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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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1 **Running Title:** Community Burden of ARIs

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

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30 ABSTRACT

31 Purpose

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

36 Participants

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

48 Findings to date

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

54 Future plans

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

61
62 **Keywords:** Cohort Studies, Influenza, Respiratory Syncytial Virus, SARS-CoV-2, Respiratory

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64 **Strengths and limitations of this study**

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

77 INTRODUCTION

78 Acute respiratory infections (ARIs) are a leading cause of morbidity and mortality worldwide^{1 2}.
79 The great majority of deaths from respiratory infections are caused by lower respiratory tract
80 infections (LRTIs), causing 2.5 million deaths in 2019.³ The Coronavirus Disease 2019 (COVID-
81 19) pandemic had a profound impact on global health,⁴ causing 14.83 million excess deaths in 2021.⁵
82 With its continuous evolution and adaptation, SARS-CoV-2 has established a biological niche in
83 the human respiratory tract and cocirculates with other endemic respiratory pathogens such as
84 influenza virus, respiratory syncytial virus, and rhinovirus.^{6 7} Changing influenza and respiratory
85 syncytial virus (RSV) epidemiology was observed during the COVID-19 pandemic⁷⁻¹⁰ that was a
86 consequence of non-pharmaceutical interventions and viral interference.¹¹ Understanding the
87 burden and transmission dynamics of common respiratory pathogens associated ARIs in a general
88 population can inform ongoing control efforts in communities and guide future interventions (i.e.,
89 vaccines, diagnostics, and therapeutic drugs) in the post-COVID-19 era.

90 In China, a nationwide sentinel-hospital-based Surveillance for Etiology of Respiratory Infections
91 (SERI) system was established in 2009.¹² Study prior to the COVID-19 pandemic found that across
92 all age groups, the viruses most frequently causing ARIs were influenza, RSV, and rhinoviruses.¹²
93 Influenza, RSV, and other viral respiratory pathogens activities were significantly suppressed or
94 interrupted during the COVID-19 pandemic.^{4 8} Most of these SERI-based studies were conducted
95 in hospital settings and focused on prevalence of etiological agents in patients, which can be biased
96 by healthcare-seeking behavior and underestimate disease burden.¹² Studies on the incidence of
97 influenza in pregnant women found that community incidences were 0.7, 1.0, and 2.1 per 100
98 person-months for 2015-2016, 2016-2017, and 2017-2018 seasons, respectively, in Suzhou,
99 China.¹³ In Jiangsu Province, China, studies conducted during the 2015-2016 and 2016-2017
100 respiratory virus seasons among individuals aged 60–89 years found that cumulative incidences
101 were 0.8% and 6.1% for influenza-associated ARIs and 0.5% and 1.0% for RSV-associated ARIs.¹⁴
102 These studies focused on special populations (pregnant women and the elderly), investigated only
103 one or two respiratory pathogens, and were conducted before the COVID-19 pandemic.^{13 15}
104 Rigorously conducted prospective cohort studies of multiple respiratory pathogens in large

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4 105 communities are urgently needed to understand true burdens, transmission dynamics, and natural
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6 106 histories of influenza, RSV, SARS-CoV-2, and other respiratory pathogens causing ARIs,
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8 107 especially in the post-COVID-19 era.
9

10 108 We designed the **Community Burden of Acute Respiratory Infections in Shanghai (CAREIS)** study
11
12 109 as a three-year, prospective, age-stratified, community-based longitudinal cohort study to assess the
13
14 110 true burden of symptomatic infections caused by influenza virus, RSV, and SARS-CoV-2 in a
15
16 111 community in Shanghai Pudong New Area District (Pudong). The primary objective was to estimate
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18 112 age-stratified (children aged six months to 18 years, adults aged 19-64 years, and elderly aged 65+
19
20 113 years) community incidences of influenza virus, RSV, and SARS-CoV-2 associated ARIs.
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22 114 Secondary objectives include: i) investigating community prevalences of 37 common respiratory
23
24 115 pathogens causing ARI; ii) determining illness course and clinical features by pathogen and age
25
26 116 group; and iii) measuring proportions of community ARI cases seeking ambulatory care (outpatient
27
28 117 visits and emergency department visits) and proportions of community ARI cases hospitalized
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30 118 (admitted or staying in the hospital for 24 hours or more) by pathogen and age group. Exploratory
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32 119 study objectives include evaluating the proportion of community ARI cases with severe outcomes
33
34 120 and factors associated with severe outcomes. We defined severe ARIs as admission to an intensive
35
36 121 care unit (ICU) with any of the following: requiring mechanical ventilation, respiratory failure, acute
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38 122 respiratory distress syndrome, shock, or death. We present the study protocol and description of the
39
40 123 cohort.

41 42 124 **COHORT DESCRIPTION**

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44
45 125 CAREIS is an ongoing prospective longitudinal cohort study being conducted in Pudong, Shanghai,
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47 126 China. The cohort was established in October 2024 and will be followed through September 2027.
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49 127 At enrolment, study staff evaluated eligibility of study participants and conducted baseline
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51 128 assessments of socio-demographics, underlying medical conditions, household information,
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53 129 vaccination history, and self-rated health data. During the follow-up period, events of interest in
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55 130 each participant, i.e., symptoms of ARI, are being closely monitored and ascertained, and respiratory
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57 131 samples are obtained from identified ARI cases for timely laboratory testing. Multiplex respiratory
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59 132 pathogen real-time quantitative PCR (RT-qPCR) assays are used to confirm presence of influenza
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4 133 virus type-A, type-B, RSV, SARS-CoV-2, and other respiratory pathogens in upper respiratory tract
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6 134 specimens from ARI cases. All ARI cases are followed for 28 days after ascertainment to identify
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8 135 illness course and clinical outcome. Study activities and procedures are shown in Figure 1.
9

10 136 ***Study site and population***

11
12 137 Pudong New Area is a municipality in eastern China with a census-based population of 5.7 million
13
14 138 in 2024, among which 1.2 million residents are adults aged 60 years and over. Pudong is served by
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16 139 47 community health service centers, all of which participate in the study. Influenza vaccine
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18 140 coverage is moderate in Pudong (17.68% in the 2021–2022 season).¹⁶ Pudong was selected as the
19
20 141 study site for several reasons: the local health authority is actively involved, willing to provide
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22 142 support, and willing to be responsible for coordinating study activities; vaccination histories can be
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24 143 obtained by linking subjects' identification numbers (ID) to the Immunization Management
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26 144 Information System and to electronic medical records in hospitals via the Regional Healthcare Big
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28 145 Data Center; and Pudong CDC has been involved in SERI studies since 2009 and has experienced,
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30 146 well-trained staff and laboratory technicians to conduct study activities.

