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Preplanned Studies

Predictors for Treatment Outcomes in Patients with Multi-drug Resistant Tuberculosis — China, 2018–2020

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Summary

What is already known about this topic?

Multi-drug resistant tuberculosis (MDR-TB) is a critical global public health problem.

What is added by this report?

Sputum cultures and lung images show a strong association with treatment outcomes, serving as a multi-dimensional approach to identify MDR-TB patients with poor outcomes.

What are the implications for public health practice?

The results imply that funds and policy investments should be increased by early monitoring of MDR-TB patients, especially regarding imaging and sputum bacterium. By informing physicians on changes to the therapeutic schedule, treatment outcomes can be improved.

Multi-drug resistant tuberculosis (MDR-TB) is caused by the *Mycobacterium tuberculosis* that is resistant to rifampicin and isoniazid (*1*). MDR-TB has become a global public health concern, which seriously threatens the realization of the goal of stopping the tuberculosis (TB) epidemic by 2035 (*1–3*). China is a country with a high burden of MDR-TB (*1*). The coronavirus disease 2019 (COVID-19) pandemic poses significant challenges to controlling MDR-TB in China (*1*,*4–5*). Therefore, a model based on multi-modal data may predict the treatment outcome in the early treatment phase. The results of the study suggest that physicians should pay special attention to dynamic changes of the sputum bacterium and lung images at the intensive stage, and it may help physicians adapt the therapeutic schedule to improve the cure rate.

A multi-center retrospective study was conducted in twenty-three sentinel hospitals selected from sixteen provincial level administration divisions (PLADs) in China. There were 6 hospitals in the east, 3 hospitals in the west, 5 hospitals in the south, 4 hospitals in the north and 5 hospitals in the middle region of China. Among them, there were 8 tertiary hospitals, 10 second-grade hospitals, and 5 community hospitals.

These treatment outcomes were based on World Health Organization (WHO) recommendations, defined as follows: 1) ‘Cured’ meant the course of treatment was completed according to the national guidelines without evidence of treatment failure, and the sputum culture was negative for 3 consecutive times or more at least 30 days after the enhancement period. 2) ‘Treatment failure’ was defined as treatment terminated due to the following reasons: at least two anti-TB drugs in the treatment protocol needed to be permanently changed, no negative conversion after the enhancement period, reversed bacteriological test results in the continuing period after negative conversion, evidence indicating acquired drug resistance to fluoroquinolones or second-line injections, adverse drug reactions, or death directly associated with MDR-TB (*2*).

All patients with MDR-TB who visited one of the 23 sentinel hospitals between January 2018 and December 2020 were considered as possible subjects. Patients who met the following inclusion criteria were considered: 1) MDR-TB patients, with the definition of MDR-TB as presented by the WHO was used (*2*). 2) Signed informed consent. Exclusion criteria included the following: 1) Patients with other serious diseases (mental diseases, various cancers, hepatitis patients, serious skin diseases, severe metabolic disease, human immunodeficiency virus/acquired immunodeficiency syndrome, etc). 2) Pregnant or lactating patients and patients with pneumonia, pneumoconiosis or other lung diseases.

MDR-TB treatment was defined as receiving recommended regimen in the national MDR-TB control program (*2–3*). For each MDR-TB case, sputum smear, sputum culture, drug sensitivity test (DST), physical examination and routine blood counts, biochemical tests, and urinalyses were recorded through monthly examinations. Chest-computed tomography (CT) was performed during the intensive phase and continuation phase to all patients according to the National TB Program (NTP) of China. Sputum specimens were collected and examined through direct smear microscopy for the presence of acid-fast bacilli (AFB) using Ziehl-Neelsen staining. A conventional DST was performed using the agar proportion method on enriched Middle-Brook 7H10 medium against first-line anti-TB drugs (FLDs). The rapid DST (Xpert MTB/RIF®) assay was performed to detect rifampicin resistance (RR) in smear-positive sputum samples. Second-line anti-TB drugs (SLDs) (*1*), such as Ethambutol, Streptomycin, Kanamycin, Ofloxacin, P-aminosalicylic acid, and Pyrazinamide, were also included. All positive cultures were submitted to the upper-level laboratory in the prefectural Center for Disease Control and Prevention (CDC).

As to all-round utilization of our clinical data, electronic medical record systems and questionnaires with telephone surveys, and underlying prognostic variables were collected with structured questionnaire using REDCap (version 10.0, Vanderbilt University, Nashville, USA). The questionnaire involved socio-demographic characteristics, risk factors, MDR-TB diagnosis and a history of TB, comorbidities, clinical laboratory indicators, and drug resistance at month zero. Data were cleaned in Microsoft Office Excel (version 2020, Microsoft Corp, Washington, USA) and analyzed with SAS (version 9.4, SAS Institute Inc, Cary, USA). Univariable analysis was done for computing odds ratios (ORs) and their 95% confidence intervals (CIs). The level of significance was assessed by the Wald χ^2 test. Variables with P<0.05 were entered into a multivariable logistic regression model to examine their independent effects through stepwise deletion of variables. P<0.05 was considered significant using a two-tailed test.

A total of 556 patients completed the therapeutic process, including cured patients (n=389) and patients with treatment failure (n=167). The average age of cured patients was lower than that of treatment failure patients (37.1, 40.2, Z=−3.844, P<0.001). The number of lobes involved in the pulmonary lobe in month 0 of the cured patients were less than that of non-cured patients (3, 5, Z=−6.695, P<0.001). Furthermore, the cavity count in the initial month in cured patients was lower compared to that in failure patients (1, 2, Z=−4.689, P<0.001).

Single factor analysis showed that variables related to the negative prognosis of MDR-TB patients included age, marriage, irregular treatment, lesions involving lung lobes in month zero, cavities counts in month zero, time from TB diagnosis to MDR-TB diagnosis, time from MDR-TB diagnosis to treatment, time from TB diagnosis to MDR-TB treatment, leukocytes, platelets, erythrocytes, sedimentation rate, streptomycin resistance, Ofloxacin resistance, Para-aminosalicylic acid treatment, Pyrazinamide treatment, Moxifloxacin treatment, and Kanamycin treatment (Table 1). In addition, sputum culture results and lung images (lesion absorption, cavity closure) were associated with unsuccessful treatment outcomes, including a sputum culture at month 1, a sputum culture at month 2, a sputum culture at month 3, a sputum culture at month 6, lesion absorption at month 6, and cavity closure at month 6 (Table 1). Finally, age, irregular treatment, time from MDR-TB diagnosis to treatment, erythrocyte sedimentation rate, Ofloxacin resistance, sputum culture month 3, lesions in the pulmonary lobe month zero, cavity count month zero, and cavity closure month 6 were associated with treatment outcome (Table 2).

TABLE 1. Predictors for MDR-TB treatment outcome using univariate analysis.

Predictor	Subgroup	Failure n=167 n (%)	Cured n=389 n (%)	χ^2	*P*	OR (95% CI)
Socio-demographic characteristics						
Age (year)	≥50 years (n=109)	47 (28.1)	62 (15.9)	11.044	0.001	0.484 (0.314, 0.746)
Gender	Female (n=182)	52 (31.1)	130 (33.4)	0.276	0.599	1.110 (0.752, 1.639)
Residential area	Urban (n=236)	70 (41.9)	166 (42.7)	0.027	0.868	1.032 (0.715, 1.489)
Marriage	Alone (n=166)	39 (23.4)	127 (32.6)	4.821	0.028	0.629 (0.415, 0.953)
Occupation	Farmer (n=240)	75 (44.9)	165 (42.4)	0.296	0.586	1.665 (1.156, 2.400)
Education	≥ High school (n=214)	58 (34.7)	156 (40.1)	1.424	0.233	1.258 (0.863, 1.836)
MDR-TB risk factors						
Smoking	Yes (n=213)	67 (40.1)	146 (37.5)	0.331	0.565	0.897 (0.619, 1.300)
Alcohol addiction	Yes (n=242)	77 (46.1)	165 (42.4)	0.648	0.421	0.861 (0.598, 1.240)
History of TB disease	Retreatment (n=406)	121 (72.5)	285 (73.3)	0.039	0.844	1.042 (0.693, 1.565)
Medical insurance	Yes (n=544)	161 (96.4)	383 (98.5)	2.326	0.127	2.379 (0.756, 7.487)

TABLE 1. (Continued)

Predictor	Subgroup	Failure n=167 n (%)	Cured n=389 n (%)	χ^2	*P*	OR (95% CI)
Current MDR-TB diagnosis and history of TB disease						
Liver protective drugs	Yes (n=178)	62 (37.1)	116 (29.8)	2.865	0.091	0.731 (0.499, 1.073)
Irregular treatment	Yes (n=116)	59 (35.3)	57 (14.7)	30.254	<0.001	0.314 (0.206, 0.480)
AFB smear month 0 (sputum grading)	High (>+++, n=192)	67 (40.1)	125 (32.1)	3.296	0.069	0.707 (0.485, 1.029)
Lesions in the pulmonary lobe month 0	≥3 (n=395)	140 (83.8)	255 (65.6)	18.978	<0.001	0.367 (0.231, 0.583)
Cavities month 0	Yes (n=321)	114 (68.3)	207 (53.2)	10.845	0.001	0.529（0.361, 0.775)
Time from TB diagnosis to MDR-TB diagnosis	≥1 year (n=271)	93 (55.7)	178 (45.8)	4.612	0.032	0.671 (0.466, 0.967)
Time from MDR-TB diagnosis to treatment	≥1 year (n=64)	38 (22.8)	26 (6.7)	29.625	<0.001	0.243 (0.142, 0.416)
Time from TB diagnosis to MDR-TB diagnosis	≥1 year (n=302)	108 (64.7)	194 (49.9)	10.313	0.001	0.544 (0.374, 0.790)
Comorbidities						
Diabetes	Yes (n=16)	7 (4.2)	9 (2.3)	1.474	0.224	0.541 (0.198, 1.478)
Hypertension	Yes (n=80)	28 (16.8)	52 (13.4)	1.131	0.288	0.766 (0.465, 1.263)
COPD	Yes (n=36)	12 (7.2)	24 (6.2)	0.199	0.655	0.849 (0.414, 1.741)
Malignancy	Yes (n=4)	3 (1.2)	2 (0.5)	0.764	0.382	0.283 (0.049, 1.707)
Clinical laboratory indicators at the beginning of treatment for MDR-TB cases						
Leukocytes	Above normal (n=45)	22 (13.2)	23 (5.9)	8.281	0.004	0.414 (0.224, 0.766)
Platelets	Below normal (n=122)	46 (27.5)	76 (19.5)	4.375	0.036	0.639 (0.419, 0.974)
Red blood cells	Below normal (n=14)	2 (1.2)	12 (3.1)	1.695	0.193	2.626 (0.581, 11.865)
Urinary protein	Above normal (n=61)	20 (12.0)	41 (10.5)	0.247	0.619	0.866 (0.491, 1.529)
Erythrocyte sedimentation rate	Above normal (n=266)	116 (69.5)	150 (38.6)	44.709	<0.001	0.276 (0.187, 0.770)
Drug resistance at the beginning of treatment for MDR-TB cases						
Ethambutol resistance	Yes (n=161)	53 (31.7)	108 (27.8)	0.897	0.344	0.827 (0.557, 1.226)
Streptomycin resistance	Yes (n=301)	101 (60.5)	200 (51.4)	3.867	0.049	0.692 (0.478, 0.999)
Pyrazinamide resistance	Yes (n=254)	73 (43.7)	181 (46.5)	0.374	0.551	1.121 (0.778, 1.614)
Kanamycin resistance	Yes (n=30)	10 (6.0)	20 (5.1)	0.164	0.684	3.095 (1.433, 6.686)
Ofloxacin resistance	Yes (n=89)	46 (27.5)	43 (11.1)	23.633	<0.001	0.327 (0.206, 0.521)
Sputum bacteria and imaging indicators in intensive phase of the treatment						
Sputum culture month 1	Positive (n=381)	144 (86.2)	237 (60.9)	34.681	<0.001	0.716 (0.650, 0.789)
Sputum culture month 2	Positive (n=315)	125 (74.9)	190 (48.8)	80.478	<0.001	0.731 (0.657, 0.813)
Sputum culture month 3	Positive (n=295)	137 (82.0)	158 (40.6)	7.302	0.007	0.605 (0.540, 0.679)
Sputum culture month 6	Positive (n=215)	102 (61.1)	113 (29.0)	16.085	<0.001	0.649 (0.566, 0.775)
Lesion absorption month 6	Absorbed (n=296)	75 (44.9)	221 (56.8)	6.649	0.011	1.156 (1.033, 1.292)
Cavity closure month 6	Absorbed (n=214)	53 (31.7)	161 (41.4)	4.597	0.032	1.129 (1.014, 1.256)
Drugs used during treatment procession						
Ofloxacin	Yes (n=393)	103 (61.7)	290 (74.6)	9.344	0.002	1.820 (1.237, 2.679)
Para-aminosalicylic acid	Yes (n=283)	72 (43.1)	211 (54.2)	5.789	0.016	1.564 (1.085, 2.254)
Pyrazinamide	Yes (n=469)	133 (79.6)	336 (86.4)	4.015	0.045	1.621 (1.008, 2.607)
Moxifloxacin	Yes (n=105)	41 (24.6)	64 (16.5)	5.002	0.025	0.605 (0.389, 0.942)
Kanamycin	Yes (n=8)	5 (3.0)	3 (0.8)	4.071	0.044	0.252 (0.060, 1.066)
Ethionamide	Yes (n=10)	4 (2.4)	6 (1.5)	0.481	0.488	0.638 (0.178, 2.292)
Clofazimine	Yes (n=7)	2 (1.2)	5 (1.3)	0.007	0.932	1.074 (0.206, 5.592)
Isoniazid	Yes (n=79)	20 (12.0)	59 (15.2)	0.976	0.323	1.314 (0.763, 2.262)
Clarithromycin	Yes (n=27)	9 (5.4)	18 (4.6)	0.147	0.702	0.852 (0.375, 1.937)
Rifapentine	Yes (n=45)	9 (5.4)	36 (9.3)	2.347	0.126	1.790 (0.842, 3.806)
Pasniazid	Yes (n=3)	1 (0.6)	2 (0.5)	0.016	0.901	0.858 (0.077, 9.527)

