Characterising the changes in RSV epidemiology in Beijing, China during 2015–2023: results from a prospective, multi-centre, hospital-based surveillance and serology study

Maozhong Li,[a,b,h] Bingbing Cong,[c,h] Xiaofeng Wei,[a,d,h] Yiting Wang,[a,b] Lu Kang,[a,b] Cheng Gong,[a,b] Qi Huang,[a,d] Xin Wang,[e,f,i,***] You Li,[c,f,g,i,**] and Fang Huang[a,b,d,i,*]

[a]Beijing Center for Disease Prevention and Control, Beijing Academy for Preventive Medicine, Beijing Institute of Tuberculosis Control Research and Prevention, Beijing, 100013, People's Republic of China
[b]Beijing Research Center for Respiratory Infectious Diseases, Beijing, 100013, People's Republic of China
[c]Department of Epidemiology, National Vaccine Innovation Platform, School of Public Health, Nanjing Medical University, Nanjing, 211166, People's Republic of China
[d]School of Public Health, Capital Medical University, Beijing, 100069, People's Republic of China
[e]Department of Biostatistics, National Vaccine Innovation Platform, School of Public Health, Nanjing Medical University, Nanjing, 211166, People's Republic of China
[f]Centre for Global Health, Usher Institute, University of Edinburgh, Edinburgh, EH8 9AG, United Kingdom
[g]Changzhou Third People's Hospital, Changzhou Medical Centre, Nanjing Medical University, Changzhou, 213000, People's Republic of China

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Summary

Background Respiratory syncytial virus (RSV) has posed substantial morbidity and mortality burden to young children and older adults globally. The coronavirus disease 2019 (COVID-19) pandemic was reported to have altered RSV epidemiology and could have important implications for RSV prevention and control strategies. We aimed to compare RSV epidemiology in different phases of the COVID-19 pandemic with the pre-pandemic period by leveraging epidemiological, molecular, and serological data collected from a prospective respiratory pathogen surveillance and serology study.

Methods This study was based on the data during July 1, 2015 to November 30, 2023 from the Respiratory Pathogen Surveillance System (RPSS), a sentinel-hospital based surveillance system of acute respiratory infections consisting of 35 hospitals that represent residents of all ages from all 16 districts in Beijing, China. RSV infection status was tested by RT-PCR and gene sequencing and phylogenetic analysis was conducted among the identified RSV strains. We further supplemented RPSS data with three serology surveys conducted during 2017–2023 that tested RSV IgG levels from serum specimens. RSV detection rate was calculated by calendar month and compared across RSV seasons (defined as the July 1 through June 30 of the following year). RSV IgG positivity proportion was calculated by quarter of the year and was correlated with quarterly aggregated RSV detection rate for understanding the relationship between infection and immunity at the population level.

Findings Overall, a total of 52,931 respiratory specimens were collected and tested over the study period. RSV detection rates ranged from 1.24% (94/7594) in the 2017–2018 season to 2.80% (219/7824) in the 2018–2019 season, and from 1.06% (55/5165) in the 2022–2023 season to 2.98% (147/4938) in the 2021–2022 season during the pre-pandemic and pandemic period, respectively. ON1 and BA9 remained the predominant genotypes during the pandemic period; no novel RSV strains were identified. RSV circulation followed a winter-months seasonal pattern in most seasons. One exception was the 2020–2021 season when an extensive year-round circulation was observed, possibly associated with partial relaxation of non-pharmaceutical interventions (NPIs). The other exception was the 2022–2023 season when very low RSV activity was observed during the usual winter months (possibly due to the concurrent local COVID-19 epidemic), and followed by an out-of-season resurgence in the

*Corresponding author. Beijing Center for Disease Prevention and Control, Beijing Academy for Preventives Medicine, Beijing Institute of Tuberculosis Control Research and Prevention, No.16 Hepingli Middle St, Dongcheng District, Beijing, 100013, People's Republic of China.
**Corresponding author. Changzhou Third People's Hospital, Changzhou Medical Center, Nanjing Medical University, 300 Lanling North Road, Changzhou, 213000, People's Republic of China.
***Corresponding author. Department of Biostatistics, National Vaccine Innovation Platform, School of Public Health, Nanjing Medical University, 101 Longmian Avenue, Nanjing, 211166, People's Republic of China.
E-mail addresses: hhffxdd@126.com (F. Huang), you.li@njmu.edu.cn (Y. Li), xin.wang@njmu.edu.cn (X. Wang).
[h]Contributed equally to this work.
[i]Joint senior authors.

spring, with RSV detection persisting to the end of the study period (November 2023). During the two seasons above, we noted an age-group related asynchrony in the RSV detection rate; the RSV detection rate in young children remained similar (or even increased with borderline significance; 43/594, 7.24%, and 42/556, 7.55% *vs* 292/5293, 5.52%; $P = 0.10$ and $P = 0.06$, respectively) compared with the pre-pandemic seasons whereas the detection rate in older adults decreased significantly (8/1779, 0.45%, and 3/2021, 0.15% *vs* 160/10,348, 1.55%; $P < 0.001$ in two comparisons). Results from serology surveys showed significantly declined RSV IgG positivity in the 2022–2023 season compared to the pre-pandemic seasons (9.32%, 29/311 vs 20.16%, 100/496; $P < 0.001$); older adults had significantly higher RSV IgG positivity than young children in both pre-pandemic and pandemic periods (P values < 0.001).

Interpretation Our study documented the trajectory of RSV detection along with the changes in the stringency of NPIs, measured IgG positivity, and local COVID-19 epidemics. The findings suggest the interplay between contact patterns, immunity dynamics, and SARS-CoV-2 infection in shaping the RSV epidemics of population of different ages. These findings provide novel insights into the potential drivers of RSV circulating patterns and have important implications for RSV prevention and control strategies.

