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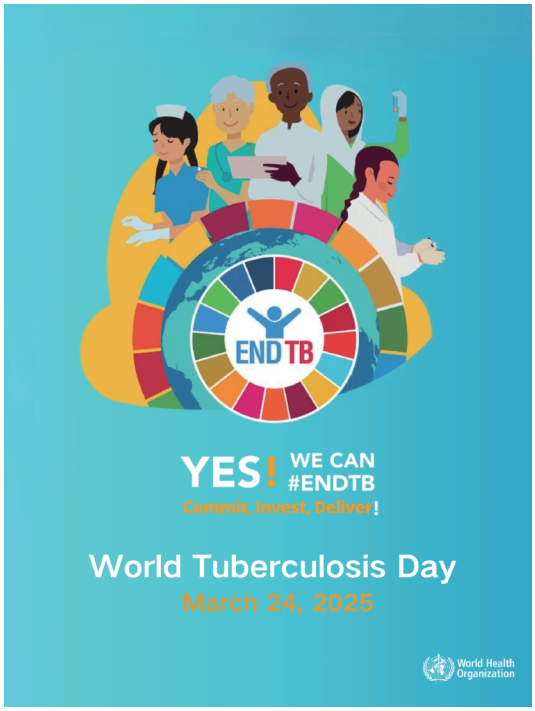

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Perspectives

Commit, Invest and Deliver: Towards Achieving End Tuberculosis Strategy Goals Through Active Case Finding and Preventive Treatment in China

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ABSTRACT

This paper addresses the World Tuberculosis (TB) Day 2025 theme, "Yes! We can end TB! Commit, Invest, Deliver". Through comprehensive analysis of China's TB epidemic landscape and associated challenges, we align with the "National TB Prevention and Control Plan (2024–2030)" which emphasizes that building Zero-TB communities through the integration of "active case finding" and "TB preventive treatment (TPT)" represents a viable pathway toward ending the TB epidemic. Active case finding serves as a critical intervention for early detection and transmission reduction, while TPT constitutes an essential strategy for decreasing latent TB infection incidence. By facilitating the rapid expansion of Zero-TB communities through governmental commitment, strategic resource allocation, and coordinated implementation, we anticipate achieving the ultimate goal of TB epidemic elimination.

CHALLENGES AND OPPORTUNITIES IN TB PREVENTION AND CONTROL

Tuberculosis (TB) remains one of the most significant global public health challenges. China continues to bear a substantial TB burden, with approximately 741,000 new cases reported in 2023, representing 6.8% of global cases and an incidence rate of 52 per 100,000 population (*1*). The TB epidemic in China exhibits marked geographic and demographic heterogeneity. In 2023, 289 counties — approximately 10% of all counties nationwide — reported high incidence rates exceeding 80 per 100,000 population, with these hotspots predominantly concentrated in western regions. The disease disproportionately affects the youth and middle-aged workforce, while incidence rates progressively increase with age among elderly populations. Despite significant advances in TB control efforts in recent years, achieving the World Health Organization's (WHO) goal of "ending TB epidemic by 2030" faces considerable challenges. These include insufficient and delayed case detection — with 95% of TB patients in China identified through passive surveillance, leaving nearly 20% of cases undetected and half experiencing diagnostic delays (*2*). Additionally, the implementation of TB preventive treatment (TPT) remains inadequate, and the adoption of innovative technologies is suboptimal. At the current rate of TB incidence decline in China, the trajectory is insufficient to achieve the 2030 target of ending the TB epidemic.

To address these challenges proactively, the National Bureau of Disease Prevention and Control, in collaboration with eight other ministries and commissions, has issued the "National TB Prevention and Control Plan (2024–2030)" (*3*) (hereinafter referred to as the "Plan"), which establishes strategic priorities for TB control in China. Complementing this national initiative, the WHO has designated the theme for World TB Day 2025 as "Yes! We can end TB! Commit, Invest, Deliver," emphasizing the critical importance of governmental commitment, financial investment, and effective service delivery. Active case finding and TPT represent cornerstone interventions for achieving these ambitious goals. Active case finding — the systematic screening of high-risk populations — facilitates early TB detection and reduces diagnostic delays, while TPT significantly diminishes TB risk among vulnerable populations. The integration of these approaches within Zero-TB communities creates a comprehensive framework that can accelerate TB incidence reduction.

CONDUCT COMMUNITY-AND FACILITY-BASED ACTIVE SCREENING TO ENHANCE TB CASE DETECTION

Early detection of tuberculosis is crucial for controlling the spread of the epidemic. However,

currently, a substantial proportion of TB patients worldwide remain undetected in a timely manner. It is estimated that approximately 20% of TB patients are undiagnosed or unreported each year (*2*). This not only adversely affects treatment outcomes for the patients themselves but also significantly increases the risk of epidemic transmission. In high-burden regions, effective active case finding faces numerous challenges due to insufficient medical resources, limited public awareness of TB, and constraints in detection methodologies. China needs to strategically enhance its active case finding approaches through precise targeting of high-risk populations, implementation of innovative screening methods, and optimization of screening protocols.

Scientifically and Accurately Identify the Targets for Active Case Finding

Despite China's TB detection rate in 2023 achieving approximately 82.7%, which is notably higher than the global average of 75.9%, a significant proportion of patients — nearly 20% — remain unidentified, highlighting substantial gaps in the current detection framework (*2*). Notably, a significant proportion of these undetected cases are asymptomatic TB. At the current stage, active case finding should prioritize key populations including close contacts of TB patients, people living with HIV/AIDS (PLWHA), previously treated TB patients, the elderly, and individuals with diabetes. Previous studies have demonstrated that TB detection rates through active screening among close family contacts of smear-positive and smear-negative TB patients are approximately 3.6% and 1.3% respectively, both substantially higher than those observed in the general population. Implementing active case finding strategies can increase patient detection by 2.5-fold and reduce mortality rates by 40% (*4*). PLWHA face an 18-fold higher risk of tuberculosis, yet there exists a 44% detection gap (*2*). A systematic review found that TB is the cause of death for 37.2% of PLWHA. The risk of TB reinfection in previously treated patients is 4 times higher than in other populations, with a 10.2-fold increased risk of developing drug-resistant TB. Due to declining immune function and physiological deterioration, the elderly constitute a high-risk group for tuberculosis, with prevalence rates approximately 2–3 times higher than other age groups (*5-6*). Facility-based active case finding should be implemented among PLWHA, previous tuberculosis patients, the elderly, and individuals with diabetes. For close contacts of TB patients, disease control and prevention institutions should organize community-based active screening initiatives.

Schools, correctional facilities, social welfare institutions, juvenile rescue and protection agencies, psychiatric hospitals, and industrial and mining enterprises are designated as key settings for TB screening. The rationale behind this designation lies in the fact that within these densely populated environments, TB cases can rapidly lead to widespread transmission and potentially trigger public health emergencies. Previous studies have demonstrated that the risk of TB among individuals in correctional facilities is 23 times higher than in the general population (*7*). In certain industrial and mining enterprises, particularly among miners exposed to silica in the workplace, silicosis is prevalent. The relative risk of TB in silicosis patients varies by disease severity, ranging from approximately 2.8 to 39-fold higher than the general population. Moreover, TB patients with silicosis face a 3-fold increased mortality risk. Furthermore, medical resources in these settings are often limited, increasing the likelihood of diagnostic and treatment delays following TB onset. Therefore, it is recommended to incorporate TB examination as a mandatory component of enrollment physical examinations for these facilities and to include TB screening in annual health assessments. Depending on the epidemiological situation and available resources, regions with appropriate capabilities should also consider implementing infection screening protocols. For high-risk individuals who have been confirmed not to have active TB, TPT should be administered to further advance disease prevention. The implementation of active case finding in key settings requires coordinated cooperation across multiple departments, with particular attention to protocols governing class suspension, work suspension, resumption of classes, and resumption of work.

WHO recommends that in regions where the estimated TB prevalence rate is 0.5% or higher, active case finding should be conducted among the general population (*8*). This approach holds significant implications for both individual and community health outcomes. The "Plan" indicates that approximately 10% of counties in China remain high-prevalence areas (reporting incidence >80/100,000). In these highly prevalent TB regions, it is essential to establish evidence-based protocols regarding target populations and screening frequency. Comprehensive evaluation

should be initiated after a minimum of three consecutive years of screening implementation. Once prevalence levels decline to moderate levels, it would be prudent to consider transitioning from community-based general population screening to facility-based screening focused on high-risk populations. Furthermore, in high-incidence areas with resource constraints, facility-based active case finding targeting high-risk groups represents a viable alternative approach.

Innovating Active Screening Methods

WHO recommends rapid molecular diagnostic techniques as the initial diagnostic tool for TB to enhance both sensitivity and specificity of diagnosis. Current screening methodologies primarily encompass symptom screening, chest imaging examinations, C-reactive protein (CRP) testing, and molecular testing. Symptom screening — a preliminary assessment that identifies long-term (chronic) cough, cough of any duration, or any TB symptoms — offers implementation simplicity but demonstrates limited sensitivity and specificity, necessitating combination with complementary screening approaches. Chest X-ray examination represents the predominant technical modality for tuberculosis screening, exhibiting high sensitivity and specificity. For large-scale population screening initiatives, integration with computer-aided detection (CAD) technology is recommended to optimize diagnostic efficiency and accuracy. CRP testing is predominantly utilized in PLWHA, demonstrating superior accuracy compared to symptom screening, with optimal sensitivity achieved using a 5 mg/L threshold. Molecular diagnostic platforms, including Xpert MTB/RIF® and sputum Truenat® methodologies, facilitate rapid diagnosis with high sensitivity and specificity, albeit at relatively higher cost.

Optimizing the Active Screening Process

Implementation of active case finding requires development of cost-effective screening protocols tailored to local epidemiological patterns and available resources, with specific consideration for diverse high-risk populations and settings. In high-incidence regions, continuous dynamic evaluation of community epidemic levels should inform timely adjustments to screening strategies and processes. For populations already integrated into basic public health service management, such as the elderly and individuals with diabetes, chest imaging examinations can be strategically incorporated into scheduled annual and quarterly health assessments to achieve multi-disease screening, thereby enhancing cost-effectiveness and implementation feasibility. For high-risk TB groups, including PLWHA and individuals with prior TB history, facility-based active case finding should be systematically implemented. Concurrently, efforts should focus on enhancing TB risk identification awareness among clinicians in general medical institutions while strengthening their tuberculosis screening capabilities. Active measures should be taken to increase the proportion of high-risk TB groups screened among outpatients and inpatients in general hospitals, thereby improving facility-based early detection rates.

PROMOTE TB PREVENTIVE TREATMENT THROUGH PREVENTIVE TREATMENT CLINICS

Latent TB infection (LTBI) represents a state of persistent immune response to Mycobacterium TB (MTB) antigens without clinical manifestations or radiographic evidence of active disease. Approximately one-quarter of the global population is infected with MTB, with 5%–10% of these individuals progressing to active TB during their lifetime, predominantly within the first five years post-infection. This substantial reservoir of latently infected individuals continuously contributes to the emergence of new TB cases. TPT for high-risk LTBI populations constitutes a critical intervention endorsed by the WHO to achieve the strategic objective of "ending TB epidemic." At the second United Nations High-level Meeting in 2023, a global commitment was established to provide TPT to at least 45 million individuals between 2024 and 2027. China's "Plan" similarly mandates that the TPT coverage rate for close contacts of TB patients should reach 60% by 2025.

Identification of TPT Targets via TB Incidence Risk Assessment

While TPT represents a cornerstone of the WHO's End TB Strategy, the efficacy of current preventive regimens varies from 60% to 90%. Consequently, TPT implementation necessitates careful risk-benefit assessment. Defining appropriate TPT target populations requires consideration of multiple factors, including progression risk in vulnerable groups, local

TB epidemiology, disease burden, and resource availability. From an individual protection perspective, TPT should primarily target those at elevated risk of progression following MTB infection, particularly recent infections and immunocompromised individuals. From a community incidence reduction standpoint, the proportion of the target population receiving TPT must also be considered. Based on these principles, China has clearly defined high-risk groups for TB, encompassing close contacts of TB patients, PLWHA, and those with immunosuppressive conditions, reflecting a targeted approach to disease surveillance and control. The risk of TB among PLWHA is 18 times higher than in the general population, with approximately one-third of PLWHA mortality attributable to TB. A systematic review has demonstrated that TPT reduces overall TB risk in PLWHA by 33%, with this protective effect increasing to 64% in tuberculin skin test (TST)-positive individuals. Additionally, TPT reduces all-cause mortality by 35%, with protective effects persisting beyond five years. Close contacts of TB patients, regardless of age, demonstrate significantly higher active TB risk compared to the general population, warranting TPT recommendation irrespective of local TB burden.

Research, Development and Promotion of Short-course Treatment Regimens

Currently, the recommended TPT regimens in China primarily include the 6-to-9-month isoniazid monotherapy regimen (6-9H), the 3-month isoniazid and rifapentine combined intermittent regimen (3HP), the 3-month isoniazid and rifampicin combined regimen (3HR), the 4 month rifampicin monotherapy regimen (4R), and the immunotherapy regimen. Studies have demonstrated that the protective efficacy of these TPT regimens ranges from approximately 60% to 90% (*9*). Acceptance rates among individuals with LTBI are strongly correlated with treatment duration. The acceptance rates for the 3HP and 6H regimens are only 76.3% and 63.9% (*10*), respectively, with corresponding compliance rates of 89.2% and 61.5% (*11*). Notably, research has shown that the 3HP regimen exhibits significantly reduced hepatotoxicity (*12*), suggesting that continued promotion of short-course regimens should be prioritized to enhance acceptance and compliance among patients with latent infection. Although randomized trials have confirmed the effectiveness and safety of the 1HP regimen compared to the 9H regimen, this approach has not yet been incorporated into national guidelines due to insufficient research evidence within China. Currently, several Chinese researchers are conducting relevant investigations in this area.

Standardized Establishment of TB Preventive Treatment Clinics

The Plan recommends that localities establish TPT clinics according to regional conditions and resources. From a systems perspective, effective TPT implementation requires integration within the comprehensive TB prevention and control service framework of "Center for Disease Control and Prevention (CDC) – Hospital – Primary Medical Institutions." Through optimized resource allocation and enhanced information sharing mechanisms, both active case finding and TPT initiatives should be strengthened. Within this framework, TPT clinics enable CDCs to fulfill their core functions of providing technical guidance, quality control, and outcome evaluation. Concurrently, the role of primary medical institutions in TB infection screening and TPT supervision must be clearly defined and supported. TPT should be incorporated into health management projects within the basic public health services framework, establishing a precision intervention model based on risk stratification built upon comprehensive health records. This approach should be integrated with the pilot deployment of public health practicing physicians, fully leveraging their capabilities in identifying TPT candidates, enhancing diagnostic and treatment competencies, and implementing standardized management protocols.

THE CONSTRUCTION OF "ZERO-TB COMMUNITIES" REPRESENTS THE BEST PRACTICE THAT INTEGRATES ACTIVE CASE FINDING AND PREVENTIVE TREATMENT

The Zero-TB Community initiative designates communities (such as townships, streets, schools, military units, long-term care institutions, large-scale enterprises, or public institutions) where tuberculosis incidence among permanent residents falls below 10 cases per 100,000 population, aligning with the World Health Organization's pre-elimination threshold for TB. The core framework of Zero-TB Communities

can be conceptualized as "three screenings, two managements, and one mobilization." The "three screenings" encompass active case finding in high-incidence areas and among high-risk populations; systematic TB infection testing in high-risk groups; and enhanced screening for drug-resistant TB. The "two managements" involve providing prompt, standardized anti-TB treatment with comprehensive case management for diagnosed TB and drug-resistant TB patients to minimize transmission risk, and implementing TB preventive treatment with robust monitoring for individuals with LTBI to reduce disease progression. The "one mobilization" component focuses on strengthening governmental advocacy and public health education to enhance population-wide health literacy. Since China initiated the Zero-TB Community construction in 2022, the program has expanded to 468 districts across 24 provinces. This initiative has demonstrated significant clinical and social benefits, achieving rapid reductions in TB incidence rates, protecting population health, and generating substantial societal value.

