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## Burden of Whooping Cough in China (PertussisChina): Study Protocol of a Prospective, Population-based Case-control Study

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## ABSTRACT

### Introduction

Despite high vaccination coverage with three-dose diphtheria-tetanus-pertussis (DTP3), a “rise of pertussis” emerged and poses threat to public health in China. To understand the potential reasons behind this rise, precise incidence of laboratory-confirmed pertussis and characteristics of strains from rigorously conducted, prospective, population-based studies can be useful, namely evaluating or optimizing interventions, developing new interventions, and adjusting immunization schedule and recommendations.

### Methods and analysis

This paper describes the study design of a one-year, prospective, age-stratified, and population-based case-control study, including sites selection, study population, case ascertainment and enrolment, control recruitment, follow-up of case, microbiological methods, data collection, quality control activities, and statistical methods used to generate incidence estimates. During June 2021 through May 2022, we aim to enroll 1,000 suspected pertussis cases (i.e. chronic/persistent cough) and 2,000 frequency matched healthy controls in a well characterized population, which would cover approximately 2.23 million censused populations at two sites. Our primary study outcome, the laboratory-confirmed *Bordetella Pertussis* infection, will be determined by a comprehensive laboratory methods and procedures (i.e. culture, PCR, and serological tests) in both cases and controls at enrolment and during 60-day’s follow-up visits.

### Ethics and dissemination

This study has been approved by Chinese Center for Disease Control and Prevention’s Institutional Review Board. Upon completion, the results from this study will provide valuable scientific data and some new insights into the incidence, etiology, and risk factors for severe sequelae of pertussis to academic societies and the public health authorities who is currently struggling and fighting against this burdensome disease worldwide.

**Keywords:** *Bordetella pertussis*, Case-Control Studies, Incidence, China

## Summary

### Strengths and limitations of this study

- A population-based study, approximately 1,000 suspected pertussis cases and 2,000 frequency matched healthy controls will be enrolled in a well characterized population covering approximately 2.23 million censused populations at two sites of China during June 2021 through May 2022.
- A laboratory-based study, in which a comprehensive laboratory methods and procedures (i.e. culture, PCR, and serological tests) will be used to confirm our primary study outcome, i.e. *Bordetella Pertussis* infection, allowing us to specifically measure pertussis disease burden.
- A case-control study, in which, the prevalence and population attributable fraction (AF) of *Bordetella Pertussis* infection will be acquired.
- A follow-up study, in which all cases will be followed up to 60-days to collect interesting events (i.e. adverse clinical outcomes of hospitalization or death) at 2, 4 and 8 weeks after enrolment.
- The incidence of laboratory-confirmed pertussis will be acquired by age groups (children, adolescents and adults), and by settings (community, outpatient and inpatient).

## BACKGROUND

Whooping cough (pertussis) is a highly contagious respiratory disease caused by *Bordetella Pertussis*<sup>1 2</sup>. Despite a high vaccine coverage of third dose diphtheria-tetanus-pertussis vaccine (DTP3)<sup>3</sup>, the "resurgence of pertussis" in recent years has posed a great threat to global public health<sup>4-6</sup>, as well as to Chinese infants<sup>7 8</sup>. The WHO estimates that pertussis kills about 160,700 children under 5 years old worldwide each year<sup>9</sup>. In China, three types of pertussis vaccines are available till March 31, 2021, i.e. the co-purified diphtheria and tetanus toxoids and acellular pertussis (cDTaP, used for routine immunization), DTaP/Hib (Minhai Biotechnology Co., Ltd., Beijing, China)<sup>10</sup> and DTaP-IPV/Hib (Sanofi Pasteur, Lyon, France)<sup>11 12</sup>. The coverage of DTP3 remained high above 99% for children throughout the 2010s<sup>13 14</sup>, but no school-age, adolescent or adult immunization (e.g. maternal vaccination) and post-exposure prophylaxis are recommended in the country<sup>15</sup>. The reported incidence of pertussis has risen from 0.12 per 100,000 in 2013 to 2.14 per 100,000 in 2019 (Figure 1). The rise was mainly concentrated in infants less than 1 year old (103.89 per 100,000 in 2019), and the underlying causes are unknown. It was suspected that multifactorial causes might have contributed to the rise<sup>4</sup>, e.g. the change of the whole-cell pertussis vaccine to acellular vaccine in national immunization program<sup>15 16</sup>, the adaption of the bacterium to evade immunization induced by vaccine, the increased diagnosis with the introduction of the PCRs in clinical practices, the raised awareness of reporting in doctors, as well as the rise in circulation of the pathogen among older children, adolescents and adults whose immunity from vaccination or natural infection has waned<sup>17</sup>.

Most epidemiological data on pertussis in China come from a passive reporting system, the National Notifiable Infectious Disease Surveillance System (NNIDSS)<sup>18</sup>. Because of limited diagnosis and incompleteness of reporting<sup>8 19 20</sup>, underreporting is substantial in the system and the burden of pertussis remains underrecognized. Moreover, some important data such as clinical, laboratory and vaccine information are not available, which is unfavorable for evaluating the effectiveness of vaccine and implementing of other disease control and prevention programs (such as adult vaccination, diagnostic

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3 tests and post-exposure prophylaxis of pertussis). Rigorously conducted, prospective,  
4 population-based studies can be used to strengthen the NNIDSS, by providing  
5 information on the burden of laboratory-confirmed pertussis, strains distribution, risk  
6 factors for severe sequelae and case fatality, and most importantly, to assist health  
7 authority in China to investigate the reasons behind the rising incidence of pertussis  
8 and prioritize health research investments and vaccine development.  
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15 We designed the PertussisChina study, a one-year, prospective, age-stratified,  
16 population-based longitudinal cohort (active surveillance) and case-control study,  
17 which will enroll suspected pertussis patients (i.e. chronic/persistent cough) seeking  
18 healthcare in several selected participating hospitals (SHs) at two sites of China,  
19 covering approximately 2.23 million censused population. This article describes the  
20 study design, including sites selection, study population, case ascertainment and  
21 enrolment, control recruitment, follow-up of cases and controls, microbiological  
22 methods (i.e. culture, PCR, and serological tests), data collection, quality control  
23 activities, and statistical methods used to generate incidence estimates of pertussis.  
24 We then further discuss the strengths and weaknesses of the study design.  
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## 35 **METHODS AND ANALYSIS**

### 36 **Objectives of the study**

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39 The primary objective of the study is to measure the incidence of laboratory-  
40 confirmed pertussis by age groups (children, adolescents and adults), and by settings  
41 (community, outpatient and inpatient). The secondary objectives are: 1) to describe  
42 the distribution of disease severity and outcomes across age groups; 2) to describe the  
43 patterns and factors of under-detection and under-reporting of pertussis; 3) to study  
44 the carrier (colonization) status of the *B. pertussis* in the upper respiratory tract of  
45 healthy controls, and the serum levels of anti-pertussis toxin antibodies (anti-Ptx IgG)  
46 in both patients and healthy people; and 4) to create a repository of well-characterized  
47 clinical specimens and *B. pertussis* isolates that can be used in future studies.  
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## Study sites and population

### *Site Selection Criteria*

Sites are selected based on the following criteria: 1) have strong willingness to participate; 2) have capability and resources to conduct ongoing surveillance, namely staffs to facilitate specimen collection and case investigation, previous experience in disease surveillance, infrastructures to secure data collection and specimen storage or transportation; and 3) provide a full list of healthcare facilities in the area and the information of built-in hospital information system in the facilities. Currently, there are two sites in the study, including Yongcheng, Henan and Yiwu, Zhejiang (Figure 2).

### *Study population*

In 2019, Yiwu had a permanent population of 821,000 (47,000 were children under five years of age) served by 24 health care facilities. Most hospital admissions ( $\geq 80\%$  of the total number) occurred in the three large tertiary hospitals, including a children's hospital and two general hospitals; meanwhile, Yongcheng had a permanent population of 1,411,000 (94,000 were children under five years of age) served by 41 health care facilities. Most hospital admissions occurred in the five large secondary hospitals, including four general hospitals and a maternal and pediatric hospital. In total, the two sites cover a total of 2.23 million permanent population in the study area.

### *Study overview and design*

In order to achieve our study objectives, we will conduct the following study activities at the two sites from June 2021 through May 2022, including, 1) a Healthcare Utilization and Attitudes Survey (HUAS) and a census data updating to define study population (i.e. incidence denominator), so as to set up a sampling frame for the case-control study and selecting participating hospitals (i.e. SH) for case recruitment; 2) the case-control study to acquire the prevalence of *B. pertussis* infection among suspected pertussis cases and healthy controls, as well as the calculation of population



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4 attributable fraction (AF) indicating the proportion of cases that can be prevented if  
5 *B. pertussis* was totally removed from the population; and 3) the retrieval of electronic  
6 medical records (EMRs) from hospital information system to validate the number of  
7 suspected pertussis case patient (chronic/persistent cough) enrolled in SHs (i.e.  
8 incidence numerator) (Figure 3).  
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### 13 ***Defining and calibrating study population***

#### 14 ***Census data updating***

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Population census data at the two sites will be collected and updated during the study period. Population census is conducted every ten years in China and the nearest one is in 2020. However, a intermittent survey of 1% sampling of the total population would be performed to update population census data every year between the two census. We will retain the up-to-date population data from the National Bureau of Statistics. Moreover, the population birth, mortality, and population migration is recorded by the local government. We will also contact the local health bureau quarterly to access these data to give a precise estimation of population size in the two sites.

#### 39 ***Healthcare Utilization and Attitudes Surveys (HUAS)***

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HUAS will be conducted prior to recruiting cases and controls at the two sites, which will serve three purposes, 1) to set up a sampling frame for the case-control study; 2) to select SHs in which prospective enrolment of cases will be conducted; and 3) to provide estimates of the population coverage for SHs and healthcare seeking behavior weights applied in estimating pertussis incidence.

In summary, a population-based cross-sectional study, with an age-stratified sample of 3,000 children aged 0-59 mo and 6,000 adolescents/adults aged  $\geq 5$  years, will be conducted in the community of the two sites. The sample size was calculated based on: i) for children, a monthly prevalence of cough illness,  $\pi=1\%$  (estimated from the reported incidence of lower respiratory tract infection of 0.15 per child year<sup>21</sup>), allowable error ( $\delta=0.5\%$ ), significant level ( $\alpha=0.05$ ), and design effect (deff=2); ii) and for adolescents/adults, a monthly prevalence of cough illness,  $\pi=3.3\%$ <sup>22</sup>, allowable

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3 error ( $\delta=0.66\%$ ), significant level ( $\alpha=0.05$ ), and design effect ( $deff=2$ ).  
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6 A complex sampling method will be used to select survey respondents as follows.  
7 Firstly, a probability proportionate to size sampling will be used to randomly select 50  
8 clusters (e.g. communities or villages) in the site's administrative regions. At the  
9 second sampling stage in selected communities, quota sampling will be used to recruit  
10 interviewee. The quota required in each age stratum was calculated based on the age  
11 distribution of the population in the site and the number of surveys allocated to each  
12 cluster. Trained work staff will go to the selected communities to conduct face-to-face  
13 surveys at several locations (residential areas, kindergartens and children's  
14 vaccination clinics) Monday to Sunday during daytime in the study period. All residents  
15 living in the communities or villages for at least half a year prior to survey are eligible  
16 for and invited to participate in the interview. After the quota required in each age  
17 group is complete, the interviews will stop.  
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28 The following questions (Supplementary table 1 & table 2) are asked to respondents,  
29 1) the occurrence and length of cough illness in the previous month prior to survey, 2)  
30 healthcare-seeking behavior regarding the self-reported cough illness for the most  
31 recent episodes and the sources of healthcare facilities; and 3) the willingness to seek  
32 healthcare and where would they choose to visit for an assumptive cough illness.  
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38 Based on the HUAS and census data, hospitals at which over 80% of respondents in  
39 each site choose to attend when hospital admission is required will be selected as our  
40 SHs. In case healthcare providers in the site change their practice or scope of service  
41 during our study period, for example the opening of new hospitals or the  
42 establishment of new branches of existing hospitals, an abbreviated HUAS with a  
43 smaller sample of 1,000 will be administered at the middle or the end of the year  
44 during which cases are recruiting at SHs.  
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## 52 ***Case-control study***

### 53 ***Case definition of suspected pertussis***

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58 Patients will be classified as suspected pertussis cases and offered to participate if they  
59 present chronic/persistent cough defined as cough of  $\geq 2$  weeks duration with one or  
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3 more of the following symptoms, 1) paroxysmal cough; 2) inspiratory whoop; or 3)  
4 post-tussive vomiting; Or, for children aged <1 years-old, cough (regardless of cough  
5 duration) accompanied by one or more of the following symptoms, 1) apnea; 2)  
6 paroxysmal cough; 3) inspiratory whoop; or 4) post-tussive vomiting.  
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11 We will exclude patients presenting with gastroesophageal reflux, spastic bronchitis,  
12 and clearly diagnosed tuberculosis, mycoplasma/chlamydia infection, or chronic  
13 sinusitis. Adults/adolescents with a measured body temperature of  $\geq 38.5$  °C at  
14 enrolment will also be excluded.  
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### 18 **Sample Size Considerations**

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21 We planned to enroll approximately 250 suspected cases and 2 matched controls for  
22 each case in each age stratum (i.e. children under 5 years, and adolescents/adults  
23 aged  $\geq 5$  years) at each site, which would add up to approximately 1000 suspected  
24 cases and 2000 controls at the two sites. We calculated the above sample size based  
25 on a prevalence of *B. pertussis* in chronic/persistent cough of 20% (range=12%-32%)  
26 <sup>23-25</sup>, an allowable error of 5% and a significant level of 0.05. This sample size would  
27 have a 90% power (two sided  $\alpha = 0.05$ ) to detect an odds ratio (OR) of 2 between case  
28 and control for a site and age stratum-specific comparison, if the true prevalence of  
29 *B. pertussis* is 20% in case; or an OR of 3, if the true prevalence is 10%. Although the  
30 carrier state of *B. pertussis* is transient in family contacts<sup>26 27</sup>, *B. pertussis* is rarely  
31 identified in healthy people<sup>28 29</sup>, and we expected a larger OR of  $\geq 2$  in the study. This  
32 sample size means that the laboratory would process average 115 samples per week,  
33 which is feasible and acceptable for our laboratories.  
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### 46 **Case Registry, Ascertainment and Enrollment**

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48 Case registry, ascertainment and enrollment will be conducted in SHs during the study  
49 period. Clinicians or trained nurses working in selected departments of the SHs (i.e.  
50 respiratory, pediatric, infectious disease, and emergency department) will carry out  
51 case registry of suspected pertussis cases every weekday (i.e. Monday through Sunday)  
52 except national holidays. Each outpatient visits and new hospital admission seeking  
53 healthcare in above departments will be screened for the eligibility of inclusion using  
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4 the inclusion & exclusion criteria of the suspected case definition of pertussis. Eligible  
5 ones will be ascertained and recorded by study coordinator who assist with doctors in  
6 SHs in enrolling cases using a standardized case reporting form (CRF) (Supplementary  
7 Table 3). We planned to enroll all hospital admissions and the first 1-3 outpatients  
8 each week in each hospital. After obtaining informed consent, study staff will conduct  
9 enrollment interviews, and collect nasopharyngeal (N/P) and blood specimens for  
10 each enrolled case.  
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### 17 *Controls selection*

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20 At the middle of the study year when the sample size of cases reaches a half of the  
21 total, a control is recruited in community of the study sites using approximate  
22 frequency matching, based on the following criteria, 1) similar proportion in sex strata;  
23 2) similar proportion in age strata, i.e. <1 year, 1-5 years, 6-19 years, 20-64 years and  
24  $\geq 65$  years; 3) a control/case ratio of 2:1; and 4) no cough, running nose, shortness of  
25 breath, dyspnea or other respiratory symptoms at enrolment nor have a record of  
26 healthcare for respiratory disease in previous 6 months before recruitment.  
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### 33 *60-day follow-up of case*

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35 We will follow cases from the time of enrollment to a maximum time period of 60 days  
36 after enrollment. Follow-up will be conducted at 2<sup>nd</sup>, 4<sup>th</sup> and 8<sup>th</sup> weeks after  
37 enrollment, with face-to-face interview if patient is currently hospitalized, or one  
38 telephone call each follow-up time if patient is discharged from hospital. At each  
39 follow-up visit/phone call, the study staff will ask about cough or other respiratory or  
40 systemic illness symptoms in the period since the last contact. If case is still  
41 symptomatic (cough) during follow-up, they will be encouraged to visit their doctor  
42 who enrolled them in the SHs within 24h of contact. The doctor will checkup the  
43 patient's health status and collect the swab and serum samples during the visit. If an  
44 enrolled patient does not want to visit the SHs, the study staff will arrange a household  
45 visit to collect the sample in the home.  
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### 56 *Data collection from cases and controls*

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58 At enrolment, trained physicians and the study coordinator will conduct face-to-face  
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3 interview to collect socio-demographic, clinical and epidemiological data from cases  
4 and controls using a standardized CRF (Supplementary Table 4). Demographic  
5 information includes household size (defined as a group of people who share a dinner  
6 table), average household income, rural or urban residence, age, alcohol consumption  
7 and smoking exposure, and occupation etc. A clinician will also examine all cases to  
8 document clinical signs and symptoms at enrollment, including cough characteristics  
9 [duration, paroxysms, post-tussive vomiting, exacerbation at night], body  
10 temperature, respiratory rate, heart rate, seizure, apnea, and other general  
11 respiratory symptoms, non-prescription antibiotic usage before visiting the doctor,  
12 blood test results and chest x-ray examinations. Vaccination history (i.e. band, dosing,  
13 procedure and time of administration) of children aged  $\leq 14$  years is also collected by  
14 linkage of his/her individual records on immunization in the national database  
15 (Childhood Immunization Information Management System, CIIMS)<sup>30</sup> or checking of  
16 vaccination certificate.  
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18 During follow-up visits, data on any current cough or respiratory symptoms, subjective  
19 severity of illness, illness duration, functional impairment, whether medical care was  
20 sought, and outcomes since the last visits will be collected using CRFs (Supplementary  
21 Table 5). At the end of follow-up, medical charts of each hospitalized case will be  
22 reviewed by study staff to collect information on antibiotic treatment and outcomes  
23 during hospitalization (i.e. mechanical ventilation, ICU transfer, and death)  
24 (Supplementary Table 6).  
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### 29 ***The retrieval of electronic medical records and Validation of the total*** 30 ***number of suspected pertussis case*** 31

32 Since our case registry and enrolment is conducted in selective departments (i.e.  
33 respiratory, pediatric, infectious disease and emergency departments) and on  
34 workdays, it is essential that the total number of hospital admissions and  
35 outpatient/emergency department visits for chronic/persistent cough illness in the  
36 whole of hospital is retrieved from SH's EMRs, and used to validate the number of  
37 suspected pertussis case encountered in SH (i.e. the numerator of incidence).  
38 Specifically, all hospital discharges or ambulatory visits in SHs coded for diagnosis  
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3 under the International Classification of Diseases 10th Revision (ICD-10) codes A37,  
4 J00-J22, J40-J47, R05, R09.2, P22, P28.2, P28.3, P28.4, and P28.5 will be monitored on  
5 a daily basis as registry cases, by hospital departments. At the end of the month, all  
6 the records with the above diagnosis codes will be abstracted from hospital  
7 information system (HIS) of the SHs. This data will be validated by prospectively  
8 counting data in the selective departments that conduct case enrolment to make a  
9 precise estimate of the total number of chronic/persistent cough illness outcomes in  
10 the studied population. Namely, through linking and comparing between the number  
11 of registered cases and the number of suspected pertussis case patients enrolled in  
12 the selected departments, we will calculate the  $W_{case}$ . With this  $W_{case}$ , we will narrow  
13 down the ICD-based EMRs records to the total number of suspected pertussis cases in  
14 SHs.  
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## 27 **Laboratory investigation**

### 28 ***Specimen collection and transport***

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32 When patients meet our suspected pertussis case definition or are recruited controls,  
33 they, as well as symptomatic (cough) cases during follow-up contacts, will be sampled  
34 within 24 hours. Physicians or nurses in SHs will be trained to collect nasopharyngeal  
35 swabs (N/P) and whole blood sample. Dacron or nylon swab will be used to collect N/P  
36 specimen to facilitate culture and PCR tests for *B.pertussis*<sup>31</sup>. Collected swab  
37 specimens will be plated onto selective agar or placed in transport medium (Charcoal  
38 Agar, Thermo Fisher Scientific Inc.) immediately after sampling at the SHs. Whole  
39 blood without adding any anticoagulants (>4ml for participants aged 5 years and older,  
40 and  $\geq 2$  ml for children aged <5 years) will be collected, and centrifuged to separate  
41 serum within 24h of collection. All collected swab and sera samples will be transported  
42 to the central laboratory of Chinese Center for Disease Control and Prevention (China  
43 CDC), using a cold box to maintain a temperature of 4°C. During transportation,  
44 samples are packaged and transported in accordance with the provision of  
45 International Civil Aviation Organization (ICAO) document Doc9284 and UN3373  
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### ***Processing and storage of specimen***

Upon arrival at the laboratory of China CDC, swab samples will be processed and prepared into three aliquots of swab supernatant, so will serum samples be. One of these aliquots will be analyzed and the other two aliquots will be kept for future analyses. All aliquots will be stored at -70°C temperature until the time of analysis.

### ***Laboratory testing***

In the laboratory of China CDC, Charcoal Agars will be cultured to isolate *B. pertussis* using standard method recommended by China CDC<sup>32</sup> and World Health Organization<sup>33</sup>. Swab supernatant will be analyzed for *B. pertussis*, *B. parapertussis*, *B. bronchiseptica* and *B. holmesii* using polymerase chain reaction (PCR) as recommended by US CDC<sup>34 35</sup>. Sera samples that have a minimum volume of  $\geq 1$  ml will be tested for Anti-Ptx IgG titer using a commercially available diagnostic kit (Virion\Serion, Wurzburg, Germany) according to the manufacturer's recommendations. To validate our laboratory methods and testing results, external quality assurance testing will be conducted to reach agreements with a reference laboratory on *Bordetellae* prior to study start. For serology testing, we use standard from the National Institute for Biological Standards and Control, London, UK, ([https://www.nibsc.org/products/brm\\_product\\_catalogue/detail\\_page.aspx?catid=18/146](https://www.nibsc.org/products/brm_product_catalogue/detail_page.aspx?catid=18/146)); and for PCR assays, the Wisconsin State Laboratory of Hygiene, Wisconsin, U.S. (<http://www.slh.wisc.edu/proficiency/training-and-competency/>).

Suspected pertussis cases and controls that have *B. pertussis* Isolated, positive tests of swabs in any of samples collected during enrolment and follow-up, or have a 2-fold or greater rise in anti-PT IgG antibody between sequential sera samples with at least one time point higher than 40 IU/ml of serum titer would be considered laboratory-confirmed pertussis.

### ***Data flow, management and analysis***

The data collected in the study are centrally managed at China CDC, using an online data platform (<http://eddc.chinacdc.cn/dap/>). The completed CRFs will be entered



into the information system by local study staff at the two sites and uploaded to data server through encrypted transmission via a Virtual Private Network set up by China CDC. The entered records are regularly checked for completeness, consistency, and logical errors by data manager and the site's co-principle investigator who is responsible for authorization, integrity, security, and backup of database during data collection.

### **Statistical analysis**

The collected data processing and key indicators based on which we calculate incidence are shown in figure 4. We will calculate the incidence of pertussis by age group and by settings with the following formula.

$$\text{Hospitalization incidence rate} = \sum \frac{S_i^{\text{inpatient}} \times W_i^{\text{case}} \times AF_i}{N_i \times W_i^{\text{cover}} \times W_{\text{sampling}} \times C_i}$$

$$\text{Outpatient incidence rate} = \sum \frac{S_i^{\text{outpatient}} \times W_i^{\text{case}} \times AF_i}{N_i \times W_i^{\text{cover}} \times W_{\text{sampling}} \times C_i}$$

$$\text{Community incidence rate} = \frac{\text{Outpatient incidence rate}}{r_i}$$

Where,  $S_i^{\text{inpatient}}$  and  $S_i^{\text{outpatient}}$  indicates the registered number of inpatients and outpatient visits of cough illnesses at age group  $i$ , as obtained from HIS.  $W_i^{\text{case}}$  is the weight used to adjust  $S_i^{\text{inpatient}}$  and  $S_i^{\text{outpatient}}$  to meet our case definition in age group  $i$ . This weight is calculated from the results of the prospective case-control study as a ratio of suspected pertussis cases over registered cases of cough illnesses at the selective departments of SHs.  $W_{\text{sampling}}$  is the weight used to adjust holidays in which we do not conduct active case enrollment (we only conduct case enrollment in weekdays, not holidays). It is calculated as the total days that we conduct active study divided by 365.25.  $N_i$  is the population size in age group  $i$  in census year 2020.  $W_i^{\text{cover}}$  is the weight used to adjust catchment population overlapping between participating hospitals from HUAS in age group  $i$ . It is calculated as the ratio of inhabitants who actually have reported seeking medical care in the participating hospitals for the last episodes of their cough illness over the inhabitants who have the willingness of healthcare-seeking in the participating hospitals, as obtained from the HUAS study.  $C_i$  is the proportion of population covered by participating hospitals in age group  $i$ , as



measured in the HUAS study. It is calculated as the proportion of residents who report having the willingness of healthcare-seeking in the participating hospitals over the total no. of residents responded.  $r_i$  is the proportion of community residents reporting seeking health-care for their most recent episode of cough illnesses in age group  $i$  as measured in the HUAS study.  $AF_i$  is the population attributable fraction of chronic/persistent cough due to *B. pertussis* infection in age group  $i$ , calculated based on case-control study using unconditional logistic regression model, as follows:

$$\log_e(OR) = \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3 + \dots + \beta_k x_k$$

$$OR = \exp(\beta_k)$$

$$AF_i = \Pr(Bordetella pertussis | Chronic cough) \left(1 - \frac{1}{OR}\right)$$

Note:  $\Pr(Bordetella pertussis | Chronic cough) = P_i$  is the prevalence of *B. pertussis*, calculated by dividing the number of laboratory-confirmed pertussis with the total number of chronic/persistent cough tested.  $x_1, x_2, x_3, \dots, x_k$  are variables associated with the occurrence of chronic/persistent cough, including the presence of *B. pertussis* and other social and environmental factors significant at  $p < 0.1$  in univariate analysis. OR is the odds ratio.

The 95% CI of incidence is calculated with bootstrap method with 1000 replications. Besides incidence estimates, we will also explore factors associated with severe pertussis (defined as a composite outcome of death, sepsis, invasive ventilation and Intensive Care Unit transfer), by using multivariable logistic regression. Factors significantly associated with severe pertussis at  $p < 0.1$  in univariate analysis will be included in the model. The median age of children with pertussis will be calculated by type of vaccinee, and factors predicting the age of pertussis breakthrough among children who had received DTP vaccination early in their life will be also studied by using Cox proportional hazards regression models.

## ETHICS AND DISSEMINATION

This study is designed an observational study. The risk of harm is minimal and adverse medical events are not anticipated from the procedures involved in the study. The

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3 study protocol, CRF, and consent form have been sent to and approved by China CDC's  
4 Institutional Review Board (reference no. ICDC-2019012).  
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7 The primary risk to participants is the loss of confidentiality. To help maintain  
8 confidentiality, all study investigators will sign a confidentiality agreement and receive  
9 appropriate ethics training. All interviews will be conducted at the study investigator's  
10 office, and signed consent forms and completed survey forms will be locked in a secure  
11 file cabinet at the end of each day. A very limited number of trained study staff can  
12 have the key to the locked file cabinets. Participation in every aspect of the study will  
13 be voluntary, and for all new data collection, participants will be asked to provide  
14 written informed consent. Besides, collection of specimens may cause mild discomfort  
15 to the subject during the procedure, especially drawing blood from young children. To  
16 minimize invasive procedures during sample collection, swab and blood specimens  
17 will be collected by aseptic technique and we encourage the use of leftover sera during  
18 routine medical care at the time point of enrolment.  
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30 As a benefit of participating in the study, participants with pertussis will receive senior  
31 doctor consultation during treatment on how to limit transmissions among family  
32 members and co-workmates; Patients enrolled in the study will have access to  
33 antibiotic susceptibility testing results should they have *B. pertussis* isolates acquired.  
34 This will give a guide on empirical antibiotic usages for physicians; moreover, the data  
35 generated in the study will be valuable to determine the burden of pertussis and  
36 explore risk factors for illness attributable to severe pertussis in children as well as  
37 adolescents/adults, which can be used by public health departments, healthcare  
38 providers and scientific group in China to inform policies making, implement disease  
39 control and prevention (i.e. vaccination) and improve patient care, both at the sites  
40 level and national level. In general, the minimal risks associated with physical  
41 discomfort during blood and N/P sample collection are offset by the great benefit  
42 associated with the study's ability to inform pertussis prevention and control  
43 strategies in China.  
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## 55 56 57 **DISCUSSION** 58

59 PertussisChina is an innovative and a pilot of a laboratory-based and population-based  
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3 active surveillance platform for vaccine-preventable bacterial diseases (VPBD) in China,  
4 which endeavors to establish a network of laboratories and hospitals using  
5 comparable and unified standards to provide up-to-date disease burden estimates  
6 and disease determinants for evaluating, prioritizing and optimizing the use of  
7 vaccines and for the development of new interventions against bacterial infections in  
8 the country. Pertussis is the first one of the several bacterial infections that we are  
9 planning to take this approach. In 2019, pertussis was one of the top ten diseases with  
10 highest burden in children younger than 10 years<sup>36</sup>. In response to the changing  
11 epidemiology of pertussis in China<sup>7 8 37 38</sup>, the 2019 summon of the National  
12 Immunization Advisory Committee submitted a motion to its members urging the  
13 modification of the current immunization schedule of pertussis vaccine administered  
14 at 3, 4, 5 and 18-24 months<sup>39</sup>, to vaccinate children at 2, 4, 6 and 18-24 months instead  
15 and to add a 5<sup>th</sup> booster dose at 4-6 years of age. To provide up-to-date evidence on  
16 disease burden of pertussis, this study will focus on age-specific incidence based on  
17 laboratory confirmation and will fill the data gaps on prospectively and actively  
18 collected incidence data and key information on illness severity and outcomes. We are  
19 expecting that data from this study can be served as background information  
20 augmenting NIDSS to inform NIAC's recommendations on children vaccination and  
21 further quantify the benefit of adolescent/adult vaccination to protect infants from  
22 severe outcomes in future. There are several strengths of the study.

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41 In this one year study, we will enroll suspected chronic/persistent cough patients (for  
42 infants aged less than 1 year, cough regardless of duration) from health care facilities  
43 in two sites of China, covering a censused population of 2.23 million. The catchment  
44 population utilizing health-care services at the SHs are well characterized and defined  
45 by HUAS, providing an unbiased estimates of age-stratified total person-times  
46 observed in the cohort. The prevalence of cough in regarding of illness duration and  
47 proportion of people who do not seek healthcare are measured retrospectively by  
48 HUAS. Thus by comparing between data generated from HUAS in community and case  
49 registry in SHs, we will able to measure incidence by settings (i.e. community,  
50 outpatient and inpatient), especially those in communities whose symptoms are mild  
51 or atypical after the waning of vaccine-induced immunity or those no healthcare are  
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3 sought<sup>2</sup>. Besides, all hospitalizations suspected of pertussis will be actively searched  
4 and prospectively enrolled in a timely manner, serving as a complete and  
5 and representative sample of pertussis occurred in the interested population that would  
6 have induced minimal selection bias. As for milder cases in ambulatory settings,  
7 sampling of patients with chronic/persistent cough in outpatient setting to conduct  
8 laboratory investigation is preferred. Misclassification of cases or recall bias will be  
9 minimized by the complex laboratory procedures (i.e. culture, PCR, and serology  
10 combined), unified data collection tools (i.e. CRFs) and data collection process, i.e. the  
11 60-day of follow-up during which interesting events (e.g. 2-fold titer raising) will be  
12 closely monitored by sequential sera samples. Using laboratory-confirmed pertussis  
13 as the outcome will allow us to specifically measure pertussis disease burden. To  
14 account for asymptomatic carriage of *B. pertussis*, we will recruit healthy control to  
15 investigate the proportion of population carrying *B. pertussis* in their upper respiratory  
16 tract and sero-positivity, which could be useful for calculating population attributable  
17 fraction (AF) to adjust rate estimates. In addition, the prospective cohort will provide  
18 valuable follow-up data related to risk factors for severe illness (i.e. adverse clinical  
19 outcomes of hospitalization or death). Collection of the vaccination history (including  
20 band, dosing, procedure and time of administration) from study participants will help  
21 explore the breakthrough rates of *B. pertussis* infection among different type of  
22 vaccinee, by linkage of study subjects  $\leq 14$  years old with his/her individual records on  
23 immunization in the national database. Finally, we will abstract EMR data from  
24 hospital information system, which serves as a complete and accurate record of cough  
25 illness outcomes occurred in SHs. The retrospectively collected EMR data will be  
26 validated by prospectively counting cases eligible for inclusion at selective  
27 departments of SHs on a daily basis. Using data from the EMR will allow us to  
28 determine the size of outpatient and emergency department visits for cough illness in  
29 the studied population. For most of adults and fully immunized children and  
30 adolescents, their illness is generally mild and is most likely to be encountered at the  
31 ambulatory settings in which the diagnostic capacity is generally lacking.

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Aside from acquiring incidence estimates, the prevalence and distribution of *B. pertussis* strains circulating in the population will be determined and characterized,

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3 which are reported to be evolving under the selection pressure from both vaccine and  
4 antibiotics in previous studies<sup>40</sup> and are important data for the development of novel  
5 vaccine or new therapeutics in the country. For example, as a benefit of the study, we  
6 will create a representative national and well characterized repository of strains and  
7 specimens that can be shared with other investigators for future research, the main  
8 antigenic and genotypic features of *B. pertussis* will be characterized by sequencing or  
9 other bio-molecular methods.  
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16 We realized that there are several limitations worthy of note in our study. Firstly, we  
17 will not identify all pertussis that occur in our studied population since our case  
18 definition will not capture atypical and asymptomatic manifestations associated with  
19 *B. pertussis* infection. For example, previous studies showed that about 17.4%  
20 children<sup>41</sup> and 20% adolescents/adults<sup>42</sup> with *B. pertussis* infection had a cough  
21 duration less than 3 weeks, and other symptoms/signs used in the case definition, like  
22 spasmodic cough (63%), post-tussive vomiting (42%) and whoops (8%), were  
23 infrequently presented in adults<sup>43</sup>, which will make incidence underestimated. It is  
24 argued that no symptom is sufficiently predictive for diagnosing pertussis<sup>44</sup> and there  
25 was no case definition that has been proposed for purpose of studying disease burden  
26 of pertussis. After balancing at the sensitivity and specificity of case definition  
27 commonly recommended by WHO, the U.S. and others<sup>45-47</sup> and the available  
28 laboratory capacity and resources in the study, we finally adopted the current case  
29 definition that can be used to facilitate comparison of results between studies and  
30 countries. Second, our study period is a little short. Since pertussis has showed a cyclic  
31 pattern and peaked every 3-5 years<sup>2 48</sup>, our study will not capture this feature.  
32 Moreover, our study are going to recruit cases in 2021-2022, right after COVID-19  
33 pandemic. As the epidemiology of many respiratory infections have been reported  
34 changing as a result of widely implementation of nonpharmaceutical interventions  
35 (e.g. wearing masks, social distancing, and personal health protection)<sup>49 50</sup> and the  
36 detained coverage of vaccines used in Expanded Program on Immunization during the  
37 pandemic<sup>51</sup>. The impacts of COVID-19 outbreak on incidence estimates of pertussis  
38 are not foreseeable in the study. Future studies are upcoming depending on the  
39 results of this pilot. Finally, China is a big country with large variations in population  
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3 density and across different climate, geographic and economic regions. Although we  
4 have paid careful attention to variables, like DTP3 vaccine coverage, childhood  
5 mortality and health-care delivery pattern when selecting study sites, regions with the  
6 highest and lowest reported incidence of pertussis are generally not included. This  
7 may also influence the generalizability of the incidence estimates to extrapolate to  
8 other regions.  
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15 In summary, PertussisChina is an innovative study that uses unified protocol to  
16 generate up-to-date high-quality incidence data on pertussis. The study design can  
17 secure the precision of data collection and provide insights into the prospectively  
18 conducted studies that designed to augment passive surveillance in countries where  
19 resources is limited and data is currently lacking. When completed, the results coming  
20 out this study will provide valuable scientific data on the incidence, etiology, and risk  
21 factors for severe sequelae of pertussis to academic societies and the public health  
22 authorities, who is currently struggling and fighting against this burdensome disease  
23 worldwide.  
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## 32 **Contributors**

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34 ZS is the lead and corresponding authors who conceptualized and designed the protocol and critically  
35 revised the manuscript. JY, HH and YZ took part in design of the protocol, wrote the first draft and  
36 contributed equally to this work. JX, LX, YG and ZC participated in the design of the protocol and wrote  
37 the statistical analysis plan. CC, XZ, YZ, WT and QZ commented on and revised drafts of the manuscript.  
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39 All authors contributed to reviewing, revising, and approving the final manuscript.  
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50 Association and the Sanofi Pasteur.  
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## 56 **Competing interests**

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58 The authors declare that they have no competing interests.  
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## Patient and public involvement

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

## Patient consent for publication

Not required.

