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Preplanned Studies

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Cover Photo: Eighth grade students in Shiqu High School filling out echinococcosis questionnaires in Shiqu County, Ganzi Tibetan Autonomous Prefecture, Sichuan Province, on September 2, 2020.

Preplanned Studies

Epidemiological and Clinical Features of Patients with Scrub Typhus — Guangzhou City, Guangdong Province, China, 2012–2018

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Summary

What is already known about this topic?

Scrub typhus (ST) causes public health challenges in the "tsutsugamushi triangle" in the Asia-Pacific area greater than 13 million square kilometers, affecting an estimated one million people each year.

What is added by this report?

A retrospective study based on 4,501 hospitalized patients with ST in Guangzhou City, China, described the epidemiological and clinical characteristics, laboratory findings of ST, and determined the related factors and a predictive model for severe disease.

What are the implications for public health practice?

The current study provided updated knowledge that might enable public health policymakers to formulate appropriate measures to prevent ST and medical workers to perform targeted management to recognize and treat severe ST patients.

Scrub typhus (ST) is a vector-borne rickettsial zoonosis caused by the organism *Orientia tsutsugamushi*, transmitted to humans by the bite of the larva of trombiculid mites (*1–2*). Up to the end of 2016 in China, all 31 provincial-level administrative divisions (PLADs) had recorded human cases, with the incidence increased by over 16-fold compared to that of 2006, with dramatic geographic expansions in both rural and urban areas and diversified seasonal patterns (*3*). Whether these profound epidemiological features might be related to clinical aspects remains obscure. This study described the epidemiological features and clinical outcomes of ST patients and assessed early predictors of severe disease by retrospective medical record review of 4,501 ST patients in 69 hospitals located throughout all 11 districts of Guangzhou City of southern China from January 2012 to December 2018. Severe ST was found to be associated with the decreased levels of albumin (ALB) and platelet (PLT) count and increased levels of serum creatinine (CREA) and total bilirubin (TBIL) in the blood, as well as the occurrence of dyspnea for ST patients, with estimated relative contributions more than 10% in the final boosted regression trees models, which could be helpful for the recognization and treatment of severe ST in the early clinical management.

According to the *National Scrub Typhus Control and Prevention Guideline (2009)* issued by China CDC, a total of 4,501 patients with clinically diagnosed and laboratory-confirmed ST were included in the study (Supplementary Figure S1, available in http://weekly.chinacdc.cn/). Demographic information, medical history, and exposure history were obtained by interviewing patients or their guardians. Clinical data which comprised of date of disease onset (the day when clinical signs or symptoms were noticed), signs and symptoms, laboratory measurements, imaging findings, and treatment regimens, were retrieved from medical records and collected by Epidata software (version 3.1; The EpiData Association; Odense, Denmark).

Patients who had ever developed any severe complications [multiple organ dysfunction syndromes (MODS), shock, or requiring intensive care unit (ICU) admission] during the hospitalization were defined as severe cases, and the remaining patients were defined as mild cases.

Continuous variables were summarized as medians and interquartile-range (IQR). Categorical variables were summarized as frequencies and proportions. Chi-squared test, Fisher's exact test, or nonparametric test, were used as appropriate to determine the difference between groups. Multivariate logistic regression analysis and boosted regression trees (BRT) model were performed to examine the effect of clinical manifestations and laboratory indicators on illness severity and to attain an early prediction of severe ST. The area under the receiver operating characteristic curve (AUC) was calculated to evaluate the predictive power of the BRT model. The details on variable selection and the modeling analyses of multivariate

logistic regression and BRT model were shown in the Supplementary Material and Supplementary Figure S2 (available in http://weekly.chinacdc.cn/). A 2-sided *P* value of <0.05 is considered as statistically significant. All statistical analyses were performed using R software (version 3.6.2; R Foundation; Vienna, Austria).

A total of 5,354 hospitalized patients with ST from 69 hospitals were included for medical record screening, from which 115 patients had incomplete information, 17 had other infectious diseases, and 721 had vague diagnosis were excluded, which resulted in 4,501 patients with clinically diagnosed ST being included in the final analysis (Supplementary Figure S1), accounting for 76.1% of the total number of cases in Guangzhou City reported to the national surveillance system of China CDC (Figure 1A). The median (IQR) age of the patients was 57 (46–65) years, which gradually increased from 54 (42–62) in 2012 to 59 (49–66) in 2018 (*P*<0.001). A slightly higher proportion of female patients (54.4%) was observed, but no significant difference was shown across the study years (*P*=0.882) (Table 1). Overall, 72.6% of the patients resided in rural areas, with the proportion increased from 60.4% in 2012 to 80.0% in 2018, and farmers and retirees were the main occupations (Table 1). When geographically displayed, cropland and forest regions were related to higher case incidence, such as in Conghua, Zengcheng, Huadu, and Nansha districts (Figure 1B). Approximately 88.4% of the patients occurred between May and October. The median time from symptom onset to hospital admission was 7 (IQR: 5–9) days and the median length of hospital stay was 7 (IQR: 6–10) days. Almost all patients (93.1%) had received antibiotics treatment (including doxycycline, azithromycin, chloramphenicol, or levofloxacin), in combination with the supportive therapy (1.5%).

Severe illness was determined from 366 patients, with a disease severity rate (DSR) of 8.1% (95% CI: 7.3%–8.9%), which did not differ across the studied years (Table 1, Figure 2A). Overall, 53 of the severe cases died, with a case fatality rate of 1.2% (95% CI: 0.9%–1.5%), which differed during the study years (Table 1). Patients with severe disease comprised 265 (5.9%) who developed MODS, 196 (4.4%) who were admitted to the ICU, and 139 (3.1%) who developed shock. When looking closely, children aged ≤14 years had a DSR of 11.0%, higher than that of the next age group of 15–29 years old (2.0%); thereafter, an age-dependent increase of DSR was observed with patients ≥80 years having an 8-fold risk of DSR compared with the 15–29 years age group (Figure 2B). The DSR was

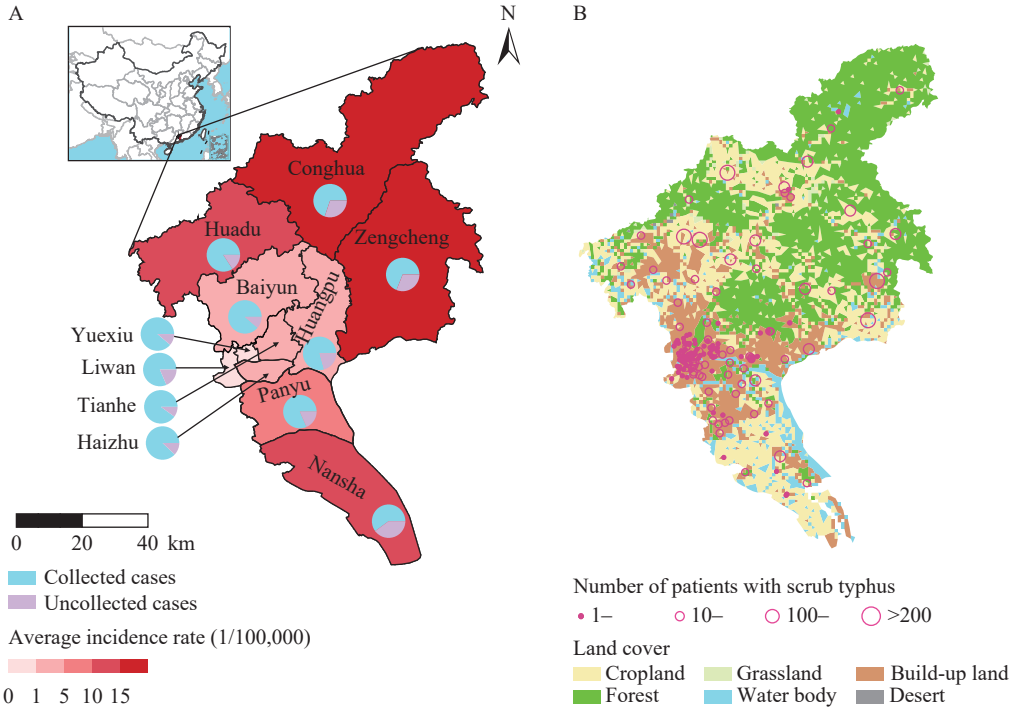

FIGURE 1. The spatial distribution of scrub typhus in Guangzhou, China, 2012–2018. (A) The percentage of currently studied cases among all reported cases in each district of Guangzhou City according to National Surveillance Data, 2012–2018; (B) The overall number of reported patients by National Surveillance Systems of Infectious Diseases for each township, 2012–2018.

TABLE 1. Baseline demographic and clinical characteristics of patients with scrub typhus in Guangzhou, China, 2012–2018.

Variables	Total (n=4,501)	2012 (n=558)	2013 (n=673)	2014 (n=731)	2015 (n=606)	2016 (n=617)	2017 (n=610)	2018 (n=706)	*P* value*
Sex, n (%)									0.882†
Female	2,450 (54.4)	310 (55.6)	371 (55.1)	394 (53.9)	323 (53.3)	348 (56.4)	323 (53.0)	381 (54.0)	
Male	2,051 (45.6)	248 (44.4)	302 (44.9)	337 (46.1)	283 (46.7)	269 (43.6)	287 (47.0)	325 (46.0)	
Age, years, median (IQR)	57 (46–65)	54 (42–62)	56 (42–63)	56 (45–64)	58 (48–64)	58 (47–65)	59 (49–66)	59 (49–66)	<0.001
Age group, years§, n (%)									<0.001†
0–14	209 (4.6)	50 (9.0)	39 (5.8)	35 (4.8)	21 (3.5)	24 (3.9)	16 (2.6)	24 (3.4)	
15–59	2,402 (53.4)	327 (58.6)	376 (55.9)	412 (56.4)	329 (54.3)	315 (51.0)	301 (49.3)	342 (48.4)	
≥60	1,890 (42.0)	181 (32.4)	258 (38.3)	284 (38.8)	256 (42.2)	278 (45.1)	293 (48.0)	340 (48.2)	
Residence, n (%)									<0.001†
Urban	1,232 (27.4)	221 (39.6)	233 (34.6)	197 (26.9)	163 (26.9)	148 (24.0)	129 (21.1)	141 (20.0)	
Rural	3,269 (72.6)	337 (60.4)	440 (65.4)	534 (73.1)	443 (73.1)	469 (76.0)	481 (78.9)	565 (80.0)	
Occupation§, n (%)									<0.001†
Farmers	1,093 (24.3)	151 (27.1)	149 (22.1)	150 (20.5)	123 (20.3)	165 (26.7)	170 (27.9)	185 (26.2)	
Retirees	1,242 (27.6)	134 (24.0)	191 (28.4)	216 (29.5)	183 (30.2)	172 (27.9)	155 (25.4)	191 (27.1)	
Children and students	240 (5.3)	52 (9.3)	47 (7.0)	42 (5.7)	24 (4.0)	31 (5.0)	20 (3.3)	24 (3.4)	
Others	848 (18.8)	107 (19.2)	141 (21.0)	136 (18.6)	93 (15.3)	114 (18.5)	128 (21.0)	129 (18.3)	
Unknown	1,078 (24.0)	114 (20.4)	145 (21.5)	187 (25.6)	183 (30.2)	135 (21.9)	137 (22.5)	177 (25.1)	
Time from symptom onset to hospital admission, days, median (IQR)	7 (5–9)	7 (5–10)	7 (5–10)	7 (5–9)	7 (5–9)	7 (4–9)	7 (4–9)	6 (4–9)	<0.001
Length of hospital stay, days, median (IQR)	7 (6–10)	8 (5–10)	8 (6–10)	8 (6–10)	7 (5–10)	7 (6–10)	7 (5–10)	7 (6–9)	0.092
Severe cases, n (%)	366 (8.1)	46 (8.2)	51 (7.6)	70 (9.6)	47 (7.8)	50 (8.1)	39 (6.4)	63 (8.9)	0.481†
Death cases, n (%)	53 (1.2)	8 (1.4)	4 (0.6)	18 (2.5)	6 (1.0)	5 (0.8)	3 (0.5)	9 (1.3)	0.013†

* *P* value relates the difference among the study years.
† *P* value calculated by use of χ^2 test.
§ Some columns do not add up to 100% because of rounding.
Abbreviation: IQR=interquartile-range.

comparable between males and females as a whole (8.2% *vs.* 8.1%, *P*=0.894). The median (IQR) time from symptom onset to hospital admission among severe patients was 8 days (6–10 days), significantly longer than that among mild patients (7 days, 4–9 days, *P*<0.001).

