory of Infectious Diseases and Biosafety Emergency Response, National Medical Center for Infectious Diseases, Huashan Hospital, Shanghai Medical College, Fudan University, Shanghai, 200040, China, 12 Wulumuqi Zhong Road, Shanghai, 200040, China.

*** Corresponding authors. NHC Key Laboratory of Systems Biology of Pathogens, Institute of Pathogen Biology, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China, State Key Laboratory of Respiratory Health and Multimorbidity, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China, 16 TianRong St, North Science Bldg, Daxing District, Beijing, 102600, China.

**** Corresponding author. Department of Infectious Diseases, Shanghai Key Laboratory of Infectious Diseases and Biosafety Emergency Response, National Medical Center for Infectious Diseases, Huashan Hospital, Shanghai Medical College, Fudan University, Shanghai, 200040, China, 12 Wulumuqi Zhong Road, Shanghai, 200040, China.

E-mail addresses: jingwenai1990@126.com (J. Ai), wangsen329@126.com (S. Wang), zqian2013@sina.com (Z. Qian), zhangwenhong@fudan.edu.cn (W. Zhang).

https://doi.org/10.1016/j.heliyon.2024.e32304

Received 20 February 2024; Received in revised form 31 May 2024; Accepted 31 May 2024

Available online 3 June 2024

2405-8440/© 2024 Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

[n] School of Life Sciences Fudan University, No. 2005 Songhu Road, Yangpu District, Shanghai, China
[o] Fudan University Library, No. 220, Handan Road, Yangpu District, Shanghai, China
[p] NHC Key Laboratory of Systems Biology of Pathogens, Institute of Pathogen Biology, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China
[q] State Key Laboratory of Respiratory Health and Multimorbidity, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China
[r] Institute of Infection and Health, Fudan University, Shanghai, China

ARTICLE INFO

Keywords:
Respiratory infections outbreak
Overlapping prevalence
Dynamic population immunity

ABSTRACT

Background: Several respiratory infections outbreaks have been observed in mainland China after reduction of non-pharmaceutical interventions. Other countries have seen increases in respiratory infections outside typical seasons post-COVID-19, warranting investigation into underlying causes.
Methods: We established monitoring networks for suspected respiratory infection in 14 tertiary hospitals nationwide. PCR for SARS-CoV-2, influenza A and B were performed on 3708 respiratory specimens and deep sequencing were conducted to identify co-infections or newly emerging microbes in 2023. Viral evolutionary analysis was completed. We retrospectively detected serum antibody level for various respiratory pathogens from 4324 adults without respiratory infections over 7 years to observe its dynamic curves.
Findings: SARS-CoV-2 and influenza A were the main pathogens during outbreaks in 2023, bacterial-virus and bacterial-bacterial co-infections were most detected, but community co-infections didn't significantly increase pneumonia incidence. Different SARS-CoV-2 and influenza variants were present in different outbreaks, and no novel pathogens were found. The epidemiological patterns of influenza A, COVID-19 and etc. were altered, exhibiting characteristics of being "staggered" compared to most global regions, and potentially led to "overlapping prevalence". Binding antibody testing showed regular fluctuation, without significant decrease against common respiratory pathogens in adults. Influenza A antibody stimulation was attenuated during the 2023 outbreak.
Conclusions: "Misaligned" alteration in seasonal respiratory disease patterns possibly caused combined epidemics, leading to cases spike in China, 2023. In adults, antibody levels didn't show significant decline, but reduced immune response to influenza during 2020–2023 emphasizes the need for consistent vaccination during pandemics.

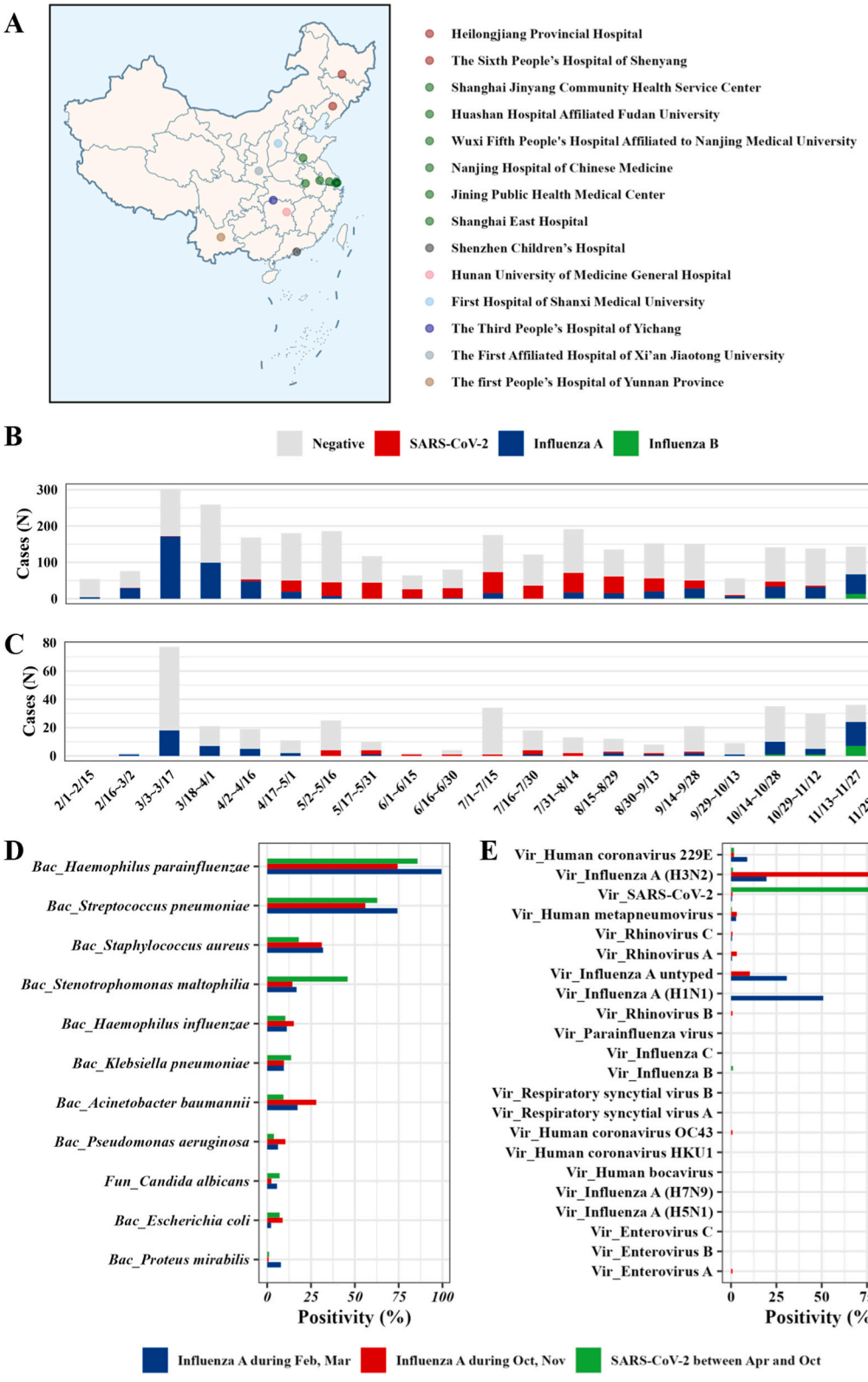
1. Introduction

A significant increase in respiratory infection cases has occurred in mainland China since the autumn-winter season of 2023 [1]. Following the gradual reduction of nonpharmaceutical interventions (NPIs) such as social distancing, travel restrictions, and home-stay policies in late 2022, the region experienced an outbreak and peak of coronavirus disease 2019 (COVID-19) cases from this time to early 2023, followed by a surge in influenza A cases during the spring of 2023 and a rapid increase in respiratory infection cases during the autumn-winter of 2023. Globally, several countries also reported an unusual rise in cases of common respiratory pathogens, such as influenza viruses (IFV), outside their typical seasons as NPI measures were relaxed or lifted post-2022 [2–4]. Before the emergence of the COVID-19 pandemic, annual seasonal fluctuations were systematically documented for a range of pathogens, including influenza A, influenza B, respiratory syncytial virus (RSV), and *Mycoplasma pneumoniae* [5–10]. Following the implementation of NPIs across various nations to curb the spread of COVID-19, certain pathogens manifested episodic outbreaks. In China, the phased relaxation of NPIs was initiated toward the end of 2022, signifying a temporal divergence from the approach adopted by most international jurisdictions.