COMMITMENTS AND INVESTMENTS SERVE AS STRONG GUARANTEES FOR THE IMPLEMENTATION OF TB PREVENTION AND CONTROL ACTIONS

Strengthening Government Commitments and Policy Guarantees

Governments at all levels should incorporate tuberculosis prevention and control into comprehensive public health strategies and foster multi-sectoral collaboration, engaging departments including healthcare, finance, and medical insurance to collectively implement TB control initiatives. TB prevention and control measures should be integrated into major and basic public health programs with clearly defined goals and action plans, and subsequently incorporated into local performance evaluation frameworks. Authorities must rigorously enforce the requirements stipulated in the Law on the Prevention and Control of Infectious Diseases, while concurrently undertaking timely revisions of relevant tuberculosis-specific regulations, such as the Administrative Measures for TB.

Increase Financial Support

A multi-channel financing approach should be maintained, utilizing diverse funding streams including allocations for major infectious disease control, basic medical insurance, local government finances, civil affairs assistance, and charitable contributions to mitigate the economic burden on TB patients. The national essential drugs list and basic medical insurance coverage should be dynamically adjusted to incorporate eligible anti-tuberculosis medications within the medical insurance framework. Implementing centralized procurement strategies and price negotiations is essential for cost reduction. For high-cost novel anti-tuberculosis therapeutics, further price reductions should be pursued through medical insurance negotiations and provincial-level centralized procurement platforms. An integrated model combining medical insurance coverage, civil affairs subsidies, and government guarantees should be promoted to substantially reduce patients' out-of-pocket expenditures.

CONCLUSION AND PROSPECTS

The 2025 World TB Day theme, "Yes! We can end TB! Commit, Invest, Deliver," establishes a clear strategic framework for tuberculosis prevention and control efforts. To achieve the goal of ending TB in China, active case finding and TB preventive treatment must serve as complementary driving forces within this comprehensive approach. By operationalizing the "Commit-Invest-Deliver" framework through evidence-based policies, scientifically rigorous prevention strategies, and efficient implementation mechanisms, China can foster meaningful integration across policy innovation, technological advancement, and community mobilization domains. Only through this multifaceted, coordinated approach can the ambitious vision of ending TB by 2030 be realized.

Conflicts of interest: No conflicts of interest.

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Vital Surveillances

Serotype Distribution, Virulence, and Antibiotic Resistance Genomic Characterization of Group B Streptococcus — China, 1998–2024

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ABSTRACT

Introduction: *Streptococcus agalactiae*, or group B Streptococcus (GBS), can cause severe infections in humans, yet comprehensive genomic characterization from China remains limited. This study presents an extensive genomic analysis of GBS isolates collected in China from 1998 to 2024.

Methods: GBS genomes were obtained from public databases and through de novo sequencing. Serotype confirmation was conducted via pan-genomic analysis, phylogenetic relationships were established using maximum-likelihood methodology, and virulence and antibiotic resistance genes were identified through the Virulence Factor Database and Comprehensive Antibiotic Resistance Database. Statistical analyses were performed using SPSS 26.0, primarily employing Fisher's exact tests.

Results: Analysis of 747 GBS genomes revealed eight serotypes (Ia, Ib, II, III, IV, V, VI, VII) and nontypeable strains. Serotypes III, Ib, Ia, V, and II constituted 96.65% of all isolates. GBS prevalence remained low from 1998–2011 but increased substantially after 2012. Geographic distribution demonstrated significant regional heterogeneity. Phylogenetic analysis categorized the 747 genomes into five distinct lineages, with lineage 5 being predominant. Six virulence factor categories encompassing 56 virulence-associated genes were identified, with 33 genes present in nearly all genomes. Twenty-seven antibiotic resistance genes spanning nine drug classes were detected, particularly those conferring resistance to peptides and macrolide antibiotics, indicating widespread antimicrobial resistance mechanisms in GBS.

Conclusions: GBS infections in China exhibit serotype distributions similar to global patterns but with notable regional variations. This comprehensive genomic characterization provides critical insights for developing targeted prevention strategies and treatment approaches for GBS infections in China.

Streptococcus agalactiae, classified as a group B streptococcus (GBS) (*1*), can exist as a commensal organism in the human gastrointestinal and genitourinary tracts while also causing severe infections in immunocompromised individuals and the elderly. In pregnant women, GBS infection is associated with maternal disease (*2*) and can cause early-onset or late-onset sepsis in newborns and hypoxic-ischemic encephalopathy in infants (*3*). The global prevalence of maternal GBS colonization is estimated at 18%, with significant regional variations. The pooled incidence of invasive GBS disease in infants is 0.49 per 1,000 live births, highest in Africa (1.12) and lowest in Asia (0.30) (*4–5*). In China, the maternal colonization rate is 8.1%, lower than the global average (*6*). GBS also represents a growing threat to immunocompromised individuals and the elderly (*7*).

Intrapartum antibiotic prophylaxis (IAP) effectively prevents GBS infections, but overuse of antibiotics contributes to increasing antibiotic resistance in GBS (*8*). Additionally, antibiotic exposure in newborns can have detrimental health effects (*9*). These concerns highlight the need for alternative treatment approaches, such as GBS vaccines. Capsular polysaccharides (CPs) are key virulence factors in GBS, with 10 recognized serotypes (Ia, Ib, II-IX) based on their immunological reactivity (*10*). Understanding the distribution of these serotypes is essential for the development of effective CPS-based vaccines (*4*). Currently, no vaccine is available for GBS infection. Clarifying GBS serotype distribution remains critical for developing effective prevention and treatment strategies, but studies in China are limited in scope and geographic coverage (*6*,*11–12*).

This study provides an extensive genomic characterization of GBS strains collected in China, aiming to investigate serotype and genotype distribution, genetic evolution, and the presence of virulence and antibiotic resistance genes. By elucidating the molecular and genomic epidemiological patterns of GBS in China, this research establishes a foundation for developing effective prevention and treatment strategies.

METHODS

Bacterial Strains, Whole-Genome Data Collection, and Sequencing

A total of 747 *Streptococcus agalactiae* genomes were analyzed in this study, comprising 721 publicly available genomes retrieved from the National Center for Biotechnology Information (NCBI) database (https://www.ncbi.nlm.nih.gov/datasets/genome/) as of April 2024, supplemented with 26 newly sequenced clinical isolates. The clinical strains were sequenced using the Illumina HiSeq 2000 platform (Novogene Technology Co., Ltd., Beijing, China), and genome annotation was performed using Prokka [version 1.13.3; Winnipeg Institute for Bacterial Genomics (PHAC), Winnipeg, Canada]. The basic information of all strains is provided in Supplementary Table S1 (available at https://weekly.chinacdc.cn/).

Identification of Serotype, Virulence, and Antibiotic Resistance-Associated Genes

Serotype determination was conducted through CPs sequence analysis using pan-genomic comparison, with a threshold of ≥95% sequence identity required for serotype confirmation (*13*–*14*). Phylogenetic analyses were performed based on core single nucleotide polymorphisms (SNPs) using IQ-TREE (version 2.3.4; Computational Evolution Lab, Ho Chi Minh City, Vietnam). Virulence and antibiotic resistance genes were identified from Prokka-generated *.gff files using Roary (version 2.3.12; University of Exeter, Exeter, UK). Virulence genes were identified through BLASTp alignment against the Virulence Factors of Pathogenic Bacteria (VFDB, https://www.mgc.ac.cn/VFs/) database, applying stringent criteria (≥60% identity, ≥ 70% coverage, E-value ≤1×10^{-5}). Antibiotic resistance genes were identified using the Resistance Gene Identifier (RGI) [version 6.0.2; Comprehensive Antibiotic Resistance Database (McMaster University), Hamilton, Canada] against the Comprehensive Antibiotic Resistance Database (CARD, https://card.mcmaster.ca/home), with thresholds of ≥80% for both identity and coverage.

Statistical Analysis and Data Availability

Statistical analyses were conducted using SPSS (version 26.0; IBM Corp., Armonk, NY). Categorical variables were assessed using Fisher's exact test, with statistical significance defined as $P<0.01$. This test was specifically employed to evaluate differences in serotype distribution of GBS across various geographical regions of China. The genome sequences of the 26 newly sequenced clinical GBS strains have been deposited in GenBank under BioProject ID PRJNA1128393.

RESULTS

Serotype and Isolation Source Distribution

A total of 747 *Streptococcus agalactiae* (GBS) strains collected in China from 1998–2024 were classified into eight distinct serotypes (Table 1). Five predominant serotypes (III, Ib, Ia, V, and II) accounted for 96.65% of all isolates, with serotype III being the most prevalent (*n*=323, 43.24%), followed by Ib (*n*=177, 23.69%) and Ia (*n*=120, 16.06%). Serotypes IV (*n*=4, 0.54%), VII (*n*=1, 0.13%), and non-typeable strains (*n*=4, 0.54%) were comparatively rare. The isolation source remained undocumented for over half of the samples (*n*=428, 57.30%). Among strains with documented sources, blood specimens were the most common origin for serotype III isolates, while genital secretions predominated in serotypes Ib and V.

Spatio-Temporal Distribution

Spatio-temporal analysis revealed a low prevalence of GBS from 1998 to 2011, followed by a significant increase starting from 2012 (Figure 1A). Serotype III has consistently been the predominant strain, while serotype Ib has shown a steady increase since 2016. Serotypes V and Ia have maintained relatively stable frequencies at lower levels (Figure 1B). Among the 623 strains with available regional data, the majority originated from Taiwan, China (35.3%); Shandong Province (18.6%); Hong Kong Special Administrative Region (SAR, 8.4%); and Henan Province (8.4%). Serotype III demonstrated clear dominance in Taiwan, China (58.71%) and Hong Kong SAR (60.32%), whereas serotype Ib was most prevalent in Shandong

TABLE 1. Serotype and isolation source distribution of GBS strains in China.

Serotype	Isolation source							Total (%)
	Blood	Genital secretion	Vaginal and rectal	Urine	Sputum	Others	Unknow	
III	59	8	20	8	4	34	190	323 (43.24)
Ib	9	34	6	6	7	13	102	177 (23.69)
Ia	11	4	2	2	6	28	67	120 (16.06)
V	3	15	2	5	3	12	41	81 (10.84)
II	2	1	0	2	1	3	12	21 (2.81)
VI	1	1	1	1	0	1	11	16 (2.14)
IV	0	0	0	1	0	2	1	4 (0.54)
VII	0	0	0	0	0	0	1	1 (0.13)
NT	0	0	0	0	0	1	3	4 (0.54)
Total	85	63	31	25	21	94	428	747 (100)

Note: Columns 1 to 5 under isolation source represent the primary sample types, all of which were collected from humans. Others: Include cervical samples, milk, skin, fish farm, bovine sources, and additional specimen types.
Abbreviation: GBS=group B Streptococcus.

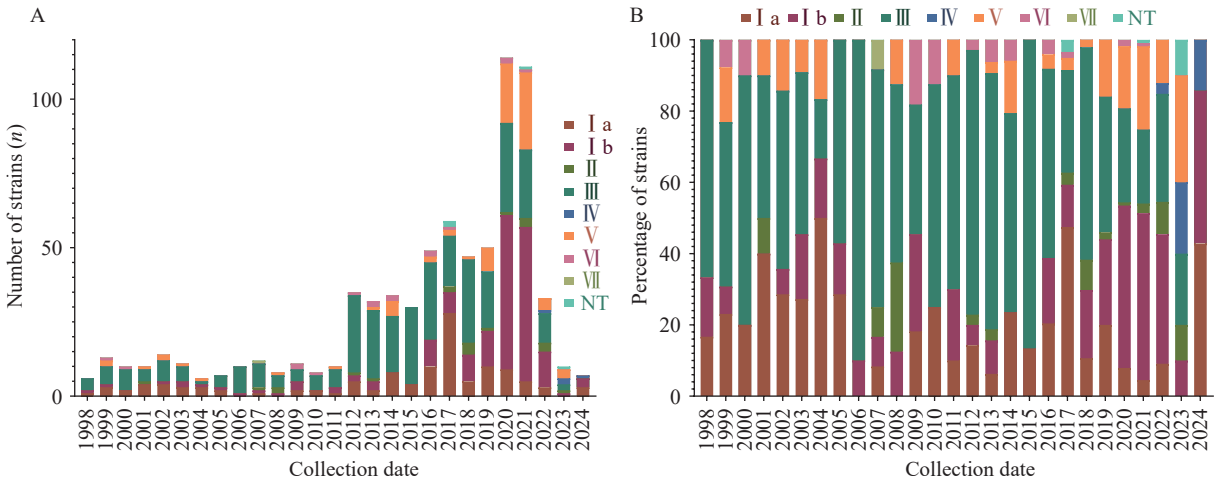


FIGURE 1. Spatio-temporal distribution of GBS in China. (A) Temporal distribution of GBS in China; (B) Temporal distribution of GBS in China, percentage stacked bar chart.
Abbreviation: GBS=group B Streptococcus.

Province (48.20%), Henan Province (53.97%), and Shanghai Municipality (44.44%). Statistical analysis revealed significant regional variations in serotype distribution (P<0.01, Table 2).

Phylogenetic Tree Construction

A maximum likelihood phylogenetic analysis of the 747 GBS genomic sequences revealed five distinct evolutionary lineages (Figure 2A). Lineage 5 comprised the largest group (n=281), predominantly containing serotypes III (n=184) and Ib (n=76). Lineage 3 encompassed 274 strains, with serotype Ib (n=176) being the most prevalent. Lineage 4 contained 141 strains, primarily consisting of serotypes III (n=93) and V (n=44). Lineage 2 was notably smaller, containing only two strains of serotype II, isolated from bovine sources in 2021. The analysis revealed no significant direct correlation between serotype classification and genetic evolutionary patterns, nor was there evidence of a relationship between phylogenetic lineage and endemic circulation patterns of the strains.

Distribution Pattern of Virulence- and ARGs- Associated Genes

A comprehensive analysis of 747 GBS genomes identified 56 virulence-associated genes, categorized into six functional groups: adherence, exoenzyme, exotoxin, immune modulation, nutritional/metabolic factors, and stress survival (Figure 2B, Table 3). Each

TABLE 2. Serotype and spatial distribution of GBS strains in China.

Region	Serotype*											Total
	Ⅰa	Ⅰb	Ⅱ	Ⅲ	Ⅳ	Ⅴ	Ⅵ	Ⅶ	Ⅷ	Ⅸ	NT	
Taiwan, China	51	22	8	155	0	16	11	1	0	0	0	264
Shandong	7	67	2	34	1	25	2	0	0	0	1	139
Henan	4	34	1	8	0	15	1	0	0	0	0	63
Hong Kong SAR	19	1	0	38	0	2	1	0	0	0	2	63
Shanghai	5	20	2	13	0	5	0	0	0	0	0	45
Beijing	2	7	0	6	0	1	0	0	0	0	0	16
Anhui	0	3	3	2	3	3	0	0	0	0	1	15
Guangdong	3	1	0	2	0	0	0	0	0	0	0	6
Jiangsu	1	1	1	0	0	1	1	0	0	0	0	5
Zhejiang	0	0	0	2	0	1	0	0	0	0	0	3
Guangxi	1	0	0	0	0	0	0	0	0	0	0	1
Hainan	1	0	0	0	0	0	0	0	0	0	0	1
Ningxia	1	0	0	0	0	0	0	0	0	0	0	1
Sichuan	0	0	0	1	0	0	0	0	0	0	0	1
Not collected	25	21	5	61	0	12	0	0	0	0	0	124
Total	120	177	22	322	4	81	16	1	0	0	4	747

Abbreviation: GBS=group B Streptococcus; Hong Kong SAR=Hong Kong Special Administrative Region.
* $P<0.001$.

genome harbored an average of 45 virulence genes, with 33 genes present in nearly all strains. While most strains carried either *fbsA* or *fbsB*, 161 strains (predominantly serotypes III and V) lacked these fibrinogen-binding genes. Notably, 48 serotype Ia and 205 serotype III strains lacked genes associated with bacterial pili (*pilA*, *pilB*, *pilC*, *setC1*, *srtC2*, *srtC3*, *srtC4*, *GBS_RS03565*, *GBS_RS03570*, *GBS_RS03585*), while 92 serotype III strains lacked the hyaluronidase gene (*hylB*). Additionally, 60 serotype Ia strains lacked the *cylX* gene, and strains of serotypes Ib (n=177), II (n=21), and V (n=81) were less likely to carry genes related to the GBS capsule. The *cba* gene was predominantly found in serotypes Ia (n=20) and Ib (n=148).