The frequently seen symptoms and signs of ST patients included fever (98.2%), eschar (74.1%), anorexia (69.9%), headache (51.1%), weakness (43.7%), and cough (41.3%) (Supplementary Table S1, available in http://weekly.chinacdc.cn/). Ulcer and skin rash were less frequently seen (among 17.4% and 14.5% of the patients). By multivariate logistic regression analysis, 12 clinical manifestations were significantly related to severe disease, among which dyspnea had the most robust effect (adjusted OR: 13.95, 95% CI: 9.94%–19.58%), followed by confusion (OR: 7.18, 95% CI: 3.29%–15.67%), dysphoria (OR: 6.76, 95% CI: 2.40%–19.10%), lethargy (OR: 5.80, 95% CI: 2.19%–15.41%), macroscopic hematuria (OR: 5.32, 95% CI: 1.03%–27.39%), and edema (OR: 4.85, 95% CI: 3.25%–7.24%) (Supplementary Table S1).

A total of 28 laboratory parameters (12 hematological and 16 biochemical) were tested on admission, among which the frequently seen abnormalities included increased levels of neutrophil (NEU) percent in the blood, and aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), γ-glutamyl transpeptidase (GGT), and C-creative protein (CRP) in the serum above the normal range, decreased levels of hematocrit (HCT) in the blood, and total protein (TP), ALB, sodium (Na), and calcium (Ca) in the serum below the normal range (Supplementary Table S2, available in http://weekly.chinacdc.cn/). Multivariate logistic regression analysis disclosed laboratory abnormalities of PLT count, ALB, CREA,

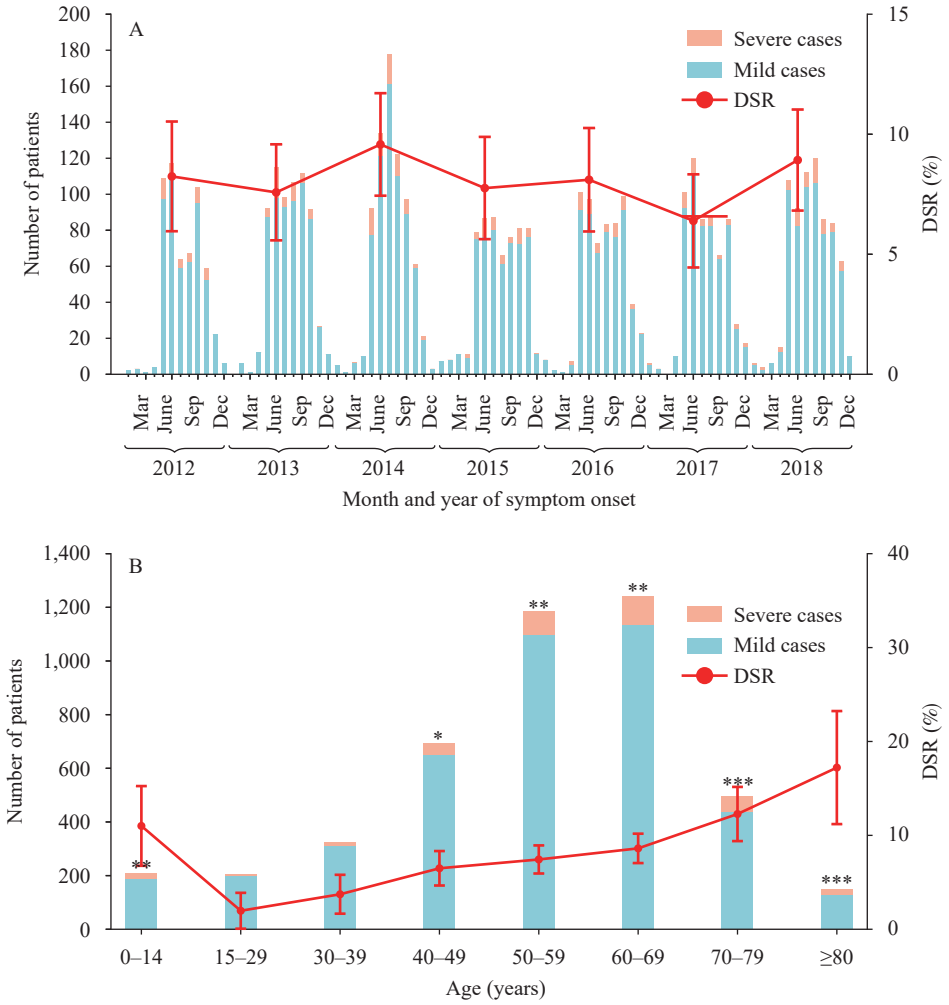

FIGURE 2. Case number and disease severity rate of patients with scrub typhus by time and age in Guangzhou, China, 2012–2018. (A) Number of scrub typhus patients and annual disease severity rate (DSR) by month and year of symptom onset. (B) Number of scrub typhus patients and DSR of patients by age groups. *P*-value indicated association between age groups and severe disease by univariate logistic regression analysis, with 15–29 years group used as reference.
*, *P*<0.05; **, *P*<0.01; ***, *P*<0.001.

TBIL, hemoglobin (HGB), and NEU count that were significantly related to severe ST (Supplementary Table S3, available in http://weekly.chinacdc.cn/).

The final BRT model that included 10 factors attained a high prediction efficiency, with the mean AUC of 0.92 (95% CI: 0.90–0.93) and an accuracy of 0.88 (95% CI: 0.86–0.89) on testing data. The highest relative contribution (RC) to severe ST was observed for ALB, estimated to be 24.77% (95% CI: 23.70–25.85), followed by dyspnea, PLT count, CREA, and TBIL with their RCs more than 10% (Supplementary Table S4, available in http://weekly.chinacdc.cn/).

DISCUSSION

To our knowledge, this study represents the largest case-cohort study on ST patients. Notably, this cohort also represented properly treated patients by antibiotics, which had a high proportion of mild disease than those studies also including untreated patients in other Asian countries (*4*–*5*). The currently determined frequency of severe complications (8.1%) was lower than that of previous cohorts (*6*–*7*), although we had exhaustively included all complications, such as MODS, shock, and ICU admission, which are the principal causes of death in patients with severe disease. Even when properly treated, the 0–14 years pediatric patients were related to a higher DSR than its next age group of 15–29 years old. Whether this discrepancy was related to the higher incidence of contact to mites or due to the lack of herd immunity in children remained to be determined. More health education on ST among children should

be implemented from schools and families in endemic areas at high risk of *Orientia tsutsugamushi* infection.

Uncommonly seen clinical complications, such as neurological manifestations, were present in 2.8% of the patients, which was based on an exhaustive search of the medical records, and were higher than those of a previous study in the Republic of Korea (1.7%) (*8*), while lower than studies in India and Thailand showing that up to 26% of ST patients had meningitis (*9*). *Orientia tsutsugamushi* has been suggested as an important cause of central nervous system infections in untreated patients. By contrast, among the properly treated patients with ST, the frequency of neurological can be significantly reduced, as displayed in the current study. The pathophysiological hallmark of ST is disseminated vasculitis, with subsequent vascular injury involved in skin, liver, brain, kidneys, and lungs, etc. Endothelial permeability may increase systemically and lead to the pathologic capillary leak syndrome resulting in tissue edema and intravascular hypovolemia (*10*). This can explain the prominent role of edema, as well as the increased laboratory abnormalities indicative of kidney and liver injury, i.e., CREA and TBIL. Decreased levels of plasma ALB and PLT count, surrogates of capillary permeability, were associated with severe disease.

Preexisting comorbidities significantly enhanced the odds of developing severe disease, with cerebral infarction showing significant effects according to the multivariate analysis. With no currently approved vaccines, aggressive treatment strategies should be applied and the treatment of a broad range of comorbidities should be advocated in those patients.

This study is subject to several limitations. Only hospitalized patients with ST were included for analysis, hence outpatients who were not admitted to hospitals warranted further investigation. Not all studied patients were laboratory-confirmed and misdiagnosis could not be completely ruled out, which could introduce uncertainty about our results.

In summary, we found that epidemiological and clinical features of ST were changing, with an increasing proportion of ST patients in the age ≥60 and in rural and higher DSR in children. Based on this knowledge, persistent surveillance and community health education should be stressed in high-risk populations, while severe ST patients could be recognized and treated in early clinical management.

Conflicts of interest: No conflicts of interest declared.

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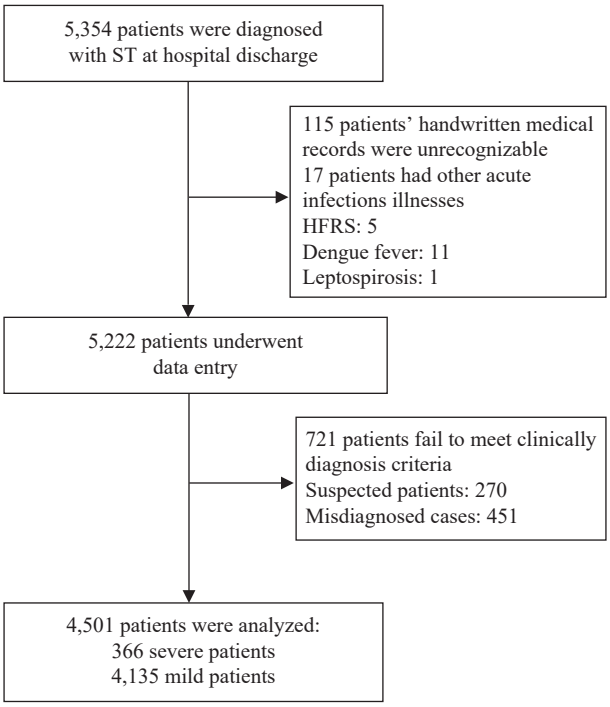
SUPPLEMENTARY METHODS