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Keywords: Respiratory syncytial virus; Epidemiology; Covid-19; Prospective studies; Sentinel surveillance; Serology

Introduction

Respiratory syncytial virus (RSV) is the most common pathogen identified in young children and older adults with lower respiratory tract infections (LRTI) and has caused substantial morbidity and mortality burden.[1,2] RSV prophylactic products including maternal vaccine, monoclonal antibodies for infants, and vaccine for older adults were licensed in Europe and the US in the recent one year, opening a new era for the prevention of RSV diseases.[3]

In China, RSV infection accounted for 16.8% of medically attended acute respiratory infections, second only to influenza virus (28.5%).[4] In the northern part of China, the annual RSV epidemics occurred during the winter–spring months. For example, in Beijing, approximately 97% of all RSV-positive cases occurred during mid-October and mid-May of the next year before the coronavirus disease 2019 (COVID-19) pandemic,[5] whereas in southern China, such as Hong Kong, the seasonality of RSV presented in spring-summer months.[6] During the COVID-19 pandemic, low RSV activity was observed globally due to the large-scale implementation of non-pharmaceutical interventions (NPIs)[7–10]; out-of-season RSV resurgence was observed following the relaxation of these measures, which might be explained by the "immune debt" characterised by the accumulated population susceptibility associated with the lack of natural infections during the pandemic.[11,12] Meanwhile, a study from Australia reported a major reduction in RSV genetic diversity following the COVID-19 pandemic.[13]

Although several reports described the epidemiological and genetic features of RSV infections in China before the COVID-19 pandemic,[14–16] there remains a knowledge gap on the post-pandemic landscape of RSV epidemiology in China. Different from most countries, China had a distinct trajectory of COVID-19 epidemics and implementation of NPIs — relatively stringent NPIs were placed throughout the first three years of the COVID-19 pandemic, and the relaxation of these NPIs at the end of 2022 resulted in a large scale COVID-19 epidemic nationwide. Therefore, it is important to understand the trajectory of RSV epidemiology in China since the COVID-19 pandemic as well as the interplay between NPIs, population immunity, and SARS-CoV-2 infection in shaping the RSV epidemic patterns.

In this prospective, multi-centre, hospital-based surveillance and serology study covering 35 sentinel hospitals from 16 districts in Beijing, China, we aimed to compare RSV epidemiology in different phases of the COVID-19 pandemic with the pre-pandemic period by leveraging epidemiological, molecular, and serological data.

Methods

Study design

This study was based on the Respiratory Pathogen Surveillance System (RPSS) of Beijing, a mega-city with over 20 million residents. RPSS is a sentinel-hospital based surveillance system consisting of 35 hospitals that represent residents of all ages from all 16 districts in Beijing.

Residents of any ages who visited any of the sentinel hospitals were potentially eligible for inclusion when they were diagnosed with upper respiratory tract

Research in context

Evidence before this study

Respiratory syncytial virus (RSV) causes substantial morbidity and mortality in young children and older adults globally and has distinct seasonal circulating patterns in most parts of the world. The COVID-19 pandemic was reportedly to have reshaped RSV transmission. We searched PubMed, with no language restrictions, for studies reporting the impact of the COVID-19 pandemic on RSV epidemiology published between Jan 1, 2020, and December 16, 2023, using the following search terms: ("COVID-19" OR "SARS-CoV-2") AND ("respiratory syncytial virus" OR "RSV") AND ("epidemiology" OR "seasonal*" OR "serology*" OR "genetic"). Existing studies highlighted the role of non-pharmaceutical interventions (NPIs) in the disruption of the seasonality of RSV; the subsequent relaxation of these NPIs were reported to be associated with the resurgence of RSV epidemics that could fall out of the typical season. Modelling studies indicated that such out-of-season resurgence could be a result of accumulated population susceptibility by the lack of exposure to natural infections, which was also supported by the reported higher proportion of RSV cases in older children during the out-of-season resurgence. Meanwhile, mixed results were reported regarding genetic diversity of RSV. Studies from Taiwan, China and Argentina reported the occurrence of new RSV variants; a study from Australia reported an initial collapse and subsequent recovery in genetic diversity of RSV; however, studies from the US, Italy and Japan reported consistent RSV strains circulating during the pandemic period with the local preexisting strains. Three studies on RSV serum IgG levels during the pandemic period were identified and all studies showed an overall decline of RSV IgG levels across all age groups. No studies were identified that simultaneously tracked down the changes in RSV detection, genetic characteristics, and serology during the COVID-19 pandemic.

Added value of this study

In this study, we leveraged epidemiological, molecular, and serological data from a sentinel-hospital-based surveillance and serology study conducted in Beijing, China for comparing RSV epidemiology in different phases of the COVID-19 pandemic with the pre-pandemic period. We showed that RSV circulating patterns at the population level changed along with the changes in the stringency of NPIs, measured IgG positivity, and local COVID-19 epidemics, suggesting the interplay between contact patterns, immunity dynamics, and SARS-CoV-2 infection in shaping RSV epidemics. Particularly, we observed that COVID-19 epidemic in the local population could completely suppress the RSV seasonal epidemic even when the population immunity level as measured by the RSV serum IgG was low and no NPIs were in place. We also noted the age-group related asynchrony in the RSV detection rate during the 2020–2021 season when RSV circulated year-round, and during the 2022–2023 season when an out-of-season RSV epidemic occurred in early 2023; the RSV detection rate in young children remained similar (or even increased with borderline significance) compared with the pre-pandemic seasons whereas the detection rate in older adults decreased significantly. Besides, older adults had significantly higher RSV IgG positivity proportions than young children in both pre-pandemic and pandemic periods according to the serology surveys. Moreover, no novel RSV strains were identified during the pandemic.

Implications of all the available evidence

Following the onset of the COVID-19 pandemic, NPIs, population immunity, and local COVID-19 epidemic all played important roles in shaping the local transmission patterns of RSV, including the atypical year-round and out-of-season circulations as well as the altered age profile of RSV detection. These important findings could provide further insights into the drivers of future RSV epidemics and help anticipate the possible impact on the RSV epidemiology across all ages when RSV immunisation programmes targeting at infants and older adults are implemented.

infections (URTI) or community-acquired pneumonia (CAP) at either outpatient or inpatient settings. URTI was defined as fever (body temperature ≥38 °C), and/or any respiratory signs or symptoms (i.e., cough or sore throat, nasal congestion, runny nose, sputum). CAP was defined according to the Guidelines of Diagnosis and Treatment for Community-Acquired Pneumonia in China,[17,18] and was further classified as severe community-acquired pneumonia (sCAP) and non-severe community-acquired pneumonia (nsCAP).[19]

While RPSS is ongoing, in this study, we focused on the time period of July 1, 2015 to November 30, 2023, during which the number of sentinel hospitals and diagnosis methods were stable.

Data collection

Respiratory specimen collection and testing

Upon enrollment, respiratory specimens were collected based on a random sampling approach where each sentinel hospital was required to collect and test at least 20 specimens per calendar month with an adult-to-children ratio of approximately 2:1. Respiratory specimens could include nasopharyngeal swab, oropharyngeal swab, sputum, bronchoalveolar lavage fluid or bronchial aspirate. Total nucleic acids were extracted from the specimens by Thermo Scientific™ KingFisher™ Flex Magnetic Particle Processors (Thermo Fisher). A multiplex combined real-time PCR detection kit was used to detect respiratory viruses (Jiangsu

Uninovo Biological Technology Co. Ltd., China), including influenza virus (A (H1N1), A (H3N2) and B), parainfluenza virus (1–4), RSV (A and B), human rhinovirus, human adenovirus, human bocavirus, human metapneumovirus, and seasonal coronavirus (NL63, OC43, 229 E, and HKU1).