31
32 147 The study population includes all permanent residents aged six months and above in Pudong, with
33
34 148 no gender restrictions. To increase coverage and representativeness, participants were enrolled at
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36 149 all 47 community health service centers by service-center family doctors. Households with multiple
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38 150 members living together are prioritized for enrollment.

40 151 ***Sample size considerations***

41
42 152 Our target sample size was 5,250 participants, including 250 infants aged six months to 2 years, 250
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44 153 preschool children aged 3-6 years, 450 school-age children aged 7-18 years, 2,150 adults aged 19-
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46 154 64 years, and 2,150 older adults aged 65+ years. Target sample sizes were calculated assuming an
47
48 155 annual cumulative incidence of symptomatic infection of 30% in infants and preschool children, 20%
49
50 156 in school-age children, and 5% in adults for influenza virus,^{17 18 19} RSV,²⁰ or SARS-CoV-2²¹.
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52 157 Accounting for loss to follow-up of up to 10%, the sample will ensure achieving a 20% relative
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54 158 precision for incidence estimates at 95% significance levels in each age strata.

56 159 ***Enrolment and baseline assessment***

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58 160 At study initiation, community residents were invited to come to family doctors' offices for
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60 161 enrolment screening, and were enrolled if they met the following eligibility criteria: i) they were

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4 162 able to understand the study procedures and provide informed consent; ii) could use the Internet and
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6 163 mobile devices to complete data collection (for young children and the elderly who are illiterate, a
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8 164 surrogate survey can be done by their parents/guardians); iii) agreed to have all family household
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10 165 members included in another study (the household transmission sub-cohort study) if they become
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12 166 confirmed with influenza virus, RSV, or SARS-CoV-2 associated ARIs during the study follow-up
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14 167 period; and iv) resided in the Pudong for at least six months.

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16 168 Participants with any of the following were excluded: i) being unwilling or not agreeing to have
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18 169 their medical records or vaccination history accessed by study staff through electronic databases
19
20 170 linkage; ii) lacking ability to adhere to study procedures as prespecified in the study protocol; or iii)
21
22 171 planning to leave Pudong for more than one month in the following year, regardless of reason.

23
24 172 After signing informed consent, study participants were assigned to the appropriate age group and
25
26 173 completed baseline questionnaires (*Supplementary Table 1*).

27 28 29 174 ***Surveillance for ARI symptoms***

30 31 175 ***Definition of ARIs***

32
33 176 Since enrollment, study participants are being actively followed for three years to identify
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35 177 occurrences of ARI. We define an ARI episode as the onset of illness in the previous seven days
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37 178 and presence of at least one systemic symptom (feeling feverish or having a measured axillary
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39 179 temperature of ≥ 37.0 °C, chills, headache, or general malaise) and at least one respiratory symptom
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41 180 (sore throat, cough lasting for ≥ 24 hours, rhinorrhea, shortness of breath, difficulty breathing or
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43 181 chest pain); or the presence of at least two respiratory symptoms. For children under two years of
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45 182 age or individuals unable to speak, ARIs are defined as the presence of an axillary temperature of
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47 183 ≥ 37.0 °C, cough, or difficulty breathing at any time in the previous seven days or observed during
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49 184 our weekly visits.

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51 185 We anticipate that participants will experience multiple ARI episodes during the three years of the
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53 186 study. To be defined as a new ARI, the onset of new symptoms should be at least seven days
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55 187 removed from the clinical recovery date of a previous ARI. Clinical recovery is defined as body
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57 188 temperature returning to normal for two consecutive days and complete disappearance of the
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59 189 following symptoms: general malaise, fatigue, cough, nasal congestion or runny nose, sore throat,
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4 190 shortness of breath, and difficulty breathing.

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6 191 *Weekly survey and passive reporting*

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8 192 Participants are monitored for ARIs with active surveillance and passive reporting. Active
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10 193 surveillance refers to a weekly survey of participants by study staff, in which the question "since
11
12 194 the last contact, have you experienced a common cold or any of the following symptoms: fever,
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14 195 cough, runny nose, sore throat, stuffy nose, or body ache?" is asked. Passive reporting refers to
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16 196 participants voluntarily reporting respiratory symptoms to study staff whenever they experience one.

17
18 197 *Case Ascertainment*

19
20 198 The study staff verify information reported by participants via phone ([Supplementary Table 2](#)). For
21
22 199 participants who meet our ARI case definition, study staff encourage the participant to go to their
23
24 200 community health service center within 24 hours to collect respiratory swab samples. If
25
26 201 inconvenient for the participant to go to the community health center, a community worker provides
27
28 202 door-to-door sample collection service within 24 hours of appointment.

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30 203 *Weekly illness updates and recovery from illness*

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32 204 Identified ARI cases are contacted weekly for 28 days to determine the illness course (i.e., symptoms
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34 205 and duration) and clinical recovery ([Supplementary Table 3](#)), starting from the case ascertainment
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36 206 day. During weekly contacts, information on ambulatory healthcare (i.e., outpatient/emergency
37
38 207 department visits) and hospital service utilization are obtained ([Supplementary Table 3](#)). For
39
40 208 hospitalized ARI cases, we collect additional information on clinical diagnosis, complications,
41
42 209 treatment, and drugs used within one week after the case has been discharged from the hospital by
43
44 210 linking participant ID number to the Pudong New Area Healthcare Big Data System ([Supplementary
45
46 211 table 4](#)).

47
48 212 *Semi-annual survey*

49
50 213 We will conduct semi-annual surveys to update participants' information that could change during
51
52 214 the study, i.e., vaccination status, household information, and overall health status ([Supplementary
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54 215 Table 5](#)).