Steps of Multivariate Logistic Regression Analysis

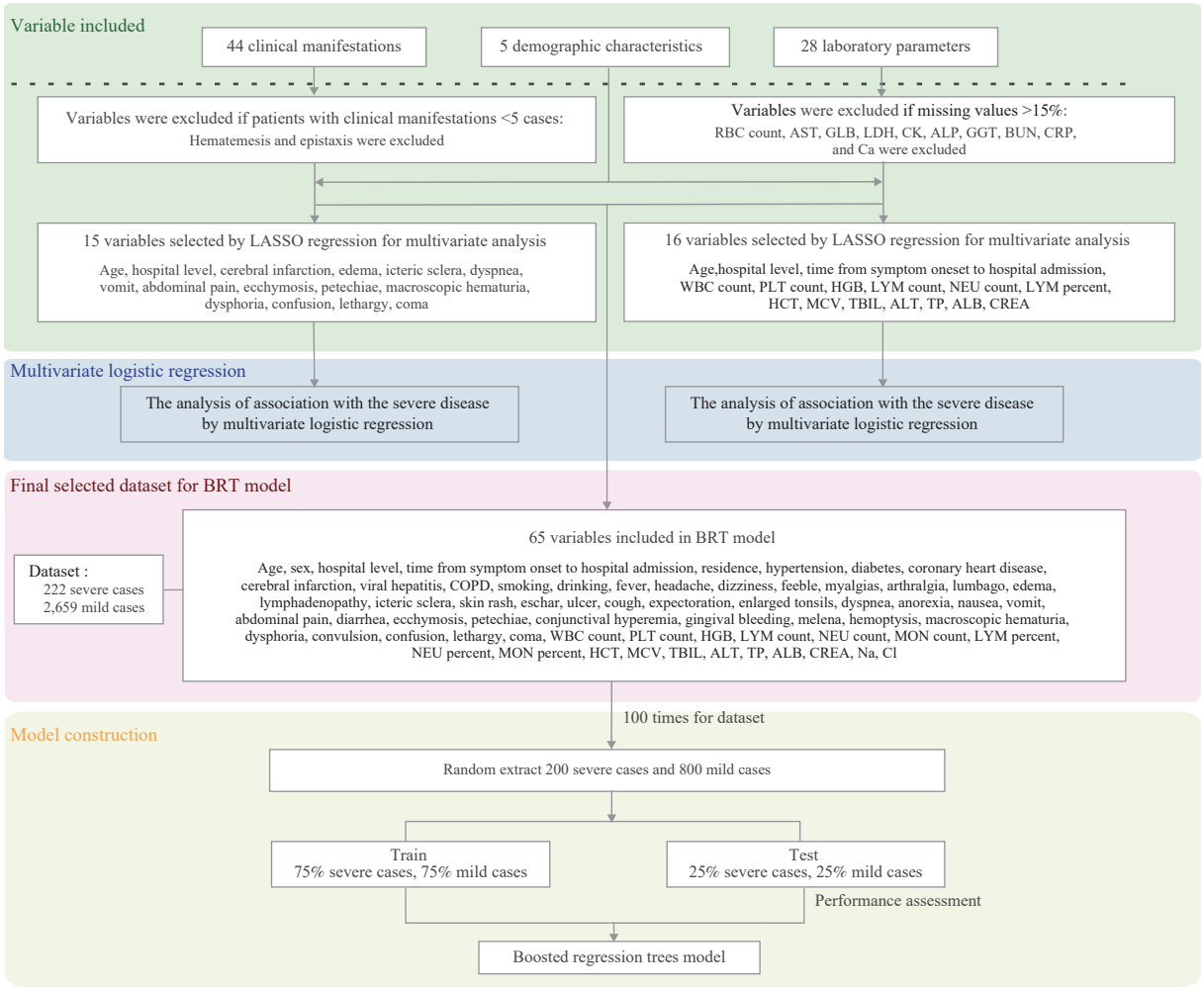
At the first step, to determine the risk factors of clinical manifestations in severe scrub typhus (ST), the presence of clinical manifestations on or before hospital admission was used for statistical analysis. Excluding variables of clinical manifestations was considered if the number of patients with a single clinical manifestation were less than five cases, and hematemesis and epistaxis were excluded. The remaining clinical manifestations, together with 5 demographic characteristics were included in Least Absolute Shrinkage and Selection Operator (LASSO) regression to select the strongest variables. Variables identified by LASSO regression analysis were entered into multivariate logistic regression analysis (Supplementary Figure S2). Meanwhile, to attain the risk factors of laboratory indicators in severe ST, the laboratory indicators result within 24 hours of hospital admission were used for statistical analysis. After excluding the laboratory indicators if the missing value was more than 15%, the laboratory indicators were also examined for their association with development of severe disease in multivariate logistic regression analysis after variable selection of LASSO regression analysis (Supplementary Figure S2). The R library "glmnet" was used for the LASSO regression. Odds ratio (OR) and the 95% confidence interval (95% CI) were estimated using maximum likelihood methods.

Variable Selection for Model Construction of the Boosted Regression Trees (BRT) Modeling

To attain an early prediction of severe ST, the clinical manifestations on or before hospital admission and the laboratory indicators result within 24 hours of hospital admission were used for model analysis. Firstly, for 44 variables of clinical manifestations, we excluded those less than five cases such as hematemesis and epistaxis. Meanwhile, for 28 laboratory parameters, we excluded those with missing values more than 15% of all patients such as RBC count, AST, GLB, LDH, CK, ALP, GGT, BUN, CRP, and Ca (Supplementary Figure S2). The remaining clinical manifestations and laboratory parameters, together with 5 demographic characteristics were included in the BRT models.



SUPPLEMENTARY FIGURE S1. The flowchart of recruited patients with scrub typhus in Guangzhou, China, 2012–2018. Abbreviations: ST=scrub typhus; HFRS=hemorrhagic fever with renal syndrome.



SUPPLEMENTARY FIGURE S2. Variable selection and model construction of the logistic regression and boosted regression trees modeling.

Notes: Demographic characteristics including age, sex, hospital level, time from symptom onset to hospital admission, and residence. Clinical manifestations including hypertension, diabetes, coronary heart disease, cerebral infarction, viral hepatitis, COPD, smoking, drinking, fever, headache, dizziness, weakness, myalgias, arthralgia, lumbago, edema, lymphadenopathy, icteric sclera, skin rash, eschar, ulcer, cough, expectoration, enlarged tonsils, dyspnea, anorexia, nausea, vomit, abdominal pain, diarrhea, ecchymosis, petechiae, conjunctival hyperemia, gingival bleeding, melena, hemoptysis, hematemesis, epistaxis, macroscopic hematuria, dysphoria, convulsion, confusion, lethargy, and coma. Laboratory parameters including WBC count, RBC count, PLT count, HGB, LYM count, NEU count, MON count, LYM percent, NEU percent, MON percent, HCT, MCV, TBIL, AST, ALT, TP, ALB, GLB, LDH, CK, ALP, GGT, CREA, BUN, CRP, Na, Cl, and Ca. Residence, rural or urban were divided according to the county address of patients, in where Huadu, Conghua, Zengcheng, Nansha, and Panyu districts were considered as rural areas, and Tianhe, Yuexiu, Liwan, Haizhu, Baiyun, and Huangpu districts were considered as urban areas (*5*).

Abbreviations: RBC=red blood cells; AST=aspartate aminotransferase; GLB=globulin; LDH=lactate dehydrogenase; CK=creatine kinase; ALP=alkaline phosphatase; GGT=γ-glutamyl transpeptidase; BUN=blood urea nitrogen; CRP=C-creative protein; Ca=calcium; LASSO=Least Absolute Shrinkage and Selection Operator; WBC=white blood cells; PLT=platelet; HGB=hemoglobin; LYM=lymphocyte; NEU=neutrophil; HCT=hematocrit; MCV=mean corpuscular volume; TBIL=total bilirubin; ALT=alanine aminotransferase; TP=total protein; ALB=albumin; CREA=creatinine; BRT=boosted regression trees; COPD=chronic obstructive pulmonary disease; MON=monocyte; Na=sodium; Cl=chlorine.

Steps of BRT Modeling

Machine learning techniques are increasingly used in developing models for vector predictions with multiple advantages, like considering nonlinearity and interactions and handling different types of predictor variables (*1–2*).

The BRT modeling was carried out in steps. First, considering the low proportion of severe outcomes, we set a 1-to-4 case-control ratio to adjust every bootstrap data. Severe cases and 4-fold num of mild cases were randomly

SUPPLEMENTARY TABLE S1. Demographic and clinical characteristics associated with severe disease for patients with scrub typhus by multivariate logistic regression.

Variables	Total (n=4,501)	Severe (n=366)	Mild (n=4,135)	Adjusted OR (95% CI)	*P* value
Sex, female	2,450 (54.4)	198 (54.1)	2,252 (54.5)		
Age, years, median (IQR)	57 (46–65)	60 (51–68)	56 (46–64)	1.01 (1.01–1.02)	0.001
Time from symptom onset to hospital admission, days, median (IQR)	7 (5–9)	8 (6–10)	7 (4–9)	2.76 (1.91–4.00)	<0.001
Length of hospital stay, days, median (IQR)	7 (6–10)	12 (8–17)	7 (5–9)		
Comorbidities					
Hypertension	718 (16.0)	77 (21.0)	641 (15.5)		
Diabetes	372 (8.3)	38 (10.4)	334 (8.1)		
Coronary heart disease	112 (2.5)	8 (2.2)	104 (2.5)		
Cerebral infarction	136 (3.0)	32 (8.7)	104 (2.5)	2.33 (1.37–3.98)	0.002
Viral hepatitis	178 (4.0)	12 (3.3)	166 (4.0)		
COPD	46 (1.0)	6 (1.6)	40 (1.0)		
Lifestyles					
Smoking	731 (16.2)	64 (17.5)	667 (16.1)		
Drinking	384 (8.5)	37 (10.1)	347 (8.4)		
Non-specific					
Fever	4,421 (98.2)	356 (97.3)	4,065 (98.3)		
Headache	2,302 (51.1)	174 (47.5)	2,128 (51.5)		
Dizziness	1,168 (25.9)	90 (24.6)	1,078 (26.1)		
Weakness	1,969 (43.7)	155 (42.3)	1,814 (43.9)		
Myalgias	1,051 (23.4)	82 (22.4)	969 (23.4)		
Arthralgia	136 (3.0)	5 (1.4)	131 (3.2)		
Lumbago	140 (3.1)	9 (2.5)	131 (3.2)		
Edema	178 (4.0)	64 (17.5)	114 (2.8)	4.85 (3.25–7.24)	<0.001
Lymphadenopathy	1,088 (24.2)	92 (25.1)	996 (24.1)		
Icteric sclera	79 (1.8)	33 (9.0)	46 (1.1)	4.67 (2.61–8.33)	<0.001
Skin					
Skin rash	653 (14.5)	61 (16.7)	592 (14.3)		
Eschar/Ulcer	3,921 (87.1)	302 (82.5)	3,619 (87.5)		
Eschar	3,335 (74.1)	260 (71.0)	3,075 (74.4)		
Ulcer	784 (17.4)	60 (16.4)	724 (17.5)		
Respiratory					
Cough	1,858 (41.3)	169 (46.2)	1,689 (40.8)		
Expectoration	1,157 (25.7)	116 (31.7)	1,041 (25.2)		
Enlarged tonsils	426 (9.5)	30 (8.2)	396 (9.6)		
Dyspnea	213 (4.7)	126 (34.4)	87 (2.1)	13.95 (9.94–19.58)	<0.001
Gastrointestinal					
Anorexia	3,148 (69.9)	270 (73.8)	2,878 (69.6)		
Nausea	791 (17.6)	69 (18.9)	722 (17.5)		
Vomit	484 (10.8)	63 (17.2)	421 (10.2)	1.45 (1.02–2.04)	0.036
Abdominal pain	361 (8.0)	64 (17.5)	297 (7.2)	1.90 (1.32–2.73)	0.001
Diarrhea	193 (4.3)	35 (9.6)	158 (3.8)		

TABLE S1. (Continued)

Variables	Total (n=4,501)	Severe (n=366)	Mild (n=4,135)	Adjusted OR (95% CI)	*P* value
Hemorrhagic manifestation*	241 (5.4)	47 (12.8)	194 (4.7)		
Ecchymosis	47 (1.0)	14 (3.8)	33 (0.8)		
Petechiae	22 (0.5)	7 (1.9)	15 (0.4)	3.45 (1.05–11.38)	0.042
Conjunctival hyperemia	108 (2.4)	20 (5.5)	88 (2.1)		
Gingival bleeding	9 (0.2)	2 (0.5)	7 (0.2)		
Melena	59 (1.3)	10 (2.7)	49 (1.2)		
Hemoptysis	10 (0.2)	3 (0.8)	7 (0.2)		
Hematemesis	3 (0.1)	1 (0.3)	2 (<0.1)		
Epistaxis	4 (0.1)	0 (0)	4 (0.1)		
Macroscopic hematuria	8 (0.2)	3 (0.8)	5 (0.1)	5.32 (1.03–27.39)	0.045
Neurological manifestation†	124 (2.8)	70 (19.3)	54 (1.3)		
Dysphoria	29 (0.6)	19 (5.2)	10 (0.2)	6.76 (2.40–19.10)	<0.001
Convulsion	27 (0.6)	15 (4.1)	12 (0.3)		
Confusion	50 (1.1)	34 (9.3)	16 (0.4)	7.18 (3.29–15.67)	<0.001
Lethargy	31 (0.7)	18 (4.9)	13 (0.3)	5.80 (2.19–15.41)	<0.001
Coma	30 (0.7)	18 (4.9)	12 (0.3)	2.90 (1.08–7.79)	0.035
Abnormal image results					
Pericardial effusion	127 (2.8)	37 (10.1)	90 (2.2)		
Pelvic effusion	42 (0.9)	14 (3.8)	28 (0.7)		
Pleural effusion	558 (12.4)	158 (43.2)	400 (9.7)		
Chest radiographic abnormality	1,062 (23.6)	167 (45.6)	895 (21.6)		
Ascites	50 (1.1)	26 (7.1)	24 (0.6)		
Splenomegaly	554 (12.3)	74 (20.2)	480 (11.6)		
Hepatomegaly	228 (5.1)	44 (12.0)	184 (4.4)		

Note: Data are n (%) until otherwise indicated. All clinical symptoms (non-specific, skin, respiratory, gastrointestinal, hemorrhagic, neurological) were reported before or at hospital admission, all abnormal image results were reported after hospital admission.
Abbreviations: COPD=chronic obstructive pulmonary disease. OR=odds ratio. CI=confidence interval; IQR=interquartile-range.
* Hemorrhagic manifestation, patients with one or more hemorrhagic symptoms.
† Neurological manifestation, patients with one or more neurological symptoms.

selected without replacement. Second, for both selected severe and mild cases, 75% of samples of each were used for training the models while the rest 25% were used for model testing. Third, a BRT model was built using the training dataset and validated using the test dataset.