RSV sequencing and phylogenetic analysis

The hypervariable region 2 (HVR2) of G gene was amplified using a One-step RT-PCR kit (Invitrogen) with primers previous reports.[14] All PCR reactions contained 5 μl RNA, 1 μl of each forward and reverse primer (20uM), 1 μl of SuperScriptTM III RT/Platinum TM Taq Mix, and 12.5 μl of 2 × Reaction Mix and were made up to a final volume of 25ul with distilled water. The amplification followed the thermocycling conditions: 50 °C for 30 min, 94 °C for 2 min, 40 cycles of denaturation at 94 °C for 30 s, annealing at 58 °C for 30 s, and extension at 72 °C for 1 min, followed by a final extension at 72 °C for 10 min. The PCR products were purified using Biological magnetic beads purification reagent (Tsingke) and then were sequenced using an ABI Prism 3730xl DNA Analyzer at Tsingke Co., Ltd (Beijing, China). The sequences were edited using Sequencher software vision 5.0 (Gene Codes, Ann Arbor, MI, USA). The maximum-likelihood (ML) phylogenetic trees of the HVR2 gene were generated and tested by MEGA 6.0 under the bootstrap method with 1000 replications. The sequences generated in this study were submitted to GenBank with accession numbers from PP024728 to PP204876. Reference sequences of RSV genotypes were provided in Appendix pp 8–10.

Serology surveys

To supplement RPSS, three serology surveys were conducted during 2017–2023 with a total of 1266 serum samples collected. Survey 1 was conducted in 2017 among 91 healthy residents of Beijing as part of an immunization program in 2017. Survey 2, spanning 2018 to 2023, was conducted among 918 patients with acute respiratory infections whose respiratory specimens were tested negative for RSV. Survey 3 was conducted in 2023 among 257 healthy residents as part of the national COVID-19 sero-epidmeiological survey. For all the three surveys, the Virion\serion® SERION ELISA classic Respiratory Syncytial Virus IgG kit was used for serum IgG antibody detection (cat. no. ESR113G; Virion\serion; Germany).

Division of RSV season

In Beijing, increased RSV activity was observed during mid-October and mid-May of the next year before COVID-19 pandemic.[5] To better compare the changes in RSV epidemic timing between different years, we defined each annual RSV season as the period from July 1 through June 30 of the following year. To compare the changes in RSV epidemiology between different periods, we used the period from July 1, 2015 to June 30 2019 as the pre-pandemic reference and further divided the COVID-19 pandemic period into the following periods: July 1, 2019 to June 30, 2020 as 2019–2020 season, July 1, 2020 to June 30, 2021 as 2020–2021 season, July 1, 2021 to June 30, 2022 as 2021–2022 season, July 1, 2022 to June 30, 2023 as 2022–2023 season and July 1, 2023 to November 30, 2023 as the latest available season.

Division of the COVID-19 pandemic phases

As RSV epidemiology was expected to change along with the occurrence of major intervention events (such as school closure and reopening) for containing the COVID-19 epidemic,[11] we divided the COVID-19 pandemic period into four phases based on the local interventions in Beijing. In Phase I (February to May 2020), a wide range of NPIs were implemented, including school closure and movement restrictions. In Phase II (June to August 2020), schools were re-opened gradually with the students on their final year returning first; kindergartens were partially re-opened. In phase 3 (September 2020 to November 2022), the "dynamic COVID-zero" strategy was in place, characterised by mass SARS-CoV-2 infection screening and reactive NPIs when there was local transmission of SARS-CoV-2; in this phase, schools and kindergartens remained fully re-opened.[20] In phase IV (December 2022 to November 2023), all NPIs were lifted.

Statistical analysis

We used detection rate as the basis for understanding the changes in RSV epidemiology, which was calculated as the number of RSV-positive samples divided by the total number of tested samples. We visualised the monthly detection rate of RSV for understanding the temporal trend of RSV infections, overall and separately by clinical diagnosis, age group and RSV subtype. We also evaluated whether clinical diagnosis and age group varied by RSV genotypes. In addition, we downloaded 97 RSV sequences (52 RSV-A and 45 RSV-B) from the GenBank database, and conducted sequence alignment and phylogenetic analysis by MEGA 6.0 and BEAST.v1.8.4.

To further explore the relationship between the serum RSV IgG antibody and the RSV detection by PCR, we aggregated data by quarter of the year, and conducted Pearson's correlation and linear regression of the RSV antibody positivity rate in the previous quarter (t-1) with the natural logarithm of RSV detection rate ratio by PCR between the current (t) and the previous quarter (t-1), based on the assumption that they followed a log-linear relationship. Based on the regression results, we predicted the minimal level of RSV IgG positivity at time t-1 for observing a decreased detection rate at time t as well as the expected RSV detection rate in the first quarter of 2024 given the RSV IgG positivity input in the last quarter of 2023.

Statistical analysis was done using SPSS software, version 21.0 and R software, version 4.2.1.

Ethic approval

This study was approved by the Ethics Committees of Beijing Center for Disease Prevention and Control. The written informed consent was obtained from each included patient, or from their legal guardians.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

A total of 52,931 respiratory specimens were collected and tested for RSV between July 1, 2015 and November 30, 2023, covering eight complete seasons (the 2015–2016 season to the 2022–2023 season) plus five months in the 2023–2024 season. RSV detection rates ranged from 1.06% (55/5165) in the 2022–2023 season to 2.98% (147/4938) in the 2021–2022 season (Table 1 and Appendix pp 3–4).

A distinct seasonal pattern was observed for laboratory-confirmed cases of RSV among patients of all ages and finer age groups from late autumn to early spring during 2015–2016 to 2018–2019 seasons. The end of the 2019–2020 season coincided with phase I of the pandemic period with stringent NPIs in place and had relatively lower detection rate compared to the pre-pandemic seasons. With the gradual relaxation of NPIs in phase II and the introduction of the "dynamic COVID-zero" strategy in phase III, a year-round detection was observed in the 2020–2021 season, followed by a normal seasonal circulation in the 2021–2022 season. In the 2022–2023 season, RSV detection was low during the winter months when all NPIs were lifted, and a massive COVID-19 epidemic occurred; an out-of-season surge was observed in April to May 2023. The detection of RSV persisted since April 2023 and an increase in the detection rate was observed at the end of the study (i.e., November 2023) (Fig. 1).