## Ethics approval

This study has been approved by Chinese Center for Disease Control and Prevention's Institutional Review Board (reference no. ICDC-2019012).

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## Figure Legends

**Figure 1. Incidence of reported pertussis from NNIDSS, China, 1952-2019.** Abbreviations: DTwP, combined diphtheria, tetanus toxoid and whole-cell pertussis vaccine; cDTaP, co-purified diphtheria, tetanus toxoid and acellular pertussis vaccine; National Notifiable Infectious Disease Surveillance System (NNIDSS).

**Figure 2. Location and population size of study sites included in PertussisChina study**

**Figure 3. Flow diagram of major study activities**

**Figure 4. Data flow chart and key indicators used to calculate incidence of pertussis**

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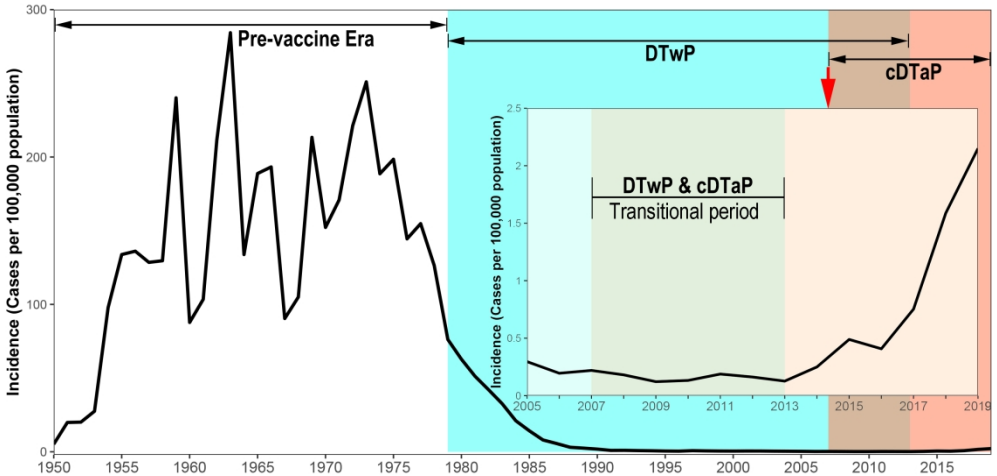


Figure 1. Incidence of reported pertussis from NNIDSS, China, 1952-2019

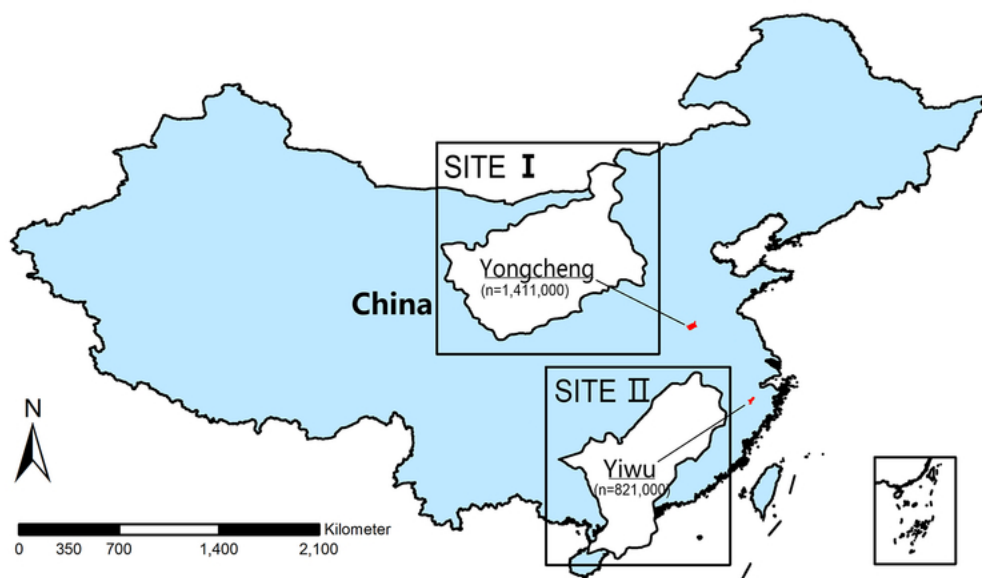


Figure 2. Location and population size of study sites included in PertussisChina study

63x38mm (300 x 300 DPI)

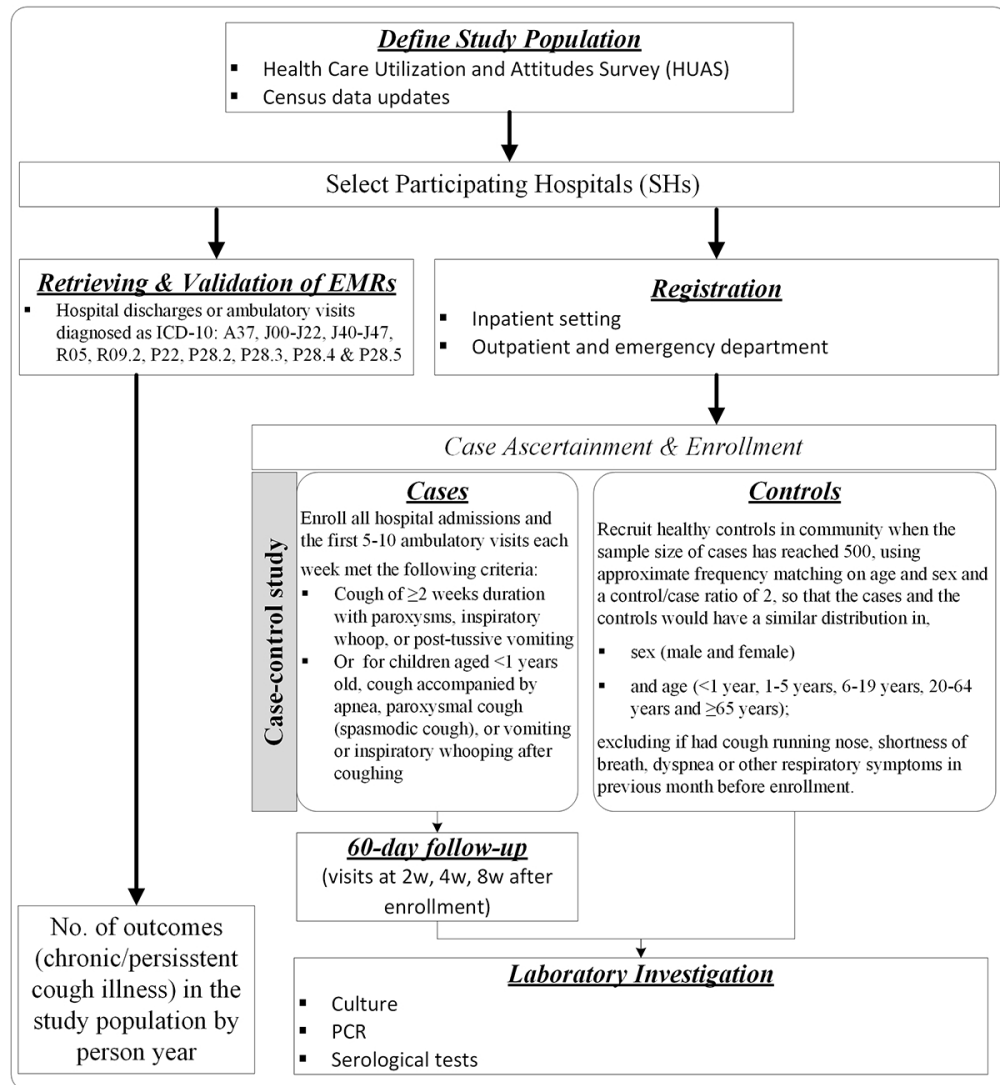


Figure 3. Flow diagram of major study activities

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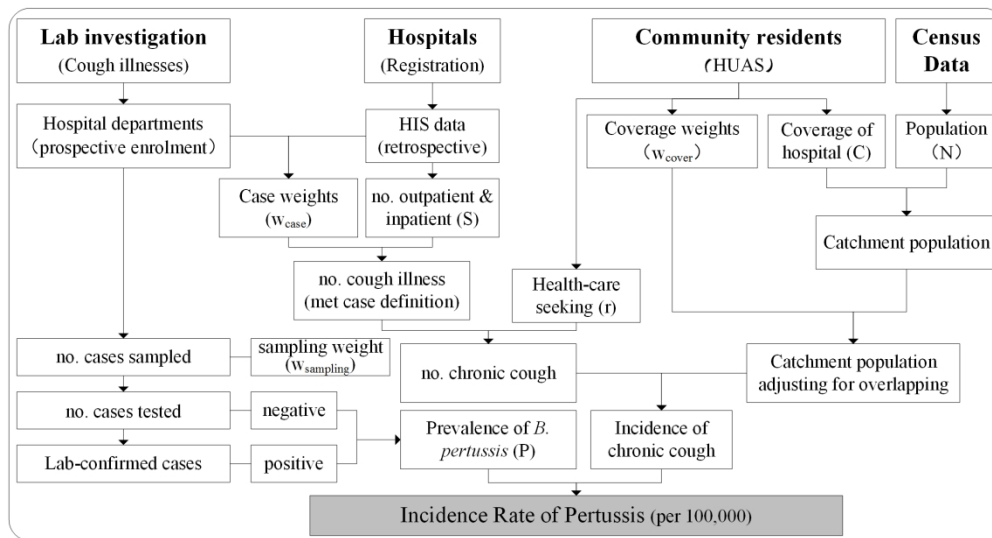


Figure 4. Data flow chart and key indicators used to calculate incidence of pertussis

187x100mm (300 x 300 DPI)



## Supplementary Appendix

**Title:** Burden of Whooping Cough in China (PertussisChina): Study Protocol of a Prospective, Population-based Case-control Study

**Running head:** PertussisChina Study, 2020

### Tables & Forms

- Supplementary Table 1. Survey questionnaire for healthcare utilization and attitudes survey of cough illness among children under 5 years old
- Supplementary Table 2. Survey questionnaire for healthcare utilization and attitudes survey of cough illness among persons aged 5 years and older
- Supplementary Table 3. Case screening and ascertainment form
- Supplementary Table 4. Baseline information of case & control (CRF—T0)
- Supplementary Table 5. Follow-up information of case (CRF—T2w/T4w/T8w)
- Supplementary Table 6. Outcome of case at the end of follow-up (CRF—Tend)

**Supplementary Table 1.** Survey questionnaire for healthcare utilization and attitudes survey of cough illness among children under 5 years old

Greetings! We are the staff of Center for Disease Control and Prevention. We sincerely invite you to participate in this questionnaire survey. The purpose of the survey is to study the utilization and attitudes of community residents towards health-care services of chronic/persistent cough, so that we can better serve you in the future.

This survey is anonymous. Your answers to these questions are kept confidential. You can choose whether to participate in the survey voluntarily or not. Refusal of the survey will not have any adverse consequences on you personally and your children. If you agree to the participate, please read each question carefully and fill in the answer on your own. Thank you for your support and cooperation!

**Part I. Basic Information**

- 1.1 Site: \_\_\_\_\_ Site ID: \_\_\_\_\_
- 1.2 Your length of time (years & months) living in the site (e.g. Yiwu or Yongcheng):  
 less than 6 months     six months and over
- 1.3 Current address: \_\_\_\_\_ county \_\_\_\_\_ street \_\_\_\_\_ community/village
- 1.4 Type of respondents in relation to the studied subject/children:  
 mother     father     grandma/grandpa     others \_\_\_\_\_
- 1.5 Date of Birth:    □□□□/□□/□□ (yyyy/MM/dd)
- 1.6 Gender:     Male     Female
- 1.7 Ethnicity:     Han     others \_\_\_\_\_
- 1.8 Did your child attend school?     yes     no
- 1.9 Your occupation (of the respondent who answered the question):  
 students     housework or unemployed     retired people     commercial & service sector workers     food handler or employees of food industry  
 specialists, including teacher, medical personnel and workers     agriculture, forestry, animal husbandry and fishery workers     others \_\_\_\_\_

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4 1.10 Your educational attainment (of the respondent who answered the question).

5 primary school or illiteracy middle school high school

6  
7 technical secondary school college level and above

8  
9 1.11 Including yourself, there are \_\_\_\_\_members in your family (defined as those  
10 who shared the same dining table in the house)?

11 Of which, there are \_\_\_\_\_children under five years old.

12  
13 1.12 Is there any smokers or ex-smokers in your family?  yes  no

14  
15  
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17  
18 **Part II. self-perceived illness and health-care seeking behavior**

19  
20  
21 2.1 Did your children experienced cough during the past one month prior to our  
22 interview?  no  yes

23  
24 2.1.1 If yes, how long did the cough last?

25  <1 week  1-2 weeks  3-4 weeks  5-8 weeks  >8 weeks

26  
27 2.1.2 If yes, what is the clinical characteristics of the last episode of cough?

28 paroxysmal cough vomiting after coughing whooping cough

29 cough worsening during the night vomiting after coughing

30 productive cough with large amount of sputum dry cough

31 cough with blood in sputum others\_\_\_\_\_

32  
33 2.1.3 If yes, what is the other concomitant symptoms?

34 productive cough running nose fever (body temperature  $\geq 37.2^{\circ}\text{C}$ )

35 belching acid reflux irritable and crying vomiting headache

36 tachypnea earache sore throat dyspnea abdominal pain

37 arthralgia chest pain myalgia fatigue lethargy

38 burn after sternum without any other discomfort others\_\_\_\_\_

39  
40 2.1.4 If yes, what do you think is the most probable cause of your cough?

41 respiratory tract infection inhalation of foreign objects in the respiratory tract

42 COPD exacerbation asthma exacerbation recurrent tuberculosis

43 chronic cardiopulmonary disease lung cancer inhalation of cold air

44 chronic bronchitis bronchiectasis I don't know others\_\_\_\_\_

2.2 Did your child visit a doctor or seek healthcare during the last episode of cough?

no     yes

2.2.1 If yes, where did your child see a doctor?

(For Yiwu site, please select the following)

- The Fourth Affiliated Hospital Zhejiang University School of Medicine
- Yiwu Fuyuan Hospital    Yiwu Maternal and Children's Hospital
- Yiwu Central Hospital    Yiwu Traditional Chinese Medicine Hospital
- Yiwu Tianxiang Medical Group Dongfang Hospital
- Chouzhou Hospital of Yiwu    The Second People's Hospital of Yiwu
- The Third People's Hospital of Yiwu    Yiting township Health Center
- Suxi Township Health Center    Beiyuan Community Health Center
- Shangxi Township Health Center    Dachen Township Health Center
- Houzhai Community Health Center    Chi'an Township Health Center
- Chengxi Community Health Center    Niansanli Community Health Center
- Yiwu Huashan Rehabilitation Hospital    Jiangdong Community Health Center
- Futian Community Health Center    Yiwu Dermatology Hospital
- Zhejiang Children's Hospital    Village clinics or private clinics
- others\_\_\_\_\_

(For Yongcheng site, please select the following)

- Yongcheng People's Hospital    Yongcheng Central Hospital
- Yongmei Group General Hospital    Henan Shenhua Group General Hospital
- Yongcheng Maternal & Child Health Hospital    Yucheng Township Health Center
- Chenji Township Health Center    Gaozhuang Township Health Center
- Yongcheng Mangdang Hospital    Lizhai Township Health Center
- Yongcheng Second People's Hospital    Liuhe Township Health Center
- Yanji Township Health Center    Dawangji Township Health Center
- Longgang Township Health Center    Shunhe Township Health Center
- Peiqiao Township Health Center    Huaihai Community Health Center
- Huangkou Township Health Center    Maqiao Township Health Center
- Jiangkou Township Health Center    Houling Township Health Center

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4 Chenguanzhuang Township Health Center  Taiqiu Township Health Center  
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6 Wolong Township Health Center  Huicun Township Health Center  
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8 Yongcheng Traditional Chinese Medicine Hospital  
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10 Shibali Township Health Center  Xuehu Township Health Center  
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12 Mamu Township Health Center  Xinqiao Township Health Center  
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14 Xunyang Township Health Center  Shuangqiao Township Health Center  
15  
16 Yongcheng Jiangkou Yongji Hospital  Miaoqiao Township Health Center  
17  
18 Yongcheng Tuberculosis Hospital  Tiaohe Township Health Center  
19  
20 Zhongyuan Road Community Health Center  Yongcheng Wuguanke Hospital  
21  
22 Mangshan Township Health Center  Luanhu Township Health Center  
23  
24 others\_\_\_\_\_

26  
27 2.2.1 If no, why did not your child see a doctor?

- 28  
29 Symptoms are mild, no need to see a doctor  
30  
31 The hospital is too far from home and the transportation is inconvenient  
32  
33 Drugs purchased in pharmacies Distrust the doctor  
34  
35 Unaffordable high medical expenses  
36  
37 Hospital facilities and environment were poor  
38  
39 others\_\_\_\_\_

40  
41 2.3 Was your child hospitalized for the last episode of cough?  no  yes

42  
43 2.3.1 If yes, where was your child hospitalized?

44  
45 (For Yiwu site, please select the following)

- 46 The Fourth Affiliated Hospital Zhejiang University School of Medicine  
47  
48 Yiwu Fuyuan Hospital Yiwu Maternal and Children's Hospital  
49  
50 Yiwu Central Hospital Yiwu Traditional Chinese Medicine Hospital  
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52 Yiwu Tianxiang Medical Group Dongfang Hospital  
53  
54 Chouzhou Hospital of Yiwu The Second People's Hospital of Yiwu  
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56 The Third People's Hospital of Yiwu Yiting township Health Center  
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58 Suxi Township Health Center Beiyuan Community Health Center  
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4  Houzhai Community Health Center  Chi'an Township Health Center  
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6  Chengxi Community Health Center  Niansanli Community Health Center  
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8  Yiwu Huashan Rehabilitation Hospital  Jiangdong Community Health Center  
9  
10  Futian Community Health Center  Yiwu Dermatology Hospital  
11  
12  Zhejiang Children's Hospital  Village clinics or private clinics  
13  
14  others \_\_\_\_\_

15 (For Yongcheng site, please select the following)

- 16  
17  Yongcheng People's Hospital  Yongcheng Central Hospital  
18  
19  Yongmei Group General Hospital  Henan Shenhua Group General Hospital  
20  
21  Yongcheng Maternal & Child Health Hospital  Yucheng Township Health Center  
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23  Chenji Township Health Center  Gaozhuang Township Health Center  
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25  Yongcheng Mangdang Hospital  Lizhai Township Health Center  
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27  Yongcheng Second People's Hospital  Liuhe Township Health Center  
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29  Yanji Township Health Center  Dawangji Township Health Center  
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31  Longgang Township Health Center  Shunhe Township Health Center  
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33  Peiqiao Township Health Center  Huaihai Community Health Center  
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35  Huangkou Township Health Center  Maqiao Township Health Center  
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37  Jiangkou Township Health Center  Houling Township Health Center  
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39  Chenguanzhuang Township Health Center  Taiqiu Township Health Center  
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41  Wolong Township Health Center  Huicun Township Health Center  
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43  Yongcheng Traditional Chinese Medicine Hospital  
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45  Shibali Township Health Center  Xuehu Township Health Center  
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49  Xunyang Township Health Center  Shuangqiao Township Health Center  
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51  Yongcheng Jiangkou Yongji Hospital  Miaoqiao Township Health Center  
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53  Yongcheng Tuberculosis Hospital  Tiaohe Township Health Center  
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55  Zhongyuan Road Community Health Center  Yongcheng Wuguanke Hospital  
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57  Mangshan Township Health Center  Luanhu Township Health Center  
58  
59  others  
60

### Part III. Attitudes towards health-care utilization

(Next, we will ask some questions about the actions you might take under some hypothetical situations that do not need to actually happen.)

3.1 If your child keeps coughing for 2 weeks but does not get better, and you have decided to see a doctor, which one of the following medical institutions would you choose to go?

(For Yiwu site, please select the following)

- The Fourth Affiliated Hospital Zhejiang University School of Medicine
- Yiwu Fuyuan Hospital    Yiwu Maternal and Children's Hospital
- Yiwu Central Hospital    Yiwu Traditional Chinese Medicine Hospital
- Yiwu Tianxiang Medical Group Dongfang Hospital
- Chouzhou Hospital of Yiwu    The Second People's Hospital of Yiwu
- The Third People's Hospital of Yiwu    Yiting township Health Center
- Suxi Township Health Center    Beiyuan Community Health Center
- Shangxi Township Health Center    Dachen Township Health Center
- Houzhai Community Health Center    Chi'an Township Health Center
- Chengxi Community Health Center    Niansanli Community Health Center
- Yiwu Huashan Rehabilitation Hospital    Jiangdong Community Health Center
- Futian Community Health Center    Yiwu Dermatology Hospital
- Zhejiang Children's Hospital    Village clinics or private clinics
- others\_\_\_\_\_

(For Yongcheng site, please select the following)

- Yongcheng People's Hospital    Yongcheng Central Hospital
- Yongmei Group General Hospital    Henan Shenhua Group General Hospital
- Yongcheng Maternal & Child Health Hospital    Yucheng Township Health Center
- Chenji Township Health Center    Gaozhuang Township Health Center
- Yongcheng Mangdang Hospital    Lizhai Township Health Center
- Yongcheng Second People's Hospital    Liuhe Township Health Center
- Yanji Township Health Center    Dawangji Township Health Center

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5  Peiqiao Township Health Center    Huaihai Community Health Center  
6  Huangkou Township Health Center    Maqiao Township Health Center  
7  Jiangkou Township Health Center    Houling Township Health Center  
8  Chenguanzhuang Township Health Center    Taiqiu Township Health Center  
9  Wolong Township Health Center    Huicun Township Health Center  
10  Yongcheng Traditional Chinese Medicine Hospital  
11  Shibali Township Health Center    Xuehu Township Health Center  
12  Mamu Township Health Center    Xinqiao Township Health Center  
13  Xunyang Township Health Center    Shuangqiao Township Health Center  
14  Yongcheng Jiangkou Yongji Hospital    Miaoqiao Township Health Center  
15  Yongcheng Tuberculosis Hospital    Tiaohe Township Health Center  
16  Zhongyuan Road Community Health Center    Yongcheng Wuguanke Hospital  
17  Mangshan Township Health Center    Luanhu Township Health Center  
18  others \_\_\_\_\_

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33 3.2 If the doctor recommends that your child be hospitalized, which one of the  
34 following medical institutions would you choose?  
35

36  
37 (For Yiwu site, please select the following)

- 38  The Fourth Affiliated Hospital Zhejiang University School of Medicine  
39  Yiwu Fuyuan Hospital    Yiwu Maternal and Children's Hospital  
40  Yiwu Central Hospital    Yiwu Traditional Chinese Medicine Hospital  
41  Yiwu Tianxiang Medical Group Dongfang Hospital  
42  Chouzhou Hospital of Yiwu    The Second People's Hospital of Yiwu  
43  The Third People's Hospital of Yiwu    Yiting township Health Center  
44  Suxi Township Health Center    Beiyuan Community Health Center  
45  Shangxi Township Health Center    Dachen Township Health Center  
46  Houzhai Community Health Center    Chi'an Township Health Center  
47  Chengxi Community Health Center    Niansanli Community Health Center  
48  Yiwu Huashan Rehabilitation Hospital    Jiangdong Community Health Center  
49  Futian Community Health Center    Yiwu Dermatology Hospital



Zhejiang Children's Hospital  Village clinics or private clinics

others \_\_\_\_\_

(For Yongcheng site, please select the following)

Yongcheng People's Hospital  Yongcheng Central Hospital

Yongmei Group General Hospital  Henan Shenhua Group General Hospital

Yongcheng Maternal & Child Health Hospital  Yucheng Township Health Center

Chenji Township Health Center  Gaozhuang Township Health Center

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Huangkou Township Health Center  Maqiao Township Health Center

Jiangkou Township Health Center  Houling Township Health Center

Chenguanzhuang Township Health Center  Taiqiu Township Health Center

Wolong Township Health Center  Huicun Township Health Center

Yongcheng Traditional Chinese Medicine Hospital

Shibali Township Health Center  Xuehu Township Health Center

Mamu Township Health Center  Xinqiao Township Health Center

Xunyang Township Health Center  Shuangqiao Township Health Center

Yongcheng Jiangkou Yongji Hospital  Miaoqiao Township Health Center

Yongcheng Tuberculosis Hospital  Tiaohe Township Health Center

Zhongyuan Road Community Health Center  Yongcheng Wuguanke Hospital

Mangshan Township Health Center  Luanhu Township Health Center

others \_\_\_\_\_

#### Part IV. Other questions

4.1 Has your child ever received the following vaccines?

influenza vaccine  pneumococcal vaccine  Haemophilus influenzae vaccine

1  
2  
3  
4  Vaccines containing pertussis components (i.e. DTP)

5 4.1.1 If received vaccines containing pertussis (i.e. DTP), what kind of the vaccine?

6  
7  cDTaP  DTaP/Hib  DTaP-IPV/Hib

8  
9 4.2 Your family's average annual income (Chinese Yuan) is,

10  
11  <50,000  50,000-90,000  100,000-190,000  200,000-490,000  ≥500,000

12  
13 4.3 Your phone number is \_\_\_\_\_

14  
15  
16 Thank you very much for taking your time. The information you provided in this  
17 interview is very valuable to help us improve our work. Wish you a happy life!  
18

19  
20 Time of survey started: □□□□/□□/□□:□□:□□ (yyyy/MM/dd hh:mm)

21  
22 Time of survey ended: □□□□/□□/□□:□□:□□ (yyyy/MM/dd hh:mm)

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24 Investigator: \_\_\_\_\_ Supervisor: \_\_\_\_\_  
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Supplementary Table 2. Survey questionnaire for healthcare utilization and attitudes survey of cough illness among persons aged 5 years and older

Greetings! We are the staff of Center for Disease Control and Prevention. We sincerely invite you to participate in this questionnaire survey. The purpose of the survey is to study the utilization and attitudes of community residents towards health-care services of chronic/persistent cough, so that we can better serve you in the future.

This survey is anonymous. Your answers to these questions are kept confidential. You can choose whether to participate in the survey voluntarily or not. Refusal of the survey will not have any adverse consequences on you personally and your children. If you agree to participate, please read each question carefully and fill in the answer on your own. Thank you for your support and cooperation!

### Part I. Basic Information

- 1.1 Site: \_\_\_\_\_ Site ID: \_\_\_\_\_
- 1.2 Your length of time (years & months) living in the site (e.g. Yiwu or Yongcheng):  
 less than 6 months     six months and over
- 1.3 Current address: \_\_\_\_\_ county \_\_\_\_\_ street \_\_\_\_\_ community/village
- 1.4 Type of respondents in relation to the studied subject:  
 respondent himself is the study subject     others \_\_\_\_\_
- 1.5 Date of Birth:    □□□□/□□/□□ (yyyy/MM/dd)
- 1.6 Gender:     Male     Female
- 1.7 Ethnicity:     Han     others \_\_\_\_\_
- 1.8 Your occupation:  
 students     housework or unemployed     retired people     commercial & service sector workers     food handler or employees of food industry  
 specialists, including teacher, medical personnel and workers     agriculture, forestry, animal husbandry and fishery workers     others \_\_\_\_\_
- 1.9 Did you ever contact with dust/chemical materials in the working environment in the past one year, such as those encountered by workers using pneumatic drills at

1  
2  
3  
4 construction sites, miners, painters, benzene solvents in leather production, etc.

5  no  yes

6  
7 1.10 Your educational attainment:

8  primary school or illiteracy  middle school  high school

9  technical secondary school  college level and above

10  
11 1.11 Including yourself, there are \_\_\_\_\_ members in your family (defined as those  
12 who shared the same dining table in the house)?

13 Of which, there are \_\_\_\_\_ children under five years old.

14  
15 1.12 Are you smoker or ex-smoker?  yes  no

16  
17  
18  
19  
20  
21  
22 **Part II. self-perceived illness and health-care seeking behavior**

23  
24 2.1 Did you experienced cough during the past one month prior to our interview?

25  no  yes

26 2.1.1 If yes, how long did the cough last?

27  <1 week  1-2 weeks  3-4 weeks  5-8 weeks  >8 weeks

28 2.1.2 If yes, what is the clinical characteristics of the last episode of cough?

29  paroxysmal cough  vomiting after coughing  whooping cough

30  cough worsening during the night  vomiting after coughing

31  productive cough with large amount of sputum  dry cough

32  cough with blood in sputum  others \_\_\_\_\_

33 2.1.3 If yes, what is the other concomitant symptoms?

34  productive cough  running nose  fever (body temperature  $\geq 37.2^{\circ}\text{C}$ )

35  belching  acid reflux  irritable and crying  vomiting  headache

36  tachypnea  earache  sore throat  dyspnea  abdominal pain

37  arthralgia  chest pain  myalgia  fatigue  lethargy

38  burn after sternum  without any other discomfort  others \_\_\_\_\_

39 2.1.4 If yes, what do you think is the most probable cause of your cough?

40  respiratory tract infection  inhalation of foreign objects in the respiratory tract

41  COPD exacerbation  asthma exacerbation  recurrent tuberculosis

chronic cardiopulmonary disease  lung cancer  inhalation of cold air

chronic bronchitis  bronchiectasis  I don't know  others\_\_\_\_\_

2.2 Did you see a doctor or seek healthcare during the last episode of cough?  no

yes

2.2.1 If yes, where did you see a doctor?

(For Yiwu site, please select the following)

The Fourth Affiliated Hospital Zhejiang University School of Medicine

Yiwu Fuyuan Hospital  Yiwu Maternal and Children's Hospital

Yiwu Central Hospital  Yiwu Traditional Chinese Medicine Hospital

Yiwu Tianxiang Medical Group Dongfang Hospital

Chouzhou Hospital of Yiwu  The Second People's Hospital of Yiwu

The Third People's Hospital of Yiwu  Yiting township Health Center

Suxi Township Health Center  Beiyuan Community Health Center

Shangxi Township Health Center  Dachen Township Health Center

Houzhai Community Health Center  Chi'an Township Health Center

Chengxi Community Health Center  Niansanli Community Health Center

Yiwu Huashan Rehabilitation Hospital  Jiangdong Community Health Center

Futian Community Health Center  Yiwu Dermatology Hospital

Zhejiang Children's Hospital  Village clinics or private clinics

others\_\_\_\_\_

(For Yongcheng site, please select the following)

Yongcheng People's Hospital  Yongcheng Central Hospital

Yongmei Group General Hospital  Henan Shenhua Group General Hospital

Yongcheng Maternal & Child Health Hospital  Yucheng Township Health Center

Chenji Township Health Center  Gaozhuang Township Health Center

Yongcheng Mangdang Hospital  Lizhai Township Health Center

Yongcheng Second People's Hospital  Liuhe Township Health Center

Yanji Township Health Center  Dawangji Township Health Center

Longgang Township Health Center  Shunhe Township Health Center

Peiqiao Township Health Center  Huaihai Community Health Center

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4 Huangkou Township Health Center    Maqiao Township Health Center  
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6 Jiangkou Township Health Center    Houling Township Health Center  
7  
8 Chenguanzhuang Township Health Center    Taiqiu Township Health Center  
9  
10 Wolong Township Health Center    Huicun Township Health Center  
11  
12 Yongcheng Traditional Chinese Medicine Hospital  
13  
14 Shibali Township Health Center    Xuehu Township Health Center  
15  
16 Mamu Township Health Center    Xinqiao Township Health Center  
17  
18 Xunyang Township Health Center    Shuangqiao Township Health Center  
19  
20 Yongcheng Jiangkou Yongji Hospital    Miaoqiao Township Health Center  
21  
22 Yongcheng Tuberculosis Hospital    Tiaohe Township Health Center  
23  
24 Zhongyuan Road Community Health Center    Yongcheng Wuguanke Hospital  
25  
26 Mangshan Township Health Center    Luanhu Township Health Center  
27  
28 others\_\_\_\_\_

29 2.2.1 If no, why did not you see a doctor?

- 30  
31 Symptoms are mild, no need to see a doctor  
32  
33 The hospital is too far from home and the transportation is inconvenient  
34  
35 Drugs purchased in pharmacies   Distrust the doctor  
36  
37 Unaffordable high medical expenses  
38  
39 Hospital facilities and environment were poor  
40  
41 others\_\_\_\_\_

42 2.3 Were you hospitalized for the last episode of cough?    no    yes

43 2.3.1 If yes, where were you hospitalized?

44 (For Yiwu site, please select the following)

- 45  
46  
47  
48 The Fourth Affiliated Hospital Zhejiang University School of Medicine  
49  
50 Yiwu Fuyuan Hospital   Yiwu Maternal and Children's Hospital  
51  
52 Yiwu Central Hospital   Yiwu Traditional Chinese Medicine Hospital  
53  
54 Yiwu Tianxiang Medical Group Dongfang Hospital  
55  
56 Chouzhou Hospital of Yiwu   The Second People's Hospital of Yiwu  
57  
58 The Third People's Hospital of Yiwu   Yiting township Health Center  
59  
60 Suxi Township Health Center   Beiyuan Community Health Center

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4 Shangxi Township Health Center Dachen Township Health Center  
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6 Houzhai Community Health Center Chi'an Township Health Center  
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8 Chengxi Community Health Center Niansanli Community Health Center  
9  
10 Yiwu Huashan Rehabilitation Hospital Jiangdong Community Health Center  
11  
12 Futian Community Health Center Yiwu Dermatology Hospital  
13  
14 Zhejiang Children's Hospital Village clinics or private clinics  
15  
16 others\_\_\_\_\_

17 (For Yongcheng site, please select the following)

- 18  
19 Yongcheng People's Hospital Yongcheng Central Hospital  
20  
21 Yongmei Group General Hospital Henan Shenhua Group General Hospital  
22  
23 Yongcheng Maternal & Child Health Hospital Yucheng Township Health Center  
24  
25 Chenji Township Health Center Gaozhuang Township Health Center  
26  
27 Yongcheng Mangdang Hospital Lizhai Township Health Center  
28  
29 Yongcheng Second People's Hospital Liuhe Township Health Center  
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31 Yanji Township Health Center Dawangji Township Health Center  
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33 Longgang Township Health Center Shunhe Township Health Center  
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35 Peiqiao Township Health Center Huaihai Community Health Center  
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37 Huangkou Township Health Center Maqiao Township Health Center  
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39 Jiangkou Township Health Center Houling Township Health Center  
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41 Chenguanzhuang Township Health Center Taiqiu Township Health Center  
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43 Wolong Township Health Center Huicun Township Health Center  
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45 Yongcheng Traditional Chinese Medicine Hospital  
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47 Shibali Township Health Center Xuehu Township Health Center  
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49 Mamu Township Health Center Xinqiao Township Health Center  
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51 Xunyang Township Health Center Shuangqiao Township Health Center  
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53 Yongcheng Jiangkou Yongji Hospital Miaoqiao Township Health Center  
54  
55 Yongcheng Tuberculosis Hospital Tiaohe Township Health Center  
56  
57 Zhongyuan Road Community Health Center Yongcheng Wuguanke Hospital  
58  
59 Mangshan Township Health Center Luanhu Township Health Center  
60  
others\_\_\_\_\_

### Part III. Attitudes towards health-care utilization

(Next, we will ask some questions about the actions you might take under some hypothetical situations that do not need to actually happen.)

3.1 If you keep coughing for 2 weeks but does not get better, and you have decided to see a doctor, which one of the following medical institutions would you choose to go?