Abbreviation: MDR-TB=multi-drug resistant tuberculosis; TB=tuberculosis; AFB=acid-fast bacilli; COPD=chronic obstructive pulmonary disease; CI=confidence interval; OR=odds ratio.

TABLE 2. Predictors for favorable MDR-TB treatment outcome using multivariate analysis.

Variable	*β*	SE	Wald χ^2	*df*	*P*	OR (95% CI)
Age	−0.589	0.279	4.470	1	0.034	0.555 (0.321, 0.958)
Irregular treatment	−0.928	0.271	11.698	1	0.001	0.395 (0.232, 0.673)
Time of MDR-TB diagnosis to treatment	−1.168	0.341	11.719	1	0.001	0.311 (0.159, 0.607)
Erythrocyte sedimentation rate	−1.215	0.247	24.286	1	<0.001	0.297 (0.183, 0.481)
Ofloxacin resistance	−1.117	0.295	14.324	1	<0.001	0.327 (0.184, 0.584)
Sputum culture month 3	−1.894	0.268	50.091	1	<0.001	0.151 (0.089, 0.254)
Lesion in the pulmonary lobe month 0	−0.588	0.295	3.967	1	0.046	0.556 (0.312, 0.991)
Cavity count month 0	−1.697	0.324	27.384	1	<0.001	0.183 (0.097, 0.346)
Cavity closure month 6	1.649	0.315	27.347	1	<0.001	5.202 (2.804, 9.652)

Abbreviation: MDR-TB=multi-drug resistant tuberculosis; SE=standard error; df=degree of freedom; CI=confidence interval; OR=odds ratio.

DISCUSSION

The findings of the study indicated that a range of risk factors were associated with poor treatment outcomes in 23 sentinel hospitals in China. Risk factors in the intensive treatment phase involved irregular treatment, pulmonary cavity and a persistent positive culture in month 6. Patients at high risk need to be given more attention by physicians to help identify patients with poor responses to treatment, so physicians can adjust the treatment plan to improve cure rates.

Etiological examination has always been the primary means of evaluating the MDR-TB treatment outcome (*4*–*5*). Sputum negative conversion is considered a reliable indicator of the loss of bacterial infectivity. Bacterial changes (change to be negative) in the sputum during treatment are a critical indicator for find patients with poor outcomes in an early stage. In addition, dynamic changes in CT findings have shown that cavities non-closure on chest CT performed at month 6 of treatment was highly predictive of treatment failure. These findings were consistent with evidence that the presence and extent of cavities at initiation were a risk factor for unfavorable treatment outcomes (*5*).

This study was subject to some limitations: 1) Some biomarkers (specific proteins and genes related to the prognosis of MDR-TB) were not included. 2) We estimated only some lung features, whereas the pathological location of the lesion, ground glass shadows, and nodules may give additional clinical significance. Hence, a large-scale multi-centers prospective cohort study based on multi-dimensional information should be conducted in future.

In conclusion, our findings showed that the first 6 months are critical in reducing an unfavorable treatment outcome. The findings implied that physicians should pay special attention to the dynamic changes of the disease at the intensive stage. Regular testing of bacteria in sputum should be performed every month in the first six months at the CDC or a designated hospital, and a CT examination should be carried out to evaluate the therapeutic effects in the early stage. These steps can optimize the treatment plans to improve the outcomes for MDR-TB patients.

Conflicts of interest: No conflicts of interest.

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Vital Surveillances

Long-Term Trend Analysis of Major Human Helminth Infections — Guangdong Province, China, 1988–2021

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ABSTRACT

Introduction: Although helminth infections threaten millions of people worldwide, the spatiotemporal characteristics remain unclear across China. This study systematically describes the spatiotemporal changes of major human helminth infections and their epidemiological characteristics from 1988 to 2021 in Guangdong Province, China.

Methods: The survey data in Guangdong Province were primarily obtained from 3 national surveys implemented during 1988–1992, 2001–2004, and 2014–2016, respectively, and from the China Information System for Disease Control and Prevention during 2019–2021. A modified Kato-Katz technique was used to detect parasite eggs in collected fecal samples.

Results: The overall standardized infection rates (SIRs) of any soil-transmitted helminths (STH) and *Clonorchis sinensis* decreased from 65.27% during 1988–1992 to 4.23% during 2019–2021. In particular, the SIRs of STH had even more of a decrease, from 64.41% during 1988–1992 to 0.31% during 2019–2021. The SIRs of *Clonorchis sinensis* in the 4 surveys were 2.40%, 12.17%, 5.20%, and 3.93%, respectively. This study observed different permutations of gender, age, occupation, and education level on the SIRs of helminths.

Conclusions: The infection rate of STH has substantially decreased. However, the infection rate of *Clonorchis sinensis* has had fewer changes, and it has become the dominant helminth.

Parasitic diseases are diseases threatening billions of people's health worldwide (*1*). There are 14 major parasitic diseases found in China, of which the top 5 are ascariasis, hookworm, trichuriasis, clonorchiasis, and paragonimiasis: all of which are infected through helminths (*2*). Notably, human helminthic infections of public health importance mainly include soil-transmitted helminths (*Ascaris lumbricoides*, hookworm, and *Trichuris trichiura*) and *Clonorchis sinensis*, which have caused a tremendous burden of diseases (*3*–*4*). It was estimated that the prevalence rates of soil-transmitted helminths caused by *Ascaris lumbricoides*, *Trichuris trichiura*, and hookworm reached 53.6% in the early 1990s, and decreased to 19.6% in the early 2000s based on national surveys (*3*); these surveys also revealed that there were 12.49 million individuals infected with *Clonorchis sinensis* across China (*4*). Guangdong Province had the highest prevalence of *Clonorchis sinensis* across China; the standardized infection rates (SIRs) in 1990 and 2003 were 2.1% and 6.2%, respectively, while the SIR was 17.5% in the endemic area (*4*). Moreover, the prevalence of any soil-transmitted helminths in Guangdong Province during 2001–2004 was 9.0% (*5*), which was higher than in many other provinces.

Chinese governments have adopted integrated control strategies to combat parasitic infection in recent decades (http://www.gov.cn/gzdt/2006-03/30/content_240456.htm). Ongoing socioeconomic development; continuous improvements in living standards, clean water, and sanitation; and greater hygiene have also substantially contributed to the reduction of parasitic infections. Several studies have summarized the efforts and effectiveness of controlling parasitic infection in China (*4*,*6*–*7*). However, there are several research gaps in previous studies: 1) most of them were based on a single or few parasites; 2) data used in those studies were from a single or few cities; and 3) the studied time spans were narrow. For example, in a study that investigated the transmission route and epidemiological characteristics of *Clonorchis sinensis* infection in Shenzhen, Guangdong Province

(*6*), Deng et al. only described the epidemic situation and prevention and control strategies in endemic areas of clonorchiasis in Guangdong Province from 1988 to 2015 (*7*). As a result, these studies did not systematically describe the temporal and spatial changes of major human helminth infections in China in the past few decades or comprehensively evaluate the efficacy of prevention and control strategies on parasitic infections. Understanding the spatiotemporal changes of major human helminth infections could help to identify the most affected regions and vulnerable people, as well as provide valuable information for the government to implement targeted prevention and control measures.

To fill in the above research gaps, this study analyzed the survey data Guangdong Province collected during 1988–1992, 2001–2004, 2014–2016, and 2019–2021, respectively, to systematically describe the spatiotemporal changes of major human helminth infections and their epidemiological characteristics over the past 3 decades, as well as investigate the overall effectiveness of prevention and control strategies.

METHODS

Survey Sites and Objects

The first 3 surveys from Guangdong Province used in this study were national surveys. In each survey, a stratified cluster random sampling method was used to select the survey sites and objects (*4*,*8*). Briefly on this, Guangdong Province was first divided into 4 regions (Supplementary Table S1, available in http://weekly.chinacdc.cn/) according to its geographical location and level of socioeconomic development. Second, all counties in each region were divided into high, medium, and low categories according to the unified economic level (per capita annual net income of farmers), and then randomly selected in each category. Each selected county was further divided into several groups according to topography, and all townships in each group were divided into high, medium, and low economic levels, which were then randomly selected. Finally, in each recruited township, survey sites (village or community) were randomly selected (Supplementary Tables S1–S2, available in http://weekly.chinacdc.cn/). Local residents and immigrants who have lived in the area for more than 6 months were recruited, but residents who have been out of the survey sites for more than 6 months were excluded.

The data used for the fourth survey from Guangdong Province were obtained from the China Information System for Disease Control and Prevention. Briefly, 10 monitoring counties were selected each year from 2019 to 2021, and 5 monitoring sites (village or community) were selected in each county (Supplementary Tables S1–S2).

Detection of Helminth Eggs in Feces

All 4 surveys used the modified Kato-Katz technique to detect the helminth (*Ascaris lumbricoides*, hookworm, *Trichuris trichiura*, and *Clonorchis sinensis*) eggs in collected fecal samples (*8*) (Supplementary Materials, available in http://weekly.chinacdc.cn/). Meanwhile, a questionnaire was used to investigate the general information of each object.

Collection of Socioeconomic Information

To examine the influence of socioeconomic development on parasitic infection, this study also collected several socioeconomic and health-related variables across Guangdong Province from recent decades (Supplementary Figure S1, available in http://weekly.chinacdc.cn/).

Statistical Analysis

The crude infection rate was calculated by dividing the number of infections by the total number of people surveyed. This study further used the sixth census data (in 2010) of Guangdong Province to calculate the SIRs of helminths by gender and age, and applied the Cochran-Armitage trend test to assess time trends. The rates were compared either by Pearson's χ^2 test or Fisher's exact test. All analyses were performed using R software (version 4.0.2, R Foundation for Statistical Computing, Vienna, Austria).

Ethics Statement

The surveys were approved by the Ethics Committee of both China CDC and Guangdong CDC. All surveyed persons provided their written informed consent, and all underage children obtained the informed consent of their guardians.