The underlying reasons for these increases in respiratory infections urgently require exploration. Potential factors contributing to this phenomenon could include the emergence of new microbes, a significant decline in immunity to a specific pathogen within the population, disruption of the typical patterns of diseases, and exacerbation of conditions due to simultaneous epidemics. A thorough understanding of the epidemiology and pathogenetic characteristics of community respiratory infections in mainland China in 2023 will provide crucial information in global public health epidemiology and aid the ongoing optimization of infectious disease prevention and control policies in China and worldwide.

This study aimed to address these questions by using established clinical monitoring networks for patients with suspected respiratory infections in 14 representative clinical medical hospitals nationwide. We conducted comprehensive PCR testing for highly contagious pathogens in all collected respiratory specimens, including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and influenza A and B. Additionally, for patients with upper and lower respiratory infections, we employed high-throughput

[1] Jingwen Ai, Hongyu Wang, Haocheng Zhang, Jieyu Song, Yi Zhang, Ke Lin, Lihong Qu, Yanliang Zhang, Shiliang Zhang contributed equally to this manuscript.



(caption on next page)

Fig. 1. Epidemiology of highly infectious and pathogenic respiratory viruses and their co-infection status in 2023. (A) Geographical distribution of 14 clinical medical institutions nationwide. Map source: Ministry of Civil Affairs of the People's Republic of China. (B) Positive cases of SARS-CoV-2, influenza A, influenza B in adult suspected of respiratory infection in 2023. (C) Positive cases of SARS-CoV-2, influenza A, influenza B in children suspected of respiratory infection in 2023. (D) Co-infection relationship between SARS-CoV-2, influenza A, influenza B and common bacterial or fungi. (E) Co-infection relationship between SARS-CoV-2, influenza A, influenza B and other respiratory virus.

sequencing to identify other pathogens and potential emerging infectious diseases. The evolutionary analysis of specific viral strains was also completed. To assess the dynamic changes in population immunity, we retrospectively conducted serum-binding antibody testing for various respiratory pathogens at different time points over the past 7 years on >4000 adults without acute respiratory infections. This analysis of data helps unveil the epidemiological and population-level immune characteristics of community respiratory infectious diseases in 2023.

2. Methods

2.1. Establishment of the clinical monitoring networks for patients with suspected respiratory infection

We established a multicenter clinical network including 14 tertiary hospitals, covering seven major regions in China. All 14 hospitals are large tertiary hospitals that routinely treat many patients with acute respiratory infections in fever clinics and emergency departments.

For the primary objective of this study, we conducted epidemiology of respiratory infections throughout our network. From February to November 2023, we collected a total of 3708 nasopharyngeal swabs from individuals with suspected respiratory virus infections at outpatient, emergency, or fever clinics in 14 research centers. We conducted testing for SARS-CoV-2 and influenza A/B viruses on nasopharyngeal swabs from all 3708 patients. Furthermore, to elucidate the coinfection status of SARS-CoV-2 and influenza A/B viruses with other respiratory pathogens during different periods in 2023, targeted next generation sequencing (tNGS) was performed on 487 samples including 179 influenza A virus samples obtained from February to March 2023, 183 SARS-CoV-2 samples from April to October 2023, and 125 influenza A virus samples since October 2023 (Supplementary Table S1 in Supplement 1). Additionally, to understand the dynamic changes in lower respiratory tract infection pathogens throughout 2023, we performed tNGS on nasopharyngeal swabs from 309 adults with community-acquired pneumonia (CAP) from the 3708 cases, with a positivity rate of 90.94 % (281/309). To explore whether the increase in respiratory infections in 2023 can be attributed to emerging pathogens and novel variants, we conducted NGS analysis on lower respiratory tract samples from 98 patients with severe pneumonia collected by our network in 2023 (Supplementary Fig. S1 in Supplement 2).

The secondary objective of this study was to conduct dynamic antibody surveillance among populations. From 2016 to 2023, we established a second longitudinal cohort without acute respiratory infections; samples were only drawn from adults because of the challenges associated with blood collection in children (Fig. 1A, Supplementary Table S2 in Supplement 2). To evaluate the association between the prevalence of community respiratory infectious diseases in 2023 and changes in population immunity, we retrospectively conducted antibody testing on all available plasma specimens collected from 4324 adults without acute respiratory infections during different seasons from 2016 to 2023 (Supplementary Fig. S2 in Supplement 2). All specimens underwent testing for antibodies against SARS-CoV-2, influenza A and B, rhinovirus, parainfluenza virus, RSV, *M. pneumoniae*, and adenovirus.

2.2. Diagnostic pathway for respiratory tract infections in clinical monitoring network

For surveillance of common highly infectious and pathogenic respiratory pathogens, samples were taken every two weeks from 30 patients, selected from various emergency and fever outpatient centers, who had experienced respiratory virus infection symptoms in the prior two weeks and met at least two of the following three criteria: First, patients with fever (body temperature >38 °C); second, patients with respiratory symptoms such as cough or sputum production; and third, patients with systemic symptoms such as myalgia and fatigue. Severe community-acquired pneumonia (SCAP) should be community-acquired and meet the ATS/IDSA criteria [11]. Samples were tested via real-time PCR (RT-PCR) for SARS-CoV-2 and influenza A/B and sequenced for further pathogen identification. For rare or emerging pathogens, we included emerging infectious diseases. In emergency observation and ward centers with cases of severe pneumonia where the above methods failed to identify the pathogen in clustered outbreaks and severe infections, high-throughput sequencing was used to evaluate specimens for comprehensive pathogen detection. All the molecular testing were done at the laboratory of the National Medical Center for Infectious Diseases.

3. Laboratory methods

3.1. Nucleic acid extraction and RT-PCR

Nucleic acid was extracted using an automatic nucleic acid extractor and nucleic acid extraction kits (Forsun, 1.13.0108) with lysis (3 min at 70 °C), washing, a second wash, elution (2 min at 70 °C), and a 10-s magnetic discard. RT-PCR for SARS-CoV-2 (Liferiver, Z-RR-0479-02-50), influenza A (Liferiver, W-RR-0051-02), and influenza B (Liferiver, W-RR-0053-02) was performed according to the manufacturer's protocol. Part of samples had gone through laboratory tests like Xpert Xpress SARS-CoV-2/Flu/RSV (Cepheid) at each

center for clinical uses. Once positive, additional RT-PCR would be further performed for confirmation at the laboratory of the National Medical Center for Infectious Diseases.

3.2. tNGS

Pathogen-specific targeted primers were used to enrich pathogenic microorganisms based on reverse transcription PCR and multiplex PCR amplification methods. Nucleic acids were extracted using a GenK© Targeted Sequencing Library Preparation Kit (2102-02), tNGS was performed using a GenK© Universal Targeted Enrichment Kit for Pathogenic Microorganisms (2062A). Rolling circle amplification was used to form DNA nano-balls. Human genomic sequences were then removed. Nonhuman sequences were aligned with target sequences to determine whether the suspected sample contains the corresponding pathogen. The tNGS detection range is listed in Supplementary 2.

3.3. High-throughput sequencing

Amplicon sequencing spanning the whole genome of SARS-CoV-2 was performed using specific primers with overlaps as previously described [12]. Qualified libraries were sequenced on an Illumina NovaSeq 6000 Platform (Illumina, USA) using a pair-end 150-base pair strategy. After assembly, fasta files were processed for pangolin lineages for typing.

3.4. Serum antibody detection

SARS-CoV-2 IgG-binding antibody (Maccura, 20203400496) was detected through magnetic chemiluminescent immunoassay using an indirect method principle. For other respiratory pathogens, including influenza A/B (ShinnyBio, SU-AN15448, SU-AN15450), adenovirus (Beier, 20163402339), parainfluenza (Beier, 20173404193), *M. pneumoniae* (Beier, 20153400153), RSV (Beier, 20163402338), and rhinovirus (ShinnyBio, SU-AN13573), enzyme-linked immunosorbent assays (ELISAs) were used, and the absorbance was detected through an automatic ELISA analyzer. Samples-to-cutoff ratios >1.00 were considered positive for all antibodies detected.