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56 216 *Loss to follow-up*

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58 217 Loss to follow-up of up to 10% was accounted for in the target sample size determination.
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60 218 Withdrawals are defined as participants who formally notify study staff that they no longer wish to

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

223 ***Laboratory investigation***

224 ***Specimen collection***

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

231 ***Processing and storage of specimens***

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

235 ***Laboratory testing***

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

246 ***Data management***

247 ***Data collection***

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

258 ***Immunization information systems***

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

263 ***Data linkage and use of electronic medical records***

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

269 **FINDINGS TO DATE**

270 We enrolled 5,387 participants into the cohort between 14 October and 22 November 2024,
271 achieving the target sample size (*Table 2*). All recruited subjects completed their baseline
272 assessments and questionnaires. Among enrollees, 2,151 (39.9%) were aged ≥ 60 years; 1,038
273 (19.3%) reported receipt of influenza vaccine in the year before enrolment; 3,543 (65.8%) reported
274 a history of COVID-19 vaccination; 611 (11.9%) participants aged 2 years and older reported a

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4 275 history of 23-valent pneumococcal polysaccharide vaccination (PPV23). Among children aged 6
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6 276 months to 5 years, 333 (65.2%) reported receipt of 13-valent pneumococcal conjugate vaccine
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8 277 (PCV13), and 363 (71.0%) reported receipt of *Haemophilus influenzae type b* (Hib) conjugate
9
10 278 vaccine. We started following participants in November 2024; they are being contacted weekly to
11
12 279 monitor ARIs for three years.

14 280 **FUTURE PLANS**

17 281 Findings from this study will be used to provide up-to-date scientific data on the community burden
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19 282 of specific respiratory infections to inform ongoing control efforts and future pandemic
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21 283 preparedness for respiratory diseases in the post-COVID-19 era in China. We completed participant
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23 284 enrolment and baseline assessment. Active follow-up, NP/OP swab collection, and laboratory
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25 285 testing are ongoing. Planned analyses include: i) analysis of annual pathogen-specific incidence by
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27 286 age group; ii) characterizing clinical presentations, illness courses, clinical recovery and outcome,
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29 287 and healthcare services utilization behavior of ARI cases; and iii) exploring factors associated with
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31 288 ARIs and severe ARIs, including vaccination history, prior infections and underlying medical
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33 289 conditions. We are also planning to assess the transmission dynamics of common respiratory
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35 290 pathogens in a household transmission sub-cohort, nested within the primary cohort. During our
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37 291 daily active follow-up, participants with laboratory-confirmed influenza, RSV, and SARS-CoV-2
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39 292 infections and all of their family members will be prospectively enrolled into a sub-cohort at the
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41 293 time of the index cases' illness ascertainment. More frequent respiratory specimen (NP/OP swab)
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43 294 sampling and symptom monitoring will be conducted on the household transmission sub-cohort for
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45 295 up to 28 days, regardless of whether they are symptomatic or asymptomatic. We plan to recruit at
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47 296 least 200 households for each of the three respiratory pathogens (influenza virus, RSV, and SARS-
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49 297 CoV-2) in the three-year study period, in order to assess epidemiological transmission parameters,
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51 298 like incubation period, latent period, generation time, serial interval, infectious period duration,
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53 299 secondary attack rate, and proportion of asymptomatic infections, for these respiratory pathogens.
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55 300 Details of the study design of the household transmission sub-cohorts will be elaborate elsewhere.

57 301 **STRENGTHS AND LIMITATIONS**

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59 302 The study design has several strengths. First, CAREIS uses standardized and unified protocol and
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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

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4 332 infections. However, we have planned another sub-cohort (the household transmission sub-cohort
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6 333 study) nested within our primary cohort. Using this sub-cohort, we can determine infection
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8 334 incidence rate and secondary attack rate, and most importantly, the proportion of participants with
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10 335 typical and asymptomatic infections.²² Second, Pudong is a highly developed and densely populated
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12 336 region in eastern China, with high average household income and vaccination coverage levels.
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14 337 Results from this study may not be generalizable to less populated or developed regions in China.
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16 338 Third, study participants are not randomly selected from the community. They are invited to
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18 339 participate and offered to join freely. Those who have high awareness of his/her health might be
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20 340 more likely to be included in our study, which can bias our estimates as they might tend to report
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22 341 more ARIs than the reference population. Fourth, our study sample size may not be sufficiently
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24 342 powered to explore risk factors of severe outcomes of influenza, RSV, and SARS-CoV-2 associated
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26 343 infections, nor can we determine the incidence of some less prevalent pathogens in the community,
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28 344 e.g., measles virus, bocavirus. Finally, our laboratory methods and the type of sample specimens
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30 345 collected may have problems for some bacterial agents (e.g., *Streptococcus pneumoniae*,
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32 346 *Haemophilus influenzae*) that commonly colonized the upper respiratory tract. Detection of these
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34 347 pathogens does not necessarily imply infection.

348 Collaborators

349 This study was a collaboration between the School of Population Medicine and Public Health,
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351 Peking Union Medical College and the Pudong New Area Center for Disease Control and
352
353 Prevention (Pudong CDC). We are open to collaboration with other researchers to use data
354
355 generated in this study as well as to use the platform to conduct further research on influenza virus,
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357 RSV, and SARS-CoV-2 to develop, evaluate and optimize interventions (i.e., vaccines and
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359 treatments). Requests of collaboration should be sent to ZL (lizhongjiecdc@163.com), accompanied
360
361 by a detailed protocol and statistical analysis plan. After reviewing scientific validity, we will
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363 contact requestors whose proposals meet the research criteria, and for which an exception does not
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365 apply, within one month of request.

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4 360 guardians, the investigators and coinvestigators, nurses, physicians, our research staff and other
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6 361 members of the community who helped us in conducting this study.
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8 362 **Data availability statement**

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11 363 De-identified individual participant-level data will be available on reasonable request, upon written
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13 364 request to the corresponding author following publication.
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25
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27
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30 372 **Contributors**

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34 373 ZL is the principal investigator on this study who conceived and critically revised the manuscript.
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36 374 CY, ZL, LH and LR conceptualized and designed the study. CY, JY, and BZ contributed equally to
37
38 375 this work. JY, XY, YL and LX wrote the first draft. LX, YX, YJ, XZ, LZ, and YW contributed to
39
40 376 the literature search. BZ, XW, YS and LR designed laboratory methods. XY, YL and LX wrote the
41
42 377 statistical analysis plan. ZL and CY received funding. YL, HX, TZ, LR, BC and WY commented
43
44 378 on and revised drafts of the manuscript. All authors contributed to reviewing, revising and approving
45
46 379 the final manuscript, and had final responsibility for the decision to submit for publication.
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48 380 **Competing interests**

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51 381 The authors declare that they have no competing interests.
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53 382 **Patient and public involvement**

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57 383 Patients and the public were not involved in this research's design, conduct, reporting, or
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59 384 dissemination plans.
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4 385 **Patient consent for publication**

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6 386 Not required.