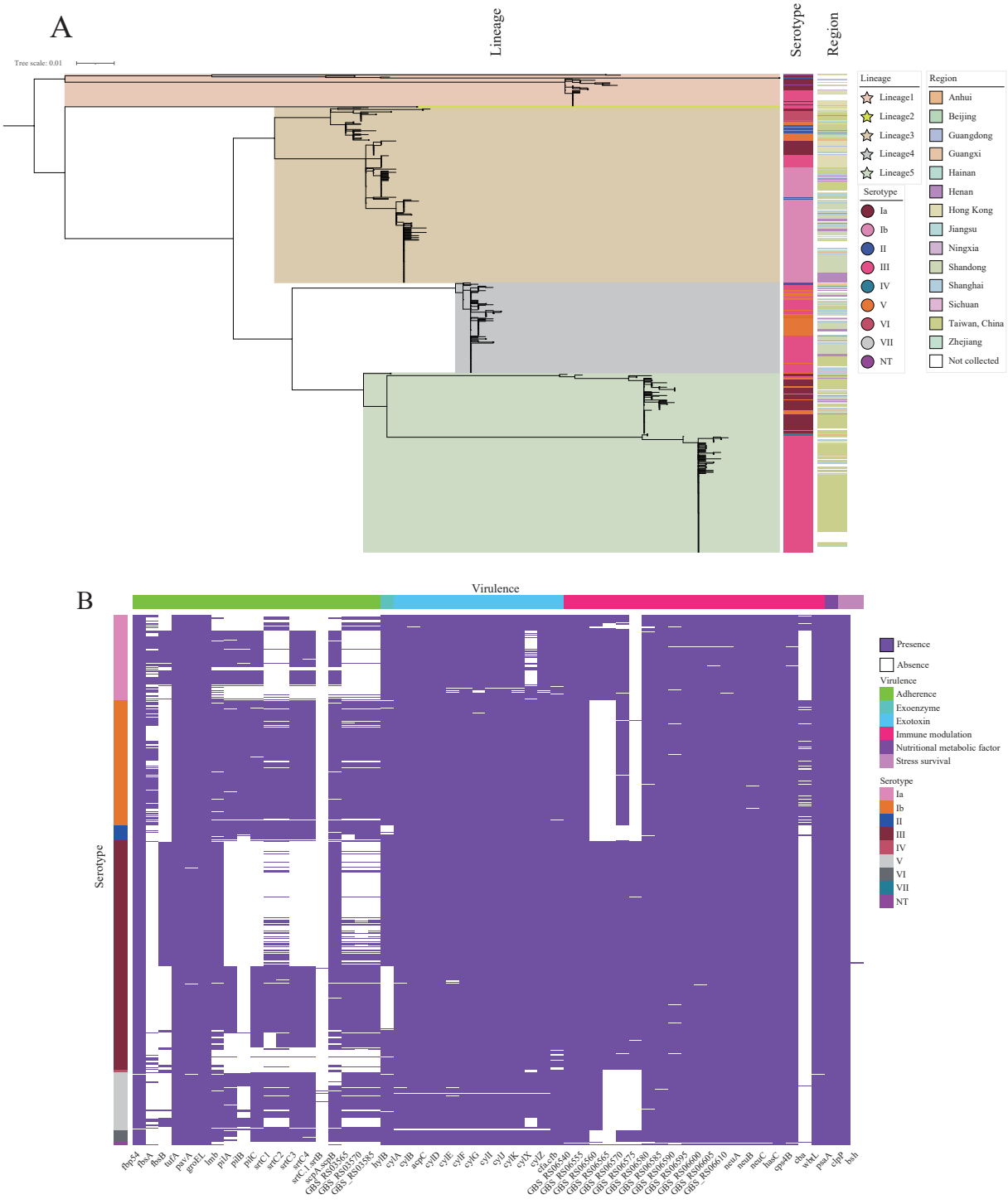
The genomic analysis revealed 27 antibiotic resistance genes (ARGs) associated with nine distinct antimicrobial drug classes (Figure 2C). Most genomes contained genes conferring resistance to peptides (*Saga_mprF*) and macrolide antibiotics (*mreA*), indicating fundamental resistance mechanisms in GBS. Over half of the strains carried genes for tetracycline resistance [*tet(M)*, n=387; serotype III, 210; Ia, 85; V, 61] and erythromycin resistance (*ermB*, n=429; serotype III, 192; Ib, 173; V, 38). Additionally, substantial proportions of strains carried genes encoding *APH3* (32.8%, n=245; serotype III, 176), *tetO* (29.6%, n=221; serotype III, 151), *aad6* (20.6%, n=154; serotype III, 102), lnub (15.8%, n=118; serotype III, 88), and *lsaE* (15.1%, n=113; serotype III, 83). Serotype III GBS strains consistently harbored the highest number of resistance genes. Detailed resistance profiles are provided in Supplementary Table S2 (available at https://weekly.chinacdc.cn/).

DISCUSSION

Among the 747 GBS strains collected in China from 1998 to 2024, we identified eight serotypes and one non-typeable serotype, with serotypes III, Ib, Ia, V, and II constituting 96.65% of all isolates. This distribution closely aligns with both global (98%) and previously reported Chinese (95.9%) distributions (*4*,*6*). Notably, the prevalence of serotype III (43.24%) in our study exceeds the global average (25%) but approximates the previously reported Chinese average (46.4%), reflecting significant regional heterogeneity within China (*4*,*6*). These findings suggest that while the overall GBS serotype distribution in China mirrors global trends, substantial intra-national variations exist. Geographic distribution analysis revealed marked regional differences, with Beijing Municipality demonstrating a high proportion of serotype III (38.3%), while Taiwan, China reported higher

prevalence of serotype VI (*11–12*). These observations underscore the pronounced geographical variations in GBS serotype distribution across China, emphasizing the necessity for region-specific surveillance studies. Temporal trend analysis indicates an increase in GBS cases, likely attributable to enhanced clinical awareness and advances in sequencing technologies, although the recent decline in case numbers may reflect the impact of coronavirus disease 2019 (COVID-19) pandemic disruptions or delays in sequencing data submission. Serotype III has maintained predominance throughout the study period, while serotype Ib has shown a notable increase in recent years, highlighting the critical importance of comprehensive serotype distribution data for targeted vaccine development strategies.

We identified six categories of virulence genes



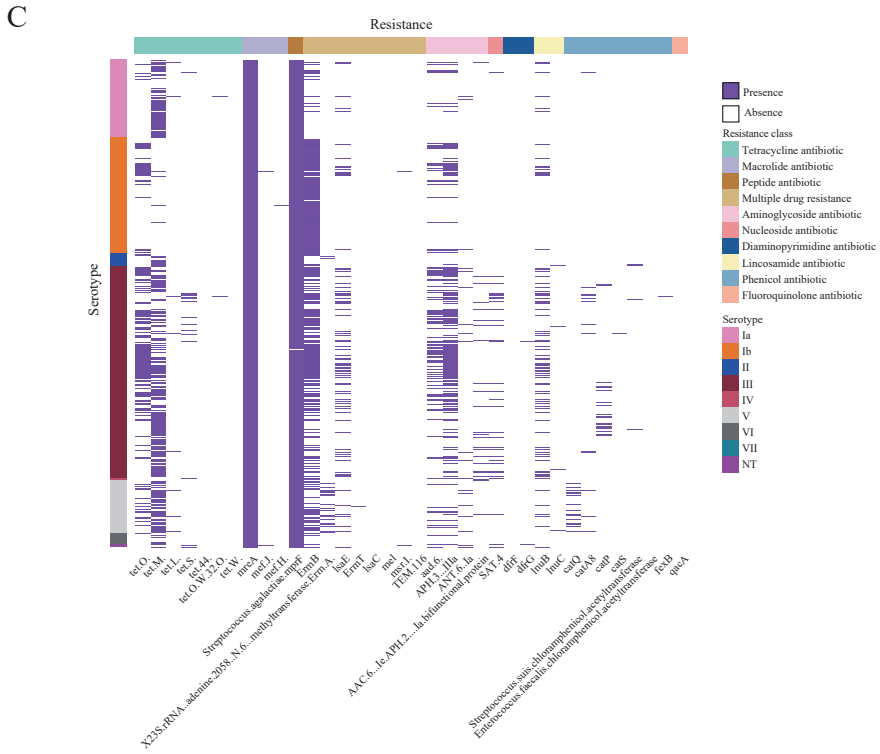


FIGURE 2. Phylogenomic tree and distribution of virulence- and ARGs-associated genes across 747 *Streptococcus agalactiae* genomes. (A) Phylogenomic tree of 747 GBS genomes constructed using maximum likelihood method based on core gene sequences; (B) Distribution of virulence-associated genes across 747 GBS genomes; (C) Distribution of antibiotic resistance genes across 747 GBS genomes.
Note: Genes with comparable functions or those belonging to the same functional class have been integrated in the visualization.
Abbreviation: GBS=group B Streptococcus.

through VFDB analysis, comprising a total of 56 genes. The adhesion protein *FbsA* facilitates GBS binding to fibrinogen, thereby protecting the pathogen from phagocytosis (*15*), while *fbsB* enhances GBS invasion into host cells and promotes vaginal colonization (*16*). Several genes (*SrtC1*, *SrtC2*, *GBS_RS03565*, *GBS_RS03570*, and *GBS_RS03585*) are associated with the pili type PI-1 structure. The PI-2a pilus comprises three subunit proteins (PilA, PilB, PilC), whose assembly requires sortases SrtC3 and SrtC4, collectively facilitating GBS invasion and colonization (*17–18*). While pili structures represent potential vaccine targets, strains lacking pili islands must be considered in vaccine development strategies (*19*). The gene encoding hyaluronidase (*hylB*) demonstrated a carriage rate of 85.68%, comparable to the 97.8% reported in Zimbabwean isolates (*20*). This enzyme enables GBS to breach the placental barrier, ascend from the vagina, and infect the fetus (*21*), while its absence significantly reduces GBS's capacity to invade fetal tissue and induce preterm delivery (*22*).

Exotoxin genes from the *cyl* gene family, *cfa*, and *cfbs*, together with the CAMP factor, are associated with β-hemolysis in GBS, causing tissue damage through lysis of human cells (*21*). The hemolytic properties of GBS play a crucial role in its pathogenesis and immune evasion mechanisms (*23*). The universal presence of cytochrome-encoding genes across all GBS strains suggests that targeting cytochrome functionality could represent a promising preventive strategy. Immunomodulatory genes, particularly those related to CPs, are critical virulence determinants, with CP-based vaccines currently under development. Our genomic analysis identified several virulence genes associated with CPs, with *GBS_RS06560*, *GBS_RS06565*, *GBS_RS06570*, and *GBS_RS06575* being notably underrepresented in serotypes Ib, II, V, and VI. Comparative analysis of capsular polysaccharide composition between these and other strains may elucidate the functional impact of these genes on the capsular structure. CPs enhance GBS virulence by facilitating immune evasion, inhibiting

TABLE 3. The classification of virulence-related factors of *Streptococcus agalactiae*.

VF category	Virulence genes	Virulence factor	Functions
Adherence	*tufA, groEL, fbp54, pavA, lmb, scpA/scpB, srtC-1/srtB, srtC3, srtC4, pilC, pilA, GBS_RS03585, srtC2, GBS_RS03565, GBS_RS03570, srtC1, pilB, fbsB, fbsA*	EF-Tu, GroEL, FBPs, PavA, Lmb, C5a peptidase, PI-2a, PI-1, FbsB, FbsA, RlrA islet	Adherence and colonization; promotes fibronectin-mediated collagen recruitment, adhesion and invasion; dissemination; impairs recruitment to sites of infection; biofilm formation; protein binding, recognizing the extracellular matrix; manipulates the host inflammatory response
Exoenzyme	*hylB*	Hyaluronidase	Dissemination, penetration
Exotoxin	*acpC, cylD, cylB, cylF, cylI, cylJ, cylA, cylK, cylZ, cylG, cfa/cfb, cylE, cylX*	Beta-haemolysin/cytolysin, CAMP factor	Forms pores in cell membrane; pro-inflammatory effects: induces apoptosis, promotes cellular invasion, and triggers iNOS and cytokine release
Immune modulation	*hasC, GBS_RS06540, GBS_RS06555, neuA, neuC, wbtL, GBS_RS06585, GBS_RS06595, GBS_RS06600, GBS_RS06605, GBS_RS06610, neuB, cps4B, GBS_RS06580, GBS_RS06590, GBS_RS06570, GBS_RS06560, GBS_RS06565, GBS_RS06575, cba*	Hyaluronic acid capsule, Capsule, LPS, Beta-C protein	Prevents phagocytosis; discourages C3b binding; binds to CD44, preventing the activation of the alternative complement pathway; inhibits complement-mediated opsonophagocytosis; LPS, resistant to complement deposition, masks cell wall-associated complement, preventing opsonophagocytosis
Nutritional/Metabolic factor	*psaA*	PsaA	Transport of Mn^{2}+ and Zn^{2}+ into bacterial cytoplasm, mutants impacts colonization and increase susceptibility to oxidative damage
Stress survival	*clpP, bsh*	ClpP, BSH	Serine protease involved in proteolysis and resisting the acute toxicity of bile and bile salts

Abbreviation: GBS=group B Streptococcus.

opsonophagocytosis, and promoting biofilm formation (*24*). The *cba* gene, predominantly found in serotypes Ia and Ib, may confer protection against opsonophagocytosis (*25*). While the virulence genes identified in this study provide valuable insights into GBS pathogenicity in China, they represent only a partial characterization, necessitating additional strain data and experimental validation for comprehensive assessment.

Antimicrobial resistance genes conferring resistance to clindamycin, erythromycin, and tetracycline were prevalent among the analyzed strains, with *Saga_mprF* specifically associated with daptomycin resistance (*26–27*). The *mreA* gene and members of the *erm* gene family were widely distributed, contributing to macrolide-lincosamide-streptogramin B resistance, particularly against clindamycin and erythromycin (*28–29*). Among 278 strains lacking erm genes, 16 harbored both *lsaE* and *lnuB*; however, their precise resistance mechanisms remain unclear due to limited sample availability. Six distinct *tet* genes were identified, with *tetM* and *tetO* encoding ribosomal protection proteins that confer tetracycline resistance (*30*). Additionally, some strains carried the *SAT-4* gene, which confers resistance to nucleoside antibiotics. While intrapartum antibiotic prophylaxis primarily targets early-onset GBS disease, the resistance profiles of GBS isolates continue to evolve, with increasing resistance to beta-lactams, erythromycin, and clindamycin, alongside emerging vancomycin-resistant strains (*31*). Comprehensive characterization of resistance gene distribution provides valuable insights into GBS resistance patterns, thereby informing the development of effective prevention and treatment strategies.

CONCLUSIONS

This study provides a comprehensive genomic characterization of *Streptococcus agalactiae* (GBS) in

China, encompassing serotype distribution, virulence factors, and antimicrobial resistance determinants. While the serotype distribution in China generally aligns with global patterns, significant regional variations exist that warrant further investigation. This research contributes essential knowledge for developing effective prevention and treatment strategies for GBS infections in China. Future studies should focus on more detailed regional and temporal analyses to inform targeted prevention approaches, treatment protocols, and vaccine development strategies.

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Vital Surveillances

The Spatiotemporal Epidemiology and Influencing Factor Analysis of Leptospirosis — Anhui Province, China, 2004–2023

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ABSTRACT

Introduction: Leptospirosis has historically been a severe public health concern across multiple Chinese provinces. Despite an overall decline in incidence in recent years, the disease continues to exhibit fluctuations and occasionally triggers localized outbreaks. This study aimed to characterize the demographic and spatiotemporal patterns of leptospirosis in Anhui Province — a historically significant epidemic region — from 2004 to 2023, to investigate potential climatic and environmental risk factors, and to identify critical targets for disease prevention and control.

Methods: Spatiotemporal cluster analysis was conducted using SaTScan software. Spearman correlation analysis was performed using SPSS to examine the short-term lagged effects of rainfall, temperature, and normalized difference vegetation index (NDVI) on leptospirosis incidence in the high-risk counties of Huaiyuan and Jingde.

