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Cohort profile: Community burden of influenza virus, respiratory syncytial virus, SARS-CoV-2, and other respiratory pathogens-associated acute respiratory infections, a longitudinal cohort study in Shanghai, China, 2024-2027

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Running Title: Community Burden of ARIs

Title: Cohort profile: Community burden of influenza virus, respiratory syncytial virus, SARS-CoV-2, and other respiratory pathogens-associated acute respiratory infections, a longitudinal cohort study in Shanghai, China, 2024-2027

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ABSTRACT

Purpose

We are conducting a longitudinal cohort study - the Community Burden of Acute Respiratory Infections in Shanghai (CAReIS) - to assess age-stratified incidence, healthcare utilization, and risk factors of influenza virus, respiratory syncytial virus (RSV), and SARS-CoV-2 associated acute respiratory infections (ARIs) in Shanghai, China.

Participants

Study participants were enrolled by family doctors in 47 community health services centers in Pudong New Area District, Shanghai, China. All permanent residents six months and older living in Pudong at least six months were eligible for enrolment; residents who planned to leave Pudong for more than one month in the first study year were excluded. During enrolment, study staff conducted baseline assessments of socio-demographics, underlying medical conditions, vaccination history, and household and self-rated health status. Study participants are being followed for ARIs for three years. Nasopharyngeal and oropharyngeal swab specimens are being obtained from suspected ARI cases. Influenza virus, RSV, SARS-CoV-2, and other respiratory pathogens are tested for by multiplex respiratory pathogen real-time quantitative PCR assays. Illness course and clinical recovery of ARI cases are assessed through weekly contact with ARI cases for 28 days post-ascertainment.

Findings to date

Between 14 October 2024 and 22 November 2024, we enrolled 5,387 community residents into the cohort, including 233 infants aged six months to 2 years, 278 preschool children aged 3-6 years, 575 school-age children aged 7-18 years, 2,150 adults aged 19-64 years, and 2,151 older adults aged 65+ years. All finished baseline assessment and started follow-up. Surveillance of ARI symptoms, collection of specimens, and laboratory testing are ongoing.

Future plans

The findings from this study will be used to provide valuable scientific data to inform ongoing control efforts and future pandemic preparedness for respiratory diseases in China. Planned analyses include analysis of annual pathogen-specific incidence by age group, and exploring healthcare seeking behavior and factors associated with ARIs and severe ARIs. We will also assess transmission dynamics of common respiratory pathogens in a household transmission sub-cohort.

Keywords: Cohort Studies, Influenza, Respiratory Syncytial Virus, SARS-CoV-2, Respiratory

Tract Infections, China

Strengths and limitations of this study

- CAReIS is a three-year, prospective, age-stratified, community-based longitudinal cohort study to assess the burden of influenza virus, RSV, and SARS-CoV-2 associated infections in community in a Chinese population aged six months and above.
- The large cohort size (over 5,200) and comprehensive laboratory methods used (RT-qPCR for detecting up to 37 respiratory pathogens) will allow us to estimate incidence by age group and pathogen, with good statistical precision.
- Weekly active follow-up contacts increase the likelihood of capturing most illness episodes, and at the same time allow for early collection of samples to undergo microbiological laboratory investigations.
- Retention and compliance may be challenging considering the study's three-year duration.
- A limitation is that CAReIS may not be sufficiently powered to study pathogens less prevalent in the community or explore risk factors associated with severe ARIs.

INTRODUCTION

Acute respiratory infections (ARIs) are a leading cause of morbidity and mortality worldwide[1 2]. The great majority of deaths from respiratory infections are caused by lower respiratory tract infections (LRTIs), causing 2.5 million deaths in 2019.[3] The Coronavirus Disease 2019 (COVID-19) pandemic had a profound impact on global health,[4] causing 14.83 million excess deaths in 2021.[5] With its continuous evolution and adaptation, SARS-CoV-2 has established a biological niche in the human respiratory tract and cocirculates with other endemic respiratory pathogens such as influenza virus, respiratory syncytial virus, and rhinovirus.[6 7] Changing influenza and respiratory syncytial virus (RSV) epidemiology was observed during the COVID-19 pandemic[7-10] that was a consequence of non-pharmaceutical interventions and viral interference.[11] Understanding the burden and transmission dynamics of common respiratory pathogens associated ARIs in a general population can inform ongoing control efforts in communities and guide future interventions (i.e., vaccines, diagnostics, and therapeutic drugs) in the post-COVID-19 era.

In China, a nationwide sentinel-hospital-based Surveillance for Etiology of Respiratory Infections (SERI) system was established in 2009.[12] Study prior to the COVID-19 pandemic found that across all age groups, the viruses most frequently causing ARIs were influenza, RSV, and rhinoviruses.[12] Influenza, RSV, and other viral respiratory pathogens activities were significantly suppressed or interrupted during the COVID-19 pandemic.[4 8] Most of these SERI-based studies were conducted in hospital settings and focused on prevalence of etiological agents in patients, which can be biased by healthcare-seeking behavior and underestimate disease burden.[12] Studies on the incidence of influenza in pregnant women found that community incidences were 0.7, 1.0, and 2.1 per 100 person-months for 2015-2016, 2016-2017, and 2017-2018 seasons, respectively, in Suzhou, China.[13] In Jiangsu Province, China, studies conducted during the 2015-2016 and 2016-2017 respiratory virus seasons among individuals aged 60–89 years found that cumulative incidences were 0.8% and 6.1% for influenza-associated ARIs and 0.5% and 1.0% for RSV-associated ARIs.[14] These studies focused on special populations (pregnant women and the elderly), investigated only one or two respiratory pathogens, and were conducted before the COVID-19 pandemic.[13 15] Rigorously conducted prospective cohort studies of multiple respiratory pathogens in large

communities are urgently needed to understand true burdens, transmission dynamics, and natural histories of influenza, RSV, SARS-CoV-2, and other respiratory pathogens causing ARIs, especially in the post-COVID-19 era.

We designed the **C**ommunity Burden of **A**cute **Re**spiratory **I**nfections in Shanghai (CAReIS) study as a three-year, prospective, age-stratified, community-based longitudinal cohort study to assess the true burden of symptomatic infections caused by influenza virus, RSV, and SARS-CoV-2 in a community in Shanghai Pudong New Area District (Pudong). The primary objective was to estimate age-stratified (children aged six months to 18 years, adults aged 19-64 years, and elderly aged 65+ years) community incidences of influenza virus, RSV, and SARS-CoV-2 associated ARIs. Secondary objectives include: i) investigating community prevalences of 37 common respiratory pathogens causing ARI; ii) determining illness course and clinical features by pathogen and age group; and iii) measuring proportions of community ARI cases seeking ambulatory care (outpatient visits and emergency department visits) and proportions of community ARI cases hospitalized (admitted or staying in the hospital for 24 hours or more) by pathogen and age group. Exploratory study objectives include evaluating the proportion of community ARI cases with severe outcomes and factors associated with severe outcomes. We defined severe ARIs as admission to an intensive care unit (ICU) with any of the following: requiring mechanical ventilation, respiratory failure, acute respiratory distress syndrome, shock, or death. We present the study protocol and description of the cohort.

COHORT DESCRIPTION

CAReIS is an ongoing prospective longitudinal cohort study being conducted in Pudong, Shanghai, China. The cohort was established in October 2024 and will be followed through September 2027. At enrolment, study staff evaluated eligibility of study participants and conducted baseline assessments of socio-demographics, underlying medical conditions, household information, vaccination history, and self-rated health data. During the follow-up period, events of interest in each participant, i.e., symptoms of ARI, are being closely monitored and ascertained, and respiratory samples are obtained from identified ARI cases for timely laboratory testing. Multiplex respiratory pathogen real-time quantitative PCR (RT-qPCR) assays are used to confirm presence of influenza

virus type-A, type-B, RSV, SARS-CoV-2, and other respiratory pathogens in upper respiratory tract specimens from ARI cases. All ARI cases are followed for 28 days after ascertainment to identify illness course and clinical outcome. Study activities and procedures are shown in Figure 1.

Study site and population

Pudong New Area is a municipality in eastern China with a census-based population of 5.7 million in 2024, among which 1.2 million residents are adults aged 60 years and over. Pudong is served by 47 community health service centers, all of which participate in the study. Influenza vaccine coverage is moderate in Pudong (17.68% in the 2021–2022 season).[16] Pudong was selected as the study site for several reasons: the local health authority is actively involved, willing to provide support, and willing to be responsible for coordinating study activities; vaccination histories can be obtained by linking subjects' identification numbers (ID) to the Immunization Management Information System and to electronic medical records in hospitals via the Regional Healthcare Big Data Center; and Pudong CDC has been involved in SERI studies since 2009 and has experienced, well-trained staff and laboratory technicians to conduct study activities.

The study population includes all permanent residents aged six months and above in Pudong, with no gender restrictions. To increase coverage and representativeness, participants were enrolled at all 47 community health service centers by service-center family doctors. Households with multiple members living together are prioritized for enrollment.

Sample size considerations

Our target sample size was 5,250 participants, including 250 infants aged six months to 2 years, 250 preschool children aged 3-6 years, 450 school-age children aged 7-18 years, 2,150 adults aged 19-64 years, and 2,150 older adults aged 65+ years. Target sample sizes were calculated assuming an annual cumulative incidence of symptomatic infection of 30% in infants and preschool children, 20% in school-age children, and 5% in adults for influenza virus,[17 18 19] RSV,[20] or SARS-CoV-2[21]. Accounting for loss to follow-up of up to 10%, the sample will ensure achieving a 20% relative precision for incidence estimates at 95% significance levels in each age strata.

Enrolment and baseline assessment

At study initiation, community residents were invited to come to family doctors' offices for enrolment screening, and were enrolled if they met the following eligibility criteria: i) they were

able to understand the study procedures and provide informed consent; ii) could use the Internet and mobile devices to complete data collection (for young children and the elderly who are illiterate, a surrogate survey can be done by their parents/guardians); iii) agreed to have all family household members included in another study (the household transmission sub-cohort study) if they become confirmed with influenza virus, RSV, or SARS-CoV-2 associated ARIs during the study follow-up period; and iv) resided in the Pudong for at least six months.

Participants with any of the following were excluded: i) being unwilling or not agreeing to have their medical records or vaccination history accessed by study staff through electronic databases linkage; ii) lacking ability to adhere to study procedures as prespecified in the study protocol; or iii) planning to leave Pudong for more than one month in the following year, regardless of reason.

After signing informed consent, study participants were assigned to the appropriate age group and completed baseline questionnaires (*Supplementary Table 1*).

Surveillance for ARI symptoms

Definition of ARIs

Since enrollment, study participants are being actively followed for three years to identify occurrences of ARI. We define an ARI episode as the onset of illness in the previous seven days and presence of at least one systemic symptom (feeling feverish or having a measured axillary temperature of ≥37.0 °C, chills, headache, or general malaise) and at least one respiratory symptom (sore throat, cough lasting for ≥24 hours, rhinorrhea, shortness of breath, difficulty breathing or chest pain); or the presence of at least two respiratory symptoms. For children under two years of age or individuals unable to speak, ARIs are defined as the presence of an axillary temperature of ≥37.0 °C, cough, or difficulty breathing at any time in the previous seven days or observed during our weekly visits.

We anticipate that participants will experience multiple ARI episodes during the three years of the study. To be defined as a new ARI, the onset of new symptoms should be at least seven days removed from the clinical recovery date of a previous ARI. Clinical recovery is defined as body temperature returning to normal for two consecutive days and complete disappearance of the following symptoms: general malaise, fatigue, cough, nasal congestion or runny nose, sore throat,

shortness of breath, and difficulty breathing.

Weekly survey and passive reporting

Participants are monitored for ARIs with active surveillance and passive reporting. Active surveillance refers to a weekly survey of participants by study staff, in which the question "since the last contact, have you experienced a common cold or any of the following symptoms: fever, cough, runny nose, sore throat, stuffy nose, or body ache?" is asked. Passive reporting refers to participants voluntarily reporting respiratory symptoms to study staff whenever they experience one.

Case Ascertainment

The study staff verify information reported by participants via phone (*Supplementary Table 2*). For participants who meet our ARI case definition, study staff encourage the participant to go to their community health service center within 24 hours to collect respiratory swab samples. If inconvenient for the participant to go to the community health center, a community worker provides door-to-door sample collection service within 24 hours of appointment.

Weekly illness updates and recovery from illness

Identified ARI cases are contacted weekly for 28 days to determine the illness course (i.e., symptoms and duration) and clinical recovery (*Supplementary Table 3*), starting from the case ascertainment day. During weekly contacts, information on ambulatory healthcare (i.e., outpatient/emergency department visits) and hospital service utilization are obtained (*Supplementary Table 3*). For hospitalized ARI cases, we collect additional information on clinical diagnosis, complications, treatment, and drugs used within one week after the case has been discharged from the hospital by linking participant ID number to the Pudong New Area Healthcare Big Data System (*Supplementary table 4*).

Semi-annual survey

We will conduct semi-annual surveys to update participants' information that could change during the study, i.e., vaccination status, household information, and overall health status (*Supplementary Table 5*).

Loss to follow-up

Loss to follow-up of up to 10% was accounted for in the target sample size determination. Withdrawals are defined as participants who formally notify study staff that they no longer wish to

continue. Study participants who do not respond to the weekly symptom survey for two consecutive weeks are contacted via text messages and phone calls. Participants who have not responded to study retention outreach for two additional consecutive weeks are de-enrolled. Participants may be re-enrolled if a response is received later.

Laboratory investigation

Specimen collection

Trained nurses or study staff use sterilized Dacron or nylon swabs to collect upper respiratory tract specimens from participants with ARI symptoms within 24 hours of onset. Two types of specimens are collected: nasopharyngeal swabs and oropharyngeal swabs (NP/OP). Swabs are placed in viral transportation medium (VTM) tubes (*Yocon Biology Technology, Beijing, Batch number: 01240229*) and transported within 24 hours of collection to the central laboratory at Pudong CDC, using a cold box to maintain a temperature of 4~8°C.

Processing and storage of specimens

Upon arrival at Pudong CDC laboratory, swab samples are processed into three aliquots of supernatant. One aliquot is analyzed and the other two are retained as backup specimens. Backup specimen is stored at -70°C, and the specimen for analysis is stored at 3-8°C until testing.