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9 387 **Ethics approval**

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12 388 This study was approved by Chinese Academy of Medical Sciences & Peking Union Medical

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14 389 College's Institutional Review Board (no. CAMS&PUMC-IEC-2024-068).

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459 **Tables**460 **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.
Post-follow-up	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
	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 <i>Haemophilus influenzae type b</i> vaccines, including doses, vaccine type, and administration date

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

463 **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)

464 IQR, interquartile range.

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

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

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

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469 **Figure Legends**

470 **Figure 1.** Flow diagram of major study activities.

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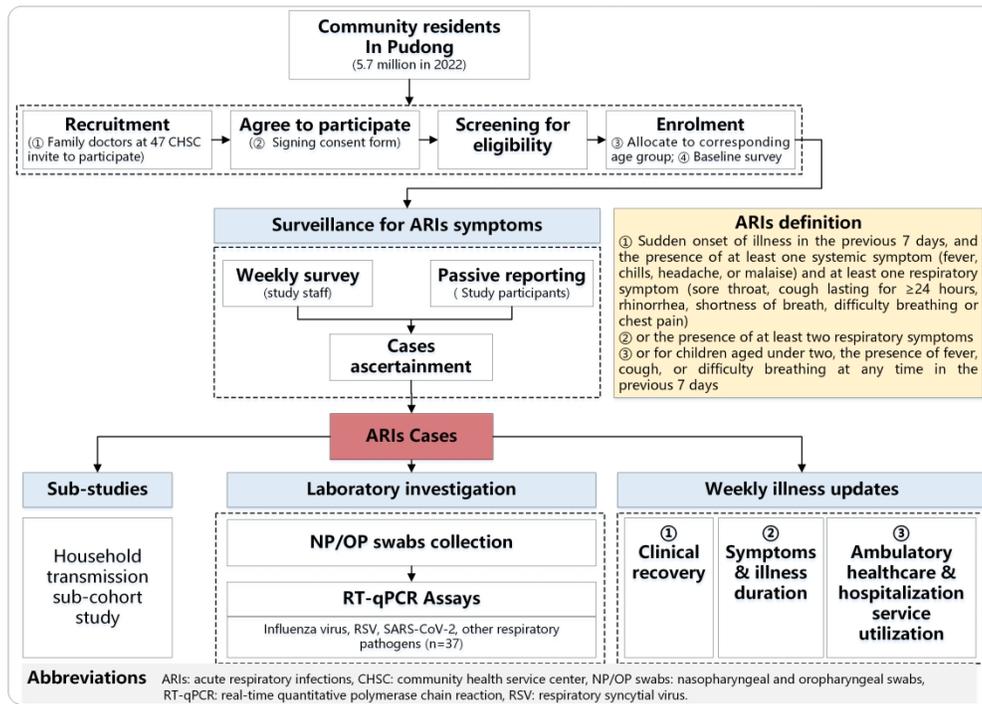


Figure 1. Flow diagram of major study activities.

289x205mm (300 x 300 DPI)

1 **Supplementary Appendix**

2 **Title:** Community burden of influenza virus, respiratory syncytial virus, SARS-CoV-
3 2, and other respiratory pathogens-associated acute respiratory infections, a
4 longitudinal cohort study in Shanghai, China, 2024-2027

5 **Running head:** Community burden of ARIs

6 **Tables & Forms**

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

15 **Supplementary Table 1. Baseline Characteristics at Enrollment**
 16 **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

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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 <i>Haemophilus influenzae type b</i> (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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18 **Supplementary Table 2. Symptoms of ARIs Monitoring Form**
 19 **(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
<i>For children under 2 years old only</i>		
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: _____		

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21 **Supplementary Table 3. Weekly Illness Updates and Clinical**
 22 **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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24 **Supplementary Table 4. Hospital Discharge Data Collection**
 25 **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							
<input type="checkbox"/> Septic shock <input type="checkbox"/> Viral pneumonia <input type="checkbox"/> Bacterial pneumonia <input type="checkbox"/> Pneumothorax							
<input type="checkbox"/> ARDS <input type="checkbox"/> Bronchiolitis <input type="checkbox"/> Respiratory failure <input type="checkbox"/> Coagulopathy							
<input type="checkbox"/> Anemia <input type="checkbox"/> Pleural effusion <input type="checkbox"/> Acute kidney injury <input type="checkbox"/> Myolysis							
<input type="checkbox"/> Bacteremia <input type="checkbox"/> Gastrointestinal bleeding <input type="checkbox"/> Encephalitis/meningitis <input type="checkbox"/> pancreatitis							
<input type="checkbox"/> Convulsion <input type="checkbox"/> Arrhythmia <input type="checkbox"/> Liver dysfunction <input type="checkbox"/> Stroke							
<input type="checkbox"/> Hyperglycemia <input type="checkbox"/> Hypoglycemia <input type="checkbox"/> Congestive heart failure <input type="checkbox"/> Heart infection							
<input type="checkbox"/> Cardiac arrest <input type="checkbox"/> Disseminated intravascular Coagulation <input type="checkbox"/> 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			

<p>4.1 Drug Name: (Please use the name of the drug. If it is a fixed compound preparation, please use the trade name.)</p> <p>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</p> <p>4.3 Route of medication: 1=oral administration, 2=intravenous injection, 3=intravenous drip, 4=intramuscular injection, 5=inhalation, 6=others</p> <p>4.4 Frequency: 1= continuous, 2= intermittent</p>							
<p>5. Patient prognosis</p> <p><input type="checkbox"/> cured</p> <p><input type="checkbox"/> improved and be discharged</p> <p><input type="checkbox"/> transferred to the other hospital</p> <p>Reasons for transfer : community rehabilitation/other (____)</p> <p><input type="checkbox"/> give up treatment</p> <p>reasons for give-up : economic reasons/illness exacerbation/other (____)</p> <p><input type="checkbox"/> death date of death : __/__/__(YYYY/mm/dd) death diagnosis : ____</p>							
<p>6. The total expenditure of your hospitalization: _____ RMB yuan</p> <p>Time of survey completion: □□□□/□□/□□:□□/□□ (YYYY/mm/dd:HH/MM)</p> <p>Name of investigator: _____</p>							

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27 **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 <i>haemophilus influenzae type b</i> (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: _____	