Over the eight complete seasons (i.e., the 2015–2016 season to the 2022–2023 season), the detection rate of RSV varied significantly by age and showed a U-shaped pattern; the lowest and highest detection rates were found in adults aged 18–<60 years and infant aged <1 year, respectively (Table 1). However, in the first five months of the latest season, children aged 2–<5 years had a significantly higher detection rate than the pre-pandemic period (8.36%, 23/275 vs 4.26%, 141/3310; $P = 0.003$). The detection rate among older adults was significantly lower in the 2020–2021 season and the 2022–2023 season (0.45%, 8/1779 and 0.15%, 3/2021 vs 1.55%, 160/10,348; $P < 0.001$ in the two comparisons); however, RSV detection rate remained similar (or even increased with borderline significance; 7.24%, 43/594 and 7.55%, 42/556 vs 5.52%, 292/5293; $P = 0.10$ and $P = 0.06$, respectively) compared with the pre-pandemic period for children young than five years during the two seasons above (Table 1, Fig. 2, Fig. 3, and Appendix pp 5–6). Patients with CAP had statistically higher RSV detection rates than those with URTI ($P < 0.001$). RSVA predominated in all seasons except for the 2020–2021 season (Fig. 2). Among those positive for RSV, RSVA was more frequently found in those with sCAP compared to URTI ($P = 0.026$; Appendix p 11).

Phylogenetic analysis of 149 sequences (from specimens taken during 2020–2023) of the RSV G gene hypervariable region 2 revealed that ON1 and BA9 were the dominant genotypes in Beijing during the COVID-19 pandemic, each having 4 distinct clades (Fig. 4 and Appendix p 6). Further comparison of the clinical diagnosis did not show any significant differences between clades and the proportion of CAP for both ON1 ($P = 0.159$) and BA9 ($P = 0.936$).

Results from serology surveys suggested significantly decreased RSV IgG positivity in the 2022–2023 season compared with the pre-pandemic seasons (9.32%, 29/311 vs 20.16%, 100/496; $P < 0.001$); older adults aged ≥60 years had significantly higher RSV IgG positivity rates than children aged <5 years in both pre-pandemic periods (27.60%, 67/243 vs 13.04%, 33/253; $P < 0.001$) and pandemic periods (21.43%, 132/616 vs 5.84%, 9/154; $P < 0.001$) (Table 1, Appendix pp 5–6). There was a temporal relationship between RSV IgG positive rates and RSV detection rates (Fig. 5, panel A; Appendix p 11). Notably, we found a significant negative log-linear correlation between RSV IgG antibody levels in the previous quarter and RSV detection rate ratio between the current quarter and the previous quarter ($r = -0.46$, $P = 0.022$) (Fig. 5, panel B). The r square of the log-linear regression of RSV IgG positivity with RSV detection rate was 0.21; with this regression results, we predicted that in order to observe reductions in RSV detection rate by PCR in the next quarter, IgG positive should above 21% (17–25%) in the current quarter. Moreover, given the RSV IgG antibody positivity rate was 28.21% in the latest quarter (i.e., 2023 Q4), based on the regression model equation of $Y = -0.1379X + 2.768$, we predicted that the PCR detection rate might decrease although the confidence interval crossed one (detection rate ratio: 0.33, 95% CI: 0.08–1.29).

Discussion

In the present study, we leveraged epidemiological, molecular, and serological data from a prospective, multi-centre, hospital-based surveillance and serology study for understanding the changes in RSV epidemiology during different phases of the COVID-19 pandemic compared to the pre-pandemic period. We showed that RSV circulating patterns at the population

	Pre-pandemic (Jul 2015–Jun 2019)		2019–2020 season (Jul 2019–Jun 2020)		2020–2021 season (Jul 2020–Jun 2021)		2021–2022 season (Jul 2021–Jun 2022)		2022–2023 season (Jul 2022–Jun 2023)		The latest available period (Jul 2023–Nov 2023)	
	No. pos/no. Tested	Detection rate, %	No. pos/no. tested	Detection rate, %	No. pos/no. tested	Detection rate, %	No. pos/no. tested	Detection rate, %	No. pos/no. tested	Detection rate, %	No. pos/no. tested	Detection rate, %
PCR testing in RPSS												
Overall	582/30,256	1.92	108/5107	2.11	62/4465	1.39	147/4938	2.98	55/5165	1.06	57/3000	1.90
RSV subtype												
RSVA	345/30,256	1.14	43/5107	0.84	12/4465	0.27	85/4938	1.72	42/5165	0.81	10/3000	0.33
RSVB	114/30,256	0.38	48/5107	0.94	48/4465	1.08	52/4938	1.05	11/5165	0.21	9/3000	0.30
RSVA + RSVB	1/30,256	<0.005	2/5107	0.04	1/4465	0.02	2/4938	0.04	0/5165	<0.005	0/3000	<0.005
Untyped	122/30,256	0.40	15/5107	0.29	1/4465	0.02	8/4938	0.16	2/5165	0.04	4/3000	0.13
Age group, y												
0–<1	91/968	9.40	25/144	17.36	12/105	11.43	22/88	25.00	6/54	11.11	1/10	10.00
1–<2	60/1015	5.91	9/129	6.98	9/101	8.91	24/169	14.20	5/90	5.56	8/73	10.96
2–<5	141/3310	4.26	29/449	6.46	22/388	5.67	46/508	9.06	31/412	7.52	23/275	8.36
5–<18	56/4150	1.35	12/874	1.37	2/381	0.52	14/557	2.51	10/735	1.36	11/769	1.43
18–<60	70/10,465	0.67	11/1700	0.65	5/1711	0.29	13/1758	0.74	0/1853	<0.005	6/896	0.67
≥60	160/10,348	1.55	19/1811	1.05	8/1779	0.45	28/1858	1.51	3/2021	0.15	8/977	0.82
Clinical diagnosis												
URTI	94/8469	1.11	18/1282	1.40	16/1709	0.94	35/1890	1.85	14/2131	0.66	17/1033	1.65
nsCAP	383/16,785	2.28	64/3078	2.08	38/2389	1.59	88/2509	3.51	33/2476	1.33	38/1595	2.38
sCAP	85/3926	2.17	22/625	3.52	3/279	1.08	18/418	4.31	7/383	1.83	1/300	0.33
Others	18/1075	1.67	1/119	0.84	1/84	1.19	6/121	4.96	1/175	0.57	1/72	1.39
Serology testing from multiple sources												
Overall	100/496	20.16	18/71	25.35	34/128	26.56	15/83	18.07	29/311	9.32	45/177	25.42
Age group, y												
<5	33/253	13.04	3/23	13.04	1/6	16.67	No data	No data	4/119	3.36	1/6	16.67
≥60	67/243	27.57	15/48	31.25	33/122	27.05	15/83	18.07	25/192	13.02	44/171	25.73

PCR, polymerase chain reaction; RPSS, the Respiratory Pathogen Surveillance System; RSV, respiratory syncytial virus; y, years; URTI, upper respiratory tract infection; nsCAP, non-severe community-acquired pneumonia; sCAP, severe community-acquired pneumonia; others, other clinical diagnosis, such as coronary heart disease, chronic bronchitis, bronchiectasis, COPD and rheumatoid arthritis; Serology samples were collected from January 2017 to October 2023.