To increase the predictive robustness of model predictions and quantify model uncertainty, we fitted an ensemble of 100 BRT models to separate bootstraps of the data. We adopted a tree complexity of 5, a learning rate of 0.005, and a bag fraction of 75% to identify the optimal trees for each bootstrap data. Herein, we modeled the severe complications as a binary classification. Each of the 100 models predicts severe risk on a continuous scale from 0 to 1, with a final prediction being generated by calculating the mean prediction across all models. To further determine the main contributing factor, we performed BRT model again after removing the factors that showed the relative contributions below 2% (*3*). The receiver-operating characteristic (ROC) curves were produced for each model based on the average of an ensemble of 100 BRT models, and the area under the receiver operating characteristic curve (AUC) was calculated to evaluate the predictive power of the models. BRT model was performed using R software (version 3.6.2; R Foundation; Vienna, Austria) with the packages of "gbm," "dismo," and "ROCR" (*4*).

SUPPLEMENTARY TABLE S2. Laboratory findings on hospital admission compared between severe patients and mild patients.

Variables	Total (n=4,501)	Severe (n=366)	Mild (n=4,135)	*P* value
Hematological indicators				
WBC count (×10^9/L) [4–10]	7.18 (5.23–9.60)	8.99 (6.50–12.92)	7.06 (5.19–9.39)	<0.001
RBC count (×10^{12}/L) [3.8–5.8]	4.23 (3.87–4.64)	3.95 (3.44–4.31)	4.26 (3.89–4.66)	<0.001
PLT count (×10^9/L) [100–300]	121.00 (81.00–172.00)	60.00 (40.00–95.50)	125.00 (86.05–178.00)	<0.001
HGB (g/L) [120–165]	121.00 (110.00–132.00)	110.90 (97.00–124.00)	121.00 (111.00–133.00)	<0.001
LYM count (×10^9/L) [1.1–3.2]	1.42 (0.78–2.57)	1.40 (0.73–2.66)	1.42 (0.79–2.56)	0.672
NEU count (×10^9/L) [1.8–6.3]	4.67 (3.23–6.55)	6.50 (4.47–9.7)	4.55 (3.17–6.36)	<0.001
MON count (×10^9/L) [0.1–0.6]	0.44 (0.28–0.69)	0.42 (0.26–0.74)	0.45 (0.28–0.69)	0.719
LYM percent (%) [20–40]	20.50 (12.90–32.30)	15.00 (8.60–26.90)	21.00 (13.30–32.80)	<0.001
NEU percent (%) [50–70]↑	71.40 (57.50–80.40)	78.40 (63.50–86.30)	71.00 (57.00–79.80)	<0.001
MON percent (%) [3–10]	6.40 (4.40–8.80)	4.90 (3.30–7.50)	6.50 (4.50–8.94)	<0.001
HCT (%) [40–50]↓	35.90 (32.50–39.20)	32.80 (28.60–35.70)	36.07 (32.80–39.40)	<0.001
MCV (FL) [82–100]	86.30 (81.70–90.01)	84.65 (79.50–89.00)	86.50 (81.90–90.20)	<0.001
Biochemical indicators				
TBIL (μmol/L) [5.1–17.1]	11.50 (8.20–16.50)	18.50 (12.38–48.35)	11.00 (8.00–15.80)	<0.001
AST (U/L) [0–40]↑	76.00 (49.00–122.00)	136.00 (88.10–218.40)	73.00 (48.00–115.00)	<0.001
ALT (U/L) [0–40]↑	67.00 (42.00–107.40)	79.50 (54.00–118.00)	65.65 (41.00–106.00)	<0.001
TP (g/L) [65–85]↓	61.20 (56.60–66.10)	54.35 (49.20–60.60)	61.80 (57.30–66.40)	<0.001
ALB (g/L) [35–55]↓	33.00 (28.90–36.70)	25.90 (22.00–29.70)	33.40 (29.60–37.00)	<0.001
GLB (g/L) [20–40]	28.20 (25.10–31.70)	29.00 (25.30–32.60)	28.11 (25.10–31.60)	0.176
LDH (U/L) [109–245]↑	459.00 (342.00–693.00)	677.00 (464.00–1,147.00)	446.50 (336.00–658.00)	<0.001
CK (U/L) [25–200]	91.00 (50.00–173.00)	110.00 (59.00–286.00)	90.00 (50.00–167.00)	<0.001
ALP (U/L) [40–150]	94.00 (67.03–143.00)	127.00 (76.00–220.50)	92.00 (67.00–138.00)	<0.001
GGT (U/L) [7–50]↑	70.00 (33.00–146.00)	98.00 (44.00–189.00)	67.00 (32.00–142.00)	<0.001
CREA (μmol/L) [53–106]	78.08 (64.00–98.00)	102.95 (72.00–193.50)	77.85 (63.10–95.10)	<0.001
BUN (mmol/L) [3.2–7.1]	4.34 (3.30–6.04)	9.00 (5.97–16.60)	4.27 (3.24–5.70)	<0.001
CRP (mg/L) [0.07–8.20]↑	45.00 (14.18–86.36)	84.05 (39.00–140.70)	42.00 (13.31–81.10)	<0.001
Na (mmol/L) [137–147]↓	135.70 (132.00–138.60)	133.00 (129.80–137.00)	136.00 (132.40–138.70)	<0.001
Cl (mmol/L) [96–108]	99.70 (96.40–102.90)	100.00 (96.00–103.90)	99.70 (96.40–102.80)	0.272
Ca (mmol/L) [2.10–2.55]↓	2.07 (1.96–2.18)	1.90 (1.79–2.03)	2.08 (1.98–2.19)	<0.001

Note: All measurements within 24 hours of hospital admission were presented as median (interquartile-range).
P value was compared between severe group and mild group by Mann-Whitney U test.
Abbreviations: WBC=white blood cells; RBC=red blood cells; PLT=platelet; HGB=hemoglobin; LYM=lymphocyte; NEU=neutrophil; MON=monocyte; HCT=hematocrit; MCV=mean corpuscular volume; TBIL=total bilirubin; AST=aspartate aminotransferase; ALT=alanine aminotransferase; TP=total protein; ALB=albumin; GLB=globulin; LDH=lactate dehydrogenase; CK=creatine kinase; ALP=alkaline phosphatase; GGT=γ-glutamyl transpeptidase; CREA=creatinine; BUN=blood urea nitrogen; CRP=C-creative protein; Na=sodium; Cl=chlorine; Ca=calcium.
↑Variable, with the median value in total population above the normal range.
↓Variable, with the median value in total population below the normal range.

SUPPLEMENTARY TABLE S3. Association between laboratory measurements and severe scrub typhus by multivariate logistic regression analysis.

Variables	Adjusted OR (95% CI)	*P* value
Hospital level	2.26 (1.50–3.43)	<0.001
Time from symptom onset to hospital admission, days	1.06 (1.01–1.10)	0.014
PLT count <100 (×10^9/L) [100–300]	4.80 (3.39–6.82)	<0.001
HGB <120 (g/L) [120–165]	2.19 (1.59–3.01)	<0.001
NEU count >6.3 (×10^9/L) [1.8–6.3]	2.03 (1.47–2.79)	<0.001
TBIL >17.1 (μmol/L) [5.1–17.1]	2.62 (1.91–3.60)	<0.001
ALB <35 (g/L) [35–55]	3.78 (1.86–7.65)	<0.001
CREA >106 (μmol/L) [53–106]	2.91 (2.12–4.00)	<0.001

Abbreviations: OR=odds ratio; CI=confidence interval; PLT=platelet; HGB=hemoglobin; NEU=neutrophil; TBIL=total bilirubin; ALB=albumin; CREA=creatinine.

SUPPLEMENTARY TABLE S4. Relative contribution of predictors estimated for the occurrence of severe complications of scrub typhus by the boosted regression trees model.

Variables	Relative contribution, % (95% CI)
ALB (g/L)	24.77 (23.70–25.85)
Dyspnea	16.63 (15.73–17.53)
PLT count (×10^9/L)	12.95 (12.16–13.74)
CREA (μmol/L)	11.34 (10.58–12.11)
TBIL (μmol/L)	10.55 (10.08–11.02)
NEU count (×10^9/L)	5.71 (5.40–6.02)
TP (g/L)	5.59 (5.20–5.98)
NEU percent (%)	5.40 (5.06–5.75)
HGB (g/L)	4.25 (3.97–4.54)
Age	2.79 (2.59–2.98)

Abbreviations: ALB=albumin; PLT=platelet; CREA=creatinine; TBIL=total bilirubin; NEU=neutrophil; TP=total protein; HGB=hemoglobin; CI=confidence interval.

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Preplanned Studies

Epidemiological Characteristics of Echinococcosis in Non-Endemic PLADs — China, 2017–2020

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Summary

What is already known about this topic?

Echinococcosis, also known as hydatid disease, is a zoonotic parasitic disease caused by the larvae of *Echinococcus granulosus*. Western China has one of the most severe epidemics worldwide. Echinococcosis is endemic in 370 counties of 9 provincial-level administrative divisions (PLADs) including Inner Mongolia, Sichuan, Yunnan, Tibet, Shaanxi, Gansu, Qinghai, Ningxia, Xinjiang and Xinjiang Production and Construction Corps (XPCC).

What is added by this report?

From 2017 to 2020, 244 cases were reported in 21 non-endemic PLADs. Of the cases reported in non-endemic PLADs, the majority were imported from endemic areas. Cases reported from non-endemic PLADs have been sporadic, and the number has increased in some areas.

What are the implications for public health practice?

Migrant workers and livestock from endemic areas may have contributed to the increased incidence of locally acquired infections in non-endemic PLADs, suggesting that health education among workers and livestock quarantine is important for the control of spread in non-endemic PLADs.

Echinococcosis, also known as hydatid disease, is a zoonotic parasitic disease caused by the larvae of *Echinococcus granulosus*. Echinococcosis has been hyperendemic in the Qinghai-Tibet Plateau, which has the highest prevalence worldwide (*1*). In recent years, the prevention and treatment of echinococcosis in China has improved. However, many difficulties and challenges remained (*2*). This study aimed to analyze the endemic distribution and epidemiological characteristics of reported cases in the non-endemic provincial-level administrative divisions (PLADs) of echinococcosis in China from 2017 to 2020. The regional distribution, age, and gender of reported cases were statistically analyzed, and onsite epidemiological investigations were conducted to clarify the sources of infection of the cases. The results showed that the epidemiological survey revealed the presence of suspected local cases in 15 PLADs, with an increasing yearly trend of reported cases in non-endemic PLADs. Endemic echinococcosis is expanding, and there may be potentially new endemic areas. Echinococcosis endemic surveillance should be strengthened, while the quality of field epidemiological investigations of echinococcosis should be improved to provide a basis for optimizing the existing prevention and control strategies and measures.