(For Yiwu site, please select the following)

- The Fourth Affiliated Hospital Zhejiang University School of Medicine
- Yiwu Fuyuan Hospital    Yiwu Maternal and Children's Hospital
- Yiwu Central Hospital    Yiwu Traditional Chinese Medicine Hospital
- Yiwu Tianxiang Medical Group Dongfang Hospital
- Chouzhou Hospital of Yiwu    The Second People's Hospital of Yiwu
- The Third People's Hospital of Yiwu    Yiting township Health Center
- Suxi Township Health Center    Beiyuan Community Health Center
- Shangxi Township Health Center    Dachen Township Health Center
- Houzhai Community Health Center    Chi'an Township Health Center
- Chengxi Community Health Center    Niansanli Community Health Center
- Yiwu Huashan Rehabilitation Hospital    Jiangdong Community Health Center
- Futian Community Health Center    Yiwu Dermatology Hospital
- Zhejiang Children's Hospital    Village clinics or private clinics
- others\_\_\_\_\_

(For Yongcheng site, please select the following)

- Yongcheng People's Hospital    Yongcheng Central Hospital
- Yongmei Group General Hospital    Henan Shenhua Group General Hospital
- Yongcheng Maternal & Child Health Hospital    Yucheng Township Health Center
- Chenji Township Health Center    Gaozhuang Township Health Center
- Yongcheng Mangdang Hospital    Lizhai Township Health Center
- Yongcheng Second People's Hospital    Liuhe Township Health Center
- Yanji Township Health Center    Dawangji Township Health Center
- Longgang Township Health Center    Shunhe Township Health Center



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4 Peiqiao Township Health Center    Huaihai Community Health Center  
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6 Huangkou Township Health Center    Maqiao Township Health Center  
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8 Jiangkou Township Health Center    Houling Township Health Center  
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10 Chenguanzhuang Township Health Center    Taiqiu Township Health Center  
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12 Wolong Township Health Center    Huicun Township Health Center  
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14 Yongcheng Traditional Chinese Medicine Hospital  
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16 Shibali Township Health Center    Xuehu Township Health Center  
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18 Mamu Township Health Center    Xinqiao Township Health Center  
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20 Xunyang Township Health Center    Shuangqiao Township Health Center  
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22 Yongcheng Jiangkou Yongji Hospital    Miaoqiao Township Health Center  
23  
24 Yongcheng Tuberculosis Hospital    Tiaohe Township Health Center  
25  
26 Zhongyuan Road Community Health Center    Yongcheng Wuguanke Hospital  
27  
28 Mangshan Township Health Center    Luanhu Township Health Center  
29  
30 others\_\_\_\_\_

31 3.2 If the doctor recommends that you should be hospitalized, which one of the  
32 following medical institutions would you choose?  
33

34  
35 (For Yiwu site, please select the following)

- 36  
37 The Fourth Affiliated Hospital Zhejiang University School of Medicine  
38  
39 Yiwu Fuyuan Hospital   Yiwu Maternal and Children's Hospital  
40  
41 Yiwu Central Hospital   Yiwu Traditional Chinese Medicine Hospital  
42  
43 Yiwu Tianxiang Medical Group Dongfang Hospital  
44  
45 Chouzhou Hospital of Yiwu   The Second People's Hospital of Yiwu  
46  
47 The Third People's Hospital of Yiwu   Yiting township Health Center  
48  
49 Suxi Township Health Center   Beiyuan Community Health Center  
50  
51 Shangxi Township Health Center   Dachen Township Health Center  
52  
53 Houzhai Community Health Center   Chi'an Township Health Center  
54  
55 Chengxi Community Health Center   Niansanli Community Health Center  
56  
57 Yiwu Huashan Rehabilitation Hospital   Jiangdong Community Health Center  
58  
59 Futian Community Health Center   Yiwu Dermatology Hospital  
60  
Zhejiang Children's Hospital   Village clinics or private clinics

others\_\_\_\_\_

(For Yongcheng site, please select the following)

- Yongcheng People's Hospital Yongcheng Central Hospital
- Yongmei Group General Hospital Henan Shenhua Group General Hospital
- Yongcheng Maternal & Child Health Hospital Yucheng Township Health Center
- Chenji Township Health Center Gaozhuang Township Health Center
- Yongcheng Mangdang Hospital Lizhai Township Health Center
- Yongcheng Second People's Hospital Liuhe Township Health Center
- Yanji Township Health Center Dawangji Township Health Center
- Longgang Township Health Center Shunhe Township Health Center
- Peiqiao Township Health Center Huaihai Community Health Center
- Huangkou Township Health Center Maqiao Township Health Center
- Jiangkou Township Health Center Houling Township Health Center
- Chenguanzhuang Township Health Center Taiqiu Township Health Center
- Wolong Township Health Center Huicun Township Health Center
- Yongcheng Traditional Chinese Medicine Hospital
- Shibali Township Health Center Xuehu Township Health Center
- Mamu Township Health Center Xinqiao Township Health Center
- Xunyang Township Health Center Shuangqiao Township Health Center
- Yongcheng Jiangkou Yongji Hospital Miaoqiao Township Health Center
- Yongcheng Tuberculosis Hospital Tiaohe Township Health Center
- Zhongyuan Road Community Health Center Yongcheng Wuguanke Hospital
- Mangshan Township Health Center Luanhu Township Health Center
- others\_\_\_\_\_

#### Part IV. Other questions

##### 4.1 Have you ever received the following vaccines?

- influenza vaccine pneumococcal vaccine Haemophilus influenzae vaccine
- Vaccines containing pertussis components (i.e. DTP)

1  
2  
3  
4 4.1.1 If received vaccines containing pertussis (i.e. DTP), what kind of the vaccine?

5 cDTaP DTaP/Hib DTaP-IPV/Hib

6  
7  
8 4.2 Your family's average annual income (Chinese Yuan) is,

9  <50,000  50,000-90,000  100,000-190,000  200,000-490,000  ≥500,000

10  
11 4.3 Your phone number is \_\_\_\_\_

12  
13  
14 Thank you very much for taking your time. The information you provided in this  
15 interview is very valuable to help us improve our work. Wish you a happy life!  
16

17  
18 Time of survey started: □□□□/□□/□□:□□:□□ (yyyy/MM/dd hh:mm)

19  
20 Time of survey ended: □□□□/□□/□□:□□:□□ (yyyy/MM/dd hh:mm)

21  
22 Investigator: \_\_\_\_\_ Supervisor: \_\_\_\_\_  
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Supplementary Table 3. Case screening and ascertainment form

Name of Hospital \_\_\_\_\_ Departments \_\_\_\_\_

Name of patient		Sex	<input type="checkbox"/> male <input type="checkbox"/> female
Birthdate		Ethnicity	
Current address		Phone number	
Date of illness onset		Date of admission	
Date of written informed consent signed			
Lists of inclusion & exclusion criteria			yes no
<b>Inclusion criteria:</b>			
<b>Patient regardless of ages:</b>			
1.cough of $\geq 2$ weeks duration;			<input type="checkbox"/> <input type="checkbox"/>
2.had one or more of the following symptoms;			<input type="checkbox"/> <input type="checkbox"/>
– paroxysmal cough;			<input type="checkbox"/> <input type="checkbox"/>
– inspiratory whoop;			<input type="checkbox"/> <input type="checkbox"/>
– post-tussive vomiting.			<input type="checkbox"/> <input type="checkbox"/>
<b>Infants less than one year old</b>			
1.cough (regardless of cough duration);			<input type="checkbox"/> <input type="checkbox"/>
2.had one or more of the following symptoms;			<input type="checkbox"/> <input type="checkbox"/>
– paroxysmal cough;			<input type="checkbox"/> <input type="checkbox"/>
– inspiratory whoop;			<input type="checkbox"/> <input type="checkbox"/>
– post-tussive vomiting.			<input type="checkbox"/> <input type="checkbox"/>
– apnea			<input type="checkbox"/> <input type="checkbox"/>
Written informed consent signed			<input type="checkbox"/> <input type="checkbox"/>
If you answer “No” to any of the above, the patient cannot enter the study.			
<b>Exclusion criteria:</b>			
1.not a permanent residents (lived longer than 6 months) at the site;			<input type="checkbox"/> <input type="checkbox"/>
2.gastroesophageal reflux;			<input type="checkbox"/> <input type="checkbox"/>
3.spastic bronchitis;			<input type="checkbox"/> <input type="checkbox"/>
4.diagnosed tuberculosis;			<input type="checkbox"/> <input type="checkbox"/>
5.lung mycoplasma/chlamydia infection;			<input type="checkbox"/> <input type="checkbox"/>
6.chronic sinusitis;			<input type="checkbox"/> <input type="checkbox"/>
7.Adults/adolescents with a measured body temperature of $\geq 38.5$ °C			<input type="checkbox"/> <input type="checkbox"/>
8. researchers considered not suitable for participating in the study			<input type="checkbox"/> <input type="checkbox"/>
If you answer Yes” to any of the above, the patient cannot enter the study.			
Whether the patient is included in the study			<input type="checkbox"/> <input type="checkbox"/>
If no, what is the reason for not included?			
– not meet the inclusion & exclusion criteria;			<input type="checkbox"/> <input type="checkbox"/>
– Refuse to participate ;			<input type="checkbox"/> <input type="checkbox"/>
If yes, what is the patient identifier no.? _____			<input type="checkbox"/> <input type="checkbox"/>



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**Vaccination history of DTP3 (for children aged under 14 years old)**

**Source of data :**  Vaccination certificate;  linkage with national database;  self-reports;

**Reasons of unvaccinated :** 1. Contraindications; 2. Under the age of vaccination; 3. Missed vaccination time; 4. Parents refused to vaccination; 5. migrating population; 6. Don't know; 7. Others \_\_\_\_\_

dose	lot number	producer	dosage		site	Date (YYYY/mm/dd)	Reasons of unvaccinated
			dose	unit			
1							
2							
3							

**hospital :** \_\_\_\_\_ **reporter :** \_\_\_\_\_ **Date of reporting :** \_\_\_\_/\_\_\_\_/\_\_\_\_(YYYY/mm/dd)

For peer review only

Supplementary Table 5. Follow-up information of case (CRF—T<sub>2w</sub>/T<sub>4w</sub>/T<sub>8w</sub>)

Patient identifier no.: _____		Type: <input type="checkbox"/> Inpatient <input type="checkbox"/> outpatient	
<b>Name :</b> _____ ( or <b>Parents' name :</b> _____ )		<b>Sex :</b> <input type="checkbox"/> male <input type="checkbox"/> female	
<b>Illness onset date :</b> ____/____/____(YYYY/mm/dd)		<b>Admission date :</b> ____/____/____(YYYY/mm/dd)	
<b>Follow-up date :</b> ____/____/____(YYYY/mm/dd)		Weeks of follow-up: <input type="checkbox"/> 2 wks <input type="checkbox"/> 4 wks <input type="checkbox"/> 8 wks	
Follow-up method: <input type="checkbox"/> hospital visits <input type="checkbox"/> telephone interview			
Outcomes			
<b>Survival:</b> <input type="checkbox"/> yes <input type="checkbox"/> no		Date of death: ____/____/____(YYYY/mm/dd) death diagnosis : _____	
<b>Hospitalized :</b> <input type="checkbox"/> yes <input type="checkbox"/> no		Re-admitted into hospital after discharge: <input type="checkbox"/> yes <input type="checkbox"/> no	
<b>Reasons for re-admission :</b> Pneumonia/heart failure/cardiogenic shock/encephalopathy/Seizure/other _____			
<b>Lost to follow-up:</b> <input type="checkbox"/> yes <input type="checkbox"/> no (refers to 3 consecutive calls to patients on different working days but no answers at all )			
Clinical characteristics (during follow-up visits)			
<input type="checkbox"/> cough ( Starting date ____/____/____ [YYYY/mm/dd] , duration ____ days )			
<input type="checkbox"/> post-tussive vomiting <input type="checkbox"/> paroxysmal cough <input type="checkbox"/> whooping cough <input type="checkbox"/> apnea <input type="checkbox"/> cyanosis <input type="checkbox"/> fever ( body temperature ____ °C )			
<input type="checkbox"/> seizure <input type="checkbox"/> cough worsening in night <input type="checkbox"/> productive cough			
Sputum color : yellow/white/black/glass like <input type="checkbox"/> hemoptysis <input type="checkbox"/> chills <input type="checkbox"/> headache <input type="checkbox"/> myalgia <input type="checkbox"/> sore throat <input type="checkbox"/> joint pain <input type="checkbox"/> chest pain			
<input type="checkbox"/> sweat <input type="checkbox"/> shortness-of-breath <input type="checkbox"/> running nose <input type="checkbox"/> lachrymation <input type="checkbox"/> fatigue <input type="checkbox"/> other( _____ )			
<b>Blood tests :</b> WBC ____ × 10 <sup>9</sup> /L; L ____ × 10 <sup>9</sup> /L; N ____ × 10 <sup>9</sup> /L; Plt ____ × 10 <sup>9</sup> /L; Hb ____ g/L; CRP ____ mg/L; GLU ____ mmol/L			
<b>Physical check :</b> body temperature : ____ °C <b>Breath rate :</b> ____ breath/min <b>Heart rate :</b> ____ beats/min			
<b>Systolic/diastolic blood pressure :</b> ____/____ mmHg <b>Pulse oximetry:</b> sPO <sub>2</sub> (if any): ____ %			
<b>Lung auscultation :</b> <input type="checkbox"/> dry rale <input type="checkbox"/> wet rale <b>Consciousness :</b> clear/lethargy/irritable/delirium/convulsions/coma			
Patient specimen collection			
<b>Specimen collected :</b> <input type="checkbox"/> yes <input type="checkbox"/> no		<b>Date of sampling :</b> ____/____/____(YYYY/mm/dd)	
<b>Type of specimen :</b> Nasopharyngeal swab <input type="checkbox"/>		amounts : _____	
Whole blood <input type="checkbox"/>		quantity : _____ ml	
<b>Reasons for not sampling :</b> <input type="checkbox"/> without coughing symptoms for 1 week <input type="checkbox"/> refusal to sampling			
<b>Hospital :</b> _____		<b>investigator :</b> _____	
<b>Date of follow-up :</b> ____/____/____(YYYY/mm/dd)			

Supplementary Table 6. Outcome of case at the end of follow-up (CRF—T<sub>end</sub>)

Patient identifier no.: \_\_\_\_\_ Type:  Inpatient  outpatient

**Name :** \_\_\_\_\_ ( or **Parents' name :** \_\_\_\_\_ ) **Sex :**  male  female **Illness onset date :** \_\_\_\_ / \_\_\_\_ / \_\_\_\_  
(YYYY/mm/dd)

**Admission date :** \_\_\_\_ / \_\_\_\_ / \_\_\_\_ (YYYY/mm/dd) **Discharge date :** \_\_\_\_ / \_\_\_\_ / \_\_\_\_ (YYYY/mm/dd)

**Discharge diagnosis :** primary diagnosis \_\_\_\_\_  
secondary diagnosis 1. \_\_\_\_\_ 2. \_\_\_\_\_ 3. \_\_\_\_\_

**Treatment during hospitalization**

**Admitting into ICU :**  yes  no \_\_\_\_ / \_\_\_\_ / \_\_\_\_ (YYYY/mm/dd)

1. **Transfer in date** \_\_\_\_ / \_\_\_\_ / \_\_\_\_ (YYYY/mm/dd) **Transfer out date** \_\_\_\_ / \_\_\_\_ / \_\_\_\_ (YYYY/mm/dd)

2. **Transfer in date** \_\_\_\_ / \_\_\_\_ / \_\_\_\_ (YYYY/mm/dd) **Transfer out date** \_\_\_\_ / \_\_\_\_ / \_\_\_\_ (YYYY/mm/dd)

3. **Transfer in date** \_\_\_\_ / \_\_\_\_ / \_\_\_\_ (YYYY/mm/dd) **Transfer out date** \_\_\_\_ / \_\_\_\_ / \_\_\_\_ (YYYY/mm/dd)

**Oxygen therapy :**  yes  no duration : \_\_\_\_\_ days

**Invasive ventilation :**  yes  no duration : \_\_\_\_\_ days (invasive ventilation refers to tracheal intubation or tracheotomy)

**Non-invasive ventilation:**  yes  no duration : \_\_\_\_\_ days

**Oscillating respirator :**  yes  no duration : \_\_\_\_\_ days

**ECMO or interventional lung adjuvant therapy ( iLA )**  yes  no **date of treatment start :** \_\_\_\_ / \_\_\_\_ / \_\_\_\_ (YYYY/mm/dd)

**Renal replacement therapy/dialysis :**  yes  no **date of treatment start :** \_\_\_\_ / \_\_\_\_ / \_\_\_\_ (YYYY/mm/dd)

**Exchange transfusion :**  yes  no **date of treatment start :** \_\_\_\_ / \_\_\_\_ / \_\_\_\_ (YYYY/mm/dd)

**Leukapheresis or leukoreduction therapy :**  yes  no **date of treatment start :** \_\_\_\_ / \_\_\_\_ / \_\_\_\_ (YYYY/mm/dd)

**Drugs**

( 1 ) Drug name : Please give the name of the drug, or the trade name if it is a fixed compound preparation

( 2 ) Category: A=antibiotic (1. Amoxicillin; 2. Amoxicillin-clavulanic acid; 3. Ampicillin; 4. Azithromycin; 5. Ceftriaxone; 6. Cefuroxime; 7. Ciprofloxacin; 8. Clarithromycin; 9. Doxycycline; 10. Erythromycin; 11. Penicillin; 12. Tetracycline; 13. Compound sulfamethoxazole); B=antiviral drugs; C=steroid hormone drugs

( 3 ) Route : 1=oral, 2=intravenous injection, 3=intravenous drip, 4=intramuscular injection, 5=inhalation, 6=other

( 4 ) Frequency : 1= continuous , 2=intermittent

Drug name (1)	Category (2)	Route (3)	Daily dose		Frequency (4)	Starting date (YYYY/mm/dd)	Stop date (YYYY/mm/dd)
			dose	unit			

**Clinical characteristics**

**Symptoms/signs :**

cough ( Starting date \_\_\_\_ / \_\_\_\_ / \_\_\_\_ [YYYY/mm/dd] , duration \_\_\_\_ days )

post-tussive vomiting  paroxysmal cough  whooping cough  apnea  cyanosis  fever ( body temperature \_\_\_\_ °C )

seizure  cough worsening in night  productive cough

Sputum color : yellow/white/black/glass like  hemoptysis  chills  headache  myalgia  sore throat  joint pain  chest pain

sweat  shortness-of-breath  running nose  lachrymation  fatigue  other( \_\_\_\_\_ )

**Complications :**

Viral pneumonia  Cardiac arrest  Bacterial pneumonia  Bacteremia  Acute lung injury/ARDS  Heart infection

Coagulation disorders  Pneumothorax  Anemia  Pleural effusion  Acute kidney injury  Myolysis



<input type="checkbox"/> Bronchiolitis	<input type="checkbox"/> Gastrointestinal hemorrhage	<input type="checkbox"/> Meningitis	<input type="checkbox"/> Pancreatitis	<input type="checkbox"/> Epilepsy	<input type="checkbox"/> Arrhythmia
<input type="checkbox"/> Liver insufficiency	<input type="checkbox"/> stroke	<input type="checkbox"/> Hyperglycemia	<input type="checkbox"/> Hypoglycemia	<input type="checkbox"/> Congestive Heart Failure	
<input type="checkbox"/> other ( _____ )					
Prognosis					
<input type="checkbox"/> Cured					
<input type="checkbox"/> Improved and be discharged					
<input type="checkbox"/> Transferred to other hospital			reasons for transfer : Community rehabilitation/other		
( _____ )					
<input type="checkbox"/> Give up treatment		reasons for give-up : Economic reasons/illness exacerbation/other ( _____ )			
<input type="checkbox"/> Death		date of death : ____ / ____ / ____ (YYYY/mm/dd)		death diagnosis : _____	
Hospital : _____		investigator : _____		Date of record : ____ / ____ / ____ (YYYY/mm/dd)	

# BMJ Open

## Burden of Whooping Cough in China (PertussisChina): Study Protocol of a Prospective, Population-based Case-control Study

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-053316.R1
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2 **Title:** Burden of Whooping Cough in China (PertussisChina): Study Protocol of a Prospective,  
3 Population-based Case-control Study

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## 25 **ABSTRACT**

### 26 **Introduction**

27 Pertussis is one of the top ten diseases of children under 10 years of age, and the few vaccine-  
28 preventable diseases who is on a rise in China in recent years; however, the true burden of  
29 pertussis, including age-stratified incidence and risk factors of severe sequelae, are  
30 underrecognized. We aim to estimate the health burden of laboratory-confirmed pertussis by  
31 age groups, considering the setting of illness onset (i.e. in community, outpatient and  
32 inpatient), in a Chinese population (~2.23 million in total) at two sites.

### 33 **Methods and analysis**

34 This paper describes the study design of a one-year, prospective, age-stratified, and  
35 population-based case-control study, including site selection, study population, case registry,  
36 ascertainment and enrolment, control recruitment, follow-up of case, microbiological  
37 methods, data collection, quality control activities, and statistical methods used to generate  
38 incidence estimates. During June 2021 through May 2022, registry of suspected pertussis  
39 cases (namely chronic/persistent cough) will be conducted in several participating hospitals  
40 (SHs) at the two sites, which are selected based on Healthcare Utilization and Attitudes  
41 Surveys (HUAS) carried out before study initiation. A case-control study will be conducted in  
42 the SHs and we aim to enroll a total of 1,000 suspected pertussis cases (i.e. all hospital  
43 admissions and the first 1-3 outpatient visits each week each hospital) and 2,000 frequency  
44 matched healthy controls in community. Our primary study outcome, the laboratory-  
45 confirmed *Bordetella Pertussis* infection, will be determined by a comprehensive laboratory  
46 methods and procedures (i.e. culture, PCR, and serological tests) in both cases and controls at  
47 enrolment and during 60-day's follow-up visits. Finally, data from HUAS (i.e. population size),  
48 case registry (i.e. the total number of suspected pertussis cases), and case-control study (i.e.  
49 the prevalence or population attributable fraction of *Bordetella Pertussis*) will be combined to  
50 calculate incidence and its 95% confidence interval through bootstrap method.  
51 Epidemiological analyses will be conducted to determine the risk factors associated with  
52 severe sequelae of pertussis.

### 53 **Ethics and dissemination**

54 This study has been approved by Chinese Center for Disease Control and Prevention's  
55 Institutional Review Board (no. ICDC-202110). Results will be disseminated via academic

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3 56 presentations and publication in peer-reviewed journals, and will provide valuable scientific  
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5 57 data and some new insights into the incidence, etiology, and risk factors for severe sequelae  
6  
7 58 of pertussis to academic societies and the public health authorities who is currently struggling  
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9 59 and fighting against this burdensome disease worldwide.

10  
11 60 **Keywords:** *Bordetella pertussis*, Case-Control Studies, Incidence, China  
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For peer review only

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3 61 **SUMMARY**  
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6 62 **Strengths and limitations of this study**  
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- 8  
9 63 ▪ PertussisChina is a population-based study at two sites, covering approximately 2.23  
10 64 million populations defined through conducting Healthcare Utilization and Attitudes  
11 65 Surveys (HUAS) in community.  
12  
13 66 ▪ PertussisChina is a laboratory-based study, in which comprehensive laboratory methods  
14 67 (i.e. culture, PCR, and serological tests) and procedures (i.e. 60-days follow-up) will be  
15 68 used to specifically measure pertussis disease burden.  
16  
17 69 ▪ PertussisChina is a case-control study in which the prevalence and population attributable  
18 70 fraction (AF) of *Bordetella Pertussis* infection can be readily acquired.  
19  
20 71 ▪ All cases will be prospectively followed up to 60-days to collect interesting events (i.e.  
21 72 adverse clinical outcomes of hospitalization or death) at 2, 4 and 8 weeks after enrolment.  
22  
23 73 ▪ Limitations are that our incidence might be underestimated and cannot be extrapolated  
24 74 to represent the whole country due to the insensitive case definition used, short study  
25 75 period and relatively small population covered.  
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## 76 BACKGROUND

77 Whooping cough (pertussis) is a highly contagious respiratory disease caused by  
78 *Bordetella Pertussis*<sup>1 2</sup>. Despite a high vaccine coverage of third dose diphtheria-  
79 tetanus-pertussis vaccine (DTP3)<sup>3</sup>, the "resurgence of pertussis" in recent years has  
80 posed a great threat to global public health<sup>4-6</sup>, as well as to Chinese infants<sup>7 8</sup>. In 2019,  
81 pertussis was one of the top ten diseases with highest burden in children younger than  
82 10 years<sup>9</sup>, and the World Health Organization estimates that pertussis kills about  
83 160,700 children under 5 years old worldwide each year<sup>10</sup>. In China, three types of  
84 pertussis vaccines are available till October 31, 2021, i.e. the co-purified diphtheria  
85 and tetanus toxoids and acellular pertussis (cDTaP, used for routine immunization),  
86 DTaP/Hib (Minhai Biotechnology Co., Ltd., Beijing, China)<sup>11</sup> and DTaP-IPV/Hib (Sanofi  
87 Pasteur, Lyon, France)<sup>12 13</sup>. The coverage of DTP3 remained high above 99% for  
88 children throughout the 2010s<sup>14 15</sup>, and the reported incidence of pertussis has been  
89 risen from 0.12 per 100,000 in 2013 to 2.14 per 100,000 in 2019 (Figure 1). Unlike the  
90 other countries who had experience resurgence of pertussis, especially in  
91 adolescents/adults, primarily due to the waning of vaccine induced immunity<sup>16-20</sup>,  
92 China observed no such changes of age distribution<sup>21</sup>. The rise of pertussis in China  
93 was mainly concentrated in infants less than 1 year old, and less than 5% of reported  
94 pertussis were adolescents and adults.

95 Since most epidemiological data on pertussis in China came from a passive reporting  
96 system, the National Notifiable Infectious Disease Surveillance System (NNIDSS)<sup>22</sup>,  
97 underreporting was substantial in the system ( $\geq 90\%$ ) because of limited diagnosis and  
98 incompleteness of reporting<sup>8 23 24</sup>. And the burden of pertussis remained  
99 underrecognized. It has been suggested that immunizing schoolchildren is the key for  
100 curtailing transmission of pertussis in population<sup>18</sup>. Due to a substantial knowledge  
101 gaps existed in age-specific burden of pertussis (i.e. incidence and severity), no  
102 adolescent or adult immunization are recommended in the country<sup>25</sup>. Moreover,  
103 some important data such as clinical, laboratory and vaccine information are also not  
104 available, which is unfavorable for evaluating the effectiveness of vaccine and  
105 implementing of other disease control and prevention programs (such as adult



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3 106 vaccination, diagnostic tests and post-exposure prophylaxis of pertussis). Rigorously  
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5 107 conducted, prospective, population-based studies can be used to strengthen the  
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7 108 NNIDSS, by providing information on the burden of laboratory-confirmed pertussis,  
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9 109 strains distribution, risk factors for severe sequelae and case fatality, and most  
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11 110 importantly, to assist health authority in China to allocate health resources, prioritize  
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13 111 health research investments, optimize interventions (i.e. vaccination) and innovate  
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15 112 vaccine development.

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17 113 We designed the PertussisChina study, a one-year, prospective, age-stratified,  
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19 114 population-based longitudinal cohort and case-control study, which will enroll  
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21 115 suspected pertussis patients (i.e. chronic/persistent cough) seeking healthcare in  
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23 116 several selected participating hospitals (SHs) at two sites of China, covering  
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25 117 approximately 2.23 million censused population. This article describes the study  
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27 118 design, including sites selection, study population, case registry, ascertainment and  
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29 119 enrolment, control recruitment, follow-up of cases and controls, microbiological  
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31 120 methods (i.e. culture, PCR, and serological tests), data collection, quality control  
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33 121 activities, and statistical methods used to generate incidence estimates of pertussis.  
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35 122 We then further discuss the strengths and weaknesses of the study design.

## 36 123 **METHODS AND ANALYSIS**

### 39 124 **Objectives of the study**

41  
42 125 The primary objective of the study is to measure the incidence of laboratory-  
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44 126 confirmed pertussis by age groups (children, adolescents and adults), and by settings  
45  
46 127 (community, outpatient and inpatient). The secondary objectives are: 1) to describe  
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48 128 the distribution of disease severity and outcomes across age groups; 2) to describe the  
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50 129 patterns and factors of under-detection and under-reporting of pertussis; 3) to study  
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52 130 the carrier (colonization) status of the *B. pertussis* in the upper respiratory tract of  
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54 131 healthy controls, and the serum levels of anti-pertussis toxin antibodies (anti-Ptx IgG)  
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56 132 in both patients and healthy people; and 4) to create a repository of well-characterized  
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58 133 clinical specimens and *B. pertussis* isolates that can be used in future studies.  
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## 134 **Study sites and population**

### 135 ***Site Selection Criteria***

136 Sites are selected based on the following criteria: 1) have strong willingness to  
137 participate; 2) have capability and resources to conduct ongoing surveillance, namely  
138 staffs to facilitate specimen collection and case investigation, previous experience in  
139 disease surveillance, infrastructures to secure data collection and specimen storage  
140 or transportation; and 3) provide a full list of healthcare facilities in the area and the  
141 information of built-in hospital information system in the facilities. Currently, there  
142 are two sites in the study, including Yongcheng, Henan and Yiwu, Zhejiang (Figure 2).

### 143 ***Study population***

144 In 2019, Yiwu had a permanent population of 821,000 (47,000 were children under  
145 five years of age) served by 24 health care facilities (i.e. three tertiary care, four  
146 secondary care, and 17 primary care hospitals). Most hospital admissions ( $\geq 80\%$  of the  
147 total number) occurred in the three large tertiary hospitals, including a children's  
148 hospital and two general hospitals; meanwhile, Yongcheng had a permanent  
149 population of 1,411,000 (94,000 were children under five years of age) served by 41  
150 health care facilities (i.e. five secondary care and 36 primary care hospitals). Most  
151 hospital admissions occurred in the five large secondary care hospitals, including four  
152 general hospitals and a maternal and pediatric hospital. In total, the two sites cover a  
153 total of 2.23 million permanent population in the study area.

### 154 **Study overview and design**

155 In order to achieve our study objectives, we will conduct the following study activities  
156 at the two sites from June 2021 through May 2022, including, 1) a Healthcare  
157 Utilization and Attitudes Survey (HUAS) and a census data updating to define study  
158 population (i.e. incidence denominator), so as to set up a sampling frame for the case-  
159 control study and selecting participating hospitals (i.e. SH) for case registry and case  
160 recruitment; 2) the case-control study to acquire the prevalence of *B. pertussis*  
161 infection among suspected pertussis cases and healthy controls, as well as the  
162 calculation of population attributable fraction (AF) indicating the proportion of cases

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4 163 that can be prevented if *B. pertussis* was totally removed from the population; and 3)  
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6 164 case registry and the retrieval of electronic medical records (EMRs) from hospital  
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8 165 information system to provide and validate the total number of suspected pertussis  
9  
10 166 case patient (chronic/persistent cough) encountered in the SHs (i.e. incidence  
11  
12 167 numerator) (Figure 3).

### 13 168 ***Defining and calibrating study population***

#### 14 169 ***Census data updating***

15  
16 169  
17 170 Population census data at the two sites will be collected and updated during the study  
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19 171 period. Population census is conducted every ten years in China and the nearest one  
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21 172 is in 2020. However, an intermittent survey of 1% sampling of the total population  
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23 173 would be performed to update population census data every year between the two  
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25 174 censuses. We will retain the up-to-date population data from the National Bureau of  
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27 175 Statistics. Moreover, the population birth, mortality, and population migration are  
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29 176 recorded by the local government. We will also contact the local health bureau  
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31 177 quarterly to access these data to give a precise estimation of population size in the  
32  
33 178 two sites.

#### 34 179 ***Healthcare Utilization and Attitudes Surveys (HUAS)***

35  
36 180 HUAS will be conducted prior to recruiting cases and controls at the two sites, which  
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38 181 will serve three purposes, 1) to set up a sampling frame for the case-control study; 2)  
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40 182 to select SHs in which prospective enrolment of cases will be conducted; and 3) to  
41  
42 183 provide estimates of the population coverage for our SHs and healthcare seeking  
43  
44 184 behavior weights applied in estimating pertussis incidence in community.

45  
46 185 In summary, a population-based cross-sectional study, with an age-stratified sample  
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48 186 of 3,000 children aged 0-59 mo and 6,000 adolescents/adults aged  $\geq 5$  years, will be  
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50 187 conducted in the community of the two sites. The sample size was calculated based  
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52 188 on: i) for children, a monthly prevalence of cough illness,  $\pi=1\%$  (estimated from the  
53  
54 189 reported incidence of lower respiratory tract infection of 0.15 per child year<sup>26</sup>),  
55  
56 190 allowable error ( $\delta=0.5\%$ ), significant level ( $\alpha=0.05$ ), and design effect (deff=2); ii) and  
57  
58 191 for adolescents/adults, a monthly prevalence of cough illness,  $\pi=3.3\%$ <sup>27</sup>, allowable  
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60 192 error ( $\delta=0.66\%$ ), significant level ( $\alpha=0.05$ ), and design effect (deff=2).

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3 193 A complex sampling method will be used to select survey respondents as follows.  
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5 194 Firstly, a probability proportionate to size sampling will be used to randomly select 50  
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7 195 clusters (e.g. communities or villages) in the site's administrative regions. At the  
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9 196 second sampling stage in selected communities, quota sampling will be used to recruit  
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11 197 interviewee. The quota required in each age stratum was calculated based on the age  
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13 198 distribution of the population in the sites and the number of surveys allocated to each  
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15 199 cluster. Trained work staff will go to the selected communities to conduct face-to-face  
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17 200 surveys at several locations (residential areas, kindergartens and children's  
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19 201 vaccination clinics) Monday to Sunday during daytime in the study period. All residents  
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21 202 living in the communities or villages for at least half a year prior to survey are eligible  
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23 203 for and invited to participate in the interview. After the quota required in each age  
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25 204 group is complete, the interviews will stop.

26 205 The following questions (Supplementary table 1 & table 2) are asked to respondents,  
27  
28 206 1) the occurrence and length of cough illness in the previous month prior to survey, 2)  
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30 207 healthcare-seeking behavior regarding the self-reported cough illness for the most  
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32 208 recent episodes and the sources of healthcare facilities; and 3) the willingness to seek  
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34 209 healthcare and where would they choose to visit for an assumptive cough illness.

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36 210 Based on the HUAS and census data, hospitals at which over 80% of respondents in  
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38 211 each site choose to attend when hospital admission is required will be selected as our  
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40 212 SHs. In case healthcare providers in the site change their practice or scope of service  
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42 213 during our study period, for example the opening of new hospitals or the  
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44 214 establishment of new branches of existing hospitals, an abbreviated HUAS with a  
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46 215 smaller sample of 1,000 will be administered at the middle or the end of the year  
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48 216 during which cases are recruiting at SHs.

### 49 217 ***Case-control study***

#### 50 51 218 ***Case definition of suspected pertussis***

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53 219 Patients will be classified as suspected pertussis cases and offered to participate if they  
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55 220 present chronic/persistent cough defined as cough of  $\geq 2$  weeks duration with one or  
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57 221 more of the following symptoms, 1) paroxysmal cough; 2) inspiratory whoop; or 3)  
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59 222 post-tussive vomiting; Or, for children aged  $< 1$  years-old, cough (regardless of cough  
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223 duration) accompanied by one or more of the following symptoms, 1) apnea; 2)  
224 paroxysmal cough; 3) inspiratory whoop; or 4) post-tussive vomiting.

225 We will exclude patients presenting with gastroesophageal reflux, spastic bronchitis,  
226 and clearly diagnosed tuberculosis, mycoplasma/chlamydia infection, or chronic  
227 sinusitis. Adults/adolescents with a measured body temperature of  $\geq 38.5$  °C at  
228 enrolment will also be excluded.

### 229 *Sample Size Considerations*

230 We planned to enroll approximately 250 suspected cases and 2 matched controls for  
231 each case in each age stratum (i.e. children under 5 years, and adolescents/adults  
232 aged  $\geq 5$  years) for laboratory investigation at each site, which would add up to  
233 approximately 1000 suspected cases and 2000 controls at the two sites. We calculated  
234 the above sample size based on a prevalence of *B. pertussis* in chronic/persistent  
235 cough of 20% (range=12%-32%)<sup>28-30</sup>, an allowable error of 5% and a significant level  
236 of 0.05. This sample size would have a 90% power (two sided  $\alpha = 0.05$ ) to detect an  
237 odds ratio (OR) of 2 between case and control for a site and age stratum-specific  
238 comparison, if the true prevalence of *B. pertussis* is 20% in case; or an OR of 3, if the  
239 true prevalence is 10%. Although the carrier state of *B. pertussis* is transient in family  
240 contacts<sup>31 32</sup>, *B. pertussis* is rarely identified in healthy people<sup>33 34</sup>, and we expected a  
241 larger OR of  $\geq 2$  in the study. This sample size means that the laboratory would process  
242 average 115 samples per week, which is feasible and acceptable for our laboratories.