RESULTS

General Characteristics of Survey Objects

A total of 61,517, 26,363, 12,401, and 31,916 people were investigated in the 4 surveys, respectively.

Out of them, the male-to-female ratios in all 4 surveys were around 1∶1. People aged below 20 years were about 40% in the 4 surveys, and people aged over 60 years were about 10%. The percentages of farmers in the 4 surveys were 51.4%, 42.0%, 35.1%, and 26.4%, respectively. In the second (2001–2004), third (2014–2016), and fourth survey (2019–2021), 85.5%, 75.3%, and 67.0% of objects had less than 10 years of education (Table 1).

Spatiotemporal Changes of the SIRs of Helminths

The overall SIRs of soil-transmitted helminths (STH) and *Clonorchis sinensis* decreased from 65.27% in 1988–1992 to 26.17% in 2001–2004, 7.47% in 2014–2016, and 4.23% in 2019–2021 (P<0.001 for trend test). Of these, the SIRs of any soil-transmitted helminths decreased from 64.41% in 1988–1992 to 15.10% in 2001–2004, 2.29% in 2014–2016, and

TABLE 1. General characteristics of survey objects in Guangdong Province, China.

Demographic characteristics	No. of survey objects (*n*, %)				χ^2	*P*
	1st (1988–1992)*	2nd (2001–2004)†	3rd (2014–2016)§	4th (2019–2021)¶		
Total	61,517 (100.0)	26,363 (100.0)	12,401 (100.0)	31,916 (100.0)	−	−
Gender						
Male	29,004 (47.1)	13,126 (49.8)	6,165 (49.7)	15,478 (48.5)	66.36	<0.001
Female	32,513 (52.9)	13,237 (50.2)	6,236 (50.3)	16,438 (51.5)		
Age (years)						
<10	15,674 (25.5)	5,297 (20.1)	2,264 (18.2)	6,843 (21.4)		
10–	11,926 (19.4)	5,570 (21.1)	1,704 (13.7)	4,125 (12.9)		
20–	8,780 (14.3)	2,698 (10.2)	1,190 (9.6)	2,571 (8.1)		
30–	9,953 (16.2)	4,491 (17.0)	1,831 (14.8)	5,395 (16.9)	4,773.40	<0.001
40–	5,809 (9.4)	3,576 (13.6)	1,858 (15.0)	4,406 (13.8)		
50–	4,683 (7.6)	2,465 (9.4)	1,656 (13.4)	3,897 (12.2)		
60–	3,172 (5.2)	1,409 (5.4)	1,230 (9.9)	2,930 (9.2)		
70–	1,247 (2.0)	690 (2.6)	473 (3.8)	1,357 (4.3)		
80–	273 (0.4)	167 (0.6)	195 (1.6)	392 (1.2)		
Occupation						
Manual worker	2,435 (4.0)	1,147 (4.4)	920 (7.4)	2,996 (9.4)		
Farmer	31,640 (51.4)	11,064 (42.0)	4,353 (35.1)	8,417 (26.4)		
Businessman	128 (0.2)	420 (1.6)	532 (4.3)	431 (1.3)		
Government official and clerk	526 (0.9)	233 (0.9)	305 (2.5)	1,098 (3.4)	16,749.00	<0.001
Medical staff and teacher	145 (0.2)	490 (1.9)	319 (2.6)	1,749 (5.5)		
Student	13,110 (21.3)	7,830 (29.6)	2,609 (21.0)	7,360 (23.1)		
Preschooler	10,793 (17.5)	2,756 (10.4)	1,368 (11.0)	3,668 (11.5)		
Others	2,740 (4.5)	2,423 (9.2)	1,995 (16.1)	6,197 (19.4)		
Education (years)						
No formal education	−	4,466 (16.9)	1,699 (13.7)	4,315 (13.5)		
1–9	−	18,090 (68.6)	7,635 (61.6)	17,089 (53.5)		
10–12	−	3,207 (12.2)	2,032 (16.4)	5,897 (18.5)	3,631.60	<0.001
≥13	−	552 (2.1)	1,032 (8.3)	4,615 (14.5)		
Missing	−	48 (0.2)	3 (0.0)	0 (0.0)		

*: The first survey was conducted during 1988–1992.
†: The second survey was conducted during 2001–2004.
§: The third survey was conducted during 2014–2016.
¶: The fourth survey was conducted during 2019–2021.
−: Unavailable.

0.31% in 2019–2021 (P<0.001 for trend test). However, the SIRs of *Clonorchis sinensis* increased from 2.40% in the first survey to 12.17% in the second survey, then decreased to 5.20% in the third survey and 3.93% in the fourth survey (P<0.001 for trend test) (Figure 1). Further, among the infected objects in 4 surveys, infection of single worm species was dominant, accounting for 57.73%, 87.10%, 98.99%, and 99.58%, respectively, followed by coinfection with two worm species (33.55%, 12.14%, 1.01%, and 0.42%) (Supplementary Table S3, available in http://weekly.chinacdc.cn/).

In all 4 surveys, there were differences in the spatial distribution of the overall SIRs of major human helminths (P<0.001). The first survey showed higher SIRs of helminths, particularly of STH, in eastern regions such as Chaozhou (88.05%) and Shantou (84.29%) cities. The SIR of *Clonorchis sinensis* also largely varied across cities (P<0.001), with higher rates in Foshan (16.37%) and Guangzhou (7.49%) cities, and lower rates in cities such as Maoming (0.00%), Shanwei (0.00%), and Zhanjiang (0.00%). The second survey showed higher overall SIRs in some cities, including Foshan (55.58%), and Zhongshan (55.50%). The SIRs of *Clonorchis sinensis* were also higher in Foshan (50.04%) and Zhongshan (43.84%), while the SIR of STH was higher in Maoming (46.89%). The third survey showed that Zhongshan (34.39%) had the highest overall SIRs of helminths, followed by Heyuan (20.74%), and *Clonorchis sinensis* was the most major human helminth in most cities (e.g., Zhongshan, Heyuan, Zhaoqing, and Qingyuan). The fourth survey showed that Heyuan, Jiangmen, and Foshan had both higher overall SIRs (13.58%, 12.20%, and 9.74%) and *Clonorchis sinensis* SIR (13.43%, 12.08%, and 9.58%), while the SIR of STH in Qingyuan (1.71%) was the highest (Figure 2 and Supplementary Table S4, available in http://weekly.chinacdc.cn/).

Modification of Demographic Characteristics on the Infection of Helminths

In the first survey, the overall SIRs of 4 major helminths were similar in people aged under 70 years, and the SIRs in females were slightly higher than in males (P<0.001). However, in the second and third

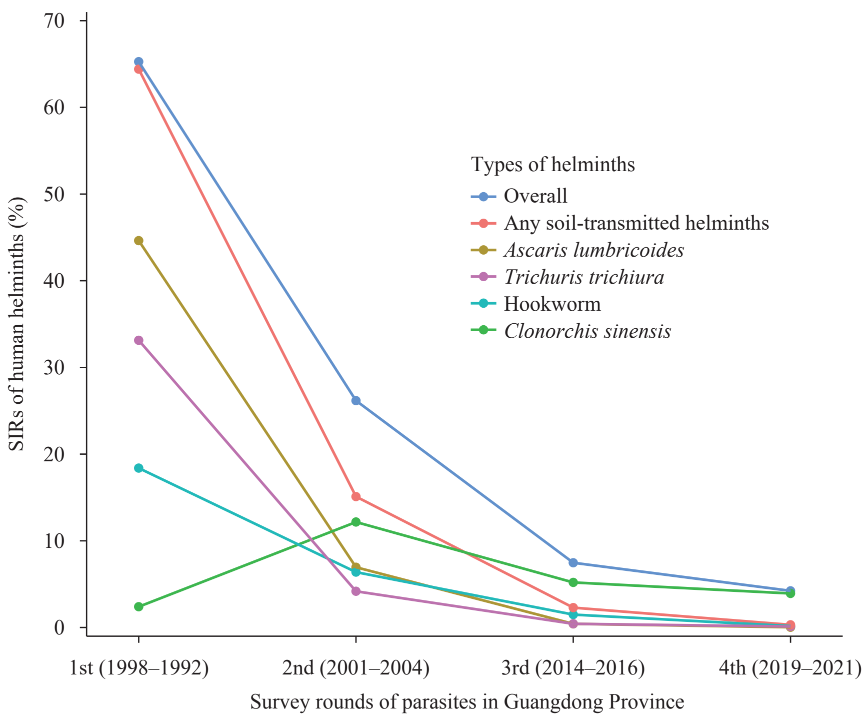

FIGURE 1. SIRs of human helminths in the four surveys in Guangdong Province, China.
Note: Any soil-transmitted helminths: Infected with at least one of *Ascaris lumbricoides*, hookworm, and *Trichuris trichiura*. 1st (1998–1992): The first survey was conducted during 1988–1992. 2nd (2001–2004): The second survey was conducted during 2001–2004. 3rd (2014–2016): The third survey was conducted during 2014–2016. 4th (2019–2021): The fourth survey was conducted during 2019–2021.
Abbreviation: SIRs=standardized infection rates.

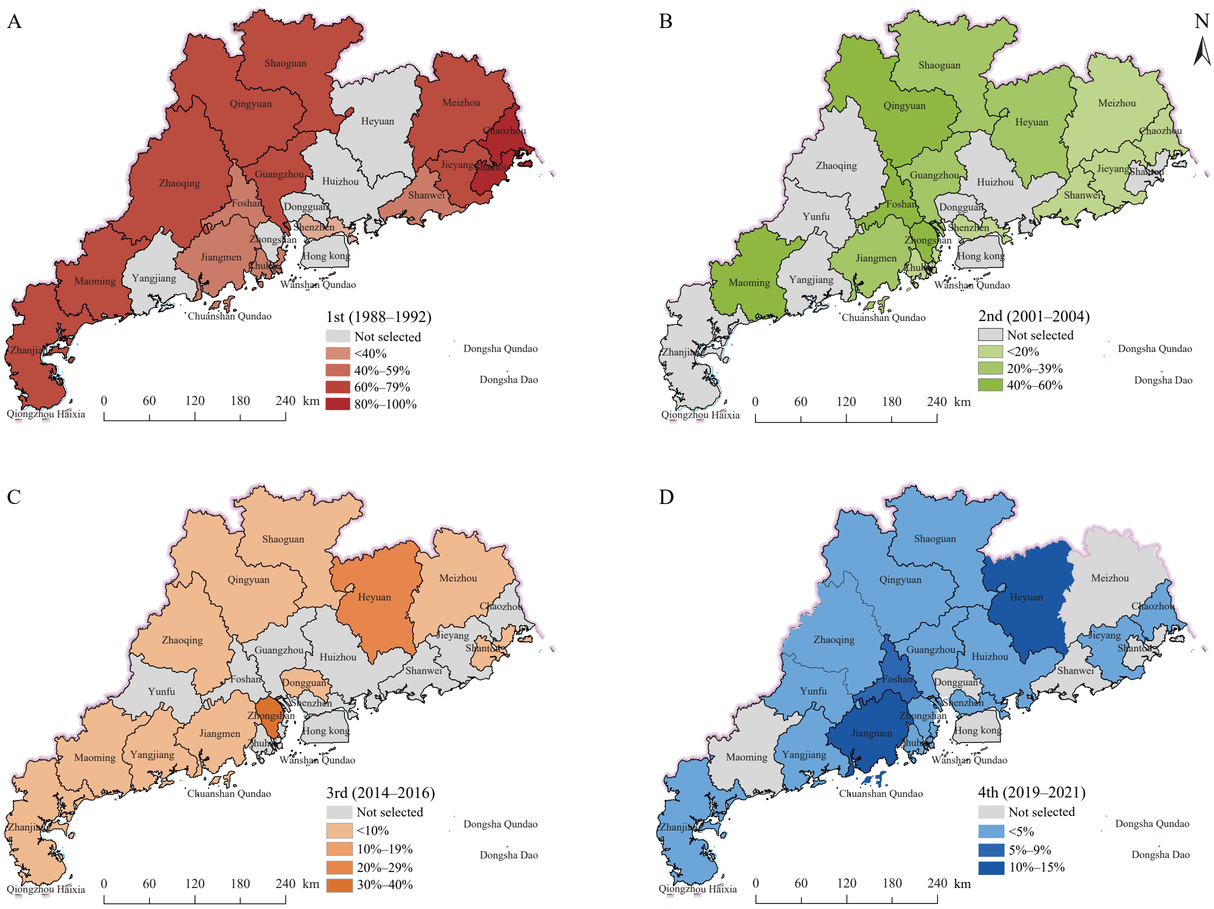

FIGURE 2. Spatial distribution of overall SIRs of human helminths in four surveys in Guangdong Province, China. (A) Spatial distribution of overall SIRs in the first survey. (B) Spatial distribution of overall SIRs in the second survey. (C) Spatial distribution of overall SIRs in the third survey. (D) Spatial distribution of overall SIRs in the fourth survey.
Note: During the first survey, Yunfu was a county that belonged to the administrative division of Zhaoqing City.
Abbreviation: SIRs=standardized infection rates.