3.5. Statistical analysis

To contrast demographical characteristics between different groups, Pearson's Chi-squared test was applied for categorical data while the Mann–Whitney *U* test and Student's t-test were employed for numerical data comparisons as appropriate. The Kolmogorov–Smirnov test was employed to assess the continuity of the variants. The results of signal-to-cutoff (S/CO) are presented as mean and SD. The significance was evaluated with two-sided p-values, and the threshold was $P < 0.05$. Data analysis was performed using R version 4.3.1 and GraphPad Prism 8 software.

4. Results

4.1. Epidemiology of highly infectious and pathogenic respiratory viruses among populations in 2023

Regardless of age group, we observed that influenza A virus was predominant from February to March 2023, followed by SARS-CoV-2 dominance from April to October, with a resurgence of influenza A virus from the end of October to November. Notably, during the three waves of the epidemic, children did not exhibit an earlier onset of pathogen prevalence compared with adults (Fig. 1B and C), which aligns with data from the Chinese CDC. In total, 1434 of the 3708 samples tested positive for at least one pathogen, indicating that the detection of these three highly infectious respiratory viruses could diagnose 38.67 % of patients with a suspected respiratory virus. Among them, three cases (0.19 %) exhibited coinfection with influenza A virus and SARS-CoV-2, highlighting the rarity of overlapping infections with these three highly infectious and pathogenic respiratory viruses.

Of the 1434 cases positive for SARS-CoV-2/influenza A/B, 487 samples with upper respiratory infections were randomly selected for further tNGS to describe coinfections between SARS-CoV-2/influenza A/B and other pathogens. The most common coinfection bacteria with influenza A virus from February to March were *Streptococcus pneumoniae* (74.30 %) and *Staphylococcus aureus* (31.84 %). For SARS-CoV-2 from April to October, prevalent coinfecting bacteria included *Haemophilus influenzae* (85.79 %), *S. pneumoniae* (62.84 %), and *Stenotrophomonas maltophilia* (45.90 %). During the resurgence of the influenza A virus since October, the coexisting bacterial species were similar to those in the earlier period (Fig. 1D). A total of 44 cases exhibited virus-virus coinfection. The most observed viral-coinfection pattern was with human coronavirus 229E and influenza A virus (16 samples, 8.94 %) in February to March, a phenomenon absent during the resurgence of influenza A virus. Otherwise, the occurrence of other virus coinfections was rare, with probabilities consistently <5 % (Fig. 1E). Notably, viral-viral coinfection did not significantly increase the occurrence of pneumonia ($P = 0.999$).

4.2. Specific pathogen monitoring and coinfection analysis in adults with community-acquired lower respiratory tract infections

Out of 3708 cases, 309 patients presented with CAP. The results of the monitoring of common pathogens in CAP is presented in Fig. 2A, Supplementary Table S3 (Supplement 3). The composition of pathogens in the winter season was more complex than the

preceding three quarters of the year. During winter 2023, the positivity rate increased for *M. pneumoniae*, rhinovirus A, rhinovirus B, parainfluenza virus in patients with pneumonia but decreased for *S. pneumoniae* and SARS-CoV-2. The positivity rates for *S. aureus*, influenza A/B virus, and coronaviruses remained stable.

Further analysis of coinfection combinations of different pathogens in the 309 cases of CAP is shown in Fig. 2B. Among 281 positive cases, 237 (83.34 %) had coinfection while 44 (15.66 %) presented as a monoinfection. Thus, virus-virus coinfections were rare in these pneumonia cases (Supplementary Fig. S3 in Supplement 2). In cases of non-SCAP, the most common coinfection combination was *H. influenzae* with *S. pneumoniae* (22.58 %), followed by *S. aureus* (9.31 %) with SARS-CoV-2 (9.31 %). In cases of SCAP, the most common coinfection combinations were *Klebsiella pneumoniae* with *S. pneumoniae* (16.67 %) and *K. pneumoniae* with *Candida albicans* (16.67 %). Furthermore, the number of cases with coinfection that progressed to SCAP was 22/237 (9.28 %), which did not significantly differ from those with monoinfection (5/44, 11.36 %) ($P = 0.879$). We conducted a comprehensive analysis of the specific

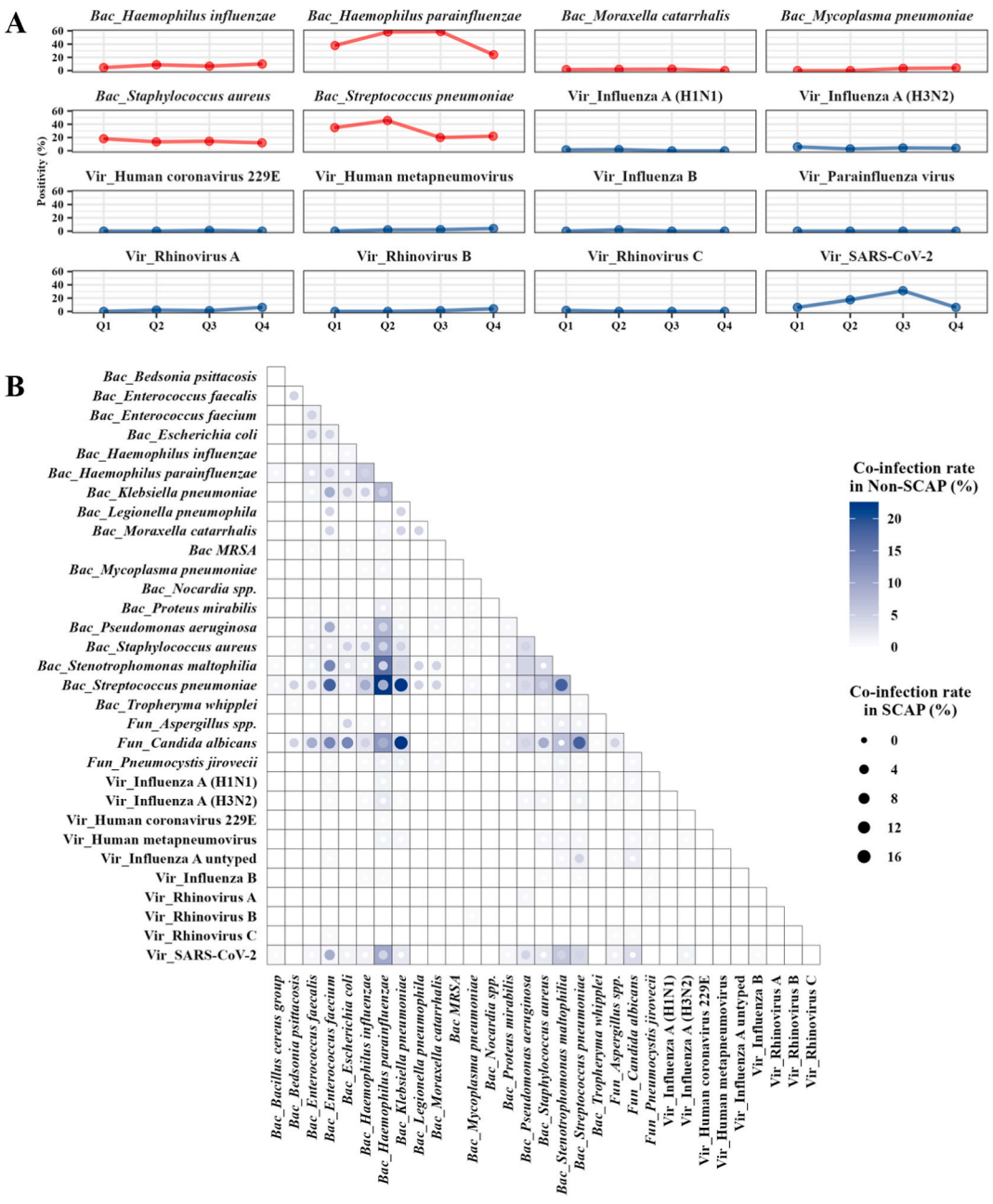


Fig. 2. Pathogen monitoring and co-Infection analysis in adult community-acquired lower respiratory tract infections. (A) Positivity of common respiratory pathogens in community-acquired pneumonia during 2023. (B) Co-Infection pattern of respiratory in community-acquired pneumonia in 2023.

underlying risk factors in patients diagnosed with CAP who also presented with coinfection and showed that 29.54 % of patients with CAP were coinfected. Among this cohort, hypertension was identified in 13 individuals, diabetes in 10, tuberculosis in 18, tumors in 3, coronary heart disease in 1, stroke in 2, chronic obstructive pulmonary disease in 21, heart failure in 1, and cirrhosis in 1.