### 243 *Case Registry, Ascertainment and Enrollment*

244 Case registry, ascertainment and enrollment for suspected case will be conducted in  
245 SHs during the study period. Clinicians or trained nurses working in selected  
246 departments of the SHs (i.e. respiratory, pediatric, infectious disease, and emergency  
247 department) will carry out case registry of suspected pertussis cases every weekday  
248 (i.e. Monday through Sunday) except national holidays. Each outpatient visits and new  
249 hospital admission seeking healthcare in above departments will be screened for the  
250 eligibility of inclusion using the inclusion & exclusion criteria of the suspected case  
251 definition of pertussis by clinicians. Eligible ones will be ascertained and recorded as  
252 suspected case by study coordinator who assist with clinicians in SHs in enrolling cases

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4 253 using a standardized case reporting form (CRF) (Supplementary Table 3). Among the  
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6 254 suspected pertussis case recorded in SHs, convenient sampling method will be used  
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8 255 to recruit cases for case-control study. We aim to enroll all hospital admissions and  
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10 256 the first 1-3 outpatient visits each week in each hospital. After obtaining informed  
11  
12 257 consent, study staff will conduct enrollment interviews, and collect nasopharyngeal  
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14 258 (N/P) and blood specimens for each enrolled case.

#### 15 259 *Controls selection*

16  
17 260 At the middle of the study year when the sample size of cases reaches a half of the  
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19 261 total (i.e. n=500), a control is recruited in community of the study sites using  
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21 262 approximate frequency matching, based on the following criteria, 1) similar  
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23 263 proportion in sex strata; 2) similar proportion in age strata, i.e. <1 year, 1-5 years, 6-  
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25 264 19 years, 20-64 years and ≥65 years; 3) a control/case ratio of 2:1; and 4) no cough,  
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27 265 running nose, shortness of breath, dyspnea or other respiratory symptoms at  
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29 266 enrolment nor have a record of healthcare for respiratory disease in previous three  
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31 267 months before recruitment.

#### 32 268 *60-day follow-up of case*

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34 269 We will follow cases from the time of enrollment to a maximum time period of 60 days  
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36 270 after enrollment. Follow-up will be conducted at 2<sup>nd</sup>, 4<sup>th</sup> and 8<sup>th</sup> weeks after  
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38 271 enrollment, with face-to-face interview if patient is currently hospitalized, or one  
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40 272 telephone call each follow-up time if patient is discharged from hospital. At each  
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42 273 follow-up visit/phone call, the study staff will ask about cough or other respiratory or  
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44 274 systemic illness symptoms in the period since the last contact. If case is still  
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46 275 symptomatic (i.e. cough) during follow-up, they will be encouraged to visit their doctor  
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48 276 who enrolled them in the SHs within 24h of contact. The doctor will checkup the  
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50 277 patient's health status and collect the swab and serum samples during the visit. If an  
51  
52 278 enrolled patient does not want to visit the SHs, the study staff will arrange a household  
53  
54 279 visit to collect the samples in the home.

#### 55 280 *Data collection from cases and controls*

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57 281 At enrolment, trained clinicians and the study coordinator will conduct face-to-face  
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59 282 interview to collect socio-demographic, clinical and epidemiological data from cases  
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3 283 and controls using a standardized CRF (Supplementary Table 4). Demographic  
4 284 information includes household size (defined as a group of people who share a dinner  
5 285 table), average household income, rural or urban residence, age, alcohol consumption  
6 286 and smoking exposure, and occupation etc. A clinician will also examine all cases to  
7 287 document clinical signs and symptoms at enrollment, including cough characteristics  
8 288 [duration, paroxysms, post-tussive vomiting, exacerbation at night], body  
9 289 temperature, respiratory rate, heart rate, seizure, apnea, and other general  
10 290 respiratory symptoms, non-prescription antibiotic usage before visiting the doctor,  
11 291 blood test results and chest x-ray examinations. Vaccination history (i.e. brand, dosing,  
12 292 procedure and time of administration) of children aged  $\leq 14$  years is also collected by  
13 293 linkage of his/her individual records on immunization in the national database  
14 294 (Childhood Immunization Information Management System, CIIMS)<sup>35</sup> or checking of  
15 295 vaccination certificate.

16 296 During follow-up visits, data on any current cough or respiratory symptoms, subjective  
17 297 severity of illness, illness duration, functional impairment, whether medical care was  
18 298 sought, and outcomes since the last visits will be collected using CRFs (Supplementary  
19 299 Table 5).

20 300 At the end of follow-up, medical charts of each hospitalized case will be reviewed by  
21 301 study staff to collect information on antibiotic treatment and outcomes during  
22 302 hospitalization (i.e. mechanical ventilation, ICU transfer, and death) (Supplementary  
23 303 Table 6).

#### 24 304 ***The retrieval of electronic medical records and Validation of the total number of*** 25 305 ***suspected pertussis case***

26 306 Since our case registry and enrolment is conducted in selective departments (i.e.  
27 307 respiratory, pediatric, infectious disease and emergency departments) and on  
28 308 workdays in SHs, it is an incomplete record of the total number of suspected cases  
29 309 encountered in the whole hospital. It is essential to calibrated the registered number  
30 310 of suspected cases to equal the total. To do this, all hospital discharges or ambulatory  
31 311 visits coded for diagnosis under the International Classification of Diseases 10th  
32 312 Revision (ICD-10) codes A37, J00-J22, J40-J47, R05, R09.2, P22, P28.2, P28.3, P28.4,  
33 313 and P28.5 will be monitored on a daily basis as registry case, by hospital departments.



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3 314 At the end of the month, the complete EMRs records with the above diagnosis codes  
4  
5 315 in the whole hospital will be abstracted from hospital information system (HIS) of the  
6  
7 316 SHs. This data will be used to calibrate the prospectively counting data of suspected  
8  
9 317 case in the selective departments that conduct case enrolment to make a precise  
10  
11 318 estimate of the total number of chronic/persistent cough illness outcomes in the  
12  
13 319 studied population. Namely, through linking and comparing between the number of  
14  
15 320 registry cases and the number of suspected pertussis case registered in the selected  
16  
17 321 departments, we will calculate the  $W_{case}$ . With this  $W_{case}$ , we will narrow down the  
18  
19 322 ICD-based EMRs records to the total number of suspected pertussis cases met our  
20  
21 323 case definition in SHs (i.e. the numerator of incidence).

## 22 23 324 **Laboratory investigation**

### 24 25 325 ***Specimen collection and transport***

26  
27 326 When patients meet our suspected pertussis case definition or are recruited controls,  
28  
29 327 they, as well as symptomatic (cough) cases during follow-up contacts, will be sampled  
30  
31 328 within 24 hours. Clinicians or nurses in SHs will be trained to collect nasopharyngeal  
32  
33 329 swabs (N/P) and whole blood sample. Dacron or nylon swab will be used to collect N/P  
34  
35 330 specimen to facilitate culture and PCR tests for *B. pertussis*<sup>36</sup>. Collected swab  
36  
37 331 specimens will be plated onto selective agar or placed in transport medium (Charcoal  
38  
39 332 Agar, Thermo Fisher Scientific Inc.) immediately after sampling at the SHs. Whole  
40  
41 333 blood without adding any anticoagulants (>4ml for participants aged 5 years and older,  
42  
43 334 and  $\geq 2$  ml for children aged <5 years) will be collected, and centrifuged to separate  
44  
45 335 serum within 24h of collection. All collected swab and sera samples will be transported  
46  
47 336 to the central laboratory of Chinese Center for Disease Control and Prevention (China  
48  
49 337 CDC), using a cold box to maintain a temperature of 4°C. During transportation,  
50  
51 338 samples are packaged and transported in accordance with the provision of  
52  
53 339 International Civil Aviation Organization (ICAO) document Doc9284 and UN3373

### 54 55 340 ***Processing and storage of specimen***

56  
57 341 Upon arrival at the laboratory of China CDC, swab samples will be processed and  
58  
59 342 prepared into three aliquots of swab supernatant, so will serum samples be. One of  
60  
343 these aliquots will be analyzed and the other two aliquots will be kept for future



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2  
3 344 analyses. All aliquots will be stored at -70°C temperature until the time of analysis.  
4  
5

### 6 345 **Laboratory testing**

7  
8 346 In the laboratory of China CDC, Charcoal Agars will be cultured to isolate *B. pertussis*  
9  
10 347 using standard method recommended by China CDC<sup>37</sup> and World Health  
11 348 Organization<sup>38</sup>. Swab supernatant will be analyzed for *B. pertussis*, *B. parapertussis*, *B.*  
12 349 *bronchiseptica* and *B. holmesii* using polymerase chain reaction (PCR) as  
13 350 recommended by US CDC<sup>39 40</sup>. Sera samples that have a minimum volume of  $\geq 1$  ml  
14 351 will be tested for Anti-Ptx IgG titer using a commercially available diagnostic kit  
15 352 (Virion\Serion, Wurzburg, Germany) according to the manufacturer's  
16 353 recommendations. To validate our laboratory methods and testing results, external  
17 354 quality assurance testing will be conducted to reach agreements with a reference  
18 355 laboratory on *Bordetellae* prior to study start. For serology testing, we use standard  
19 356 from the National Institute for Biological Standards and Control, London, UK,  
20 357 ([https://www.nibsc.org/products/brm\\_product\\_catalogue/detail\\_page.aspx?catid=1](https://www.nibsc.org/products/brm_product_catalogue/detail_page.aspx?catid=18/146)  
21 358 [8/146](https://www.nibsc.org/products/brm_product_catalogue/detail_page.aspx?catid=18/146)); and for PCR assays, the Wisconsin State Laboratory of Hygiene, Wisconsin, U.S.  
22 359 (<http://www.slh.wisc.edu/proficiency/training-and-competency/>).

23 360 Suspected pertussis cases and controls that have *B. pertussis* Isolated, positive tests  
24 361 of swabs in any of samples collected during enrolment and follow-up, or for persons  
25 362 three years of age and over have a 3-fold or greater rise in anti-Ptx IgG antibody  
26 363 between sequential sera samples with at least one time point higher than 40 IU/ml of  
27 364 serum titer would be considered laboratory-confirmed pertussis.<sup>36 41</sup>

### 28 365 **Data flow, management and analysis**

29 366 The data collected in the study are centrally managed at China CDC, using an online  
30 367 data platform (<http://eddc.chinacdc.cn/dap/>). The completed CRFs will be entered  
31 368 into the information system by local study staff at the two sites and uploaded to data  
32 369 server through encrypted transmission via a Virtual Private Network set up by China  
33 370 CDC. The entered records are regularly checked for completeness, consistency, and  
34 371 logical errors by data manager and the site's co-principle investigator who is  
35 372 responsible for authorization, integrity, security, and backup of database during data  
36 373 collection.  
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374 **Statistical analysis**

375 The collected data processing and key indicators based on which we calculate  
 376 incidence are shown in figure 4. We will calculate the incidence of pertussis by age  
 377 group and by settings with the following formula.

$$378 \quad \text{Hospitalization incidence rate} = \sum \frac{S_i^{\text{inpatient}} \times W_i^{\text{case}} \times AF_i}{N_i \times W_i^{\text{cover}} \times C_i}$$

$$379 \quad \text{Outpatient incidence rate} = \sum \frac{S_i^{\text{outpatient}} \times W_i^{\text{case}} \times AF_i}{N_i \times W_i^{\text{cover}} \times C_i}$$

$$380 \quad \text{Community incidence rate} = \frac{\text{Outpatient incidence rate}}{r_i}$$

381 Where,  $S_i^{\text{inpatient}}$  and  $S_i^{\text{outpatient}}$  indicates the registered number of inpatients and  
 382 outpatient visits of cough illnesses at age group  $i$ , as obtained from HIS.  $W_i^{\text{case}}$  is the  
 383 weight used to adjust  $S_i^{\text{inpatient}}$  and  $S_i^{\text{outpatient}}$  to meet our case definition in age group  $i$ .  
 384 This weight is calculated from the results of the prospective case-control study as a  
 385 ratio of suspected cases over registered cases of cough illnesses at the selective  
 386 departments of SHs.  $N_i$  is the population size in age group  $i$  in census year 2020.  
 387  $W_i^{\text{cover}}$  is the weight used to adjust catchment population overlapping between  
 388 participating hospitals from HUAS in age group  $i$ . It is calculated as the ratio of  
 389 community residents who have the reported seeking medical care in the participating  
 390 hospitals for the last episodes of their cough illness over the residents who have the  
 391 willingness of healthcare-seeking in the participating hospitals, as obtained from the  
 392 HUAS study.  $C_i$  is the proportion of population covered by participating hospitals in  
 393 age group  $i$ , as measured in the HUAS study. It is calculated as the proportion of  
 394 residents who report having the willingness of healthcare-seeking in the participating  
 395 hospitals over the total no. of residents responded.  $r_i$  is the proportion of  
 396 community residents reporting seeking health-care for their most recent episode of  
 397 cough illnesses in age group  $i$  as measured in the HUAS study.  $AF_i$  is the population  
 398 attributable fraction of chronic/persistent cough due to *B. pertussis* infection in age  
 399 group  $i$ , calculated based on case-control study using unconditional logistic regression

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4 400 model, as follows:

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6 401 
$$\log_e(OR) = \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3 + \dots + \beta_k x_k$$

7  
8 402 
$$OR = \exp(\beta_k)$$

9  
10  
11 403 
$$AF_i = \Pr(Bordetella pertussis | Chronic cough) (1 - \frac{1}{OR})$$

12  
13 404 Note:  $\Pr(Bordetella pertussis | Chronic cough) = P_i$  is the prevalence of *B. pertussis*,  
14  
15 405 calculated by dividing the number of laboratory-confirmed pertussis with the total  
16  
17 406 number of chronic/persist cough tested.  $x_1, x_2, x_3, \dots, x_k$  are variables associated with  
18  
19 407 the occurrence of chronic/persistent cough, including the presence of *B. pertussis* and  
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21 408 other social and environmental factors significant at  $p < 0.1$  in univariate analysis. OR  
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23 409 is the odds ratio.

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27 410 The 95% CI of incidence is calculated with bootstrap method with 1000 replications.  
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29 411 Besides incidence estimates, we will also explore factors associated with severe  
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31 412 pertussis (defined as a composite outcome of death, sepsis, invasive ventilation and  
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33 413 Intensive Care Unit transfer), by using multivariable logistic regression. Factors  
34  
35 414 significantly associated with severe pertussis at  $p < 0.1$  in univariate analysis will be  
36  
37 415 included in the model. The median age of children with pertussis will be calculated by  
38  
39 416 type of vaccinees, and factors predicting the age of pertussis breakthrough among  
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41 417 children who had received DTP vaccination early in their life will be also studied by  
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43 418 using Cox proportional hazards regression models.

#### 44 45 419 **ETHICS AND DISSEMINATION**

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48 420 This study is designed an observational study. The risk of harm is minimal and adverse  
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50 421 medical events are not anticipated from the procedures involved in the study. The  
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52 422 study protocol, CRF, and consent form have been sent to and approved by China CDC's  
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54 423 Institutional Review Board (reference no. ICDC-202110).

55  
56 424 The primary risk to participants is the loss of confidentiality. To help maintain  
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58 425 confidentiality, all study investigators will sign a confidentiality agreement and receive  
59  
60 426 appropriate ethics training. All interviews will be conducted at the study investigator's

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3 427 office, and signed consent forms and completed survey forms will be locked in a secure  
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5 428 file cabinet at the end of each day. A very limited number of trained study staff can  
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7 429 have the key to the locked file cabinets. Participation in every aspect of the study will  
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9 430 be voluntary, and for all new data collection, participants will be asked to provide  
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11 431 written informed consent. Besides, collection of specimens may cause mild discomfort  
12  
13 432 to the subject during the procedure, especially drawing blood from young children. To  
14  
15 433 minimize invasive procedures during sample collection, swab and blood specimens  
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17 434 will be collected by aseptic technique and we encourage the use of leftover sera during  
18  
19 435 routine medical care at the time point of enrolment.

20  
21 436 As a benefit of participating in the study, participants with pertussis will receive senior  
22  
23 437 doctor consultation during treatment on how to limit transmissions among family  
24  
25 438 members and co-workmates; Patients enrolled in the study will have access to  
26  
27 439 antibiotic susceptibility testing results should they have *B. pertussis* isolates acquired.  
28  
29 440 This will give a guide on empirical antibiotic usages for physicians; moreover, the data  
30  
31 441 generated in the study will be valuable to determine the burden of pertussis and  
32  
33 442 explore risk factors for illness attributable to severe pertussis in children as well as  
34  
35 443 adolescents/adults, which can be used by public health departments, healthcare  
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37 444 providers and scientific group in China to inform policies making, implement disease  
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39 445 control and prevention (i.e. vaccination) and improve patient care, both at the sites  
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41 446 level and national level. In general, the minimal risks associated with physical  
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43 447 discomfort during blood and N/P sample collection are offset by the great benefit  
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45 448 associated with the study's ability to inform pertussis prevention and control  
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47 449 strategies in China. Upon completion, results from this study will be disseminated via  
48  
49 450 academic presentations and publication in peer-reviewed journals.

## 49 451 **DISCUSSION**

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51 452 PertussisChina is an innovative and a pilot of a laboratory-based and population-based  
52  
53 453 active surveillance platform for vaccine-preventable bacterial diseases (VPBD) in China,  
54  
55 454 which endeavors to establish a network of laboratories and hospitals using  
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57 455 comparable and unified standards to provide up-to-date disease burden estimates  
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59 456 and disease determinants for evaluating, prioritizing and optimizing the use of  
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3 457 vaccines and for the development of new interventions against bacterial infections in  
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5 458 the country. Pertussis is the first one of the several bacterial infections that we are  
6  
7 459 planning to take this approach. In response to the changing epidemiology of pertussis  
8  
9 460 in China<sup>7 8 42 43</sup>, the 2019 summon of the National Immunization Advisory Committee  
10  
11 461 submitted a motion to its members urging the modification of the current  
12  
13 462 immunization schedule of pertussis vaccine administered at 3, 4, 5 and 18-24 months<sup>44</sup>,  
14  
15 463 to vaccinate children at 2, 4, 6 and 18-24 months instead and to add a 5<sup>th</sup> booster dose  
16  
17 464 at 4-6 years of age; however, partly due to knowledge gaps existed in age-specific  
18  
19 465 burden of pertussis, NIAC suspended its decision on this issue. To provide up-to-date  
20  
21 466 evidence on disease burden of pertussis, this study will focus on age-specific incidence  
22  
23 467 based on laboratory confirmation and will fill the data gaps on prospectively and  
24  
25 468 actively collected incidence data and key information on illness severity and outcomes.  
26  
27 469 We are expecting that data from this study can be served as background information  
28  
29 470 augmenting NIDSS to inform NIAC's recommendations on children vaccination and  
30  
31 471 further quantify the benefit of adolescent/adult vaccination to protect infants from  
32  
33 472 severe outcomes in future. There are several strengths of the study.

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35 473 In this one-year study, we will enroll suspected chronic/persistent cough patients (for  
36  
37 474 infants aged less than 1 year, cough regardless of duration) from health care facilities  
38  
39 475 in two sites of China, covering a censused population of 2.23 million. The catchment  
40  
41 476 population utilizing health-care services at the SHs are well characterized and defined  
42  
43 477 by HUAS, providing unbiased estimates of age-stratified total person-times observed  
44  
45 478 in the cohort. The prevalence of cough in regarding of illness duration and proportion  
46  
47 479 of people who do not seek healthcare are measured retrospectively by HUAS. Thus by  
48  
49 480 comparing between data generated from HUAS in community and case registry in SHs,  
50  
51 481 we will able to measure incidence by settings (i.e. community, outpatient and  
52  
53 482 inpatient), especially those in communities whose symptoms are mild or atypical after  
54  
55 483 the waning of vaccine-induced immunity or those no healthcare are sought<sup>2</sup>. Besides,  
56  
57 484 all hospitalizations suspected of pertussis will be actively searched and prospectively  
58  
59 485 enrolled in a timely manner in our SHs, serving as a complete and representative  
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61 486 sample of pertussis occurred in the interested population that would have induced  
62  
63 487 minimal selection bias. As for milder cases in ambulatory settings, sampling of patients

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3 488 with chronic/persistent cough in outpatient setting to conduct laboratory  
4  
5 489 investigation is preferred. Misclassification of cases or recall bias will be minimized by  
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7 490 the complex laboratory procedures (i.e. culture, PCR, and serology combined), unified  
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9 491 data collection tools (i.e. CRFs) and data collection process, i.e. the 60-day of follow-  
10  
11 492 up during which interesting events (e.g. 3-fold titer raising) will be closely monitored  
12  
13 493 by sequential sera samples. Using laboratory-confirmed pertussis as the outcome will  
14  
15 494 allow us to specifically measure pertussis disease burden. To account for  
16  
17 495 asymptomatic carriage of *B. pertussis*, we will recruit healthy control to investigate  
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19 496 the proportion of population carrying *B. pertussis* in their upper respiratory tract and  
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21 497 sero-positivity, which could be useful for calculating population attributable fraction  
22  
23 498 (AF) to adjust rate estimates. In addition, the prospective cohort will provide valuable  
24  
25 499 follow-up data related to risk factors for severe illness (i.e. adverse clinical outcomes  
26  
27 500 of hospitalization or death). Collection of the vaccination history (including band,  
28  
29 501 dosing, procedure and time of administration) from study participants will help  
30  
31 502 explore the breakthrough rates of *B. pertussis* infection among different type of  
32  
33 503 vaccinees and investigate reasons of vaccination failure, by linkage of study subjects  
34  
35 504  $\leq 14$  years old with his/her individual records on immunization in the national database.  
36  
37 505 Finally, we will abstract EMR data from hospital information system, which serves as  
38  
39 506 a complete and accurate record of cough illness outcomes occurred in SHs. The  
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41 507 retrospectively collected EMR data will be validated by prospectively counting cases  
42  
43 508 eligible for inclusion at selective departments of SHs on daily basis. Using data from  
44  
45 509 the EMR will allow us to determine the size of outpatient and emergency department  
46  
47 510 visits for cough illness in the studied population. For most of adults and fully  
48  
49 511 immunized children and adolescents, their illness is generally mild and is most likely  
50  
51 512 to be encountered at the ambulatory settings in which the diagnostic capacity is  
52  
53 513 generally lacking.

51 514 Aside from acquiring incidence estimates, the prevalence and distribution of *B.*  
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53 515 *pertussis* strains circulating in the population will be determined and characterized,  
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55 516 which are reported to be evolving under the selection pressure from both vaccine and  
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57 517 antibiotics in previous studies<sup>45</sup> and are important data for the development of novel  
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59 518 vaccine or new therapeutics in the country. For example, as a benefit of the study, we  
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3 519 will create a representative national and well characterized repository of strains and  
4 520 specimens that can be shared with other investigators for future research, the main  
5 521 antigenic and genotypic features of *B. pertussis* will be characterized by sequencing or  
6  
7 522 other bio-molecular methods.  
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11 523 We realized that there are several limitations worthy of note in our study. Firstly, we  
12 524 will not identify all pertussis that occur in our studied population since our case  
13 525 definition will not capture atypical and asymptomatic manifestations associated with  
14 526 *B. pertussis* infection. For example, previous studies showed that about 17.4%  
15 527 children<sup>46</sup> and 20% adolescents/adults<sup>47</sup> with *B. pertussis* infection had a cough  
16 528 duration less than 3 weeks, and other symptoms/signs used in the case definition, like  
17 529 spasmodic cough (63%), post-tussive vomiting (42%) and whoops (8%), were  
18 530 infrequently presented in adults<sup>48</sup>, which will make incidence underestimated. It is  
19 531 argued that no symptom is sufficiently predictive for diagnosing pertussis<sup>49</sup> and there  
20 532 was no case definition that has been proposed for purpose of studying disease burden  
21 533 of pertussis. After balancing at the sensitivity and specificity of case definition  
22 534 commonly recommended by WHO, the U.S. and others<sup>50-52</sup> and the available  
23 535 laboratory capacity and resources in the study, we finally adopted the current case  
24 536 definition that can be used to facilitate comparison of results between studies and  
25 537 countries. Second, our study period is a little short. Since pertussis has showed a cyclic  
26 538 pattern and peaked every 3-5 years<sup>2 16</sup>, our study will not capture this feature.  
27 539 Moreover, our study is going to recruit cases in 2021-2022, right after COVID-19  
28 540 pandemic. As the epidemiology of many respiratory infections have been reported  
29 541 changing as a result of widely implementation of nonpharmaceutical interventions  
30 542 (e.g. wearing masks, social distancing, and personal health protection)<sup>53 54</sup> and the  
31 543 detained coverage of vaccines used in Expanded Program on Immunization during the  
32 544 pandemic<sup>55</sup>. The impacts of COVID-19 outbreak on incidence estimates of pertussis  
33 545 are not foreseeable in the study. Future studies are upcoming depending on the  
34 546 results of this pilot. Finally, China is a big country with large variations in population  
35 547 density and across different climate, geographic and economic regions. Although we  
36 548 have paid careful attention to variables, like DTP3 vaccine coverage, childhood  
37 549 mortality and health-care delivery pattern when selecting study sites, regions with the  
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3 550 highest and lowest reported incidence of pertussis are generally not included. This  
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5 551 may also influence the generalizability of the incidence estimates to extrapolate to  
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7 552 other regions.  
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9 553 In summary, PertussisChina is an innovative study that uses unified protocol to  
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11 554 generate up-to-date high-quality incidence data on pertussis. The study design can  
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13 555 secure the precision of data collection and provide insights into the prospectively  
14  
15 556 conducted studies that designed to augment passive surveillance in countries where  
16  
17 557 resources is limited and data is currently lacking. When completed, the results coming  
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19 558 out this study will provide valuable scientific data on the incidence, etiology, and risk  
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21 559 factors for severe sequelae of pertussis to academic societies and the public health  
22  
23 560 authorities, who is currently struggling and fighting against this burdensome disease  
24  
25 561 worldwide.  
26

## 27 562 **Contributors**

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29  
30 563 ZS is the principal investigator on this study who conceived and critically revised the  
31  
32 564 manuscript. JY, HH and YZ conceptualized and designed the study, wrote the first draft  
33  
34 565 and contributed equally to this work. YG, JX, LX, and YG designed the laboratory  
35  
36 566 methods. XZ, QZ, YZ and XT wrote the statistical analysis plan. CC and ZC commented  
37  
38 567 on and revised drafts of the manuscript. All authors contributed to reviewing, revising,  
39  
40 568 and approving the final manuscript.  
41

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43  
44  
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46  
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48  
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## 51 573 **Competing interests**

52  
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54 574 The authors declare that they have no competing interests.  
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575 **Patient and public involvement**

576 Patients and/or the public were not involved in the design, or conduct, or reporting,  
577 or dissemination plans of this research.

578 **Patient consent for publication**

579 Not required.

580 **Ethics approval**

581 This study has been approved by Chinese Center for Disease Control and Prevention's  
582 Institutional Review Board (reference no. ICDC-202110).

583

For peer review only

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4 744 **Figure Legends**  
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6 745 **Figure 1. Incidence of reported pertussis from NNIDSS, China, 1952-2019.** A cDTaP  
7  
8 746 was introduced into national immunization program to replace DTwP in 2007 and the  
9  
10 747 transition was fully completed in 2013. Abbreviations: DTwP, combined diphtheria,  
11  
12 748 tetanus toxoid and whole-cell pertussis vaccine; cDTaP, co-purified diphtheria, tetanus  
13  
14 749 toxoid and acellular pertussis vaccine; National Notifiable Infectious Disease  
15  
16 750 Surveillance System (NNIDSS).  
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19 751 **Figure 2. Location and population size of study sites included in PertussisChina study**  
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22 752 **Figure 3. Flow diagram of major study activities**  
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26 753 **Figure 4. Data flow chart and key indicators used to calculate incidence of pertussis**  
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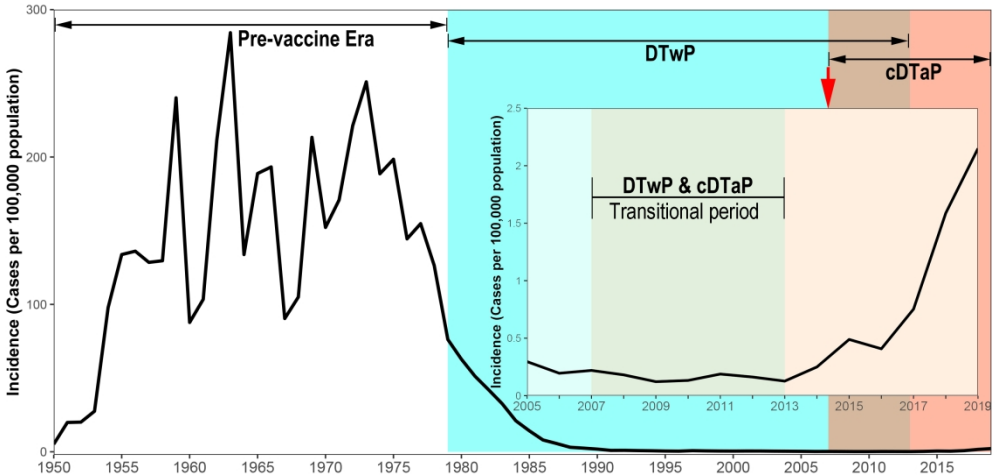


Figure 1. Incidence of reported pertussis from NNIDSS, China, 1952-2019

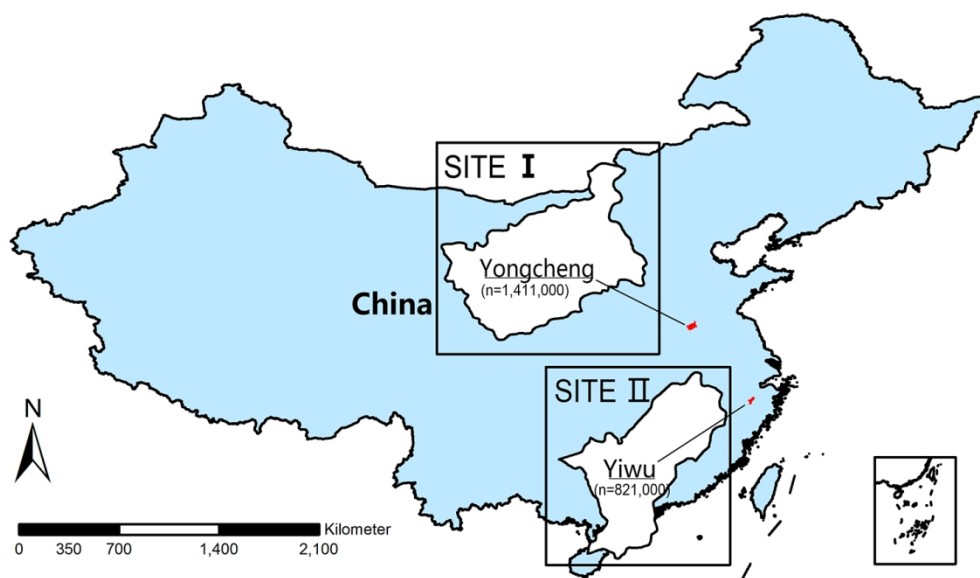


Figure 2. Location and population size of study sites included in PertussisChina study



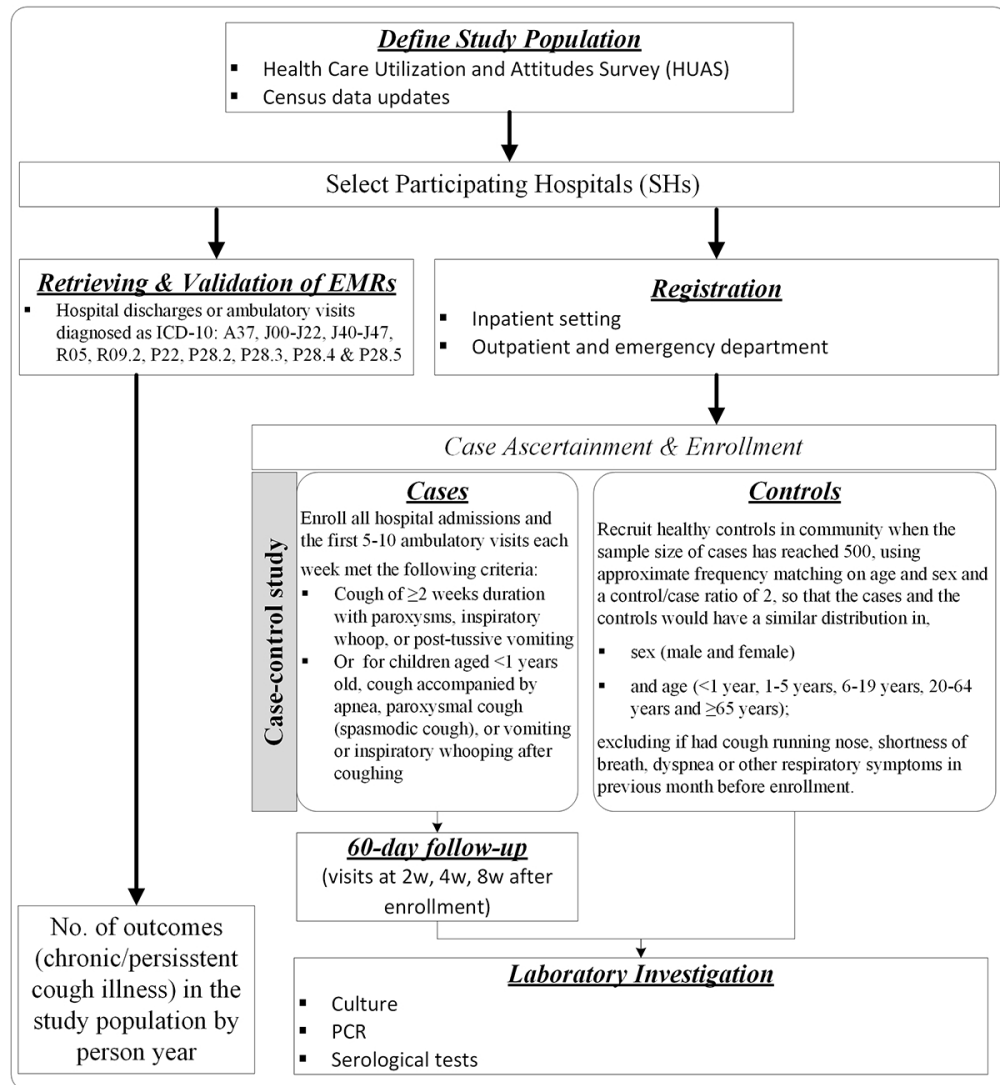


Figure 3. Flow diagram of major study activities

101x110mm (300 x 300 DPI)

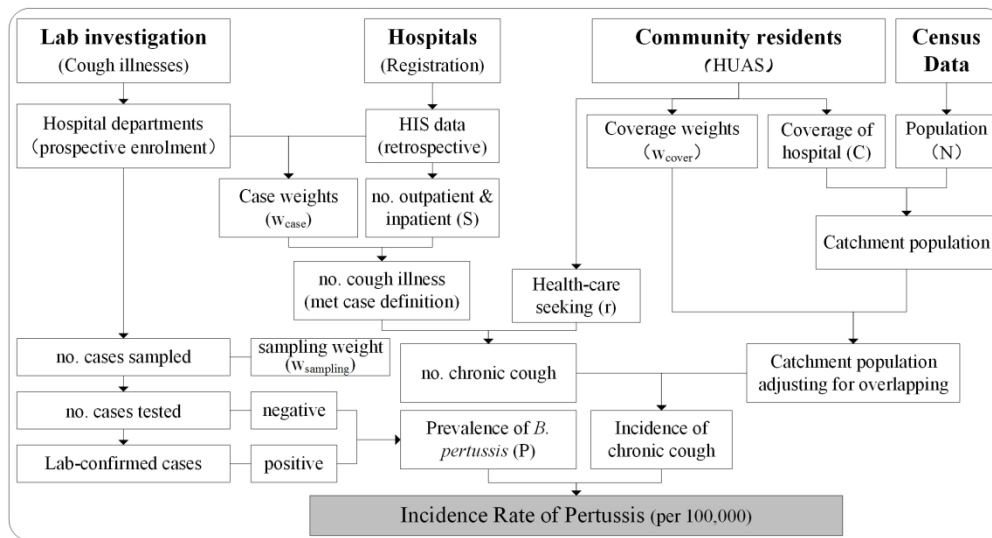


Figure 4. Data flow chart and key indicators used to calculate incidence of pertussis

187x100mm (300 x 300 DPI)

## Supplementary Appendix

**Title:** Burden of Whooping Cough in China (PertussisChina): Study Protocol of a Prospective, Population-based Case-control Study

**Running head:** PertussisChina Study, 2020

### Tables & Forms

- Supplementary Table 1. Survey questionnaire for healthcare utilization and attitudes survey of cough illness among children under 5 years old
- Supplementary Table 2. Survey questionnaire for healthcare utilization and attitudes survey of cough illness among persons aged 5 years and older
- Supplementary Table 3. Case screening and ascertainment form
- Supplementary Table 4. Baseline information of case & control (CRF—T0)
- Supplementary Table 5. Follow-up information of case (CRF—T2w/T4w/T8w)
- Supplementary Table 6. Outcome of case at the end of follow-up (CRF—Tend)

**Supplementary Table 1.** Survey questionnaire for healthcare utilization and attitudes survey of cough illness among children under 5 years old

Greetings! We are the staff of Center for Disease Control and Prevention. We sincerely invite you to participate in this questionnaire survey. The purpose of the survey is to study the utilization and attitudes of community residents towards health-care services of chronic/persistent cough, so that we can better serve you in the future.