surveys, the overall SIRs of helminths inclined in correlation with age and reached their peak in the group aged 50–60 years. In addition, males had slightly higher SIRs than females among most age groups. In the fourth survey, the overall SIRs of 4 major helminths were similar in people aged under 30 years but varied widely in people aged between 30 and 60 years, with males having higher SIRs than females (P<0.001). Longitudinal comparisons of the 4 surveys showed that STH were the major infections among all age groups in the first survey, and then substantially decreased in the next 3 surveys. In contrast, *Clonorchis sinensis* was the dominant helminth among adults in the second, third, and particularly in the fourth survey. The SIR of *Clonorchis sinensis* was higher in males than in females (P<0.001). Moreover, in the second survey, most infections of *Clonorchis sinensis* were found in adults aged over 20 years and, regardless of gender, the SIRs were higher among the groups aged 50–60 years (male: 21.66%, female: 13.89%) and 70–80 years (male: 22.92%, female: 15.42%). Meanwhile, *Clonorchis sinensis* infection was mainly found in people aged 40–60 years in the third and fourth surveys (Figure 3).

The overall SIRs of helminths were higher in farmers and manual workers in the first 3 surveys, while the overall SIR of government officials and clerks was higher in the fourth survey. However, the overall SIRs substantially decreased in most occupations (e.g., manual workers, farmers, businessmen, and students) across the 4 surveys. Similar patterns were found for each STH. The SIRs of *Clonorchis sinensis* were higher in manual workers, farmers, and businessmen in the 4 surveys (Supplementary Table S5, available in http://weekly.chinacdc.cn/), which indicates that the SIRs increased in the second survey and then decreased in the third and fourth surveys.

Moreover, the second survey showed that the overall

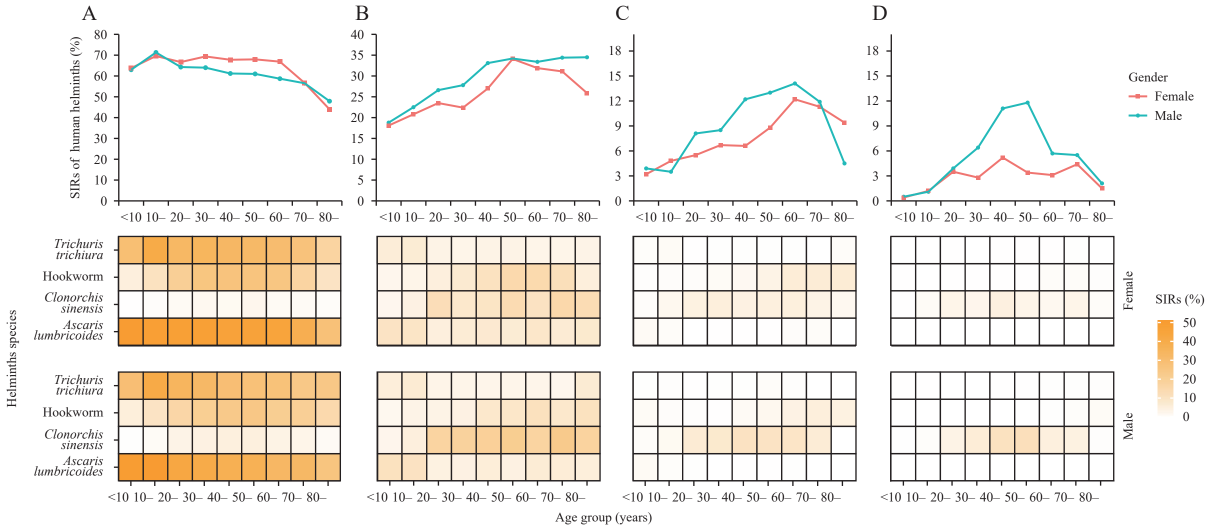

FIGURE 3. SIRs of human helminths by gender and age in four surveys in Guangdong Province, China. (A) The first survey was conducted during 1988–1992. (B) The second survey was conducted during 2001–2004. (C) The third survey was conducted during 2014–2016. (D) The fourth survey was conducted during 2019–2021.
Note: The shades of color of the box in the picture represent the SIRs of human helminths.
Abbreviation: SIRs=standardized infection rates.

SIRs of the helminths and the SIRs of STH substantially decreased from lower education groups to higher education groups. However, the SIRs of *Clonorchis sinensis* were higher in the groups with 1–12 years of education in the second survey and inclined with increases in education levels in the third and fourth surveys. Meanwhile, in each education group, the dominant helminth infection source changed from STH infection in the second survey to *Clonorchis sinensis* infection in the third and fourth surveys (Supplementary Table S6, available in http://weekly.chinacdc.cn/).

CONCLUSIONS

In the early years of China, due to lessened socioeconomic development, poor healthcare systems and facilities (Supplementary Figure S1), and people's unhealthy hygiene habits, parasitic infection was a severe public health challenge (*9*). The Chinese government has made a great effort to prevent and control these health-threatening parasitic diseases (*2*). In Guangdong Province, the prevention and control work can be divided into 3 phases (Supplementary Figure S2, available in http://weekly.chinacdc.cn/), and various control measures have been put forward and implemented. These measures improved people's mode of production and increased awareness of protection, thus substantially reducing the infection of parasites — particularly soil-transmitted helminths.

However, the epidemiological characteristics of *Clonorchis sinensis* infection were substantially different from STH. Compared with the first survey, the infection rate of *Clonorchis sinensis* increased in the second survey, which is consistent with the national infection rate (*4*). This phenomenon can be explained by several reasons. First, humans are mainly infected with *Clonorchis sinensis* by eating raw freshwater fish. Guangdong Province is in subtropical areas, and freshwater aquaculture is an important part of its industry (*10*), which gives people more opportunities to ingest food containing raw fish. Second, in earlier years in Guangdong Province, particularly in rural areas, simple lavatories without sanitary treatment were usually built adjacent to fishponds. Human excrement containing *Clonorchis sinensis* eggs was directly excreted into the ponds and contaminated the snails and fish (*11*). Third, some wrong perceptions about clonorchiasis were popular among people. For example, one myth promulgated the claim that drinking wine while eating raw freshwater fish could prevent the infection of *Clonorchis sinensis* (*12*). Fourth, the prevalence of infection is affected by the cumulative effect of long-term survival of *Clonorchis sinensis*. People infected with *Clonorchis sinensis* demonstrate appearance of the disease in a chronic process over time, and the symptoms are mostly mild and atypical in the early stages, so it is easy to be ignored by people; alongside this, the public consciousness in these areas around taking the initiative to seek medical treatment is not strong, often resulting in long-term accumulation (*7*). In addition, socio-economic development is also a key factor in the spread of *Clonorchis sinensis*. The improvement of China's economic level has provided the material conditions and convenience necessary for the expansion of freshwater aquaculture and people's consumption of raw freshwater fish (*13*). Therefore, more people eat raw freshwater fish when their income increases — which explains why the infection rate of *Clonorchis sinensis* increased sharply in the second survey during a period of economic growth (*7*).

The infection rate of *Clonorchis sinensis* slightly decreased in the third and fourth surveys compared with the second survey, which was related to the comprehensive prevention and cure measures implemented after 2000. For example, most lavatories nearby fishponds were removed, and the environments of fishponds were reconstructed to be more hygienic. However, due to deeply rooted traditions, people in many places have kept their traditional food preparation techniques despite economic development. Therefore, the infection rate of *Clonorchis sinensis* remained at a high level even in people with higher education levels.

This study further found different effects of gender, age, and occupation on the infection rate of helminths. In the early years (the 1980s–1990s) with less socioeconomic development, women and children were more vulnerable to parasites. However, with socioeconomic and healthcare system development, more efforts were made to protect women's and children's health (*14*), and their infection risks continually decreased in the second, third, and fourth surveys. By contrast, males had more exposure to parasites and a higher risk of infection due to their occupations and dietary habits (having more social activities).

These findings suggest that although most parasitic diseases have been successfully controlled or eliminated, sustained work of prevention and control is also needed, especially on clonorchiasis. A series of measures are recommended by the CDC of the USA, and the WHO, including health education, health promotion, chemotherapy, and environmental reconstruction (*15*). Health education and promotion programs could improve people's knowledge regarding the health impacts of clonorchiasis. More attention should be paid to the safety of freshwater fish, and those infected fish should be barred from markets. In addition, more research is needed to estimate the disease burden of clonorchiasis at national and regional levels, which could help make prevention and control policies better.

There are several limitations to this study. First, this study did not collect individual information on dietary habits, behaviors, living environments, and income levels, and did not investigate their impacts on the infection of helminths. Second, education information was not collected in the first survey. As a result, we did not describe the modification of education levels on the infection rate of helminths in the first survey. Third, although the Kato-Katz technique is a relatively simple and low-cost method recommended by the WHO, it may miss low-intensity infections, leading to an underestimation of the actual infection rate.

In conclusion, this study evaluated the spatiotemporal changes of major human helminth infections in the past three decades across Guangdong Province. Integrated measures are needed to maintain the low prevalence level of soil-transmitted helminths; meanwhile, more intensified comprehensive measures are urgently needed to prevent and control *Clonorchis sinensis* infection.

Conflicts of interest: No conflicts of interest.

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SUPPLEMENTARY MATERIALS

Collection of Fecal Samples

The surveys in Guangdong Province mainly aimed to investigate the infection of helminths including soil-transmitted helminths (e.g., *Ascaris lumbricoides*, hookworm, and *Trichuris trichiura*) and food-borne trematodes (e.g., *Clonorchis sinensis*). In each survey site, clean fecal bags were distributed to study objects who collected egg-sized and early-rise feces from 8:00 to 9:00 am, and sent the samples to the laboratory for detection.

SUPPLEMENTARY TABLE S1. Number of survey sites in the first, second, third, and fourth surveys in Guangdong Province, China.