Laboratory testing

All specimens are subjected to multiplex respiratory pathogen real-time quantitative PCR (RT-qPCR) testing at the Pudong CDC laboratory that can detect 37 respiratory pathogens (*Supplementary Table 6*). Multiplex testing is conducted using microfluidic chip technology combined with RT-qPCR to determine each sample's relative cycle threshold (*Crt*) values. Testing is conducted using procedures recommended by the manufacturers, i.e., nucleic acid extraction kit (*Roche (China) Holding Ltd., Catalog number: 6369750*), and pathogen detection kit (*Thermo Fish Scientific Inc., Catalog number: 4398986*). A C_{rt} threshold of 35 is used to interpret results, with C_{rt} values ≤35 considered positive for a particular pathogen and values >35 considered negative. Testing results are reported to study participants within three working days, as indicated in the informed consent document.

Data management

Data collection

The data and specimens collected at enrolment and baseline, during active follow-up and post follow-up are summarized in table 1. Data collection and questionnaire surveys are performed with an electronic data capture system, the ARIs Information Management System (ARIs-IMS). The software was custom developed for this study. Web-based surveys can be performed on a personal computer desktop or smartphone app. ARIs-IMS supports several key functions, including Participant Management (recruitment, grouping, follow-up, and sample collection appointments), Data Collection (baseline surveys, ARI symptom reporting, and case follow-up), Sample Collection and Testing Management (tracking collection, transporting, and testing of specimens), Results Feedback, Data Management and Storage, and Role Management (authorizing access to data and function module).

Immunization information systems

In addition to self-reported vaccination histories obtained during the baseline and semi-annual surveys, participants' up-to-date vaccination information is obtained by linking the participant's ID number to the National Immunization Information System. Informed consent for this linkage was obtained from participants at enrolment.

Data linkage and use of electronic medical records

For participants diagnosed with ARIs and hospitalized, their medical records are retrieved within one week after discharge by linking the participant's ID number to the Pudong New Area Healthcare Big Data System. Retrieved data include clinical laboratory results, imaging findings, medications (e.g., antibiotics, antiviral treatments), complications, and discharge diagnosis. Participants provide informed consent before data are accessed or used.

FINDINGS TO DATE

We enrolled 5,387 participants into the cohort between 14 October and 22 November 2024, achieving the target sample size (*Table 2*). All recruited subjects completed their baseline assessments and questionnaires. Among enrollees, 2,151 (39.9%) were aged ≥60 years; 1,038 (19.3%) reported receipt of influenza vaccine in the year before enrolment; 3,543 (65.8%) reported a history of COVID-19 vaccination; 611 (11.9%) participants aged 2 years and older reported a

history of 23-valent pneumococcal polysaccharide vaccination (PPV23). Among children aged 6 months to 5 years, 333 (65.2%) reported receipt of 13-valent pneumococcal conjugate vaccine (PCV13), and 363 (71.0%) reported receipt of *Haemophilus influenzae type b* (Hib) conjugate vaccine. We started following participants in November 2024; they are being contacted weekly to monitor ARIs for three years.

FUTURE PLANS

Findings from this study will be used to provide up-to-date scientific data on the community burden of specific respiratory infections to inform ongoing control efforts and future pandemic preparedness for respiratory diseases in the post-COVID-19 era in China. We completed participant enrolment and baseline assessment. Active follow-up, NP/OP swab collection, and laboratory testing are ongoing. Planned analyses include: i) analysis of annual pathogen-specific incidence by age group; ii) characterizing clinical presentations, illness courses, clinical recovery and outcome, and healthcare services utilization behavior of ARI cases; and iii) exploring factors associated with ARIs and severe ARIs, including vaccination history, prior infections and underlying medical conditions. We are also planning to assess the transmission dynamics of common respiratory pathogens in a household transmission sub-cohort, nested within the primary cohort. During our daily active follow-up, participants with laboratory-confirmed influenza, RSV, and SARS-CoV-2 infections and all of their family members will be prospectively enrolled into a sub-cohort at the time of the index cases' illness ascertainment. More frequent respiratory specimen (NP/OP swab) sampling and symptom monitoring will be conducted on the household transmission sub-cohort for up to 28 days, regardless of whether they are symptomatic or asymptomatic. We plan to recruit at least 200 households for each of the three respiratory pathogens (influenza virus, RSV, and SARS-CoV-2) in the three-year study period, in order to assess epidemiological transmission parameters, like incubation period, latent period, generation time, serial interval, infectious period duration, secondary attack rate, and proportion of asymptomatic infections, for these respiratory pathogens. Details of the study design of the household transmission sub-cohorts will be elaborate elsewhere.

STRENGTHS AND LIMITATIONS

The study design has several strengths. First, CAReIS uses standardized and unified protocol and

laboratory procedures, allowing us to generate high-quality community-level incidence data in age strata on a wide range of common respiratory pathogens in the post-COVID-19 pandemic era. The study design ensures accurate data collection and provides insights into the true burden, transmission dynamics, natural history, and risk factors of common respiratory pathogen infections. Second, our participants include permanent residents recruited from all 47 community health service centers of Pudong. The sample is representative of the local population and can reflect actual illness occurrence at the community level. Weekly follow-up contacts increase the likelihood of capturing all illness episodes in the study participants, providing us with precise incidence estimates. Third, the large cohort size (>5,200 participants) will allow us to estimate incidence by age group and respiratory pathogen with good statistical precision. The three-year follow-up period will provide information on year-to-year and season-to-season variation in incidence for most respiratory pathogens, especially influenza virus, RSV, and SARS-CoV-2, which have shown a strong seasonal and yearly cyclical pattern in other studies. Fourth, the study uses molecular laboratory methods (i.e., RT-qPCR) to investigate up to 37 respiratory pathogens. The laboratory methods used in the study can ensure that the pathogen-specific burden of respiratory infections is measured, which is valuable for developing and optimizing targeted interventions (e.g., vaccines) in the future. NP/OP specimens collected from study participants with ARIs can be analyzed, sequenced, and shared with other investigators for future research purposes. Fifth, our study uses the documented vaccination registry data and electronic medical records maintained by the local health authority. This will allow us to access historical exposure data at different times and various clinical outcomes during hospitalization. Finally, to facilitate efficient data collection and management, we customized a data information system, ARIs-IMS. Compliance of study personnel and study participants will be significantly increased because of a decreased data collection burden and simplified data collection procedures with ARIs-IMS. Participants are recruited through their family doctors who generally have a strong connection and relationship with the community that will support participant retention in the cohort through weekly contact and semi-annual surveys. Family doctors' efforts will also contribute to high compliance and cohort retention during the three years of study follow-up.

This study has limitations. First, we may not identify all respiratory infections through active surveillance of ARI symptoms since our case definitions do not capture atypical and asymptomatic

infections. However, we have planned another sub-cohort (the household transmission sub-cohort study) nested within our primary cohort. Using this sub-cohort, we can determine infection incidence rate and secondary attack rate, and most importantly, the proportion of participants with typical and asymptomatic infections. [22] Second, Pudong is a highly developed and densely populated region in eastern China, with high average household income and vaccination coverage levels. Results from this study may not be generalizable to less populated or developed regions in China. Third, study participants are not randomly selected from the community. They are invited to participate and offered to join freely. Those who have high awareness of his/her health might be more likely to be included in our study, which can bias our estimates as they might tend to report more ARIs than the reference population. Fourth, our study sample size may not be sufficiently powered to explore risk factors of severe outcomes of influenza, RSV, and SARS-CoV-2 associated infections, nor can we determine the incidence of some less prevalent pathogens in the community, e.g., measles virus, bocavirus. Finally, our laboratory methods and the type of sample specimens collected may have problems for some bacterial agents (e.g., *Streptococcus pneumoniae, Haemophilus influenzae*) that commonly colonized the upper respiratory tract. Detection of these pathogens does not necessarily imply infection.

Collaborators

This study was a collaboration between the School of Population Medicine and Public Health, Peking Union Medical College and the Pudong New Area Center for Disease Control and Prevention (Pudong CDC). We are open to collaboration with other researchers to use data generated in this study as well as to use the platform to conduct further research on influenza virus, RSV, and SARS-CoV-2 to develop, evaluate and optimize interventions (i.e., vaccines and treatments). Requests of collaboration should be sent to ZL (lizhongjiecdc@163.com), accompanied by a detailed protocol and statistical analysis plan. After reviewing scientific validity, we will contact requestors whose proposals meet the research criteria, and for which an exception does not apply, within one month of request.

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Data availability statement

De-identified individual participant-level data will be available on reasonable request, upon written request to the corresponding author following publication.

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Contributors

ZL is the principal investigator on this study who conceived and critically revised the manuscript. CY, ZL, LH and LR conceptualized and designed the study. CY, JY, and BZ contributed equally to this work. JY, XY, YL and LX wrote the first draft. LX, YX, YJ, XZ, LZ, and YW contributed to the literature search. BZ, XW, YS and LR designed laboratory methods. XY, YL and LX wrote the statistical analysis plan. ZL and CY received funding. YL, HX, TZ, LR, BC and WY commented on and revised drafts of the manuscript. All authors contributed to reviewing, revising and approving the final manuscript, and had final responsibility for the decision to submit for publication.

Competing interests

The authors declare that they have no competing interests.

Patient and public involvement

Patients and the public were not involved in this research's design, conduct, reporting, or dissemination plans.

Patient consent for publication

Not required.

Ethics approval

This study was approved by Chinese Academy of Medical Sciences & Peking Union Medical College's Institutional Review Board (no. CAMS&PUMC-IEC-2024-068).

REFERENCES

1. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet* 2020;396(10258):1204-22. doi: 10.1016/s0140-6736(20)30925-9 [published Online First: 2020/10/19]
2. Global burden of 288 causes of death and life expectancy decomposition in 204 countries and territories and 811 subnational locations, 1990-2021: a systematic analysis for the Global Burden of Disease Study 2021. *Lancet* 2024;403(10440):2100-32. doi: 10.1016/s0140-6736(24)00367-2 [published Online First: 2024/04/07]
3. Evaluation IfHMa. Visualization of Global Burden of Diseases results: Institute for Health Metrics and Evaluation; 2024 [Available from: https://vizhub.healthdata.org/gbd-results/ accessed September 30 2024.
4. Li ZJ, Yu LJ, Zhang HY, et al. Broad Impacts of Coronavirus Disease 2019 (COVID-19) Pandemic on Acute Respiratory Infections in China: An Observational Study. *Clinical infectious diseases* 2022;75(1):e1054-e62. doi: 10.1093/cid/ciab942 [published Online First: 2021/11/18]
5. Msemburi W, Karlinsky A, Knutson V, et al. The WHO estimates of excess mortality associated with the COVID-19 pandemic. *Nature* 2023;613(7942):130-37. doi: 10.1038/s41586-022-05522-2 [published Online First: 2022/12/15]
6. Markov PV, Ghafari M, Beer M, et al. The evolution of SARS-CoV-2. *Nature reviews Microbiology* 2023;21(6):361-79. doi: 10.1038/s41579-023-00878-2 [published Online First: 2023/04/06]
7. Chow EJ, Uyeki TM, Chu HY. The effects of the COVID-19 pandemic on community respiratory virus activity. *Nature reviews Microbiology* 2023;21(3):195-210. doi: 10.1038/s41579-022-00807-9 [published Online First: 2022/10/18]
8. Feng L, Zhang T, Wang Q, et al. Impact of COVID-19 outbreaks and interventions on influenza in China and the United States. *Nature communications* 2021;12(1):3249. doi: 10.1038/s41467-021-23440-1 [published Online First: 2021/06/02]
9. Olsen SJ, Azziz-Baumgartner E, Budd AP, et al. Decreased influenza activity during the COVID-19 pandemic-United States, Australia, Chile, and South Africa, 2020. *American journal of transplantation* 2020;20(12):3681-85. doi: 10.1111/ajt.16381 [published Online First: 2020/12/03]
10. Olsen SJ, Winn AK, Budd AP, et al. Changes in Influenza and Other Respiratory Virus Activity During the COVID-19 Pandemic - United States, 2020-2021. *MMWR Morbidity and mortality weekly report* 2021;70(29):1013-19. doi: 10.15585/mmwr.mm7029a1 [published Online First: 2021/07/23]
11. Piret J, Boivin G. Viral Interference between Respiratory Viruses. *Emerging infectious diseases* 2022;28(2):273-81. doi: 10.3201/eid2802.211727 [published Online First: 2022/01/26]
12. Li ZJ, Zhang HY, Ren LL, et al. Etiological and epidemiological features of acute respiratory infections in China. *Nature communications* 2021;12(1):5026. doi: 10.1038/s41467-021-25120-6 [published Online First: 2021/08/20]
13. Chen L, Zhou S, Zhang Z, et al. Cohort profile: China respiratory illness surveillance among pregnant women (CRISP), 2015-2018. *BMJ open* 2018;8(4):e019709. doi: 10.1136/bmjopen-2017-019709 [published Online First: 2018/05/01]
14. Leung NHL, Zhang H, Zhang J, et al. Incidence, symptoms and medical care for influenza virus and respiratory syncytial virus illnesses among older adults in Eastern China: Findings from the China Ageing Respiratory Infections Study (CARES), 2015-2017. *medRxiv : the preprint server for health sciences* 2024 doi: https://doi.org/10.1101/2024.07.03.24309873 [published Online First: July 3]

15. Cowling BJ, Xu C, Tang F, et al. Cohort profile: the China Ageing REespiratory infections Study (CARES), a prospective cohort study in older adults in Eastern China. *BMJ open* 2017;7(10):e017503. doi: 10.1136/bmjopen-2017-017503 [published Online First: 2017/11/03]

16. Sun G, Zhang L, Qiu Y, et al. Changes of influenza vaccination rate and associated influencing factors after the COVID-19 pandemic in Shanghai, China. *Human vaccines & immunotherapeutics* 2024;20(1):2287294. doi: 10.1080/21645515.2023.2287294 [published Online First: 2024/02/01]

17. Jefferson T, Rivetti A, Di Pietrantonj C, et al. Vaccines for preventing influenza in healthy children. *The Cochrane database of systematic reviews* 2018;2(2):Cd004879. doi: 10.1002/14651858.CD004879.pub5 [published Online First: 2018/02/02]

18. Demicheli V, Jefferson T, Ferroni E, et al. Vaccines for preventing influenza in healthy adults. *The Cochrane database of systematic reviews* 2018;2(2):Cd001269. doi: 10.1002/14651858.CD001269.pub6 [published Online First: 2018/02/02]

19. Demicheli V, Jefferson T, Di Pietrantonj C, et al. Vaccines for preventing influenza in the elderly. *The Cochrane database of systematic reviews* 2018;2(2):Cd004876. doi: 10.1002/14651858.CD004876.pub4 [published Online First: 2018/02/02]

20. Cohen C, Kleynhans J, Moyes J, et al. Incidence and transmission of respiratory syncytial virus in urban and rural South Africa, 2017-2018. *Nature communications* 2024;15(1):116. doi: 10.1038/s41467-023-44275-y [published Online First: 2024/01/04]

21. Cohen C, Kleynhans J, von Gottberg A, et al. SARS-CoV-2 incidence, transmission, and reinfection in a rural and an urban setting: results of the PHIRST-C cohort study, South Africa, 2020–21. *The Lancet Infectious Diseases* 2022;22(6):821-34. doi: 10.1016/s1473-3099(22)00069-x [published Online First: 2021/12/16]

22. Tsang TK, Wang C, Fang VJ, et al. Reconstructing household transmission dynamics to estimate the infectiousness of asymptomatic influenza virus infections. *Proceedings of the National Academy of Sciences of the United States of America* 2023;120(33):e2304750120. doi: 10.1073/pnas.2304750120 [published Online First: 2023/08/07]

Tables

Table 1. Data and samples collected in the Community Burden of Acute Respiratory Infections in Shanghai (CAReIS) study, 2024–2027.