This survey is anonymous. Your answers to these questions are kept confidential. You can choose whether to participate in the survey voluntarily or not. Refusal of the survey will not have any adverse consequences on you personally and your children. If you agree to the participate, please read each question carefully and fill in the answer on your own. Thank you for your support and cooperation!

**Part I. Basic Information**

- 1.1 Site: \_\_\_\_\_ Site ID: \_\_\_\_\_
- 1.2 Your length of time (years & months) living in the site (e.g. Yiwu or Yongcheng):  
 less than 6 months     six months and over
- 1.3 Current address: \_\_\_\_\_ county \_\_\_\_\_ street \_\_\_\_\_ community/village
- 1.4 Type of respondents in relation to the studied subject/children:  
 mother     father     grandma/grandpa     others \_\_\_\_\_
- 1.5 Date of Birth:    / /  (yyyy/MM/dd)
- 1.6 Gender:     Male     Female
- 1.7 Ethnicity:     Han     others \_\_\_\_\_
- 1.8 Did your child attend school?     yes     no
- 1.9 Your occupation (of the respondent who answered the question):  
 students     housework or unemployed     retired people     commercial & service sector workers     food handler or employees of food industry  
 specialists, including teacher, medical personnel and workers     agriculture, forestry, animal husbandry and fishery workers     others \_\_\_\_\_

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4 1.10 Your educational attainment (of the respondent who answered the question).

- 5 primary school or illiteracy middle school high school  
6  
7 technical secondary school college level and above  
8

9  
10 1.11 Including yourself, there are\_\_\_\_\_members in your family (defined as those  
11 who shared the same dining table in the house)?  
12

13 Of which, there are\_\_\_\_\_children under five years old.  
14

15 1.12 Is there any smokers or ex-smokers in your family?  yes  no  
16  
17

18 **Part II. self-perceived illness and health-care seeking behavior**  
19

20  
21 2.1 Did your children experienced cough during the past one month prior to our  
22 interview?  no  yes  
23

24  
25 2.1.1 If yes, how long did the cough last?

- 26  <1 week  1-2 weeks  3-4 weeks  5-8 weeks  >8 weeks  
27  
28

29 2.1.2 If yes, what is the clinical characteristics of the last episode of cough?

- 30 paroxysmal cough vomiting after coughing whooping cough  
31  
32 cough worsening during the night vomiting after coughing  
33  
34 productive cough with large amount of sputum dry cough  
35  
36 cough with blood in sputum others\_\_\_\_\_

37  
38 2.1.3 If yes, what is the other concomitant symptoms?

- 39 productive cough running nose fever (body temperature  $\geq 37.2^{\circ}\text{C}$ )  
40  
41 belching acid reflux irritable and crying vomiting headache  
42  
43 tachypnea earache sore throat dyspnea abdominal pain  
44  
45 arthralgia chest pain myalgia fatigue lethargy  
46  
47 burn after sternum without any other discomfort others\_\_\_\_\_

48  
49 2.1.4 If yes, what do you think is the most probable cause of your cough?

- 50 respiratory tract infection inhalation of foreign objects in the respiratory tract  
51  
52 COPD exacerbation asthma exacerbation recurrent tuberculosis  
53  
54 chronic cardiopulmonary disease lung cancer inhalation of cold air  
55  
56 chronic bronchitis bronchiectasis I don't know others\_\_\_\_\_

2.2 Did your child visit a doctor or seek healthcare during the last episode of cough?

no     yes

2.2.1 If yes, where did your child see a doctor?

(For Yiwu site, please select the following)

- The Fourth Affiliated Hospital Zhejiang University School of Medicine
- Yiwu Fuyuan Hospital    Yiwu Maternal and Children's Hospital
- Yiwu Central Hospital    Yiwu Traditional Chinese Medicine Hospital
- Yiwu Tianxiang Medical Group Dongfang Hospital
- Chouzhou Hospital of Yiwu    The Second People's Hospital of Yiwu
- The Third People's Hospital of Yiwu    Yiting township Health Center
- Suxi Township Health Center    Beiyuan Community Health Center
- Shangxi Township Health Center    Dachen Township Health Center
- Houzhai Community Health Center    Chi'an Township Health Center
- Chengxi Community Health Center    Niansanli Community Health Center
- Yiwu Huashan Rehabilitation Hospital    Jiangdong Community Health Center
- Futian Community Health Center    Yiwu Dermatology Hospital
- Zhejiang Children's Hospital    Village clinics or private clinics
- others \_\_\_\_\_

(For Yongcheng site, please select the following)

- Yongcheng People's Hospital    Yongcheng Central Hospital
- Yongmei Group General Hospital    Henan Shenhua Group General Hospital
- Yongcheng Maternal & Child Health Hospital    Yucheng Township Health Center
- Chenji Township Health Center    Gaozhuang Township Health Center
- Yongcheng Mangdang Hospital    Lizhai Township Health Center
- Yongcheng Second People's Hospital    Liuhe Township Health Center
- Yanji Township Health Center    Dawangji Township Health Center
- Longgang Township Health Center    Shunhe Township Health Center
- Peiqiao Township Health Center    Huaihai Community Health Center
- Huangkou Township Health Center    Maqiao Township Health Center
- Jiangkou Township Health Center    Houling Township Health Center

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4 Chenguanzhuang Township Health Center  Taiqiu Township Health Center  
5  
6 Wolong Township Health Center  Huicun Township Health Center  
7  
8 Yongcheng Traditional Chinese Medicine Hospital  
9  
10 Shibali Township Health Center  Xuehu Township Health Center  
11  
12 Mamu Township Health Center  Xinqiao Township Health Center  
13  
14 Xunyang Township Health Center  Shuangqiao Township Health Center  
15  
16 Yongcheng Jiangkou Yongji Hospital  Miaoqiao Township Health Center  
17  
18 Yongcheng Tuberculosis Hospital  Tiaohu Township Health Center  
19  
20 Zhongyuan Road Community Health Center  Yongcheng Wuguanke Hospital  
21  
22 Mangshan Township Health Center  Luanhu Township Health Center  
23  
24 others \_\_\_\_\_  
25  
26

27 2.2.1 If no, why did not your child see a doctor?  
28

- 29 Symptoms are mild, no need to see a doctor  
30  
31 The hospital is too far from home and the transportation is inconvenient  
32  
33 Drugs purchased in pharmacies Distrust the doctor  
34  
35 Unaffordable high medical expenses  
36  
37 Hospital facilities and environment were poor  
38  
39 others \_\_\_\_\_  
40

41 2.3 Was your child hospitalized for the last episode of cough?  no  yes  
42

43 2.3.1 If yes, where was your child hospitalized?  
44

45 (For Yiwu site, please select the following)

- 46 The Fourth Affiliated Hospital Zhejiang University School of Medicine  
47  
48 Yiwu Fuyuan Hospital Yiwu Maternal and Children's Hospital  
49  
50 Yiwu Central Hospital Yiwu Traditional Chinese Medicine Hospital  
51  
52 Yiwu Tianxiang Medical Group Dongfang Hospital  
53  
54 Chouzhou Hospital of Yiwu The Second People's Hospital of Yiwu  
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56 The Third People's Hospital of Yiwu Yiting township Health Center  
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58 Suxi Township Health Center Beiyuan Community Health Center  
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60 Shangxi Township Health Center Dachen Township Health Center

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4  Houzhai Community Health Center     Chi'an Township Health Center  
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6  Chengxi Community Health Center     Niansanli Community Health Center  
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8  Yiwu Huashan Rehabilitation Hospital     Jiangdong Community Health Center  
9  
10  Futian Community Health Center     Yiwu Dermatology Hospital  
11  
12  Zhejiang Children's Hospital     Village clinics or private clinics  
13  
14  others\_\_\_\_\_

15  
16 (For Yongcheng site, please select the following)

- 17  Yongcheng People's Hospital     Yongcheng Central Hospital  
18  
19  Yongmei Group General Hospital     Henan Shenhua Group General Hospital  
20  
21  Yongcheng Maternal & Child Health Hospital     Yucheng Township Health Center  
22  
23  Chenji Township Health Center     Gaozhuang Township Health Center  
24  
25  Yongcheng Mangdang Hospital     Lizhai Township Health Center  
26  
27  Yongcheng Second People's Hospital     Liuhe Township Health Center  
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29  Yanji Township Health Center     Dawangji Township Health Center  
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31  Longgang Township Health Center     Shunhe Township Health Center  
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33  Peiqiao Township Health Center     Huaihai Community Health Center  
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35  Huangkou Township Health Center     Maqiao Township Health Center  
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37  Jiangkou Township Health Center     Houling Township Health Center  
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39  Chenguanzhuang Township Health Center     Taiqiu Township Health Center  
40  
41  Wolong Township Health Center     Huicun Township Health Center  
42  
43  Yongcheng Traditional Chinese Medicine Hospital  
44  
45  Shibali Township Health Center     Xuehu Township Health Center  
46  
47  Mamu Township Health Center     Xinqiao Township Health Center  
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49  Xunyang Township Health Center     Shuangqiao Township Health Center  
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51  Yongcheng Jiangkou Yongji Hospital     Miaoqiao Township Health Center  
52  
53  Yongcheng Tuberculosis Hospital     Tiaohe Township Health Center  
54  
55  Zhongyuan Road Community Health Center     Yongcheng Wuguanke Hospital  
56  
57  Mangshan Township Health Center     Luanhu Township Health Center  
58  
59  others  
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### Part III. Attitudes towards health-care utilization

(Next, we will ask some questions about the actions you might take under some hypothetical situations that do not need to happen.)

3.1 If your child keeps coughing for 2 weeks but does not get better, and you have decided to see a doctor, which one of the following medical institutions would you choose to go?

(For Yiwu site, please select the following)

- The Fourth Affiliated Hospital Zhejiang University School of Medicine
- Yiwu Fuyuan Hospital    Yiwu Maternal and Children's Hospital
- Yiwu Central Hospital    Yiwu Traditional Chinese Medicine Hospital
- Yiwu Tianxiang Medical Group Dongfang Hospital
- Chouzhou Hospital of Yiwu    The Second People's Hospital of Yiwu
- The Third People's Hospital of Yiwu    Yiting township Health Center
- Suxi Township Health Center    Beiyuan Community Health Center
- Shangxi Township Health Center    Dachen Township Health Center
- Houzhai Community Health Center    Chi'an Township Health Center
- Chengxi Community Health Center    Niansanli Community Health Center
- Yiwu Huashan Rehabilitation Hospital    Jiangdong Community Health Center
- Futian Community Health Center    Yiwu Dermatology Hospital
- Zhejiang Children's Hospital    Village clinics or private clinics
- others\_\_\_\_\_

(For Yongcheng site, please select the following)

- Yongcheng People's Hospital    Yongcheng Central Hospital
- Yongmei Group General Hospital    Henan Shenhua Group General Hospital
- Yongcheng Maternal & Child Health Hospital    Yucheng Township Health Center
- Chenji Township Health Center    Gaozhuang Township Health Center
- Yongcheng Mangdang Hospital    Lizhai Township Health Center
- Yongcheng Second People's Hospital    Liuhe Township Health Center
- Yanji Township Health Center    Dawangji Township Health Center

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4  Longgang Township Health Center    Shunhe Township Health Center  
5  Peiqiao Township Health Center    Huaihai Community Health Center  
6  Huangkou Township Health Center    Maqiao Township Health Center  
7  Jiangkou Township Health Center    Houling Township Health Center  
8  Chenguanzhuang Township Health Center    Taiqiu Township Health Center  
9  Wolong Township Health Center    Huicun Township Health Center  
10  Yongcheng Traditional Chinese Medicine Hospital  
11  Shibali Township Health Center    Xuehu Township Health Center  
12  Mamu Township Health Center    Xinqiao Township Health Center  
13  Xunyang Township Health Center    Shuangqiao Township Health Center  
14  Yongcheng Jiangkou Yongji Hospital    Miaoqiao Township Health Center  
15  Yongcheng Tuberculosis Hospital    Tiaohu Township Health Center  
16  Zhongyuan Road Community Health Center    Yongcheng Wuguanke Hospital  
17  Mangshan Township Health Center    Luanhu Township Health Center  
18  others\_\_\_\_\_

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32  
33 3.2 If the doctor recommends that your child be hospitalized, which one of the  
34 following medical institutions would you choose?  
35

36 (For Yiwu site, please select the following)

- 37  
38  
39  The Fourth Affiliated Hospital Zhejiang University School of Medicine  
40  Yiwu Fuyuan Hospital    Yiwu Maternal and Children's Hospital  
41  Yiwu Central Hospital    Yiwu Traditional Chinese Medicine Hospital  
42  Yiwu Tianxiang Medical Group Dongfang Hospital  
43  Chouzhou Hospital of Yiwu    The Second People's Hospital of Yiwu  
44  The Third People's Hospital of Yiwu    Yiting township Health Center  
45  Suxi Township Health Center    Beiyuan Community Health Center  
46  Shangxi Township Health Center    Dacheng Township Health Center  
47  Houzhai Community Health Center    Chi'an Township Health Center  
48  Chengxi Community Health Center    Niansanli Community Health Center  
49  Yiwu Huashan Rehabilitation Hospital    Jiangdong Community Health Center  
50  Futian Community Health Center    Yiwu Dermatology Hospital  
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Zhejiang Children's Hospital  Village clinics or private clinics

others \_\_\_\_\_

(For Yongcheng site, please select the following)

Yongcheng People's Hospital  Yongcheng Central Hospital

Yongmei Group General Hospital  Henan Shenhua Group General Hospital

Yongcheng Maternal & Child Health Hospital  Yucheng Township Health Center

Chenji Township Health Center  Gaozhuang Township Health Center

Yongcheng Mangdang Hospital  Lizhai Township Health Center

Yongcheng Second People's Hospital  Liuhe Township Health Center

Yanji Township Health Center  Dawangji Township Health Center

Longgang Township Health Center  Shunhe Township Health Center

Peiqiao Township Health Center  Huaihai Community Health Center

Huangkou Township Health Center  Maqiao Township Health Center

Jiangkou Township Health Center  Houling Township Health Center

Chenguanzhuang Township Health Center  Taiqiu Township Health Center

Wolong Township Health Center  Huicun Township Health Center

Yongcheng Traditional Chinese Medicine Hospital

Shibali Township Health Center  Xuehu Township Health Center

Mamu Township Health Center  Xinqiao Township Health Center

Xunyang Township Health Center  Shuangqiao Township Health Center

Yongcheng Jiangkou Yongji Hospital  Miaoqiao Township Health Center

Yongcheng Tuberculosis Hospital  Tiaohe Township Health Center

Zhongyuan Road Community Health Center  Yongcheng Wuguanke Hospital

Mangshan Township Health Center  Luanhu Township Health Center

others \_\_\_\_\_

#### Part IV. Other questions

4.1 Has your child ever received the following vaccines?

influenza vaccine  pneumococcal vaccine  Haemophilus influenzae vaccine

1  
2  
3  
4  Vaccines containing pertussis components (i.e. DTP)

5 4.1.1 If received vaccines containing pertussis (i.e. DTP), what kind of the vaccine?

6  
7  cDTaP  DTaP/Hib  DTaP-IPV/Hib

8  
9 4.2 Your family's average annual income (Chinese Yuan) is,

10  
11  <50,000  50,000-90,000  100,000-190,000  200,000-490,000  ≥500,000

12  
13 4.3 Your phone number is \_\_\_\_\_

14  
15  
16  
17  
18 Thank you very much for taking your time. The information you provided in this  
19 interview is very valuable to help us improve our work. Wish you a happy life!  
20

21  
22 Time of survey started: □□□□/□□/□□:□□:□□ (yyyy/MM/dd hh:mm)

23  
24 Time of survey ended: □□□□/□□/□□:□□:□□ (yyyy/MM/dd hh:mm)

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26 Investigator: \_\_\_\_\_ Supervisor: \_\_\_\_\_  
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Supplementary Table 2. Survey questionnaire for healthcare utilization and attitudes survey of cough illness among persons aged 5 years and older

Greetings! We are the staff of Center for Disease Control and Prevention. We sincerely invite you to participate in this questionnaire survey. The purpose of the survey is to study the utilization and attitudes of community residents towards health-care services of chronic/persistent cough, so that we can better serve you in the future.

This survey is anonymous. Your answers to these questions are kept confidential. You can choose whether to participate in the survey voluntarily or not. Refusal of the survey will not have any adverse consequences on you personally and your children. If you agree to the participate, please read each question carefully and fill in the answer on your own. Thank you for your support and cooperation!

### Part I. Basic Information

1.1 Site: \_\_\_\_\_ Site ID: \_\_\_\_\_

1.2 Your length of time (years & months) living in the site (e.g. Yiwu or Yongcheng):

less than 6 months     six months and over

1.3 Current address: \_\_\_\_\_ county \_\_\_\_\_ street \_\_\_\_\_ community/village

1.4 Type of respondents in relation to the studied subject:

respondent himself is the study subject     others \_\_\_\_\_

1.5 Date of Birth: □□□□/□□/□□ (yyyy/MM/dd)

1.6 Gender:     Male     Female

1.7 Ethnicity:     Han     others \_\_\_\_\_

1.8 Your occupation:

students     housework or unemployed     retired people     commercial & service sector workers     food handler or employees of food industry  
 specialists, including teacher, medical personnel and workers     agriculture, forestry, animal husbandry and fishery workers     others \_\_\_\_\_

1.9 Did you ever contact with dust/chemical materials in the working environment in the past one year, such as those encountered by workers using pneumatic drills at

1  
2  
3  
4 construction sites, miners, painters, benzene solvents in leather production, etc.

5  no  yes

6  
7 1.10 Your educational attainment:

8  primary school or illiteracy  middle school  high school

9  technical secondary school  college level and above

10  
11 1.11 Including yourself, there are \_\_\_\_\_ members in your family (defined as those  
12 who shared the same dining table in the house)?

13 Of which, there are \_\_\_\_\_ children under five years old.

14  
15 1.12 Are you smoker or ex-smoker?  yes  no

16  
17  
18  
19  
20  
21  
22 **Part II. self-perceived illness and health-care seeking behavior**

23  
24 2.1 Did you experienced cough during the past one month prior to our interview?

25  no  yes

26 2.1.1 If yes, how long did the cough last?

27  <1 week  1-2 weeks  3-4 weeks  5-8 weeks  >8 weeks

28 2.1.2 If yes, what is the clinical characteristics of the last episode of cough?

29  paroxysmal cough  vomiting after coughing  whooping cough

30  cough worsening during the night  vomiting after coughing

31  productive cough with large amount of sputum  dry cough

32  cough with blood in sputum  others \_\_\_\_\_

33 2.1.3 If yes, what is the other concomitant symptoms?

34  productive cough  running nose  fever (body temperature  $\geq 37.2^{\circ}\text{C}$ )

35  belching  acid reflux  irritable and crying  vomiting  headache

36  tachypnea  earache  sore throat  dyspnea  abdominal pain

37  arthralgia  chest pain  myalgia  fatigue  lethargy

38  burn after sternum  without any other discomfort  others \_\_\_\_\_

39 2.1.4 If yes, what do you think is the most probable cause of your cough?

40  respiratory tract infection  inhalation of foreign objects in the respiratory tract

41  COPD exacerbation  asthma exacerbation  recurrent tuberculosis

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2  
3  
4 chronic cardiopulmonary disease lung cancer inhalation of cold air  
5  
6 chronic bronchitis bronchiectasis I don't know others\_\_\_\_\_

7  
8 2.2 Did you see a doctor or seek healthcare during the last episode of cough?

- 9  no  yes

10  
11 2.2.1 If yes, where did you see a doctor?

12  
13 (For Yiwu site, please select the following)

- 14  
15 The Fourth Affiliated Hospital Zhejiang University School of Medicine  
16  
17 Yiwu Fuyuan Hospital Yiwu Maternal and Children's Hospital  
18  
19 Yiwu Central Hospital Yiwu Traditional Chinese Medicine Hospital  
20  
21 Yiwu Tianxiang Medical Group Dongfang Hospital  
22  
23 Chouzhou Hospital of Yiwu The Second People's Hospital of Yiwu  
24  
25 The Third People's Hospital of Yiwu Yiting township Health Center  
26  
27 Suxi Township Health Center Beiyuan Community Health Center  
28  
29 Shangxi Township Health Center Dachen Township Health Center  
30  
31 Houzhai Community Health Center Chi'an Township Health Center  
32  
33 Chengxi Community Health Center Niansanli Community Health Center  
34  
35 Yiwu Huashan Rehabilitation Hospital Jiangdong Community Health Center  
36  
37 Futian Community Health Center Yiwu Dermatology Hospital  
38  
39 Zhejiang Children's Hospital Village clinics or private clinics  
40  
41 others\_\_\_\_\_

42  
43 (For Yongcheng site, please select the following)

- 44  
45 Yongcheng People's Hospital Yongcheng Central Hospital  
46  
47 Yongmei Group General Hospital Henan Shenhua Group General Hospital  
48  
49 Yongcheng Maternal & Child Health Hospital Yucheng Township Health Center  
50  
51 Chenji Township Health Center Gaozhuang Township Health Center  
52  
53 Yongcheng Mangdang Hospital Lizhai Township Health Center  
54  
55 Yongcheng Second People's Hospital Liuhe Township Health Center  
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57 Yanji Township Health Center Dawangji Township Health Center  
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59 Longgang Township Health Center Shunhe Township Health Center  
60  
Peiqiao Township Health Center Huaihai Community Health Center

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4 Huangkou Township Health Center  Maqiao Township Health Center  
5  
6 Jiangkou Township Health Center  Houling Township Health Center  
7  
8 Chenguanzhuang Township Health Center  Taiqiu Township Health Center  
9  
10 Wolong Township Health Center  Huicun Township Health Center  
11  
12 Yongcheng Traditional Chinese Medicine Hospital  
13  
14 Shibali Township Health Center  Xuehu Township Health Center  
15  
16 Mamu Township Health Center  Xinqiao Township Health Center  
17  
18 Xunyang Township Health Center  Shuangqiao Township Health Center  
19  
20 Yongcheng Jiangkou Yongji Hospital  Miaoqiao Township Health Center  
21  
22 Yongcheng Tuberculosis Hospital  Tiaohe Township Health Center  
23  
24 Zhongyuan Road Community Health Center  Yongcheng Wuguanke Hospital  
25  
26 Mangshan Township Health Center  Luanhu Township Health Center  
27  
28 others\_\_\_\_\_

29 2.2.1 If no, why did not you see a doctor?

- 30  
31 Symptoms are mild, no need to see a doctor  
32  
33 The hospital is too far from home and the transportation is inconvenient  
34  
35 Drugs purchased in pharmacies Distrust the doctor  
36  
37 Unaffordable high medical expenses  
38  
39 Hospital facilities and environment were poor  
40  
41 others\_\_\_\_\_

42 2.3 Were you hospitalized for the last episode of cough?  no  yes

43 2.3.1 If yes, where were you hospitalized?

44 (For Yiwu site, please select the following)

- 45  
46  
47  
48 The Fourth Affiliated Hospital Zhejiang University School of Medicine  
49  
50 Yiwu Fuyuan Hospital Yiwu Maternal and Children's Hospital  
51  
52 Yiwu Central Hospital Yiwu Traditional Chinese Medicine Hospital  
53  
54 Yiwu Tianxiang Medical Group Dongfang Hospital  
55  
56 Chouzhou Hospital of Yiwu The Second People's Hospital of Yiwu  
57  
58 The Third People's Hospital of Yiwu Yiting township Health Center  
59  
60 Suxi Township Health Center Beiyuan Community Health Center



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4 Shangxi Township Health Center Dachen Township Health Center  
5  
6 Houzhai Community Health Center Chi'an Township Health Center  
7  
8 Chengxi Community Health Center Niansanli Community Health Center  
9  
10 Yiwu Huashan Rehabilitation Hospital Jiangdong Community Health Center  
11  
12 Futian Community Health Center Yiwu Dermatology Hospital  
13  
14 Zhejiang Children's Hospital Village clinics or private clinics  
15  
16 others\_\_\_\_\_

17 (For Yongcheng site, please select the following)

- 18  
19 Yongcheng People's Hospital Yongcheng Central Hospital  
20  
21 Yongmei Group General Hospital Henan Shenhua Group General Hospital  
22  
23 Yongcheng Maternal & Child Health Hospital Yucheng Township Health Center  
24  
25 Chenji Township Health Center Gaozhuang Township Health Center  
26  
27 Yongcheng Mangdang Hospital Lizhai Township Health Center  
28  
29 Yongcheng Second People's Hospital Liuhe Township Health Center  
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31 Yanji Township Health Center Dawangji Township Health Center  
32  
33 Longgang Township Health Center Shunhe Township Health Center  
34  
35 Peiqiao Township Health Center Huaihai Community Health Center  
36  
37 Huangkou Township Health Center Maqiao Township Health Center  
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39 Jiangkou Township Health Center Houling Township Health Center  
40  
41 Chenguanzhuang Township Health Center Taiqiu Township Health Center  
42  
43 Wolong Township Health Center Huicun Township Health Center  
44  
45 Yongcheng Traditional Chinese Medicine Hospital  
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47 Shibali Township Health Center Xuehu Township Health Center  
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49 Mamu Township Health Center Xinqiao Township Health Center  
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51 Xunyang Township Health Center Shuangqiao Township Health Center  
52  
53 Yongcheng Jiangkou Yongji Hospital Miaoqiao Township Health Center  
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55 Yongcheng Tuberculosis Hospital Tiaohe Township Health Center  
56  
57 Zhongyuan Road Community Health Center Yongcheng Wuguanke Hospital  
58  
59 Mangshan Township Health Center Luanhu Township Health Center  
60  
others\_\_\_\_\_

### Part III. Attitudes towards health-care utilization

(Next, we will ask some questions about the actions you might take under some hypothetical situations that do not need to happen.)

3.1 If you keep coughing for 2 weeks but does not get better, and you have decided to see a doctor, which one of the following medical institutions would you choose to go?

(For Yiwu site, please select the following)

- The Fourth Affiliated Hospital Zhejiang University School of Medicine
- Yiwu Fuyuan Hospital    Yiwu Maternal and Children's Hospital
- Yiwu Central Hospital    Yiwu Traditional Chinese Medicine Hospital
- Yiwu Tianxiang Medical Group Dongfang Hospital
- Chouzhou Hospital of Yiwu    The Second People's Hospital of Yiwu
- The Third People's Hospital of Yiwu    Yiting township Health Center
- Suxi Township Health Center    Beiyuan Community Health Center
- Shangxi Township Health Center    Dachen Township Health Center
- Houzhai Community Health Center    Chi'an Township Health Center
- Chengxi Community Health Center    Niansanli Community Health Center
- Yiwu Huashan Rehabilitation Hospital    Jiangdong Community Health Center
- Futian Community Health Center    Yiwu Dermatology Hospital
- Zhejiang Children's Hospital    Village clinics or private clinics
- others\_\_\_\_\_

(For Yongcheng site, please select the following)

- Yongcheng People's Hospital    Yongcheng Central Hospital
- Yongmei Group General Hospital    Henan Shenhua Group General Hospital
- Yongcheng Maternal & Child Health Hospital    Yucheng Township Health Center
- Chenji Township Health Center    Gaozhuang Township Health Center
- Yongcheng Mangdang Hospital    Lizhai Township Health Center
- Yongcheng Second People's Hospital    Liuhe Township Health Center
- Yanji Township Health Center    Dawangji Township Health Center
- Longgang Township Health Center    Shunhe Township Health Center

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4  Peiqiao Township Health Center    Huaihai Community Health Center  
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6  Huangkou Township Health Center    Maqiao Township Health Center  
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8  Jiangkou Township Health Center    Houling Township Health Center  
9  
10  Chenguanzhuang Township Health Center    Taiqiu Township Health Center  
11  
12  Wolong Township Health Center    Huicun Township Health Center  
13  
14  Yongcheng Traditional Chinese Medicine Hospital  
15  
16  Shibali Township Health Center    Xuehu Township Health Center  
17  
18  Mamu Township Health Center    Xinqiao Township Health Center  
19  
20  Xunyang Township Health Center    Shuangqiao Township Health Center  
21  
22  Yongcheng Jiangkou Yongji Hospital    Miaoqiao Township Health Center  
23  
24  Yongcheng Tuberculosis Hospital    Tiaohe Township Health Center  
25  
26  Zhongyuan Road Community Health Center    Yongcheng Wuguanke Hospital  
27  
28  Mangshan Township Health Center    Luanhu Township Health Center  
29  
30  others\_\_\_\_\_

31 3.2 If the doctor recommends that you should be hospitalized, which one of the  
32 following medical institutions would you choose?  
33

34 (For Yiwu site, please select the following)

- 35  
36  
37  The Fourth Affiliated Hospital Zhejiang University School of Medicine  
38  
39  Yiwu Fuyuan Hospital    Yiwu Maternal and Children's Hospital  
40  
41  Yiwu Central Hospital    Yiwu Traditional Chinese Medicine Hospital  
42  
43  Yiwu Tianxiang Medical Group Dongfang Hospital  
44  
45  Chouzhou Hospital of Yiwu    The Second People's Hospital of Yiwu  
46  
47  The Third People's Hospital of Yiwu    Yiting township Health Center  
48  
49  Suxi Township Health Center    Beiyuan Community Health Center  
50  
51  Shangxi Township Health Center    Dachen Township Health Center  
52  
53  Houzhai Community Health Center    Chi'an Township Health Center  
54  
55  Chengxi Community Health Center    Niansanli Community Health Center  
56  
57  Yiwu Huashan Rehabilitation Hospital    Jiangdong Community Health Center  
58  
59  Futian Community Health Center    Yiwu Dermatology Hospital  
60  
 Zhejiang Children's Hospital    Village clinics or private clinics

others\_\_\_\_\_

(For Yongcheng site, please select the following)

- Yongcheng People's Hospital Yongcheng Central Hospital
- Yongmei Group General Hospital Henan Shenhua Group General Hospital
- Yongcheng Maternal & Child Health Hospital Yucheng Township Health Center
- Chenji Township Health Center Gaozhuang Township Health Center
- Yongcheng Mangdang Hospital Lizhai Township Health Center
- Yongcheng Second People's Hospital Liuhe Township Health Center
- Yanji Township Health Center Dawangji Township Health Center
- Longgang Township Health Center Shunhe Township Health Center
- Peiqiao Township Health Center Huaihai Community Health Center
- Huangkou Township Health Center Maqiao Township Health Center
- Jiangkou Township Health Center Houling Township Health Center
- Chenguanzhuang Township Health Center Taiqiu Township Health Center
- Wolong Township Health Center Huicun Township Health Center
- Yongcheng Traditional Chinese Medicine Hospital
- Shibali Township Health Center Xuehu Township Health Center
- Mamu Township Health Center Xinqiao Township Health Center
- Xunyang Township Health Center Shuangqiao Township Health Center
- Yongcheng Jiangkou Yongji Hospital Miaoqiao Township Health Center
- Yongcheng Tuberculosis Hospital Tiaohe Township Health Center
- Zhongyuan Road Community Health Center Yongcheng Wuguanke Hospital
- Mangshan Township Health Center Luanhu Township Health Center
- others\_\_\_\_\_

#### Part IV. Other questions

##### 4.1 Have you ever received the following vaccines?

- influenza vaccine pneumococcal vaccine Haemophilus influenzae vaccine
- Vaccines containing pertussis components (i.e. DTP)

1  
2  
3  
4 4.1.1 If received vaccines containing pertussis (i.e. DTP), what kind of the vaccine?