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

no.	Viruses	no.	Bacteria
1	Influenza A	27	<i>Bordetella holmesii</i>
2	Influenza B	28	<i>Bordetella pertussis</i>
3	Respiratory syncytial virus subtype A/B	29	<i>Chlamydophila pneumoniae</i>
4	SARS-Cov-2	30	<i>Haemophilus influenzae</i>
5	Human Coronavirus-229E	31	<i>Klebsiella pneumoniae</i>
6	Human Coronavirus- HKU1	32	<i>Legionella pneumophila</i>
7	Human Coronavirus- NL63	33	<i>Moraxella catarrhalis</i>
8	Human Coronavirus- OC43	34	<i>Mycoplasma pneumoniae</i>
9	MERS-CoV	35	<i>Staphylococcus aureus</i>
10	SARS-CoV	36	<i>Streptococcus pneumoniae</i>
11	Adenovirus	37	<i>Pneumocystis jirovecii</i>
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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BMJ Open

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

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Primary Subject Heading:	Epidemiology
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Keywords:	China, Respiratory infections < THORACIC MEDICINE, Epidemiology < INFECTIOUS DISEASES, EPIDEMIOLOGIC STUDIES, INFECTIOUS DISEASES

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1 **Running Title:** Community Burden of ARIs

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

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28 **Word count:** abstract =324; text=3,880

29 ABSTRACT

30 Purpose

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

35 Participants

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

47 Findings to date

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

53 Future plans

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

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

62 **Strengths and limitations of this study**

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

77 INTRODUCTION

78 Acute respiratory infections (ARIs) are a leading cause of morbidity and mortality worldwide^{1 2}.
79 The great majority of deaths from respiratory infections are caused by lower respiratory tract
80 infections (LRTIs), causing 2.5 million deaths in 2019.³ The Coronavirus Disease 2019 (COVID-
81 19) pandemic had a profound impact on global health,⁴ causing 14.83 million excess deaths in 2021.⁵
82 With its continuous evolution and adaptation, SARS-CoV-2 has established a biological niche in
83 the human respiratory tract and cocirculates with other endemic respiratory pathogens such as
84 influenza virus, respiratory syncytial virus, and rhinovirus.^{6 7} Due to widely used non-
85 pharmaceutical interventions and viral interference,⁸ changing influenza and respiratory syncytial
86 virus (RSV) epidemiology was observed during the COVID-19 pandemic.⁷⁻¹¹ Understanding the
87 burden and transmission dynamics of common respiratory pathogens associated ARIs in a
88 community population can inform ongoing control efforts in communities and guide future
89 interventions (i.e., vaccines, diagnostics, and therapeutic drugs) in the post-COVID-19 era.

90 A nationwide sentinel-hospital-based Surveillance for Etiology of Respiratory Infections (SERI)
91 system was established in China in 2009.¹² Study prior to the COVID-19 pandemic found that across
92 all age groups, the viruses most frequently causing ARIs were influenza, RSV, and rhinoviruses.¹²
93 Influenza, RSV, and other viral respiratory pathogens activities were significantly suppressed or
94 interrupted during the COVID-19 pandemic.^{4 9} Most of these SERI-based studies were conducted
95 in hospital settings and focused on prevalence of etiological agents in patients, which can be biased
96 by healthcare-seeking behavior and underestimate disease burden.¹² Studies on the incidence of
97 influenza in pregnant women found that community incidences were 0.7, 1.0, and 2.1 per 100
98 person-months for 2015-2016, 2016-2017, and 2017-2018 seasons, respectively, in Suzhou,
99 China.¹³ In Jiangsu Province, China, studies conducted during the 2015-2016 and 2016-2017
100 respiratory virus seasons among individuals aged 60–89 years found that cumulative incidences
101 were 0.8% and 6.1% for influenza-associated ARIs and 0.5% and 1.0% for RSV-associated ARIs.¹⁴
102 These studies focused on special populations (pregnant women and the elderly), investigated only
103 one or two respiratory pathogens, and were conducted before the COVID-19 pandemic.^{13 15}
104 Rigorously conducted prospective cohort studies of multiple respiratory pathogens in large

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4 105 communities are urgently needed to understand true burdens, transmission dynamics, and natural
5
6 106 histories of influenza, RSV, SARS-CoV-2, and other respiratory pathogens causing ARIs,
7
8 107 especially in the post-COVID-19 era.
9

10 108 We designed the **Community Burden of Acute Respiratory Infections in Shanghai (CAREIS)** study
11
12 109 as a three-year, prospective, age-stratified, community-based longitudinal cohort study to assess the
13
14 110 true burden of symptomatic infections caused by influenza virus, RSV, and SARS-CoV-2 in a
15
16 111 community in Shanghai Pudong New Area District (Pudong, for short). The primary objective was
17
18 112 to estimate age-stratified (children aged six months to 18 years, adults aged 19-64 years, and elderly
19
20 113 aged 65+ years) community incidences of influenza virus, RSV, and SARS-CoV-2 associated ARIs.
21
22 114 Secondary objectives include: i) investigating community prevalences of influenza virus, RSV, and
23
24 115 SARS-CoV-2 causing ARI; ii) determining illness course and clinical features by pathogen and age
25
26 116 group; and iii) measuring proportions of community ARI cases seeking ambulatory care (outpatient
27
28 117 visits and emergency department visits) and proportions of community ARI cases hospitalized
29
30 118 (admitted or staying in the hospital for 24 hours or more) by pathogen and age group. Exploratory
31
32 119 study objectives include: i) studying prevalence of other common respiratory pathogens causing
33
34 120 ARI, other than influenza virus, RSV, and SARS-CoV-2, in the community; ii) and evaluating the
35
36 121 proportion of community ARI cases with severe outcomes and factors associated with severe
37
38 122 outcomes. We defined severe ARIs as admission to an intensive care unit (ICU) with any of the
39
40 123 following: requiring mechanical ventilation, respiratory failure, acute respiratory distress syndrome,
41
42 124 shock, or death. We present the study protocol and description of the cohort.

43 44 125 **COHORT DESCRIPTION**

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47 126 CAREIS is an ongoing prospective longitudinal cohort study being conducted in Pudong, Shanghai,
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49 127 China. The cohort was established in October 2024 and will be followed through September 2027.
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51 128 At enrolment, study staff evaluated eligibility of potential participants and conducted baseline
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53 129 assessments of socio-demographics, underlying medical conditions, household information,
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55 130 vaccination history, and self-rated health data of eligible, consenting individuals. During the follow-
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57 131 up period, events of interest in each participant, i.e., symptoms of ARI, are being closely monitored
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59 132 and ascertained, and respiratory samples are obtained from identified ARI cases for timely
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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.