Study period	Tools and methods	Participants	Measurement
Baseline	Structured questionnaire to participant/guardians (ARIs-IMS assisted personal interview)	All participants	Demographics, education attainment, socioeconomic status, anthropometry, underlying medical conditions, tobacco and alcohol use, self-rated health, household information, overcrowding, vaccination history
During active follow-up	Weekly surveillance	All participants	ARI symptoms since last contact, symptom onset date
	Combined nasopharyngeal and oropharyngeal (NP/OP) swab	Participants reporting an ARI	Multiplex respiratory pathogen real-time quantitative PCR (RT-qPCR) for influenza virus, RSV, SARS-CoV-2 and other 34 respiratory pathogens.
	Structured questionnaire to participant/guardians (ARIs-IMS assisted personal interview)	Participants with an ascertained ARI	ARI symptoms, symptom onset and diminish date, healthcare services utilization (outpatient and emergency department visits, and hospital admission), work and school absent, clinical outcomes
Post-follow-up	Hospital medical records (data linkage)	Participants hospitalized during study	Length of hospital stay, discharge diagnosis, clinical laboratory testing results, intensive care unit admission, clinical outcome, complications, prescriptions, costs, clinical recovery and in-hospital deaths.
	Immunization information system records (data linkage)	All participants	History of COVID-19 vaccines, pneumococcal vaccines, influenza vaccines, and *Haemophilus influenzae type b* vaccines, including doses, vaccine type, and administration date

Abbreviations. ARI, acute respiratory infection; ARIs-IMS, the ARIs Information Management System; PCR, Polymerase Chain Reaction; RSV, respiratory syncytial virus.

Table 2. Characteristics of study participants at baseline

Characteristics	Sex, no. (%)		Total, no. (%)
	Male	Female	
Number of participants	2595	2792	5387
Median age in years (IQR)	58(33-70)	60(34-69)	60(34-70)
Age group			
6-35 months	122(4.7)	111(4.0)	233(4.3)
3-6 years	136(5.2)	142(5.1)	278(5.2)
7-18 years	308(11.9)	267(9.6)	575(10.7)
19-59 years	1020(39.3)	1130(40.5)	2150(39.9)
60+ years	1009(38.9)	1142(40.9)	2151(39.9)
Underlying medical conditions			
Diabetes mellitus	232(8.9)	223(8.0)	455(8.4)
Hypertension	633(24.4)	656(23.5)	1289(23.9)
Heart disease	104(4.0)	130(4.7)	234(4.3)
Asthma	18(0.7)	15(0.5)	33(0.6)
Chronic bronchitis	60(2.3)	44(1.6)	104(1.9)
Chronic obstructive pulmonary disease	13(0.5)	4(0.1)	17(0.3)
Chronic kidney disease	6(0.2)	8(0.3)	14(0.3)
Myocardial infarction	13(0.5)	3(0.1)	16(0.3)
Stroke	28(1.1)	21(0.8)	49(0.9)
Cancer	37(1.4)	43(1.5)	80(1.5)
Other	46(1.8)	58(2.1)	104(1.9)
Vaccinations received			
Influenza vaccine	480(18.5)	558(20.0)	1038(19.3)
COVID-19 vaccine	1661(64.0)	1882(67.4)	3543(65.8)
PPV23 #	284(11.5)	327(12.2)	611(11.9)
PCV13 *	158(61.2)	175(69.2)	333(65.2)
Hib vaccine §	184(71.3)	179(70.8)	363(71.0)

IQR, interquartile range.

PPV23, 23-valent pneumococcal polysaccharide vaccine. Numbers counted in participants aged 2 years and older.

* PCV13, 13-valent pneumococcal conjugate vaccine. Numbers counted in children aged 6 months to 6 years old.

§ Hib vaccine, *Haemophilus influenzae type b* (Hib) conjugate vaccine. Numbers counted in children aged 6 months to 6 years old.

Figure Legends

Figure 1. Flow diagram of major study activities.

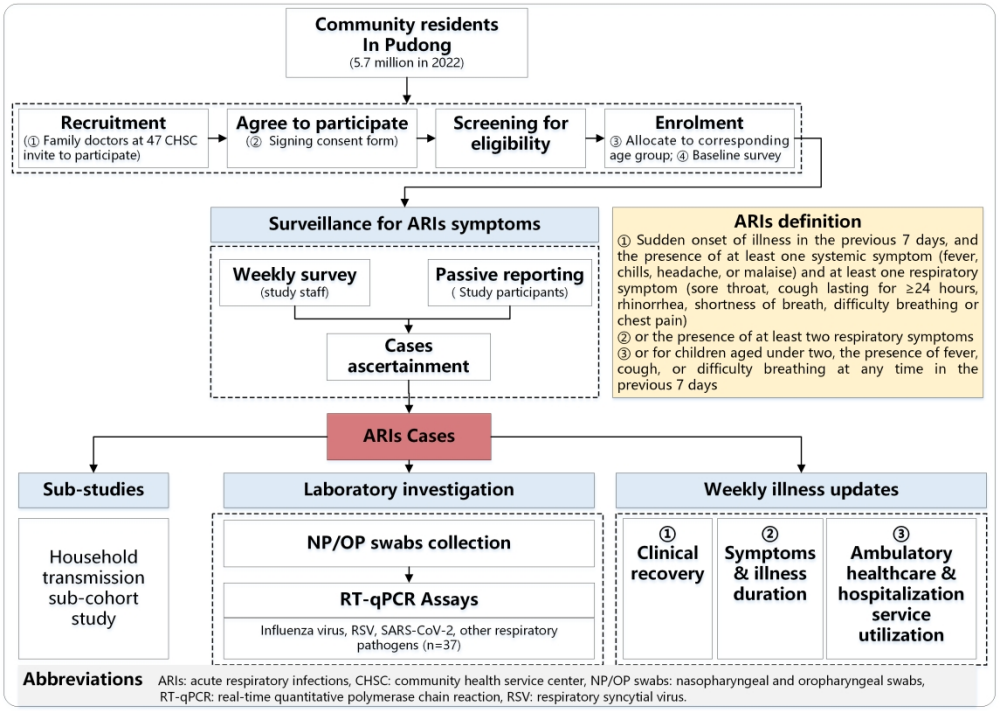

Figure 1. Flow diagram of major study activities.

289x205mm (300 x 300 DPI)

Supplementary Appendix

Title: Community burden of influenza virus, respiratory syncytial virus, SARS-CoV-2, and other respiratory pathogens-associated acute respiratory infections, a longitudinal cohort study in Shanghai, China, 2024-2027

Running head: Community burden of ARIs

Tables & Forms

- Supplementary Table 1. Baseline Characteristics at Enrollment Survey (CRF01)
- Supplementary Table 2. Symptoms of ARIs Monitoring Form (CRF02)
- Supplementary Table 3. Weekly Illness Updates and Clinical Recovery Follow-up (D07/D14/D21/D28) Data Form (CRF03)
- Supplementary Table 4. Hospital Discharge Data Collection Form (CRF04)
- Supplementary Table 5. Semi-annual Survey Data Form (CRF05)
- Supplementary Table 6. Lists of respiratory pathogens tested for in the study

Supplementary Table 1. Baseline Characteristics at Enrollment Survey (CRF01)

Date of signing informed consent: □□□□/□□/□□(YYYY/mm/dd)
Participant ID: □□□□□□ Family ID: □□□□□□
1. Basic Characteristics
1.1 Name of participants:_____ 1.2 Sex: 1=male; 2=female 1.3 Your identification number: □□□□□□□□□□□□□□ 1.4 Your date of birth: □□□□/□□/□□(YYYY/mm/dd) 1.5 Your home address (to street) :_____ 1.6 Place where your residence is registered? 1=Shanghai; 2=Other provinces 1.7 Your occupation: 1=school student; 2=housewife and unemployment; 3=retired; 4= service workers/food delivery; 5=security guards; 6=house keeping; 7=medical staff; 8=office clerk; 9=others_____ 1.8 Your education attainment: 1=primary school level and under; 2=Junior high school; 3= high school/technical secondary school; 4= university/college level or above 1.9 Are you covered by the following insurance (multiple choice allowed)? 1= basic medical insurance for urban workers; 2=basic medical insurance for urban residents; 3= new rural cooperative medical care; 4= commercial medical insurance; 5= uninsured; 6= others_
2. Overall health status
2.1 Your height:_____ cm 2.2 Your weight:_____ kg 2.3 Are you pregnant ? 1=Yes; 0=No; 9=Unknown If yes, your gestational age is_____weeks. 2.4 Are your children a premature baby (for children 6 years and under) ? 1=Yes; 0=No; 9=Unknown (A premature baby is defined as a child born at less than 37 weeks of gestational age.) 2.5 Are your children born a low-birth-weight baby (for children 6 years and under) ? 1=Yes; 0=No; 9=Unknown (A low-birth-weight baby is defined as a baby weighing less than 2500 grams within 1 hour of birth.) 2.6 Do you have or have had any of the following underlying conditions (multiple choice allowed): 1= diabetes mellitus; 2= hypertension; 3= heart disease; 4=asthma; 5= chronic bronchitis/bronchitis; 6=COPD; 7= chronic kidney disease; 8= myocardial infarction; 9= cerebral stroke; 10=cancer; 11=others_____; 12=no medical underlying conditions 2.7 Do you smoke? 1=current smoking; 2= used to smoke, but not smoke now; 3=never smoke; 4= exposure to second-hand smoke 2.8 Do you drink alcohol ? 1=never; 2=occasionally; 3=drink often (once per week); 4=drink everyday 2.9 During the past three months, have you experienced a common cold or any of the following symptoms, e.g., fever, cough, runny nose, sore throat, stuffy nose, and body aches? 1=Yes; 0=No If yes, the nearest date of symptom onset: □□□□/□□/□□ (YYYY/mm/dd); If yes, how many episodes have you experienced?_____ times. 2.10 During the past one year，have you ever visited a doctor? 1=Yes; 0=No If yes, how many visits?_____ visits. 2.11 During the past one year，have you ever been hospitalized? 1=Yes; 0=No

If yes, How many days have you been hospitalized?_____ days.
3. Household information
3.1 Total number of members living in your family:_____(persons) 3.2 The number of children aged <5 years in your family:_____(persons) 3.3 The number of people aged≥65 years in your family:_____(persons) 3.4 Total living area of your family:_____m^2 3.5 Per capita living area of your family:_____m^2 3.6 What is the average monthly income of your family? 1=less than 5000 Chinese yuan; 2=5000-9999 Chinese yuan; 3=10000-19999 Chinese yuan; 4=≥20000 Chinese yuan; 9= Unknown 3.1 Total number of members living in your family:_____(persons) 3.2 The number of children aged <5 years in your family:_____(persons) 3.3 The number of people aged≥65 years in your family:_____(persons)
4. Vaccination history (self-reported)
4.1 Have you ever received the flu vaccine since October 2023? 1=Yes; 0=No; 9=Unknown 4.2 Have you ever received a Covid-19 vaccine? 1=Yes; 0=No; 9=Unknown If yes, how many doses have been administered cumulatively? 1=1 dose; 2=2 doses; 3=3 doses; 4=4 doses and more 4.3 Have you received the 23 valent pneumococcal polysaccharide vaccine? 1=Yes; 0=No; 9=Unknown 4.4 Have you received the 13 valent pneumococcal conjugate vaccine? 1=Yes; 0=No; 9=Unknown 4.5 Have you received the *Haemophilus influenzae type b* (Hib) conjugate vaccine? 1=Yes; 0=No; 9=Unknown
Time of survey completion: □□□□/□□/□□:□□/□□ (YYYY/mm/dd:HH/MM) Name of investigator:_____

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Supplementary Table 2. Symptoms of ARIs Monitoring Form (CRF02)

Participant ID: □□□□□□ Family ID: □□□□□□		
1. Occurrence of ARIs		
1.1 Since our last contact, have you experienced any cold symptoms (such as fever, cough, nasal congestion or discharge, sore throat, body or muscle aches and pain, etc.)? 1=Yes; 0=No If "no", survey ends. If "yes", please fill in the following information.		
2. ARI Symptoms/Signs (multiple choices allowed)		
Symptoms/Signs	**Symptoms/Signs**	**If "yes", onset time (days ago)**
Fever	1=Yes 0=No	_____ days ago
Chills	1=Yes 0=No	_____ days ago
Headache	1=Yes 0=No	_____ days ago
Body or muscle aches	1=Yes 0=No	_____ days ago
Sore throat	1=Yes 0=No	_____ days ago
Fatigue	1=Yes 0=No	_____ days ago
Nasal congestion or discharge	1=Yes 0=No	_____ days ago
Wheezing, or dyspnea	1=Yes 0=No	_____ days ago
Cough	1=Yes 0=No	_____ days ago
Sputum production	1=Yes 0=No	_____ days ago
Chest Pain	1=Yes 0=No	_____ days ago
Other	Please specify_____	_____ days ago
For children under 2 years old only		
Chest wall indrawing	1=Yes 0=No	_____ days ago
Head nodding	1=Yes 0=No	_____ days ago
Central cyanosis	1=Yes 0=No	_____ days ago
Apnea or difficulty in breathing	1=Yes 0=No	_____ days ago
Crying can't be eased by parents	1=Yes 0=No	_____ days ago
Unable to feed or choke while breastfeeding	1=Yes 0=No	_____ days ago
Lethargy or difficulty to wake up	1=Yes 0=No	_____ days ago
2.1 Does the subject meet the ARIs' case definition? 1=Yes; 0=No. If yes, please provide the onset date □□□□/□□/□□ (Format: YYYY/mm/dd).		
3. Sampling Information		
3.1 Is a swab sampling scheduled? 1=Yes ; 0=No If yes, please provide the following information: 3.2 Name of the Community Healthcare Center for scheduled swab sampling: _____ 3.3 Scheduled swab sampling time: □□□□/□□/□□ (Format: YYYY/mm/dd)		
Time of survey completion: □□□□/□□/□□:□□/□□ (YYYY/mm/dd:HH/MM) Name of investigator:_____		