Regions in Guangdong Province	1st (1988–1992)		2nd (2001–2004)		3rd (2014–2016)		4th (2019–2021)	
	Cities/ counties	Number of survey sites	Cities/ counties	Number of survey sites	Cities/ counties	Number of survey sites	Cities/ counties	Number of survey sites
North	Shixing	3	Shixing	3	Lechang	3	Shixing	5
	Shaoguan	4	Qingyuan	3	Wengyuan	1	Ruyuan	5
	Yangshan	3	Xingning	3	Lianshan	2	Yuancheng	5
	Liannan	3	−	−	Qingyuan	2	Heping	5
	−	−	−	−	−	−	Longchuan	5
	−	−	−	−	−	−	Qingcheng	5
	−	−	−	−	−	−	Lianzhou	5
	−	−	−	−	−	−	Liannan	5
East	Meizhou	3	Longchuan	3	Longchuan	1	Chaoan	5
	Xingning	4	Chaoan	3	Xingning	1	Jiedong	5
	Fengshun	4	Jiexi	3	Pingyuan	4	−	−
	Dabu	4	Puning	3	Nanao	3	−	−
	Wuhua	4	Luhe	3	Shantou	2	−	−
	Chenghai	4	−	−	−	−	−	−
	Chaozhou	4	−	−	−	−	−	−
	Jieyang	5	−	−	−	−	−	−
	Puning	4	−	−	−	−	−	−
	Luhe	3	−	−	−	−	−	−
West	Kaiping	4	Gaozhou	3	Xinyi	4	Xuwen	5
	Taishan	1	Dianbai	3	Huazhou	3	Chikan	5
	Yunan	4	−	−	Yangxi	3	Luoding	5
	Fengkai	4	−	−	Wuchuan	1	Yangchun	5
	Suixi	4	−	−	Zhanjiang	2	−	−
	Lianjiang	4	−	−	Lianjiang	3	−	−
	Wuchuan	4	−	−	−	−	−	−
	Gaozhou	4	−	−	−	−	−	−
	Dianbai	4	−	−	−	−	−	−
Pearl River Delta	Zhuhai	4	Zhuhai	3	Kaiping	2	Huadu	5
	Naihai	4	Foshan	3	Zhongshan	4	Panyu	5
	Panyu	4	Panyu	3	Dongguan	5	Xiangzhou	5
	Huaxian	4	Kaiping	3	Zhaoqing	2	Doumen	5
	Xinhui	5	Xinhui	3	−	−	Jinwan	5
	Luohu	5	Shenzhen	3	−	−	Xinhui	10
	Zhaoqing	4	Zhongshan	3	−	−	Zhongshan	10
	Qingyuan	5	−	−	−	−	Pingshan	5
	−	−	−	−	−	−	Dapeng New Area	5
	−	−	−	−	−	−	Nanshan	5
	−	−	−	−	−	−	Duanzhou	5
	−	−	−	−	−	−	Dinghu	5
	−	−	−	−	−	−	Chancheng	5
	−	−	−	−	−	−	Huidong	5
Total	31	120	17	51	19	48	28	150

−: No survey site was selected.

SUPPLEMENTARY TABLE S2. Number of study objects in selected cities in the first, second, third, and fourth survey in Guangdong Province, China.

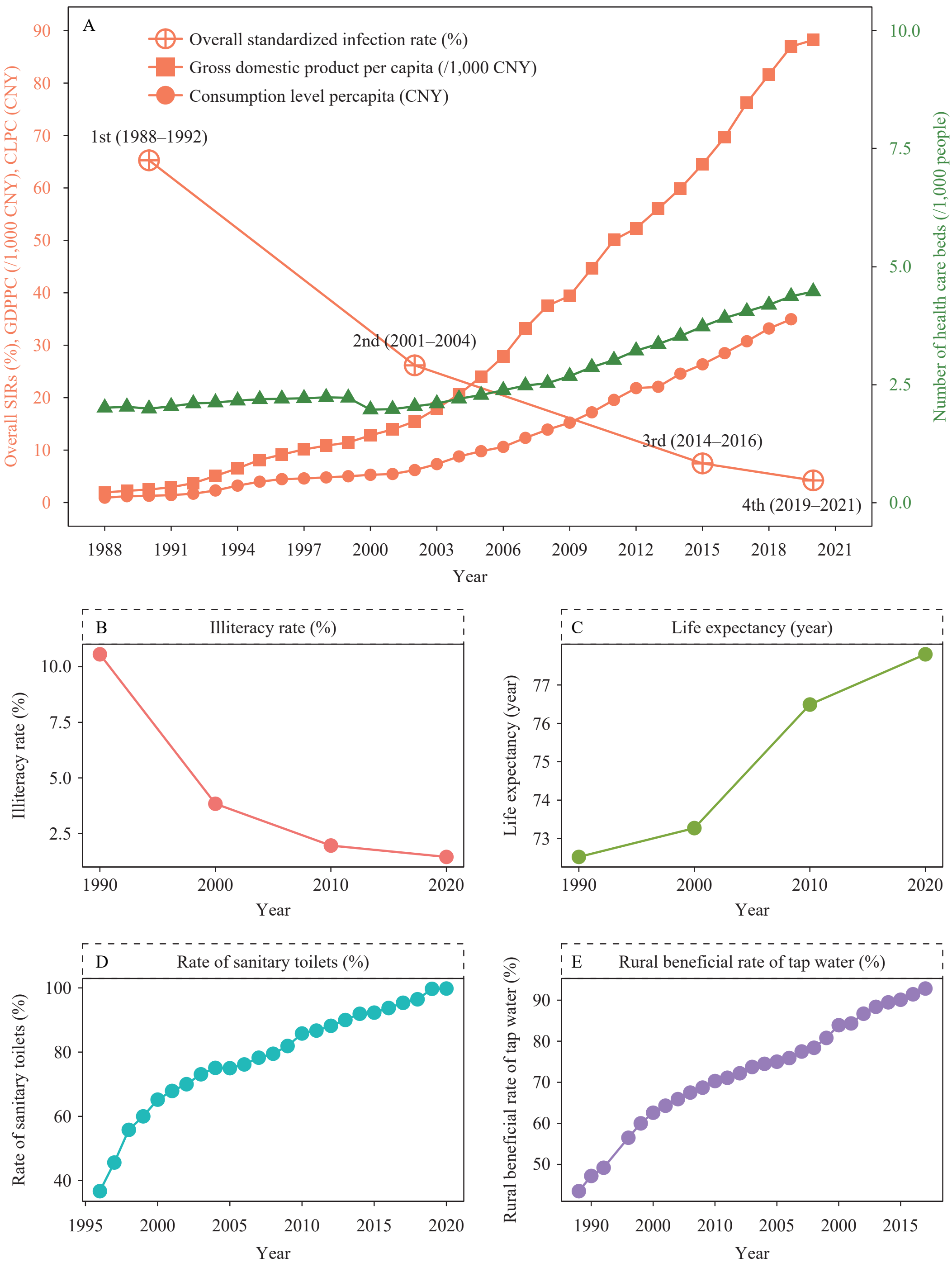
City	Study objects							
	1st (1988–1992)*		2nd (2001–2004)†		3rd (2014–2016)§		4th (2019–2021)¶	
	N	%	N	%	N	%	N	%
Total	61,517	100.0	26,363	100.0	12,401	100.0	31,916	100.0
Chaozhou	2,027	3.3	1,503	5.7	−	−	1,000	3.1
Foshan	2,032	3.3	1,561	5.9	−	−	1,015	3.2
Guangzhou	4,267	6.9	1,583	6.0	−	−	2,034	6.4
Jiangmen	5,108	8.3	3,037	11.5	541	4.4	2,065	6.5
Jieyang	4,569	7.4	3,099	11.8	−	−	1,062	3.3
Maoming	4,118	6.7	3,038	11.5	1,796	14.5	−	−
Meizhou	9,680	15.7	1,663	6.3	1,271	10.2	−	−
Qingyuan	5,735	9.3	1,506	5.7	1,024	8.3	3,131	9.8
Shantou	2,011	3.3	−	−	1,272	10.3	−	−
Shanwei	1,541	2.5	1,624	6.2	−	−	−	−
Shaoguan	3,584	5.8	1,537	5.8	1,033	8.3	2,342	7.3
Shenzhen	2,497	4.1	1,666	6.3	−	−	3,428	10.8
Yunfu	−	−	−	−	−	−	1,077	3.4
Zhanjiang	6,122	10.0	−	−	1,556	12.5	2,188	6.9
Zhaoqing	6,105	9.9	−	−	513	4.1	2,006	6.3
Zhuhai	2,121	3.4	1,494	5.7	−	−	3,076	9.6
Yangjiang	−	−	−	−	769	6.2	1,004	3.1
Zhongshan	−	−	1,500	5.7	1,073	8.7	2,042	6.4
Dongguan	−	−	−	−	1,297	10.5	−	−
Huizhou	−	−	−	−	−	−	1,024	3.2
Heyuan	−	−	1,552	5.9	256	2.1	3,422	10.7

*: The first survey was conducted during 1988–1992, when Yunfu was a county belonged to the administrative division of Zhaoqing City.
†: The second survey was conducted during 2001–2004.
§: The third survey was conducted during 2014–2016.
¶: The fourth survey was conducted during 2019–2021.
−: No survey site was selected.

SUPPLEMENTARY TABLE S3. Proportion of human helminth single infection and coinfection in Guangdong Province, China.

Survey rounds	No. of objects	No. of infections	Infected with only one parasite (%)	Infected with two parasites (%)	Infected with three parasites (%)	Infected with four parasites (%)	Coinfection of parasites (%)		
1st (1988–1992)*	61,517	40,426	57.73	33.55	8.52	0.20	*Ascaris lumbricoides* and *Trichuris trichura* (47.4)	*Ascaris lumbricoides* and hookworm (18.8)	*Ascaris lumbricoides*, hookworm, and *Trichuris trichura* (18.4)
2nd (2001–2004)†	26,363	6,619	87.10	12.14	0.73	0.03	*Ascaris lumbricoides* and *Trichuris trichura* (30.2)	*Ascaris lumbricoides* and hookworm (25.7)	*Clonorchis sinensis*, and hookworm (15.7)
3rd (2014–2016)§	12,401	950	98.99	1.01	0.00	0.00	*Ascaris lumbricoides* and hookworm (43.1)	*Trichuris trichura* and *Clonorchis sinensis* (29.5)	*Trichuris trichura*, and hookworm (12.8)
4th (2019–2021)¶	31,916	1,260	99.58	0.42	0.00	0.00	*Trichuris trichura* and *Clonorchis sinensis* (46.6)	*Trichuris trichura*, and hookworm (33.2)	*Ascaris lumbricoides* and *Trichuris trichura* (20.2)
P for trend**	−	−	<0.001	<0.001	<0.001	<0.001	−	−	−

*: The first survey was conducted during 1988–1992.
†: The second survey was conducted during 2001–2004.
§: The third survey was conducted during 2014–2016.
¶: The fourth survey was conducted during 2019–2021.
**: Cochran-Armitage trend test.
−: Not applicable.



SUPPLEMENTARY FIGURE S1. Temporal change of major socioeconomic and health status during 1988–2021 in Guangdong Province, China. (A) Temporal changes of overall standardized infection rate of human helminths in the four surveys, and gross domestic product per capita (/1,000 CNY), consumption level per capita (CNY), and number of health care beds (/1,000 people) from 1988 to 2021.

(B) Temporal change of illiteracy rate (%) from 1990 to 2020.

(C) Temporal change of life expectancy (year) from 1990 to 2020.

(D) Temporal change of rate of sanitary toilets (%) from 1996 to 2020.

(E) Temporal change of rural beneficial rate of tap water (%) from 1989 to 2020.

Note: (A) Data were collected from Guangdong Statistical Yearbook. (B–C) Data were collected from the 4th to 7th census data of Guangdong Province. (D–E) Data were collected from China Health Statistical Yearbook.

Abbreviation: SIRs=standardized infection rates. GDPPC=gross domestic product per capita. CLPC=consumption level per capita.