Results: A total of 458 leptospirosis cases were reported across Anhui Province during the 20-year study period. Middle-aged individuals (40–59 years), males, and agricultural workers constituted the primary high-risk populations. Spatiotemporal scanning identified nine adjacent hotspots in southern Anhui during 2004–2012, with a subsequent shift to Huaiyuan County in the northern Huaihe River Basin during 2016–2021. Significant associations were observed between leptospirosis cases and temperature, rainfall, and NDVI in both Huaiyuan and Jingde counties.

Conclusion: This study revealed significant spatial heterogeneity, distinct spatiotemporal clustering patterns, and potential climatic and environmental risk factors for leptospirosis in Anhui Province during 2004–2023. These findings provide critical information regarding target regions, high-risk populations, and climatic and environmental factors to inform early warning systems and enhance prevention and control strategies for leptospirosis.

Leptospirosis is a globally neglected zoonotic disease, predominantly prevalent in Southeast Asia, Oceania, and Central and South America (*1*). Caused by pathogenic *Leptospira*, the disease accounts for approximately one million human cases and 60,000 deaths annually worldwide (*1–2*). Humans acquire infection through direct or indirect exposure to urine from reservoir animals, including pigs, dogs, and rodents (*2*). Since its classification as a notifiable infectious disease in China in 1955, leptospirosis has caused numerous outbreaks throughout history, primarily affecting central and southern regions including Anhui, Sichuan, Jiangxi, and Hunan provinces (*3*). Despite a significant decrease in overall incidence in recent years, small-scale outbreaks and sporadic cases continue to occur frequently across China (*4*). As a historically significant epidemic region, leptospirosis was first documented in Anhui Province in 1962. Severe outbreaks occurred in the Huaihe River Basin between 1970–1972 following heavy rainfall and flooding, with incidence peaking at 255.91 per 100,000 population in 1971, accounting for 30% of national cases (*3*). The disease exhibited distinct geographical shifts, predominantly affecting southern mountainous areas between 1960–1980 before transitioning to the northern Basin between 1980–2000. Jingde County emerged as a significant high-risk region, reporting the highest morbidity of 175.50 per 100,000 population in 1990 (*5*). Huaiyuan County represents another persistent hotspot, having reported peak morbidity of 56.73 per 100,000 population in 1972. Recent outbreaks in Huaiyuan, with 40 and 27 cases reported in 2016 and 2021

respectively, underscore that this region remains a significant leptospirosis hotspot in Anhui [data obtained from the China Information System for Diseases Control and Prevention (CISDCP)]. These epidemiological patterns indicate that leptospirosis continues to pose a serious yet neglected public health challenge warranting further investigation to identify high-risk regions and temporal clusters in Anhui Province.

To date, few comprehensive long-term studies have focused on demographic and spatiotemporal clustering analysis of leptospirosis in Anhui Province. To identify epidemiological characteristics and potential spatiotemporal hotspots, we conducted descriptive and geographical analyses spanning 2004–2023. Previous research has demonstrated that extreme weather events (e.g., heavy rainfall, flooding, and hurricanes), climatic factors (e.g., humidity and temperature), and environmental variables (e.g., land cover variations, presence of water bodies) may significantly influence leptospirosis transmission dynamics (*1*–*2*). To explore potential risk factors and their short-term effects on disease incidence, we performed correlation analyses between local climatic and environmental factors and leptospirosis cases in two high-risk counties — Huaiyuan and Jingde. The detailed characterization of epidemiological patterns, spatiotemporal hotspots, and identification of high-risk populations, climatic and environmental factors provides a scientific foundation for developing targeted prevention and control strategies for leptospirosis.

METHODS

Surveillance data of leptospirosis from January 2004 to December 2023 in Anhui Province, including both clinically diagnosed and laboratory-confirmed cases based on the Diagnostic Criteria for Leptospirosis (WS 2902008), were obtained from the CISDCP. The data included comprehensive demographic information such as age, gender, occupation, residential address, and date of illness onset for all leptospirosis patients. Demographic data for Anhui Province were obtained from the National Bureau of Statistics of China.

A descriptive analysis of county-level surveillance data was conducted to characterize the epidemiological features of leptospirosis. Spatiotemporal scanning analyses were performed using SaTScan (version 9.6, Information Management Services, Maryland, USA) based on spatial dynamic window scanning methodology. Relative risk (RR) and log-likelihood ratio (LLR) were calculated to quantify the elevated risk within scanning windows compared to areas outside these windows. The scanning window with the highest LLR value was designated as the primary cluster, while other windows with statistically significant LLRs were classified as secondary clusters. To investigate potential risk factors and their short-term effects on leptospirosis incidence, Spearman correlation analysis was conducted between local precipitation, temperature, normalized difference vegetation index (NDVI) and reported leptospirosis cases in two high-risk counties (Huaiyuan and Jingde) from 2004 to 2023 using SPSS (version 22.0, IBM Corp., Armonk, NY, USA). Monthly climatic data were obtained from the National Tibetan Plateau Data Center (https://data.tpdc.ac.cn/). Monthly NDVI data were sourced from the National Aeronautics and Space Administration (https://www.nasa.gov/). All statistical analyses were performed using SPSS, and circular heatmaps were generated using chiplot (https://www.chiplot.online/). Results were considered statistically significant when P values were less than 0.05.

RESULTS

Epidemiological Characteristics of Human Leptospirosis in Anhui

From 2004 to 2023, a total of 458 cases from 45 counties were reported in Anhui, with an annual average incidence rate of 0.037 per 100,000 population (Figure 1). Overall, leptospirosis incidence remained low throughout the study period, with notable spikes occurring in 2007, 2008, 2010, 2016, and 2021. Annual incidence rates fluctuated between 0.01 and 0.09 per 100,000 population.

Leptospirosis cases were documented across all age groups, with the highest prevalence observed among adults aged 40–59 years (n=222, 48.47%). Farmers constituted the predominant occupational category (n=405, 88.43%), followed by students (n=15, 3.28%). The male-to-female ratio was 2.14∶1. Leptospirosis cases were reported in every month except February, with August and September (n=349, 76.20%) representing the primary peak season annually, demonstrating distinct single-peak seasonal characteristics (Figure 2).

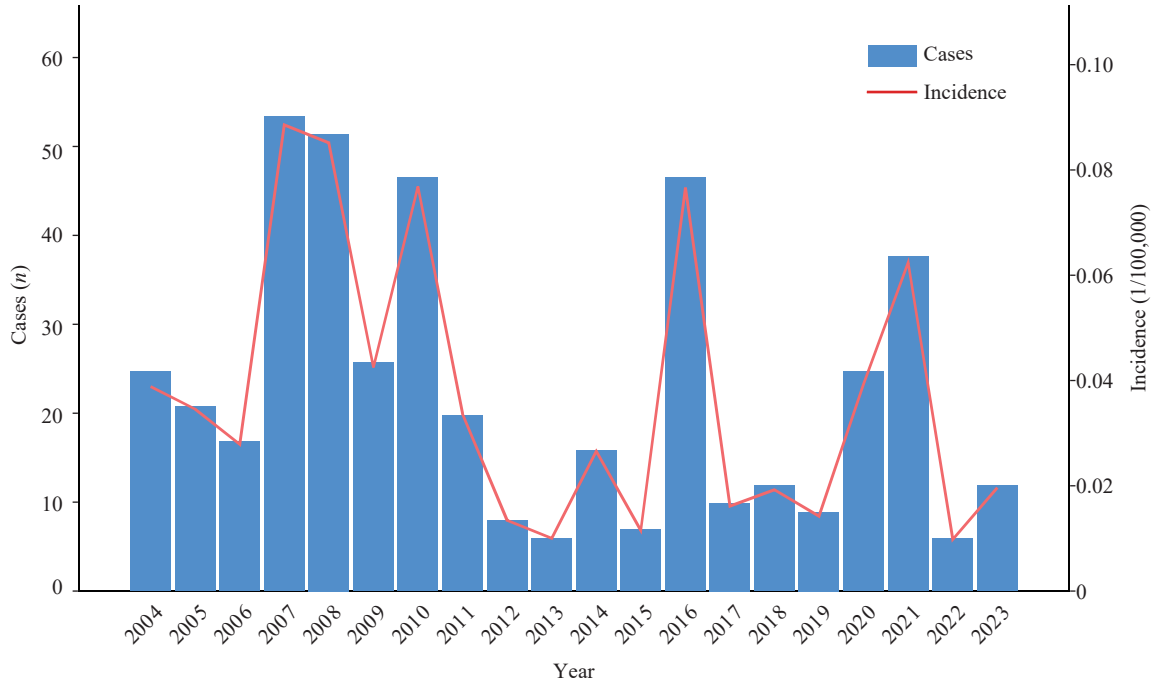

FIGURE 1. Annual distribution of leptospirosis cases in Anhui Province, China, 2004–2023.

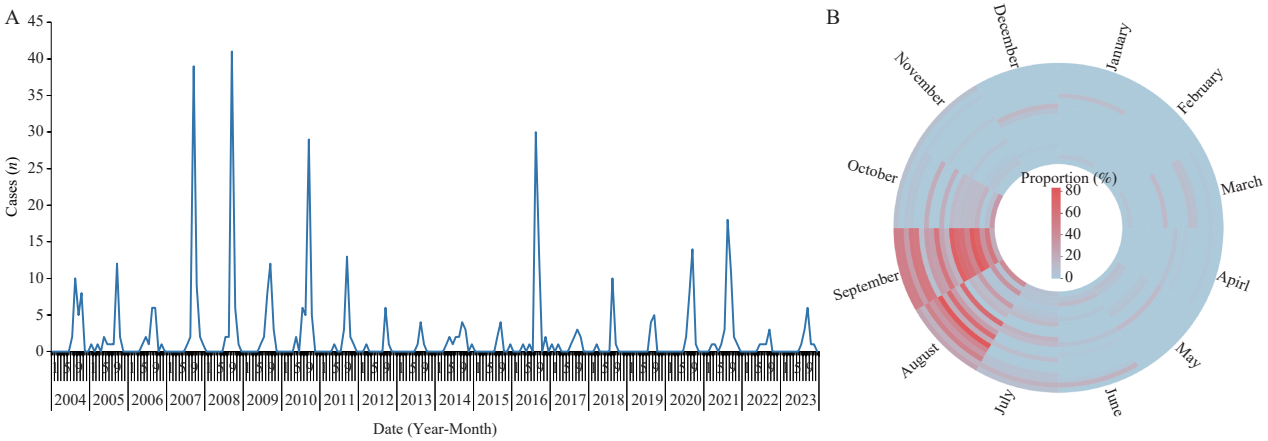

FIGURE 2. The monthly reported cases of leptospirosis in Anhui Province, China, 2004–2023, (A) Monthly distribution of leptospirosis cases each year; (B) Circular heatmap of the proportion of monthly leptospirosis cases each year.
Note: The order of the circles from the inside to the outside is represented 2004–2023.

Spatiotemporal Analysis of Human Leptospirosis in Anhui

Significant spatial heterogeneity was observed in the distribution of leptospirosis cases across counties in Anhui Province between 2004–2023, with Huaiyuan and Jingde emerging as the two highest-risk counties based on cumulative case numbers over the 20-year period (Supplementary Table S1, available at https://weekly.chinacdc.cn/). Multiple small-scale outbreaks occurred throughout this timeframe. Jingde County reported the highest incidence rates of 14.49, 8.98, and 15.26 per 100,000 population, accounting for 38.89%, 25.00%, and 46.81% of all Anhui cases in 2007, 2008, and 2010, respectively. Huaiyuan County subsequently emerged as a major hotspot, with incidence rates of 4.12 and 2.89 per 100,000 population, representing 85.11% and 72.97% of total provincial cases in 2016 and 2021, respectively. Spatiotemporal scan analysis revealed non-random distribution of leptospirosis across geographical areas and time periods, identifying one most likely cluster and one secondary cluster (Table 1). The most likely cluster was concentrated in the southern mountainous

TABLE 1. The results of spatiotemporal scan analysis of leptospirosis in Anhui Province, China, 2004–2023.

Cluster types	Year	Counties
Most likely cluster	2004–2012	Qimen, Yixian, Huangshan, Jingde, Jixi, Xiuning, Tunxi, Huizhou, Shexian.
Secondary cluster	2016–2021	Huaiyuan

areas, encompassing 9 adjacent counties (Qimen, Yixian, Huangshan, Jingde, Jixi, Xiuning, Tunxi, Huizhou, and Shexian) from 2004–2012 (LLR= 737.62, RR=88.06, P<0.001). The secondary cluster was localized to Huaiyuan in the northern Huaihe River Basin from 2016–2021 (LLR=330.76, RR=65.60, P<0.001).

The Correlations Between Climatic, Environmental Factors and Leptospirosis in Huaiyuan and Jingde Counties

Based on the results of Spearman correlation analysis in Huaiyuan and Jingde, significantly positive correlations were observed between the numbers of reported case and average temperature, maximum temperature, and minimum temperature at lag periods of 0–3 and 6 months (P<0.05) (Table 2). Positive correlations were identified between leptospirosis and NDVI at lag periods of 0–1, 4, and 5 months in Huaiyuan, and at lag periods of 0–3, 5, and 6 months in Jingde, respectively (P<0.05) (Table 2). Similarly, positive correlations were observed between leptospirosis and rainfall at lag periods of 0–3 and 6 months in Huaiyuan, and at lag periods of 1–4 months in Jingde (P<0.05) (Table 2).

DISCUSSION

In this study, we analyzed the epidemiological characteristics and spatiotemporal patterns of leptospirosis in Anhui Province from 2004 to 2023, and explored potential climatic and environmental factors influencing disease transmission in high-risk regions. Throughout the 20-year study period, leptospirosis maintained a generally low incidence with significant spatial heterogeneity. Our findings suggest that temperature, rainfall, and NDVI may play substantial roles in driving increased leptospirosis incidence in Huaiyuan and Jingde Counties. This represents the first comprehensive analysis based on an extensive surveillance dataset to elucidate the predominant spatiotemporal patterns, identify key high-risk regions, and determine potential risk factors for leptospirosis in Anhui Province.

The significantly higher incidence among males compared to females in Anhui aligns with previous epidemiological studies (*3*–*4*). Middle-aged adults (40–59 years), males, and farmers — who constitute the primary local workforce — face elevated exposure risk to Leptospira-contaminated environments through activities such as rice harvesting, livestock management, fishing, and swimming (*4*,*6*). These findings underscore the necessity for enhanced health education targeting these vulnerable populations, particularly in rural communities. Our analysis revealed a distinct single-peak seasonal pattern of leptospirosis transmission, consistent with previous studies in Anhui (*7*). This peak coincides with the agricultural harvesting season and periods of high rainfall, further supporting the relationship between environmental conditions and disease transmission.

In this study, significant spatial heterogeneity was revealed. The high-incidence regions were predominantly concentrated in the southern mountainous areas and the northern Huaihe River Basin. Anhui, as a significant epidemic region, is traversed by both the Yangtze and Huaihe Rivers. The abundant rainfall, moist subtropical climate, and diverse host animal populations provide favorable environmental conditions for leptospirosis transmission. Notably, nine adjacent counties in the southern mountainous areas of Anhui formed the most likely high-risk cluster during 2004–2012, but the hotspots subsequently shifted to Huaiyuan in the northern Huaihe River Basin during 2016–2021. Rodents constituted the primary reservoir hosts in both high-risk regions of Huaiyuan and Jingde. The increased leptospirosis morbidity in Huaiyuan may be attributed to higher rodent densities and carrier rates, altered rodent species composition, and expanded rice cultivation areas (*8*–*10*). Three critical risk factors — rodent density exceeding 15%, rodent carrier rate exceeding 15%, and antibody levels against leptospirosis in the local population below 15% — precipitated the 2016 leptospirosis outbreak in Huaiyuan (*7*). Mechanized harvesting practices may have concurrently reduced human contact with contaminated environments in recent years (*4*). Consequently, more targeted control efforts are needed in these high-risk areas through enhanced epidemiological surveillance, promotion of protective

TABLE 2. Correlation coefficients between climatic, environmental factors and the numbers of reported cases in Huaiyuan and Jingde counties, Anhui Province, China, 2004–2023.