Supplementary Table 3. Weekly Illness Updates and Clinical Recovery Follow-up (D07/D14/D21/D28) Data Form (CRF03)

Participant ID: □□□□□□ Family ID: □□□□□□				
1. ARI Symptoms/Signs (multiple choices allowed)				
1.1 Since our last contact, have you experienced any of the following symptoms? 1=Yes, please specify the symptoms (multiple choices allowed); 0=No				
ARI Symptoms/Signs	**Day 7**	**Day 14**	**Day 21**	**Day 28**
Fever	1=Yes 0=No	1=Yes 0=No	1=Yes 0=No	1=Yes 0=No
Chills	1=Yes 0=No	1=Yes 0=No	1=Yes 0=No	1=Yes 0=No
Headache	1=Yes 0=No	1=Yes 0=No	1=Yes 0=No	1=Yes 0=No
Body or muscle aches	1=Yes 0=No	1=Yes 0=No	1=Yes 0=No	1=Yes 0=No
Sore throat	1=Yes 0=No	1=Yes 0=No	1=Yes 0=No	1=Yes 0=No
Fatigue	1=Yes 0=No	1=Yes 0=No	1=Yes 0=No	1=Yes 0=No
Nasal congestion or discharge	1=Yes 0=No	1=Yes 0=No	1=Yes 0=No	1=Yes 0=No
Wheezing, or dyspnea	1=Yes 0=No	1=Yes 0=No	1=Yes 0=No	1=Yes 0=No
Cough	1=Yes 0=No	1=Yes 0=No	1=Yes 0=No	1=Yes 0=No
Sputum production	1=Yes 0=No	1=Yes 0=No	1=Yes 0=No	1=Yes 0=No
Chest Pain	1=Yes 0=No	1=Yes 0=No	1=Yes 0=No	1=Yes 0=No
Other	Please specify___	Please specify___	Please specify___	Please specify___
For children aged under 2 years old only				
Chest wall indrawing	1=Yes 0=No	1=Yes 0=No	1=Yes 0=No	1=Yes 0=No
Head nodding	1=Yes 0=No	1=Yes 0=No	1=Yes 0=No	1=Yes 0=No
Central cyanosis	1=Yes 0=No	1=Yes 0=No	1=Yes 0=No	1=Yes 0=No
Apnea or difficulty in breathing	1=Yes 0=No	1=Yes 0=No	1=Yes 0=No	1=Yes 0=No
Crying can't be eased by parents	1=Yes 0=No	1=Yes 0=No	1=Yes 0=No	1=Yes 0=No
Unable to feed or choke while breastfeeding	1=Yes 0=No	1=Yes 0=No	1=Yes 0=No	1=Yes 0=No
Lethargy or difficulty to wake up	1=Yes 0=No	1=Yes 0=No	1=Yes 0=No	1=Yes 0=No
2. Healthcare Utilization 2.1 Since our last contact, have you ever experienced any of the following? (Multiple choices allowed)				
Healthcare Utilization	**Day 7**	**Day 14**	**Day 21**	**Day 28**
Outpatient/clinic visit	1=Yes 0=No	1=Yes 0=No	1=Yes 0=No	1=Yes 0=No
Emergency department visit	1=Yes 0=No	1=Yes 0=No	1=Yes 0=No	1=Yes 0=No
Hospital admission	1=Yes 0=No	1=Yes 0=No	1=Yes 0=No	1=Yes 0=No
Absent from school or work	1=Yes 0=No	1=Yes 0=No	1=Yes 0=No	1=Yes 0=No
2.2 Outpatient and Emergency Department Visits				
2.2.1 Total number of visits to outpatient and emergency Department: ___times 2.2.2 Name of the hospital or clinic for the first visit: _____ 2.2.3 Date of the first visit: □□□□/□□/□□ (Format: YYYY/mm/dd) 2.2.4 Diagnosis from the first visit:_____ 2.2.5 Total cumulative expenditure: 1=Below 200 yuan; 2=200-499 yuan; 3=500-999 yuan; 4=1000 yuan and above				
2.3 Hospitalization				
2.3.1 Name of the Hospital：_____ 2.3.2 Admission Date：□□□□/□□/□□ (Format: YYYY/mm/dd)				
2.4 Absence from Work/School				
2.4.1 Total number of days absent from work or school due to the illness:____				
3. Clinical Outcome 3.1 By the end of the follow-up period, the clinical outcome for the subject is: 1=Clinical recovery; 2=Improvement or remission; 3=Worsening or Hospitalization; 4=Death.				

(Note: Clinical recovery is defined as a normal body temperature for two consecutive days and the complete disappearance of symptoms such as body or muscle aches and pain, fatigue, cough, nasal congestion or discharge, sore throat, and wheezing, or dyspnea. Improvement/Remission is defined as an improvement in systemic and/or respiratory symptoms by the 28-day follow-up, but without complete resolution. Worsening or Hospitalization is defined as being admitted to the hospital during the follow-up period)
Time of survey completion: □□□□/□□/□□:□□/□□ (YYYY/mm/dd:HH/MM) Name of investigator:_____

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Supplementary Table 4. Hospital Discharge Data Collection Form (CRF04)

Participant No. □□□□□□ Family No. □□□□□□

1. Basic information of admission

1.1 Hospital name:_____

1.2 Date of admission:□□□□/□□/□□ (Format: YYYY/mm/dd)

1.3 Admitting diagnosis:_____

1.4 Date of discharge:□□□□/□□/□□ (Format: YYYY/mm/dd)

1.5 Discharge diagnosis:

Principal diagnosis 1._____

Secondary diagnosis 1._____; 2._____; 3._____

2. Clinical examination results

2.1 Signs/symptoms and physical examinations

Temperature:___C° Respiratory rate:__beats/min Heart rate:___beats/min

Blood pressure:___ /__mmHg

Pulse oxygen saturation (oxygen inhalation) sPO_2:____%

Pulse oxygen saturation (without oxygen) sPO_2:____%

Pulmonary auscultation: 1=dry rales; 2=wet rales; 3=normal

Mental status: 1=clear; 2=drowsiness; 3=irritability; 4=delirium; 5=convulsion; 6=coma; 7=normal

2.2 Blood examination: WBC_____×10^9/L; L_____×10^9/L; N_____×10^9/L; Plt _____×10^9/L; Hb____ g/L;

2.3 Blood biochemical examination: CRP_____mg/L; GLU_____mmol/L; BUN_____ mmol/L; PCT____μg/L

2.4 Clinical laboratory testing for respiratory pathogens was performed. 1=Yes; 0=No

2.4.1 If yes, the name of pathogen was tested for_____

2.4.2 If yes, the method of laboratory testing: 1=PCR; 2=antigen testing; 3=antibody testing

2.4.3 If yes, the result of laboratory testing: 1=positive; 0=negative

2.5 Whether chest radiography or other chest imaging was performed? 1=Yes; 0=No

If yes, is there a sign of pneumonia? 1=Yes; 0=No

2.6 Complications

☐Septic shock ☐Viral pneumonia ☐Bacterial pneumonia ☐Pneumothorax
☐ARDS ☐Bronchiolitis ☐Respiratory failure ☐Coagulopathy
☐Anemia ☐Pleural effusion ☐Acute kidney injury ☐Myolysis
☐Bacteremia ☐Gastrointestinal bleeding ☐Encephalitis/meningitis ☐pancreatitis
☐Convulsion ☐Arrhythmia ☐Liver dysfunction ☐Stroke
☐Hyperglycemia ☐Hypoglycemia ☐Congestive heart failure ☐Heart infection
☐Cardiac arrest ☐Disseminated intravascular Coagulation ☐Other (_____)

3. Treatment during hospitalization

3.1 Was oxygen therapy administered during hospitalization? 1=Yes; 0=No

If yes, the method of treatment: 1=nasal cannula or mask oxygen; 2=high-flow nasal cannula; 3=non-invasive mechanical ventilation; 4=invasive mechanical ventilation; 5= Other_____

3.2 Admission to the ICU? 1=Yes; 0=No

If yes, the length of ICU admission (_____days)

3.3 Were vasopressors administered? 1=Yes; 0=No

3.4 Were extracorporeal membrane oxygenation (ECMO) administered? 1=Yes; 0=No

3.5 Were Continuous renal replacement therapy(CRRT) administered? 1=Yes; 0=No

4. Drugs administered

Drug name	Category	Route	Daily dose		Frequency	Starting date (YYYY/mm/dd)	Stop date (YYYY/mm/dd)
			Dose	Unit			

4.1 Drug Name: (Please use the name of the drug. If it is a fixed compound preparation, please use the trade name.)
4.2 Category: A=antibiotics; B=antiviral drugs; C=steroid hormone drugs; D=angiotensin-converting enzyme inhibitors (ACE-Is) or angiotensin-receptor blockers (ARBs); E=Statins
4.3 Route of medication: 1=oral administration, 2=intravenous injection, 3=intravenous drip, 4=intramuscular injection, 5=inhalation, 6=others
4.4 Frequency: 1= continuous, 2= intermittent

5. Patient prognosis

☐ cured
☐ improved and be discharged
☐ transferred to the other hospital

Reasons for transfer：community rehabilitation/other（____）

☐ give up treatment

reasons for give-up：economic reasons/illness exacerbation/other（____）

☐ death date of death：___/___/___(YYYY/mm/dd) death diagnosis：___

6. The total expenditure of your hospitalization:_____RMB yuan

Time of survey completion: □□□□/□□/□□:□□/□□ (YYYY/mm/dd:HH/MM)
Name of investigator:_____

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Supplementary Table 5. Semi-annual Survey Data Form (CRF05)

Participant No. □□□□□□ Family No. □□□□□□
1. **Update of family information**
1.1 Total number of members living in your family:_____(persons) 1.2 The number of children aged <5 years in your family:_____(persons) 1.3 The number of people aged≥65 years in your family:_____(persons)
2. **Update of vaccination information during the study**
2.1 Have you received the flu vaccine during your participation in the study? 1=Yes; 0=No; 9=Unknown 2.2 Have you received the Covid-19 vaccine during your participation in the study? 1=Yes; 0=No; 9=Unknown If yes, how many doses have been administered cumulatively? 1=1 dose; 2=2 doses; 3=3 doses; 4=4 doses and more 2.3 Have you received the 23 valent pneumococcal polysaccharide vaccine during your participation in the study? 1=Yes; 0=No; 9=Unknown 2.4 Have you received the 13 valent pneumococcal conjugate vaccine during your participation in the study? 1=Yes; 0=No; 9=Unknown 2.5 Have you received the *haemophilus influenzae type b* (Hib) conjugate vaccine during your participation in the study? 1=Yes; 0=No; 9=Unknown
Time of survey completion: □□□□/□□/□□:□□/□□ (YYYY/mm/dd:HH/MM) Name of investigator:_____

Supplementary Table 6. Lists of respiratory pathogens tested for in the study

no.	**Viruses**	no.	**Bacteria**
1	Influenza A	27	*Bordetella holmesii*
2	Influenza B	28	*Bordetella pertussis*
3	Respiratory syncytial virus subtype A/B	29	*Chlamydophila pneumoniae*
4	SARS-Cov-2	30	*Haemophilus influenzae*
5	Human Coronavirus-229E	31	*Klebsiella pneumoniae*
6	Human Coronavirus- HKU1	32	*Legionella pneumophila*
7	Human Coronavirus- NL63	33	*Moraxella catarrhalis*
8	Human Coronavirus- OC43	34	*Mycoplasma pneumoniae*
9	MERS-CoV	35	*Staphylococcus aureus*
10	SARS-CoV	36	*Streptococcus pneumoniae*
11	Adenovirus	37	*Pneumocystis jirovecii*
12	Human parainfluenza virus serotype 1		
13	Human parainfluenza virus serotype 2		
14	Human parainfluenza virus serotype 3		
15	Human parainfluenza virus serotype 4		
16	Human metapneumovirus		
17	Rhinovirus		
18	Enterovirus		
19	Bocavirus		
20	varicella-zoster virus		
21	Epstein-Barr virus		
22	Cytomegalovirus		
23	Human herpesvirus 6		
24	Measles virus		
25	Mumps virus		
26	Parechovirus		

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Cohort profile: Community Burden of Acute Respiratory Infections in Shanghai, a longitudinal cohort study in respiratory pathogens, China, 2024-2027

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Running Title: Community Burden of ARIs

Title: Cohort profile: Community Burden of Acute Respiratory Infections in Shanghai, a longitudinal cohort study in respiratory pathogens, China, 2024-2027

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ABSTRACT

Purpose

We are conducting a longitudinal cohort study - the Community Burden of Acute Respiratory Infections in Shanghai (CAReIS) - to assess age-stratified incidence, healthcare utilization, and risk factors of influenza virus, respiratory syncytial virus (RSV), and SARS-CoV-2 associated acute respiratory infections (ARIs) in Shanghai, China.

Participants

Study participants were enrolled by family doctors in all 47 community health services centers in Pudong New Area District, Shanghai, China. All permanent residents six months and older living in Pudong at least six months were eligible for enrolment; residents who planned to leave Pudong for more than one month in the first study year were excluded. During enrolment, study staff conducted baseline assessments of socio-demographics, underlying medical conditions, vaccination history, and household and self-rated health status. Study participants are being followed for ARIs for three years. Nasopharyngeal and oropharyngeal swab specimens are being obtained from suspected ARI cases. Influenza virus, RSV, SARS-CoV-2, and other respiratory pathogens are tested for by multiplex respiratory pathogen real-time quantitative PCR assays. Illness courses and clinical recoveries of ARI cases are assessed through weekly contact with ARI cases for 28 days post-ascertainment.

Findings to date

Between 14 October 2024 and 22 November 2024, we enrolled 5,387 community residents into the cohort, including 233 children aged six months to 2 years, 278 preschool children aged 3-6 years, 575 school-age children aged 7-18 years, 2,150 adults aged 19-64 years, and 2,151 older adults aged 65+ years. All finished baseline assessment and started follow-up. Surveillance of ARI symptoms, collection of specimens, and laboratory testing are ongoing.