SUPPLEMENTARY TABLE S4. SIRs of human helminths in the selected cities/counties in Guangdong Province, China

City	1st (1988–1992)*						2nd (2001–2004)†						3rd (2014–2016)§						4th (2019–2021)¶					
	Total	Soil-transmitted helminths			Any soil-transmitted helminths	*Clonorchis sinensis*	Total	Soil-transmitted helminths			Any soil-transmitted helminths	*Clonorchis sinensis*	Total	Soil-transmitted helminths			Any soil-transmitted helminths	*Clonorchis sinensis*	Total	Soil-transmitted helminths			Any soil-transmitted helminths	*Clonorchis sinensis*
		Ascaris lumbricoides	Hookworm	*Trichuris trichiura*				*Ascaris lumbricoides*	Hookworm	*Trichuris trichiura*				*Ascaris lumbricoides*	Hookworm	*Trichuris trichiura*				*Ascaris lumbricoides*	Hookworm	*Trichuris trichiura*		
Chaozhou	88.05	45.08	40.65	74.62	87.99	2.48	11.15	1.82	2.70	6.18	10.25	1.30	–	–	–	–	–	–	0.00	0.00	0.00	0.00	0.00	0.00
Foshan	56.22	31.98	8.22	30.21	49.56	16.37	55.58	2.35	5.08	2.21	8.91	50.04	–	–	–	–	–	–	9.74	0.12	0.04	0.00	0.16	9.58
Guangzhou	70.72	43.87	22.68	42.83	69.91	7.49	23.01	0.80	3.30	0.54	4.64	19.89	–	–	–	–	–	–	1.26	0.00	0.00	0.03	0.03	1.22
Jiangmen	46.48	23.05	13.06	22.26	44.64	3.35	22.78	2.19	3.24	0.63	5.94	17.42	2.11	0.00	0.00	0.00	0.00	2.11	12.20	0.00	0.00	0.19	0.19	12.08
Jieyang	78.74	38.73	21.73	67.23	78.74	0.02	15.72	2.57	11.12	3.32	15.67	0.05	–	–	–	–	–	–	0.23	0.13	0.00	0.23	0.23	0.00
Maoming	65.47	52.34	24.47	31.57	65.47	0.00	46.90	22.43	19.93	18.86	46.89	0.13	8.96	0.76	7.70	0.37	8.71	0.25	–	–	–	–	–	–
Meizhou	67.38	49.08	17.28	30.99	67.13	0.54	11.71	6.35	3.52	2.61	11.39	0.32	0.55	0.00	0.23	0.06	0.29	0.26	–	–	–	–	–	–
Qingyuan	61.01	51.04	21.68	7.08	59.60	2.29	43.98	28.62	12.06	1.52	36.88	7.88	5.21	0.32	0.00	0.41	0.68	4.58	2.45	0.00	1.44	0.31	1.71	0.74
Shantou	84.29	52.25	8.49	75.19	84.29	0.05	–	–	–	–	–	–	0.06	0.06	0.00	0.00	0.06	0.00	–	–	–	–	–	–
Shanwei	57.24	41.64	27.16	10.36	57.24	0.00	5.68	2.46	3.02	0.73	5.68	0.00	–	–	–	–	–	–	–	–	–	–	–	–
Shaoguan	68.71	57.50	13.05	27.22	65.82	6.96	27.45	16.75	5.16	5.04	24.98	3.24	2.97	0.26	0.82	0.24	1.33	1.64	0.11	0.00	0.04	47.88	0.09	0.00
Shenzhen	38.64	10.65	12.95	23.63	38.52	0.17	3.51	1.26	0.40	0.72	2.31	1.23	–	–	–	–	–	–	1.09	0.00	0.00	0.07	0.07	1.04
Yunfu	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	0.17	0.00	0.07	0.11	0.17	0.00
Zhanjiang	66.61	56.13	20.48	23.44	66.61	0.00	–	–	–	–	–	–	6.61	1.87	2.53	1.85	6.19	0.41	0.15	0.05	0.00	0.11	0.15	0.00
Zhaoqing	68.21	56.75	8.61	30.82	67.93	0.84	–	–	–	–	–	–	9.36	0.00	1.18	0.08	1.27	8.19	1.45	0.00	0.00	0.00	0.00	1.45
Zhuhai	59.89	19.57	26.71	38.21	58.56	3.69	9.39	0.43	3.10	0.78	4.22	5.84	–	–	–	–	–	–	3.23	0.02	0.00	0.05	0.07	3.16
Yangjiang	–	–	–	–	–	–	–	–	–	–	–	–	2.74	0.00	1.89	0.97	2.74	0.00	0.91	0.00	0.00	0.91	0.91	0.00
Zhongshan	–	–	–	–	–	–	55.50	6.02	8.38	7.51	18.68	43.84	34.39	0.00	0.00	0.18	0.18	34.39	4.61	0.15	0.00	0.00	0.15	4.46
Dongguan	–	–	–	–	–	–	–	–	–	–	–	–	0.61	0.00	0.00	0.00	0.00	0.61	–	–	–	–	–	–
Huizhou	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	0.00	0.00	0.00	0.00	0.00	0.00
Heyuan	–	–	–	–	–	–	20.58	2.02	3.52	0.06	5.35	16.18	20.74	0.00	0.00	0.00	0.00	20.74	13.58	0.00	0.04	0.12	0.15	13.43
*P***	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

Note: Any soil-transmitted helminths: Infected with at least one of *Ascaris lumbricoides*, hookworm, and *Trichuris trichiura*.

−: No survey site was selected.

Abbreviation: SIRs=standardized infection rates.

*: The first survey was conducted during 1988–1992.

†: The second survey was conducted during 2001–2004.

§: The third survey was conducted during 2014–2016.

¶: The fourth survey was conducted during 2019–2021.

**: Pearson's χ^2 test.

SUPPLEMENTARY TABLE S5. SIRs of human helminths by occupation in four surveys in Guangdong Province, China.

Occupation	1st (1988–1992)*						2nd (2001–2004)†						3rd (2014–2016)§						4th (2019–2021)¶					
	Total	Soil-transmitted helminths			Any soil-transmitted helminths	*Clonorchis sinensis*	Total	Soil-transmitted helminths			Any soil-transmitted helminths	*Clonorchis sinensis*	Total	Soil-transmitted helminths			Any soil-transmitted helminths	*Clonorchis sinensis*	Total	Soil-transmitted helminths			Any soil-transmitted helminths	*Clonorchis sinensis*
		Ascaris lumbricoides	Hookworm	*Trichuris trichiura*				*Ascaris lumbricoides*	Hookworm	*Trichuris trichiura*				*Ascaris lumbricoides*	Hookworm	*Trichuris trichiura*				*Ascaris lumbricoides*	Hookworm	*Trichuris trichiura*		
Manual worker	41.46	26.98	4.58	26.32	40.29	2.36	26.82	3.21	4.81	2.47	9.21	18.99	8.24	0.22	0.55	0.33	0.88	7.42	3.03	0.04	0.09	0.06	0.20	2.85
Farmer	70.82	47.33	22.68	36.08	70.07	2.36	27.40	7.84	8.50	3.20	15.22	11.68	7.21	0.31	2.19	0.26	2.71	4.54	3.31	0.01	0.37	0.20	0.56	2.76
Businessman	33.47	22.46	1.15	19.69	31.81	1.67	24.93	1.59	4.04	1.90	6.86	19.54	4.32	0.00	0.28	0.08	0.36	3.96	1.91	0.00	0.00	0.00	0.00	1.91
Government official and clerk	33.46	16.33	1.66	15.33	30.42	4.36	15.47	3.93	2.04	0.46	5.61	9.87	5.16	0.00	0.00	0.24	0.24	4.92	8.31	0.00	0.00	0.00	0.00	8.31
Medical staff and teacher	17.82	9.40	1.33	7.10	15.69	2.12	13.59	1.26	1.96	1.64	4.13	9.68	3.52	0.00	0.62	0.00	0.62	2.89	6.12	0.03	0.00	0.08	0.11	6.05
Student	34.15	22.23	7.21	18.33	34.11	1.23	9.33	3.83	1.98	2.63	7.19	2.44	2.05	0.32	0.28	0.21	0.79	1.26	0.97	0.01	0.02	0.03	0.05	0.92
Preschooler	15.92	11.32	1.42	6.92	14.45	1.48	1.62	0.94	0.19	0.43	1.40	0.27	0.30	0.12	0.03	0.05	0.20	0.11	0.05	0.00	0.01	0.01	0.03	0.02
Others	44.05	26.31	6.45	25.82	43.15	1.74	19.90	3.11	4.86	3.63	10.10	10.73	10.01	0.03	0.83	0.29	1.15	8.86	4.53	0.00	0.01	0.02	0.02	4.51
P**	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

Note: Any soil-transmitted helminths: Infected with at least one of *Ascaris lumbricoides*, hookworm, and *Trichuris trichiura*.

Abbreviation: SIRs=standardized infection rates.

*: The first survey was conducted during 1988–1992.

†: The second survey was conducted during 2001–2004.

§: The third survey was conducted during 2014–2016.

¶: The fourth survey was conducted during 2019–2021.

**: Pearson's χ^2 test.

SUPPLEMENTARY TABLE S6. SIRs of human helminths by education level in the second, third and fourth surveys in Guangdong Province, China.

Education (years)	2nd (2001–2004)*						3rd (2014–2016)†						4th (2019–2021)§					
	Total	Soil-transmitted helminths			Any soil-transmitted helminths	*Clonorchis sinensis*	Total	Soil-transmitted helminths			Any soil-transmitted helminths	*Clonorchis sinensis*	Total	Soil-transmitted helminths			Any soil-transmitted helminths	*Clonorchis sinensis*
		Ascaris lumbricoides	Hookworm	*Trichuris trichiura*				*Ascaris lumbricoides*	Hookworm	*Trichuris trichiura*				*Ascaris lumbricoides*	Hookworm	*Trichuris trichiura*		
No formal education	30.28	10.56	10.15	8.96	23.47	7.29	4.12	0.12	0.56	0.06	0.74	3.38	2.69	0.00	0.09	0.01	0.11	2.58
1–9	27.85	7.96	6.97	4.70	16.85	12.18	7.35	0.44	2.17	0.47	3.01	4.38	3.30	0.02	0.20	0.19	0.39	2.91
10–12	26.17	3.08	8.22	2.87	12.72	14.55	6.82	0.32	0.28	0.42	1.03	5.79	5.48	0.04	0.11	0.10	0.24	5.24
≥13	11.00	1.17	2.75	1.52	4.24	7.17	8.95	0.00	0.10	0.15	0.25	8.69	5.45	0.00	0.02	0.04	0.06	5.42
Missing	18.73	2.99	8.94	0.00	11.93	6.80	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
P¶	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

Note: Education information was not investigated in the first survey.

Any soil-transmitted helminths: Infected with at least one of *Ascaris lumbricoides*, hookworm, and *Trichuris trichiura*.

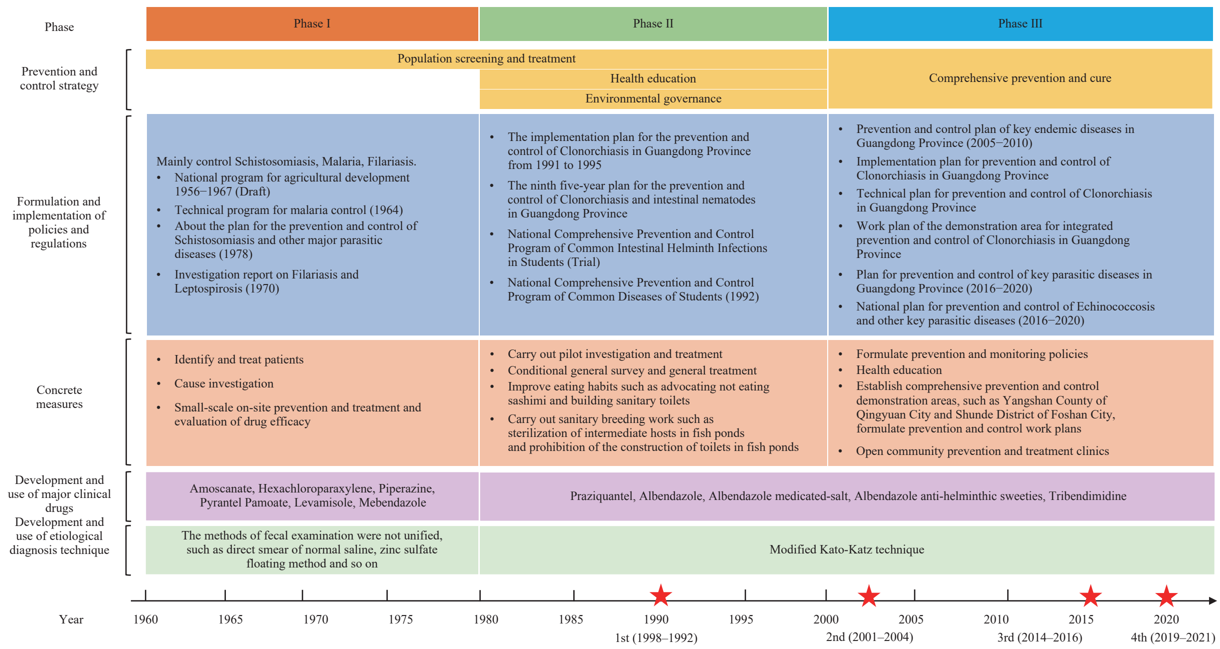
Abbreviation: SIRs=standardized infection rates.

*: The second survey was conducted during 2001–2004.

†: The third survey was conducted during 2014–2016.

§: The fourth survey was conducted during 2019–2021.