Characteristics	Lag (months)						
	0	1	2	3	4	5	6
Huaiyuan							
Average temperature (℃)	0.340**	0.439**	0.374**	0.223**	0.056	−0.096	−0.266**
Rainfall (mm)	0.279**	0.389**	0.339**	0.182**	0.038	−0.05	−0.147*
NDVI	0.377**	0.342**	0.116	0.108	0.208**	0.155*	−0.029
Maximum temperature (℃)	0.336**	0.437**	0.375**	0.224**	0.056	−0.094	−0.269**
Minimum temperature (℃)	0.340**	0.441**	0.375**	0.229**	0.065	−0.096	−0.264**
Jingde							
Average temperature (℃)	0.232**	0.410**	0.431**	0.293**	0.122	−0.063	−0.236**
Rainfall (mm)	−0.027	0.190**	0.272**	0.343**	0.234**	0.113	0.018
NDVI	0.248**	0.394**	0.398**	0.246**	0.048	−0.178**	−0.178**
Maximum temperature (℃)	0.243**	0.411**	0.430**	0.284**	0.123	−0.054	−0.230**
Minimum temperature (℃)	0.220**	0.409**	0.435**	0.304**	0.120	−0.072	−0.239**

Abbreviation: NDVI=normalized difference vegetation index.
* $P<0.050$
** $P<0.001$.

equipment (rubber boots and gloves), and implementation of leptospirosis immunization when warranted.

Significant associations between leptospirosis, and climatic and environmental risk factors — including average humidity, precipitation, temperature, and difference water index — have been documented in previous research, though the reported lag effects vary considerably from weeks to months or even years (*1*,*11*). Our results demonstrate that the numbers of reported cases were significantly associated with temperature, rainfall, and NDVI in the two high-risk counties of Huaiyuan and Jingde. The strongest positive correlations were observed between leptospirosis and concurrent NDVI, with local temperature and rainfall showing strongest associations at a one-month lag in Huaiyuan. Compared to July measurements in 2015 and 2020, Huaiyuan experienced substantial rainfall increases of 47.06% and 19.83% in 2016 and 2021, respectively. The lagged effects of local precipitation likely constituted the primary risk factor for subsequent leptospirosis outbreaks in Huaiyuan, consistent with findings from Lezhi, China (*12*). Humid and warm conditions favor *Leptospira* survival, increase animal reservoir abundance, and facilitate environmental transmission of the pathogen. NDVI correlates with vegetation cover, livestock grazing patterns, animal reservoir abundance, and agricultural activities. Therefore, systematic monitoring and early-warning systems, coupled with locally-tailored intervention measures, are essential to reduce the burden of leptospiral infection in Huaiyuan.

In summary, our findings revealed significant spatial heterogeneity and distinct spatiotemporal clustering of leptospirosis in Anhui Province from 2004 to 2023. These results provide important insights for characterizing high-risk areas and strengthening ongoing surveillance and control efforts. However, this study has several limitations. Potential socioeconomic factors, host animal density, and *Leptospira*-carrying rates that may influence leptospirosis transmission were not included in the analysis. Additional risk factors should be explored in future investigations.

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SUPPLEMENTARY MATERIAL

SUPPLEMENTARY TABLE S1. The regions with top five highest numbers of annual reported cases in Anhui Province, China, 2004–2023.

Year	1	2	3	4	5
2004	Xiuning	Jingde, Shexian	Huangshan	Yixian, Qimen	Jixi
2005	Jingde	Shexian	Xiuning	Mingguang	Huangshan, Fengyang
2006	Jingde	Shexian	Xiuning, Mingguang, Huangshan, Qimen, Huizhou, Wuhe		
2007	Jingde	Shexian	Yixian	Qimen	Xiuning
2008	Jingde	Shexian	Yixian, Qimen	Huangshan	Xiuning
2009	Shexian	Jingde	Huaiyuan	Xiuning, Huizhou	Yixian, Qingyang
2010	Jingde	Xiuning, Huangshan	Shexian	Huaiyuan	Qimen, Dangtu, Huaining, Yizhou
2011	Jingde, Huangshan	Yixian	Xiuning	Huaiyuan, Mingguang, Lixin, Yingdong	
2012	Jingde	Yixian	Huaiyuan		
2013	Shexian	Jingde, Xiuning, Tianchang, Huaiyuan			
2014	Jingde	Xiuning, Huangshan	Shexian, Yixian, Yongqiao, Tunxi, Daguan		
2015	Jingde	Xiuning, Huaiyuan, Tianchang, Tongcheng, Jixi			
2016	Huaiyuan	Huangshan,Taihe	Xiuning, Yixian, Nanqiao		
2017	Huaiyuan	Jingde, Shexian	Yixian, Sixian, Congyang		
2018	Huaiyuan	Guichi			
2019	Huaiyuan	Jingde			
2020	Huaiyuan	Jingde, Sixian, Yingshang, Yeji, Jinghu, Yingzhou			
2021	Huaiyuan	Yian, Fengtai	Sixian, Lixin, Wuhe, Xiejiaji, Tianjiaan, Shucheng, Nanling		
2022	Qingyang	Huaiyuan, Yixian, Guangde, Yingquan			
2023	Guichi	Qingyang, Huaiyuan, Sixian, Yingshang, Xiuning, Tongcheng, Dongzhi, Lingbi, Linquan			

Preplanned Studies

Differences Between the Local and Migrant Populations in Healthcare Service Use and Direct Cost of Tuberculosis Treatment — Shanghai Municipality, China, 2020–2021

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Summary

What is already known about this topic?

Tuberculosis (TB) disproportionately affects socially vulnerable populations, particularly the migrant population. Shanghai has implemented a policy providing additional reimbursement for TB diagnosis and treatment beyond standard health insurance coverage for residents. However, comprehensive evidence on TB care utilization patterns and treatment costs remains limited, especially on the disparities between local and migrant populations

What is added by this report?

From 2020 to 2021, local and migrant TB patients in Shanghai demonstrated comparable outpatient visit frequencies with an overall hospitalization rate of 85.7%. Migrant TB patients without resident permits are ineligible for government reimbursement, resulting in over half of the patients encountering out-of-pocket costs that exceed 20% of their annual household income for TB treatments.

What are the implications for public health practice?

The government's reimbursement policy should be expanded to include the most vulnerable populations, specifically migrant patients without residency permits, to strengthen the financial risk protection for TB patients.

ABSTRACT

Background: Tuberculosis (TB) disproportionately impacts socially vulnerable populations, including migrants. This study aimed to investigate the utilization of TB care services and the financial burden on TB patients during 2020–2021 in Shanghai and to examine differences between local and migrant patients.

Methods: A retrospective survey was conducted in three districts of Shanghai among drug-sensitive TB patients who initiated treatment on or after January 24, 2020, and had completed treatment by the time of the interview in 2021. The study used a designed sampling ratio of 1∶1 for both local and migrant populations, and examined the use of outpatient and inpatient care, as well as the direct costs of treatment. Descriptive analyses and statistical tests were utilized to assess differences in patient characteristics between locals and migrants, with and without a residence permit. Logistic regression was used to examine the impact of migrant status on service usage and financial burden, after adjusting for demographic and socio-economic factors.

Results: The study included a total of 196 TB patients, comprising 88 locals and 108 migrants. No significant differences in the average number of outpatient visits were observed between migrant and local patients. Migrants with a residence permit (RP) had the highest hospitalization rate (92.86%), followed by migrants without an RP (86.84%), and then local patients (79.55%). The median out-of-pocket (OOP) payment for the entire treatment course, including medical and non-medical costs, was 15,845 yuan for migrants without an RP, with descending amounts for migrants with an RP, and then local patients (P<0.001). The proportion of patients incurring OOP payments exceeding 20% of their annual household income was also highest among migrants without an RP (57.14%). Regression analysis indicated that migrants without an RP faced the highest financial risk during TB treatment. Even migrants with an RP showed significantly higher financial risk compared to local patients (P<0.05).

Conclusions: During 2020–2021, the utilization of TB care in Shanghai was high among both local and migrant TB patients. Nevertheless, significant financial burdens were more pronounced among migrant patients without RP.

Tuberculosis (TB) remains a significant global health challenge that disproportionally affects socially vulnerable populations. Studies from low-income and middle-income countries have demonstrated that domestic migrant workers face higher risk of TB and often encounter financial hardships when seeking treatment (*1*–*4*). Global TB service capacity experienced disruption between 2020 and 2022 due to coronavirus disease 2019 (COVID-19) pandemic (*5*–*6*). In 2018, Shanghai Municipality, China, implemented a policy providing government reimbursement, after health insurance reimbursement, for out-of-pocket (OOP) payments related to essential TB diagnosis and treatment services. This policy extends to both local and migrant patients holding a Shanghai Resident Permit (RP). Within this policy framework, migrant TB patients are defined as individuals without permanent registered residence in Shanghai, who reside in the city, and are managed by the Shanghai CDC. This study analyzed TB care utilization and its associated costs from 2020 to 2021 by linking the data from a TB patient survey with the Shanghai TB registry and government reimbursement records. Specifically comparing these aspects between the local and migrant populations. The findings revealed that the average number of outpatient visits was 11.48 for local patients, 11.33 for migrant patients with an RP, and 9.92 for migrant patients without an RP, while the overall hospitalization rate was at 85.7%. Migrant patients without an RP incurred the highest OOP payments for complete TB treatment, with over half of them experiencing OOP payments exceeding 20% of their annual household income.

A TB patient survey was conducted across three districts in Shanghai, selected based on local patient registration volumes and varying economic levels. The survey data were integrated with the Shanghai TB registry and government financial records to evaluate treatment utilization patterns and associated expenses. The study specifically focused on rifampicin-sensitive patients who initiated treatment after January 25, 2020, and completed their treatment course by the interview date. To ensure robust comparative analysis, the study design aimed for equal representation between local and migrant patients. Sample size calculations were performed using Stata's 'sampsi' command, targeting the detection of a minimum 15% difference in the proportion of patients experiencing high financial burden between local and migrant populations, assuming a 30% baseline incidence among local patients. With parameters set at 0.05 significance level and 80% power, the required sample size was calculated at 252 participants, with a target enrollment of 300 to ensure adequate statistical power. Patient enrollment followed chronological order based on registration dates, and participants completed a structured questionnaire capturing: 1) demographic and socioeconomic information; 2) TB treatment care utilization patterns; and 3) comprehensive direct medical and non-medical treatment costs.

Care utilization assessment encompassed multiple metrics: outpatient visit frequency, hospitalization rates, total hospital stays, and average length of hospital stays. The total OOP payment for complete TB treatment included both medical and non-medical expenses. OOP medical payments were calculated by subtracting health insurance and government reimbursements from total medical costs. Non-medical payments encompassed transportation, caregiver fees, food, and accommodation expenses incurred during treatment. A high financial risk threshold was established at the point when total OOP payments exceed 20% of annual household income.

To analyze differences in TB care utilization, OOP expenses, and financial burden among three residential groups — locals, migrants with RP, and migrants without RP — multiple statistical approaches were employed. Chi-square tests and F-tests were applied where appropriate, while the Kruskal-Wallis H test was specifically used for analyzing non-normally distributed expense data. Linear regression models were constructed to examine the factors associated with OOP costs for TB treatment, while logistic regression was utilized to investigate the factors associated with TB-related hospitalization and elevated financial risk from care utilization. The identification of relevant demographic, socioeconomic, and disease-related covariates for multivariate analysis was conducted through stepwise regressions using forward selection, with a threshold *P*-value of 0.15.

Due to logistical constraints, 196 TB patients were enrolled, comprising of 88 locals and 108 migrants (70 with resident permits). Approximately 90% were new TB cases (Table 1). Migrant patients were significantly younger than local patients ($P<0.001$). Comorbidities were present in over one-third of local patients compared to approximately 12% of migrant patients ($P<0.001$). While more than half of local patients were

TABLE 1. Demographic and socioeconomic characteristics of TB patients.

Characteristics	Total		Local		Migrant with RP		Migrant without RP		*P*
	N	%	*N*	%	*N*	%	*N*	%	
All	196		88	44.9	70	35.7	38	19.4	
District									
Baoshan	82	41.84	29	32.95	29	41.43	24	63.16	<0.001
Hongkou	41	20.92	32	36.36	9	12.86	0	0	
Jingan	73	37.24	27	30.68	32	45.71	14	36.84	
Age (years)									
<30	64	32.65	13	14.77	25	35.71	26	68.42	<0.001
30 –59	81	41.33	33	37.5	38	54.29	10	26.32	
≥60	51	26.02	42	47.73	7	10	2	5.46	
Sex									
Female	85	43.37	32	36.36	37	52.86	16	42.11	0.114
Male	111	56.63	56	63.64	33	47.14	22	57.89	
Education									
Primary school or secondary school	13	6.63	8	9.09	3	4.29	2	5.26	0.275
High school or vocational school	84	42.86	43	48.86	27	38.37	14	36.84	
College or university and above	99	50.51	37	42.05	40	57.14	22	57.89	
Employment status after the pandemic									
Employed	111	56.63	27	30.68	55	78.57	29	76.32	<0.001
Retired	57	29.08	48	54.55	8	11.43	1	2.63	
Others	28	14.29	13	14.77	7	10	8	21.05	
Annual income*									
Below average	47	23.98	17	19.12	16	22.86	14	36.84	0.103
Above average	149	76.02	71	80.68	54	77.14	24	63.16	
Medical insurance†									
No insurance	10	5.21	1	1.18	5	7.25	4	10.53	<0.001
Shanghai UEBMI	113	58.85	54	63.53	45	65.22	14	36.84	
Shanghai URRBMI	31	16.15	25	29.41	4	5.80	2	5.26	
Medical insurance at hometown	27	14t.06	–	–	11	15.94	15	39.47	
Others	11	5.73	4	4.71	4	5.80	3	7.89	
Patient type									
New	178	90.82	78	88.64	66	94.29	34	89.47	0.451
Relapse	18	9.18	10	11.36	4	5.71	4	10.53	
Diagnosis results§									
Positive	114	58.16	53	60.23	37	52.86	24	63.16	0.508
Negative	82	41.84	35	39.77	33	47.14	14	36.84	
Comorbidities¶									
No comorbidity	149	76.41	54	62.07	62	88.57	33	86.84	<0.001
≥1 Comorbidity	46	23.59	33	37.93	8	11.43	5	13.16	

Note: "–" means not applicable.
Abbreviation: TB=tuberculosis; RP=residence permit; UEBMI=urban employee basic medical insurance; URRBMI=urban and rural resident basic medical insurance; CNY=Chinese Yuan.
* Shanghai's 2020 per capita urban disposable income: 72,232 CNY.
† Medical insurance data were missing for 4 local patients and 1 migrant with an RP.
§ Diagnosis results were negative, including TB patients for whom etiological test results are not available.
¶ Data on comorbidities were missing for one local patient.

retired, over 75% of migrant patients were employed (P<0.001). Notably, 76% of participants reported incomes exceeding Shanghai's 2020 per capita urban disposable income. Among migrant patients, 7.25% with an RP and 10.53% without an RP lacked medical insurance coverage.

Regarding TB treatment utilization, patients averaged 11.12 outpatient visits, with an overall hospitalization rate of 85.71%. Among patient subgroups, migrants holding an RP demonstrated the highest hospitalization rate (92.86%), followed by migrants without an RP (86.84%), and local patients (79.55%). The mean hospital stay duration was 7.79 days, with migrants without an RP experiencing the longest stays. However, these differences did not reach statistical significance.

Analysis of medical expenditure revealed that migrants without an RP incurred the highest total OOP payments (median 15,845 Chinese Yuan), followed by migrants with an RP, and then local patients (P<0.001) (Table 2). Outpatient care comprised 57.46% of total OOP payments before government reimbursements. Dunn's tests demonstrated statistically significant differences in both total and medical OOP payments among all three residential groups (P<0.001). Significant differences in both outpatient and inpatient payments were observed between local patients and both migrant groups (P<0.001), though no significant differences emerged between the two migrant groups. The proportion of patients experiencing catastrophic health expenditure (OOP payments exceeding 20% of annual household income) was markedly higher among migrants without an RP (57.14%, 16/28) compared to local patients (2.60%, 2/77).

Multivariate analysis (Table 3) revealed that migrants with an RP had significantly higher odds of hospitalization [odds ratio (OR)=4.12, P<0.05], while migrants without an RP incurred significantly higher OOP payments compared to locals (P<0.05). Shanghai basic medical insurance enrollment and above-average income were also associated with higher OOP payments (P<0.05). Migrants without an RP faced the highest financial risk during TB treatment, and even migrants with an RP demonstrated significantly higher financial risk compared to local patients (P<0.05).