Future plans

Findings from this study will be used to provide valuable scientific data to inform ongoing control efforts and future pandemic preparedness for respiratory diseases in China. Planned analyses include analysis of annual pathogen-specific incidence by age group and exploration of healthcare seeking behavior and factors associated with ARIs and severe ARIs. We will also assess transmission dynamics of common respiratory pathogens in a household transmission sub-cohort.

Keywords: Cohort Studies, Influenza, Respiratory Syncytial Virus, SARS-CoV-2, Respiratory Tract Infections, China

Strengths and limitations of this study

- CAReIS is a three-year, prospective, age-stratified, community-based longitudinal cohort study to assess the burden of influenza virus, RSV, and SARS-CoV-2 associated community infections in a Chinese population aged six months and above.
- Our comprehensive laboratory methods (RT-qPCR) help us measure pathogen specific disease burdens caused by up to 37 respiratory pathogens.
- The large cohort size (over 5,200) allows us to estimate incidence by age group and pathogen, with good statistical precision.
- Weekly active follow-up of contacts increases the likelihood of capturing most illness episodes and allows for early collection of samples for microbiological laboratory investigation.
- Retention and compliance may be challenging considering the study's three-year duration and large number of participants.
- A limitation is that CAReIS may not be sufficiently powered to study pathogens less prevalent in the community or explore risk factors associated with severe ARIs.

INTRODUCTION

Acute respiratory infections (ARIs) are a leading cause of morbidity and mortality worldwide[1 2]. The great majority of deaths from respiratory infections are caused by lower respiratory tract infections (LRTIs), causing 2.5 million deaths in 2019.[3] The Coronavirus Disease 2019 (COVID-19) pandemic had a profound impact on global health,[4] causing 14.83 million excess deaths in 2021.[5] With its continuous evolution and adaptation, SARS-CoV-2 has established a biological niche in the human respiratory tract and cocirculates with other endemic respiratory pathogens such as influenza virus, respiratory syncytial virus, and rhinovirus.[6 7] Due to widely used non-pharmaceutical interventions and viral interference,[8] changing influenza and respiratory syncytial virus (RSV) epidemiology was observed during the COVID-19 pandemic.[7 9-11] Understanding the burden and transmission dynamics of common respiratory pathogens associated ARIs in a community population can inform ongoing control efforts in communities and guide future interventions (i.e., vaccines, diagnostics, and therapeutic drugs) in the post-COVID-19 era.

A nationwide sentinel-hospital-based Surveillance for Etiology of Respiratory Infections (SERI) system was established in China in 2009.[12] Study prior to the COVID-19 pandemic found that across all age groups, the viruses most frequently causing ARIs were influenza, RSV, and rhinoviruses.[12] Influenza, RSV, and other viral respiratory pathogens activities were significantly suppressed or interrupted during the COVID-19 pandemic.[4 9] Most of these SERI-based studies were conducted in hospital settings and focused on prevalence of etiological agents in patients, which can be biased by healthcare-seeking behavior and underestimate disease burden.[12] Studies on the incidence of influenza in pregnant women found that community incidences were 0.7, 1.0, and 2.1 per 100 person-months for 2015-2016, 2016-2017, and 2017-2018 seasons, respectively, in Suzhou, China.[13] In Jiangsu Province, China, studies conducted during the 2015-2016 and 2016-2017 respiratory virus seasons among individuals aged 60–89 years found that cumulative incidences were 0.8% and 6.1% for influenza-associated ARIs and 0.5% and 1.0% for RSV-associated ARIs.[14] These studies focused on special populations (pregnant women and the elderly), investigated only one or two respiratory pathogens, and were conducted before the COVID-19 pandemic.[13 15] Rigorously conducted prospective cohort studies of multiple respiratory pathogens in large

communities are urgently needed to understand true burdens, transmission dynamics, and natural histories of influenza, RSV, SARS-CoV-2, and other respiratory pathogens causing ARIs, especially in the post-COVID-19 era.

We designed the **C**ommunity Burden of **A**cute **Re**spiratory **I**nfections in Shanghai (CAReIS) study as a three-year, prospective, age-stratified, community-based longitudinal cohort study to assess the true burden of symptomatic infections caused by influenza virus, RSV, and SARS-CoV-2 in a community in Shanghai Pudong New Area District (Pudong, for short). The primary objective was to estimate age-stratified (children aged six months to 18 years, adults aged 19-64 years, and elderly aged 65+ years) community incidences of influenza virus, RSV, and SARS-CoV-2 associated ARIs. Secondary objectives include: i) investigating community prevalences of influenza virus, RSV, and SARS-CoV-2 causing ARI; ii) determining illness course and clinical features by pathogen and age group; and iii) measuring proportions of community ARI cases seeking ambulatory care (outpatient visits and emergency department visits) and proportions of community ARI cases hospitalized (admitted or staying in the hospital for 24 hours or more) by pathogen and age group. Exploratory study objectives include: i) studying prevalence of other common respiratory pathogens causing ARI, other than influenza virus, RSV, and SARS-CoV-2, in the community; ii) and evaluating the proportion of community ARI cases with severe outcomes and factors associated with severe outcomes. We defined severe ARIs as admission to an intensive care unit (ICU) with any of the following: requiring mechanical ventilation, respiratory failure, acute respiratory distress syndrome, shock, or death. We present the study protocol and description of the cohort.

COHORT DESCRIPTION

CAReIS is an ongoing prospective longitudinal cohort study being conducted in Pudong, Shanghai, China. The cohort was established in October 2024 and will be followed through September 2027. At enrolment, study staff evaluated eligibility of potential participants and conducted baseline assessments of socio-demographics, underlying medical conditions, household information, vaccination history, and self-rated health data of eligible, consenting individuals. During the follow-up period, events of interest in each participant, i.e., symptoms of ARI, are being closely monitored and ascertained, and respiratory samples are obtained from identified ARI cases for timely

laboratory testing. Multiplex respiratory pathogen real-time quantitative PCR (RT-qPCR) assays are used to confirm presence of influenza virus type-A, type-B, RSV, SARS-CoV-2, and other respiratory pathogens in upper respiratory tract specimens from ARI cases. All ARI cases are followed for 28 days after ascertainment to identify illness course and clinical outcome. The primary outcome of the study is incidence of influenza virus, RSV, and SARS-CoV-2 associated ARIs. Secondary outcomes are incidences of medically attended ARIs, including outpatient and emergency department visits and hospital admission caused by influenza virus, RSV, or SARS-CoV-2. Exploratory outcomes include incidences of severe ARIs caused by influenza virus, RSV, or SARS-CoV-2, and ARIs caused by other common respiratory pathogens investigated in the study. Study activities and procedures are shown in Figure 1.

Study site and population

Our study site, Pudong, is located in subtropical southeast China and is the largest and most populous district in Shanghai City. It had a census-based population of 5.7 million in 2024, among which 1.2 million residents were adults aged 60 years and over. Pudong is a well-developed area served by 47 community health service centers, all of which participate in the study. Influenza vaccine coverage is moderate in Pudong (17.68% in the 2021–2022 season).[16] RSV vaccination is not available in the region or China as a whole. Pudong was selected as the study site for several reasons: the local health authority is actively involved, willing to provide support, and willing to be responsible for coordinating study activities; vaccination histories can be obtained by linking subjects' identification numbers (ID) to the Immunization Management Information System and to electronic medical records in hospitals via the Regional Healthcare Big Data Center; and Pudong CDC has been involved in SERI studies since 2009 and has experienced, well-trained staff and laboratory technicians to conduct study activities.

The study population includes all permanent residents aged six months and above in Pudong, with no gender restrictions. To increase coverage and representativeness, participants were enrolled at all 47 community health service centers by service-center family doctors. People who are interested in participating in the study came to their family doctor and joined freely on site. Households with multiple members living together were prioritized for enrollment.

Sample size considerations

Our target sample size was 5,250 participants, including 250 children aged six months to 2 years, 250 preschool children aged 3-6 years, 450 school-age children aged 7-18 years, 2,150 adults aged 19-64 years, and 2,150 older adults aged 65+ years. Target sample sizes were calculated assuming an annual cumulative incidence of symptomatic infection of 30% in infants and preschool children, 20% in school-age children, and 5% in adults for influenza virus,[17 18 19] RSV,[20] or SARS-CoV-2[21]. Accounting for loss to follow-up of up to 10%, the sample will ensure achieving a 20% relative precision for incidence estimates at 95% significance levels in each age strata.

Enrolment and baseline assessment

At study initiation, community residents were invited to come to family doctors' offices for enrolment screening, and were enrolled if they met the following eligibility criteria: they i) were able to understand the study procedures and provide informed consent; ii) could use the Internet and mobile devices to complete data collection (for young children and elderly who are illiterate, a surrogate survey is done by their parents/guardians); iii) agreed to have all family household members included in another study (the household transmission sub-cohort study) if they become confirmed with influenza virus, RSV, or SARS-CoV-2 associated ARIs during the study follow-up period; and iv) were permanent residents of the community, defined as persons who resided in the Pudong New Area District for at least six months.

Participants with any of the following were excluded: i) being unwilling or not agreeing to have their medical records or vaccination history accessed by study staff through electronic databases linkage; ii) lacking ability to adhere to study procedures as prespecified in the study protocol; or iii) planning to leave Pudong for more than one month in the following year, regardless of reason (i.e., having high risks of losing to follow-up early).

After signing informed consent, study participants were assigned to the appropriate age group and completed baseline questionnaires (*Supplementary Table 1*). Full consent was obtained from all children and adult participants. Older illiterate people gave oral consent, children aged 6 months to 8 years of age gave written consent from their parents/guardians, while children aged 9 years to 18 years of age gave written consent themselves along with their parents/guardians.

Surveillance for ARI symptoms

Definition of ARIs

Since enrollment, study participants are being actively followed for three years to identify occurrences of ARI. We define an ARI episode as the onset of illness in the previous seven days and presence of at least one systemic symptom (feeling feverish or having a measured axillary temperature of ≥37.0 °C, chills, headache, or general malaise) and at least one respiratory symptom (sore throat, cough lasting for ≥24 hours, rhinorrhea, shortness of breath, difficulty breathing or chest pain); or the presence of at least two respiratory symptoms. For children under two years of age or individuals unable to speak, ARIs are defined as the presence of an axillary temperature of ≥37.0 °C, cough, or difficulty breathing at any time in the previous seven days or observed during our weekly visits.

We anticipate that participants will experience multiple ARI episodes during the three years of the study. To be defined as a new ARI, the onset of new symptoms should be at least seven days removed from the clinical recovery date of a previous ARI. Clinical recovery is defined as body temperature returning to normal (a measured axillary temperature of <37.0 °C) for two consecutive days and complete disappearance of the following symptoms: general malaise, fatigue, cough, nasal congestion or runny nose, sore throat, shortness of breath, and difficulty breathing.

Weekly survey and passive reporting

Participants are monitored for ARIs with active surveillance and passive reporting. Active surveillance refers to a weekly survey of participants by study staff, in which the question "since the last contact, have you experienced a common cold or any of the following symptoms: fever, cough, runny nose, sore throat, stuffy nose, or body ache?" is asked. Passive reporting refers to participants voluntarily reporting respiratory symptoms to study staff whenever they experience one.

Case Ascertainment

The study staff verify information reported by participants via phone (*Supplementary Table 2*). For participants who meet our ARI case definition, study staff encourage the participant to go to their community health service center within 24 hours to collect respiratory swab samples. If inconvenient for the participant to go to the community health center, a community worker provides door-to-door sample collection service within 24 hours of appointment.

Weekly illness updates and recovery from illness

Identified ARI cases are contacted weekly for 28 days to determine the illness course (i.e., symptoms and duration) and clinical recovery (*Supplementary Table 3*), starting from the case ascertainment day. Since by definition ARI cases have symptoms, the weekly survey for ARI symptoms is interrupted until clinical recovery. Instead, during weekly contacts, information on ambulatory healthcare (i.e., outpatient/emergency department visits) and hospital service utilization is obtained (*Supplementary Table 3*). For hospitalized ARI cases, we collect additional information on clinical diagnosis, complications, treatment, and drugs used within one week after the case has been discharged from the hospital by linking participant ID number to the Pudong New Area Healthcare Big Data System (*Supplementary table 4*).

Semi-annual survey

We will conduct semi-annual surveys to update participants' information that could change during the study, i.e., vaccination status, household information, and overall health status (*Supplementary Table 5*).

Withdrawals and loss to follow-up

Withdrawals are defined as participants who formally notify study staff that they no longer wish to continue in the study. Participants who do not respond to the weekly symptom survey for two consecutive weeks are contacted via text messages and phone calls, and those who have not responded to study retention outreach for two additional consecutive weeks are de-enrolled. Participants may be re-enrolled if a response is received later. Loss to follow-up of up to 10% was accounted for in the target sample size determination.

Laboratory investigation

Specimen collection

Trained nurses or study staff use sterilized Dacron or nylon swabs to collect upper respiratory tract specimens from participants with ARI symptoms within 24 hours of onset. Two types of specimens are collected: nasopharyngeal swabs and oropharyngeal swabs (NP/OP). Swabs are placed in viral transportation medium (VTM) tubes (*Yocon Biology Technology, Beijing, Batch number: 01240229*) and transported within 24 hours of collection to the central laboratory at Pudong CDC, using a cold

box to maintain a temperature of 4~8°C.

Processing and storage of specimens

Upon arrival at Pudong CDC laboratory, swab samples are processed into three aliquots of supernatant. One aliquot is analyzed and the other two are retained as backup specimens. Backup specimens are stored at -70°C, and specimens for immediate analysis are stored at 3-8°C until tested.

Laboratory testing

All specimens are subjected to multiplex respiratory pathogen real-time quantitative PCR (RT-qPCR) testing at the Pudong CDC laboratory that can detect 37 respiratory pathogens (*Supplementary Table 6*). Multiplex testing is conducted using microfluidic chip technology combined with RT-qPCR to determine each sample's relative cycle threshold (*Crt*) values. Testing is conducted using procedures recommended by the manufacturers, i.e., nucleic acid extraction kit (*Roche (China) Holding Ltd., Catalog number: 6369750*), and pathogen detection kit (*Thermo Fish Scientific Inc., Catalog number: 4398986*). A C_{rt} threshold of 35 is used to interpret results, with C_{rt} values ≤35 considered positive for a particular pathogen and values >35 considered negative. Test results are reported to study participants within three working days, as indicated in the informed consent document.