In China, echinococcosis is currently classified as a Category C infectious disease. Cases of echinococcosis have also been reported in non-endemic PLADs and consisted of both suspected local cases and imported cases. In this study, the cases of echinococcosis reported to the National Notifiable Diseases Reporting System (NNDRS) of the China CDC from non-endemic PLADs from 2017 to 2020 were analyzed. Specifically, this study included onsite epidemiological investigations, an assessment of the epidemic status and epidemiological characteristics, and identification of the sources of infections in order to provide a basis for optimizing the prevention and control strategies for echinococcosis. Microsoft Excel (version 2016, Microsoft Corp, Redmond, USA), SAS Software (version 9.4, SAS Institute Inc., NC, USA) were used for basic descriptive statistical analyses. The geographic distribution of cases, age, gender, and source of infection were analyzed using the chi-squared test (P<0.05). Based on the 2012–2016 national echinococcosis epidemiological survey results, 9 PLADs and XPCC were identified as echinococcosis endemic PLADs (*3*) (Figure 1). Locally-acquired cases refer to no history of living in endemic areas. For cases reported in non-endemic PLADs, investigations and verifications were carried out by staff from national and provincial offices of CDC for the Prevention and

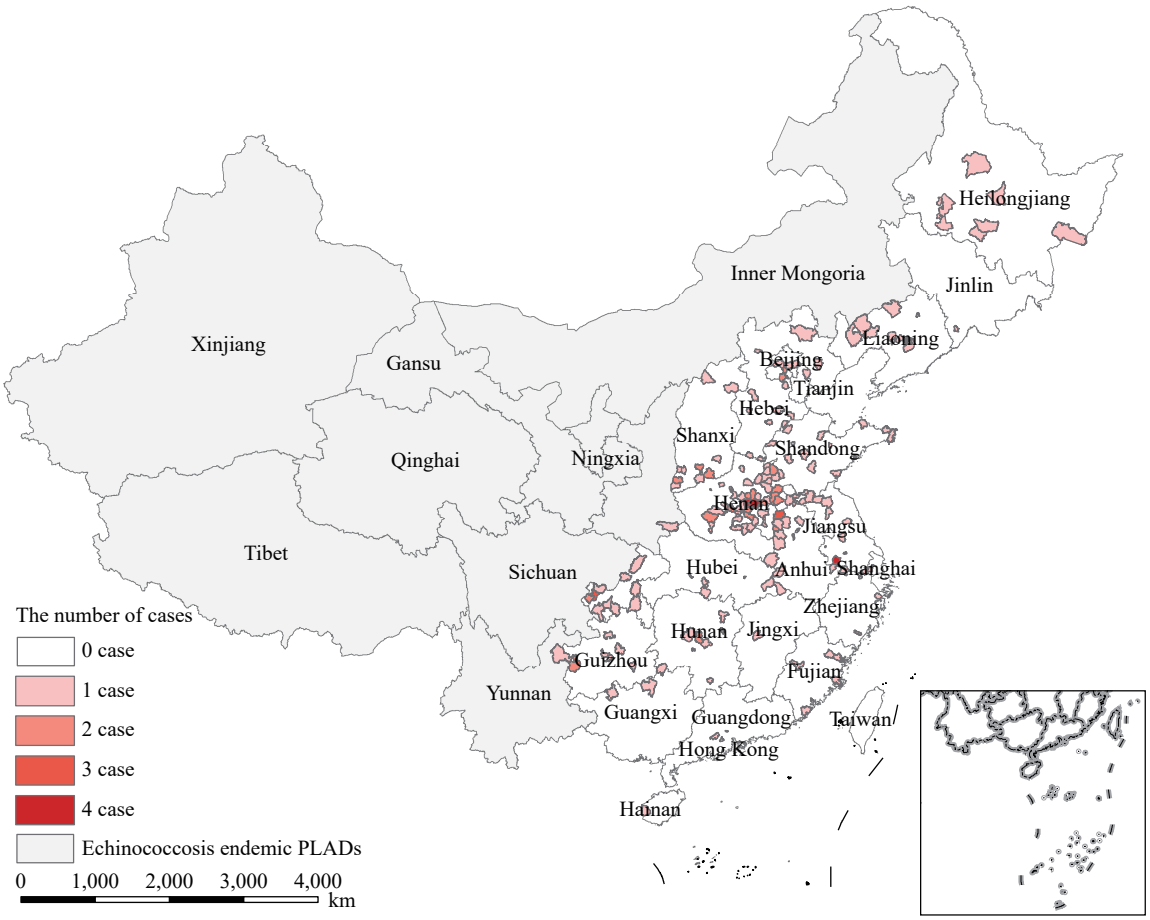

FIGURE 1. The regional distribution of reported cases of echinococcosis in non-endemic counties of PLADs' of China from 2017 to 2020.
Abbreviation: PLADs=provincial-level administrative divisions.

Control of Parasitic Diseases. Reported cases of echinococcosis from 2017 to 2020 were extracted from the China CDC NNDRS and duplicate reports were excluded.

From 2017 to 2020, 19,948 cases of echinococcosis were reported nationwide, of which 19,704 cases were reported in endemic PLADs. Of the cases from endemic areas, the majority (80.85%) were reported in Sichuan, Qinghai, and Xinjiang. The remaining 244 cases were reported in 21 non-endemic PLADs (Figure 1) and were mainly distributed in Henan, Shandong, Anhui, Shanxi, Jiangsu, Chongqing, and Hebei, among which Henan Province had the highest number of non-endemic cases (28.28%) (Table 1). Cases were reported throughout the year with no significant seasonal variation. However, the number of non-endemic reported cases were sporadic and locally increasing. (Figure 1).

The age ranged from 3 to 85 years with a mean age of 44.5±16.2 years. The age distribution of cases was as follows (χ^2=52.1211, P<0.05): <10 years (n=10; 4.10%), 10–19 years (n=6; 2.46%), 20–29 years (n=32; 13.11%), 30–39 years (n=30; 12.30%), 40–49 years (n=68; 27.87%), 50–59 years (n=60; 24.59%), and ≥60 years (n=38; 15.57%). There was no significant difference between men and women [54.1% and 45.9%, (χ^2=0.8211, P>0.05)].

The most frequently reported occupational categories were (χ^2=170.3174, P<0.05): farmers (n=114; 46.72%), domestic and unemployed individuals (n=50; 20.49%), retired individuals (n=18; 7.38%), and others (n=14; 5.74%). No other occupational category had more than 10 cases.

Of the 244 cases reported in non-endemic PLADs, there were 58 locally-acquired cases (23.77%), 165 imported cases (67.62%), and 21 cases (8.61%) that were lost to follow-up. The sources of the imported cases were as follows: 3 (1.23%) from Gansu, 16 (6.56%) from Inner Mongolia, 2 (0.82%) from Ningxia, 15 (6.15%) from Tibet, 109 (44.67%) from

TABLE 1. The number of reported cases of echinococcosis in non-endemic PLADs — China, 2017–2020.

PLADs	Cumulative cases (n)	Composition ratio (%)	Locally cumulative acquired cases (n)	Cumulative imported cases (n)	Cumulative missing cases (n)
Beijing	7	2.87	0	6	1
Hebei	13	5.33	2	10	1
Shanxi	14	5.74	7	6	1
Liaoning	8	3.28	3	3	2
Jilin	1	0.41	0	1	0
Heilongjiang	8	3.28	1	6	1
Shanghai	2	0.82	0	1	1
Jiangsu	14	5.74	6	8	0
Zhejiang	5	2.05	1	4	0
Anhui	18	7.38	3	12	3
Fujian	7	2.87	6	1	0
Jiangxi	1	0.41	1	0	0
Shandong	27	11.07	8	19	0
Henan	69	28.28	8	59	2
Hubei	7	2.87	0	6	1
Hunan	10	4.10	1	7	2
Guangdong	4	1.64	0	4	0
Guangxi	3	1.23	3	0	0
Hainan	1	0.41	1	0	0
Chongqing	14	5.74	0	10	4
Guizhou	11	4.51	7	2	2
Total	244	100.00	58	165	21

Abbreviation: PLADs=provincial-level administrative divisions.

Xinjiang, 1 (0.41%) from Yunnan, 7 (2.87%) from Sichuan, 10 (4.10%) from Qinghai, and 2 (0.82%) from other countries (Figure 2). Furthermore, there were also cases of locally-acquired infections reported in 15 PLADs, imported cases in 18 PLADs, and cases that were lost to follow-up in 11 PLADs (Table 1).

DISCUSSION

The results of this study showed the dynamic changes and epidemiological characteristics of reported echinococcosis cases in China from 2017 to 2020. There were 19,948 cases of echinococcosis reported nationwide from 2017 to 2020, of which 244 cases were reported in 21 non-endemic PLADs. Henan Province reported the largest number of cases. Cases were distributed across all age groups, with the majority of cases occurring in people aged >20 years. Furthermore, the majority of patients were farmers. The epidemiological investigation found that of the cases reported in non-endemic PLADs, the majority were imported and less than one-quarter were confirmed to have been locally acquired. The largest source of imported cases was Xinjiang. There were locally acquired cases reported in 11 non-endemic PLADs. According to the China Statistical Yearbook (*4*), from 2000 to 2019, the migrant population in China increased from 121 million to 236 million, the number of domestic tourists increased from 744 million to 6.006 billion, meat production increased from 60.139 million tons to 77.588 million tons, and the total output value of the livestock industry grew from 739.31 billion CNY to 3,306.43 billion CNY. The increase in population migration (due to work, tourism, and labor) and the circulation of livestock and other products between regions could pave the way for the spread of echinococcosis from pasturing areas to agricultural and urban areas.

This increase in the number of cases reported in non-endemic PLADs has been reported previously (*5*), and it is expected that this trend will continue. This increase is likely to be attributable to the gradual

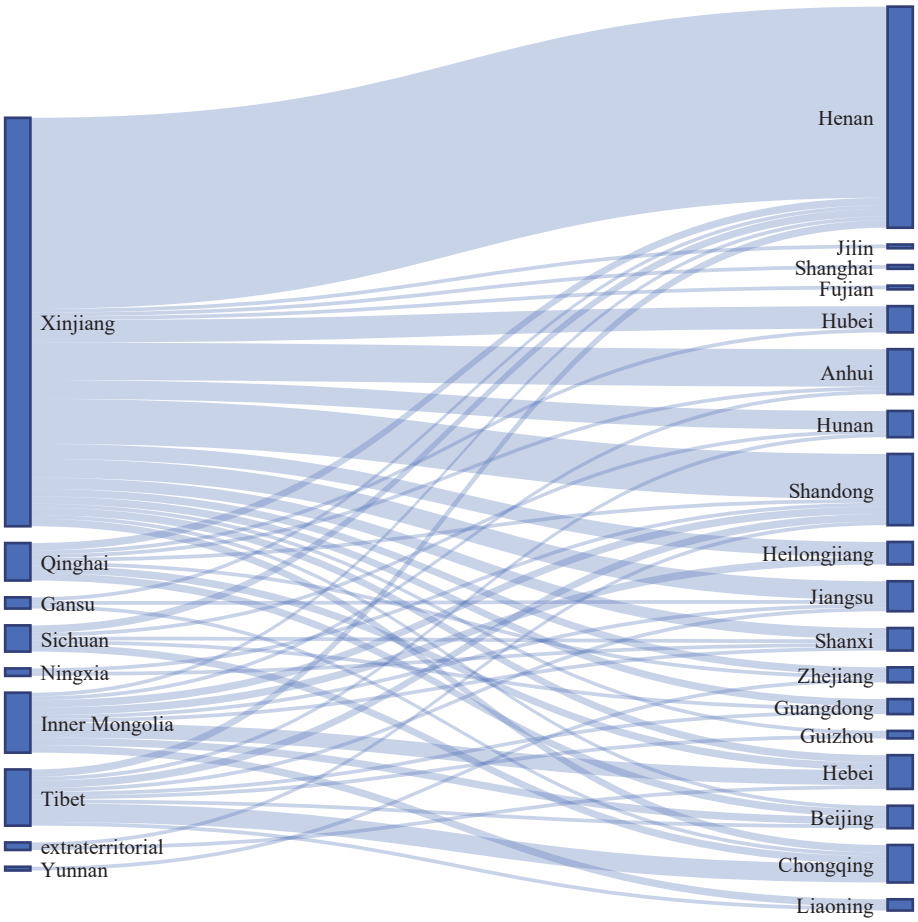

FIGURE 2. The Sankey diagram of exported PLADs and imported non-endemic PLADs of echinococcosis in China from 2017 to 2020.
Abbreviation: PLADs=provincial-level administrative divisions.

increase in the detection of echinococcosis through screening and improved health-seeking behavior. Moreover, hospitals and county-level CDCs have strengthened the awareness of reporting notifiable diseases and cases. According to the results of the epidemiological investigation of suspected local cases, no infected dogs were found, and the cases were sporadic. However, some local livestock originated from endemic areas. It is speculated that the humans were infected by ingesting insect eggs on animal fur or by people feeding diseased organs to dogs in non-endemic areas which led to the spread of echinococcosis. Infected individuals in non-endemic PLADs were mainly those of working age, the possibility of infection when they were working in endemic areas cannot be ruled out. This suggests that health education for people working in endemic areas should be strengthened. Some of the locally acquired cases in non-endemic PLADs may have been related to work, such as fur processing. Most cases from non-endemic PLADs were reported from Henan, Heilongjiang, and Jiangsu (*6*), which suggests that echinococcosis may also be endemic in parts of China where it is not currently recognized as endemic and there is still a risk of locally acquired infections. More detailed onsite investigation needs to be the next step, including mass screening of high-risk population and surveys of intermediate and final. The National Echinococcosis Control Expert Group should determine if there are new endemic areas based on the field investigation results.