DISCUSSION

This study revealed that from 2020 to 2021, the majority of patients with drug-sensitive TB in Shanghai adhered to prescribed outpatient treatment regimens and hospitalization schedules. While migrant TB patients demonstrated a higher propensity for hospitalization, their overall length of hospital stays was comparable to local patients. Both migrant groups — those with and without an RP — incurred significantly higher OOP costs compared to local patients. Furthermore, migrant patients without an RP faced the highest risk of experiencing severe financial burden due to TB treatment.

TB care utilization in Shanghai was maintained at adequate levels from 2020 to 2021. However, according to clinical guidelines, inpatient care might not be medically necessary for most TB patients (*7*). The findings revealed higher hospitalization rates and OOP payments among migrant patients, despite their notably younger demographic profile and lower

TABLE 2. OOP Payment for TB Treatment by Residence Type.

OOP payment	Total (n=168)		Local (n=77)		Migrant with RP (n=63)		Migrant without RP (n=28)		P (KW H test)
	Median	(Q1, Q3)	Median	(Q1, Q3)	Median	(Q1, Q3)	Median	(Q1, Q3)	
Total OOP payment	6,199	(3,120, 12.436)	4,264	(2,242, 7,335)	7,410	(4,511, 15,135)	15,845	(8,601, 31,611)	<0.001
Medical OOP before government reimbursement	7,685	(4,774, 13,000)	5,834	(3,800, 9,122)	8,285	(5,650, 16,900)	15,820	(8,501, 30,505)	<0.001
Outpatient (%)	3,925 (57.46)	(2,116, 6,094)	3,000 (57.86)	(1,800, 4,511)	4,565 (58.89)	(2,700, 8,400)	5,750 (55.05)	(3,850, 17,400)	<0.001
Inpatient (%)	3,241 (42.54)	(1,200, 5,384)	2,294 (42.14)	(639, 4,991)	3,602 (41.11)	(1,723, 6,500)	5,497 (44.95)	(1,411, 14,500)	<0.01
Government reimbursement	1,286	(0, 2,666)	2,070	(1,070, 2,845)	1529	(0, 2,819)	–		0.13
Non-medical payment	30	(4,258)	2	(4,233)	60	(6,360)	40	(0, 238)	0.51

Note: "–" means not applicable

Abbreviation: TB=tuberculosis; OOP=out-of-pocket; RP=residence permit; SD=standard deviation; KW=Kruskal-Wallis;

TABLE 3. Factors associated with TB-related hospitalization, OOP payments, and financial burden.

Factors	Hospitalization incidence				OOP				OOP payment exceeding 20% of the annual household income			
	OR	*P*	95% *CI*		Coef.	*P*	95% *CI*		*OR*	*P*	95% *CI*	
Residential type												
Local	ref.								ref.			
Migrant with RP	4.12	0.014	1.34	12.72	0.317	0.155	−0.121,	0.755	9.14	0.012	1.63,	51.22
Migrant without RP	1.96	0.293	0.56	6.83	0.698	0.028	0.078,	1.319	53.25	0.000	7.50,	378.24
Age (years)												
<30	ref.								ref.			
30–59	1.31	0.620	0.45	3.74	−0.162	0.441	−0.577,	0.253	0.36	0.106	0.11,	1.24
≥60	1.57	0.471	0.46	5.34	0.099	0.781	−0.602,	0.799	0.42	0.382	0.06,	2.92
Sex												
Male					−0.272	0.104	−0.601,	0.057				
Etiological diagnosis												
Positive	2.20	0.063	0.96	5.07								
Annual income												
Above average					−0.507	0.009	−0.888,	−0.126				
Education												
Below high school									ref.			
High school/vocational									0.60	0.665	0.06,	6.20
College and above									0.12	0.096	0.01,	1.46
Medical insurance												
Insurance outside SH					ref.							
UEBMI					−0.631	0.024	−1.178,	−0.085				
URRBMI					−0.905	0.007	−1.560,	−0.250				
Others					−0.552	0.098	−1.208,	0.104				
Employment status												
Employed					ref.							
Retired					−0.392	0.207	−1.002,	0.219				
Others					−0.020	0.940	−0.535,	0.495				

Abbreviation: TB=tuberculosis; OOP=out-of-pocket payment; OR=odds ratio; *CI*=confidence interval; ref.=reference; coef.=coefficient; RP=residence permit; SH=Shanghai; UEBMI=urban employee basic medical insurance; URRBMI=urban and rural resident basic medical insurance.

comorbidity rates — factors that should theoretically indicate less need for intensive treatment. This paradox may be explained by several factors. Firstly, younger migrants may prioritize rapid recovery to resume employment, which is unlike the predominantly retired local population. Secondly, the migrant patients in this study, who reported higher incomes compared to other regions, often sought care at top-tier hospitals where comprehensive testing is mandatory for accurate diagnosis and exclusion of conditions, such as endobronchial TB. Thirdly, higher reimbursement rates for inpatient services may incentivize hospitalization for comprehensive diagnostics and treatment. These patterns suggest potential service overprovision, especially in younger migrants who demonstrate a greater willingness to incur healthcare costs. This aligns with previous empirical research documenting provider-induced demand within China's TB treatment system (*8*–*9*). Moreover, the absence of local health insurance office oversight for

healthcare services and associated costs among uninsured migrant patients in Shanghai may further contribute to service overprovision for this demographic.

This study underscores the critical role of government reimbursement policies in mitigating financial risk as these policies covered 25% of OOP medical payments for local patients, with only two individuals experiencing high financial burden. In stark contrast, more than half of the migrant patients without RP remain ineligible for reimbursement, facing substantial financial risks.

A nationwide cross-sectional survey conducted in 2020 among TB patients in China similarly revealed significant financial burdens persisting despite the implementation of a basic free TB care package (*10*). These findings strongly suggest the need to expand government reimbursement policies to encompass all TB patients, including migrants without an RP, targeting support to low-income patients.

Several limitations warrant consideration in this study. First, the target sample size of this study could not be achieved due to COVID-19 prevention and control measures in Shanghai during the data collection period. The healthcare workers in primary healthcare centers who were responsible for patient interview, were unable to complete interviews due to their pandemic-related commitments, necessitating early termination of recruitment. Additionally, cost analysis was limited to 168 samples due to patients' inability to recall expenses or locate receipts. Furthermore, this study included only migrant TB patients who remained in Shanghai for treatment. Lower-income migrant workers, particularly those facing temporary unemployment, may have returned to their hometowns due to Shanghai's high living costs, potentially introducing selection bias. Consequently, these findings may not be generalizable to the broader migrant population.

Nevertheless, this research has revealed both substantial financial risks for migrant patients and potential TB care overutilization — patterns likely to be replicated in other urban cities with significant high-income migrant populations. Given these limitations, future research should prioritize investigating migrant patients from lower socioeconomic backgrounds to identify effective interventions promoting TB treatment completion.

Conflicts of interest: The authors declare that they have no competing interests.

Ethical statement: Approved by the Institutional Review Board (IRB) of Duke Kunshan University (No. FWA00021580). Informed consent was obtained from all participants who participated in this study.

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Preplanned Studies

Using Phylogenetic Analysis to Detect National and International Dimensions of Hepatitis C Virus 1b Transmission Clusters — China, 1989–2021

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Summary

What is already known about this topic?

Phylogenetic analysis has revolutionized the detection and understanding of Hepatitis C Virus (HCV) transmission patterns.

What is added by this report?

Three distinct transmission cluster patterns were identified across China: a large cluster with nationwide distribution, two medium clusters predominantly in the Central and Eastern China, and 103 small clusters scattered across 19 provincial-level administrative divisions (PLADs). Each cluster type exhibited unique characteristics of expansion risk and inter-provincial transmission patterns. No genetic linkages were found between Chinese sequences and those from other countries.

What are the implications for public health practice?

These findings underscore the critical need for a comprehensive national molecular epidemiological surveillance network.

ABSTRACT

Introduction: Data on inter-regional transmission clusters of Hepatitis C Virus (HCV) helps optimize targeted preventive strategies. This study aims to detect the national and international dimensions of HCV 1b transmission clusters.

Methods: Available published HCV 1b non-structural protein 5B sequences sampled between 1989 and 2021 were collected, including 1,750 sequences from China and 482 comparable sequences from other countries. Network-based and tree-based approaches were introduced to detect transmission clusters and infer their relationships.

Results: Three distinct transmission cluster patterns were identified across China: a large cluster with nationwide distribution, two medium clusters predominantly in the Central and Eastern China, and 103 small clusters scattered across 19 provincial-level administrative divisions. No genetic linkages were found between Chinese sequences and those from other countries. The medium clusters exhibited a similar expansion risk compared with the large cluster [adjusted odds ratio (a*OR*)=1.247, 95% confidence interval (*CI*): 0.862, 1.804, *P*=0.241], but showed significantly lower inter-provincial transmission (a*OR*=0.255, 95% *CI*: 0.077, 0.798, *P*=0.019). The small clusters demonstrated faster expansion [adjusted hazard ratio (a*HR)*=1.327, 95% *CI*: 1.050, 1.676, *P*=0.018] and markedly reduced inter-provincial transmission (a*OR*=0.006, 95% *CI*: 0.002, 0.014, *P*<0.001) compared to the large cluster. The Northeast China groups showed significantly higher inter-provincial transmission risk compared to the Central China groups (a*OR*=11.461, 95% *CI*: 2.262, 87.014, *P*=0.006).

Conclusions: This study emphasizes the urgent need to establish a national molecular epidemiological surveillance network for detecting hidden transmission chains and monitoring the emergence of variants.

In an era of globalization and hyperconnectivity, eliminating the Hepatitis C Virus (HCV) faces challenges from continuous external introductions and emerging transmission clusters. While routine notifiable disease reporting systems struggle to detect hidden transmission patterns, phylogenetic analysis offers the potential for characterizing HCV transmission clusters in China. To investigate this approach, we analyzed 1,750 published HCV 1b non-structural protein 5B (NS5B) sequences from China (China sequences), collected between 2002 and 2019; alongside 482 comparable sequences from other

countries (foreign sequences), sampled between 1989 and 2021. Using both network-based and tree-based approaches, we detected transmission clusters and inferred their relationships. Our analysis revealed three distinct types of clusters within China, each exhibiting unique expansion risks and inter-provincial transmission patterns. Notably, these clusters showed no linkages to sequences from other countries. These findings highlight HCV transmission patterns in China and provide insights for optimizing preventive strategies.

While phylogenetic analysis have been employed in multi-center and single-center studies to investigate transmission patterns, results have varied in its scope and implications. A study analyzing whole-genome HCV sequences from 8 high-income countries demonstrated ongoing HCV 1a and 4d transmission among men who have sex with men (MSM) at both local and international levels (*1*). HCV subtypes show geographical diversity with HCV 1b having worldwide distribution. In China, 5 dominant HCV subtypes account for 98.84% of infections: with 1b (52.18%) predominating, followed by 2a (28.69%), 3b (7.06%), 6a (6.41%), and 3a (4.62%) (*2*). While researchers have successfully used HCV partial genome sequences to infer local or inter-regional transmissions (*3*–*5*), detection capabilities are often constrained by limited temporal and geographic sampling ranges. Building on previous studies' strengths and limitations, we designed a comprehensive secondary analysis method integrating published sequences.

HCV NS5B sequences (AF009606 coordinates: 8,276–8,615 nt, searched on July 11, 2024) and associated epidemiological data were retrieved from the Los Alamos HCV sequence database (https://hcv.lanl.gov/) and the National Center for Biotechnology Information (https://www.ncbi.nlm.nih.gov/). Inclusion criteria required sequences to be annotated with country, provincial-level administrative division (PLAD, for sequences from China), and sampling year. For individuals with multiple sequences, only the earliest sequence was retained. Sequences that were synthetic, contaminated, or contained high non-ACTG content were excluded. China sequences were aligned with reference sequences of representative subtypes 1a–6k. HCV 1b subtype sequences were identified through approximate maximum likelihood phylogenetic (ML) tree analysis using IQ-TREE (version 1.6.12, IQ-TREE Development team, Canberra, ACT, Australia)(*6*). The analysis set was constructed by dividing China HCV 1b sequences and foreign sequences into query and search sets, respectively, then extracting the five most similar target sequences for each query sequence using the Basic Local Alignment Search Tool (version 2.15.0, National Center for Biotechnology Information, National Library of Medicine, National Institutes of Health, Bethesda, USA). The sequence screening process is detailed in Supplementary Figure S1 (available athttps://weekly.chinacdc.cn/).

Transmission cluster analysis employed network-based and tree-based approaches to detect clusters and infer relationships between major clusters, respectively. For the network-based approach, Tamura-Nei 93 pairwise nucleotide genetic distances (GD) were calculated to construct a molecular network using MicrobeTrace (version 0.9.0, Centers for Disease Control and Prevention, Atlanta, Georgia, USA). A sensitivity analysis, using GD thresholds from 0.0001–0.0300 substitutions/site, was conducted to determine the optimal threshold (Supplementary Table S1, available at https://weekly.chinacdc.cn/). The GD threshold of 0.001 substitutions/site was selected based on the optimal balance between maximum cluster numbers and the ratio of nodes in the largest to second-largest clusters (*7*). For the tree-based approach, sequences from major clusters in the molecular network were analyzed using ML tree inference with a significant bootstrap support of ≥84% (1,000 repetitions) (*8*). Transmission characteristics were compared among clusters by calculating adjusted hazard ratios (a*HR*) and 95% confidence interval (*CI*) for expansion risk, which were assessed through linked pairs from the older sequences to their first linkages. Adjusted odds ratios (a*OR*) and 95% *CI* were calculated to evaluate inter-provincial transmission risk by analyzing linked pairs from different PLADs.

A total of 2,232 HCV 1b NS5B sequences (1,750 China sequences and 482 foreign sequences) sampled between 1989 and 2021 were analyzed, with 20.3% forming clusters in the molecular network (Supplementary Table S2, available at https://weekly.chinacdc.cn/). The sequences were distributed across large (≥50 nodes; 127 sequences), medium (10–49 nodes; 42 sequences), and small clusters (<10 nodes; 284 sequences). The molecular network comprised 126 distinct clusters ranging from 2 to 127 nodes (Supplementary Figure S2, available athttps://weekly.chinacdc.cn/).