Data management and analysis

Data collection

Data and specimens collected at enrolment and baseline and during active follow-up and post follow-up are summarized in table 1. Data collection and questionnaire surveys are performed with an electronic data capture system, the ARIs Information Management System (ARIs-IMS). The software was custom developed for this study. Web-based surveys can be performed on a personal computer desktop or smartphone app. ARIs-IMS supports several key functions, including Participant Management (recruitment, grouping, follow-up, and sample collection appointments), Data Collection (baseline surveys, ARI symptom reporting, and case follow-up), Sample Collection and Testing Management (tracking collection, transporting, and testing of specimens), Test Results Feedback, Data Management and Storage, and Role Management (authorizing access to data and function module).

Immunization information systems

In addition to self-reported vaccination histories obtained during the baseline and semi-annual surveys, participants' up-to-date vaccination information is obtained by linking the participant's ID number to the National Immunization Information System. Informed consent for this linkage was obtained from participants at enrolment.

Data linkage and use of electronic medical records

For participants diagnosed with an ARI and hospitalized, their medical records are retrieved within one week after discharge by linking the participant's ID number to the Pudong New Area Healthcare Big Data System. Retrieved data include clinical laboratory results, imaging findings, medications (e.g., antibiotics, antiviral treatments), complications, and discharge diagnosis. Participants provide informed consent before data are accessed or used at enrolment.

FINDINGS TO DATE

Between 14 October and 22 November 2024, we enrolled 5,387 participants into the cohort (*Table 2*). Among the participants, 2,595 (48.2%) were male and 2,792 (51.8%) were female. There were 1,086 (20.2%) children aged six months to 18 years, 2,150 (39.9%) adults aged 19-64 years, and 2,151 (39.9%) elderly aged ≥60 years. Among the 5,387 enrollees, 1,038 (19.3%) reported receipt of influenza vaccine in the year before enrolment; 3,543 (65.8%) reported a history of COVID-19 vaccination; 611 (11.9%) participants aged 2 years and older reported a history of 23-valent pneumococcal polysaccharide vaccination (PPV23). Among children aged 6 months to 5 years, 333 (65.2%) reported receipt of 13-valent pneumococcal conjugate vaccine (PCV13), and 363 (71.0%) reported receipt of *Haemophilus influenzae type b* (Hib) conjugate vaccine. All recruited subjects completed their baseline assessments and questionnaires, and we started following participants in November 2024; they are being contacted weekly to monitor ARIs for three years.

FUTURE PLANS

Findings from this study will be used to provide up-to-date scientific data on the community burden of specific respiratory infections to inform ongoing control efforts and future pandemic preparedness for respiratory diseases in the post-COVID-19 era in China. We have completed participant enrolment and baseline assessment. Active follow-up, NP/OP swab collection, and

laboratory testing are ongoing. Planned analyses include: i) analysis of annual pathogen-specific incidence by age group; ii) characterizing clinical presentations, illness courses, clinical recovery and outcome, and healthcare services utilization behavior of ARI cases; and iii) exploring factors associated with ARIs and severe ARIs, including vaccination history, prior infections and underlying medical conditions. Pathogen-specific incidence rates will be calculated as the number of episodes of influenza virus, RSV, or SARS-CoV-2 associated ARIs divided by the total person-time at risk contributed by all study participants during the follow-up period. To make precise rate calculations, the number of days with ARI illness or lost to follow-up will be subtracted from total person-time. The 95% confidence intervals (95% CI) of rates will be calculated assuming a Poisson distribution. We will present pathogen-specific incidences by age group (i.e., children aged six months to 18 years, adults aged 19-64 years, and elderly aged 65+ years), vaccination status (influenza vaccines, COVID-19 vaccines, and pneumococcal vaccines), season, and history of prior infection. Since a wide range of case definitions of ARIs exist in literature, that can impact on our incidence estimates, we will use the WHO's ARIs definition[22] and re-calculate incidences to make comparisons. Factors associated with ARIs and severe ARIs (i.e., age, sex, underlying medical conditions, smoking status, having a child in the household, vaccination history, prior infections) will be assessed using a generalized linear mixed model (GLMM) with logit-link function. The GLMM includes a random intercept for each individual nested within each household and community. Seasonality will be controlled by including sinusoidal functions with annual and semiannual cycles for the weeks of the year as fixed effectors.

We are also planning to assess the transmission dynamics of common respiratory pathogens in a household transmission sub-cohort, nested within the primary cohort. During our daily active follow-up, participants with laboratory-confirmed influenza, RSV, and SARS-CoV-2 infections and all of their family members will be prospectively enrolled into a sub-cohort at the time of the index cases' illness ascertainment. More frequent respiratory specimen (NP/OP swab) sampling and symptom monitoring will be conducted on the household transmission sub-cohort for up to 28 days, regardless of whether they are symptomatic or asymptomatic. We plan to recruit at least 200 households for each of the three respiratory pathogens (influenza virus, RSV, and SARS-CoV-2) in the three-year study period, in order to assess epidemiological transmission parameters, like

incubation period, latent period, generation time, serial interval, infectious period duration, secondary attack rate, and proportion of asymptomatic infections, for these respiratory pathogens. Details of the study design of the household transmission sub-cohorts will be elaborated elsewhere.

STRENGTHS AND LIMITATIONS

The study design has several strengths. First, CAReIS uses a standardized and unified protocol and laboratory procedures, allowing us to generate high-quality community-level incidence data in age strata on a wide range of common respiratory pathogens in the post-COVID-19 pandemic era. The study design ensures accurate data collection and provides insights into the true burden, transmission dynamics, natural history, and risk factors of common respiratory pathogen infections. Second, our participants include permanent residents recruited from all 47 community health service centers of Pudong. The sample is representative of the local population and can reflect actual illness occurrence at the community level. Weekly follow-up of contacts increases the likelihood of capturing all illness episodes in the study participants, providing us with precise incidence estimates. Third, the large cohort size (>5,200 participants) will allow us to estimate incidence by age group and respiratory pathogen with good statistical precision. The three-year follow-up period will provide information on year-to-year and season-to-season variation in incidence for most respiratory pathogens, especially influenza virus, RSV, and SARS-CoV-2, which have shown a strong seasonal and yearly cyclical pattern in other studies. Fourth, the study uses molecular laboratory methods (i.e., RT-qPCR) to investigate up to 37 respiratory pathogens. The laboratory methods used in the study can ensure that the pathogen-specific burden of respiratory infections is measured, which is valuable for developing and optimizing targeted interventions (e.g., vaccinations) in the future. NP/OP specimens collected from study participants with ARIs can be analyzed, sequenced, and shared with other investigators for future research purposes. Fifth, our study uses the documented vaccination registry data and electronic medical records maintained by the local health authority. This will allow us to access historical exposure data at different times and various clinical outcomes during hospitalization. Finally, to facilitate efficient data collection and management, we customized a data information system, ARIs-IMS. Compliance of study personnel and study participants will be significantly increased because of a decreased data collection burden and simplified data collection procedures with ARIs-IMS. Participants are recruited through their family

doctors who generally have a strong connection and relationship with the community that will support participant retention in the cohort through weekly contact and semi-annual surveys. Family doctors' efforts will also contribute to high compliance and cohort retention during the three years of study follow-up.

This study has limitations. First, we may not identify all respiratory infections through active surveillance of ARI symptoms since our case definitions do not capture atypical and asymptomatic infections. However, we have planned another sub-cohort (the household transmission sub-cohort study) nested within our primary cohort. Using this sub-cohort, we can determine infection incidence rate and secondary attack rate, and most importantly, the proportion of participants with typical and asymptomatic infections. [23] Second, Pudong is a highly developed and densely populated region in eastern China, with high average household income and vaccination coverage levels. Results from this study may not be generalizable to less populated or developed regions in China. Third, our study participants were not randomly selected from the community. They were invited to participate and offered to join freely. Those who have high awareness of his/her health might be more likely to be included in our study, which may bias our estimates as they might tend to report more ARIs than a reference population. Fourth, our study sample size may not be sufficiently powered to determine the burden of hospitalization or severe illnesses and explore risk factors of severe outcomes of influenza, RSV, and SARS-CoV-2 associated infections, nor can we determine the incidence of some less prevalent pathogens in the community, e.g., measles virus, bocavirus. Fifth, specimen test results, whether positive or negative, will be automatically communicated to participants through ARIs-IMS via a smartphone mini-program. Study participants can access their information by themselves. Since the study is observational and healthcare seeking behavior will be decided by the participants themselves, we cannot know how this action will impact the healthcare seeking behavior of participants. Finally, our laboratory methods and the type of sample specimens collected may have problems for some bacterial agents (e.g., *Streptococcus pneumoniae, Haemophilus influenzae*) that commonly colonized the upper respiratory tract. Detection of these pathogens does not necessarily imply infection.

Collaboration

This study is a collaboration between the School of Population Medicine and Public Health, Peking Union Medical College and the Pudong New Area Center for Disease Control and Prevention (Pudong CDC). We are open to collaboration with other researchers to use data generated in this study and to use the platform to conduct further research on influenza virus, RSV, and SARS-CoV-2 to develop, evaluate and optimize interventions (i.e., vaccinations and treatments). Requests of collaboration should be sent to ZL (lizhongjiecdc@163.com), accompanied by a detailed protocol and statistical analysis plan. After reviewing for scientific validity, we will contact requestors whose proposals meet the research criteria, and for whom an exception does not apply, within one month of request.

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Data availability statement

De-identified individual participant-level data will be available on reasonable request, upon written request to the corresponding author following publication.

Funding declaration

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Contributors

ZL is the principal investigator on this study who conceived and critically revised the manuscript

and is the guarantor of the study. CY, ZL, LH and LR conceptualized and designed the study. CY, JY, and BZ contributed equally to this work. JY, XY, YL and LX wrote the first draft. LZ, YX, YJ, XZ, LHZ, and YW contributed to the literature search. BZ, XW, YS and LR designed laboratory methods. XY, YL and LX wrote the statistical analysis plan. ZL, WY and CY received funding. YL, HX, TZ, LR, BC and WY commented on and revised drafts of the manuscript. All authors contributed to reviewing, revising and approving the final manuscript, and had final responsibility for the decision to submit for publication.

Competing interests

ZL reports receiving research funding from Ministry of Science and Technology of People' s Republic of China. WY received research funding from Chinese Academy of Medical Sciences (CAMS). CY reports receiving research funding from Science and Technology Economic Commission and Health Commission of Pudong New Area District, Shanghai. All other authors declare no competing interests.

Patient and public involvement

Patients and the public were not involved in this research's design, conduct, reporting, or dissemination plans.

Patient consent for publication

Not required.

Ethics approval

This study was approved by Chinese Academy of Medical Sciences & Peking Union Medical College’s Institutional Review Board (no. CAMS&PUMC-IEC-2024-068).

REFERENCES

1. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet (London, England)* 2020;396(10258):1204-22. doi: 10.1016/s0140-6736(20)30925-9 [published Online First: 2020/10/19]
2. Global burden of 288 causes of death and life expectancy decomposition in 204 countries and territories and 811 subnational locations, 1990-2021: a systematic analysis for the Global Burden of Disease Study 2021. *Lancet (London, England)* 2024;403(10440):2100-32. doi: 10.1016/s0140-6736(24)00367-2 [published Online First: 2024/04/07]
3. Institute for Health Metrics and Evaluation. Visualization of Global Burden of Diseases results: Institute for Health Metrics and Evaluation; 2024 [Available from: https://vizhub.healthdata.org/gbd-results/ accessed September 30 2024.
4. Li ZJ, Yu LJ, Zhang HY, et al. Broad Impacts of Coronavirus Disease 2019 (COVID-19) Pandemic on Acute Respiratory Infections in China: An Observational Study. *Clinical infectious diseases* 2022;75(1):e1054-e62. doi: 10.1093/cid/ciab942 [published Online First: 2021/11/18]
5. Msemburi W, Karlinsky A, Knutson V, et al. The WHO estimates of excess mortality associated with the COVID-19 pandemic. *Nature* 2023;613(7942):130-37. doi: 10.1038/s41586-022-05522-2 [published Online First: 2022/12/15]
6. Markov PV, Ghafari M, Beer M, et al. The evolution of SARS-CoV-2. *Nature reviews Microbiology* 2023;21(6):361-79. doi: 10.1038/s41579-023-00878-2 [published Online First: 2023/04/06]
7. Chow EJ, Uyeki TM, Chu HY. The effects of the COVID-19 pandemic on community respiratory virus activity. *Nature reviews Microbiology* 2023;21(3):195-210. doi: 10.1038/s41579-022-00807-9 [published Online First: 2022/10/18]
8. Piret J, Boivin G. Viral Interference between Respiratory Viruses. *Emerging infectious diseases* 2022;28(2):273-81. doi: 10.3201/eid2802.211727 [published Online First: 2022/01/26]
9. Feng L, Zhang T, Wang Q, et al. Impact of COVID-19 outbreaks and interventions on influenza in China and the United States. *Nature communications* 2021;12(1):3249. doi: 10.1038/s41467-021-23440-1 [published Online First: 2021/06/02]
10. Olsen SJ, Azziz-Baumgartner E, Budd AP, et al. Decreased influenza activity during the COVID-19 pandemic-United States, Australia, Chile, and South Africa, 2020. *American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons* 2020;20(12):3681-85. doi: 10.1111/ajt.16381 [published Online First: 2020/12/03]
11. Olsen SJ, Winn AK, Budd AP, et al. Changes in Influenza and Other Respiratory Virus Activity During the COVID-19 Pandemic - United States, 2020-2021. *MMWR Morbidity and mortality weekly report* 2021;70(29):1013-19. doi: 10.15585/mmwr.mm7029a1 [published Online First: 2021/07/23]
12. Li ZJ, Zhang HY, Ren LL, et al. Etiological and epidemiological features of acute respiratory infections in China. *Nature communications* 2021;12(1):5026. doi: 10.1038/s41467-021-25120-6 [published Online First: 2021/08/20]
13. Chen L, Zhou S, Zhang Z, et al. Cohort profile: China respiratory illness surveillance among pregnant women (CRISP), 2015-2018. *BMJ open* 2018;8(4):e019709. doi: 10.1136/bmjopen-2017-019709 [published Online First: 2018/05/01]
14. Leung NHL, Zhang H, Zhang J, et al. Incidence, symptoms and medical care for influenza virus and respiratory syncytial virus illnesses among older adults in Eastern China: Findings from the China Ageing Respiratory Infections Study (CARES), 2015-2017. *medRxiv : the preprint server for health sciences* 2024