5 cDTaP DTaP/Hib DTaP-IPV/Hib

6  
7  
8 4.2 Your family's average annual income (Chinese Yuan) is,

9  <50,000  50,000-90,000  100,000-190,000  200,000-490,000  ≥500,000

10  
11 4.3 Your phone number is \_\_\_\_\_

12  
13  
14  
15  
16 Thank you very much for taking your time. The information you provided in this  
17 interview is very valuable to help us improve our work. Wish you a happy life!  
18

19  
20 Time of survey started: □□□□/□□/□□:□□:□□ (yyyy/MM/dd hh:mm)

21  
22 Time of survey ended: □□□□/□□/□□:□□:□□ (yyyy/MM/dd hh:mm)

23  
24 Investigator: \_\_\_\_\_ Supervisor: \_\_\_\_\_  
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Supplementary Table 3. Case screening and ascertainment form

Name of Hospital \_\_\_\_\_ Departments \_\_\_\_\_

Name of patient		Sex	<input type="checkbox"/> male <input type="checkbox"/> female
Birthdate		Ethnicity	
Current address		Phone number	
Date of illness onset		Date of admission	
Date of written informed consent signed			
Lists of inclusion & exclusion criteria			yes no
<b>Inclusion criteria:</b>			
<b>Patient regardless of ages:</b>			
1.cough of $\geq 2$ weeks duration;			<input type="checkbox"/> <input type="checkbox"/>
2.had one or more of the following symptoms;			<input type="checkbox"/> <input type="checkbox"/>
- paroxysmal cough;			<input type="checkbox"/>
- inspiratory whoop;			<input type="checkbox"/>
- post-tussive vomiting.			<input type="checkbox"/>
<b>Infants less than one year old</b>			
1.cough (regardless of cough duration);			<input type="checkbox"/> <input type="checkbox"/>
2.had one or more of the following symptoms;			<input type="checkbox"/> <input type="checkbox"/>
- paroxysmal cough;			<input type="checkbox"/>
- inspiratory whoop;			<input type="checkbox"/>
- post-tussive vomiting;			<input type="checkbox"/>
- apnea.			<input type="checkbox"/>
Written informed consent signed			<input type="checkbox"/> <input type="checkbox"/>
If you answer "No" to any of the above, the patient cannot enter the study.			
<b>Exclusion criteria:</b>			
1.not a permanent resident (lived less than 6 months at the site);			<input type="checkbox"/> <input type="checkbox"/>
2.gastroesophageal reflux;			<input type="checkbox"/> <input type="checkbox"/>
3.spastic bronchitis;			<input type="checkbox"/> <input type="checkbox"/>
4.diagnosed tuberculosis;			<input type="checkbox"/> <input type="checkbox"/>
5.lung mycoplasma/chlamydia infection;			<input type="checkbox"/> <input type="checkbox"/>
6.chronic sinusitis;			<input type="checkbox"/> <input type="checkbox"/>
7.adults/adolescents with a measured body temperature of $\geq 38.5$ °C;			<input type="checkbox"/> <input type="checkbox"/>
8. researchers considered not suitable for participating in the study.			<input type="checkbox"/> <input type="checkbox"/>
If you answer Yes" to any of the above, the patient cannot enter the study.			
Whether the patient is included in the study			<input type="checkbox"/> <input type="checkbox"/>
If no, what is the reason for not included?			
- not meet the inclusion & exclusion criteria;			<input type="checkbox"/> <input type="checkbox"/>
- Refuse to participate ;			<input type="checkbox"/> <input type="checkbox"/>
If yes, what is the patient identifier no.? _____			<input type="checkbox"/> <input type="checkbox"/>



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<b>Vaccination history of DTP3 (for children aged under 14 years old)</b>							
<b>Source of data :</b> <input type="checkbox"/> vaccination certificate <input type="checkbox"/> linkage with national database <input type="checkbox"/> self-reports							
<b>Reasons of unvaccinated :</b> 1. Contraindications; 2. Under the age of vaccination; 3. Missed vaccination time; 4. Parents refused to vaccination; 5. migrating population; 6. Don't know; 7. Others _____							
dose	lot number	producer	dosage		site	Date (YYYY/mm/dd)	Reasons of unvaccinated
			dose	unit			
1							
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<b>Patient specimen collection</b>							
<b>Specimen collected :</b> <input type="checkbox"/> yes <input type="checkbox"/> no							
<b>Date of sampling :</b> ____ / ____ / ____ (YYYY/mm/dd)							
<b>Type of specimen :</b> Nasopharyngeal swab <input type="checkbox"/> amounts : _____							
Whole blood <input type="checkbox"/> quantity : _____ ml							
<b>Hospital :</b> _____ <b>Investigator :</b> _____ <b>Date of reporting :</b> ____ / ____ / ____ (YYYY/mm/dd)							

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Supplementary Table 5. Follow-up information of case (CRF—T<sub>2w</sub>/T<sub>4w</sub>/T<sub>8w</sub>)

Patient identifier no.: \_\_\_\_\_ Type:  Inpatient  outpatient

**Name :** \_\_\_\_\_ ( or **Parents' name :** \_\_\_\_\_ ) **Sex :**  male  female

**Illness onset date :** \_\_\_\_ / \_\_\_\_ / \_\_\_\_ (YYYY/mm/dd) **Admission date :** \_\_\_\_ / \_\_\_\_ / \_\_\_\_ (YYYY/mm/dd)

**Follow-up date :** \_\_\_\_ / \_\_\_\_ / \_\_\_\_ (YYYY/mm/dd) **Weeks of follow-up:**  2 wks  4 wks  8 wks

**Follow-up method:**  hospital visits  home visits

**Outcomes**

**Survival:**  yes  no Date of death: \_\_\_\_ / \_\_\_\_ / \_\_\_\_ (YYYY/mm/dd) death diagnosis : \_\_\_\_\_

**Hospitalized :**  yes  no **Re-admitted into hospital after discharge:**  yes  no

**Reasons for re-admission :** Pneumonia/heart failure/cardiogenic shock/encephalopathy/Seizure/other \_\_\_\_\_

**Lost to follow-up:**  yes  no (refers to 3 consecutive phone calls to patients on different working days but no answers at all )

**Clinical characteristics (during follow-up visits)**

cough ( Starting date \_\_\_\_ / \_\_\_\_ / \_\_\_\_ [YYYY/mm/dd] , duration \_\_\_\_ days )

post-tussive vomiting  paroxysmal cough  whooping cough  apnea  cyanosis  fever ( body temperature \_\_\_\_ °C )

cough worsening in night  productive cough; Sputum color : yellow/white/black/glass like

seizure  hemoptysis  chills  headache  myalgia  sore throat  joint pain  chest pain

sweat  shortness-of-breath  running nose  lachrymation  fatigue  other( \_\_\_\_\_ )

**Blood tests :** WBC \_\_\_\_ × 10<sup>9</sup>/L; L \_\_\_\_ × 10<sup>9</sup>/L; N \_\_\_\_ × 10<sup>9</sup>/L; Plt \_\_\_\_ × 10<sup>9</sup>/L; Hb \_\_\_\_ g/L; CRP \_\_\_\_ mg/L; GLU \_\_\_\_ mmol/L

**Physical check :** body temperature : \_\_\_\_ °C **Breath rate :** \_\_\_\_ breath/min **Heart rate :** \_\_\_\_ beats/min

**Systolic/diastolic blood pressure :** \_\_\_\_ / \_\_\_\_ mmHg **Pulse oximetry:** sPO<sub>2</sub> (if any): \_\_\_\_ %

**Lung auscultation :**  dry rale  wet rale **Consciousness :** clear/lethargy/irritable/delirium/convulsions/coma

**Patient specimen collection**

**Specimen collected :**  yes  no **Date of sampling :** \_\_\_\_ / \_\_\_\_ / \_\_\_\_ (YYYY/mm/dd)

**Type of specimen :** Nasopharyngeal swab  amounts : \_\_\_\_\_

Whole blood  quantity : \_\_\_\_\_ ml

**Reasons for not sampling :**  without coughing symptoms for 1 week  refusal to sampling

**Hospital :** \_\_\_\_\_ **Investigator :** \_\_\_\_\_ **Date of follow-up :** \_\_\_\_ / \_\_\_\_ / \_\_\_\_ (YYYY/mm/dd)

Supplementary Table 6. Outcome of case at the end of follow-up (CRF—T<sub>end</sub>)

Patient identifier no.: \_\_\_\_\_ Type:  inpatient  outpatient

Name : \_\_\_\_\_ ( or Parents' name : \_\_\_\_\_ ) Sex :  male  female Illness onset date : \_\_\_\_ / \_\_\_\_ / \_\_\_\_ (YYYY/mm/dd)  
 Admission date : \_\_\_\_ / \_\_\_\_ / \_\_\_\_ (YYYY/mm/dd) Discharge date : \_\_\_\_ / \_\_\_\_ / \_\_\_\_ (YYYY/mm/dd)  
 Discharge diagnosis : primary diagnosis \_\_\_\_\_  
 secondary diagnosis 1. \_\_\_\_\_ 2. \_\_\_\_\_ 3. \_\_\_\_\_

**Treatment during hospitalization**

Admitting into ICU :  yes  no \_\_\_\_ / \_\_\_\_ / \_\_\_\_ (YYYY/mm/dd)  
 1. Transfer in date \_\_\_\_ / \_\_\_\_ / \_\_\_\_ (YYYY/mm/dd) Transfer out date \_\_\_\_ / \_\_\_\_ / \_\_\_\_ (YYYY/mm/dd)  
 2. Transfer in date \_\_\_\_ / \_\_\_\_ / \_\_\_\_ (YYYY/mm/dd) Transfer out date \_\_\_\_ / \_\_\_\_ / \_\_\_\_ (YYYY/mm/dd)  
 3. Transfer in date \_\_\_\_ / \_\_\_\_ / \_\_\_\_ (YYYY/mm/dd) Transfer out date \_\_\_\_ / \_\_\_\_ / \_\_\_\_ (YYYY/mm/dd)  
 Oxygen therapy :  yes  no duration : \_\_\_\_\_ days  
 Invasive ventilation :  yes  no duration : \_\_\_\_\_ days (invasive ventilation refers to tracheal intubation or tracheotomy)  
 Non-invasive ventilation:  yes  no duration : \_\_\_\_\_ days  
 Oscillating respirator :  yes  no duration : \_\_\_\_\_ days  
 ECMO or interventional lung adjuvant therapy ( iLA )  yes  no date of treatment start : \_\_\_\_ / \_\_\_\_ / \_\_\_\_ (YYYY/mm/dd)  
 Renal replacement therapy/dialysis :  yes  no date of treatment start : \_\_\_\_ / \_\_\_\_ / \_\_\_\_ (YYYY/mm/dd)  
 Exchange transfusion :  yes  no date of treatment start : \_\_\_\_ / \_\_\_\_ / \_\_\_\_ (YYYY/mm/dd)  
 Leukapheresis or leukoreduction therapy :  yes  no date of treatment start : \_\_\_\_ / \_\_\_\_ / \_\_\_\_ (YYYY/mm/dd)

**Drugs**

- ( 1 ) Drug name : Please give the name of the drug, or the trade name if it is a fixed compound preparation
- ( 2 ) Category: A=antibiotic (1. Amoxicillin; 2. Amoxicillin-clavulanic acid; 3. Ampicillin; 4. Azithromycin; 5. Ceftriaxone; 6. Cefuroxime; 7. Ciprofloxacin; 8. Clarithromycin; 9. Doxycycline; 10. Erythromycin; 11. Penicillin; 12. Tetracycline; 13. Compound sulfamethoxazole); B=antiviral drugs; C=steroid hormone drugs
- ( 3 ) Route : 1=oral, 2=intravenous injection, 3=intravenous drip, 4=intramuscular injection, 5=inhalation, 6=other
- ( 4 ) Frequency : 1= continuous , 2=intermittent

drug name (1)	category (2)	route (3)	daily dose		frequency (4)	starting date (YYYY/mm/dd)	stop date (YYYY/mm/dd)
			dose	unit			

**Clinical characteristics**

**Symptoms/signs :**  
 cough ( Starting date \_\_\_\_ / \_\_\_\_ / \_\_\_\_ [YYYY/mm/dd] , duration \_\_\_\_\_ days )  
 post-tussive vomiting  paroxysmal cough  whooping cough  apnea  cyanosis  fever ( body temperature \_\_\_\_\_ °C )  
 cough worsening in night  productive cough; Sputum color : yellow/white/black/glass like  
 seizure  hemoptysis  chills  headache  myalgia  sore throat  joint pain  chest pain  
 sweat  shortness-of-breath  running nose  lachrymation  fatigue  other( \_\_\_\_\_ )

**Complications :**  
 viral pneumonia  cardiac arrest  bacterial pneumonia  bacteremia  acute lung injury/ARDS  heart infection  
 coagulation disorders  pneumothorax  anemia  pleural Effusion  acute kidney injury  myolysis  
 bronchiolitis  gastrointestinal hemorrhage  meningitis  pancreatitis  epilepsy  arrhythmia

<input type="checkbox"/> liver insufficiency	<input type="checkbox"/> stroke	<input type="checkbox"/> hyperglycemia	<input type="checkbox"/> hypoglycemia	<input type="checkbox"/> congestive Heart Failure
<input type="checkbox"/> other ( _____ )				
<b>Patient Prognosis</b>				
<input type="checkbox"/> cured				
<input type="checkbox"/> improved and be discharged				
<input type="checkbox"/> transferred to other hospital      reasons for transfer : community rehabilitation/other ( _____ )				
<input type="checkbox"/> give up treatment      reasons for give-up : economic reasons/illness exacerbation/other ( _____ )				
<input type="checkbox"/> death      date of death : ____ / ____ / ____ (YYYY/mm/dd)      death diagnosis : _____				
Hospital : _____		Investigator : _____		Date of record : ____ / ____ / ____ (YYYY/mm/dd)

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# BMJ Open

## Burden of Whooping Cough in China (PertussisChina): Study Protocol of a Prospective, Population-based Case-control Study

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<b>Primary Subject Heading</b>:	Epidemiology
Secondary Subject Heading:	Infectious diseases
Keywords:	EPIDEMIOLOGY, Paediatric infectious disease & immunisation < PAEDIATRICS, Epidemiology < THORACIC MEDICINE, Epidemiology < INFECTIOUS DISEASES

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1 **Running Title:** PertussisChina Study, 2020

2 **Title:** Burden of Whooping Cough in China (PertussisChina): Study Protocol of a Prospective,  
3 Population-based Case-control Study

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24 **Word count:** abstract =388; text=5,619

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3     25     **ABSTRACT**  
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6     26     **Introduction**  
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8     27     Pertussis is one of the top ten diseases of children under 10 years of age, and the few vaccine-  
9     28     preventable diseases who is on a rise in China in recent years; however, the true burden of  
10    29     pertussis, including age-stratified incidence and risk factors of severe sequelae, are  
11    30     underrecognized. We aim to estimate the health burden of laboratory-confirmed pertussis by  
12    31     age groups, considering the setting of illness onset (i.e. in community, outpatient and  
13    32     inpatient), in a Chinese population (~2.23 million in total) at two sites.

14    33     **Methods and analysis**  
15

16    34     This paper describes the study design of a one-year, prospective, age-stratified, and  
17    35     population-based case-control study, including site selection, study population, case registry,  
18    36     ascertainment and enrolment, control recruitment, follow-up of case, microbiological  
19    37     methods, data collection, quality control activities, and statistical methods used to generate  
20    38     incidence estimates. During June 2021 through May 2022, registry of suspected pertussis  
21    39     cases (namely chronic/persistent cough) will be conducted in several participating hospitals  
22    40     (SHs) at the two sites, which are selected based on Healthcare Utilization and Attitudes  
23    41     Surveys (HUAS) carried out before study initiation. A case-control study will be conducted in  
24    42     the SHs and we aim to enroll a total of 1,000 suspected pertussis cases (i.e. all hospital  
25    43     admissions and the first 1-3 outpatient visits each week each hospital) and 2,000 frequency  
26    44     matched healthy controls in community. Our primary study outcome, the laboratory-  
27    45     confirmed *Bordetella Pertussis* infection, will be determined by a comprehensive laboratory  
28    46     methods and procedures (i.e. culture, PCR, and serological tests) in both cases and controls at  
29    47     enrolment and during 60-day's follow-up visits. Finally, data from HUAS (i.e. population size),  
30    48     case registry (i.e. the total number of suspected pertussis cases), and case-control study (i.e.  
31    49     the prevalence or population attributable fraction of *Bordetella Pertussis*) will be combined to  
32    50     calculate incidence and its 95% confidence interval through bootstrap method.  
33    51     Epidemiological analyses will be conducted to determine the risk factors associated with  
34    52     severe sequelae of pertussis.

35    53     **Ethics and dissemination**  
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37    54     This study has been approved by Chinese Center for Disease Control and Prevention's  
38    55     Institutional Review Board (no. ICDC-202110). Results will be disseminated via academic  
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3 56 presentations and publication in peer-reviewed journals, and will provide valuable scientific  
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5 57 data and some new insights into the incidence, etiology, and risk factors for severe sequelae  
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7 58 of pertussis to academic societies and the public health authorities who is currently struggling  
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9 59 and fighting against this burdensome disease worldwide.

10  
11 60 **Keywords:** *Bordetella pertussis*, Case-Control Studies, Incidence, China  
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3 61 **SUMMARY**  
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6 62 **Strengths and limitations of this study**  
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- 8  
9 63 ▪ PertussisChina is a population-based study at two sites, covering approximately 2.23  
10 64 million populations defined through conducting Healthcare Utilization and Attitudes  
11 65 Surveys (HUAS) in community.  
12  
13 66 ▪ PertussisChina is a laboratory-based study, in which comprehensive laboratory methods  
14 67 (i.e. culture, PCR, and serological tests) and procedures (i.e. 60-days follow-up) will be  
15 68 used to specifically measure pertussis disease burden.  
16  
17 69 ▪ PertussisChina is a case-control study in which the prevalence and population attributable  
18 70 fraction (AF) of *Bordetella Pertussis* infection can be readily acquired.  
19  
20 71 ▪ All cases will be prospectively followed up to 60-days to collect interesting events (i.e.  
21 72 adverse clinical outcomes of hospitalization or death) at 2, 4 and 8 weeks after enrolment.  
22  
23 73 ▪ Limitations are that our incidence might be underestimated and cannot be extrapolated  
24 74 to represent the whole country due to the insensitive case definition used, short study  
25 75 period and relatively small population covered.  
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## 76 BACKGROUND

77 Whooping cough (pertussis) is a highly contagious respiratory disease caused by  
78 *Bordetella Pertussis*<sup>1 2</sup>. Despite a high vaccine coverage of third dose diphtheria-  
79 tetanus-pertussis vaccine (DTP3)<sup>3</sup>, the "resurgence of pertussis" in recent years has  
80 posed a great threat to global public health<sup>4-6</sup>, as well as to Chinese infants<sup>7 8</sup>. In 2019,  
81 pertussis was one of the top ten diseases with highest burden in children younger than  
82 10 years<sup>9</sup>, and the World Health Organization estimates that pertussis kills about  
83 160,700 children under 5 years old worldwide each year<sup>10</sup>. In China, three types of  
84 pertussis vaccines are available till October 31, 2021, i.e. the co-purified diphtheria  
85 and tetanus toxoids and acellular pertussis (cDTaP, used for routine immunization),  
86 DTaP/Hib (Minhai Biotechnology Co., Ltd., Beijing, China)<sup>11</sup> and DTaP-IPV/Hib (Sanofi  
87 Pasteur, Lyon, France)<sup>12 13</sup>. The coverage of DTP3 remained high above 99% for  
88 children throughout the 2010s<sup>14 15</sup>, and the reported incidence of pertussis has been  
89 risen from 0.12 per 100,000 in 2013 to 2.14 per 100,000 in 2019 (Figure 1). Unlike the  
90 other countries who had experience resurgence of pertussis, especially in  
91 adolescents/adults, primarily due to the waning of vaccine induced immunity<sup>16-20</sup>,  
92 China observed no such changes of age distribution<sup>21</sup>. The rise of pertussis in China  
93 was mainly concentrated in infants less than 1 year old, and less than 5% of reported  
94 pertussis were adolescents and adults.

95 Since most epidemiological data on pertussis in China came from a passive reporting  
96 system, the National Notifiable Infectious Disease Surveillance System (NNIDSS)<sup>22</sup>,  
97 underreporting was substantial in the system ( $\geq 90\%$ ) because of limited diagnosis and  
98 incompleteness of reporting<sup>8 23 24</sup>. And the burden of pertussis remained  
99 underrecognized. It has been suggested that immunizing schoolchildren is the key for  
100 curtailing transmission of pertussis in population<sup>18</sup>. Due to a substantial knowledge  
101 gaps existed in age-specific burden of pertussis (i.e. incidence and severity), no  
102 adolescent or adult immunization are recommended in the country<sup>25</sup>. Moreover,  
103 some important data such as clinical, laboratory and vaccine information are also not  
104 available, which is unfavorable for evaluating the effectiveness of vaccine and  
105 implementing of other disease control and prevention programs (such as adult

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3 106 vaccination, diagnostic tests and post-exposure prophylaxis of pertussis). Rigorously  
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5 107 conducted, prospective, population-based studies can be used to strengthen the  
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7 108 NNIDSS, by providing information on the burden of laboratory-confirmed pertussis,  
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9 109 strains distribution, risk factors for severe sequelae and case fatality, and most  
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11 110 importantly, to assist health authority in China to allocate health resources, prioritize  
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13 111 health research investments, optimize interventions (i.e. vaccination) and innovate  
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15 112 vaccine development.

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17 113 We designed the PertussisChina study, a one-year, prospective, age-stratified,  
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19 114 population-based longitudinal cohort and case-control study, which will enroll  
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21 115 suspected pertussis patients (i.e. chronic/persistent cough) seeking healthcare in  
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23 116 several selected participating hospitals (SHs) at two sites of China, covering  
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25 117 approximately 2.23 million censused population. This article describes the study  
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27 118 design, including sites selection, study population, case registry, ascertainment and  
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29 119 enrolment, control recruitment, follow-up of cases and controls, microbiological  
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31 120 methods (i.e. culture, PCR, and serological tests), data collection, quality control  
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33 121 activities, and statistical methods used to generate incidence estimates of pertussis.  
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35 122 We then further discuss the strengths and weaknesses of the study design.

## 36 123 **METHODS AND ANALYSIS**

### 37 38 39 124 **Objectives of the study**

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42 125 The primary objective of the study is to measure the incidence of laboratory-  
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44 126 confirmed pertussis by age groups (children, adolescents and adults), and by settings  
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46 127 (community, outpatient and inpatient). The secondary objectives are: 1) to describe  
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48 128 the distribution of disease severity and outcomes across age groups; 2) to describe the  
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50 129 patterns and factors of under-detection and under-reporting of pertussis; 3) to study  
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52 130 the carrier (colonization) status of the *B. pertussis* in the upper respiratory tract of  
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54 131 healthy controls, and the serum levels of anti-pertussis toxin antibodies (anti-Ptx IgG)  
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56 132 in both patients and healthy people; and 4) to create a repository of well-characterized  
57  
58 133 clinical specimens and *B. pertussis* isolates that can be used in future studies.  
59  
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## 134 **Study sites and population**

### 135 ***Site Selection Criteria***

136 Sites are selected based on the following criteria: 1) have strong willingness to  
137 participate; 2) have capability and resources to conduct ongoing surveillance, namely  
138 staffs to facilitate specimen collection and case investigation, previous experience in  
139 disease surveillance, infrastructures to secure data collection and specimen storage  
140 or transportation; and 3) provide a full list of healthcare facilities in the area and the  
141 information of built-in hospital information system in the facilities. Currently, there  
142 are two sites in the study, including Yongcheng, Henan and Yiwu, Zhejiang (Figure 2).

### 143 ***Study population***

144 In 2019, Yiwu had a permanent population of 821,000 (47,000 were children under  
145 five years of age) served by 24 health care facilities (i.e. three tertiary care, four  
146 secondary care, and 17 primary care hospitals). Most hospital admissions ( $\geq 80\%$  of the  
147 total number) occurred in the three large tertiary hospitals, including a children's  
148 hospital and two general hospitals; meanwhile, Yongcheng had a permanent  
149 population of 1,411,000 (94,000 were children under five years of age) served by 41  
150 health care facilities (i.e. five secondary care and 36 primary care hospitals). Most  
151 hospital admissions occurred in the five large secondary care hospitals, including four  
152 general hospitals and a maternal and pediatric hospital. In total, the two sites cover a  
153 total of 2.23 million permanent population in the study area.

### 154 **Study overview and design**

155 In order to achieve our study objectives, we will conduct the following study activities  
156 at the two sites from June 2021 through May 2022, including, 1) a Healthcare  
157 Utilization and Attitudes Survey (HUAS) and a census data updating to define study  
158 population (i.e. incidence denominator), so as to set up a sampling frame for the case-  
159 control study and selecting participating hospitals (i.e. SH) for case registry and case  
160 recruitment; 2) the case-control study to acquire the prevalence of *B. pertussis*  
161 infection among suspected pertussis cases and healthy controls, as well as the  
162 calculation of population attributable fraction (AF) indicating the proportion of cases

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3  
4 163 that can be prevented if *B. pertussis* was totally removed from the population; and 3)  
5  
6 164 case registry and the retrieval of electronic medical records (EMRs) from hospital  
7  
8 165 information system to provide and validate the total number of suspected pertussis  
9  
10 166 case patient (chronic/persistent cough) encountered in the SHs (i.e. incidence  
11  
12 167 numerator) (Figure 3).

### 13 14 168 ***Defining and calibrating study population***

#### 15 16 169 ***Census data updating***

17 170 Population census data at the two sites will be collected and updated during the study  
18  
19 171 period. Population census is conducted every ten years in China and the nearest one  
20  
21 172 is in 2020. However, an intermittent survey of 1% sampling of the total population  
22  
23 173 would be performed to update population census data every year between the two  
24  
25 174 censuses. We will retain the up-to-date population data from the National Bureau of  
26  
27 175 Statistics. Moreover, the population birth, mortality, and population migration are  
28  
29 176 recorded by the local government. We will also contact the local health bureau  
30  
31 177 quarterly to access these data to give a precise estimation of population size in the  
32  
33 178 two sites.

#### 34 35 179 ***Healthcare Utilization and Attitudes Surveys (HUAS)***

36  
37 180 HUAS will be conducted prior to recruiting cases and controls at the two sites, which  
38  
39 181 will serve three purposes, 1) to set up a sampling frame for the case-control study; 2)  
40  
41 182 to select SHs in which prospective enrolment of cases will be conducted; and 3) to  
42  
43 183 provide estimates of the population coverage for our SHs and healthcare seeking  
44  
45 184 behavior weights applied in estimating pertussis incidence in community.

46  
47 185 In summary, a population-based cross-sectional study, with an age-stratified sample  
48  
49 186 of 3,000 children aged 0-59 mo and 6,000 adolescents/adults aged  $\geq 5$  years, will be  
50  
51 187 conducted in the community of the two sites. The sample size was calculated based  
52  
53 188 on: i) for children, a monthly prevalence of cough illness,  $\pi=1\%$  (estimated from the  
54  
55 189 reported incidence of lower respiratory tract infection of 0.15 per child year<sup>26</sup>),  
56  
57 190 allowable error ( $\delta=0.5\%$ ), significant level ( $\alpha=0.05$ ), and design effect (deff=2); ii) and  
58  
59 191 for adolescents/adults, a monthly prevalence of cough illness,  $\pi=3.3\%$ <sup>27</sup>, allowable  
60  
192 error ( $\delta=0.66\%$ ), significant level ( $\alpha=0.05$ ), and design effect (deff=2).

1  
2  
3 193 A complex sampling method will be used to select survey respondents as follows.  
4  
5 194 Firstly, a probability proportionate to size sampling will be used to randomly select 50  
6  
7 195 clusters (e.g. communities or villages) in the site's administrative regions. At the  
8  
9 196 second sampling stage in selected communities, quota sampling will be used to recruit  
10  
11 197 interviewee. The quota required in each age stratum was calculated based on the age  
12  
13 198 distribution of the population in the sites and the number of surveys allocated to each  
14  
15 199 cluster. Trained work staff will go to the selected communities to conduct face-to-face  
16  
17 200 surveys at several locations (residential areas, kindergartens and children's  
18  
19 201 vaccination clinics) Monday to Sunday during daytime in the study period. All residents  
20  
21 202 living in the communities or villages for at least half a year prior to survey are eligible  
22  
23 203 for and invited to participate in the interview. After the quota required in each age  
24  
25 204 group is complete, the interviews will stop.

26 205 The following questions (Supplementary table 1 & table 2) are asked to respondents,  
27  
28 206 1) the occurrence and length of cough illness in the previous month prior to survey, 2)  
29  
30 207 healthcare-seeking behavior regarding the self-reported cough illness for the most  
31  
32 208 recent episodes and the sources of healthcare facilities; and 3) the willingness to seek  
33  
34 209 healthcare and where would they choose to visit for an assumptive cough illness.

35  
36 210 Based on the HUAS and census data, hospitals at which over 80% of respondents in  
37  
38 211 each site choose to attend when hospital admission is required will be selected as our  
39  
40 212 SHs. In case healthcare providers in the site change their practice or scope of service  
41  
42 213 during our study period, for example the opening of new hospitals or the  
43  
44 214 establishment of new branches of existing hospitals, an abbreviated HUAS with a  
45  
46 215 smaller sample of 1,000 will be administered at the middle or the end of the year  
47  
48 216 during which cases are recruiting at SHs.

### 49 217 ***Case-control study***

#### 50 51 218 ***Case definition of suspected pertussis***

52  
53 219 Patients will be classified as suspected pertussis cases and offered to participate if they  
54  
55 220 present chronic/persistent cough defined as cough of  $\geq 2$  weeks duration with one or  
56  
57 221 more of the following symptoms, 1) paroxysmal cough; 2) inspiratory whoop; or 3)  
58  
59 222 post-tussive vomiting; Or, for children aged  $< 1$  years-old, cough (regardless of cough  
60

223 duration) accompanied by one or more of the following symptoms, 1) apnea; 2)  
224 paroxysmal cough; 3) inspiratory whoop; or 4) post-tussive vomiting.

225 We will exclude patients presenting with gastroesophageal reflux, spastic bronchitis,  
226 and clearly diagnosed tuberculosis, mycoplasma/chlamydia infection, or chronic  
227 sinusitis. Adults/adolescents with a measured body temperature of  $\geq 38.5$  °C at  
228 enrolment will also be excluded.

### 229 *Sample Size Considerations*

230 We planned to enroll approximately 250 suspected cases and 2 matched controls for  
231 each case in each age stratum (i.e. children under 5 years, and adolescents/adults  
232 aged  $\geq 5$  years) for laboratory investigation at each site, which would add up to  
233 approximately 1000 suspected cases and 2000 controls at the two sites. We calculated  
234 the above sample size based on a prevalence of *B. pertussis* in chronic/persistent  
235 cough of 20% (range=12%-32%)<sup>28-30</sup>, an allowable error of 5% and a significant level  
236 of 0.05. This sample size would have a 90% power (two sided  $\alpha = 0.05$ ) to detect an  
237 odds ratio (OR) of 2 between case and control for a site and age stratum-specific  
238 comparison, if the true prevalence of *B. pertussis* is 20% in case; or an OR of 3, if the  
239 true prevalence is 10%. Although the carrier state of *B. pertussis* is transient in family  
240 contacts<sup>31 32</sup>, *B. pertussis* is rarely identified in healthy people<sup>33 34</sup>, and we expected a  
241 larger OR of  $\geq 2$  in the study. This sample size means that the laboratory would process  
242 average 115 samples per week, which is feasible and acceptable for our laboratories.

### 243 *Case Registry, Ascertainment and Enrollment*

244 Case registry, ascertainment and enrollment for suspected case will be conducted in  
245 SHs during the study period. Clinicians or trained nurses working in selected  
246 departments of the SHs (i.e. respiratory, pediatric, infectious disease, and emergency  
247 department) will carry out case registry of suspected pertussis cases every weekday  
248 (i.e. Monday through Sunday) except national holidays. Each outpatient visits and new  
249 hospital admission seeking healthcare in above departments will be screened for the  
250 eligibility of inclusion using the inclusion & exclusion criteria of the suspected case  
251 definition of pertussis by clinicians. Eligible ones will be ascertained and recorded as  
252 suspected case by study coordinator who assist with clinicians in SHs in enrolling cases



1  
2  
3  
4 253 using a standardized case reporting form (CRF) (Supplementary Table 3). Among the  
5  
6 254 suspected pertussis case recorded in SHs, convenient sampling method will be used  
7  
8 255 to recruit cases for case-control study. We aim to enroll all hospital admissions and  
9  
10 256 the first 1-3 outpatient visits each week in each hospital. After obtaining informed  
11  
12 257 consent, study staff will conduct enrollment interviews, and collect nasopharyngeal  
13  
14 258 (N/P) and blood specimens for each enrolled case.

#### 15 259 *Controls selection*

16  
17 260 At the middle of the study year when the sample size of cases reaches a half of the  
18  
19 261 total (i.e. n=500), a control is recruited in community of the study sites using  
20  
21 262 approximate frequency matching, based on the following criteria, 1) similar  
22  
23 263 proportion in sex strata; 2) similar proportion in age strata, i.e. <1 year, 1-5 years, 6-  
24  
25 264 19 years, 20-64 years and ≥65 years; 3) a control/case ratio of 2:1; and 4) no cough,  
26  
27 265 running nose, shortness of breath, dyspnea or other respiratory symptoms at  
28  
29 266 enrolment nor have a record of healthcare for respiratory disease in previous three  
30  
31 267 months before recruitment.

#### 32 268 *60-day follow-up of case*

33  
34 269 We will follow cases from the time of enrollment to a maximum time period of 60 days  
35  
36 270 after enrollment. Follow-up will be conducted at 2<sup>nd</sup>, 4<sup>th</sup> and 8<sup>th</sup> weeks after  
37  
38 271 enrollment, with face-to-face interview if patient is currently hospitalized, or one  
39  
40 272 telephone call each follow-up time if patient is discharged from hospital. At each  
41  
42 273 follow-up visit/phone call, the study staff will ask about cough or other respiratory or  
43  
44 274 systemic illness symptoms in the period since the last contact. If case is still  
45  
46 275 symptomatic (i.e. cough) during follow-up, they will be encouraged to visit their doctor  
47  
48 276 who enrolled them in the SHs within 24h of contact. The doctor will checkup the  
49  
50 277 patient's health status and collect the swab and serum samples during the visit. If an  
51  
52 278 enrolled patient does not want to visit the SHs, the study staff will arrange a household  
53  
54 279 visit to collect the samples in the home.

#### 55 280 *Data collection from cases and controls*

56  
57 281 At enrolment, trained clinicians and the study coordinator will conduct face-to-face  
58  
59 282 interview to collect socio-demographic, clinical and epidemiological data from cases  
60



1  
2  
3 283 and controls using a standardized CRF (Supplementary Table 4). Demographic  
4  
5 284 information includes household size (defined as a group of people who share a dinner  
6  
7 285 table), average household income, rural or urban residence, age, alcohol consumption  
8  
9 286 and smoking exposure, and occupation etc. A clinician will also examine all cases to  
10  
11 287 document clinical signs and symptoms at enrollment, including cough characteristics  
12  
13 288 [duration, paroxysms, post-tussive vomiting, exacerbation at night], body  
14  
15 289 temperature, respiratory rate, heart rate, seizure, apnea, and other general  
16  
17 290 respiratory symptoms, non-prescription antibiotic usage before visiting the doctor,  
18  
19 291 blood test results and chest x-ray examinations. Vaccination history (i.e. brand, dosing,  
20  
21 292 procedure and time of administration) of children aged  $\leq 14$  years is also collected by  
22  
23 293 linkage of his/her individual records on immunization in the national database  
24  
25 294 (Childhood Immunization Information Management System, CIIMS)<sup>35</sup> or checking of  
26  
27 295 vaccination certificate.

27 296 During follow-up visits, data on any current cough or respiratory symptoms, subjective  
28  
29 297 severity of illness, illness duration, functional impairment, whether medical care was  
30  
31 298 sought, and outcomes since the last visits will be collected using CRFs (Supplementary  
32  
33 299 Table 5).

34 300 At the end of follow-up, medical charts of each hospitalized case will be reviewed by  
35  
36 301 study staff to collect information on antibiotic treatment and outcomes during  
37  
38 302 hospitalization (i.e. mechanical ventilation, ICU transfer, and death) (Supplementary  
39  
40 303 Table 6).

41  
42 304 ***The retrieval of electronic medical records and Validation of the total number of***  
43  
44 305 ***suspected pertussis case***

45 306 Since our case registry and enrolment is conducted in selective departments (i.e.  
46  
47 307 respiratory, pediatric, infectious disease and emergency departments) and on  
48  
49 308 workdays in SHs, it is an incomplete record of the total number of suspected cases  
50  
51 309 encountered in the whole hospital. It is essential to calibrated the registered number  
52  
53 310 of suspected cases to equal the total. To do this, all hospital discharges or ambulatory  
54  
55 311 visits coded for diagnosis under the International Classification of Diseases 10th  
56  
57 312 Revision (ICD-10) codes A37, J00-J22, J40-J47, R05, R09.2, P22, P28.2, P28.3, P28.4,  
58  
59 313 and P28.5 will be monitored on a daily basis as registry case, by hospital departments.  
60

1  
2  
3 314 At the end of the month, the complete EMRs records with the above diagnosis codes  
4  
5 315 in the whole hospital will be abstracted from hospital information system (HIS) of the  
6  
7 316 SHs. This data will be used to calibrate the prospectively counting data of suspected  
8  
9 317 case in the selective departments that conduct case enrolment to make a precise  
10  
11 318 estimate of the total number of chronic/persistent cough illness outcomes in the  
12  
13 319 studied population. Namely, through linking and comparing between the number of  
14  
15 320 registry cases and the number of suspected pertussis case registered in the selected  
16  
17 321 departments, we will calculate the  $W_{case}$ . With this  $W_{case}$ , we will narrow down the  
18  
19 322 ICD-based EMRs records to the total number of suspected pertussis cases met our  
20  
21 323 case definition in SHs (i.e. the numerator of incidence).

## 22 23 324 **Laboratory investigation**

### 24 25 325 ***Specimen collection and transport***

26  
27 326 When patients meet our suspected pertussis case definition or are recruited controls,  
28  
29 327 they, as well as symptomatic (cough) cases during follow-up contacts, will be sampled  
30  
31 328 within 24 hours. Clinicians or nurses in SHs will be trained to collect nasopharyngeal  
32  
33 329 swabs (N/P) and whole blood sample. Dacron or nylon swab will be used to collect N/P  
34  
35 330 specimen to facilitate culture and PCR tests for *B. pertussis*<sup>36</sup>. Collected swab  
36  
37 331 specimens will be plated onto selective agar or placed in transport medium (Charcoal  
38  
39 332 Agar, Thermo Fisher Scientific Inc.) immediately after sampling at the SHs. Whole  
40  
41 333 blood without adding any anticoagulants (>4ml for participants aged 5 years and older,  
42  
43 334 and  $\geq 2$  ml for children aged <5 years) will be collected, and centrifuged to separate  
44  
45 335 serum within 24h of collection. All collected swab and sera samples will be transported  
46  
47 336 to the central laboratory of Chinese Center for Disease Control and Prevention (China  
48  
49 337 CDC), using a cold box to maintain a temperature of 4°C. During transportation,  
50  
51 338 samples are packaged and transported in accordance with the provision of  
52  
53 339 International Civil Aviation Organization (ICAO) document Doc9284 and UN3373

### 54 55 340 ***Processing and storage of specimen***

56  
57 341 Upon arrival at the laboratory of China CDC, swab samples will be processed and  
58  
59 342 prepared into three aliquots of swab supernatant, so will serum samples be. One of  
60  
343 these aliquots will be analyzed and the other two aliquots will be kept for future

1  
2  
3 344 analyses. All aliquots will be stored at -70°C temperature until the time of analysis.  
4  
5

### 6 345 **Laboratory testing**

7  
8 346 In the laboratory of China CDC, Charcoal Agars will be cultured to isolate *B. pertussis*  
9  
10 347 using standard method recommended by China CDC<sup>37</sup> and World Health  
11 348 Organization<sup>38</sup>. Swab supernatant will be analyzed for *B. pertussis*, *B. parapertussis*, *B.*  
12 349 *bronchiseptica* and *B. holmesii* using polymerase chain reaction (PCR) as  
13 350 recommended by US CDC<sup>39 40</sup>. Sera samples that have a minimum volume of  $\geq 1$  ml  
14 351 will be tested for Anti-Ptx IgG titer using a commercially available diagnostic kit  
15 352 (Virion\Serion, Wurzburg, Germany) according to the manufacturer's  
16 353 recommendations. To validate our laboratory methods and testing results, external  
17 354 quality assurance testing will be conducted to reach agreements with a reference  
18 355 laboratory on *Bordetellae* prior to study start. For serology testing, we use standard  
19 356 from the National Institute for Biological Standards and Control, London, UK,  
20 357 ([https://www.nibsc.org/products/brm\\_product\\_catalogue/detail\\_page.aspx?catid=1](https://www.nibsc.org/products/brm_product_catalogue/detail_page.aspx?catid=18/146)  
21 358 [8/146](https://www.nibsc.org/products/brm_product_catalogue/detail_page.aspx?catid=18/146)); and for PCR assays, the Wisconsin State Laboratory of Hygiene, Wisconsin, U.S.  
22 359 (<http://www.slh.wisc.edu/proficiency/training-and-competency/>).