The China sequences formed 106 clusters, consisting of one large cluster, two medium clusters, and 103 small clusters (Figure 1). The sampling

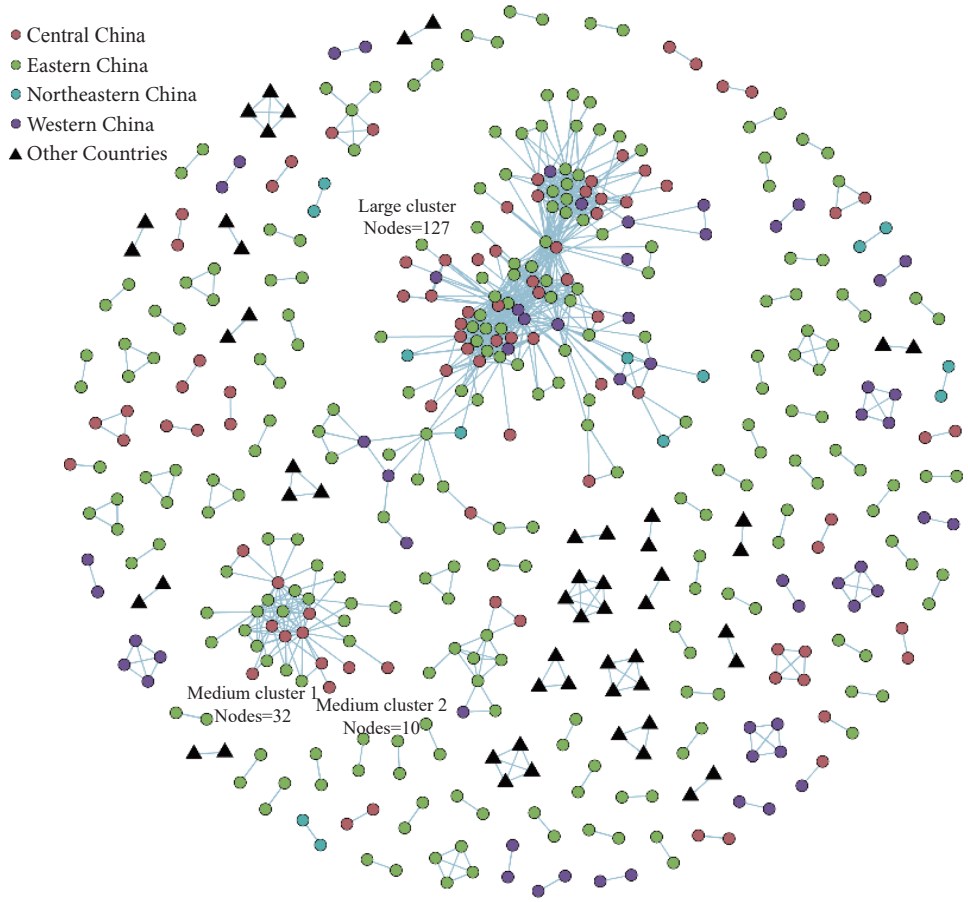

FIGURE 1. Clusters in the Hepatitis C Virus 1b molecular network, China, 1989–2021.
Note: China sequences clustered in the molecular network are distributed across 26 PLADs. Central China: Anhui, Henan, Hubei, Hunan, and Jiangxi PLADs; eastern China: Beijing, Fujian, Guangdong, Hainan, Hebei, Hong Kong, Jiangsu, Shandong, Shanghai, and Zhejiang PLADs; northeastern China: Heilongjiang, Jilin, and Liaoning PLADs; western China: Gansu, Guangxi, Ningxia, Qinghai, Sichuan, Xinjiang, and Yunnan PLADs.
Abbreviation: PLADs=provincial-level administrative divisions.

periods for these three cluster types spanned 2002–2014, 2002–2013, and 1992–2017, respectively. All three cluster types shared a median sampling year of 2009 (interquartile range: 2009–2010, Kruskal-Wallis chi-squared=3.589, *P*=0.166). The large cluster encompassed sequences from the central China (38 sequences), eastern China (67 sequences), northeastern China (5 sequences), and western China (17 sequences). The two medium clusters contained sequences primarily from the central China (13 sequences) and eastern China (28 sequences), with 1 sequence from the western China. The 103 small clusters included sequences from the central China (38 sequences), eastern China (147 sequences), northeastern China (8 sequences), and western China (39 sequences). While foreign sequences from 10 countries formed 20 distinct clusters, none of which clustered with sequences from China.

The maximum likelihood (ML) tree analysis revealed two distinct phylogenetic groups (bootstrap support=1.000). Group A comprised 127 sequences from the large cluster, representing samples from the central, eastern, northeastern, and western China. Group B contained 42 sequences from the two medium clusters, with samples originating from the Central, Eastern, and Western China. The sequences within the two medium clusters demonstrated high genetic homology (bootstrap support=0.852), suggesting that they likely diverged from similar geographical origins (Figure 2).

The medium clusters exhibited a similar expansion risk compared with the large cluster (a*HR*=1.247, 95% *CI*: 0.862, 1.804, *P*=0.241), but showed significantly lower inter-provincial transmission (a*OR*=0.255, 95% *CI*: 0.077, 0.798, *P*=0.019). The small clusters demonstrated faster expansion (a*HR*=1.327, 95% *CI*:

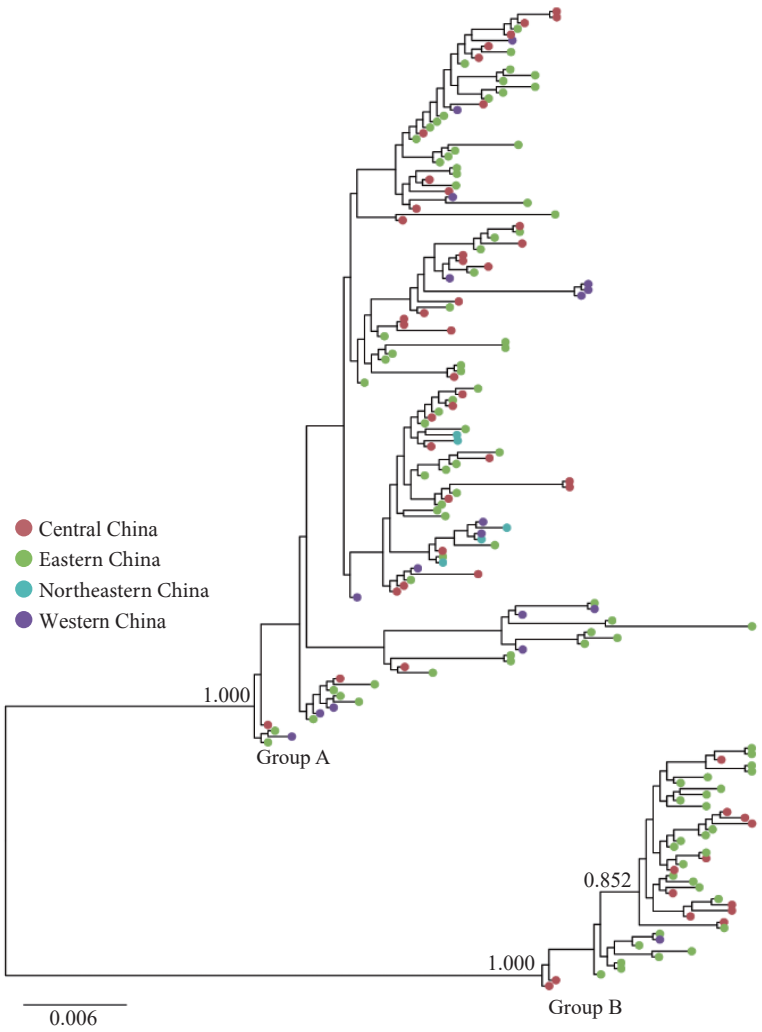

FIGURE 2. The approximate maximum likelihood phylogenetic tree with sequences presented in the large and medium clusters in the Hepatitis C Virus 1b molecular network, China, 1989–2021.
Note: China sequences in the approximate maximum likelihood phylogenetic tree were distributed in 25 PLADs. Central China: Anhui, Henan, Hubei, Hunan, Jiangxi, and Shanxi PLADs; eastern China: Beijing, Fujian, Guangdong, Hainan, Hebei, Hong Kong, Jiangsu, Shandong, Shanghai, and Zhejiang PLADs; northeastern China: Heilongjiang and Liaoning PLADs; western China: Gansu, Guangxi, Ningxia, Qinghai, Sichuan, Xinjiang, and Yunnan PLADs.
Abbreviation: PLAD=provincial-level administrative division.

1.050, 1.676, *P*=0.018) and markedly reduced inter-provincial transmission (a*OR*=0.006, 95% *CI*: 0.002, 0.014, *P*<0.001) compared to the large cluster. The Northeast China groups showed significantly higher inter-provincial transmission risk compared to the Central China groups (a*OR*=11.461, 95% *CI*: 2.262, 87.014, *P*=0.006) (Table 1).

DISCUSSION

This study integrated globally published sequences with China sequences to characterize the national and international dimensions of HCV 1b transmission clusters in China. The analysis revealed three distinct cluster types with unique transmission characteristics. The sequences from China showed no linkages with foreign sequences, providing valuable insights for developing targeted HCV preventive strategies.

A previous investigation analyzing HCV NS5B sequences to infer molecular networks in China employed a genetic distance threshold of 0.01 substitutions/site, reporting a clustering proportion of 33.1% (*5*). Our study utilized a more stringent threshold which resulted in a lower sensitivity for cluster detection. Based on established estimates, HCV 1b NS5B sequences evolve at approximately 0.0005 substitutions/site/year (*9*). Therefore, our chosen threshold of 0.001 substitutions/site will likely capture

TABLE 1. The expansion risk and risk of inter-provincial transmission among clusters in the Hepatitis C Virus 1b molecular network, China, 1989–2021.

Characteristics	Expansion risk		Risk of inter-provincial transmission	
	a*HR* (95% *CI*)	*P*	a*OR* (95% *CI*)	*P*
Type of cluster				
Large	1		1	
Medium	1.247 (0.862, 1.804)	0.241	0.255 (0.077, 0.798)	0.019
Small	1.327 (1.050, 1.676)	0.018	0.006 (0.002, 0.014)	<0.001
Region				
Central China	1		1	
Eastern China	0.929 (0.711, 1.214)	0.589	0.32 (0.135, 0.745)	0.009
Northeastern China	0.727 (0.384, 1.374)	0.326	11.461 (2.262, 87.014)	0.006
Western China	1.022 (0.716, 1.460)	0.904	1.703 (0.631, 4.641)	0.293

Note: Adjusted by sampling year. Clusters are classified into three categories: large (≥50 nodes), medium (10–49 nodes), and small (<10 nodes). Sequences clustered in the molecular network were distributed in 26 PLADs. Central China: Anhui, Henan, Hubei, Hunan, and Jiangxi PLADs; eastern China: Beijing, Fujian, Guangdong, Hainan, Hebei, Hong Kong, Jiangsu, Shandong, Shanghai, and Zhejiang PLADs; northeastern China: Heilongjiang, Jilin, and Liaoning PLADs; western China: Gansu, Guangxi, Ningxia, Qinghai, Sichuan, Xinjiang, and Yunnan PLADs.
Abbreviation: a*OR*=adjusted odds ratios; a*HR*=adjusted hazard ratios; *CI*=confidence interval.

transmission relationships within two years, offering enhanced specificity for identifying key transmission chains.

Another previous research has documented two HCV 1b groups that underwent exponential expansion during the 1970s to 1990s (*8*,*10*). Our analysis incorporates newly sampled sequences, which confirmed the widely persistence distribution of the group throughout China. However, the group's previous dominance in the Central and Eastern China have now diverged into two distinct clusters based on genetic distance thresholds. These findings not only suggest the continued presence of major transmission chains, but also the potential emergence of new HCV 1b variants in the Central and Eastern China.

Despite similar temporal distributions across cluster sizes, the transmission characteristics varied significantly among large, medium, and small clusters. The small clusters exhibited faster transmission rates and reduced inter-provincial spread compared to the large cluster. Given our molecular network's two-year transmission relationship threshold, these small clusters likely represented localized outbreaks. Furthermore, the Northeastern China demonstrated higher inter-provincial transmission probability compared to the Central China, which could be attributed to two factors. Firstly, while HCV 2a predominates in the Northeastern China (*2*), the direct genetic linkages of numerous HCV 1b sequences from this region to the other parts of China suggests external introductions. Secondly, the relatively sparse sampling from the Northeastern China compared to the Central China may create a sampling bias, potentially overestimating the direct genetic linkages when intermediate sequences are missing.

This study has several limitations. First, the published sequences represent a small fraction of HCV cases in China, introducing inevitable sampling biases. However, our optimized genetic distance threshold helps mitigate potential biases in the key transmission cluster inference. Second, achieving balanced temporal and regional sample distribution proved challenging. To address this, we implemented multiple analytical approaches to assess transmission characteristics while controlling for potential confounding factors.

In conclusion, this study successfully identified and characterized HCV 1b transmission clusters within China. Our findings emphasize the urgent need to establish a national molecular epidemiological surveillance network for detecting hidden transmission chains and monitoring the emergence of variants.

Conflicts of interest: No conflicts of interest.

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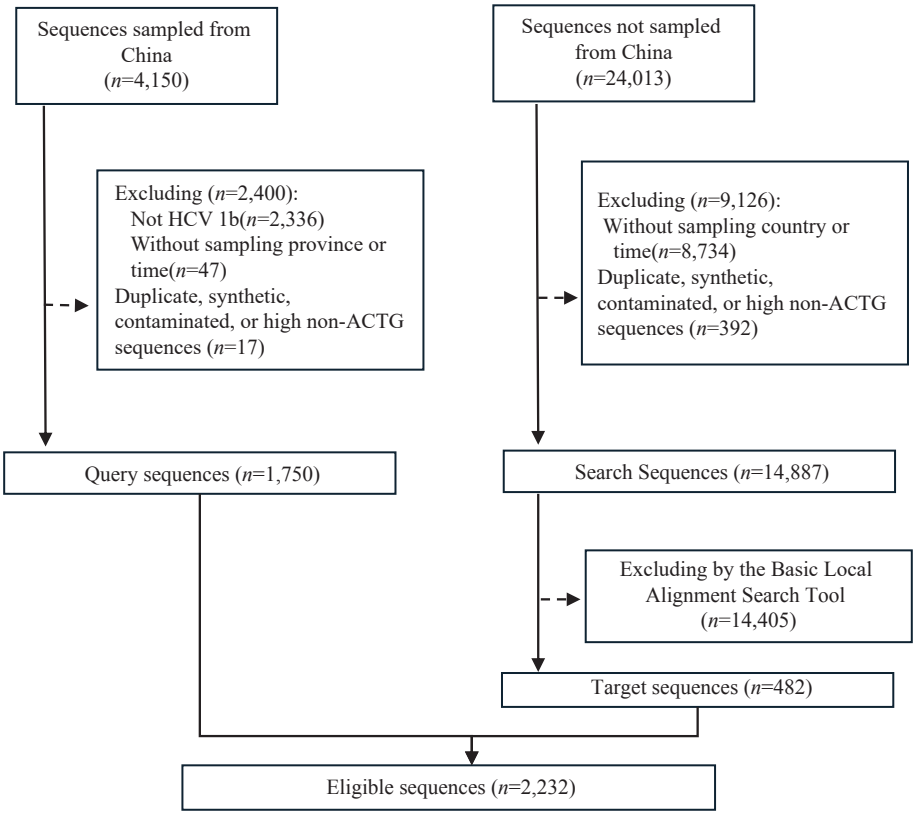
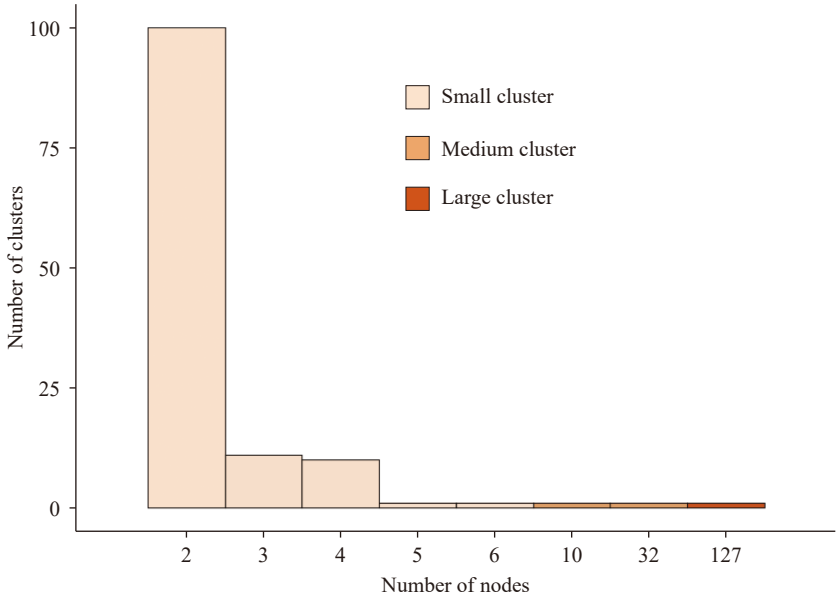
Supplemental Materials



SUPPLEMENTARY FIGURE S1. Flowchart of screening HCV 1b non-structural protein 5B sequences, worldwide, 1989–2021.



SUPPLEMENTARY FIGURE S2. Distribution and composition of clusters in the Hepatitis C Virus 1b molecular network, worldwide, 1989–2021.

SUPPLEMENTARY TABLE S1. Selection of Tamura-Nei 93 pairwise nucleotide genetic distances threshold for constructing the Hepatitis C Virus 1b molecular network, worldwide, 1989–2021.

Threshold (substitution /site)	No. of nodes	No. of links	No. of clusters	Nodes in the largest clusters	Nodes in the second-largest clusters	The ratio of the nodes in the largest- and second-largest clusters
0.0001	453	935	126	127	32	3.97
0.0005	453	935	126	127	32	3.97
0.0010	453	935	126	127	32	3.97
0.0050	669	3889	114	289	106	2.73
0.0100	1173	23775	100	559	271	2.06
0.0150	1480	63834	86	682	400	1.71
0.0200	1645	106130	69	934	448	2.08
0.0250	1879	184005	40	1781	7	254.43
0.0300	1984	223766	26	1929	5	385.80

Note: To better capture the main transmission clusters, a pairwise nucleotide genetic distances threshold was selected based on the maximum ratio of nodes in the largest- and second-largest clusters, as well as the maximum number of clusters presented in the molecular network. When the threshold is set at 0.0010 substitutions per site, the maximum values of these two parameters were balanced.