4.3. High-throughput sequencing of lower respiratory samples from patients with severe pneumonia and lineage analysis of SARS-CoV-2– and influenza A–positive specimens

Among patients with severe pneumonia, 89/98 (90.82 %) cases had identifiable pathogens, 7 (7.9 %) cases were ruled out for pulmonary infections, and 2 (2.04 %) cases had undetermined diagnoses. No newly emerging microbes were identified in this analysis.

We next analyzed the lineage landscape and characteristics of the two SARS-CoV-2 waves. China experienced the first wave from December 2022 to February 2023 with the dropping of all COVID-19 restrictions. In these three months, most of the variants comprised BA.5.2.48 and BF.7.14 and their sublineages (95.71 %). DY.2 accounted for the most prevalent variant (46.07 %), followed by BF.7.14 (28.93 %), BA.5.2.48 (6.07 %), and DY.4 (5.00 %) (Fig. 3A). From the second epidemic period from mid-April to mid-October 2023, FU.1 was the most prevalent variant (25.35 %), followed by EG.5.1 (14.08 %), EG.5.1.1 (6.34 %), and XBB.1.5 (5.63 %) (Fig. 3B). We then analyzed the mutations in the spike protein among the lineages with at least 5 % detection and found a distinct pattern of spike protein mutations between the two waves, with DEL69/70, V213G, G339D, L452R, and F486V mutations only present in BA.5.2.48 and BF.7 sublineages. However, the XBB and associated sublineages possessed mutations including V83A, DEL144/144, H146Q, Q183F, V213E, G252V, N460K, F486P, and F490S (Fig. 3C). Genotyping of influenza A virus for all 2023 samples is illustrated in Fig. 3D. H1N1 and H3N2 were cocirculating from February to March 2023 while H3N2 dominated from October to November 2023.

4.4. Global and Chinese trends in the epidemiology of respiratory infectious diseases reveals coepidemics during the COVID-19 outbreak

In this study, we initially reviewed the official World Health Organization website and international published research to summarize the global patterns of common respiratory pathogens over the past several years. Before the COVID-19 pandemic, pathogens such as influenza A, influenza B, RSV, and *M. pneumoniae* exhibited annual seasonal trends (Table 1, Fig. 4A–C) [2–10]. Following the implementation of COVID-19–related NPI measures in multiple countries, some pathogens experienced short-term outbreaks. In mainland China, the gradual easing of NPI measures commenced at the end of 2022, marking a time lag compared with most regions worldwide. Consequently, the epidemiological patterns of influenza A and COVID-19 exhibited a characteristic of being "staggered" compared with most global regions. Additionally, clinical surveillance during the autumn-winter respiratory disease outbreak in 2023

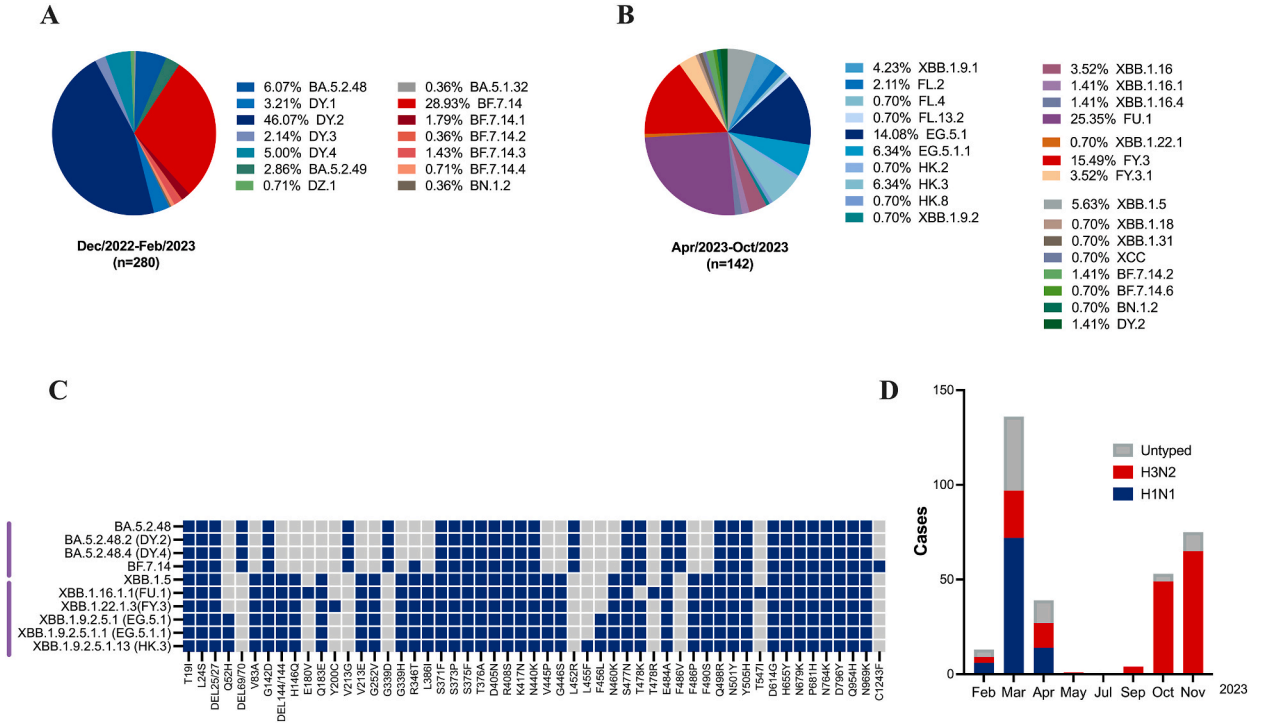


Fig. 3. The distributions of SARS-CoV-2 lineages and spike mutation comparisons in COVID-19 epidemic periods. (A) The proportion of SARS-CoV-2 lineages from December 2022 to February 2023. (B) The proportion of SARS-CoV-2 lineages from April 2023 to October 2023. (C) comparisons of mutations at spike protein of epidemic strains (proportion >5 %) in these two periods. (D) The proportion of influenza lineages from February 2023 to November 2023.

Table 1
Epidemiological patterns of common respiratory infectious pathogens in some regions of the world and China since 2017.

Pathogen	Region	Population	Began pandemic seasons	End of pandemic seasons	Peak
SARS-CoV-2	Global [2]	All ages	April 2020	January 2021	January 2021
			March 2021	May 2021	April 2021
			July 2021	September 2021	August 2021
			December 2021	April 2022	January 2022
			July 2022	August 2022	July 2022
			December 2022	January 2023	December 2022
	China [2]	All ages	December 2022	January 2023	December 2022
			April 2023	July 2023	June 2023
Influenza A	Global [3]	All ages	December 2016	April 2017	January 2017
			June 2017	August 2017	July 2017
			December 2017	April 2018	January 2018
			December 2018	April 2019	February 2019
			June 2019	July 2019	June 2019
			November 2019	March 2020	February 2020
			November 2021	February 2022	December 2021
			March 2022	June 2022	March 2022
			October 2022	February 2023	December 2022
			March 2023	May 2023	March 2023
			September 2023	a	a
	China [3]	All ages	December 2017	March 2018	January 2018
			December 2018	March 2019	January 2019
			December 2019	January 2020	December 2019
			June 2022	August 2022	July 2022
			February 2023	May 2023	March 2023
			October 2023	a	a
Influenza B	Global [3]	All ages	January 2017	May 2017	March 2017
			October 2017	May 2018	January 2018
			March 2019	June 2019	April 2019
			November 2019	March 2020	January 2020
			November 2021	March 2022	January 2022
			October 2022	May 2023	February 2023
			October 2023	a	a
	China [3]	All ages	November 2017	March 2018	January 2018
			March 2019	July 2019	April 2019
			December 2019	January 2020	January 2020
			November 2021	March 2022	January 2022
			October 2023	a	a
Mycoplasma pneumoniae	Global [4,5]	All ages	August 2017	March 2018	November 2017–January 2018
			October 2018	January 2019	November–December 2018
			March 2019	July 2019	May 2020
			August 2019	April 2020	November 2019–February 2020
			May 2023	b	b
	Beijing, China [6]	All ages	August–January 2015–2019	/	October of the same year
Respiratory Syncytial Virus	United States [7]	All ages	October 2017–2019	April 2018/2019/ 2020	December of the same year
			May 2021	January 2022	July 2021
			June 2022	January 2023	November 2022
	Hangzhou, China [8]	0–14 years	late autumn-early winter October 2017–February 2021	/	November of the same year- January of the next year
Adenovirus	United States [9]	All ages	April 2017–2019	August of the same year	June–July of the same year
			November 2017–2019	December of the same year	November of the same year
			May 2021	c	c
Adenovirus	Hangzhou, China [8]	All ages	prevalent throughout the year October 2017–February 2021	/	Summer
Rhinovirus	United States [9]	All ages	May 2017–2019	June of the same year	May of the same year
			August 2017–2019	December of the same year	September of the same year
			May 2021	c	c
	China [10]	Children	prevalent throughout the year September 2019–January 2022	/	April and November
Parainfluenza Virus	United States [9]	All ages	April 2017–2019	July of the same year	May–June of the same year