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4 161 ***Sample size considerations***

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6 162 Our target sample size was 5,250 participants, including 250 children aged six months to 2 years,
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8 163 250 preschool children aged 3-6 years, 450 school-age children aged 7-18 years, 2,150 adults aged
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10 164 19-64 years, and 2,150 older adults aged 65+ years. Target sample sizes were calculated assuming
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12 165 an annual cumulative incidence of symptomatic infection of 30% in infants and preschool children,
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14 166 20% in school-age children, and 5% in adults for influenza virus,^{17 18 19} RSV,²⁰ or SARS-CoV-2²¹.
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16 167 Accounting for loss to follow-up of up to 10%, the sample will ensure achieving a 20% relative
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18 168 precision for incidence estimates at 95% significance levels in each age strata.

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20 169 ***Enrolment and baseline assessment***

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22 170 At study initiation, community residents were invited to come to family doctors' offices for
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24 171 enrolment screening, and were enrolled if they met the following eligibility criteria: they i) were
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26 172 able to understand the study procedures and provide informed consent; ii) could use the Internet and
27
28 173 mobile devices to complete data collection (for young children and elderly who are illiterate, a
29
30 174 surrogate survey is done by their parents/guardians); iii) agreed to have all family household
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32 175 members included in another study (the household transmission sub-cohort study) if they become
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34 176 confirmed with influenza virus, RSV, or SARS-CoV-2 associated ARIs during the study follow-up
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36 177 period; and iv) were permanent residents of the community, defined as persons who resided in the
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38 178 Pudong New Area District for at least six months.

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40 179 Participants with any of the following were excluded: i) being unwilling or not agreeing to have
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42 180 their medical records or vaccination history accessed by study staff through electronic databases
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44 181 linkage; ii) lacking ability to adhere to study procedures as prespecified in the study protocol; or iii)
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46 182 planning to leave Pudong for more than one month in the following year, regardless of reason (i.e.,
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48 183 having high risks of losing to follow-up early).

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50 184 After signing informed consent, study participants were assigned to the appropriate age group and
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52 185 completed baseline questionnaires (*Supplementary Table 1*). Full consent was obtained from all
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54 186 children and adult participants. Older illiterate people gave oral consent, children aged 6 months to
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56 187 8 years of age gave written consent from their parents/guardians, while children aged 9 years to 18
57
58 188 years of age gave written consent themselves along with their parents/guardians.

189 *Surveillance for ARI symptoms*

190 *Definition of ARIs*

191 Since enrollment, study participants are being actively followed for three years to identify
192 occurrences of ARI. We define an ARI episode as the onset of illness in the previous seven days
193 and presence of at least one systemic symptom (feeling feverish or having a measured axillary
194 temperature of ≥ 37.0 °C, chills, headache, or general malaise) and at least one respiratory symptom
195 (sore throat, cough lasting for ≥ 24 hours, rhinorrhea, shortness of breath, difficulty breathing or
196 chest pain); or the presence of at least two respiratory symptoms. For children under two years of
197 age or individuals unable to speak, ARIs are defined as the presence of an axillary temperature of
198 ≥ 37.0 °C, cough, or difficulty breathing at any time in the previous seven days or observed during
199 our weekly visits.

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

206 *Weekly survey and passive reporting*

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

212 *Case Ascertainment*

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

218 ***Weekly illness updates and recovery from illness***

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

228 ***Semi-annual survey***

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

232 ***Withdrawals and loss to follow-up***

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

239 ***Laboratory investigation***

240 ***Specimen collection***

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

246 box to maintain a temperature of 4–8°C.

247 *Processing and storage of specimens*

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

251 *Laboratory testing*

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

262 *Data management and analysis*

263 *Data collection*

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

274 *Immunization information systems*

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

279 *Data linkage and use of electronic medical records*

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

285 **FINDINGS TO DATE**

286 Between 14 October and 22 November 2024, we enrolled 5,387 participants into the cohort ([Table](#)
287 [2](#)). Among the participants, 2,595 (48.2%) were male and 2,792 (51.8%) were female. There were
288 1,086 (20.2%) children aged six months to 18 years, 2,150 (39.9%) adults aged 19-64 years, and
289 2,151 (39.9%) elderly aged ≥ 60 years. Among the 5,387 enrollees, 1,038 (19.3%) reported receipt
290 of influenza vaccine in the year before enrolment; 3,543 (65.8%) reported a history of COVID-19
291 vaccination; 611 (11.9%) participants aged 2 years and older reported a history of 23-valent
292 pneumococcal polysaccharide vaccination (PPV23). Among children aged 6 months to 5 years, 333
293 (65.2%) reported receipt of 13-valent pneumococcal conjugate vaccine (PCV13), and 363 (71.0%)
294 reported receipt of *Haemophilus influenzae type b* (Hib) conjugate vaccine. All recruited subjects
295 completed their baseline assessments and questionnaires, and we started following participants in
296 November 2024; they are being contacted weekly to monitor ARIs for three years.

297 **FUTURE PLANS**

298 Findings from this study will be used to provide up-to-date scientific data on the community burden
299 of specific respiratory infections to inform ongoing control efforts and future pandemic
300 preparedness for respiratory diseases in the post-COVID-19 era in China. We have completed
301 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 definition²² 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

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4 331 incubation period, latent period, generation time, serial interval, infectious period duration,
5 332 secondary attack rate, and proportion of asymptomatic infections, for these respiratory pathogens.
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7 333 Details of the study design of the household transmission sub-cohorts will be elaborated elsewhere.
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10 334 **STRENGTHS AND LIMITATIONS**