¶: Pearson's χ^2 test.



SUPPLEMENTARY FIGURE S2. The comprehensive prevention and control measures on human helminth infections in Guangdong Province, China (*1*–*5*).

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Outbreak Reports

A Poisoning Outbreak Caused by *Anisodus tanguticus* — Maqin County, Qinghai Province, China, July 2021

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Summary

What is already known about this topic?

Anisodus tanguticus belongs to the Solanaceae family. The plant is toxic due to the tropane alkaloids it contains and can cause poisoning when it is ingested or used inappropriately.

What is added by this report?

A poisoning outbreak involved 10 patients, and one death was caused by *Anisodus tanguticus*. The etiological association of plant exposure and poisoning was confirmed with evidence from an epidemiological investigation, clinical manifestations, plant identification and a toxin analysis.

What are the implications for public health practice?

The risk of poisoning caused by mistakenly collecting and ingesting tropane alkaloid-containing plants should be highlighted, and public health practitioners should be on alert.

At 4:40 am on July 17, 2021, the Qinghai CDC received a telephone report from Guoluo Prefecture CDC of 10 patients with similar complaints and spatiotemporal aggregation who were admitted to Guoluo Prefecture People's Hospital in 2 sessions from 23:00 on July 16 to 1:00 on July 17. They assumed this outbreak was due to food poisoning and initiated an investigation. The Qinghai CDC evaluated and verified the outbreak promptly and sent a team with 2 epidemiologists and 1 laboratory expert to the incident site to cooperate with the local government and the CDC to respond to the incident. According to the clinical syndrome and the information provided by the local CDC, this outbreak was probably caused by tropane alkaloid-containing plants, and the researchers contacted the China CDC for further confirmation. Then, field epidemiological and hygiene investigations were conducted, and plant samples were collected in collaboration with provincial, prefecture, and county CDC staff. The plant samples were identified as *Anisodus tanguticus* by morphological identification and molecular analysis.

INVESTIGATION AND RESULTS

The outbreak occurred in a remote village located on the Tibetan Plateau at an average altitude of 3,500 m. It is approximately 60 km away from the Maqin county seat, and travel is inconvenient. A total of 69 households with more than 300 people are in the village. All the patients (9 males, 1 female, ages: 27–57 years old) were migrant workers from a construction company in Henan Province who engaged in road maintenance in the second bid and lived in 3 tents around the construction site on a temporary base.

On July 16, approximately 30 min after dinner at 20:00, the first case appeared and was characterized by stagger, fatigue, dizziness, and nausea; subsequently, another 9 workers exhibited similar symptoms and signs, and only 1 worker had no symptoms. Then, all the patients were sent to Guoluo People's Hospital from 23:00 on July 16 to approximately 1:00 on July 17. Four patients had severe neurotoxic symptoms with unconsciousness and dilated pupils, and the other 6 patients had dizziness, fatigue, nausea, blurred vision, irritability, and tachycardia. The clinical presentation resembled atropine poisoning, which probably indicated that the poisoning outbreak was caused by atropine-containing plants. The first patient vomited twice by stimulating his pharynx with his fingers when feeling discomfort. All patients in Guoluo People's Hospital underwent gastric lavage, monitoring with electrocardiography, and fluid infusion therapy. A 49-year-old male patient suddenly developed dysphoria and choking cough and then suffered cardiac arrest with loss of consciousness and facial cyanosis when pumping his stomach. Endotracheal intubation and mechanical ventilation were performed, while external cardiac compression and intravenous administration of adrenaline were performed to restore the beating of the heart. Unfortunately, the patient died after 45 minutes of rescue. During intubation, a large quantity of gastric contents filled his mouth, which might have resulted in suffocation and further aggravated the condition. Because 1 patient died, the other 9 patients were transferred to Qinghai People's Hospital and Qinghai Red Cross Hospital in Xining City for further treatment. A patient treated at Qinghai Red Cross Hospital underwent hemoperfusion. When arriving at Xining, the vital signs of the patients were stable; after symptomatic and supportive treatment, the patients were discharged from the hospital from July 22 to 25.

The latency period of the first case was 30 min, and the longest latency period was approximately 40 min. The average latency was 35 min. The temporal, spatial, and population distributions and correlations of the patients revealed that this outbreak may have been a food-borne outbreak. The field and food hygiene investigation showed that 10 male migrant workers lived in 2 tents, while another tent was the kitchen and the living room of the female migrant worker as chef; their living and sanitary conditions were poor. Their drinking water was obtained from the river beside their residence, and all vegetables and ingredients were purchased in Maqin County every 2 days. Their living conditions and food supply had not changed compared to previous ones, and their residence was isolated from outsiders. The only difference in the dinner was excess consumption of cold wild vegetables; all the patients had ingested the cold dish, while the worker who did not develop the disease did not eat the cold dish. This outbreak was a single exposure, and no new cases occurred after the consumption of wild vegetables was stopped. The result of the field epidemiological investigation indicated that the cold wild vegetables may be the cause of this outbreak.

The wild vegetables were picked by 3 migrant workers belonging to Sichuan Province, from neighboring areas to the construction site. Approximately 1 kg was blanched by the chef, and then a cold dish was prepared. Guoluo CDC took pictures and videos of the wild vegetables immediately to allow the plant to be recognized and identified. Then, the pictures and videos were sent to the China National Center for Food Safety Risk Assessment, Institute of Occupational Health and Poisoning Control (National Poison Control Center), and the College of Pharmacy at Qinghai Nationalities University for further expert support. All the experts had a preliminary consensus opinion that the plant belongs to the *Anisodus* genus. The plant specimens were collected in the field and then identified as *Anisodus tanguticus* (Figure 1) by morphological and molecular identification. A voucher specimen was deposited in the Poisonous Plants Herbarium affiliated with the National Poison Control Center (No: 2021071701).

The remainder of the dinner, plants, and vomitus were collected to screen and confirm the toxicants. The results of the tests for organophosphorus pesticides, carbamate pesticides, tetramine, fluoroacetamide, and nitrite were negative. According to the epidemiological investigation result, the distinct toxins of the wild plants were analyzed using high-performance liquid chromatography coupled to tandem mass spectrometry. The main tropane alkaloids, atropine, anisodamine, scopolamine, and anisodine, in the cold dish were present at concentrations of 107.4, 0.58, 12.6, and 39.8 mg/kg, respectively, and at 107.0, 1.498, 15.4, and 95.8 mg/kg, respectively, in the wild vegetable plant. The contents of atropine, anisodamine, and anisodine in a vomitus sample were 0.492, 0.07, and 0.802 μg/kg, respectively, and scopolamine was undetected (Table 1). Cardiac blood and stomach content samples of the death patient were collected and tested by the police agency, and atropine, anisodamine, scopolamine and anisodine were detected in the biological samples. All four toxins were positive in all the aforementioned samples.

DISCUSSION

This poisoning outbreak was responded to and investigated by the national, provincial and local CDCs with multidisciplinary experts in clinical

FIGURE 1. The *Anisodus tanguticus* plant that caused a poisoning outbreak in Maqin County, Qinghai Province. (A) Collection of the plant sample; (B) The *Anisodus tanguticus* plant; (C) The *Anisodus tanguticus* flower; (D) The *Anisodus tanguticus* seeds.

TABLE 1. The contents of tropane alkaloids in the remainder of the cold dish, plants and vomitus sample from one patient in the poisoning outbreak caused by *Anisodus tanguticus*.

Sample	Atropine	Anisodamine	Scopolamine	Anisodine
Remainder of the cold dish (mg/kg)	107.4	0.580	12.6	39.8
Wild vegetable plant(mg/kg)	107.0	1.498	15.4	95.8
Vomitus* (μg/kg)	0.492	0.070	Undetected	0.802

* Only vomitus sample from one patient was obtained and analyzed.

toxicology, analytical toxicology, epidemiology and plant taxonomy. Clearly, the incident was a food-borne poisoning outbreak caused by eating the wild plant *Anisodus tanguticus* as a vegetable. According to the solid results from the epidemiological investigation, hygienic investigation, clinical diagnosis and treatment, laboratory tests, and wild plant morphological identification analysis, tropane alkaloids in the plant were confirmed as the etiological toxins. This outbreak indicated that eating *Anisodus tanguticus* by mistake as a wild vegetable might cause severe public health problems, and the public should be alerted and educated to avoid poisoning incidents.

The clinical manifestations of patients with poisoning were explained by the anticholinergic activity of tropane alkaloids. Unlike one etiological chemical associated with anticholinergic drug overdose or poisoning, more tropane alkaloids are usually present in plants, and differences exist in the effects exerted by the different toxins, all of which should be included in the poisoning hypothesis formation and validation. In this outbreak, 4 tropane alkaloids were tested to explain the poisoning. *Anisodus tanguticus* belongs to the *Anisodus* genus of the Solanaceae family and is mainly distributed in Qinghai, Gansu, Sichuan (northwest and southwest), Tibet (east), Yunnan (northwest) of China and Nepal (*1*). *Anisodus tanguticus* is the most important species used in Tibetan medicine (*2*), and the whole plant, especially the roots, contains a variety of tropane alkaloids, such as hyoscyamine, scopolamine, cuscohygrine, anisodamine and anisodine. These alkaloids allow the plants to be used as medicinal plants and important sources of anticholinergic drugs, and these alkaloids are also the main cause of their toxicity.

In China, tropane alkaloid-containing plant poisoning is due to people mistakenly picking plants as vegetables and using them as drugs for therapy. Poisoning caused by another tropane-containing plant, *Datura stramonium,* is more common. Tropane alkaloid-containing plant poisoning has been reported in other countries and regions. In Germany (*3*), the United Kingdom (*4*), and Morocco (*5*), poisoning caused by berries of *Atropa belladonna* has been reported. In Uganda in 2009, a batch of super cereals was contaminated with *Datura* seeds, resulting in a series of food poisoning outbreaks; 278 cases and 5 deaths occurred, and atropine and scopolamine were detected as the main toxins (*6*). In Turkey (*7*), Iran (*8*), and Israel (*9*), tropane alkaloid poisoning was caused by *Datura stramonium.*

As we noted, this report is the first to document tropane alkaloid poisoning caused by eating the stems and leaves of *Anisodus tanguticus*, and the poisoned population was migrant workers. With the rapid development in China, many people working in different locations may be exposed to a different environment; thus, the possibility of harvesting and ingesting wild poisonous plants has significantly increased. The public should be alerted and educated to increase their awareness of self-protection and avoid eating unfamiliar or unknown wild plants to cope with this challenge.

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Policy Notes

Consideration of Monkeypox Surveillance in China, 2022

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BACKGROUND AND CONSIDERATIONS FOR MONKEYPOX SURVEILLANCE STRATEGIES

Since the first monkeypox cases were confirmed in England in May 2022 (*1*), 100 countries worldwide have reported 53,027 confirmed cases and 15 deaths as of September 2 (*2*). This is the largest and most widespread monkeypox epidemic in the world since monkeypox virus was discovered and identified in 1958, involving the largest number of countries and transmitting primarily in non-endemic countries (*3*). Moreover, the currently ongoing monkeypox epidemic also has some characteristics that are different from previous outbreaks (*4*). For example, most cases have a history of sexual contact, with an overwhelming majority of men who have sex with men (MSM) (*5*). On July 23, the WHO declared the global monkeypox outbreak a Public Health Emergency of International Concern (PHEIC) in order to address the ongoing outbreak with the required urgency (*6*).

So far, except for three and one imported cases of monkeypox virus infection in Taiwan, China, and Hong Kong Special Administrative Region (SAR), China, respectively (*2,7–9*), in the mainland of China, the first monkeypox case, who was imported from an European country, was detected and reported in Chongqing on September 14, 2022 (*10*), indicating that current monkeypox surveillance in the mainland of China was effective. In consideration of the frequent contacts between China and other countries in trade, business, tourism, and overseas study (*11–12*), the risk of monkeypox being imported into China and subsequently transmitted locally remains. With the rapid development of the monkeypox epidemic in the world, coupled with the gradual recovery of communication between countries, the risk of monkeypox being imported into China may continue to increase.