doi: https://doi.org/10.1101/2024.07.03.24309873 [published Online First: July 3]
15. Cowling BJ, Xu C, Tang F, et al. Cohort profile: the China Ageing REespiratory infections Study (CARES), a prospective cohort study in older adults in Eastern China. *BMJ open* 2017;7(10):e017503. doi: 10.1136/bmjopen-2017-017503 [published Online First: 2017/11/03]
16. Sun G, Zhang L, Qiu Y, et al. Changes of influenza vaccination rate and associated influencing factors after the COVID-19 pandemic in Shanghai, China. *Human vaccines & immunotherapeutics* 2024;20(1):2287294. doi: 10.1080/21645515.2023.2287294 [published Online First: 2024/02/01]
17. Jefferson T, Rivetti A, Di Pietrantonj C, et al. Vaccines for preventing influenza in healthy children. *The Cochrane database of systematic reviews* 2018;2(2):Cd004879. doi: 10.1002/14651858.CD004879.pub5 [published Online First: 2018/02/02]
18. Demicheli V, Jefferson T, Ferroni E, et al. Vaccines for preventing influenza in healthy adults. *The Cochrane database of systematic reviews* 2018;2(2):Cd001269. doi: 10.1002/14651858.CD001269.pub6 [published Online First: 2018/02/02]
19. Demicheli V, Jefferson T, Di Pietrantonj C, et al. Vaccines for preventing influenza in the elderly. *The Cochrane database of systematic reviews* 2018;2(2):Cd004876. doi: 10.1002/14651858.CD004876.pub4 [published Online First: 2018/02/02]
20. Cohen C, Kleynhans J, Moyes J, et al. Incidence and transmission of respiratory syncytial virus in urban and rural South Africa, 2017-2018. *Nature communications* 2024;15(1):116. doi: 10.1038/s41467-023-44275-y [published Online First: 2024/01/04]
21. Cohen C, Kleynhans J, von Gottberg A, et al. SARS-CoV-2 incidence, transmission, and reinfection in a rural and an urban setting: results of the PHIRST-C cohort study, South Africa, 2020–21. *The Lancet Infectious Diseases* 2022;22(6):821-34. doi: 10.1016/s1473-3099(22)00069-x [published Online First: 2021/12/16]
22. World Health Orgainzation. "ARI" case definition for community-based sureillance for RSV infection: World Health Organization; 2025 [Available from: https://www.who.int/teams/global-influenza-programme/global-respiratory-syncytial-virus-surveillance/case-definitions accessed April 22 2025.
23. Tsang TK, Wang C, Fang VJ, et al. Reconstructing household transmission dynamics to estimate the infectiousness of asymptomatic influenza virus infections. *Proceedings of the National Academy of Sciences of the United States of America* 2023;120(33):e2304750120. doi: 10.1073/pnas.2304750120 [published Online First: 2023/08/07]

Tables

Table 1. Data and samples collected in the Community Burden of Acute Respiratory Infections in Shanghai (CAReIS) study, 2024–2027.

Study period	Tools and methods	Participants	Measurement
Baseline	Structured questionnaire to participant/guardians (ARIs-IMS assisted personal interview)	All participants	Demographics, education attainment, socioeconomic status, anthropometry, underlying medical conditions, tobacco and alcohol use, self-rated health, household information, overcrowding, vaccination history
During active follow-up	Weekly surveillance	All participants	ARI symptoms since last contact, symptom onset date
	Combined nasopharyngeal and oropharyngeal (NP/OP) swab	Participants reporting an ARI	Multiplex respiratory pathogen real-time quantitative PCR (RT-qPCR) for influenza virus, RSV, SARS-CoV-2 and other 34 respiratory pathogens.
	Structured questionnaire to participant/guardians (ARIs-IMS assisted personal interview)	Participants with an ascertained ARI	ARI symptoms, symptom onset and diminish date, healthcare services utilization (outpatient and emergency department visits, and hospital admission), work and school absent, clinical outcomes
Post-follow-up	Hospital medical records (data linkage)	Participants hospitalized during study	Length of hospital stay, discharge diagnosis, clinical laboratory testing results, intensive care unit admission, clinical outcome, complications, prescriptions, costs, clinical recovery and in-hospital deaths.
	Immunization information system records (data linkage)	All participants	History of COVID-19 vaccines, pneumococcal vaccines, influenza vaccines, and *Haemophilus influenzae type b* vaccines, including doses, vaccine type, and administration date

Abbreviations. ARI, acute respiratory infection; ARIs-IMS, the ARIs Information Management System; PCR, Polymerase Chain Reaction; RSV, respiratory syncytial virus.

Table 2. Characteristics of study participants at baseline

Characteristics	Sex, no. (%)		Total, no. (%)
	Male	Female	
Number of participants	2595	2792	5387
Median age in years (IQR)	58(33-70)	60(34-69)	60(34-70)
Age group			
6-35 months	122(4.7)	111(4.0)	233(4.3)
3-6 years	136(5.2)	142(5.1)	278(5.2)
7-18 years	308(11.9)	267(9.6)	575(10.7)
19-59 years	1020(39.3)	1130(40.5)	2150(39.9)
60+ years	1009(38.9)	1142(40.9)	2151(39.9)
Underlying medical conditions			
Diabetes mellitus	232(8.9)	223(8.0)	455(8.4)
Hypertension	633(24.4)	656(23.5)	1289(23.9)
Heart disease	104(4.0)	130(4.7)	234(4.3)
Asthma	18(0.7)	15(0.5)	33(0.6)
Chronic bronchitis	60(2.3)	44(1.6)	104(1.9)
Chronic obstructive pulmonary disease	13(0.5)	4(0.1)	17(0.3)
Chronic kidney disease	6(0.2)	8(0.3)	14(0.3)
Myocardial infarction	13(0.5)	3(0.1)	16(0.3)
Stroke	28(1.1)	21(0.8)	49(0.9)
Cancer	37(1.4)	43(1.5)	80(1.5)
Other	46(1.8)	58(2.1)	104(1.9)
Vaccinations received			
Influenza vaccine	480(18.5)	558(20.0)	1038(19.3)
COVID-19 vaccine	1661(64.0)	1882(67.4)	3543(65.8)
PPV23 #	284(11.5)	327(12.2)	611(11.9)
PCV13 *	158(61.2)	175(69.2)	333(65.2)
Hib vaccine §	184(71.3)	179(70.8)	363(71.0)

IQR, interquartile range.

PPV23, 23-valent pneumococcal polysaccharide vaccine. Numbers counted in participants aged 2 years and older.

* PCV13, 13-valent pneumococcal conjugate vaccine. Numbers counted in children aged 6 months to 6 years old.

§ Hib vaccine, *Haemophilus influenzae type b* (Hib) conjugate vaccine. Numbers counted in children aged 6 months to 6 years old.

Figure Legends

Figure 1. Flow diagram of major study activities.

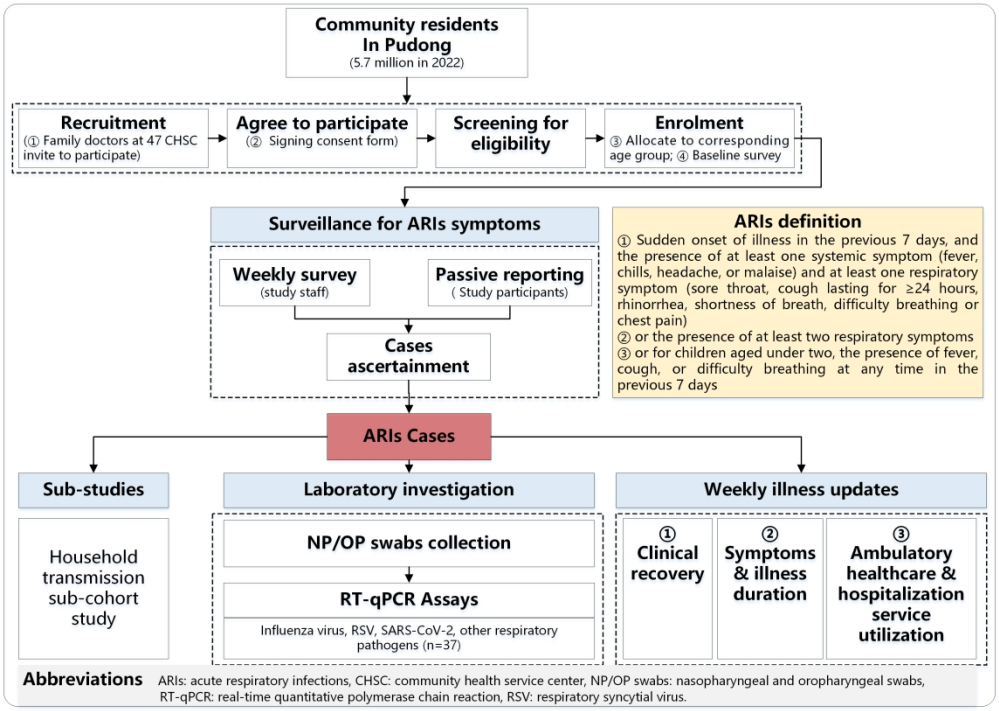

Figure 1. Flow diagram of major study activities.

289x205mm (300 x 300 DPI)

Supplementary Appendix

Title: Cohort profile: Community Burden of Acute Respiratory Infections in Shanghai, a longitudinal cohort study in respiratory pathogens, China, 2024-2027

Running head: Community burden of ARIs

Tables & Forms

- Supplementary Table 1. Baseline Characteristics at Enrollment Survey (CRF01)
- Supplementary Table 2. Symptoms of ARIs Monitoring Form (CRF02)
- Supplementary Table 3. Weekly Illness Updates and Clinical Recovery Follow-up (D07/D14/D21/D28) Data Form (CRF03)
- Supplementary Table 4. Hospital Discharge Data Collection Form (CRF04)
- Supplementary Table 5. Semi-annual Survey Data Form (CRF05)
- Supplementary Table 6. Lists of respiratory pathogens tested for in the study

Supplementary Table 1. Baseline Characteristics at Enrollment Survey (CRF01)

Date of signing informed consent: □□□□/□□/□□(YYYY/mm/dd)
Participant ID: □□□□□□ Family ID: □□□□□□
1. Basic Characteristics
1.1 Name of participants:_____ 1.2 Sex: 1=male; 2=female 1.3 Your identification number: □□□□□□□□□□□□□□ 1.4 Your date of birth: □□□□/□□/□□(YYYY/mm/dd) 1.5 Your home address (to street) :_____ 1.6 Place where your residence is registered? 1=Shanghai; 2=Other provinces 1.7 Your occupation: 1=school student; 2=housewife and unemployment; 3=retired; 4= service workers/food delivery; 5=security guards; 6=house keeping; 7=medical staff; 8=office clerk; 9=others_____ 1.8 Your education attainment: 1=primary school level and under; 2=Junior high school; 3= high school/technical secondary school; 4= university/college level or above 1.9 Are you covered by the following insurance (multiple choice allowed)? 1= basic medical insurance for urban workers; 2=basic medical insurance for urban residents; 3= new rural cooperative medical care; 4= commercial medical insurance; 5= uninsured; 6= others_
2. Overall health status
2.1 Your height:_____ cm 2.2 Your weight:_____ kg 2.3 Are you pregnant ? 1=Yes; 0=No; 9=Unknown If yes, your gestational age is_____weeks. 2.4 Are your children a premature baby (for children 6 years and under) ? 1=Yes; 0=No; 9=Unknown (A premature baby is defined as a child born at less than 37 weeks of gestational age.) 2.5 Are your children born a low-birth-weight baby (for children 6 years and under) ? 1=Yes; 0=No; 9=Unknown (A low-birth-weight baby is defined as a baby weighing less than 2500 grams within 1 hour of birth.) 2.6 Do you have or have had any of the following underlying conditions (multiple choice allowed): 1= diabetes mellitus; 2= hypertension; 3= heart disease; 4=asthma; 5= chronic bronchitis/bronchitis; 6=COPD; 7= chronic kidney disease; 8= myocardial infarction; 9= cerebral stroke; 10=cancer; 11=immunocompromised (defined as having received a solid organ or hematopoietic stem cell transplant, undergoing cancer chemotherapy, having a history of HIV or AIDS, or using steroids for >30 days); 12=others_____; 13=no medical underlying conditions 2.7 Do you smoke? 1=current smoking; 2= used to smoke, but not smoke now; 3=never smoke; 4= exposure to second-hand smoke 2.8 Do you drink alcohol ? 1=never; 2=occasionally; 3=drink often (once per week); 4=drink everyday 2.9 During the past three months, have you experienced a common cold or any of the following symptoms, e.g., fever, cough, runny nose, sore throat, stuffy nose, and body aches? 1=Yes; 0=No If yes, the nearest date of symptom onset: □□□□/□□/□□ (YYYY/mm/dd); If yes, how many episodes have you experienced?_____ times. 2.10 During the past one year , have you ever visited a doctor? 1=Yes; 0=No If yes, how many visits?_____ visits.