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13 335 The study design has several strengths. First, CAREIS uses a standardized and unified protocol and
14 336 laboratory procedures, allowing us to generate high-quality community-level incidence data in age
15 337 strata on a wide range of common respiratory pathogens in the post-COVID-19 pandemic era. The
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17 338 study design ensures accurate data collection and provides insights into the true burden,
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19 339 transmission dynamics, natural history, and risk factors of common respiratory pathogen infections.
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21 340 Second, our participants include permanent residents recruited from all 47 community health service
22 341 centers of Pudong. The sample is representative of the local population and can reflect actual illness
23 342 occurrence at the community level. Weekly follow-up of contacts increases the likelihood of
24 343 capturing all illness episodes in the study participants, providing us with precise incidence estimates.
25
26 344 Third, the large cohort size (>5,200 participants) will allow us to estimate incidence by age group
27 345 and respiratory pathogen with good statistical precision. The three-year follow-up period will
28 346 provide information on year-to-year and season-to-season variation in incidence for most respiratory
29 347 pathogens, especially influenza virus, RSV, and SARS-CoV-2, which have shown a strong seasonal
30 348 and yearly cyclical pattern in other studies. Fourth, the study uses molecular laboratory methods
31 349 (i.e., RT-qPCR) to investigate up to 37 respiratory pathogens. The laboratory methods used in the
32 350 study can ensure that the pathogen-specific burden of respiratory infections is measured, which is
33 351 valuable for developing and optimizing targeted interventions (e.g., vaccinations) in the future.
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35 352 NP/OP specimens collected from study participants with ARIs can be analyzed, sequenced, and
36 353 shared with other investigators for future research purposes. Fifth, our study uses the documented
37 354 vaccination registry data and electronic medical records maintained by the local health authority.
38
39 355 This will allow us to access historical exposure data at different times and various clinical outcomes
40 356 during hospitalization. Finally, to facilitate efficient data collection and management, we
41 357 customized a data information system, ARIs-IMS. Compliance of study personnel and study
42 358 participants will be significantly increased because of a decreased data collection burden and
43 359 simplified data collection procedures with ARIs-IMS. Participants are recruited through their family
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4 360 doctors who generally have a strong connection and relationship with the community that will
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6 361 support participant retention in the cohort through weekly contact and semi-annual surveys. Family
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8 362 doctors' efforts will also contribute to high compliance and cohort retention during the three years
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10 363 of study follow-up.

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12 364 This study has limitations. First, we may not identify all respiratory infections through active
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14 365 surveillance of ARI symptoms since our case definitions do not capture atypical and asymptomatic
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16 366 infections. However, we have planned another sub-cohort (the household transmission sub-cohort
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18 367 study) nested within our primary cohort. Using this sub-cohort, we can determine infection
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20 368 incidence rate and secondary attack rate, and most importantly, the proportion of participants with
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22 369 typical and asymptomatic infections.²³ Second, Pudong is a highly developed and densely populated
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24 370 region in eastern China, with high average household income and vaccination coverage levels.
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26 371 Results from this study may not be generalizable to less populated or developed regions in China.
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28 372 Third, our study participants were not randomly selected from the community. They were invited
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30 373 to participate and offered to join freely. Those who have high awareness of his/her health might be
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32 374 more likely to be included in our study, which may bias our estimates as they might tend to report
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34 375 more ARIs than a reference population. Fourth, our study sample size may not be sufficiently
35
36 376 powered to determine the burden of hospitalization or severe illnesses and explore risk factors of
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38 377 severe outcomes of influenza, RSV, and SARS-CoV-2 associated infections, nor can we determine
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40 378 the incidence of some less prevalent pathogens in the community, e.g., measles virus, bocavirus.
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42 379 Fifth, specimen test results, whether positive or negative, will be automatically communicated to
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44 380 participants through ARIs-IMS via a smartphone mini-program. Study participants can access their
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46 381 information by themselves. Since the study is observational and healthcare seeking behavior will be
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48 382 decided by the participants themselves, we cannot know how this action will impact the healthcare
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50 383 seeking behavior of participants. Finally, our laboratory methods and the type of sample specimens
51
52 384 collected may have problems for some bacterial agents (e.g., *Streptococcus pneumoniae*,
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54 385 *Haemophilus influenzae*) that commonly colonized the upper respiratory tract. Detection of these
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56 386 pathogens does not necessarily imply infection.
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387 **Collaboration**

388 This study is a collaboration between the School of Population Medicine and Public Health, Peking
389 Union Medical College and the Pudong New Area Center for Disease Control and Prevention
390 (Pudong CDC). We are open to collaboration with other researchers to use data generated in this
391 study and to use the platform to conduct further research on influenza virus, RSV, and SARS-CoV-
392 2 to develop, evaluate and optimize interventions (i.e., vaccinations and treatments). Requests of
393 collaboration should be sent to ZL (lizhongjiecdc@163.com), accompanied by a detailed protocol
394 and statistical analysis plan. After reviewing for scientific validity, we will contact requestors whose
395 proposals meet the research criteria, and for whom an exception does not apply, within one month
396 of request.

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401 **Data availability statement**

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

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411 **Contributors**

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

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4 413 and is the guarantor of the study. CY, ZL, LH and LR conceptualized and designed the study. CY,
5 414 JY, and BZ contributed equally to this work. JY, XY, YL and LX wrote the first draft. LZ, YX, YJ,
6 415 XZ, LHZ, and YW contributed to the literature search. BZ, XW, YS and LR designed laboratory
7 416 methods. XY, YL and LX wrote the statistical analysis plan. ZL, WY and CY received funding.
8 417 YL, HX, TZ, LR, BC and WY commented on and revised drafts of the manuscript. All authors
9 418 contributed to reviewing, revising and approving the final manuscript, and had final responsibility
10 419 for the decision to submit for publication.

18 420 **Competing interests**

21 421 ZL reports receiving research funding from Ministry of Science and Technology of People' s
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24 424 Commission and Health Commission of Pudong New Area District, Shanghai. All other authors
25 425 declare no competing interests.

31 426 **Patient and public involvement**

34 427 Patients and the public were not involved in this research's design, conduct, reporting, or
35 428 dissemination plans.

39 429 **Patient consent for publication**

41 430 Not required.

44 431 **Ethics approval**

46 432 This study was approved by Chinese Academy of Medical Sciences & Peking Union Medical
47 433 College's Institutional Review Board (no. CAMS&PUMC-IEC-2024-068).

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508 **Tables**509 **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.
Post-follow-up	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
	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 <i>Haemophilus influenzae type b</i> vaccines, including doses, vaccine type, and administration date

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

512 **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)

513 IQR, interquartile range.

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

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

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

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518 **Figure Legends**

519 **Figure 1.** Flow diagram of major study activities.