(*continued on next page*)

Table 1 (*continued*)

Pathogen	Region	Population	Began pandemic seasons	End of pandemic seasons	Peak
			September 2017–2019	December of the same year	October–November of the same year
			May 2021	c	c
	China [10]	Children	March 2019/2021	July of the same year	May
			September 2019–2021	February of the next year	November

The global data for SARS-CoV-2, Influenza A, and Influenza B include China.
a As of December 6, 2023, this part of the data is not available.
b The original data was up to September of the same year, and this part of the data is not available.
c The original data was up to May of the same year, and this part of the data is not available.

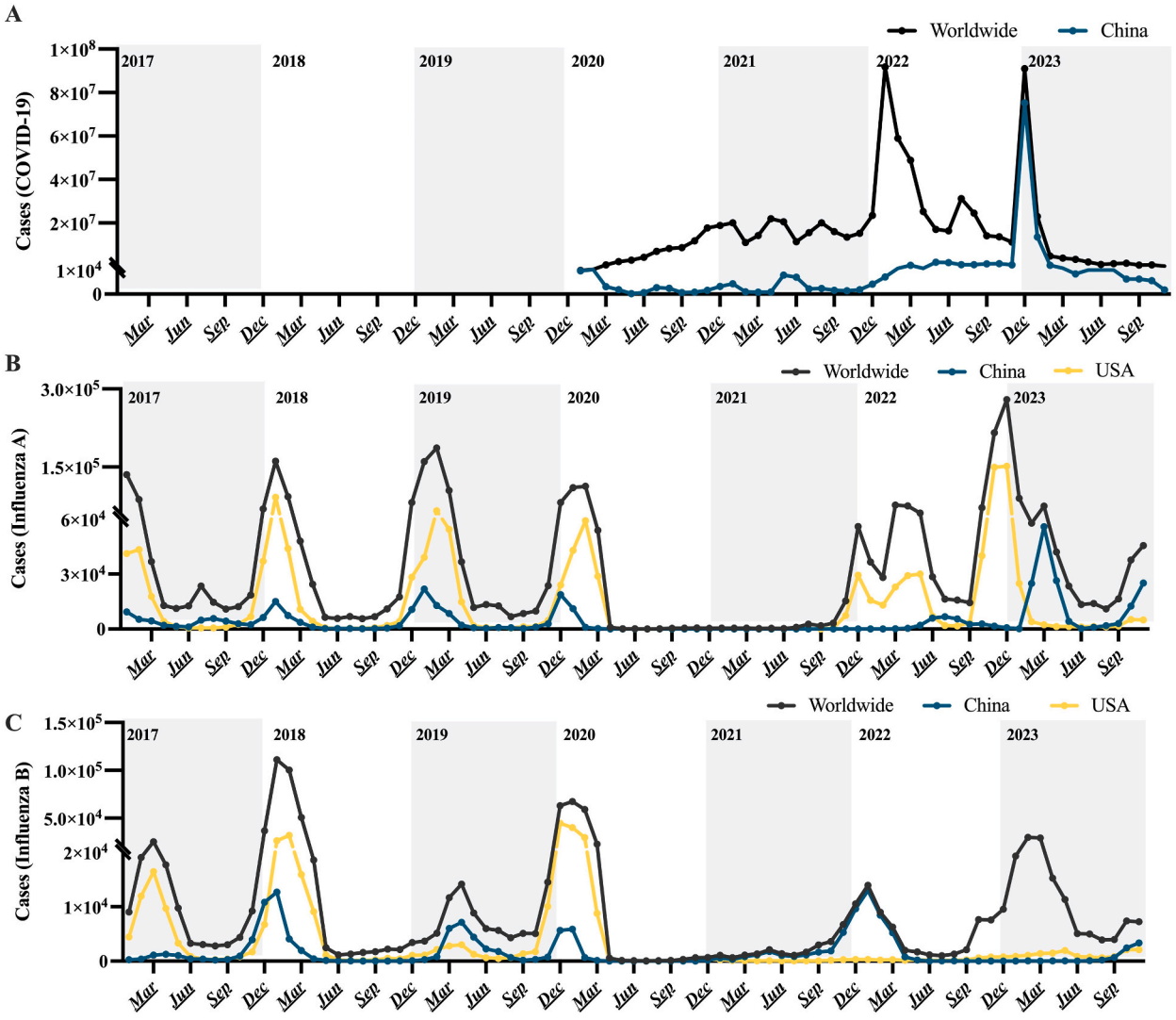


Fig. 4. Monthly new confirmed (A) COVID-19 (B) Influenza A and (C) Influenza B cases in mainland China and globally.
Data Source: WHO COVID-19 Dashboard (https://data.who.int/) ; WHOFlunet (https://www.who.int/tools/flunet)

revealed cases of "coepidemics" involving influenza A and *M. pneumoniae*.

4.5. Dynamic assessment of pathogen antibody levels in the adults without acute respiratory infections in China, 2016–2023

The antibody distribution chart reveals a regular seasonal variation in the levels of seven pathogens (excluding SARS-CoV-2 before 2020). Taking influenza A virus antibody variation as an example, before 2020, the antibody levels exhibited a noticeable increase during the winter-spring seasons coinciding with an epidemic of influenza A. The mean antibody titer during the winter-spring seasons in 2019 was 4.05 S/CO, with a low value of 0.97 S/CO in the summer of 2018. After 2020, the seasonal trend was disrupted because of the onset of the COVID-19 epidemic. From March to May 2023, during the influenza A seasonal outbreak, the average antibody level rose to 1.59 S/CO, which was below the levels observed before 2020. Interestingly, over the past seven years, the antibody levels against every respiratory pathogen in the adult population have remained at a certain level, showing no significant decrease compared with their pre-COVID-19 pandemic levels regardless of the implementation of NPI measures. For instance, for *M. pneumoniae*, although the fluctuation rhythm changed, the antibody levels fluctuated between 2.06 and 4.25 S/CO before the pandemic and 1.62–5.97 S/CO after 2021, with no significant difference (Fig. 5, Supplementary Fig. S4 in Supplement 2).

5. Discussion

During the COVID-19 pandemic, many countries implemented NPIs to mitigate or block the spread of SARS-CoV-2. However, after the gradual relaxation and lifting of NPIs, an anomalous increase in common respiratory pathogens (such as RSV and IFV) during nonpeak seasons has been observed globally from 2022 to 2023 [2–6]. In China, the concentrated prevalence of respiratory pathogens such as SARS-CoV-2 and influenza was noted in 2023.

Our monitoring revealed that SARS-CoV-2 and influenza A were the main pathogens causing the outbreaks in 2023. To exclude the possibility of newly emerging microbes, we conducted high-throughput sequencing on samples from patients with pneumonia that had been collected from multiple clinical institutions in 2023. We found no evidence supporting the notion that a novel pathogen had led to an increase in community cases of respiratory tract infections.