Table 1: **Detection rate of respiratory syncytial virus in 52,931 patients presenting with acute respiratory tract infection and IgG antibody positivity rate in 1266 serum samples during July 1, 2015 to November 30, 2023.**

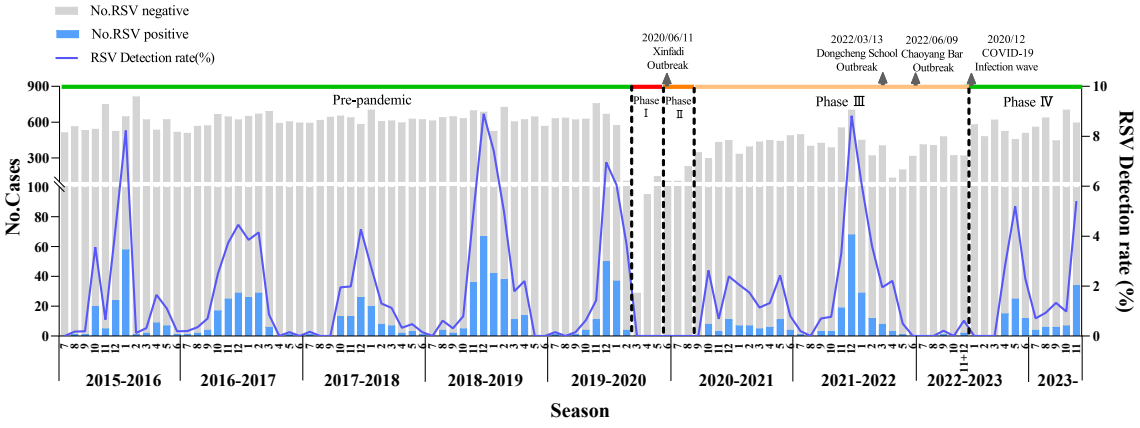

Fig. 1: Monthly distribution of tested samples for (bars) and detection rates of (lines) respiratory syncytial virus in 52,931 patients presenting with acute respiratory tract infection during July 1, 2015 to November 30, 2023. RSV, Respiratory syncytial virus.

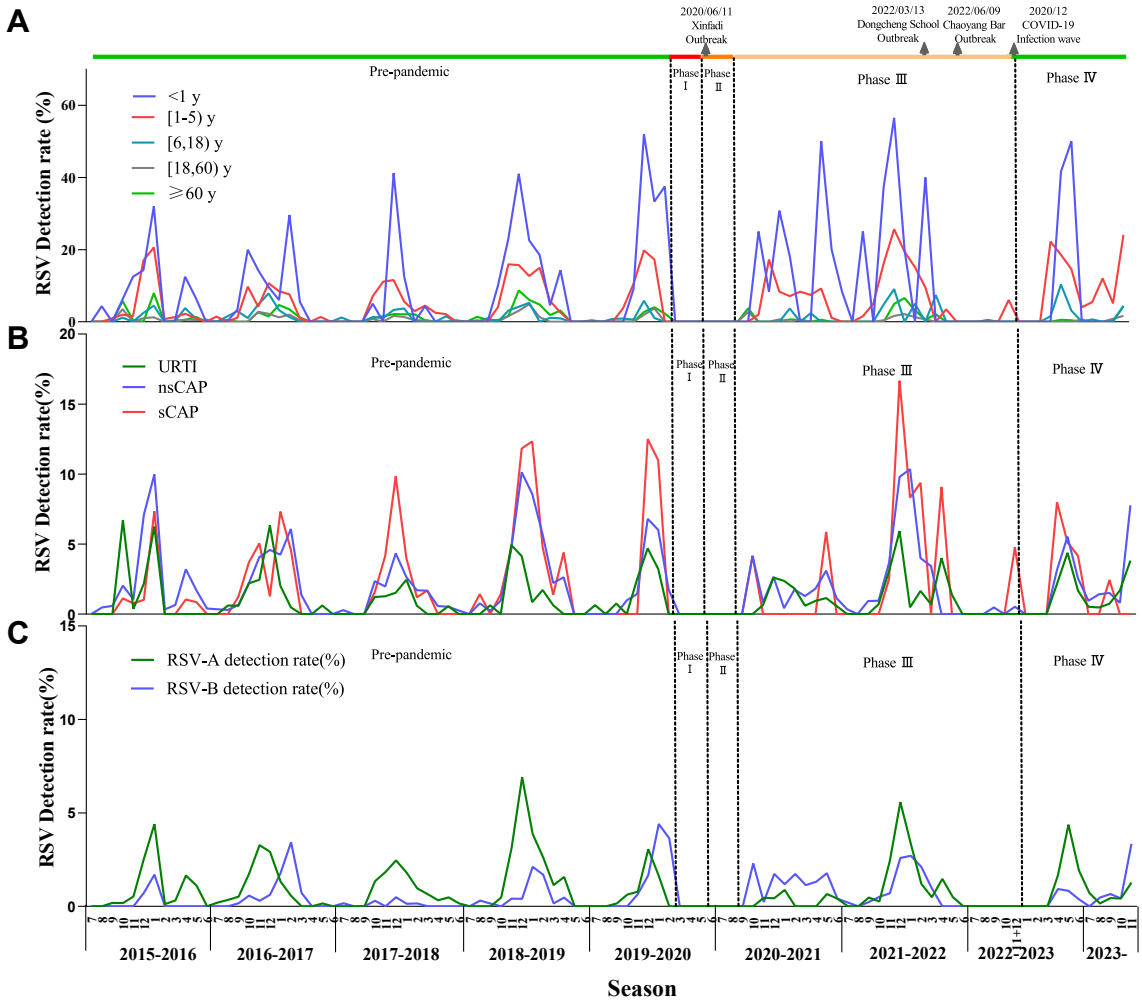

Fig. 2: Monthly distribution of tested samples for (bars) and detection rates of (lines) respiratory syncytial virus in 52,931 patients presented with acute respiratory tract infection during July 1, 2015 to November 30, 2023, by age group (panel A), clinical diagnosis (panel B), and RSV subtype (panel C). y, years; RSV, Respiratory syncytial virus; URTI, upper respiratory tract infection.