The study was subject to some limitations. Because echinococcosis is a chronic disease (*7*), of which there are two types including cystic echinococcosis (CE) and alveolar echinococcosis (AE), the progression of the disease is hard to classify due to different imaging features (*8*–*10*). The NNDRS did not specify whether these cases were CE or AE, so the prevalence of echinococcosis in China may not be fully reflected by the number of cases as some may be misclassified or

missed due to limitations in the surveillance system.

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Preplanned Studies

Rapid Assessment on Potential Risks of Schistosomiasis Transmission — 7 PLADs, China, 2019 and 2021

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Summary

What is already known about this topic?

Oncomelania hupensis (*O. hupensis*) and livestock are main infection sources of schistosomiasis. The schistosome infected *O. hupensis* and livestock's feces are important risk factors in the transmission of schistosomiasis.

What is added by this report?

The potential risks of schistosomiasis transmission remain prevalent, giving an early warning to local government with information on existing transmission risks. It is expected that the effectiveness and efficiency of schistosomiasis surveillance could be improved by conducting rapid risk assessment at the beginning of transmission season.

What are the implications for public health practice?

Rapid risk assessment is essential in early detection and the active monitoring of indicators of the transmission risks of schistosomiasis in endemic areas. This could work synergistically with surveillance system to minimize infections and prevent rebounds of endemic schistosomiasis outbreaks.

Schistosomiasis was endemic to 12 provincial-level administrative divisions (PLADs) in the middle and lower reaches of the Yangtze River and southern China. *Oncomelania hupensis* (*O. hupensis*) was the only intermediate snail host of *Schistosoma japonicum* (*1*). Previous studies had illustrated that the contribution of cattle feces to the transmission of schistosomiasis had accounted for 75% (*2*). In order to detect these potential risks of schistosomiasis transmission, indicators including distribution and infection rates of *O. hupensis* and livestock's feces around *O. hupensis* habitats were assessed at the beginning of transmission season in the 7 PLADs where schistosomiasis elimination had not achieved the national criteria (*3*). The rapid assessments were conducted in the spring of 2019 and 2021. The *O. hupensis* survey was performed by means of environmental sampling, and livestock feces samples were collected in surveyed *O. hupensis* habitats. Loop-mediated isothermal amplification (LAMP) assay and miracidial hatching were used to detect for *O. hupensis* infection and livestock's feces samples, respectively. In 2021, 2 surveyed environments detected nucleic acids of schistosomes among *O. hupensis* snails by LAMP assay. Schistosome eggs were found in cattle feces collected from snail habitats both in 2019 and 2021. These results indicated that the distribution and infections of *O. hupensis* and livestock's feces may cause concerns in endemic areas, which also gave an early warning that rapid response measures should be implemented in key environments to eliminate the potential risks of schistosomiasis transmission as soon as possible.

The assessments were conducted in the schistosomiasis endemic areas of Hunan, Hubei, Jiangxi, Anhui, Jiangsu, Sichuan, and Yunnan Provinces. Stratified random sampling was used to select surveyed environments. In each surveyed environment, over 50 square frames of 0.1 m^2 were used to capture all *O. hupensis* within the frame. Every 10 specimens of captured *O. hupensis* were pooled in 1 centrifuge tube (1 tube for less than 10 *O. hupensis*) for DNA extraction, and DNA extracted from 50 *O. hupensis* samples were pooled for LAMP assay to detect *S. japonicum.* Surveyed environments with LAMP-tested positive *O. hupensis* were categorized as a positive environment. Livestock's feces found in surveyed *O. hupensis* fields were all collected. Stool samples were categorized as positive if schistosome miracidia was detected by the hatching test (3 bottles for 1 sample). The proportion of frames with living *O. hupensis* to total surveyed frames, rate of positive *O. hupensis* habitats, and positive livestock-feces samples were calculated.

A total of 33 administrative villages in 14 counties of the 7 PLADs were sampled in 2019 and 2021 without

duplicate sampled counties (Table 1–2). In 2019, 68 *O. hupensis* inhabited environments were surveyed, in which 41.18% (28/68) environments had *O. hupensis* captured. Out of the total of 3,115 surveyed frames, living *O. hupensis* occurred in 324 frames. A total of 1,919 *O. hupensis* were living of all 2,076 captured, and an irrigation ditch in Laoguanju Village (Hubei Province) had the highest number of living *O. hupensis* in single frame at 69/frame. The LAMP assay detected no positive environments from all surveyed fields. A total of 56 stool samples were found in 7 sampled counties' surveyed environments, including 53 (94.64%) cattle-feces samples and 3 (5.36%) sheep-feces samples. A total of 4 cattle-feces sample from a marshland in Minglang Village (Hunan Province) tested positive by miracidial hatching, with a 7.14% (4/56) positivity rate of livestock-feces samples (Table 1).

In 2021, 74 *O. hupensis* inhabited environments were surveyed, in which 50% (37/74) of environments had *O. hupensis* captured. Of the total of 3,532 surveyed frames, living *O. hupensis* occurred in 292 frames. In addition, of all 1,958 *O. hupensis* captured, 1,870 were living. In marshland and lake endemic areas, an irrigation ditch in Lianyi Village (Hubei Province) had the highest number of living *O. hupensis* in a single frame at 94/frame. In mountainous and hilly endemic areas, a tobacco field in Yunfeng Village (Yunnan Province) had the highest number of living *O. hupensis* in a single frame at 31/frame. The LAMP assay detected 2 positive environments where the nucleic acids of a schistosome were found in *O. hupensis*, including a marshland in Wufeng Village (Jiangxi Province) and an irrigation ditch in Lianyi Village (Hubei Province), with a 2.70% (2/74) positivity rate of *O. hupensis* habitats. A total of 54 stool samples were found in 13 surveyed environments in 9 sampled counties, including cattle feces, sheep feces, and other mammal's feces, accounting for 42.59% (23/54), 38.89% (21/54), and 18.52% (10/54), respectively. One cattle-feces sample from a marshland in Lianxu Village (Jiangxi Province) tested positive by miracidial hatching, with a 1.85% (1/54) positivity rate of livestock-feces samples (Table 2).

TABLE 1. Results of rapid assessments on potential risks of schistosomiasis transmission in 7 PLADs, China, Spring 2019.

Province	County/City/ District	Number of investigated villages	Number of surveyed environments	*O. hupensis* survey result		Livestock's feces survey result	
				Frames with living *O. hupensis*/total surveyed frames	LAMP result*	Count	Miracidial hatching positive
Jiangsu	Jiangning District	2	7	52/204	0	0	0
	Pukou District	4	6	39/187	0	0	0
Anhui	Wuwei County	2	4	3/210	0	8	0
	Sanshan District	2	3	0/160	0	0	0
Jiangxi	Pengze County	2	4	13/222	0	0	0
	Ruichang City	3	5	30/271	0	0	0
Hubei	Chibi City	3	6	30/303	0	3	0
	Jiayu County	3	6	20/306	0	0	0
Hunan	Ziyang District	2	4	81/205	0	18	4
	Nan County	2	4	32/203	0	20	0
Sichuan	Dechang County	2	5	2/205	0	0	0
	Xichang City	2	6	19/239	0	3	0
Yunnan	Yongsheng County	2	4	3/200	0	2	0
	Jianchuan County	2	4	0/200	0	2	0
Total		33	68	324/3,115	0	56	4

Note: Based on national schistosomiasis epidemic data in the last 2 years, 2 epidemic counties (cities, districts) with relatively intense history of epidemics were selected from each province, 2 towns were selected from each sampled county (city, district), 1 village with intense history of epidemics and large extant areas of *O. hupensis* habitats was selected from each sampled town, and 2 possible *O. hupensis* inhabited environments were selected from each sampled village to conduct the field survey.

Abbreviations: PLADs=provincial-level administrative divisions; LAMP=loop-mediated isothermal amplification; *O. hupensis*=*Oncomelania hupensis*.

* LAMP results: 1: Positive, 0: Negative.

TABLE 2. Results of rapid assessments on potential risks of schistosomiasis transmission in 7 PLADs, China, Spring 2021.

Province	County/City/ District	Number of investigated villages	Number of surveyed environments	*O. hupensis* survey result		Livestock's feces survey result	
				Frames with living *O. hupensis*/total surveyed frames	LAMP result*	Count	Miracidial hatching positive
Jiangsu	New Zhenjiang District	2	4	2/213	0	1	0
	Yangzhong City	2	4	3/208	0	3	0
Anhui	Wanzhi Distrcit	2	6	31/223	0	21	0
	Xuanzhou District	2	9	14/219	0	0	0
Jiangxi	Jinxian County	2	3	0/162	0	4	0
	Nanchang County	3	5	11/293	1	13	1
Hubei	Shashi District	3	8	1/439	0	1	0
	Jingzhou District	3	6	42/187	1	2	0
Hunan	Hanshou District	2	4	8/209	0	0	0
	Dincheng District	3	4	18/209	0	6	0
Sichuan	Mianzhu City	2	4	88/240	0	0	0
	Jingyang District	2	4	63/233	0	0	0
Yunnan	Heqing County	3	8	0/435	0	3	0
	Dali City	2	5	11/262	0	0	0
Total		33	74	292/3,532	2	54	1

Note: Based on national schistosomiasis epidemic data in the last 2 years, 2 epidemic counties (cities, districts) with relatively intense history of epidemics were selected from each province, 2 towns were selected from each sampled county (city, district), 1 village with intense history of epidemics and large extant areas of *O. hupensis* habitats was selected from each sampled town, and 2 possible *O. hupensis* inhabited environments were selected from each sampled village to conduct the field survey.

* LAMP results: 1: Positive, 0: Negative.

Abbreviations: PLADs=provincial-level administrative divisions; LAMP=loop-mediated isothermal amplification; *O. hupensis*=*Oncomelania hupensis*.

DISCUSSION

Even though the current prevalence of schistosomiasis was relatively low across China (*3*), rapid assessments in 2019 and 2021 have found that the density of *O. hupensis* distribution remained high in several *O. hupensis* habitats and surrounding environments where fecal contamination was also observed. In addition, the infections of *O. hupensis* and livestock's feces were both detected in the assessments. The potential risks of schistosomiasis transmission are likely remaining prevalent, which is an early warning of the transmission risks of schistosomiasis at the beginning of transmission season. This finding further indicated that low sensitivity existed in schistosomiasis surveillance system. By conducting rapid risk assessments before the beginning of transmission season, the effectiveness and efficiency of schistosomiasis surveillance may be improved.