Whether coinfections increase the severity of infection is a crucial factor in assessing the impact of epidemics. We found that coinfections with multiple respiratory pathogens are relatively common in community-acquired acute respiratory infections. Viral and bacterial coinfections, as well as bacterial-bacterial coinfections, were the most observed, whereas coinfections between viruses were

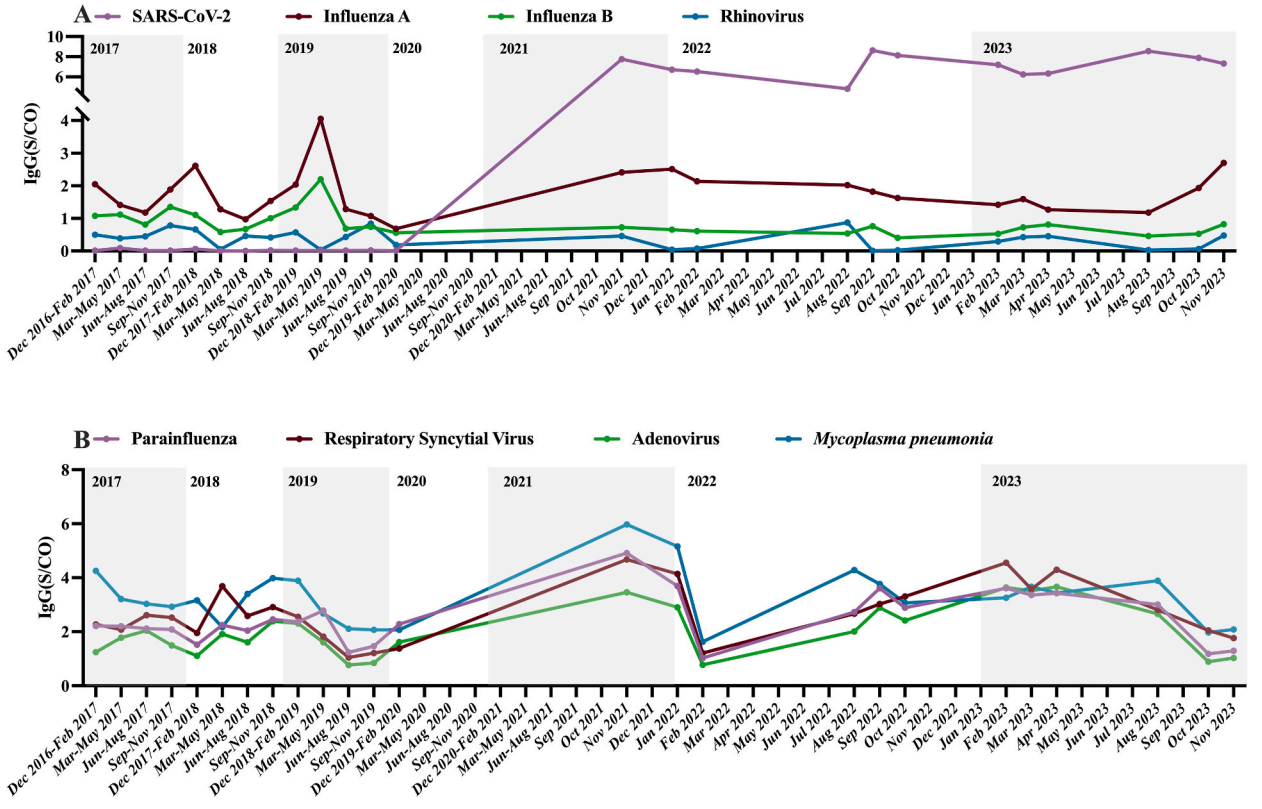


Fig. 5. Distribution of signal-to-cutoff(S/CO) antibody values over the seven yearly samples among adults are shown for eight pathogens. Each point represents the mean S/CO level for the samples at the timepoint.

relatively rare. In our multicenter data, tNGS analysis found that the incidence of SCAP among cases with coinfection was 9.7 %, which was not significantly higher than that with monoinfection, suggesting that coinfection did not increase SCAP incidence in patients with CAP.

Previous studies have reported that patients with SCAP, especially children and the elderly, are more prone to viral-bacterial coinfections, while adults are mainly associated with bacterial-bacterial coinfections [13,14]. Several reports suggest that the impact of coinfections on clinical outcomes varies depending on the pathogen. For instance, during SARS-CoV-2 infection, bacterial coinfections are less common, but coinfections with IFVs may increase disease severity [15–18]. Although our study did not find a direct relationship between respiratory coinfection and an increased incidence of SCAP, which may be due to the low incidence of viral-viral coinfections, monitoring pathogen coinfections remains of significant importance for assessing disease severity and guiding treatment strategies.

This winter in China, the predominant subtype of influenza A had become H3N2. In our study, 8.12 % of cases of pneumonia were caused by influenza A (H3N2), which was significantly higher than the 3.26 % of cases caused by influenza A (H1N1pdm) ($P = 0.209$), which agrees with previous studies [19,20]. For the two SARS-CoV-2 epidemics in China in 2023, the BA.5 variant was reported to have a higher risk of hospitalization compared with that of the BA.2 variant [21,22] and showed a similar severity to that of BA.1 but reduced clinical severity compared with that of the Delta variants [23]. For the XBB subvariants, no significant association has been indicated between XBB variants and admission rate compared with other circulating variants [24].

In 2023, the prevalence patterns of influenza A and SARS-CoV-2 in China exhibited a “staggered” trend compared to those in most other regions globally. This situation might be attributed to China gradually lifting NPIs towards the end of 2022, which was several months later than other global regions. Additionally, we observed a “coepidemic” pattern of influenza A and *M. pneumoniae* during the autumn-winter season in 2023. Previous international studies have also indicated that the implementation of NPIs not only disrupted the transmission of SARS-CoV-2 but also altered the seasonal patterns of other respiratory pathogens [25,26]. The timing and impact of RSV peaks varied across multiple countries in the northern and southern hemispheres after the relaxation of NPIs [26]. Therefore, the relaxation of NPIs caused a phenomenon of “overlapping prevalence” with multiple pathogens. This may be a significant factor in the substantial increase in cases of respiratory infections during the autumn and winter seasons in 2023.

The hypothesis of NPIs leading to “immune debt” was explored in this study to reveal that antibody levels did not significantly decline compared with those during 2018–2020. The antibody titers against pathogens such as RSV and *M. pneumoniae* exhibited intermittent trends of initial increase followed by decrease, indicating partial population-level prevalence over recent years. However, from March to May 2023, during the influenza A seasonal outbreak, we did not observe a significant stimulation of antibody levels among adults, indicating that the attenuated immune stimulation may have also contributed to the influenza surge. The possible reasons for attenuated immune stimulation could be due to the decreased prevalence of influenza A during the past 3 years or reduced influenza A vaccination rates globally. However, we should also consider the positive impact of NPI measures during the pandemics, which significantly reduced the number of infections and the consumption of medical resources during the peak of the pandemic [27,28]. Therefore, the decision to implement or lift NPIs should be made based on a range of epidemiological, social, economic, and public health factors.

In other studies, antibodies to RSV have been used to measure immunity in children [29]. A children’s hospital in Jiangsu, China, reported a significant reduction in antibody levels in children after the removal of NPIs [30]. Additionally, a study in Lombardy, Italy, using RSV catalytic modeling, determined a 60.8 % increase in RSV susceptibility in the 1–5 age group after NPI implementation [31]. Moreover, infants born during the NPI period tended to have lower levels of maternally derived antibodies [32,33]. NPI implementation may have also disrupted routine vaccination schedules, leading to lower antibody levels compared with those in the same period in previous years [34].

Our study focused on immunity to common respiratory pathogens in adult populations. Existing published cohort studies primarily focused on children and suggested an “immune gap” in the 1–5 age group after NPI implementation. Adults generally experience long-term seasonal prevalence, and routine influenza vaccination is more common. Therefore, adults were less susceptible to short-term NPIs, extended intervals between vaccine doses, and maternal antibody interference. However, the attenuated immune stimulation should raise our awareness, especially recalling the importance of routine vaccinations even during a global pandemic.