23 360 Suspected pertussis cases and controls that have *B. pertussis* Isolated, positive tests  
24 361 of swabs in any of samples collected during enrolment and follow-up, or for persons  
25 362 three years of age and over have a 3-fold or greater rise in anti-Ptx IgG antibody  
26 363 between sequential sera samples with at least one time point higher than 40 IU/ml of  
27 364 serum titer would be considered laboratory-confirmed pertussis.<sup>36 41</sup>

### 28 365 **Data flow, management and analysis**

29 366 The data collected in the study are centrally managed at China CDC, using an online  
30 367 data platform (<http://eddc.chinacdc.cn/dap/>). The completed CRFs will be entered  
31 368 into the information system by local study staff at the two sites and uploaded to data  
32 369 server through encrypted transmission via a Virtual Private Network set up by China  
33 370 CDC. The entered records are regularly checked for completeness, consistency, and  
34 371 logical errors by data manager and the site's co-principle investigator who is  
35 372 responsible for authorization, integrity, security, and backup of database during data  
36 373 collection.  
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374 **Statistical analysis**

375 The collected data processing and key indicators based on which we calculate  
 376 incidence are shown in figure 4. We will calculate the incidence of pertussis by age  
 377 group and by settings with the following formula.

$$378 \quad \text{Hospitalization incidence rate} = \sum \frac{S_i^{\text{inpatient}} \times W_i^{\text{case}} \times AF_i}{N_i \times W_i^{\text{cover}} \times C_i}$$

$$379 \quad \text{Outpatient incidence rate} = \sum \frac{S_i^{\text{outpatient}} \times W_i^{\text{case}} \times AF_i}{N_i \times W_i^{\text{cover}} \times C_i}$$

$$380 \quad \text{Community incidence rate} = \frac{\text{Outpatient incidence rate}}{r_i}$$

381 Where,  $S_i^{\text{inpatient}}$  and  $S_i^{\text{outpatient}}$  indicates the registered number of inpatients and  
 382 outpatient visits of cough illnesses at age group  $i$ , as obtained from HIS.  $W_i^{\text{case}}$  is the  
 383 weight used to adjust  $S_i^{\text{inpatient}}$  and  $S_i^{\text{outpatient}}$  to meet our case definition in age group  $i$ .  
 384 This weight is calculated from the results of the prospective case-control study as a  
 385 ratio of suspected cases over registered cases of cough illnesses at the selective  
 386 departments of SHs.  $N_i$  is the population size in age group  $i$  in census year 2020.  
 387  $W_i^{\text{cover}}$  is the weight used to adjust catchment population overlapping between  
 388 participating hospitals from HUAS in age group  $i$ . It is calculated as the ratio of  
 389 community residents who have the reported seeking medical care in the participating  
 390 hospitals for the last episodes of their cough illness over the residents who have the  
 391 willingness of healthcare-seeking in the participating hospitals, as obtained from the  
 392 HUAS study.  $C_i$  is the proportion of population covered by participating hospitals in  
 393 age group  $i$ , as measured in the HUAS study. It is calculated as the proportion of  
 394 residents who report having the willingness of healthcare-seeking in the participating  
 395 hospitals over the total no. of residents responded.  $r_i$  is the proportion of  
 396 community residents reporting seeking health-care for their most recent episode of  
 397 cough illnesses in age group  $i$  as measured in the HUAS study.  $AF_i$  is the population  
 398 attributable fraction of chronic/persistent cough due to *B. pertussis* infection in age  
 399 group  $i$ , calculated based on case-control study using unconditional logistic regression

1  
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3  
4 400 model, as follows:

5  
6 401 
$$\log_e(OR) = \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3 + \dots + \beta_k x_k$$

7  
8 402 
$$OR = \exp(\beta_k)$$

9  
10  
11 403 
$$AF_i = \Pr(Bordetella pertussis | Chronic cough) (1 - \frac{1}{OR})$$

12  
13 404 Note:  $\Pr(Bordetella pertussis | Chronic cough) = P_i$  is the prevalence of *B. pertussis*,  
14  
15 405 calculated by dividing the number of laboratory-confirmed pertussis with the total  
16  
17 406 number of chronic/persist cough tested.  $x_1, x_2, x_3, \dots, x_k$  are variables associated with  
18  
19 407 the occurrence of chronic/persistent cough, including the presence of *B. pertussis* and  
20  
21 408 other social and environmental factors significant at  $p < 0.1$  in univariate analysis. OR  
22  
23 409 is the odds ratio.

24  
25  
26  
27 410 The 95% CI of incidence is calculated with bootstrap method with 1000 replications.  
28  
29 411 Besides incidence estimates, we will also explore factors associated with severe  
30  
31 412 pertussis (defined as a composite outcome of death, sepsis, invasive ventilation and  
32  
33 413 Intensive Care Unit transfer), by using multivariable logistic regression. Factors  
34  
35 414 significantly associated with severe pertussis at  $p < 0.1$  in univariate analysis will be  
36  
37 415 included in the model. The median age of children with pertussis will be calculated by  
38  
39 416 type of vaccinees, and factors predicting the age of pertussis breakthrough among  
40  
41 417 children who had received DTP vaccination early in their life will be also studied by  
42  
43 418 using Cox proportional hazards regression models. For sensitivity analysis, we will use  
44  
45 419 a two-fold or greater increase of anti-Ptx IgG antibody as the cut-off threshold for our  
46  
47 420 serological assays and calculate incidence again.

48  
49 421 **ETHICS AND DISSEMINATION**

50  
51 422 This study is designed an observational study. The risk of harm is minimal and adverse  
52  
53 423 medical events are not anticipated from the procedures involved in the study. The  
54  
55 424 study protocol, CRF, and consent form have been sent to and approved by China CDC's  
56  
57 425 Institutional Review Board (reference no. ICDC-202110).

58  
59 426 The primary risk to participants is the loss of confidentiality. To help maintain

1  
2  
3 427 confidentiality, all study investigators will sign a confidentiality agreement and receive  
4  
5 428 appropriate ethics training. All interviews will be conducted at the study investigator's  
6  
7 429 office, and signed consent forms and completed survey forms will be locked in a secure  
8  
9 430 file cabinet at the end of each day. A very limited number of trained study staff can  
10  
11 431 have the key to the locked file cabinets. Participation in every aspect of the study will  
12  
13 432 be voluntary, and for all new data collection, participants will be asked to provide  
14  
15 433 written informed consent. Besides, collection of specimens may cause mild discomfort  
16  
17 434 to the subject during the procedure, especially drawing blood from young children. To  
18  
19 435 minimize invasive procedures during sample collection, swab and blood specimens  
20  
21 436 will be collected by aseptic technique and we encourage the use of leftover sera during  
22  
23 437 routine medical care at the time point of enrolment.

24  
25 438 As a benefit of participating in the study, participants with pertussis will receive senior  
26  
27 439 doctor consultation during treatment on how to limit transmissions among family  
28  
29 440 members and co-workmates; Patients enrolled in the study will have access to  
30  
31 441 antibiotic susceptibility testing results should they have *B. pertussis* isolates acquired.  
32  
33 442 This will give a guide on empirical antibiotic usages for physicians; moreover, the data  
34  
35 443 generated in the study will be valuable to determine the burden of pertussis and  
36  
37 444 explore risk factors for illness attributable to severe pertussis in children as well as  
38  
39 445 adolescents/adults, which can be used by public health departments, healthcare  
40  
41 446 providers and scientific group in China to inform policies making, implement disease  
42  
43 447 control and prevention (i.e. vaccination) and improve patient care, both at the sites  
44  
45 448 level and national level. In general, the minimal risks associated with physical  
46  
47 449 discomfort during blood and N/P sample collection are offset by the great benefit  
48  
49 450 associated with the study's ability to inform pertussis prevention and control  
50  
51 451 strategies in China. Upon completion, results from this study will be disseminated via  
52  
53 452 academic presentations and publication in peer-reviewed journals.

## 54 453 **DISCUSSION**

55 454 PertussisChina is an innovative and a pilot of a laboratory-based and population-based  
56  
57 455 active surveillance platform for vaccine-preventable bacterial diseases (VPBD) in China,  
58  
59 456 which endeavors to establish a network of laboratories and hospitals using  
60

1  
2  
3 457 comparable and unified standards to provide up-to-date disease burden estimates  
4  
5 458 and disease determinants for evaluating, prioritizing and optimizing the use of  
6  
7 459 vaccines and for the development of new interventions against bacterial infections in  
8  
9 460 the country. Pertussis is the first one of the several bacterial infections that we are  
10  
11 461 planning to take this approach. In response to the changing epidemiology of pertussis  
12  
13 462 in China<sup>7 8 42 43</sup>, the 2019 summon of the National Immunization Advisory Committee  
14  
15 463 submitted a motion to its members urging the modification of the current  
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17 464 immunization schedule of pertussis vaccine administered at 3, 4, 5 and 18-24 months<sup>44</sup>,  
18  
19 465 to vaccinate children at 2, 4, 6 and 18-24 months instead and to add a 5<sup>th</sup> booster dose  
20  
21 466 at 4-6 years of age; however, partly due to knowledge gaps existed in age-specific  
22  
23 467 burden of pertussis, NIAC suspended its decision on this issue. To provide up-to-date  
24  
25 468 evidence on disease burden of pertussis, this study will focus on age-specific incidence  
26  
27 469 based on laboratory confirmation and will fill the data gaps on prospectively and  
28  
29 470 actively collected incidence data and key information on illness severity and outcomes.  
30  
31 471 We are expecting that data from this study can be served as background information  
32  
33 472 augmenting NIDSS to inform NIAC's recommendations on children vaccination and  
34  
35 473 further quantify the benefit of adolescent/adult vaccination to protect infants from  
36  
37 474 severe outcomes in future. There are several strengths of the study.

37 475 In this one-year study, we will enroll suspected chronic/persistent cough patients (for  
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39 476 infants aged less than 1 year, cough regardless of duration) from health care facilities  
40  
41 477 in two sites of China, covering a censused population of 2.23 million. The catchment  
42  
43 478 population utilizing health-care services at the SHs are well characterized and defined  
44  
45 479 by HUAS, providing unbiased estimates of age-stratified total person-times observed  
46  
47 480 in the cohort. The prevalence of cough in regarding of illness duration and proportion  
48  
49 481 of people who do not seek healthcare are measured retrospectively by HUAS. Thus by  
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51 482 comparing between data generated from HUAS in community and case registry in SHs,  
52  
53 483 we will able to measure incidence by settings (i.e. community, outpatient and  
54  
55 484 inpatient), especially those in communities whose symptoms are mild or atypical after  
56  
57 485 the waning of vaccine-induced immunity or those no healthcare are sought<sup>2</sup>. Besides,  
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59 486 all hospitalizations suspected of pertussis will be actively searched and prospectively  
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487 enrolled in a timely manner in our SHs, serving as a complete and representative



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3 488 sample of pertussis occurred in the interested population that would have induced  
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5 489 minimal selection bias. As for milder cases in ambulatory settings, sampling of patients  
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7 490 with chronic/persistent cough in outpatient setting to conduct laboratory  
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9 491 investigation is preferred. Misclassification of cases or recall bias will be minimized by  
10  
11 492 the complex laboratory procedures (i.e. culture, PCR, and serology combined), unified  
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13 493 data collection tools (i.e. CRFs) and data collection process, i.e. the 60-day of follow-  
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15 494 up during which interesting events (e.g. 3-fold titer raising) will be closely monitored  
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17 495 by sequential sera samples. Using laboratory-confirmed pertussis as the outcome will  
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19 496 allow us to specifically measure pertussis disease burden. To account for  
20  
21 497 asymptomatic carriage of *B. pertussis*, we will recruit healthy control to investigate  
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23 498 the proportion of population carrying *B. pertussis* in their upper respiratory tract and  
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25 499 sero-positivity, which could be useful for calculating population attributable fraction  
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27 500 (AF) to adjust rate estimates. In addition, the prospective cohort will provide valuable  
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29 501 follow-up data related to risk factors for severe illness (i.e. adverse clinical outcomes  
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31 502 of hospitalization or death). Collection of the vaccination history (including band,  
32  
33 503 dosing, procedure and time of administration) from study participants will help  
34  
35 504 explore the breakthrough rates of *B. pertussis* infection among different type of  
36  
37 505 vaccinees and investigate reasons of vaccination failure, by linkage of study subjects  
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39 506  $\leq 14$  years old with his/her individual records on immunization in the national database.  
40  
41 507 Finally, we will abstract EMR data from hospital information system, which serves as  
42  
43 508 a complete and accurate record of cough illness outcomes occurred in SHs. The  
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45 509 retrospectively collected EMR data will be validated by prospectively counting cases  
46  
47 510 eligible for inclusion at selective departments of SHs on daily basis. Using data from  
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49 511 the EMR will allow us to determine the size of outpatient and emergency department  
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51 512 visits for cough illness in the studied population. For most of adults and fully  
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53 513 immunized children and adolescents, their illness is generally mild and is most likely  
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55 514 to be encountered at the ambulatory settings in which the diagnostic capacity is  
56  
57 515 generally lacking.

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59 516 Aside from acquiring incidence estimates, the prevalence and distribution of *B.*  
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517 *pertussis* strains circulating in the population will be determined and characterized,  
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which are reported to be evolving under the selection pressure from both vaccine and



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3 519 antibiotics in previous studies<sup>45</sup> and are important data for the development of novel  
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5 520 vaccine or new therapeutics in the country. For example, as a benefit of the study, we  
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7 521 will create a representative national and well characterized repository of strains and  
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9 522 specimens that can be shared with other investigators for future research, the main  
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11 523 antigenic and genotypic features of *B. pertussis* will be characterized by sequencing or  
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13 524 other bio-molecular methods.

14  
15 525 We realized that there are several limitations worthy of note in our study. Firstly, we  
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17 526 will not identify all pertussis that occur in our studied population since our case  
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19 527 definition will not capture atypical and asymptomatic manifestations associated with  
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21 528 *B. pertussis* infection. For example, previous studies showed that about 17.4%  
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23 529 children<sup>46</sup> and 20% adolescents/adults<sup>47</sup> with *B. pertussis* infection had a cough  
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25 530 duration less than 3 weeks, and other symptoms/signs used in the case definition, like  
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27 531 spasmodic cough (63%), post-tussive vomiting (42%) and whoops (8%), were  
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29 532 infrequently presented in adults<sup>48</sup>, which will make incidence underestimated. It is  
30  
31 533 argued that no symptom is sufficiently predictive for diagnosing pertussis<sup>49</sup> and there  
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33 534 was no case definition that has been proposed for purpose of studying disease burden  
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35 535 of pertussis. After balancing at the sensitivity and specificity of case definition  
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37 536 commonly recommended by WHO, the U.S. and others<sup>50-52</sup> and the available  
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39 537 laboratory capacity and resources in the study, we finally adopted the current case  
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41 538 definition that can be used to facilitate comparison of results between studies and  
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43 539 countries. Second, our study period is a little short. Since pertussis has showed a cyclic  
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45 540 pattern and peaked every 3-5 years<sup>2 16</sup>, our study will not capture this feature.  
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47 541 Moreover, our study is going to recruit cases in 2021-2022, right after COVID-19  
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49 542 pandemic. As the epidemiology of many respiratory infections have been reported  
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51 543 changing as a result of widely implementation of nonpharmaceutical interventions  
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53 544 (e.g. wearing masks, social distancing, and personal health protection)<sup>53 54</sup> and the  
54  
55 545 detained coverage of vaccines used in Expanded Program on Immunization during the  
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57 546 pandemic<sup>55</sup>. The impacts of COVID-19 outbreak on incidence estimates of pertussis  
58  
59 547 are not foreseeable in the study. Future studies are upcoming depending on the  
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548 results of this pilot. Finally, China is a big country with large variations in population  
549 density and across different climate, geographic and economic regions. Although we

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3 550 have paid careful attention to variables, like DTP3 vaccine coverage, childhood  
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5 551 mortality and health-care delivery pattern when selecting study sites, regions with the  
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7 552 highest and lowest reported incidence of pertussis are generally not included. This  
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9 553 may also influence the generalizability of the incidence estimates to extrapolate to  
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11 554 other regions.

12  
13 555 In summary, PertussisChina is an innovative study that uses unified protocol to  
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15 556 generate up-to-date high-quality incidence data on pertussis. The study design can  
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17 557 secure the precision of data collection and provide insights into the prospectively  
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19 558 conducted studies that designed to augment passive surveillance in countries where  
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21 559 resources is limited and data is currently lacking. When completed, the results coming  
22  
23 560 out this study will provide valuable scientific data on the incidence, etiology, and risk  
24  
25 561 factors for severe sequelae of pertussis to academic societies and the public health  
26  
27 562 authorities, who is currently struggling and fighting against this burdensome disease  
28  
29 563 worldwide.

#### 30 564 **Contributors**

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33 565 Zhujun Shao is the principal investigator on this study who conceived and critically  
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35 566 revised the manuscript. Jianxing Yu, Hanqing He and Yanyang Zhang conceptualized  
36  
37 567 and designed the study, wrote the first draft and contributed equally to this work.  
38  
39 568 Yuan Gao, Juan Xu, Li Xu, and Yonghao Guo designed the laboratory methods. Xiaoxiao  
40  
41 569 Zhang, Qianqian Zhou, Yao Zhu and Xuewen Tang wrote the statistical analysis plan.  
42  
43 570 Chuanwei Chen and Zhiping Chen commented on and revised drafts of the manuscript.  
44  
45 571 All authors contributed to reviewing, revising, and approving the final manuscript.  
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578 **Competing interests**

579 The authors declare that they have no competing interests.

580 **Patient and public involvement**

581 Patients and/or the public were not involved in the design, or conduct, or reporting,  
582 or dissemination plans of this research.

583 **Patient consent for publication**

584 Not required.

585 **Ethics approval**

586 This study has been approved by Chinese Center for Disease Control and Prevention's  
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4 749 **Figure Legends**  
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6 750 **Figure 1. Incidence of reported pertussis from NNIDSS, China, 1952-2019.** A cDTaP  
7  
8 751 was introduced into national immunization program to replace DTwP in 2007 and the  
9  
10 752 transition was fully completed in 2013. Abbreviations: DTwP, combined diphtheria,  
11  
12 753 tetanus toxoid and whole-cell pertussis vaccine; cDTaP, co-purified diphtheria, tetanus  
13  
14 754 toxoid and acellular pertussis vaccine; National Notifiable Infectious Disease  
15  
16 755 Surveillance System (NNIDSS).  
17

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19 756 **Figure 2. Location and population size of study sites included in PertussisChina study**  
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23 757 **Figure 3. Flow diagram of major study activities**  
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26 758 **Figure 4. Data flow chart and key indicators used to calculate incidence of pertussis**  
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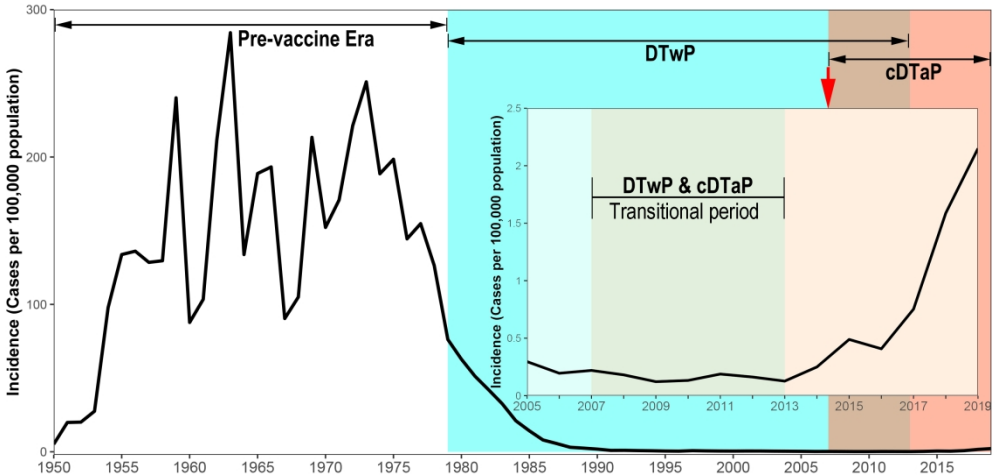


Figure 1. Incidence of reported pertussis from NNIDSS, China, 1952-2019

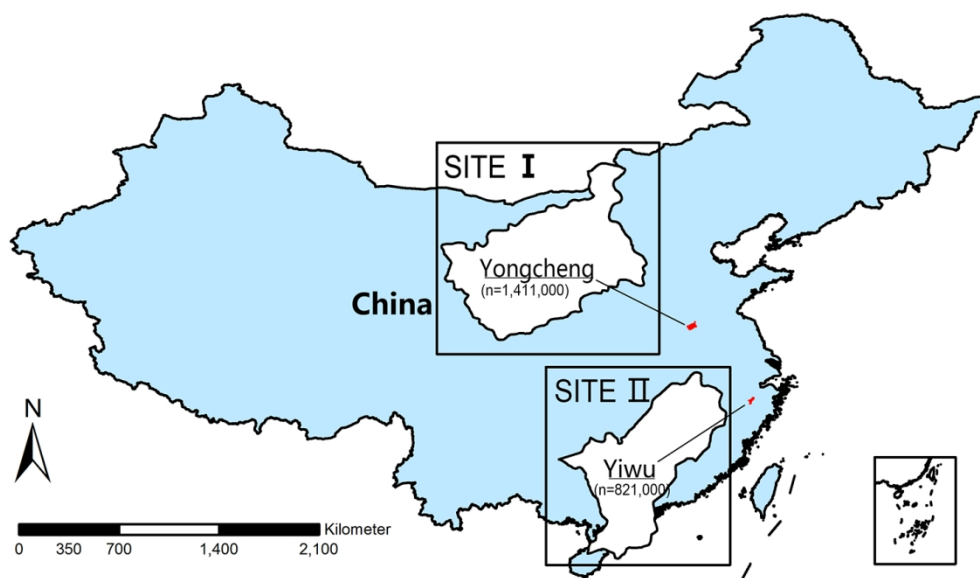


Figure 2. Location and population size of study sites included in PertussisChina study

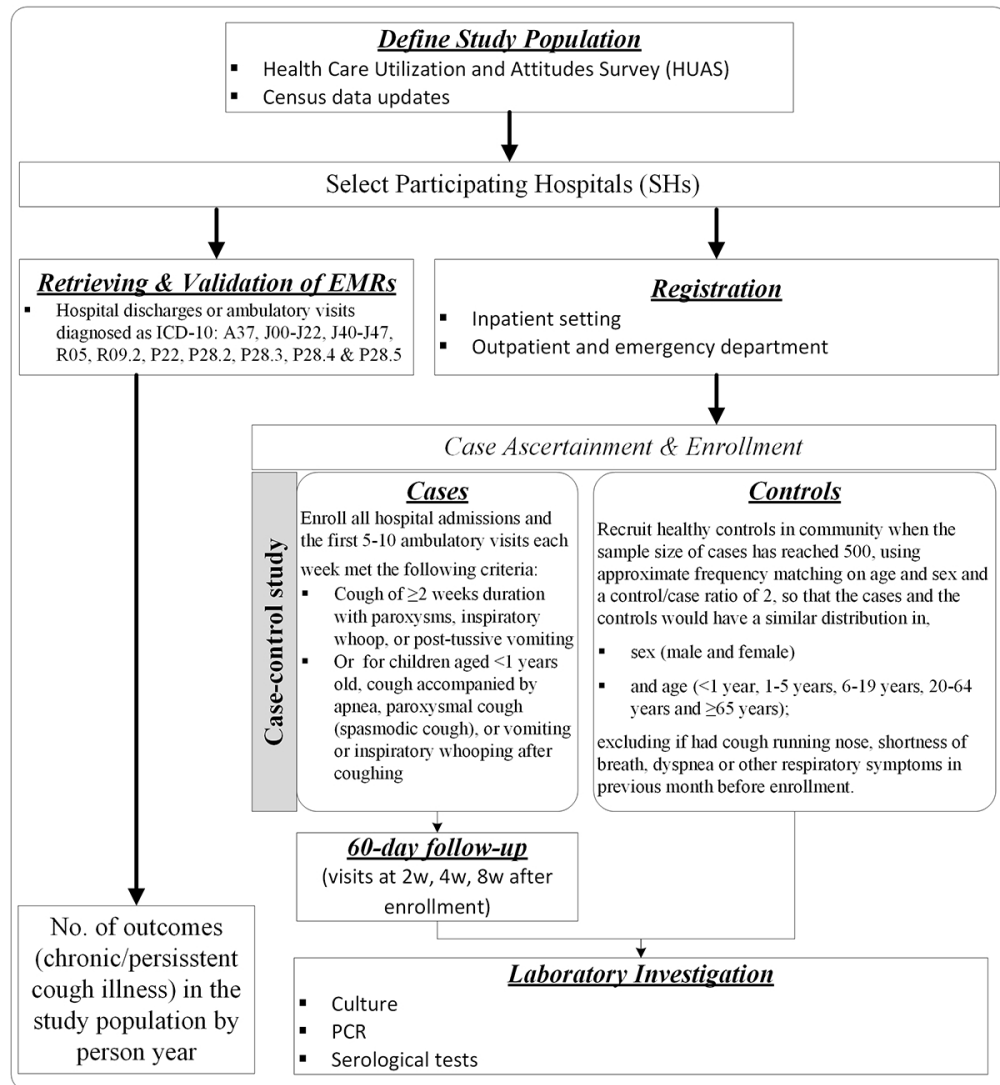


Figure 3. Flow diagram of major study activities

101x110mm (300 x 300 DPI)

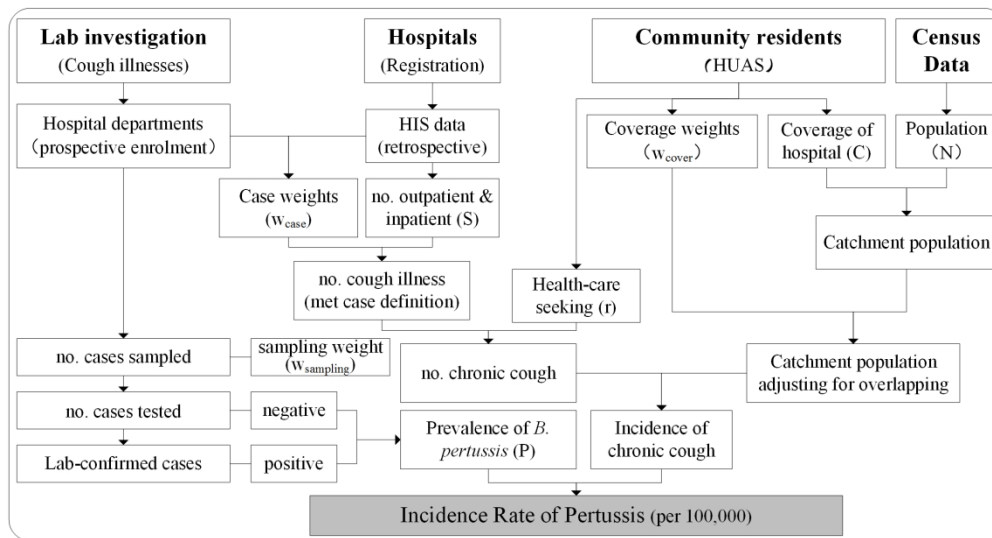


Figure 4. Data flow chart and key indicators used to calculate incidence of pertussis

187x100mm (300 x 300 DPI)

## Supplementary Appendix

**Title:** Burden of Whooping Cough in China (PertussisChina): Study Protocol of a Prospective, Population-based Case-control Study

**Running head:** PertussisChina Study, 2020

### Tables & Forms

- Supplementary Table 1. Survey questionnaire for healthcare utilization and attitudes survey of cough illness among children under 5 years old
- Supplementary Table 2. Survey questionnaire for healthcare utilization and attitudes survey of cough illness among persons aged 5 years and older
- Supplementary Table 3. Case screening and ascertainment form
- Supplementary Table 4. Baseline information of case & control (CRF—T0)
- Supplementary Table 5. Follow-up information of case (CRF—T2w/T4w/T8w)
- Supplementary Table 6. Outcome of case at the end of follow-up (CRF—Tend)

**Supplementary Table 1.** Survey questionnaire for healthcare utilization and attitudes survey of cough illness among children under 5 years old

Greetings! We are the staff of Center for Disease Control and Prevention. We sincerely invite you to participate in this questionnaire survey. The purpose of the survey is to study the utilization and attitudes of community residents towards health-care services of chronic/persistent cough, so that we can better serve you in the future.

This survey is anonymous. Your answers to these questions are kept confidential. You can choose whether to participate in the survey voluntarily or not. Refusal of the survey will not have any adverse consequences on you personally and your children. If you agree to the participate, please read each question carefully and fill in the answer on your own. Thank you for your support and cooperation!

**Part I. Basic Information**

- 1.1 Site: \_\_\_\_\_ Site ID: \_\_\_\_\_
- 1.2 Your length of time (years & months) living in the site (e.g. Yiwu or Yongcheng):  
 less than 6 months     six months and over
- 1.3 Current address: \_\_\_\_\_ county \_\_\_\_\_ street \_\_\_\_\_ community/village
- 1.4 Type of respondents in relation to the studied subject/children:  
 mother     father     grandma/grandpa     others \_\_\_\_\_
- 1.5 Date of Birth:    □□□□/□□/□□ (yyyy/MM/dd)
- 1.6 Gender:     Male     Female
- 1.7 Ethnicity:     Han     others \_\_\_\_\_
- 1.8 Did your child attend school?     yes     no
- 1.9 Your occupation (of the respondent who answered the question):  
 students     housework or unemployed     retired people     commercial & service sector workers     food handler or employees of food industry  
 specialists, including teacher, medical personnel and workers     agriculture, forestry, animal husbandry and fishery workers     others \_\_\_\_\_

1  
2  
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4 1.10 Your educational attainment (of the respondent who answered the question).

5 primary school or illiteracy middle school high school

6  
7 technical secondary school college level and above

8  
9 1.11 Including yourself, there are\_\_\_\_\_members in your family (defined as those  
10 who shared the same dining table in the house)?

11 Of which, there are\_\_\_\_\_children under five years old.

12  
13 1.12 Is there any smokers or ex-smokers in your family?  yes  no

14  
15  
16  
17  
18 **Part II. self-perceived illness and health-care seeking behavior**

19  
20 2.1 Did your children experienced cough during the past one month prior to our  
21 interview?  no  yes

22 2.1.1 If yes, how long did the cough last?

23  <1 week  1-2 weeks  3-4 weeks  5-8 weeks  >8 weeks

24 2.1.2 If yes, what is the clinical characteristics of the last episode of cough?

25 paroxysmal cough vomiting after coughing whooping cough

26 cough worsening during the night vomiting after coughing

27 productive cough with large amount of sputum dry cough

28 cough with blood in sputum others\_\_\_\_\_

29 2.1.3 If yes, what is the other concomitant symptoms?

30 productive cough running nose fever (body temperature  $\geq 37.2^{\circ}\text{C}$ )

31 belching acid reflux irritable and crying vomiting headache

32 tachypnea earache sore throat dyspnea abdominal pain

33 arthralgia chest pain myalgia fatigue lethargy

34 burn after sternum without any other discomfort others\_\_\_\_\_

35 2.1.4 If yes, what do you think is the most probable cause of your cough?

36 respiratory tract infection inhalation of foreign objects in the respiratory tract

37 COPD exacerbation asthma exacerbation recurrent tuberculosis

38 chronic cardiopulmonary disease lung cancer inhalation of cold air

39 chronic bronchitis bronchiectasis I don't know others\_\_\_\_\_

2.2 Did your child visit a doctor or seek healthcare during the last episode of cough?

no     yes

2.2.1 If yes, where did your child see a doctor?

(For Yiwu site, please select the following)

- The Fourth Affiliated Hospital Zhejiang University School of Medicine
- Yiwu Fuyuan Hospital    Yiwu Maternal and Children's Hospital
- Yiwu Central Hospital    Yiwu Traditional Chinese Medicine Hospital
- Yiwu Tianxiang Medical Group Dongfang Hospital
- Chouzhou Hospital of Yiwu    The Second People's Hospital of Yiwu
- The Third People's Hospital of Yiwu    Yiting township Health Center
- Suxi Township Health Center    Beiyuan Community Health Center
- Shangxi Township Health Center    Dachen Township Health Center
- Houzhai Community Health Center    Chi'an Township Health Center
- Chengxi Community Health Center    Niansanli Community Health Center
- Yiwu Huashan Rehabilitation Hospital    Jiangdong Community Health Center
- Futian Community Health Center    Yiwu Dermatology Hospital
- Zhejiang Children's Hospital    Village clinics or private clinics
- others \_\_\_\_\_

(For Yongcheng site, please select the following)

- Yongcheng People's Hospital    Yongcheng Central Hospital
- Yongmei Group General Hospital    Henan Shenhua Group General Hospital
- Yongcheng Maternal & Child Health Hospital    Yucheng Township Health Center
- Chenji Township Health Center    Gaozhuang Township Health Center
- Yongcheng Mangdang Hospital    Lizhai Township Health Center
- Yongcheng Second People's Hospital    Liuhe Township Health Center
- Yanji Township Health Center    Dawangji Township Health Center
- Longgang Township Health Center    Shunhe Township Health Center
- Peiqiao Township Health Center    Huaihai Community Health Center
- Huangkou Township Health Center    Maqiao Township Health Center
- Jiangkou Township Health Center    Houling Township Health Center



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4 Chenguanzhuang Township Health Center  Taiqiu Township Health Center  
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6 Wolong Township Health Center  Huicun Township Health Center  
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8 Yongcheng Traditional Chinese Medicine Hospital  
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10 Shibali Township Health Center  Xuehu Township Health Center  
11  
12 Mamu Township Health Center  Xinqiao Township Health Center  
13  
14 Xunyang Township Health Center  Shuangqiao Township Health Center  
15  
16 Yongcheng Jiangkou Yongji Hospital  Miaoqiao Township Health Center  
17  
18 Yongcheng Tuberculosis Hospital  Tiaohu Township Health Center  
19  
20 Zhongyuan Road Community Health Center  Yongcheng Wuguanke Hospital  
21  
22 Mangshan Township Health Center  Luanhu Township Health Center  
23  
24 others \_\_\_\_\_  
25  
26

27 2.2.1 If no, why did not your child see a doctor?  
28

- 29 Symptoms are mild, no need to see a doctor  
30  
31 The hospital is too far from home and the transportation is inconvenient  
32  
33 Drugs purchased in pharmacies Distrust the doctor  
34  
35 Unaffordable high medical expenses  
36  
37 Hospital facilities and environment were poor  
38  
39 others \_\_\_\_\_  
40

41 2.3 Was your child hospitalized for the last episode of cough?  no  yes  
42

43 2.3.1 If yes, where was your child hospitalized?  
44

45 (For Yiwu site, please select the following)

- 46 The Fourth Affiliated Hospital Zhejiang University School of Medicine  
47  
48 Yiwu Fuyuan Hospital Yiwu Maternal and Children's Hospital  
49  
50 Yiwu Central Hospital Yiwu Traditional Chinese Medicine Hospital  
51  
52 Yiwu Tianxiang Medical Group Dongfang Hospital  
53  
54 Chouzhou Hospital of Yiwu The Second People's Hospital of Yiwu  
55  
56 The Third People's Hospital of Yiwu Yiting township Health Center  
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58 Suxi Township Health Center Beiyuan Community Health Center  
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60 Shangxi Township Health Center Dachen Township Health Center

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4  Houzhai Community Health Center    Chi'an Township Health Center  
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6  Chengxi Community Health Center    Niansanli Community Health Center  
7  
8  Yiwu Huashan Rehabilitation Hospital    Jiangdong Community Health Center  
9  
10  Futian Community Health Center    Yiwu Dermatology Hospital  
11  
12  Zhejiang Children's Hospital    Village clinics or private clinics  
13  
14  others\_\_\_\_\_

15 (For Yongcheng site, please select the following)

- 16  
17  Yongcheng People's Hospital    Yongcheng Central Hospital  
18  
19  Yongmei Group General Hospital    Henan Shenhua Group General Hospital  
20  
21  Yongcheng Maternal & Child Health Hospital    Yucheng Township Health Center  
22  
23  Chenji Township Health Center    Gaozhuang Township Health Center  
24  
25  Yongcheng Mangdang Hospital    Lizhai Township Health Center  
26  
27  Yongcheng Second People's Hospital    Liuhe Township Health Center  
28  
29  Yanji Township Health Center    Dawangji Township Health Center  
30  
31  Longgang Township Health Center    Shunhe Township Health Center  
32  
33  Peiqiao Township Health Center    Huaihai Community Health Center  
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35  Huangkou Township Health Center    Maqiao Township Health Center  
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37  Jiangkou Township Health Center    Houling Township Health Center  
38  
39  Chenguanzhuang Township Health Center    Taiqiu Township Health Center  
40  
41  Wolong Township Health Center    Huicun Township Health Center  
42  
43  Yongcheng Traditional Chinese Medicine Hospital  
44  
45  Shibali Township Health Center    Xuehu Township Health Center  
46  
47  Mamu Township Health Center    Xinqiao Township Health Center  
48  
49  Xunyang Township Health Center    Shuangqiao Township Health Center  
50  
51  Yongcheng Jiangkou Yongji Hospital    Miaoqiao Township Health Center  
52  
53  Yongcheng Tuberculosis Hospital    Tiaohe Township Health Center  
54  
55  Zhongyuan Road Community Health Center    Yongcheng Wuguanke Hospital  
56  
57  Mangshan Township Health Center    Luanhu Township Health Center  
58  
59  others  
60

### Part III. Attitudes towards health-care utilization

(Next, we will ask some questions about the actions you might take under some hypothetical situations that do not need to happen.)