In the index system for rapid assessment of environments with high transmission risk of schistosomiasis, morbidity in livestock and *O. hupensis* were regarded as the primary indices, and the secondary indices included the infection rate of livestock, areas with infected *O. hupensis*, and density of infected *O. hupensis* (*4*). This index system showed the importance of assessing transmission risks related to *O. hupensis* and livestock in not only building a comprehensive risk assessment system but also in realizing earlier detection and response to further reduce the possible infection in *O. hupensis* and livestock. Thus, the distribution and infection of *O. hupensis* and livestock's feces were assessed as essential indicators in the rapid assessments and surveillance on schistosomiasis transmission.

The existence and reemergence of *O. hupensis* can greatly affect the transmission of schistosomiasis across endemic areas in 12 southern PLADs (*1*). The optimal temperature for living *O. hupensis* is 20–25 ℃, and their main multiplying stage is between April and June (*5*), during which people and livestock may be more susceptible to schistosomiasis infections. Especially in marshland and lake endemic areas, the distribution of *O. hupensis* and the transmission of schistosomiasis may be facilitated after encountering flood disasters (*6*). In the risk assessment of 5 PLADs affected by

flood disasters in the summer of 2020, 3,240 living *O. hupensis* were captured out of all 8,904 captured, and 1 LAMP-tested positive *O. hupensis*-inhabited environment was detected in the 64 assessed environments (*7*). The flood also caused *O. hupensis* to reemerge in a few environments where no *O. hupensis* distribution had been reported over the past 20 years at least, extending the distribution of *O. hupensis* (*7*).

Livestock is another key factor that causes schistosomiasis transmission. It is reported that cattle feces infected with the schistosome eggs can account for 80% to 90% of schistosomiasis transmission (*8*). Even though several measures have been taken to prevent schistosomiasis transmission caused by livestock activities, such as replacing farming cattle with machines, prohibiting grazing on *O. hupensis*-infested grassland and marshland (*2*), a few livestock, including cattle and sheep, were found grazing around *O. hupensis* habitats during the assessments. The reemergence of livestock activities may lead to a rebound of schistosomiasis infections in endemic areas (*9*). In terms of positive feces detected, harmless disposal of feces was conducted to prevent the transmission. The management of livestock activities should be strengthened as well.

This study was subjected to some limitations. First, the assessment was not conducted in 2020 due to the coronavirus disease 2019 (COVID-19) pandemic, which affected the continuity of assessments. There was 1 case of acute schistosomiasis reported in 2020 (*3*); therefore, assessing environments with transmission risks of schistosomiasis annually is needed based on historical reports and data to avoid infections (*10*). Second, only environmental sampling was applied in investigating *O. hupensis* habitats, which was not as comprehensive as systematic sampling applied in regular risk surveillance. Although our findings can point out potential risks by reporting the distribution and infection of these indicators in endemic regions, further assessment and surveillance should be performed on a broader scale.

In conclusion, in order to achieve the goal of eliminating schistosomiasis in China before 2030 (*2*), environments with potential risks of schistosomiasis transmission need prompt and efficient detection and surveillance to minimize the possibility of schistosomiasis infection in both humans and livestock. Rapid risk assessment should also be applied to actively monitor indicators of the transmission risks of schistosomiasis and prevent the rebound of the endemic schistosomiasis outbreaks.

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Preplanned Studies

Reappearance of Risk of Schistosomiasis Transmission and the Response After 27 Years of Interrupted Transmission — Guangdong Province, China, 2019

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Summary

What is already known about this topic?

No live specimens of the snail *Oncomelania hupensis* (*O. hupensis*) and indigenous infected cases of schistosomiasis japonicum have been found in Guangdong Province since 1993, but live *O. hupensis* was found again in 2019. This study conducted *O. hupensis* identification and elimination.

What is added by this report?

In 2019, live *O. hupensis* specimens were detected by routine surveillance in areas in Qujiang of Shaoguan City and Yingde of Qingyuan City, and an emergency response was launched immediately.

What are the implications for public health practice?

The suspected habitat of *O. hupensis* in originally endemic areas of schistosomiasis in Guangdong is still complicated, so it is necessary to record suspected habitats comprehensively and carry out scientific routine surveillance for *O. hupensis*.

Oncomelania hupensis (*O. hupensis*) is the only intermediate host of *Schistosoma japonicum* (*1*). Guangdong Province is also a province with endemic *O. hupensis*, and there used to be an estimated 110 million square meters of original habitat for *O. hupensis* (*2*). In order to eliminate schistosomiasis, a team in Guangdong modified the environment to undertake *O. hupensis* control measures, and since 1993, live *O. hupensis* have disappeared in Guangdong (*3*). Unexpectedly, live *O. hupensis* were found during the spring *O. hupensis* survey in Qujiang District of Shaoguan City and Yingde City of Qingyuan City of Guangdong in early April of 2019 (Figure 1). In order to maintain the state of no live *O. hupensis* in Guangdong Province and to eliminate the risk of possible recurrence of schistosomiasis, a team in Guangdong was dispatched to carry out prevention and control measures to eliminate *O. hupensis* and modify its breeding area from April to August 2019 in this study.

The first *O. hupensis* habitat area was located in the junction area of Changjiang Dam of Shakou Town, Yingde (county-level jurisdiction), Qingyuan City, and Qunxing Village of Zhangshi Town, Qujiang District (county-level jurisdiction), Shaoguan City, which was originally an *O. hupensis* habitat area (Figure 1), with diverse and complex surrounding environments. The *O. hupensis* density survey was carried out by 5 meter systematic sampling combined with 2-frame environmental sampling. Both dead and live snails were identified, and the infection rate of *Schistosoma japonicum* cercariae in live snails was detected by anatomical microscope, polymerase chain reaction (PCR), and loop-mediated isothermal amplification (*4*). At the same time, the whole mitochondrial genome DNA of snails was sequenced and phylogenetic analysis was carried out using next generation sequencing. In order to further understand the schistosomiasis infection status of people and livestock in the affected areas, the venous blood and feces of people and cattle were collected, and schistosomiasis antibodies were detected for using indirect haemagglutination assay (IHA). The feces were detected by metacercaria incubation method and Kato Katz. In addition, in order to completely eliminate the snails, comprehensive environmental treatment was adopted in the response process. The main measures include the following: comprehensively managing ditches by weeding and clearing the surface; spraying the area with 26% metaldehyde and niclosamide suspension concentrate combined with either black ground rubber film cover or with soaking to eliminate *O. hupensis*; and filling old ditches and constructing new ditches and hardening three sides with smooth surfaces.

The results showed a total of 1,847 suspected

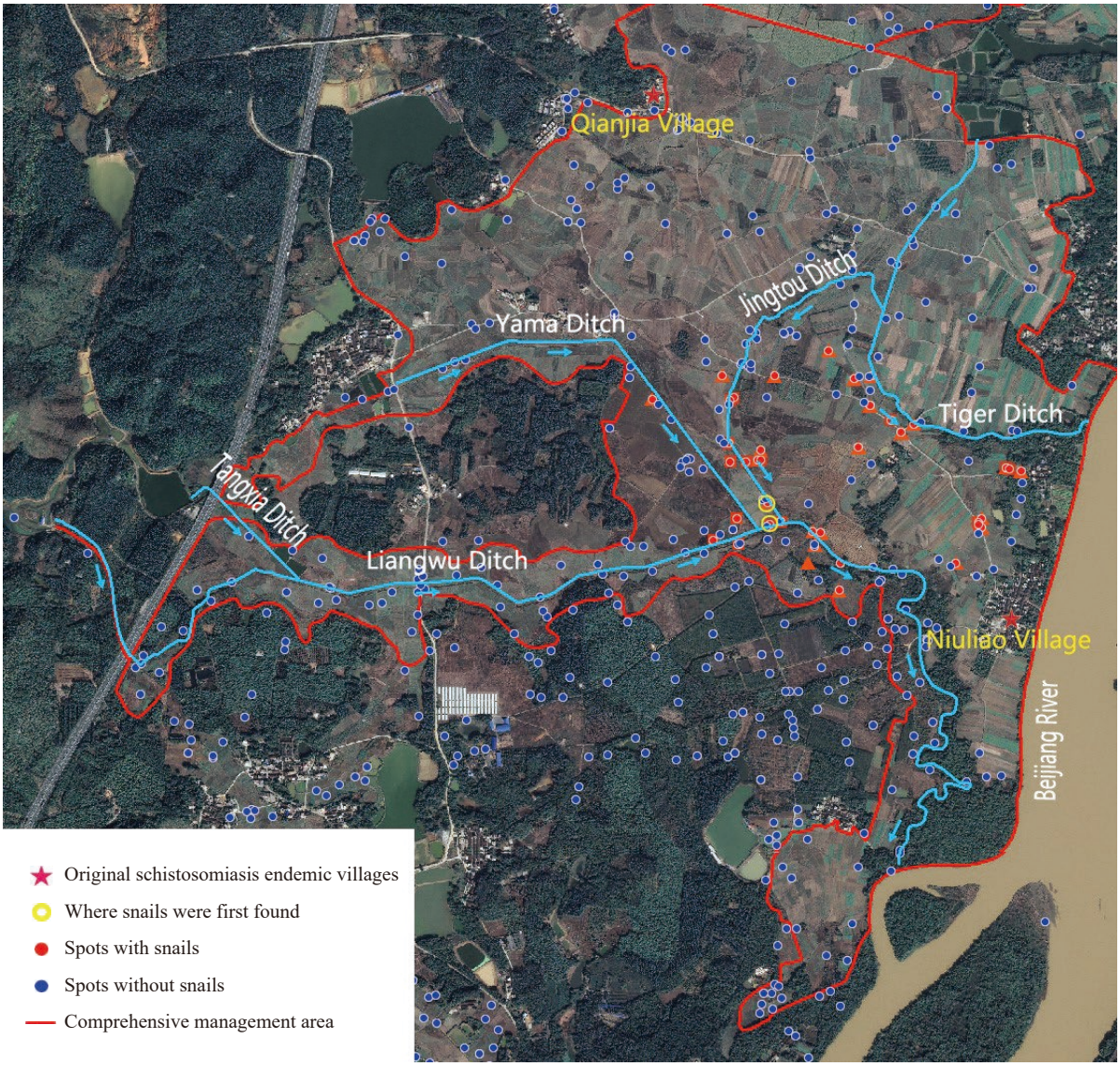

FIGURE 1. The map of comprehensive management of *Oncomelania hupensis* in Guangdong Province in 2019.

environments suitable for *O. hupensis* habitat that were investigated, with a total area of about 2.26 million square meters. A total of 40 environments with *O. hupensis* were identified covering an area of about 124.7 thousand square meters. The occurrence rate of the survey frames with *O. hupensis* in the habitat environment was 0.32%–66.09%, and the density of live *O. hupensis* was 0.01–7.66/frame (Table 1). A total of 8,612 snails were collected and identified as live snails. The whole mitochondrial genome sequence (15,850 bp) of *O. hupensis* was obtained by second-generation deep sequencing. The results of identification and evolutionary analysis showed that *O. hupensis* in Guangdong Province and the Yangzhou (JF284688.1) strain in Jiangsu Province were located in the same evolutionary branch, and identification with the strain at the nucleotide level was 100% (Figure 2). A total of 4,861 human blood samples were collected, with a test response rate of more than 95%. The IHA test results were positive for schistosomiasis antibody in 14 people (0.29%), and the stool samples of 14 IHA positive people were negative for schistosomiasis eggs and metacercaria. The blood and fecal samples of 269 buffalo in all affected areas were collected, and the examination rate was 100%. No *Schistosoma* antibodies, eggs, and cercariae were found. In the process of environmental treatment, a total of 51.94 km of canals were newly built and repaired, 3 screw basins were newly built, 27 culverts were rebuilt, and more than 3,000 acres of farmland remediation and rehabilitation were completed. The cumulative drug snail extermination area was 1.45 million square

TABLE 1. Investigation on *Oncomelania hupensis* and its breeding area in the affected areas of Qujiang and Yingde, Guangdong Province from April to August 2019.