China has taken a series of proactive measures to respond to the global monkeypox epidemic. In June 2022, the National Health Commission formulated and issued the *Monkeypox Diagnosis and Treatment Protocol* (2022 Edition) (*13*) (hereinafter referred to as Protocol) and the *Technical Guidelines for the Prevention and Control of Monkeypox* (2022 Edition) (*14*) (hereinafter referred to as Guidelines) to strengthen the detection and reporting of monkeypox patients in medical institutions. The Customs issued its *Circular on Preventing Monkeypox from being Introduced into China* (Circular No. 65 of the General Administration of Customs in 2022) (*15*), further tightening controls over the quarantine of people and animals entering China and surveillance of animal reservoirs.

To achieve the goal of early detection of cases and timely blocking of possible transmission, based on the epidemic situation of monkeypox abroad and the risk of importation into China, China's current surveillance strategy focuses on early detection of imported cases and subsequent transmission, increasing the sensitivity of surveillance, and syndromic surveillance of target populations (Figure 1).

CONSIDERATIONS FOR OBJECTS AND SCOPE OF SURVEILLANCE

As monkeypox virus infection has already been imported and detected in the mainland of China (*10*) and the COVID-19 prevention and control is still under great pressure, surveillance of symptoms of monkeypox cases in focus populations, medical facilities and regions is an important supplement to the routine surveillance of probable and confirmed monkeypox cases, which is carried out in health care facilities at all levels and of all types across the country (Table 1).

Focus Populations

The focus populations include international travelers and MSM. First, international travelers are asked to voluntarily declare to the customs at the border entry whether they have any monkeypox-like symptoms or any epidemiological exposure history, such as close

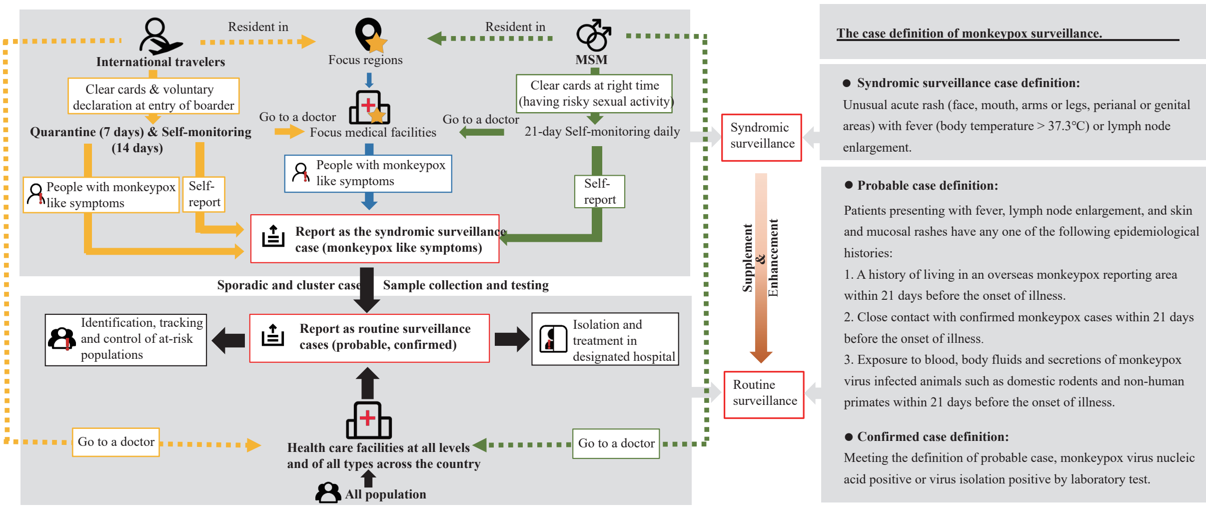

FIGURE 1. The framework and the case definition of monkeypox surveillance in the mainland of China, 2022.
Abbreviation: MSM=men who have sex with men.

TABLE 1. Monkeypox surveillance scope, target, object, location and content in the mainland of China, 2022.

Surveillance scope and coverage	Objects or locations of surveillance	Contents of surveillance
Focus populations	International travelers and MSM	1) People coming from abroad are asked to voluntarily declare to the customs at the entry of border 2) People coming from abroad are quarantined at a designated hotel for 7 days after entry 3) People coming from abroad are asked to do a self-monitoring for 14 days after completing the 7-day quarantine at hotel 4) MSM are asked to do a 21-day self-monitoring daily after having any risky sexual activity
Focus medical facilities	Dermatology hospitals, dermatology clinics and STD clinics, including VCT clinics	Doctors and nurses monitor whether patients visiting facilities develop monkeypox-like symptoms, and then promptly report to jurisdictional CDC
Focus regions	Provincial capitals (including municipalities directly under the Central Government)	Implement syndromic surveillance in focus medical facilities in provincial capitals or municipalities
Across the country	Healthcare facilities at all levels and of all types	1) Doctors and nurses monitor whether patients visiting facilities at all levels and of all types meet diagnosis definition of probable and confirmed monkeypox cases, and then promptly report to jurisdictional CDC 2) Both sporadic and cluster cases meeting the definition of monkeypox syndromic surveillance are promptly reported

Abbreviation: MSM=men who have sex with mem; STD=sexually transmitted disease; VCT=HIV voluntary counseling & testing; CDC=center for disease control and prevention.

contact with someone infected with monkeypox. Second, international travelers are required to have a 7-day quarantine at a designated hotel, in which they will be monitored for monkeypox-like symptoms. Third, international travelers are asked to do self-monitoring for monkeypox-like symptoms for 14 days after they have completed the 7-day quarantine at hotel and to promptly report any possible symptoms to the local CDC.

In addition, given the high proportion of cases involving MSM in the current monkeypox epidemic (*16*) and the clear role of sexual contact and having multiple sexual partners in the spread of monkeypox (*17–18*), although no domestic transmission has been detected in the mainland of China at present, from a forward-looking perspective of monkeypox surveillance, in addition to the international travelers, MSM are also included in focus populations in focus regions to improve the sensitivity of surveillance for case detection. MSM are asked to do daily self-monitoring for 21 days after having any risky sexual activity and promptly report possible infection to the local CDC.

Focus Medical Facilities

Focus medical facilities mainly include dermatology hospitals, dermatology clinics, and sexually transmitted disease (STD) clinics, including HIV Voluntary Counseling & Testing (VCT) clinics. As in the monkeypox case series, most persons presented with a rash, and the most common anatomical sites were the anogenital area, the trunk, arms, legs, and the palms or soles (*19*), these medical facilities are considered the focus for monkeypox surveillance to improve the probability of detection.

Focus Regions

Considering the distribution of ports of entry, mobility of people, MSM population size and activity, and China's efforts in relevant disease prevention and control, all provincial capitals (including municipalities directly under the Central Government) are selected as areas for monkeypox syndromic surveillance in medical facilities.

SURVEILLANCE CASE DEFINITION

Three types of case definition are used (Figure 1). Probable cases and confirmed cases are defined clearly in the Protocol (*13*), but the clinical manifestations defined in the Protocol are too technical and are more applicable to clinical diagnosis instead of surveillance; furthermore, the epidemiological history in the definition is too concerned with overseas exposures. Therefore, on the basis of the definition in the Protocol, the simplified and more sensitive description of monkeypox-like symptoms is adopted for syndromic surveillance case definition in the country: unusual acute rash (face, mouth, arms or legs, perianal or genital areas) with fever (body temperature >37.3 ℃) or lymph node enlargement.

CONSIDERATIONS FOR SURVEILLANCE IMPLEMENTATION

At-Risk Populations: Self-Monitoring and Active Reporting

Given the potentially large populations of international travelers and MSM, and unknown prevalence of monkeypox virus, *clear cards* are issued to international travelers at the border entry and to MSM at right time, letting them carry out a self-monitoring for a period of 21 days after entering the country or having a risky sexual activity, respectively, consistent with the maximum incubation period of monkeypox virus infection (*20*).

The process of self-monitoring is equivalent to the publicity and education of monkeypox prevention and control knowledge. In the focus regions, media campaigns and other means are used to increase MSM education on symptoms of monkeypox, so that they can carry out self-monitoring of monkeypox-like symptoms, and avoid unprotected sex to prevent the risk of monkeypox virus infection and transmission.

Focus Regions and Focus Medical Facilities: Combination

Although no domestic monkeypox case has yet been reported, the risk of importation has still been the major challenge of monkeypox in the mainland of China. Provincial capitals or municipalities were selected to carry out monkeypox syndromic surveillance as they have more immigrants, more active MSM personnel, and strong diagnostic, treatment, and detection capabilities in hospitals and clinics. Syndromic surveillance is implemented at dermatology hospitals, dermatology clinics, or STD clinics, including VCT clinics in provincial capitals or municipalities.

Across the Country: Routine and Syndromic Surveillance, Targeting Both Sporadic and Cluster Cases

Monkeypox syndromic surveillance is a supplement and enhancement to routine surveillance. According to the Protocol, doctors and nurses monitor whether patients visiting facilities at all levels and of all types meet diagnostic criteria of probable and confirmed monkeypox case, and then promptly report these cases to jurisdictional CDC. In addition, both sporadic and cluster cases meeting the definition of monkeypox syndromic surveillance are also promptly reported across the country. Secondary monkeypox cases will follow the same procedures as the primary cases, and be given a thorough field epidemiological investigation.

Specimen Collection and Testing

Monkeypox virus is a Biosafety Level 1 pathogen in China (*21*), for patients with monkeypox-like symptoms and probable cases, inactivated throat swabs are first collected for biosafety and efficiency. If throat swabs of individuals who have monkeypox-like symptoms are negative, specimens of the skin rash will be sampled for diagnosis. If the laboratory test is positive, multiple non-inactivated specimens, including specimens of skin rash, herpes surface or exudate, blister fluid, scab or scleroderma, will be collected immediately for subsequent work such as virus isolation and gene sequencing. Serum samples during the acute phase (within 7 days of onset) and the convalescent phase (2–3 weeks apart) respectively will be collected for antibody testing.

It is necessary for medical facilities and CDCs at all levels in the mainland of China to establish a stable and sustainable capacity of nucleic acid testing for detection of monkeypox virus as soon as possible. The National Institute for Viral Diseases Control and Prevention (IVDC) of China CDC has developed a nucleic acid testing method for detection of monkeypox virus, completed the development of nucleic acid detection reagents, and distributed the first batch of monkeypox virus detection reagents to provincial CDCs in the mainland of China in August, 2022. At present, many domestic reagent companies have initiated research, development, and production of test kits for monkeypox virus.

Considerations for Diagnostic and Reporting Processes

According to the Protocol (*13*) and the Guidelines (*14*), probable cases should be transferred to designated medical facilities for cubicle treatment, and the identification, tracking, and control of at-risk populations should be carried out immediately. Groups of experts on monkeypox diagnosis should be established at all levels of medical facilities and health authorities to study probable cases so as to improve the specificity of monkeypox surveillance and the accuracy of monkeypox diagnosis and to avoid excessive response or waste of epidemic control resources. The medical facilities first organize resident expert group consultations when they detect monkeypox-like symptoms or probable cases, and then, if necessary, refer to local or superior expert groups for consultations.

CONSIDERATIONS FOR ADJUSTMENT OF MONKEYPOX SURVEILLANCE STRATEGIES AND IMPLEMENTATION PLAN

China's current monkeypox surveillance strategy and implementation plan are based on the current global monkeypox epidemic and domestic situation and subject to timely adjustment according to changes in the characteristics of monkeypox virus and disease, the situational changes of surveillance implementation, case reports in China, and strategic changes to prevent and control infectious diseases.

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Erratum

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In the article entitled 'Building a Chronic Diseases Prevention and Rehabilitation System Throughout the Life Span to Proactively Respond to the Challenges of Accelerated Population Aging' [2022, 4(39): 863-864. doi: 10.46234/ccdcw2022.178], the third author affiliation on page 864 'Research Center of Population Health and Social Development, University of Health and Rehabilitation Sciences, Beijing, China' should be 'Research Center of Population Health and Social Development, University of Health and Rehabilitation Sciences/Soft Science Research Base of Public Policy on Population Health in Shandong Province, Qingdao City, Shandong Province, China'.

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