level changed along with the changes in the stringency of NPIs, measured IgG positivity, and local COVID-19 epidemics, suggesting the interplay between contact patterns, immunity dynamics, and SARS-CoV-2 infection in shaping RSV epidemics. We also noted the age-group related asynchrony in the RSV detection rate during the 2020–2021 season when RSV circulated year-round, and during the 2022–2023 season when an out-of-season RSV epidemic occurred in early 2023, with an overall similar RSV detection rates seen in young children (or even increased with borderline significance) and significantly decreased detection rate in older adults who had higher RSV IgG positivity proportions compared to young children in both pre-pandemic and pandemic periods. These findings provide novel insights into the potential drivers of RSV circulating patterns and have important implications for RSV prevention and control strategies.

Compared to the distinct winter-months circulation, we observed an unusual RSV circulating trajectory since the onset of the COVID-19 pandemic in Beijing. In the 2020–2021 season, RSV detection remained at a low level as a result of the large-scale implementation of non-pharmaceutical interventions, such as school closure, mask wearing and reduced social activities, and showed an atypical year-round detection that lasted for approximately nine months. A similar year-round circulation was reported by Löwensteyn and colleagues recently in Netherlands, a country with a typical winter-months RSV season[21]; through model simulation, the authors concluded that the year-round transmission of RSV was associated with the waning immunity due to

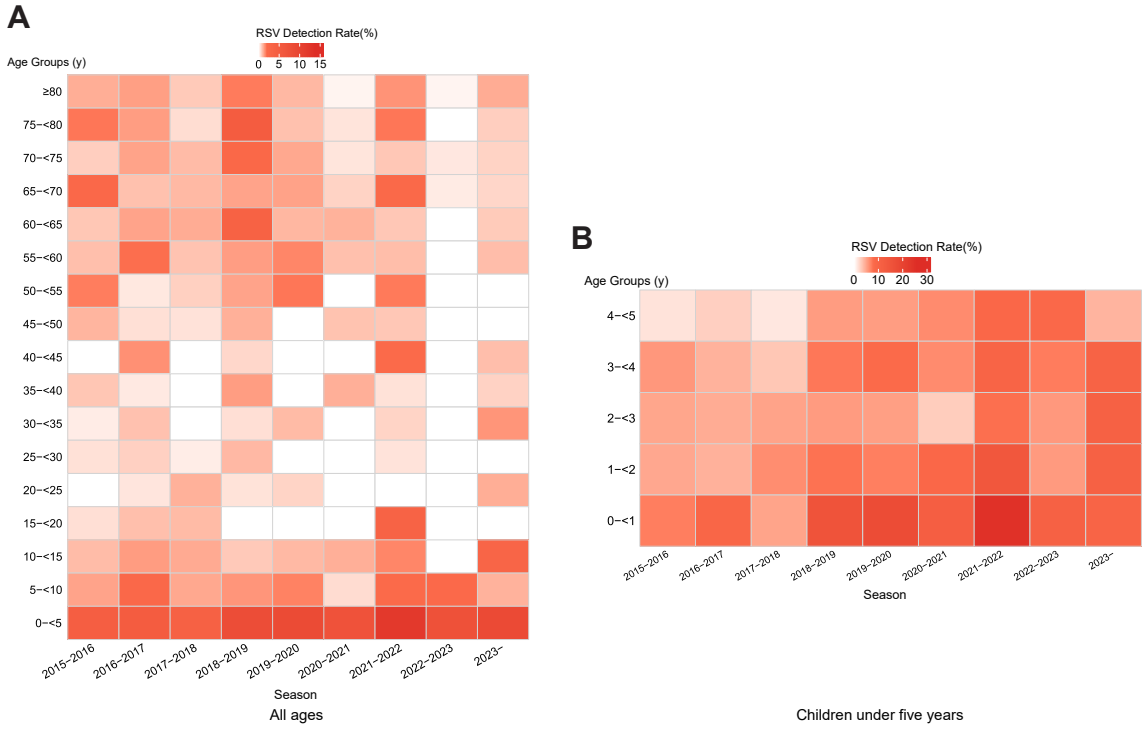

Fig. 3: Heatmaps of RSV detection rate during different seasons in 52,931 patients presenting with acute respiratory tract infection, grouped by all ages (A) and children under five years old (B), during July 1, 2015 to November 30, 2023. Higher detection rate associates with redder colorings. y, years; RSV, Respiratory syncytial virus.

the period of very low RSV circulation in the country. In this study, however, we found that the IgG positivity rate remained relatively high when RSV circulated year-round in the 2020–2021 season, suggesting that other factors than immunity could have played a role in the circulation, such as the phased reopening of schools as well as social distancing and mask wearing that were widely adopted by the population during that period. The atypical year-round circulation of RSV in the 2020–2021 season was followed by an apparently typical seasonal circulation in the 2021–2022 season, when the "dynamic COVID-zero" policy was still in place. This was largely due to the fact that no major local transmission of SARS-CoV-2 was reported during the winter months of the 2021–2022 season, not triggering any large-scale implementation of NPIs that suppressed the transmission of RSV.

Interestingly, in the winter months of the 2022–2023 season when all NPIs were lifted, very low level of RSV detection was observed. Meanwhile, there was a massive COVID-19 epidemic locally in Beijing. Different from the year-round circulation observed earlier in the 2020–2021 season and the low circulation at the beginning year of the pandemic observed globally, the very low level of RSV detection in the 2022–2023 winter months could not be explained by NPIs (in fact, all NPIs were lifted in December 2022), nor could it be explained by population immunity given that the RSV IgG positivity rate was at a low level (7.69% in 2022 Q4). A possible explanation is that the local COVID-19 epidemic suppressed the RSV circulation. We previously observed a similar effect on the RSV circulation by the 2009 influenza H1N1 pandemic where we showed that the influenza pandemic delayed the onset of the RSV season by 0.58 months on average (95% CI: 0.42–0.73; maximum delay: 2.5 months).[22] Although the underlying mechanism for the suppressed or delayed RSV season by a pandemic of another virus is not known, we speculated that the non-specific immunity induced by infection with the virus that causes the pandemic could have played a role; for example, influenza vaccines were reportedly to protect against SARS-CoV-2 infection and severe COVID-19[23,24] and RSV-confirmed hospitalisations[25]; and live attenuated influenza vaccine (CAIV) induces local innate immune responses that provide a broad range of antiviral immunity in a mouse infection model.[26] The suppressed RSV circulation in winter months of the 2022–2023 season was followed by an unprecedented out-of-season RSV resurgence. The resurgence, as was reported in other studies, was likely due to the "immunity debt"[12,27]— the RSV-naïve population in 2022 remained susceptible until the end of the massive COVID-19 epidemic in the end of 2022 and the beginning of