County-level jurisdiction	No. of snail environment	Environment type	Environmental area (m^2)	No. of survey system frames	No. of live snail frames	Rate of live snail frames	No. of live snails collected	Live *Oncomelania* density (No./ frame)
Qujiang	1	Ditch	78	43	6	13.95	147	3.42
Qujiang	2	Ditch	1,575	12	1	8.33	1	0.08
Qujiang	3	Ditch	400	23	5	21.74	11	0.48
Qujiang	4	Ditch	800	174	115	66.09	794	4.56
Qujiang	5	Ditch	60	26	1	3.85	1	0.04
Qujiang	6	Waste land	865	66	1	1.52	1	0.02
Qujiang	7	Waste land	5,004	133	2	1.50	2	0.02
Qujiang	8	Ditch	50	13	2	15.38	5	0.38
Qujiang	9	Ditch	50	12	4	33.33	20	1.67
Qujiang	10	Ditch	320	308	1	0.32	17	0.06
Qujiang	11	Ditch	65	28	4	14.29	16	0.57
Qujiang	12	Ditch	175	33	3	9.09	6	0.18
Qujiang	13	Waste land	2,200	262	4	1.53	16	0.06
Qujiang	14	Ditch	240	83	1	1.20	1	0.01
Qujiang	15	Waste land	30	11	3	27.27	15	1.36
Qujiang	16	Waste land	50	11	2	18.18	15	1.36
Qujiang	17	Waste land	7,178	414	54	13.04	97	0.23
Yingde	18	Waste land	10,525	32	11	34.38	164	5.13
Yingde	19	Ditch	1,592	31	8	25.81	63	2.03
Yingde	20	Waste land	22,056	55	17	30.91	179	3.25
Yingde	21	Waste land	2,653	111	26	23.42	144	1.30
Yingde	22	Waste land	1,781	70	25	35.17	154	2.20
Yingde	23	Waste land	2,164	77	7	9.09	590	7.66
Yingde	24	Waste land	7,676	77	12	15.58	28	0.36
Yingde	25	Waste land	13,603	98	21	21.43	300	3.06
Yingde	26	Waste land	8,935	36	11	30.56	28	0.78
Yingde	27	Waste land	2,175	73	5	6.85	25	0.34
Yingde	28	Ditch	4,064	138	11	7.97	37	0.27
Yingde	29	Waste land	1,752	17	2	11.76	13	0.76
Yingde	30	Waste land	337	18	8	44.44	90	5.00
Yingde	31	Ditch	259	99	42	42.42	629	6.35
Yingde	32	Waste land	10,599	347	18	5.19	89	0.26
Yingde	33	Waste land	6,215	147	4	2.72	33	0.22
Yingde	34	Waste land	6,245	162	10	6.17	189	1.17
Yingde	35	Ditch	278	175	102	58.29	726	4.15
Yingde	36	Ditch	250	43	8	18.60	25	0.58
Yingde	37	Ditch	620	169	1	0.59	1	0.01
Yingde	38	Ditch	1,370	238	44	18.49	1,312	5.51
Yingde	39	Ditch	200	35	20	57.14	76	2.17
Yingde	40	Ditch	300	107	1	0.93	1	0.01
Total			124,789	4,007	623	15.55	6,061	1.51

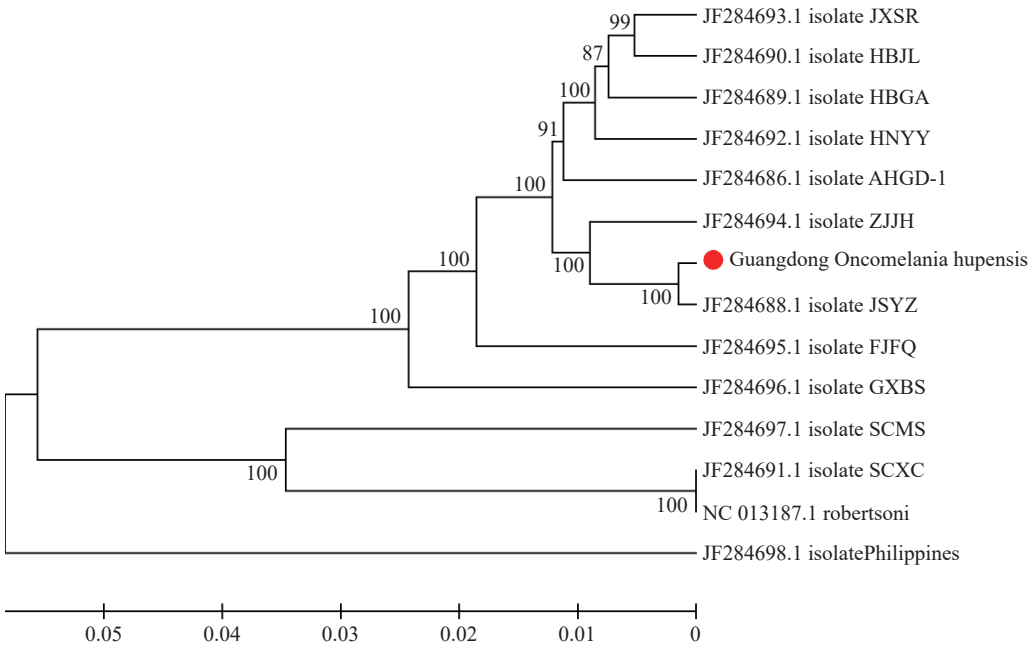

FIGURE 2. Phylogenetic tree of *Oncomelania hupensis* mitochondrial genomic DNA obtained from Qujiang in 2019 in Guangdong Province, China.
Notes: A total of 14 sequences were used for phylogenetic tree reconstructions. The Guangdong Oncomelania hupensis strain was indicated by red circle.

meters. From December 2020 to May 2021, 40 environments with *O. hupensis* and the surrounding environments were monitored and evaluated several times, and no more live *O. hupensis* were detected.

DISCUSSION

Schistosomiasis epidemic areas in Guangdong Province were mainly distributed in the middle and lower reaches of the Beijiang River in the Pearl River System (*2*). Guangdong Province announced the elimination of schistosomiasis in 1985 as there were no *O. hupensis* found in 7 years. Since then, in 1992, an outbreak of *O. hupensis* reappeared in Caozhai Village, Sanshui District, Foshan City. It was found that there were 2000 m^2 of *O. hupensis* and 3 persons with positive fecal eggs, including 1 case of previous infection and 2 cases of new infection (*5*). No *O. hupensis* had been reported in affected area in Yingde since 1982, and no sick cattle have been found since 1983 (*5*). Fortunately, we did not find any human and animal infections, so we inferred that the possible reasons for the recurrence of *O. hupensis* were as follows. First, there might be some remaining *O. hupensis* still living in the local environments at that time, and the environmental conditions were suitable for the reproduction of *O. hupensis*, which reached a certain density after many years. Second, the environment was low-lying and waterlogged during the flood season, resulting in abandoned fields and overgrown weeds, forming an environment suitable for *O. hupensis* habitation. Third, the environmental terrain and its altitude, the mode of production and grazing, etc., were all possible factors causing *O. hupensis* to spread in a large area in this region. Fourth, the local reporting of suspicious environment suitable for *O. hupensis* habitat was not comprehensive enough, which might have resulted in insufficient monitoring coverage and missed investigation for many years (*6*). In 2018, Yingde strengthened the reporting efforts and monitored the environment of the newly built datasets in 2018, subsequently finding the *O. hupensis* habitats. Of the 40 areas affected by *O. hupensis*, half were distributed along the water system, and the other half were distributed at independent points. It is analyzed that the habitat and diffusion of the remaining snails in this area might be categorized in three passive diffusion modes (*7*): 1) carried and spread by water flow along the river system, flooding, and waterlogging water; 2) carried by human production and living activities; and 3) carried by activity of grazing animals in affected areas.

The following points were learned and implemented in this emergency response: 1) the monitoring system

must be maintained and be effective by adhering to surveillance procedures, team training, and quality evaluation every year; 2) the reoccurrence of the *O. hupensis* epidemic was confirmed quickly, and the provincial, municipal and county levels immediately launched emergency response, quickly established multidepartment joint management mechanisms, and took emergency implementation measures; 3) according to the characteristics of the environments with *O. hupensis*, molluscacide was utilized with environmental reforms to eliminate *O. hupensis* rapidly and consolidate the effects of *O. hupensis* eradication; 4) environments containing *O. hupensis*, surrounding water systems, and suspected environments must be comprehensively managed to reduce suspected environments suitable for *O. hupensis* breeding and minimize the risk of *O. hupensis* breeding and diffusion in the affected places, and relevant departments must be synchronized and collaborate on their work.

There are some limitations in the snail disposal. Firstly, the limitation of snail traceability. At present, there is no whole genome sequence of oncomelania, so it can only be compared according to the mitochondrial genome sequence. Secondly, the limitation of snail distribution survey. Based on the current method of snail investigation, probability of missing inspection is high in the environment with low density; There may also be very few residual snails in the environment after snail disposal.

Strengthening surveillance is an important measure to consolidate and eliminate schistosomiasis. In order to consolidate the *O. hupensis* control effect, it is necessary to further strengthen the effect evaluation and monitoring, improve the environmental management, and conduct sustainable environmental management. In schistosomiasis surveillance areas, it is necessary to further strengthen the comprehensive reporting and registration of suspected environments suitable for *O. hupensis* habitation, strive to fully grasp the distribution and quantity of suspicious habitat environments, simultaneously carry out dynamic filing management, carry out rational *O. hupensis* monitoring, ensure monitoring coverage and *O. hupensis* survey quality, and prevent missing investigations.

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Notifiable Infectious Diseases Reports

Reported Cases and Deaths of National Notifiable Infectious Diseases — China, October, 2021

Diseases	Cases	Deaths
Plague	0	0
Cholera	2	0
SARS-CoV	0	0
Acquired immune deficiency syndrome*	5,357	1,849
Hepatitis	118,664	43
Hepatitis A	940	0
Hepatitis B	95,942	33
Hepatitis C	19,157	10
Hepatitis D	24	0
Hepatitis E	1,846	0
Other hepatitis	755	0
Poliomyelitis	0	0
Human infection with H5N1 virus	0	0
Measles	88	0
Epidemic hemorrhagic fever	678	5
Rabies	19	10
Japanese encephalitis	39	1
Dengue	6	0
Anthrax	38	0
Dysentery	3,745	0
Tuberculosis	61,391	126
Typhoid fever and paratyphoid fever	655	1
Meningococcal meningitis	7	0
Pertussis	825	0
Diphtheria	0	0
Neonatal tetanus	3	0
Scarlet fever	1,634	0
Brucellosis	3,622	0
Gonorrhea	10,720	1
Syphilis	40,900	2
Leptospirosis	81	1
Schistosomiasis	6	0
Malaria	46	0
Human infection with H7N9 virus	0	0
COVID-19[†]	1,081	0
Influenza	53,346	1
Mumps	11,116	0

Continued

Diseases	Cases	Deaths
Rubella	101	0
Acute hemorrhagic conjunctivitis	1,994	0
Leprosy	21	0
Typhus	190	0
Kala azar	11	0
Echinococcosis	207	0
Filariasis	0	0
Infectious diarrhea[§]	74,343	0
Hand, foot and mouth disease	132,070	0
Total	**523,006**	**2,040**

* The number of deaths of Acquired immune deficiency syndrome is the number of all-cause deaths reported in the month by cumulative reported AIDS patients.
† The data were from the website of the National Health Commission of the People's Republic of China.
§ Infectious diarrhea excludes cholera, dysentery, typhoid fever and paratyphoid fever.
The number of cases and cause-specific deaths refer to data recorded in National Notifiable Disease Reporting System in China, which includes both clinically-diagnosed cases and laboratory-confirmed cases. Only reported cases of the 31 provincial-level administrative divisions in the mainland of China are included in the table, whereas data of Hong Kong Special Administrative Region, Macau Special Administrative Region, and Taiwan are not included. Monthly statistics are calculated without annual verification, which were usually conducted in February of the next year for de-duplication and verification of reported cases in annual statistics. Therefore, 12-month cases could not be added together directly to calculate the cumulative cases because the individual information might be verified via National Notifiable Disease Reporting System according to information verification or field investigations by local CDCs.

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