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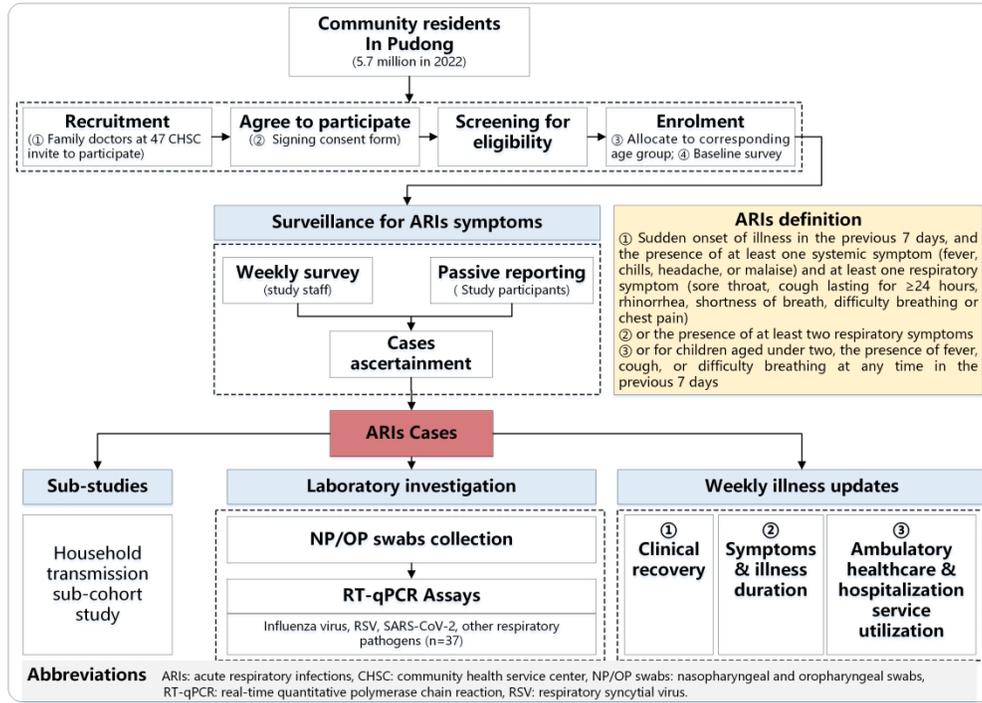


Figure 1. Flow diagram of major study activities.

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5 **1 Supplementary Appendix**
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11 **2 Title:** Cohort profile: Community Burden of Acute Respiratory Infections in Shanghai,
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14 **3 a longitudinal cohort study in respiratory pathogens, China, 2024-2027**
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20 **4 Running head:** Community burden of ARIs
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55 **13**

14 **Supplementary Table 1. Baseline Characteristics at Enrollment**
 15 **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.

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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 <i>Haemophilus influenzae type b</i> (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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17 **Supplementary Table 2. Symptoms of ARIs Monitoring Form**
 18 **(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
<i>For children under 2 years old only</i>		
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: _____		

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20 **Supplementary Table 3. Weekly Illness Updates and Clinical**
 21 **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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23 **Supplementary Table 4. Hospital Discharge Data Collection**
 24 **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							
<input type="checkbox"/> Septic shock <input type="checkbox"/> Viral pneumonia <input type="checkbox"/> Bacterial pneumonia <input type="checkbox"/> Pneumothorax							
<input type="checkbox"/> ARDS <input type="checkbox"/> Bronchiolitis <input type="checkbox"/> Respiratory failure <input type="checkbox"/> Coagulopathy							
<input type="checkbox"/> Anemia <input type="checkbox"/> Pleural effusion <input type="checkbox"/> Acute kidney injury <input type="checkbox"/> Myolysis							
<input type="checkbox"/> Bacteremia <input type="checkbox"/> Gastrointestinal bleeding <input type="checkbox"/> Encephalitis/meningitis <input type="checkbox"/> pancreatitis							
<input type="checkbox"/> Convulsion <input type="checkbox"/> Arrhythmia <input type="checkbox"/> Liver dysfunction <input type="checkbox"/> Stroke							
<input type="checkbox"/> Hyperglycemia <input type="checkbox"/> Hypoglycemia <input type="checkbox"/> Congestive heart failure <input type="checkbox"/> Heart infection							
<input type="checkbox"/> Cardiac arrest <input type="checkbox"/> Disseminated intravascular Coagulation <input type="checkbox"/> 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			

<p>4.1 Drug Name: (Please use the name of the drug. If it is a fixed compound preparation, please use the trade name.)</p> <p>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</p> <p>4.3 Route of medication: 1=oral administration, 2=intravenous injection, 3=intravenous drip, 4=intramuscular injection, 5=inhalation, 6=others</p> <p>4.4 Frequency: 1= continuous, 2= intermittent</p>							
<p>5. Patient prognosis</p> <p><input type="checkbox"/> cured</p> <p><input type="checkbox"/> improved and be discharged</p> <p><input type="checkbox"/> transferred to the other hospital</p> <p>Reasons for transfer : community rehabilitation/other (____)</p> <p><input type="checkbox"/> gave up treatment</p> <p>reasons for giving-up : economic reasons/illness exacerbation/other (____)</p> <p><input type="checkbox"/> death date of death : __/__/__(YYYY/mm/dd) death diagnosis : __</p>							
<p>6. The total expenditure of your hospitalization: _____RMB yuan</p> <p>Time of survey completion: □□□□/□□/□□:□□/□□ (YYYY/mm/dd:HH/MM)</p> <p>Name of investigator: _____</p>							

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26 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 <i>Haemophilus influenzae type b</i> (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: _____	

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

no.	Viruses	no.	Bacteria
1	Influenza A	27	<i>Bordetella holmesii</i>
2	Influenza B	28	<i>Bordetella pertussis</i>
3	Respiratory syncytial virus subtype A/B	29	<i>Chlamydomphila pneumoniae</i>
4	SARS-Cov-2	30	<i>Haemophilus influenzae</i>
5	Human Coronavirus-229E	31	<i>Klebsiella pneumoniae</i>
6	Human Coronavirus- HKU1	32	<i>Legionella pneumophila</i>
7	Human Coronavirus- NL63	33	<i>Moraxella catarrhalis</i>
8	Human Coronavirus- OC43	34	<i>Mycoplasma pneumoniae</i>
9	MERS-CoV	35	<i>Staphylococcus aureus</i>
10	SARS-CoV	36	<i>Streptococcus pneumoniae</i>
11	Adenovirus		Fungus
12	Human parainfluenza virus serotype 1	37	<i>Pneumocystis jirovecii</i>
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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