3.1 If your child keeps coughing for 2 weeks but does not get better, and you have decided to see a doctor, which one of the following medical institutions would you choose to go?

(For Yiwu site, please select the following)

- The Fourth Affiliated Hospital Zhejiang University School of Medicine
- Yiwu Fuyuan Hospital    Yiwu Maternal and Children's Hospital
- Yiwu Central Hospital    Yiwu Traditional Chinese Medicine Hospital
- Yiwu Tianxiang Medical Group Dongfang Hospital
- Chouzhou Hospital of Yiwu    The Second People's Hospital of Yiwu
- The Third People's Hospital of Yiwu    Yiting township Health Center
- Suxi Township Health Center    Beiyuan Community Health Center
- Shangxi Township Health Center    Dachen Township Health Center
- Houzhai Community Health Center    Chi'an Township Health Center
- Chengxi Community Health Center    Niansanli Community Health Center
- Yiwu Huashan Rehabilitation Hospital    Jiangdong Community Health Center
- Futian Community Health Center    Yiwu Dermatology Hospital
- Zhejiang Children's Hospital    Village clinics or private clinics
- others\_\_\_\_\_

(For Yongcheng site, please select the following)

- Yongcheng People's Hospital    Yongcheng Central Hospital
- Yongmei Group General Hospital    Henan Shenhua Group General Hospital
- Yongcheng Maternal & Child Health Hospital    Yucheng Township Health Center
- Chenji Township Health Center    Gaozhuang Township Health Center
- Yongcheng Mangdang Hospital    Lizhai Township Health Center
- Yongcheng Second People's Hospital    Liuhe Township Health Center
- Yanji Township Health Center    Dawangji Township Health Center

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4  Longgang Township Health Center    Shunhe Township Health Center  
5  Peiqiao Township Health Center    Huaihai Community Health Center  
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7  Huangkou Township Health Center    Maqiao Township Health Center  
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9  Jiangkou Township Health Center    Houling Township Health Center  
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11  Chenguanzhuang Township Health Center    Taiqiu Township Health Center  
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13  Wolong Township Health Center    Huicun Township Health Center  
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15  Yongcheng Traditional Chinese Medicine Hospital  
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17  Shibali Township Health Center    Xuehu Township Health Center  
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19  Mamu Township Health Center    Xinqiao Township Health Center  
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21  Xunyang Township Health Center    Shuangqiao Township Health Center  
22  
23  Yongcheng Jiangkou Yongji Hospital    Miaoqiao Township Health Center  
24  
25  Yongcheng Tuberculosis Hospital    Tiaohu Township Health Center  
26  
27  Zhongyuan Road Community Health Center    Yongcheng Wuguanke Hospital  
28  
29  Mangshan Township Health Center    Luanhu Township Health Center  
30  
31  others\_\_\_\_\_

32  
33 3.2 If the doctor recommends that your child be hospitalized, which one of the  
34 following medical institutions would you choose?  
35

36  
37 (For Yiwu site, please select the following)

- 38  
39  The Fourth Affiliated Hospital Zhejiang University School of Medicine  
40  
41  Yiwu Fuyuan Hospital    Yiwu Maternal and Children's Hospital  
42  
43  Yiwu Central Hospital    Yiwu Traditional Chinese Medicine Hospital  
44  
45  Yiwu Tianxiang Medical Group Dongfang Hospital  
46  
47  Chouzhou Hospital of Yiwu    The Second People's Hospital of Yiwu  
48  
49  The Third People's Hospital of Yiwu    Yiting township Health Center  
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51  Suxi Township Health Center    Beiyuan Community Health Center  
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53  Shangxi Township Health Center    Dacheng Township Health Center  
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55  Houzhai Community Health Center    Chi'an Township Health Center  
56  
57  Chengxi Community Health Center    Niansanli Community Health Center  
58  
59  Yiwu Huashan Rehabilitation Hospital    Jiangdong Community Health Center  
60  
 Futian Community Health Center    Yiwu Dermatology Hospital

Zhejiang Children's Hospital    Village clinics or private clinics

others \_\_\_\_\_

(For Yongcheng site, please select the following)

Yongcheng People's Hospital    Yongcheng Central Hospital

Yongmei Group General Hospital    Henan Shenhua Group General Hospital

Yongcheng Maternal & Child Health Hospital    Yucheng Township Health Center

Chenji Township Health Center    Gaozhuang Township Health Center

Yongcheng Mangdang Hospital    Lizhai Township Health Center

Yongcheng Second People's Hospital    Liuhe Township Health Center

Yanji Township Health Center    Dawangji Township Health Center

Longgang Township Health Center    Shunhe Township Health Center

Peiqiao Township Health Center    Huaihai Community Health Center

Huangkou Township Health Center    Maqiao Township Health Center

Jiangkou Township Health Center    Houling Township Health Center

Chenguanzhuang Township Health Center    Taiqiu Township Health Center

Wolong Township Health Center    Huicun Township Health Center

Yongcheng Traditional Chinese Medicine Hospital

Shibali Township Health Center    Xuehu Township Health Center

Mamu Township Health Center    Xinqiao Township Health Center

Xunyang Township Health Center    Shuangqiao Township Health Center

Yongcheng Jiangkou Yongji Hospital    Miaoqiao Township Health Center

Yongcheng Tuberculosis Hospital    Tiaohe Township Health Center

Zhongyuan Road Community Health Center    Yongcheng Wuguanke Hospital

Mangshan Township Health Center    Luanhu Township Health Center

others \_\_\_\_\_

#### **Part IV. Other questions**

4.1 Has your child ever received the following vaccines?

influenza vaccine    pneumococcal vaccine    Haemophilus influenzae vaccine

1  
2  
3  
4  Vaccines containing pertussis components (i.e. DTP)

5 4.1.1 If received vaccines containing pertussis (i.e. DTP), what kind of the vaccine?

6  
7  cDTaP  DTaP/Hib  DTaP-IPV/Hib

8  
9 4.2 Your family's average annual income (Chinese Yuan) is,

10  
11  <50,000  50,000-90,000  100,000-190,000  200,000-490,000  ≥500,000

12  
13 4.3 Your phone number is \_\_\_\_\_

14  
15  
16  
17  
18 Thank you very much for taking your time. The information you provided in this  
19 interview is very valuable to help us improve our work. Wish you a happy life!  
20

21  
22 Time of survey started: □□□□/□□/□□:□□:□□ (yyyy/MM/dd hh:mm)

23  
24 Time of survey ended: □□□□/□□/□□:□□:□□ (yyyy/MM/dd hh:mm)

25  
26 Investigator: \_\_\_\_\_ Supervisor: \_\_\_\_\_  
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Supplementary Table 2. Survey questionnaire for healthcare utilization and attitudes survey of cough illness among persons aged 5 years and older

Greetings! We are the staff of Center for Disease Control and Prevention. We sincerely invite you to participate in this questionnaire survey. The purpose of the survey is to study the utilization and attitudes of community residents towards health-care services of chronic/persistent cough, so that we can better serve you in the future.

This survey is anonymous. Your answers to these questions are kept confidential. You can choose whether to participate in the survey voluntarily or not. Refusal of the survey will not have any adverse consequences on you personally and your children. If you agree to the participate, please read each question carefully and fill in the answer on your own. Thank you for your support and cooperation!

### Part I. Basic Information

1.1 Site: \_\_\_\_\_ Site ID: \_\_\_\_\_

1.2 Your length of time (years & months) living in the site (e.g. Yiwu or Yongcheng):

less than 6 months     six months and over

1.3 Current address: \_\_\_\_\_ county \_\_\_\_\_ street \_\_\_\_\_ community/village

1.4 Type of respondents in relation to the studied subject:

respondent himself is the study subject     others \_\_\_\_\_

1.5 Date of Birth: □□□□/□□/□□ (yyyy/MM/dd)

1.6 Gender:     Male     Female

1.7 Ethnicity:     Han     others \_\_\_\_\_

1.8 Your occupation:

students     housework or unemployed     retired people     commercial & service sector workers     food handler or employees of food industry  
 specialists, including teacher, medical personnel and workers     agriculture, forestry, animal husbandry and fishery workers     others \_\_\_\_\_

1.9 Did you ever contact with dust/chemical materials in the working environment in the past one year, such as those encountered by workers using pneumatic drills at

construction sites, miners, painters, benzene solvents in leather production, etc.

no  yes

1.10 Your educational attainment:

primary school or illiteracy  middle school  high school

technical secondary school  college level and above

1.11 Including yourself, there are \_\_\_\_\_ members in your family (defined as those who shared the same dining table in the house)?

Of which, there are \_\_\_\_\_ children under five years old.

1.12 Are you smoker or ex-smoker?  yes  no

## Part II. self-perceived illness and health-care seeking behavior

2.1 Did you experienced cough during the past one month prior to our interview?

no  yes

2.1.1 If yes, how long did the cough last?

<1 week  1-2 weeks  3-4 weeks  5-8 weeks  >8 weeks

2.1.2 If yes, what is the clinical characteristics of the last episode of cough?

paroxysmal cough  vomiting after coughing  whooping cough

cough worsening during the night  vomiting after coughing

productive cough with large amount of sputum  dry cough

cough with blood in sputum  others \_\_\_\_\_

2.1.3 If yes, what is the other concomitant symptoms?

productive cough  running nose  fever (body temperature  $\geq 37.2^{\circ}\text{C}$ )

belching  acid reflux  irritable and crying  vomiting  headache

tachypnea  earache  sore throat  dyspnea  abdominal pain

arthralgia  chest pain  myalgia  fatigue  lethargy

burn after sternum  without any other discomfort  others \_\_\_\_\_

2.1.4 If yes, what do you think is the most probable cause of your cough?

respiratory tract infection  inhalation of foreign objects in the respiratory tract

COPD exacerbation  asthma exacerbation  recurrent tuberculosis



- 1  
2  
3  
4 chronic cardiopulmonary disease lung cancer inhalation of cold air  
5  
6 chronic bronchitis bronchiectasis I don't know others\_\_\_\_\_

7  
8 2.2 Did you see a doctor or seek healthcare during the last episode of cough?

- 9  no  yes

10  
11 2.2.1 If yes, where did you see a doctor?

12  
13 (For Yiwu site, please select the following)

- 14  
15 The Fourth Affiliated Hospital Zhejiang University School of Medicine  
16  
17 Yiwu Fuyuan Hospital Yiwu Maternal and Children's Hospital  
18  
19 Yiwu Central Hospital Yiwu Traditional Chinese Medicine Hospital  
20  
21 Yiwu Tianxiang Medical Group Dongfang Hospital  
22  
23 Chouzhou Hospital of Yiwu The Second People's Hospital of Yiwu  
24  
25 The Third People's Hospital of Yiwu Yiting township Health Center  
26  
27 Suxi Township Health Center Beiyuan Community Health Center  
28  
29 Shangxi Township Health Center Dachen Township Health Center  
30  
31 Houzhai Community Health Center Chi'an Township Health Center  
32  
33 Chengxi Community Health Center Niansanli Community Health Center  
34  
35 Yiwu Huashan Rehabilitation Hospital Jiangdong Community Health Center  
36  
37 Futian Community Health Center Yiwu Dermatology Hospital  
38  
39 Zhejiang Children's Hospital Village clinics or private clinics  
40  
41 others\_\_\_\_\_

42 (For Yongcheng site, please select the following)

- 43  
44 Yongcheng People's Hospital Yongcheng Central Hospital  
45  
46 Yongmei Group General Hospital Henan Shenhua Group General Hospital  
47  
48 Yongcheng Maternal & Child Health Hospital Yucheng Township Health Center  
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50 Chenji Township Health Center Gaozhuang Township Health Center  
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52 Yongcheng Mangdang Hospital Lizhai Township Health Center  
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54 Yongcheng Second People's Hospital Liuhe Township Health Center  
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56 Yanji Township Health Center Dawangji Township Health Center  
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58 Longgang Township Health Center Shunhe Township Health Center  
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60 Peiqiao Township Health Center Huaihai Community Health Center

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4 Huangkou Township Health Center  Maqiao Township Health Center  
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6 Jiangkou Township Health Center  Houling Township Health Center  
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8 Chenguanzhuang Township Health Center  Taiqiu Township Health Center  
9  
10 Wolong Township Health Center  Huicun Township Health Center  
11  
12 Yongcheng Traditional Chinese Medicine Hospital  
13  
14 Shibali Township Health Center  Xuehu Township Health Center  
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16 Mamu Township Health Center  Xinqiao Township Health Center  
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18 Xunyang Township Health Center  Shuangqiao Township Health Center  
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20 Yongcheng Jiangkou Yongji Hospital  Miaoqiao Township Health Center  
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22 Yongcheng Tuberculosis Hospital  Tiaohe Township Health Center  
23  
24 Zhongyuan Road Community Health Center  Yongcheng Wuguanke Hospital  
25  
26 Mangshan Township Health Center  Luanhu Township Health Center  
27  
28 others\_\_\_\_\_

29 2.2.1 If no, why did not you see a doctor?

- 30  
31 Symptoms are mild, no need to see a doctor  
32  
33 The hospital is too far from home and the transportation is inconvenient  
34  
35 Drugs purchased in pharmacies Distrust the doctor  
36  
37 Unaffordable high medical expenses  
38  
39 Hospital facilities and environment were poor  
40  
41 others\_\_\_\_\_

42 2.3 Were you hospitalized for the last episode of cough?  no  yes

43 2.3.1 If yes, where were you hospitalized?

44 (For Yiwu site, please select the following)

- 45  
46  
47  
48 The Fourth Affiliated Hospital Zhejiang University School of Medicine  
49  
50 Yiwu Fuyuan Hospital Yiwu Maternal and Children's Hospital  
51  
52 Yiwu Central Hospital Yiwu Traditional Chinese Medicine Hospital  
53  
54 Yiwu Tianxiang Medical Group Dongfang Hospital  
55  
56 Chouzhou Hospital of Yiwu The Second People's Hospital of Yiwu  
57  
58 The Third People's Hospital of Yiwu Yiting township Health Center  
59  
60 Suxi Township Health Center Beiyuan Community Health Center

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4 Shangxi Township Health Center Dachen Township Health Center  
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6 Houzhai Community Health Center Chi'an Township Health Center  
7  
8 Chengxi Community Health Center Niansanli Community Health Center  
9  
10 Yiwu Huashan Rehabilitation Hospital Jiangdong Community Health Center  
11  
12 Futian Community Health Center Yiwu Dermatology Hospital  
13  
14 Zhejiang Children's Hospital Village clinics or private clinics  
15  
16 others\_\_\_\_\_

17 (For Yongcheng site, please select the following)

- 18  
19 Yongcheng People's Hospital Yongcheng Central Hospital  
20  
21 Yongmei Group General Hospital Henan Shenhua Group General Hospital  
22  
23 Yongcheng Maternal & Child Health Hospital Yucheng Township Health Center  
24  
25 Chenji Township Health Center Gaozhuang Township Health Center  
26  
27 Yongcheng Mangdang Hospital Lizhai Township Health Center  
28  
29 Yongcheng Second People's Hospital Liuhe Township Health Center  
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31 Yanji Township Health Center Dawangji Township Health Center  
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33 Longgang Township Health Center Shunhe Township Health Center  
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35 Peiqiao Township Health Center Huaihai Community Health Center  
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37 Huangkou Township Health Center Maqiao Township Health Center  
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39 Jiangkou Township Health Center Houling Township Health Center  
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41 Chenguanzhuang Township Health Center Taiqiu Township Health Center  
42  
43 Wolong Township Health Center Huicun Township Health Center  
44  
45 Yongcheng Traditional Chinese Medicine Hospital  
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47 Shibali Township Health Center Xuehu Township Health Center  
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49 Mamu Township Health Center Xinqiao Township Health Center  
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51 Xunyang Township Health Center Shuangqiao Township Health Center  
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53 Yongcheng Jiangkou Yongji Hospital Miaoqiao Township Health Center  
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55 Yongcheng Tuberculosis Hospital Tiaohe Township Health Center  
56  
57 Zhongyuan Road Community Health Center Yongcheng Wuguanke Hospital  
58  
59 Mangshan Township Health Center Luanhu Township Health Center  
60  
others\_\_\_\_\_

### Part III. Attitudes towards health-care utilization

(Next, we will ask some questions about the actions you might take under some hypothetical situations that do not need to happen.)

3.1 If you keep coughing for 2 weeks but does not get better, and you have decided to see a doctor, which one of the following medical institutions would you choose to go?

(For Yiwu site, please select the following)

- The Fourth Affiliated Hospital Zhejiang University School of Medicine
- Yiwu Fuyuan Hospital    Yiwu Maternal and Children's Hospital
- Yiwu Central Hospital    Yiwu Traditional Chinese Medicine Hospital
- Yiwu Tianxiang Medical Group Dongfang Hospital
- Chouzhou Hospital of Yiwu    The Second People's Hospital of Yiwu
- The Third People's Hospital of Yiwu    Yiting township Health Center
- Suxi Township Health Center    Beiyuan Community Health Center
- Shangxi Township Health Center    Dachen Township Health Center
- Houzhai Community Health Center    Chi'an Township Health Center
- Chengxi Community Health Center    Niansanli Community Health Center
- Yiwu Huashan Rehabilitation Hospital    Jiangdong Community Health Center
- Futian Community Health Center    Yiwu Dermatology Hospital
- Zhejiang Children's Hospital    Village clinics or private clinics
- others\_\_\_\_\_

(For Yongcheng site, please select the following)

- Yongcheng People's Hospital    Yongcheng Central Hospital
- Yongmei Group General Hospital    Henan Shenhua Group General Hospital
- Yongcheng Maternal & Child Health Hospital    Yucheng Township Health Center
- Chenji Township Health Center    Gaozhuang Township Health Center
- Yongcheng Mangdang Hospital    Lizhai Township Health Center
- Yongcheng Second People's Hospital    Liuhe Township Health Center
- Yanji Township Health Center    Dawangji Township Health Center
- Longgang Township Health Center    Shunhe Township Health Center

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4  Peiqiao Township Health Center    Huaihai Community Health Center  
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10  Chenguanzhuang Township Health Center    Taiqiu Township Health Center  
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12  Wolong Township Health Center    Huicun Township Health Center  
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14  Yongcheng Traditional Chinese Medicine Hospital  
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20  Xunyang Township Health Center    Shuangqiao Township Health Center  
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22  Yongcheng Jiangkou Yongji Hospital    Miaoqiao Township Health Center  
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24  Yongcheng Tuberculosis Hospital    Tiaohe Township Health Center  
25  
26  Zhongyuan Road Community Health Center    Yongcheng Wuguanke Hospital  
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28  Mangshan Township Health Center    Luanhu Township Health Center  
29  
30  others\_\_\_\_\_

31 3.2 If the doctor recommends that you should be hospitalized, which one of the  
32 following medical institutions would you choose?  
33

34 (For Yiwu site, please select the following)

- 35  
36  
37  The Fourth Affiliated Hospital Zhejiang University School of Medicine  
38  
39  Yiwu Fuyuan Hospital    Yiwu Maternal and Children's Hospital  
40  
41  Yiwu Central Hospital    Yiwu Traditional Chinese Medicine Hospital  
42  
43  Yiwu Tianxiang Medical Group Dongfang Hospital  
44  
45  Chouzhou Hospital of Yiwu    The Second People's Hospital of Yiwu  
46  
47  The Third People's Hospital of Yiwu    Yiting township Health Center  
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49  Suxi Township Health Center    Beiyuan Community Health Center  
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51  Shangxi Township Health Center    Dachen Township Health Center  
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53  Houzhai Community Health Center    Chi'an Township Health Center  
54  
55  Chengxi Community Health Center    Niansanli Community Health Center  
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57  Yiwu Huashan Rehabilitation Hospital    Jiangdong Community Health Center  
58  
59  Futian Community Health Center    Yiwu Dermatology Hospital  
60  
 Zhejiang Children's Hospital    Village clinics or private clinics

others\_\_\_\_\_

(For Yongcheng site, please select the following)

- Yongcheng People's Hospital Yongcheng Central Hospital
- Yongmei Group General Hospital Henan Shenhua Group General Hospital
- Yongcheng Maternal & Child Health Hospital Yucheng Township Health Center
- Chenji Township Health Center Gaozhuang Township Health Center
- Yongcheng Mangdang Hospital Lizhai Township Health Center
- Yongcheng Second People's Hospital Liuhe Township Health Center
- Yanji Township Health Center Dawangji Township Health Center
- Longgang Township Health Center Shunhe Township Health Center
- Peiqiao Township Health Center Huaihai Community Health Center
- Huangkou Township Health Center Maqiao Township Health Center
- Jiangkou Township Health Center Houling Township Health Center
- Chenguanzhuang Township Health Center Taiqiu Township Health Center
- Wolong Township Health Center Huicun Township Health Center
- Yongcheng Traditional Chinese Medicine Hospital
- Shibali Township Health Center Xuehu Township Health Center
- Mamu Township Health Center Xinqiao Township Health Center
- Xunyang Township Health Center Shuangqiao Township Health Center
- Yongcheng Jiangkou Yongji Hospital Miaoqiao Township Health Center
- Yongcheng Tuberculosis Hospital Tiaohe Township Health Center
- Zhongyuan Road Community Health Center Yongcheng Wuguanke Hospital
- Mangshan Township Health Center Luanhu Township Health Center
- others\_\_\_\_\_

#### Part IV. Other questions

##### 4.1 Have you ever received the following vaccines?

- influenza vaccine pneumococcal vaccine Haemophilus influenzae vaccine
- Vaccines containing pertussis components (i.e. DTP)

1  
2  
3  
4 4.1.1 If received vaccines containing pertussis (i.e. DTP), what kind of the vaccine?

5 cDTaP DTaP/Hib DTaP-IPV/Hib

6  
7  
8 4.2 Your family's average annual income (Chinese Yuan) is,

9  <50,000  50,000-90,000  100,000-190,000  200,000-490,000  ≥500,000

10  
11 4.3 Your phone number is \_\_\_\_\_

12  
13  
14  
15  
16 Thank you very much for taking your time. The information you provided in this  
17 interview is very valuable to help us improve our work. Wish you a happy life!  
18

19  
20 Time of survey started: □□□□/□□/□□:□□:□□ (yyyy/MM/dd hh:mm)

21  
22 Time of survey ended: □□□□/□□/□□:□□:□□ (yyyy/MM/dd hh:mm)

23  
24 Investigator: \_\_\_\_\_ Supervisor: \_\_\_\_\_

Supplementary Table 3. Case screening and ascertainment form

Name of Hospital \_\_\_\_\_ Departments \_\_\_\_\_

Name of patient		Sex	<input type="checkbox"/> male <input type="checkbox"/> female
Birthdate		Ethnicity	
Current address		Phone number	
Date of illness onset		Date of admission	
Date of written informed consent signed			
Lists of inclusion & exclusion criteria			yes no
<b>Inclusion criteria:</b>			
<b>Patient regardless of ages:</b>			
1.cough of $\geq 2$ weeks duration;			<input type="checkbox"/> <input type="checkbox"/>
2.had one or more of the following symptoms;			<input type="checkbox"/> <input type="checkbox"/>
- paroxysmal cough;			<input type="checkbox"/>
- inspiratory whoop;			<input type="checkbox"/>
- post-tussive vomiting.			<input type="checkbox"/>
<b>Infants less than one year old</b>			
1.cough (regardless of cough duration);			<input type="checkbox"/> <input type="checkbox"/>
2.had one or more of the following symptoms;			<input type="checkbox"/> <input type="checkbox"/>
- paroxysmal cough;			<input type="checkbox"/>
- inspiratory whoop;			<input type="checkbox"/>
- post-tussive vomiting;			<input type="checkbox"/>
- apnea.			<input type="checkbox"/>
Written informed consent signed			<input type="checkbox"/> <input type="checkbox"/>
If you answer "No" to any of the above, the patient cannot enter the study.			
<b>Exclusion criteria:</b>			
1.not a permanent resident (lived less than 6 months at the site);			<input type="checkbox"/> <input type="checkbox"/>
2.gastroesophageal reflux;			<input type="checkbox"/> <input type="checkbox"/>
3.spastic bronchitis;			<input type="checkbox"/> <input type="checkbox"/>
4.diagnosed tuberculosis;			<input type="checkbox"/> <input type="checkbox"/>
5.lung mycoplasma/chlamydia infection;			<input type="checkbox"/> <input type="checkbox"/>
6.chronic sinusitis;			<input type="checkbox"/> <input type="checkbox"/>
7.adults/adolescents with a measured body temperature of $\geq 38.5$ °C;			<input type="checkbox"/> <input type="checkbox"/>
8. researchers considered not suitable for participating in the study.			<input type="checkbox"/> <input type="checkbox"/>
If you answer Yes" to any of the above, the patient cannot enter the study.			
Whether the patient is included in the study			<input type="checkbox"/> <input type="checkbox"/>
If no, what is the reason for not included?			
- not meet the inclusion & exclusion criteria;			<input type="checkbox"/> <input type="checkbox"/>
- Refuse to participate ;			<input type="checkbox"/> <input type="checkbox"/>
If yes, what is the patient identifier no.? _____			<input type="checkbox"/> <input type="checkbox"/>





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Vaccination history of DTP3 (for children aged under 14 years old)							
<b>Source of data :</b> <input type="checkbox"/> vaccination certificate <input type="checkbox"/> linkage with national database <input type="checkbox"/> self-reports <b>Reasons of unvaccinated :</b> 1. Contraindications; 2. Under the age of vaccination; 3. Missed vaccination time; 4. Parents refused to vaccination; 5. migrating population; 6. Don't know; 7. Others _____							
dose	lot number	producer	dosage		site	Date (YYYY/mm/dd)	Reasons of unvaccinated
			dose	unit			
1							
2							
3							
Patient specimen collection							
<b>Specimen collected :</b> <input type="checkbox"/> yes <input type="checkbox"/> no <b>Date of sampling :</b> ____/____/____(YYYY/mm/dd)							
<b>Type of specimen :</b> Nasopharyngeal swab <input type="checkbox"/> amounts : _____ Whole blood <input type="checkbox"/> quantity : _____ ml							
<b>Hospital :</b> _____ <b>Investigator :</b> _____ <b>Date of reporting :</b> ____/____/____(YYYY/mm/dd)							

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Supplementary Table 5. Follow-up information of case (CRF—T<sub>2w</sub>/T<sub>4w</sub>/T<sub>8w</sub>)

Patient identifier no.: \_\_\_\_\_ Type:  Inpatient  outpatient

**Name :** \_\_\_\_\_ ( or **Parents' name :** \_\_\_\_\_ ) **Sex :**  male  female

**Illness onset date :** \_\_\_\_ / \_\_\_\_ / \_\_\_\_ (YYYY/mm/dd) **Admission date :** \_\_\_\_ / \_\_\_\_ / \_\_\_\_ (YYYY/mm/dd)

**Follow-up date :** \_\_\_\_ / \_\_\_\_ / \_\_\_\_ (YYYY/mm/dd) **Weeks of follow-up:**  2 wks  4 wks  8 wks

**Follow-up method:**  hospital visits  home visits

**Outcomes**

**Survival:**  yes  no Date of death: \_\_\_\_ / \_\_\_\_ / \_\_\_\_ (YYYY/mm/dd) death diagnosis : \_\_\_\_\_

**Hospitalized :**  yes  no **Re-admitted into hospital after discharge:**  yes  no

**Reasons for re-admission :** Pneumonia/heart failure/cardiogenic shock/encephalopathy/Seizure/other \_\_\_\_\_

**Lost to follow-up:**  yes  no (refers to 3 consecutive phone calls to patients on different working days but no answers at all )

**Clinical characteristics (during follow-up visits)**

cough ( Starting date \_\_\_\_ / \_\_\_\_ / \_\_\_\_ [YYYY/mm/dd] , duration \_\_\_\_ days )

post-tussive vomiting  paroxysmal cough  whooping cough  apnea  cyanosis  fever ( body temperature \_\_\_\_ °C )

cough worsening in night  productive cough; Sputum color : yellow/white/black/glass like

seizure  hemoptysis  chills  headache  myalgia  sore throat  joint pain  chest pain

sweat  shortness-of-breath  running nose  lachrymation  fatigue  other( \_\_\_\_\_ )

**Blood tests :** WBC \_\_\_\_ × 10<sup>9</sup>/L; L \_\_\_\_ × 10<sup>9</sup>/L; N \_\_\_\_ × 10<sup>9</sup>/L; Plt \_\_\_\_ × 10<sup>9</sup>/L; Hb \_\_\_\_ g/L; CRP \_\_\_\_ mg/L; GLU \_\_\_\_ mmol/L

**Physical check :** body temperature : \_\_\_\_ °C **Breath rate :** \_\_\_\_ breath/min **Heart rate :** \_\_\_\_ beats/min

**Systolic/diastolic blood pressure :** \_\_\_\_ / \_\_\_\_ mmHg **Pulse oximetry:** sPO<sub>2</sub> (if any): \_\_\_\_ %

**Lung auscultation :**  dry rale  wet rale **Consciousness :** clear/lethargy/irritable/delirium/convulsions/coma

**Patient specimen collection**

**Specimen collected :**  yes  no **Date of sampling :** \_\_\_\_ / \_\_\_\_ / \_\_\_\_ (YYYY/mm/dd)

**Type of specimen :** Nasopharyngeal swab  amounts : \_\_\_\_\_

Whole blood  quantity : \_\_\_\_\_ ml

**Reasons for not sampling :**  without coughing symptoms for 1 week  refusal to sampling

**Hospital :** \_\_\_\_\_ **Investigator :** \_\_\_\_\_ **Date of follow-up :** \_\_\_\_ / \_\_\_\_ / \_\_\_\_ (YYYY/mm/dd)

Supplementary Table 6. Outcome of case at the end of follow-up (CRF—T<sub>end</sub>)

Patient identifier no.: \_\_\_\_\_ Type:  inpatient  outpatient

Name : \_\_\_\_\_ ( or Parents' name : \_\_\_\_\_ ) Sex :  male  female Illness onset date : \_\_\_\_ / \_\_\_\_ / \_\_\_\_ (YYYY/mm/dd)  
 Admission date : \_\_\_\_ / \_\_\_\_ / \_\_\_\_ (YYYY/mm/dd) Discharge date : \_\_\_\_ / \_\_\_\_ / \_\_\_\_ (YYYY/mm/dd)  
 Discharge diagnosis : primary diagnosis \_\_\_\_\_  
 secondary diagnosis 1. \_\_\_\_\_ 2. \_\_\_\_\_ 3. \_\_\_\_\_

**Treatment during hospitalization**

Admitting into ICU :  yes  no \_\_\_\_ / \_\_\_\_ / \_\_\_\_ (YYYY/mm/dd)  
 1. Transfer in date \_\_\_\_ / \_\_\_\_ / \_\_\_\_ (YYYY/mm/dd) Transfer out date \_\_\_\_ / \_\_\_\_ / \_\_\_\_ (YYYY/mm/dd)  
 2. Transfer in date \_\_\_\_ / \_\_\_\_ / \_\_\_\_ (YYYY/mm/dd) Transfer out date \_\_\_\_ / \_\_\_\_ / \_\_\_\_ (YYYY/mm/dd)  
 3. Transfer in date \_\_\_\_ / \_\_\_\_ / \_\_\_\_ (YYYY/mm/dd) Transfer out date \_\_\_\_ / \_\_\_\_ / \_\_\_\_ (YYYY/mm/dd)  
 Oxygen therapy :  yes  no duration : \_\_\_\_\_ days  
 Invasive ventilation :  yes  no duration : \_\_\_\_\_ days (invasive ventilation refers to tracheal intubation or tracheotomy)  
 Non-invasive ventilation:  yes  no duration : \_\_\_\_\_ days  
 Oscillating respirator :  yes  no duration : \_\_\_\_\_ days  
 ECMO or interventional lung adjuvant therapy ( iLA )  yes  no date of treatment start : \_\_\_\_ / \_\_\_\_ / \_\_\_\_ (YYYY/mm/dd)  
 Renal replacement therapy/dialysis :  yes  no date of treatment start : \_\_\_\_ / \_\_\_\_ / \_\_\_\_ (YYYY/mm/dd)  
 Exchange transfusion :  yes  no date of treatment start : \_\_\_\_ / \_\_\_\_ / \_\_\_\_ (YYYY/mm/dd)  
 Leukapheresis or leukoreduction therapy :  yes  no date of treatment start : \_\_\_\_ / \_\_\_\_ / \_\_\_\_ (YYYY/mm/dd)

**Drugs**

- ( 1 ) Drug name : Please give the name of the drug, or the trade name if it is a fixed compound preparation
- ( 2 ) Category: A=antibiotic (1. Amoxicillin; 2. Amoxicillin-clavulanic acid; 3. Ampicillin; 4. Azithromycin; 5. Ceftriaxone; 6. Cefuroxime; 7. Ciprofloxacin; 8. Clarithromycin; 9. Doxycycline; 10. Erythromycin; 11. Penicillin; 12. Tetracycline; 13. Compound sulfamethoxazole); B=antiviral drugs; C=steroid hormone drugs
- ( 3 ) Route : 1=oral, 2=intravenous injection, 3=intravenous drip, 4=intramuscular injection, 5=inhalation, 6=other
- ( 4 ) Frequency : 1= continuous , 2=intermittent

drug name (1)	category (2)	route (3)	daily dose		frequency (4)	starting date (YYYY/mm/dd)	stop date (YYYY/mm/dd)
			dose	unit			

**Clinical characteristics**

**Symptoms/signs :**  
 cough ( Starting date \_\_\_\_ / \_\_\_\_ / \_\_\_\_ [YYYY/mm/dd] , duration \_\_\_\_ days )  
 post-tussive vomiting  paroxysmal cough  whooping cough  apnea  cyanosis  fever ( body temperature \_\_\_\_ °C )  
 cough worsening in night  productive cough; Sputum color : yellow/white/black/glass like  
 seizure  hemoptysis  chills  headache  myalgia  sore throat  joint pain  chest pain  
 sweat  shortness-of-breath  running nose  lachrymation  fatigue  other( \_\_\_\_\_ )

**Complications :**  
 viral pneumonia  cardiac arrest  bacterial pneumonia  bacteremia  acute lung injury/ARDS  heart infection  
 coagulation disorders  pneumothorax  anemia  pleural Effusion  acute kidney injury  myolysis  
 bronchiolitis  gastrointestinal hemorrhage  meningitis  pancreatitis  epilepsy  arrhythmia

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<input type="checkbox"/> liver insufficiency <input type="checkbox"/> stroke <input type="checkbox"/> hyperglycemia <input type="checkbox"/> hypoglycemia <input type="checkbox"/> congestive Heart Failure <input type="checkbox"/> other ( _____ )
<b>Patient Prognosis</b>
<input type="checkbox"/> cured <input type="checkbox"/> improved and be discharged <input type="checkbox"/> transferred to other hospital    reasons for transfer : community rehabilitation/other ( _____ ) <input type="checkbox"/> give up treatment    reasons for give-up : economic reasons/illness exacerbation/other ( _____ ) <input type="checkbox"/> death    date of death : ____ / ____ / ____ (YYYY/mm/dd)    death diagnosis : _____
<b>Hospital :</b> _____ <b>Investigator :</b> _____ <b>Date of record :</b> ____ / ____ / ____ (YYYY/mm/dd)

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