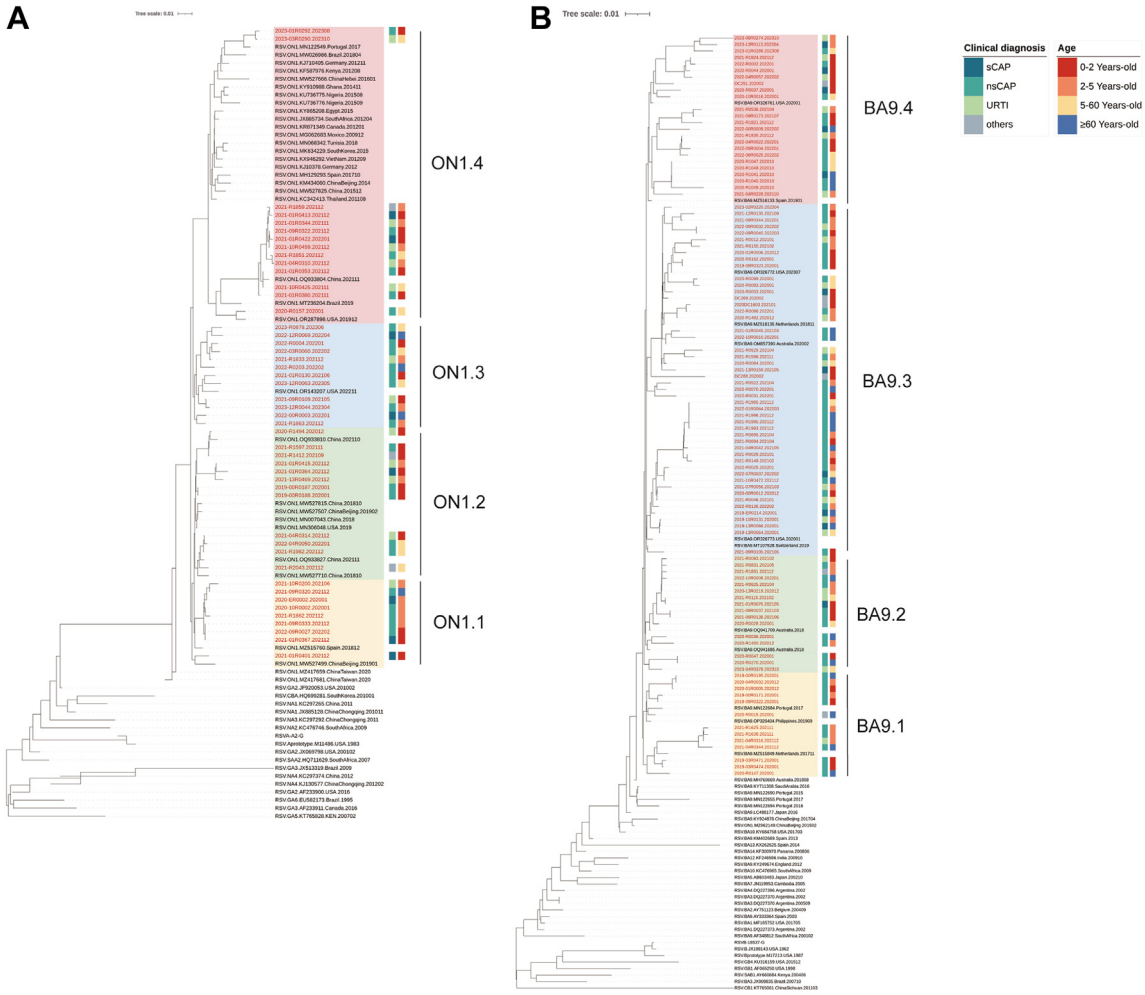

Fig. 4: Phylogenetic analysis of the G gene of RSV-A (A) and RSV-B (B). Different colors indicate different lineages. sCAP, severe community-acquired pneumonia; nsCAP, non-severe community-acquired pneumonia; URTI, upper respiratory tract infection.

2023. During the out-of-season resurgence, RSV detection rate was similar (or even increased with borderline significance) to the pre-pandemic period for younger children and decreased among the older adults who generally had a higher RSV IgG positivity as observed in this study.

Our latest data demonstrated an increasing trend of RSV detection rate during October to November 2023, despite the previous out-of-season circulation just several months away. Similar circulating patterns were observed in other countries with out-of-season RSV epidemics followed by an increase in the RSV detection during the local typical circulating season, such as England,[9] Australia,[28] and South Africa,[29] while Netherlands observed year-round circulation of RSV after an out-of-season surge.[21] It remains a challenge to forecast how the detection rate of RSV would be in the next few months in Beijing as we learnt from this study that NPIs, population immunity and COVID-19 epidemics could all affect RSV transmission, in addition to meteorological factors that were previously widely acknowledged.[30] Based on the observed correlation between RSV IgG positivity and the changes in the RSV detection rate, with the available RSV IgG positivity data in the last quarter of 2023, our prediction for the first quarter in 2024 did not yield a definitive answer to the question, with confidence interval crossing one (0.08–1.29), indicating that the detection rate could further increase or decrease.