6. Limitations

Our study has several limitations. First, the clinical respiratory infection specimens were collected from outpatient, emergency, or fever clinics across 14 clinical institutions covered by our research, which may not fully represent the situation in every city in China, especially for hospital-acquired infections. Second, the sample size was limited when analyzing the disease pathogenesis between mono- and coinfections. Furthermore, because of limitations in sample quantity, neutralizing antibody testing of the blood was not performed, and high-throughput sequencing for monitoring emerging infectious diseases was conducted only in 98 cases of pneumonia. During the dynamic assessment of antibody levels, we could not collect enough peripheral blood specimens from children as only one children’s hospital is in our network. Another limitation was that clustering of cases was not reported in a standardized manner as of November 2023. A standardized reporting pathway for the clustering of cases should be established for closer surveillance.

Our research found no significant decline in the overall antibody levels, indicating the absence of a population-wide immune attenuation. However, for individuals, coinfections may occur because of factors such as age, comorbidities, and individual circumstances, which need more in-depth studies at the individual level in the future. Lastly, the adult blood samples were not obtained from a fixed long-term follow-up cohort but from a different population of patients with nonrespiratory infections at different timepoints.

Although we increased the sample size to minimize the bias, further fixed-cohort follow-up studies may be required.

7. Conclusion

The significant increase in cases of respiratory infectious diseases during the fall and winter of 2023 may be due to the overlapping prevalence of seasonal respiratory infectious diseases in China. The termination of NPIs caused a "misaligned" alteration in the traditional pathogen prevalence pattern, similar to the reported anomalous fluctuations in common respiratory infections in other countries. Our study found no evidence of emerging novel pathogens in this round of disease prevalence, and with the influenza or COVID-19 prevalence, bacterial-bacterial coinfections were the most common coinfections among patients who developed CAP. Our study revealed that NPI measures did not cause a significant decrease in binding antibody levels in the adult population. Attenuated immune stimulation for influenza was observed among the adult population, suggesting the importance of maintaining vaccine coverage even during a pandemic. The impact of the pandemic on the global seasonal prevalence pattern of infectious diseases requires closer monitoring and observation in the future.

Ethical approval

This study was reviewed and approved by [Huashan Institutional Review Board], with the approval number: [KY2017-338, KY2020-688, KY2021-450, KY2021-749, KY2021-958, KY2022-721, KY2022-1011]. All participants/patients (or their proxies/legal guardians) written informed consent in the study.

Funding

This work was supported by the following fundings, National Key Research and Development Program [2023YFC3043500] and [2022YFF1202105], Autonomous deployment project of Shanghai Sci-Tech InnoCenter for Infection and Immunity [SSIII- 202401], and Shanghai three-year action plan for public health [GWVI-2.1].

Data availability statement

Source data were included in article and supplementary materials, and the data associated with this study have not been deposited in a publicly available repository.

CRediT authorship contribution statement

Jingwen Ai: Writing – review & editing, Writing – original draft, Validation, Methodology, Investigation, Conceptualization. **Hongyu Wang:** Writing – original draft, Methodology, Formal analysis, Data curation, Visualization, Conceptualization. **Haocheng Zhang:** Writing – original draft, Methodology, Formal analysis, Data curation, Visualization, Conceptualization. **Jieyu Song:** Writing – original draft, Formal analysis. **Yi Zhang:** Writing – original draft, Visualization, Data curation, Formal analysis. **Ke Lin:** Writing – original draft, Formal analysis. **Lihong Qu:** Writing – original draft, Formal analysis. **Yanliang Zhang:** Writing – original draft, Formal analysis. **Shiliang Zhang:** Writing – original draft, Formal analysis. **Qiyun Xiang:** Data curation. **Jiawei Geng:** Data curation. **Guangxia Jin:** Data curation. **Wei Song:** Data curation. **Liaoyun Zhang:** Data curation. **Xiaoli Hu:** Data curation. **Hongyan Liu:** Data curation. **Guanmin Yuan:** Data curation. **Ning Jiang:** Formal analysis. **Yang Zhou:** Formal analysis. **Yuanyuan Xu:** Formal analysis. **Jun Ying:** Formal analysis. **Jiqin Wu:** Data curation. **Yajiao Xing:** Data curation. **Kai Fang:** Data curation. **Hui Yan:** Data curation. **Feiying Chen:** Data curation. **Tailin Xu:** Data curation. **Sen Wang:** Methodology, Investigation, Conceptualization. **Zhaohui Qian:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Wenhong Zhang:** Writing – review & editing, Methodology, Investigation, Conceptualization, Funding acquisition.

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.

Acknowledgements

We thank Hongyang Li, Wen Liu, Yan Miao, Yanqiu Zhao, Kejie Zhu, Zhide Liu, and Haoyang Xue for data collection and analysis. We thank Huashan Hospital Affiliated Fudan University, Shanghai East Hospital, Nanjing Hospital of Chinese Medicine, Wuxi Fifth People's Hospital Affiliated to Nanjing Medical University, Heilongjiang Provincial Hospital, Jining Public Health Medical Center, First Hospital of Shanxi Medical University, The Sixth People's Hospital of Shenyang, The Third People's Hospital of Yichang, The first People's Hospital of Yunnan Province, Shanghai Jinyang Community Health Service Center, Hunan University of Medicine General Hospital, Shenzhen Children's Hospital, and The First Affiliated Hospital of Xi'an Jiaotong University, all 14 institutions for sample collection of nasopharyngeal swabs. We thank Shanghai ZJ Bio-Tech Co., Ltd. and Hangzhou DIAN Biotechnology Co., Ltd for their technology support during the study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e32304.