2.11 During the past one year，have you ever been hospitalized? 1=Yes; 0=No If yes, how many days have you been hospitalized?_____ days.
3. Household information
3.1 Total number of members living in your family:_____(persons) 3.2 The number of children aged <5 years in your family:_____(persons) 3.3 The number of people aged≥65 years in your family:_____(persons) 3.4 Total living area of your family:_____m^2 3.5 Per capita living area of your family:_____m^2 3.6 What is the average monthly income of your family? 1=less than 5000 Chinese yuan; 2=5000-9999 Chinese yuan; 3=10000-19999 Chinese yuan; 4=≥20000 Chinese yuan; 9= Unknown 3.1 Total number of members living in your family:_____(persons) 3.2 The number of children aged <5 years in your family:_____(persons) 3.3 The number of people aged≥65 years in your family:_____(persons)
4. Vaccination history (self-reported)
4.1 Have you ever received the flu vaccine since October 2023? 1=Yes; 0=No; 9=Unknown 4.2 Have you ever received a Covid-19 vaccine? 1=Yes; 0=No; 9=Unknown If yes, how many doses have been administered cumulatively? 1=1 dose; 2=2 doses; 3=3 doses; 4=4 doses and more 4.3 Have you received the 23 valent pneumococcal polysaccharide vaccine? 1=Yes; 0=No; 9=Unknown 4.4 Have you received the 13 valent pneumococcal conjugate vaccine? 1=Yes; 0=No; 9=Unknown 4.5 Have you received the *Haemophilus influenzae type b* (Hib) conjugate vaccine? 1=Yes; 0=No; 9=Unknown
Time of survey completion: □□□□/□□/□□:□□/□□ (YYYY/mm/dd:HH/MM) Name of investigator:_____

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Supplementary Table 2. Symptoms of ARIs Monitoring Form (CRF02)

Participant ID: □□□□□□ Family ID: □□□□□□		
1. Occurrence of ARIs		
1.1 Since our last contact, have you experienced any cold symptoms (such as fever, cough, nasal congestion or discharge, sore throat, body or muscle aches and pain, etc.)? 1=Yes; 0=No If "no", survey ends. If "yes", please fill in the following information.		
2. ARI Symptoms/Signs (multiple choices allowed)		
Symptoms/Signs	**Symptoms/Signs**	**If "yes", onset time (days ago)**
Fever	1=Yes 0=No	_____ days ago
Chills	1=Yes 0=No	_____ days ago
Headache	1=Yes 0=No	_____ days ago
Body or muscle aches	1=Yes 0=No	_____ days ago
Sore throat	1=Yes 0=No	_____ days ago
Fatigue	1=Yes 0=No	_____ days ago
Nasal congestion or discharge	1=Yes 0=No	_____ days ago
Wheezing, or dyspnea	1=Yes 0=No	_____ days ago
Cough	1=Yes 0=No	_____ days ago
Sputum production	1=Yes 0=No	_____ days ago
Chest Pain	1=Yes 0=No	_____ days ago
Other	Please specify_____	_____ days ago
For children under 2 years old only		
Chest wall indrawing	1=Yes 0=No	_____ days ago
Head nodding	1=Yes 0=No	_____ days ago
Central cyanosis	1=Yes 0=No	_____ days ago
Apnea or difficulty in breathing	1=Yes 0=No	_____ days ago
Crying can't be eased by parents	1=Yes 0=No	_____ days ago
Unable to feed or choked while breastfeeding	1=Yes 0=No	_____ days ago
Lethargy or difficulty to wake up	1=Yes 0=No	_____ days ago
2.1 Does the subject meet the ARIs' case definition? 1=Yes; 0=No. If yes, please provide the onset date □□□□/□□/□□ (Format: YYYY/mm/dd).		
3. Sampling Information		
3.1 Is a swab sampling scheduled? 1=Yes ; 0=No If yes, please provide the following information: 3.2 Name of the Community Healthcare Center for scheduled swab sampling: _____ 3.3 Scheduled swab sampling time: □□□□/□□/□□ (Format: YYYY/mm/dd)		
Time of survey completion: □□□□/□□/□□:□□/□□ (YYYY/mm/dd:HH/MM) Name of investigator:_____		

Supplementary Table 3. Weekly Illness Updates and Clinical Recovery Follow-up (D07/D14/D21/D28) Data Form (CRF03)

Participant ID: □□□□□□ Family ID: □□□□□□

1. ARI Symptoms/Signs (multiple choices allowed)

1.1 Since our last contact, have you experienced any of the following symptoms?
1=Yes, please specify the symptoms (multiple choices allowed); 0=No

ARI Symptoms/Signs	Day 7	Day 14	Day 21	Day 28
Fever	1=Yes 0=No	1=Yes 0=No	1=Yes 0=No	1=Yes 0=No
Chills	1=Yes 0=No	1=Yes 0=No	1=Yes 0=No	1=Yes 0=No
Headache	1=Yes 0=No	1=Yes 0=No	1=Yes 0=No	1=Yes 0=No
Body or muscle aches	1=Yes 0=No	1=Yes 0=No	1=Yes 0=No	1=Yes 0=No
Sore throat	1=Yes 0=No	1=Yes 0=No	1=Yes 0=No	1=Yes 0=No
Fatigue	1=Yes 0=No	1=Yes 0=No	1=Yes 0=No	1=Yes 0=No
Nasal congestion or discharge	1=Yes 0=No	1=Yes 0=No	1=Yes 0=No	1=Yes 0=No
Wheezing, or dyspnea	1=Yes 0=No	1=Yes 0=No	1=Yes 0=No	1=Yes 0=No
Cough	1=Yes 0=No	1=Yes 0=No	1=Yes 0=No	1=Yes 0=No
Sputum production	1=Yes 0=No	1=Yes 0=No	1=Yes 0=No	1=Yes 0=No
Chest Pain	1=Yes 0=No	1=Yes 0=No	1=Yes 0=No	1=Yes 0=No
Other	Please specify___	Please specify___	Please specify___	Please specify___
For children aged under 2 years old only				
Chest wall indrawing	1=Yes 0=No	1=Yes 0=No	1=Yes 0=No	1=Yes 0=No
Head nodding	1=Yes 0=No	1=Yes 0=No	1=Yes 0=No	1=Yes 0=No
Central cyanosis	1=Yes 0=No	1=Yes 0=No	1=Yes 0=No	1=Yes 0=No
Apnea or difficulty in breathing	1=Yes 0=No	1=Yes 0=No	1=Yes 0=No	1=Yes 0=No
Crying can't be eased by parents	1=Yes 0=No	1=Yes 0=No	1=Yes 0=No	1=Yes 0=No
Unable to feed or choked while breastfeeding	1=Yes 0=No	1=Yes 0=No	1=Yes 0=No	1=Yes 0=No
Lethargy or difficulty to wake up	1=Yes 0=No	1=Yes 0=No	1=Yes 0=No	1=Yes 0=No

2. Healthcare Utilization

2.1 Since our last contact, have you ever experienced any of the following? (Multiple choices allowed)

Healthcare Utilization	Day 7	Day 14	Day 21	Day 28
Outpatient/clinic visit	1=Yes 0=No	1=Yes 0=No	1=Yes 0=No	1=Yes 0=No
Emergency department visit	1=Yes 0=No	1=Yes 0=No	1=Yes 0=No	1=Yes 0=No
Hospital admission	1=Yes 0=No	1=Yes 0=No	1=Yes 0=No	1=Yes 0=No
Absent from school or work	1=Yes 0=No	1=Yes 0=No	1=Yes 0=No	1=Yes 0=No

2.2 Outpatient and Emergency Department Visits

2.2.1 Total number of visits to outpatient and emergency Department: ___times
2.2.2 Name of the hospital or clinic for the first visit: _____
2.2.3 Date of the first visit: □□□□/□□/□□ (Format: YYYY/mm/dd)
2.2.4 Diagnosis from the first visit:_____
2.2.5 Total cumulative expenditure: 1=Below 200 yuan; 2=200-499 yuan; 3=500-999 yuan; 4=1000 yuan and above

2.3 Hospitalization

2.3.1 Name of the Hospital：_____
2.3.2 Admission Date：□□□□/□□/□□ (Format: YYYY/mm/dd)

2.4 Absence from Work/School

2.4.1 Total number of days absent from work or school due to the illness:____

3. Clinical Outcome

3.1 By the end of the follow-up period, the clinical outcome for the subject is:
1=Clinical recovery; 2=Improvement or remission; 3=Worsening or Hospitalization; 4=Death.

(Note: Clinical recovery is defined as a normal body temperature for two consecutive days and the complete disappearance of symptoms such as body or muscle aches and pain, fatigue, cough, nasal congestion or discharge, sore throat, and wheezing, or dyspnea. Improvement/Remission is defined as an improvement in systemic and/or respiratory symptoms by the 28-day follow-up, but without complete resolution. Worsening or Hospitalization is defined as being admitted to the hospital during the follow-up period)
Time of survey completion: □□□□/□□/□□:□□/□□ (YYYY/mm/dd:HH/MM) Name of investigator:_____

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Supplementary Table 4. Hospital Discharge Data Collection Form (CRF04)

Participant No. □□□□□□ Family No. □□□□□□

1. Basic information of admission

1.1 Hospital name:_____

1.2 Date of admission:□□□□/□□/□□ (Format: YYYY/mm/dd)

1.3 Admitting diagnosis:_____

1.4 Date of discharge:□□□□/□□/□□ (Format: YYYY/mm/dd)

1.5 Discharge diagnosis:

Principal diagnosis 1._____

Secondary diagnosis 1._____; 2._____; 3._____

2. Clinical examination results

2.1 Signs/symptoms and physical examinations

Temperature:___C° Respiratory rate:__beats/min Heart rate:___beats/min

Blood pressure:___ /___mmHg

Pulse oxygen saturation (oxygen inhalation) sPO_2:____%

Pulse oxygen saturation (without oxygen) sPO_2:____%

Pulmonary auscultation: 1=dry rales; 2=wet rales; 3=normal

Mental status: 1=clear; 2=drowsiness; 3=irritability; 4=delirium; 5=convulsion; 6=coma; 7=normal

2.2 Blood examination: WBC_____×10^9/L; L_____×10^9/L; N_____×10^9/L; Plt _____×10^9/L; Hb____ g/L;

2.3 Blood biochemical examination: CRP_____mg/L; GLU_____mmol/L; BUN_____ mmol/L; PCT____μg/L

2.4 Clinical laboratory testing for respiratory pathogens was performed. 1=Yes; 0=No

2.4.1 If yes, the name of pathogen was tested for_____

2.4.2 If yes, the method of laboratory testing: 1=PCR; 2=antigen testing; 3=antibody testing

2.4.3 If yes, the result of laboratory testing: 1=positive; 0=negative

2.5 Whether chest radiography or other chest imaging was performed? 1=Yes; 0=No

If yes, is there a sign of pneumonia? 1=Yes; 0=No

2.6 Complications

☐Septic shock ☐Viral pneumonia ☐Bacterial pneumonia ☐Pneumothorax
☐ARDS ☐Bronchiolitis ☐Respiratory failure ☐Coagulopathy
☐Anemia ☐Pleural effusion ☐Acute kidney injury ☐Myolysis
☐Bacteremia ☐Gastrointestinal bleeding ☐Encephalitis/meningitis ☐pancreatitis
☐Convulsion ☐Arrhythmia ☐Liver dysfunction ☐Stroke
☐Hyperglycemia ☐Hypoglycemia ☐Congestive heart failure ☐Heart infection
☐Cardiac arrest ☐Disseminated intravascular Coagulation ☐Other (_____)

3. Treatment during hospitalization

3.1 Was oxygen therapy administered during hospitalization? 1=Yes; 0=No

If yes, the method of treatment: 1=nasal cannula or mask oxygen; 2=high-flow nasal cannula; 3=non-invasive mechanical ventilation; 4=invasive mechanical ventilation; 5= Other_____

3.2 Admission to the ICU? 1=Yes; 0=No

If yes, the length of ICU admission (_____days)

3.3 Were vasopressors administered? 1=Yes; 0=No

3.4 Were extracorporeal membrane oxygenation (ECMO) administered? 1=Yes; 0=No

3.5 Were Continuous renal replacement therapy(CRRT) administered? 1=Yes; 0=No

4. Drugs administered

Drug name	Category	Route	Daily dose		Frequency	Starting date (YYYY/mm/dd)	Stop date (YYYY/mm/dd)
			Dose	Unit			

4.1 Drug Name: (Please use the name of the drug. If it is a fixed compound preparation, please use the trade name.)
4.2 Category: A=antibiotics; B=antiviral drugs; C=steroid hormone drugs; D=angiotensin-converting enzyme inhibitors (ACE-Is) or angiotensin-receptor blockers (ARBs); E=Statins
4.3 Route of medication: 1=oral administration, 2=intravenous injection, 3=intravenous drip, 4=intramuscular injection, 5=inhalation, 6=others
4.4 Frequency: 1= continuous, 2= intermittent

5. Patient prognosis

☐ cured
☐ improved and be discharged
☐ transferred to the other hospital

Reasons for transfer：community rehabilitation/other（____）

☐ gave up treatment

reasons for giving-up：economic reasons/illness exacerbation/other（____）

☐ death date of death：___/___/___(YYYY/mm/dd) death diagnosis：___

6. The total expenditure of your hospitalization:_____RMB yuan

Time of survey completion: □□□□/□□/□□:□□/□□ (YYYY/mm/dd:HH/MM)

Name of investigator:_____

Supplementary Table 5. Semi-annual Survey Data Form (CRF05)

Participant No. □□□□□□ Family No. □□□□□□
1. **Update of family information**
1.1 Total number of members living in your family:_____(persons) 1.2 The number of children aged <5 years in your family:_____(persons) 1.3 The number of people aged≥65 years in your family:_____(persons)
2. **Update of vaccination information during the study**
2.1 Have you received the flu vaccine during your participation in the study? 1=Yes; 0=No; 9=Unknown 2.2 Have you received the Covid-19 vaccine during your participation in the study? 1=Yes; 0=No; 9=Unknown If yes, how many doses have been administered cumulatively? 1=1 dose; 2=2 doses; 3=3 doses; 4=4 doses and more 2.3 Have you received the 23 valent pneumococcal polysaccharide vaccine during your participation in the study? 1=Yes; 0=No; 9=Unknown 2.4 Have you received the 13 valent pneumococcal conjugate vaccine during your participation in the study? 1=Yes; 0=No; 9=Unknown 2.5 Have you received the *Haemophilus influenzae type b* (Hib) conjugate vaccine during your participation in the study? 1=Yes; 0=No; 9=Unknown
Time of survey completion: □□□□/□□/□□:□□/□□ (YYYY/mm/dd:HH/MM) Name of investigator:_____

Supplementary Table 6. Lists of respiratory pathogens tested for in the study

no.	**Viruses**	no.	**Bacteria**
1	Influenza A	27	*Bordetella holmesii*
2	Influenza B	28	*Bordetella pertussis*
3	Respiratory syncytial virus subtype A/B	29	*Chlamydophila pneumoniae*
4	SARS-Cov-2	30	*Haemophilus influenzae*
5	Human Coronavirus-229E	31	*Klebsiella pneumoniae*
6	Human Coronavirus- HKU1	32	*Legionella pneumophila*
7	Human Coronavirus- NL63	33	*Moraxella catarrhalis*
8	Human Coronavirus- OC43	34	*Mycoplasma pneumoniae*
9	MERS-CoV	35	*Staphylococcus aureus*
10	SARS-CoV	36	*Streptococcus pneumoniae*
11	Adenovirus		**Fungus**
12	Human parainfluenza virus serotype 1	37	*Pneumocystis jirovecii*
13	Human parainfluenza virus serotype 2		
14	Human parainfluenza virus serotype 3		
15	Human parainfluenza virus serotype 4		
16	Human metapneumovirus		
17	Rhinovirus		
18	Enterovirus		
19	Bocavirus		
20	varicella-zoster virus		
21	Epstein-Barr virus		
22	Cytomegalovirus		
23	Human herpesvirus 6		
24	Measles virus		
25	Mumps virus		
26	Parechovirus		