We found that ON1 and BA9 were the prevalent genotypes in Beijing after the onset of the pandemic, consistent with the reported distribution of genotypes during 2015–2019 from our previous study.[14] Through the analysis of HVR2 of G gene, we found that RSV in Beijing was closely related to the circulating strains in several regions, all prevalent before the COVID-19

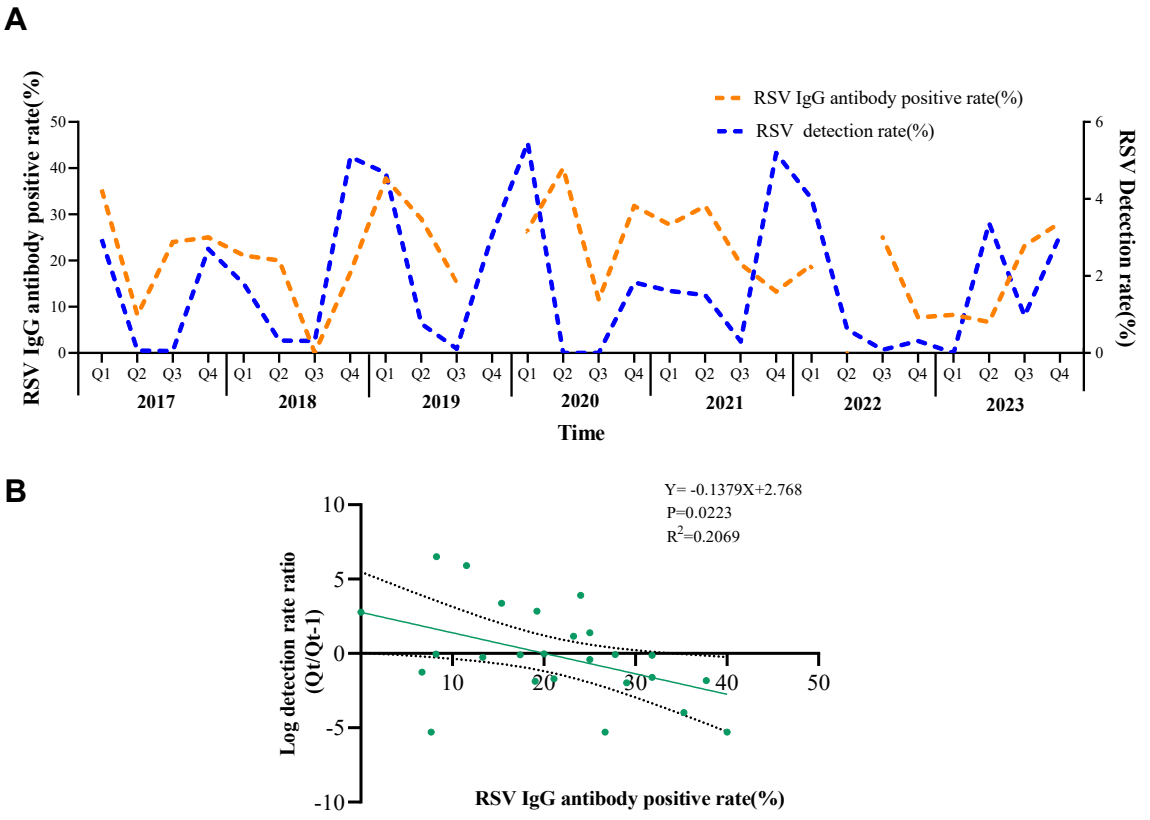

Fig. 5: (A) Changes of RSV IgG antibody positive rate and detection rate during January 1, 2017 to November 30, 2023. (B) Comparison of RSV IgG antibody positive rate and detection rate by PCR. Q, quarter; RSV, Respiratory syncytial virus. In Panel B, Y-axis are displayed in log scale (with base natural logarithm). Q_t represents RSV detection rate in the current quarter. Q_{t-1} represents RSV detection rate in the previous quarter. The number in the X-axis represents RSV IgG antibody positivity rate in the previous quarter.

epidemic. These results indicated that the RSV strains circulating in Beijing were composed of most preexisting strains, which was consistent with the reports in the United States.[31,32] However, Eden. et al. reported major reductions in RSV genomic diversity in Australia during the COVID-19 pandemic; they identified two genetically distinct RSV-A clades during the out-of-season RSV outbreaks in New South Wales and Australian Captial Territory, presumably introduced from overseas.[13] By comparison, all strains obtained by sequencing were previously prevalent and no novel genotypes were identified in our study, which suggests that it is the susceptibility of the populations, rather than any inherent changes in transmissibility or pathogenicity characteristics of the RSV strains, that allowed RSV epidemics to occur in Beijing.

This study has several limitations. First, although data from our RPSS network were designed to be presentative, the serology surveys were not conducted under the same sampling framework and might be less representative both geographically and temporally, which could lead to selection bias. In addition, as a passive surveillance, RPSS was subject to possible changes in the healthcare seeking behaviours associated with the COVID-19 pandemic; nonetheless, as a prospective surveillance, RPSS was stable in terms of applications of consistent case definitions, specimen collection and testing, as well as quality control, ensuring the comparability between the pandemic and the pre-pandemic periods. Second, our interference regarding the roles of NPIs, population immunity and SARS-CoV-2 infection was based on a quasi-experiment design, and we acknowledged the challenges in fully disentangling the roles of these factors in shaping the epidemiology of RSV. Third, the serology data used in this study were used as proxies of population immunity levels and we acknowledged that serum IgG levels were not necessarily indicative of protection against RSV infections and that serology data came from different study populations; this could explain the relatively low r square in the regression analysis of IgG positivity with RSV detection by PCR, suggesting that the predicted changes in RSV detection rate should be interpreted with caution. Moreover, an inactivated preparation of

RSV was used for serum IgG antibody detection, there would be possible cross-reactions with other respiratory viruses[33]; we would not expect this potential misclassification to significantly affect RSV antibody positivity estimates.

In summary, our study provides an overview of the dynamics of RSV epidemiology in Beijing, China during the COVID-19 pandemic with comparison to the pre-pandemic period. We revealed the important role of NPIs, population immunity, and local COVID-19 epidemic in shaping the local transmission patterns of RSV, including the atypical year-round and out-of-season circulations as well as the altered age profile of RSV detection. These findings could provide further insights into the drivers of RSV epidemics and help anticipate the possible impact on the RSV epidemiology across all ages when RSV immunisation programmes targeting infants and older adults are implemented.

Contributors

FH, YL and XW conceived and designed the study. All authors were responsible for acquisition of data. ML, BC, XW led the data analysis and visualisation and wrote the first draft of the manuscript. ML, BC, XW, YW, LK, CG, QH analysed and interpreted the data. FH, YL and XW reviewed and revised the report. All authors approved of the final version. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Data sharing statement

Data for plotting the main figure is available online for download (Supplemental Files). Individual-level data will not be made publicly available with this article. Requests for sharing of de-identified patient dataset for scientific research can be directed to HF (hhffxdd@126.com). All proposals will be subject to scientific review and institutional review board approval at Beijing CDC, and all approved data requestors will need to sign a data use agreement.

Declaration of interests

XW reports grants from GSK (to institution), and personal fees from Pfizer, outside the submitted work. YL reports grants from GSK, WHO, and Wellcome Trust (all to institution), and personal fees from Pfizer and WHO, outside the submitted work. Other authors declare no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanwpc.2024.101050.

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