References

[1] Nov 10, Chinese Center for Disease, C. National Epidemic of Novel Coronavirus Infections (October 2023) (2023). December 6, 2023]; Available from: https://www.chinacdc.cn/jkzt/crb/zl/szkb_11803/jszl_13141/202311/t20231110_270578.html.
[2] W.H. Organization, WHO COVID-19 Dashboard, 6 December 2023. December 6, 2023. Available from: https://covid19.who.int/data.
[3] W.H. Organization, FluNet, December 6, 2023. Available from: https://www.who.int/tools/flunet.
[4] P.M. Meyer Sauteur, M.L. Beeton, Mycoplasma pneumoniae: delayed re-emergence after COVID-19 pandemic restrictions, Lancet Microbe 5 (2) (2024) e100–e101, https://doi.org/10.1016/s2666-5247(23)00344-0.
[5] P.M.M. Sauteur, M.L. Beeton, S.A. Uldum, N. Bossuyt, M. Vermeulen, K. Loens, et al., Mycoplasma pneumoniae detections before and during the COVID-19 pandemic: results of a global survey, 2017 to 2021, Euro Surveill. 27 (19) (2022) 2100746, https://doi.org/10.2807/1560-7917.ES.2022.27.19.2100746.
[6] X. Wang, M. Li, M. Luo, Q. Luo, L. Kang, H. Xie, et al., Mycoplasma pneumoniae triggers pneumonia epidemic in autumn and winter in Beijing: a multicentre, population-based epidemiological study between 2015 and 2020, Emerg Microbes Infect 11 (1) (2022) 1508–1517, https://doi.org/10.1080/22221751.2022.2078228.
[7] S. Hamid, A. Winn, R. Parikh, J.M. Jones, M. McMorrow, M.M. Prill, et al., Seasonality of respiratory syncytial virus - United States, 2017-2023, MMWR Morb. Mortal. Wkly. Rep. 72 (14) (2023) 355–361, https://doi.org/10.15585/mmwr.mm7214a1.
[8] X. Du, G. Wu, Y. Zhu, S. Zhang, Exploring the epidemiological changes of common respiratory viruses since the COVID-19 pandemic: a hospital study in Hangzhou, China, Arch. Virol. 166 (11) (2021) 3085–3092, https://doi.org/10.1007/s00705-021-05214-8.
[9] S.J. Olsen, A.K. Winn, A.P. Budd, M.M. Prill, J. Steel, C.M. Midgley, et al., Changes in influenza and other respiratory virus activity during the COVID-19 pandemic - United States, 2020-2021, MMWR Morb. Mortal. Wkly. Rep. 70 (29) (2021) 1013–1019, https://doi.org/10.15585/mmwr.mm7029a1.
[10] H. Wang, Y. Zheng, M.I. de Jonge, R. Wang, L.M. Verhagen, Y. Chen, et al., Lockdown measures during the COVID-19 pandemic strongly impacted the circulation of respiratory pathogens in Southern China, Sci. Rep. 12 (1) (2022) 16926, https://doi.org/10.1038/s41598-022-21430-x.
[11] J.P. Metlay, G.W. Waterer, A.C. Long, A. Anzueto, J. Brozek, K. Crothers, et al., Diagnosis and treatment of adults with community-acquired pneumonia. An official clinical practice guideline of the American thoracic society and infectious diseases society of America, Am. J. Respir. Crit. Care Med. 200 (7) (2019) e45–e67, https://doi.org/10.1164/rccm.201908-1581ST.
[12] X. Zhang, Y. Tan, Y. Ling, G. Lu, F. Liu, Z. Yi, et al., Viral and host factors related to the clinical outcome of COVID-19, Nature 583 (7816) (2020) 437–440, https://doi.org/10.1038/s41586-020-2355-0.
[13] Y.-N. Liu, Y.-F. Zhang, Q. Xu, Y. Qiu, Q.-B. Lu, T. Wang, et al., Infection and co-infection patterns of community-acquired pneumonia in patients of different ages in China from 2009 to 2020: a national surveillance study, The Lancet Microbe 4 (5) (2023) e330–e339.
[14] Y. Mandelia, G.W. Procop, S.S. Richter, S. Worley, W. Liu, F. Esper, Dynamics and predisposition of respiratory viral co-infections in children and adults, Clin. Microbiol. Infect. 27 (4) (2021) 631 e1–e631 e6, https://doi.org/10.1016/j.cmi.2020.05.042.
[15] S. Liu, W. Li, S. Jiang, Disease of influenza virus and SARS-CoV-2 coinfection: flurona or Flucovid? J. Med. Virol. 94 (9) (2022) 4056–4057, https://doi.org/10.1002/jmv.27874.
[16] Y. Liu, L. Ling, S.H. Wong, M.H. Wang, J.R. Fitzgerald, X. Zou, et al., Outcomes of respiratory viral-bacterial co-infection in adult hospitalized patients, EClinicalMedicine 37 (2021) 100955, https://doi.org/10.1016/j.eclinm.2021.100955.
[17] L. Lansbury, B. Lim, V. Baskaran, W.S. Lim, Co-infections in people with COVID-19: a systematic review and meta-analysis, J. Infect. 81 (2) (2020) 266–275, https://doi.org/10.1016/j.jinf.2020.05.046.
[18] M.C. Swets, C.D. Russell, E.M. Harrison, A.B. Docherty, N. Lone, M. Girvan, et al., SARS-CoV-2 co-infection with influenza viruses, respiratory syncytial virus, or adenoviruses, Lancet 399 (10334) (2022) 1463–1464, https://doi.org/10.1016/S0140-6736(22)00383-X.
[19] J.G. Yoon, J.Y. Noh, W.S. Choi, J. Lee, J.S. Lee, S.H. Wie, et al., A comparison of epidemiology and clinical outcomes between influenza A H1N1pdm09 and H3N2 based on multicenter surveillance from 2014 to 2018 in South Korea, Influenza Other Respir Viruses 15 (1) (2021) 99–109, https://doi.org/10.1111/irv.12795.
[20] A. Fall, L. Han, M. Yunker, Y.N. Gong, T.J. Li, J.M. Norton, et al., Evolution of influenza A(H3N2) viruses in 2 consecutive seasons of genomic surveillance, 2021-2023, Open Forum Infect. Dis. 10 (12) (2023) ofad577, https://doi.org/10.1093/ofid/ofad577.
[21] C.H. Hansen, N.U. Friis, P. Bager, M. Stegger, J. Fonager, A. Fomsgaard, et al., Risk of reinfection, vaccine protection, and severity of infection with the BA.5 omicron subvariant: a nation-wide population-based study in Denmark, Lancet Infect. Dis. 23 (2) (2023) 167–176, https://doi.org/10.1016/S1473-3099(22)00595-3.
[22] C. Robertson, S. Kerr, A. Sheikh, Severity of Omicron BA.5 variant and protective effect of vaccination: national cohort and matched analyses in Scotland, Lancet Reg Health Eur 28 (2023) 100638, https://doi.org/10.1016/j.lanepe.2023.100638.
[23] N. Wolter, W. Jassat, S. Walaza, R. Welch, H. Moultrie, M.J. Groome, et al., Clinical severity of SARS-CoV-2 Omicron BA.4 and BA.5 lineages compared to BA.1 and Delta in South Africa, Nat. Commun. 13 (1) (2022) 5860, https://doi.org/10.1038/s41467-022-33614-0.
[24] E.Y. Klein, A. Fall, J.M. Norton, R.E. Eldesouki, O. Abdullah, L. Han, et al., Severity outcomes associated with SARS-CoV-2 XBB variants, an observational analysis, J. Clin. Virol. 165 (2023) 105500, https://doi.org/10.1016/j.jcv.2023.105500.
[25] R. Cohen, C. Levy, A. Rybak, F. Angoulvant, N. Ouldali, E. Grimprel, Immune debt: recrudescence of disease and confirmation of a contested concept, Infect Dis Now 53 (2) (2023) 104638, https://doi.org/10.1016/j.idnow.2022.12.003.
[26] T.C. Williams, I. Sinha, I.G. Barr, M. Zambon, Transmission of paediatric respiratory syncytial virus and influenza in the wake of the COVID-19 pandemic, Euro Surveill. 26 (29) (2021) 2100186, https://doi.org/10.2807/1560-7917.ES.2021.26.29.2100186.
[27] N.M. Ferguson, D. Laydon, G. Nedjati-Gilani, N. Imai, K. Ainslie, M. Baguelin, et al., Impact of Non-pharmaceutical Interventions (NPIs) to Reduce COVID-19 Mortality and Healthcare Demand, 16-03, Imperial College London, 2020, https://doi.org/10.25561/77482.
[28] S. Lai, N.W. Ruktanonchai, L. Zhou, O. Prosper, W. Luo, J.R. Floyd, et al., Effect of non-pharmaceutical interventions to contain COVID-19 in China, nature 585 (7825) (2020) 410–413.
[29] M.N. Billard, L.J. Bont, Quantifying the RSV immunity debt following COVID-19: a public health matter, Lancet Infect. Dis. 23 (1) (2023) 3–5, https://doi.org/10.1016/S1473-3099(22)00544-8.
[30] W. Jiang, L. Xu, Y. Wang, C. Hao, Exploring immunity debt: dynamic alterations in RSV antibody levels in children under 5 years during the COVID-19 pandemic, J. Infect. (2023), https://doi.org/10.1016/j.jinf.2023.10.019. Oct 29: p. S0163-4453(23)00550-9.
[31] H.J. Ang, F. Menegale, G. Preziosi, E. Pariani, M. Migliari, L. Pellegrinelli, et al., Reconstructing the impact of COVID-19 on the immunity gap and transmission of respiratory syncytial virus in Lombardy, Italy, EBioMedicine 95 (2023) 104745, https://doi.org/10.1016/j.ebiom.2023.104745.

[32] B. Abu-Raya, F. Reicherz, C. Michalski, M. Vineta Paramo, A. Majdoubi, L. Golding, et al., Loss of respiratory syncytial virus antibody functions during the peak of the COVID-19 pandemic mitigation measures, J Pediatric Infect Dis Soc 12 (10) (2023) piad099, https://doi.org/10.1093/jpids/piad099.
[33] F. Reicherz, R.Y. Xu, B. Abu-Raya, A. Majdoubi, C. Michalski, L. Golding, et al., Waning immunity against respiratory syncytial virus during the coronavirus disease 2019 pandemic, J. Infect. Dis. 226 (12) (2022) 2064–2068, https://doi.org/10.1093/infdis/jiac192.
[34] R. Cohen, M. Ashman, M.K. Taha, E. Varon, F. Angoulvant, C. Levy, et al., 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? Infect Dis Now 51 (5) (2021) 418–423, https://doi.org/10.1016/j.idnow.2021.05.004.