SUPPLEMENTARY TABLE S2. The number of eligible sequences for analysis and sequences clustered in the Hepatitis C Virus 1b molecular network, worldwide, 1989–2021.

Sampling area	Period of sampling (year)	Eligible sequences for analysis	Sequences clustered in the molecular network	Sequences in three types of clusters large	Medium	Small
China						
Anhui	2009–2010	47	13	7	0	6
Beijing	2002–2010	47	3	3	0	0
Fujian	2009–2012	24	4	2	0	2
Gansu	2009–2013	37	20	6	0	14
Guangdong	2002–2017	739	177	35	28	114
Guangxi	2009–2009	16	3	3	0	0
Hainan	2009–2012	40	7	2	0	5
Hebei	2009–2009	29	2	2	0	0
Heilongjiang	2010–2010	21	6	3	0	3
Henan	2002–2010	44	10	5	2	3
Hong Kong	2004–2019	10	1	1	0	0
Hubei	2010–2014	55	16	4	4	8
Hunan	2004–2010	46	8	2	3	3
Jiangsu	2009–2009	33	11	9	0	2
Jiangxi	2010–2012	35	19	7	3	9
Jilin	2010–2010	23	5	0	0	5
Liaoning	2002–2002	8	2	2	0	0
Inner Mongolia	2009–2010	32	0	0	0	0
Ningxia	2009–2013	28	14	2	0	12
Qinghai	2009–2013	27	11	1	0	10
Shandong	2010–2010	34	9	1	0	8
Shanghai	2003–2015	112	18	4	0	14
Shanxi	2004–2013	93	23	13	1	9
Sichuan	2005–2010	24	4	1	0	3
Tianjin	2010–2010	37	0	0	0	0
Xinjiang	2004–2009	35	1	1	0	0
Yunnan	2002–2010	42	4	3	1	0
Zhejiang	2010–2010	32	10	8	0	2
Asia (not including China)	1997–2019	97	11	0	0	11
Africa	2003–2019	8	0	0	0	0
Europe	1996–2021	231	22	0	0	22
North America	1989–2016	94	15	0	0	15
Oceania	2008–2016	12	0	0	0	0
South America	2007–2017	40	4	0	0	4

Note: Foreign sequences for analysis: Asia (not including China): Afghanistan, Azerbaijan, Cambodia, Indonesia, Iran, Japan, Laos, Thailand, Turkey, and Vietnam. Africa: Benin, Madagascar, South Africa, and Tunisia. Europe: Austria, Belgium, Croatia, France, Germany, Greece, Hungary, Ireland, Israel, Italy, Netherlands, Portugal, Romania, Russia, Spain, Switzerland, Ukraine, and the United Kingdom. North America: Canada and the United States. Oceania: Australia and New Zealand. South America: Brazil, Colombia, and Uruguay.
Foreign sequences clustered in the molecular network: Asia (not including China): Cambodia, Iran, and Japan. Africa: Belgium, Ireland, Italy, Russia, and Switzerland. North America: the United States. South America: Brazil.

Preplanned Studies

Current Status and Factors of Vaccine Hesitancy in Tetanus Vaccination Among Traumatic Patients — China, 2024

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Summary

What is already known about this topic?

The incidence of tetanus in China remains significantly higher than in economically developed regions. Tetanus vaccination represents the most scientifically validated and efficient approach to tetanus prevention. However, vaccine hesitancy presents substantial barriers to the widespread implementation of non-neonatal tetanus vaccination programs across China.

What is added by this report?

This study constitutes the first comprehensive investigation of tetanus vaccine hesitancy in China, documenting its current prevalence and underlying determinants. Findings reveal that limited knowledge about tetanus vaccines, complacency regarding tetanus risk, advanced age, and other factors significantly contribute to vaccination hesitancy. The research demonstrates that medical institutions and healthcare providers offering evidence-based information about tetanus prevention may substantially enhance vaccination uptake.

What are the implications for public health practice?

By elucidating the specific reasons for tetanus vaccine refusal among trauma patients, this study provides critical insights for government agencies and health policymakers to develop contextually appropriate interventions aligned with China's national circumstances, ultimately facilitating improved tetanus vaccination coverage.

ABSTRACT

Introduction: Tetanus remains a significant public health concern in China, with a notable proportion of injured patients declining tetanus vaccination. This study aims to investigate the prevalence and determinants of tetanus vaccine hesitancy and identify effective strategies to address this critical public health challenge.

Methods: We calculated tetanus vaccine hesitancy rates among trauma patients presenting at eight hospitals across China from April 1 to June 30, 2024. A comprehensive questionnaire survey was conducted from June 3 to June 27, 2024, targeting patients aged 11 years and older who had open wounds requiring tetanus immunization but refused vaccination. The survey assessed participants' sociodemographic characteristics, knowledge, attitudes, and practices regarding tetanus and tetanus vaccines. Statistical analyses included Pearson's Chi-squared tests, multiple response analyses, and goodness of fit tests.

Results: Among 8,993 trauma patients requiring tetanus vaccination, 26.78% declined immunization. Analysis of 503 consecutively collected questionnaires revealed low overall awareness of tetanus and tetanus vaccines, with only 20.1% of respondents demonstrating comprehensive knowledge of tetanus-related questions. The predominant reason for vaccine hesitancy (34.5%) was the perception that post-injury tetanus risk was minimal. Across all age groups, medical institutions and healthcare professionals were consistently identified as the most effective sources for tetanus prevention information.

Conclusion: This study demonstrates that enhancing public awareness about tetanus and its vaccines while addressing complacency are fundamental to reducing vaccine hesitancy. Targeted educational interventions delivered by healthcare institutions and professionals can significantly improve public knowledge and acceptance of tetanus vaccination.

Tetanus is an acute, specific, toxic disease caused by *Clostridium tetani* (*1*). The condition is preventable through vaccination and post-exposure prophylaxis (*2*). While the incidence of tetanus has declined substantially in developed countries (*3*), it remains a significant public health challenge in regions with

inadequately implemented immunization programs and in middle- and low-income countries (*3*).

Since the 1970s, China has prioritized tetanus prevention and control, progressively implementing policies to enhance vaccine accessibility. In 2019, guided by the World Health Organization (WHO) "Tetanus vaccines: WHO position paper, February 2017 — Recommendations" (*4*) and considering China's healthcare landscape, the National Health Commission of the People's Republic of China issued the "Diagnostic and Treatment Protocol for Non-Neonatal Tetanus (2019 edition)" and the "Guidelines for the Use of Tetanus Vaccine and Passive Immunizing Agents After Injury (2019 edition)" (*5*–*6*). These guidelines, revised in October 2024, established the first clear standards for post-trauma tetanus vaccination. They stipulate that patients with unreliable or absent tetanus immunization history should complete the full immunization schedule, while those vaccinated more than 5–10 years prior should receive a booster dose. However, emergency physicians in China generally possess limited knowledge of tetanus treatment and prevention, resulting in overutilization of tetanus immune globulin (TIG) or tetanus antitoxin (TAT) in clinical practice, while vaccines are often neglected (*2*). Additionally, a significant proportion of trauma patients continue to refuse tetanus vaccination for complex and poorly understood reasons.

In 2012, the WHO defined vaccine hesitancy as the delay in acceptance or refusal of vaccines despite their availability (*7*–*8*). Multiple factors influence vaccine hesitancy, including the recipient's perception of disease risk, trust in healthcare systems, cost considerations, and socioeconomic factors (*7*,*9*). Public health and vaccine policies, healthcare practitioners' communication skills, and vaccine promotion channels all interact with vaccine hesitancy (*9*). This hesitancy can ultimately contribute to the resurgence and spread of preventable infectious diseases.

This study represents the first investigation in China to examine knowledge (K), attitudes (A), and vaccination intentions (practice, P) (*10*) among patients exhibiting hesitancy toward tetanus vaccination following injury. Conducted across eight hospitals in seven cities, the research explores the underlying reasons for tetanus vaccine refusal among trauma patients, providing valuable insights for developing targeted tetanus prevention strategies tailored to China's specific national context.

METHODS

Data Collection

From April 1, 2024, to June 30, 2024, this study documented the number of trauma patients requiring tetanus vaccination across eight hospitals, tallied those who refused vaccination, and calculated the vaccine hesitancy rate. The primary descriptive cross-sectional study was conducted consecutively with patients who met the following criteria: aged over 11 years, presenting with open wounds requiring tetanus immunization, and refusing the recommended vaccination. Participants were recruited from eight hospitals: Peking University First Hospital, Dezhou Municipal Hospital, Changshu Hospital Affiliated to Nanjing University of Chinese Medicine, Dazhou City Center Hospital (Sichuan Province), Qingdao Children and Women's Hospital, Qingdao Eighth People's Hospital, Norinco General Hospital, and The First People's Hospital of Lanzhou City. The questionnaire study was administered face-to-face between June 3, 2024, and June 27, 2024. Participation was entirely voluntary.

Sample Size Calculation

The formula $n=Z^2_{a/2}\times p\times(1-p)/\varepsilon^2$ was employed, where $Z_{a/2}$ represents the value of the standard normal distribution, ε represents the margin of error, and p denotes the prevalence of tetanus. Assuming a=0.05, then $Z_{a/2}=1.96$ with a margin error of 5%, a minimum of 385 participants were required. Since the prevalence of tetanus in China was indeterminate, we opted for the most conservative estimate by assuming $p=0.5$, thereby maximizing the sample size for calculations.

Survey Content

The questionnaire comprised sections on sociodemographic characteristics (Questions 1–5), knowledge of tetanus disease and tetanus vaccine (Questions 6–9), reasons for vaccine hesitancy (Question 10), and practices regarding tetanus vaccination (Questions 11–13). The complete questionnaire is available in Supplementary Table S1 (available at https://weekly.chinacdc.cn/).

Statistical Analysis

Data analysis was performed using SPSS Statistics (version 29.0.2.0, IBM, Chicago, United States). Categorical variables were expressed as percentages and compared using Pearson's Chi-squared test. Goodness

of fit test and multiple response analysis were employed for multiple-choice questions. Statistical significance was defined as $P<0.05$.

RESULTS

From April 1, 2024, to June 30, 2024, a total of 8,993 trauma patients required tetanus vaccination across the eight participating medical institutions. Among these patients, 2,408 (26.78%) refused vaccination, while 6,585 (73.22%) accepted it. During the focused survey period from June 3, 2024, to June 27, 2024, we collected 503 completed questionnaires from vaccine-hesitant patients. Table 1 presents the demographic and socioeconomic characteristics of the respondents.

Table 2 summarizes participant responses to four key questions regarding tetanus and tetanus vaccination. Overall, participants demonstrated low awareness levels, with higher educational attainment correlating positively with better understanding of tetanus and tetanus vaccines (Supplementary Figure S1, available at https://weekly.chinacdc.cn/). As detailed in Supplementary Table S2 (available at

TABLE 1. Characteristics of participants of the survey (*N*=503).

Characteristics	*N* (%)
Age (years)	
11–17	25 (5.0)
18–45	261 (51.9)
46–65	166 (33.0)
>65	51 (10.1)
Gender	
Female	276 (54.9)
Male	227 (45.1)
Education background	
Postgraduates	41 (8.2)
Graduates	125 (24.9)
College graduates	50 (9.9)
High school graduates	77 (15.3)
Junior high school graduates	78 (15.5)
Primary school graduates	63 (12.5)
Other	69 (13.7)
Hospital	
Peking University First Hospital	58 (11.5)
Dezhou Municipal Hospital	88 (17.5)
Changshu Hospital Affiliated to Nanjing University of Chinese Medicine	49 (9.7)
Dazhou City Center Hospital, Sichuan Province	10 (2.0)
Qingdao Children and Women's Hospital	7 (1.4)
Qingdao Eighth People's Hospital	112 (22.3)
Norinco General Hospital	163 (32.4)
The First People's Hospital of Lanzhou City	16 (3.2)
Regional economic level	
High-income cities	226 (44.9)
Upper-middle income cities	277 (55.1)

Note: The eight participating hospitals are strategically distributed across northern, southern, eastern, and western regions of China. According to World Bank classification standards and based on 2023 per capita GDP, 3 of the 7 cities represent high-income areas (Beijing: 200,000 CNY, Changshu: 166,000 CNY, and Qingdao: 152,000 CNY), while 4 cities fall into the upper-middle-income category (Dezhou: 69,000 CY, Dazhou: 50,000 CNY, Xi'an: 92,000 CNY, and Lanzhou: 79,000 CNY).
Abbreviation: GDP=gross domestic product; CNY=Chinese Yuan.

TABLE 2. Knowledge of participants about tetanus disease and tetanus vaccine in different educational background.

Education background	Question 6		Question 7		Question 8		Question 9	
	Yes, *N* (%)	No, *N* (%)	Yes, *N* (%)	No, *N* (%)	Yes, *N* (%)	No, *N* (%)	Yes, *N* (%)	No, *N* (%)
Postgraduates	32 (78.0)	9 (22.0)	16 (39.0)	25 (61.0)	31 (75.6)	10 (24.4)	14 (34.1)	27 (65.9)
Graduates	99 (79.2)	26 (20.8)	58 (46.4)	67 (53.6)	86 (68.8)	39 (31.2)	48 (38.4)	77 (61.6)
College graduates	43 (86.0)	7 (14.0)	21 (42.0)	29 (58.0)	30 (60.0)	20 (40.0)	25 (50.0)	25 (50.0)
High school graduates	59 (76.6)	18 (23.4)	20 (26.0)	57 (74.0)	24 (31.2)	53 (68.8)	16 (20.8)	61 (79.2)
Junior high school graduates	51 (65.4)	27 (34.6)	15 (19.2)	63 (80.8)	21 (26.9)	57 (73.1)	16 (20.5)	62 (79.5)
Primary school graduates	24 (38.1)	39 (61.9)	3 (4.8)	60 (95.2)	7 (11.1)	56 (88.9)	1 (1.6)	62 (98.4)
Other	27 (39.1)	42 (60.9)	16 (23.2)	53 (76.8)	18 (26.1)	51 (73.9)	21 (30.4)	48 (69.6)
Sum	335 (66.6)	168 (33.4)	149 (29.6)	354 (70.4)	217 (43.1)	286 (56.9)	141 (28.0)	362 (72.0)
$\chi 2$	46.010		44.416		93.735		45.766	
P	<0.001		<0.001		<0.001		<0.001	

Note: Question 6: Did you know that you may develop tetanus after trauma or animal scratches (bites)? Question 7: Did you know that TIG or TAT provides only short-term protection and cannot completely prevent tetanus infection? Question 8: Did you know that the "DTP vaccine" administered during childhood includes tetanus vaccine? Question 9: After completing the full course of tetanus vaccination, immunity remains effective for at least 5–10 years. Only one booster dose is needed when reinjury occurs more than 5 years after the full-course vaccination. Were you aware of this information?

https://weekly.chinacdc.cn/), only 20.1% of respondents demonstrated comprehensive awareness by correctly answering all four tetanus-related questions (Questions 6–9), while 25.6% were completely unaware of any of the queried information.

For the multiple-choice question regarding reasons for refusing the tetanus vaccine (Figure 1), 503 participants provided a total of 1,073 responses. The goodness-of-fit test showed statistical significance (χ^2=324.486, *P*<0.001), indicating substantial differences in the distribution of response choices. The predominant reason for tetanus vaccine refusal, cited by 34.5% of respondents, was the belief that "there is little risk of tetanus infection after this injury." Only 4.9% of respondents expressed concerns about the quality and effectiveness of tetanus vaccines as their rationale for refusal. Cross-analysis revealed significant associations between educational level and reasons for vaccine refusal (χ^2=69.647, *P*<0.001), demonstrating that vaccine hesitancy motivations varied substantially across educational strata. Participants with graduate and postgraduate degrees expressed greater concerns about vaccine side effects compared to those with other educational backgrounds (31.2% and 43.9%, respectively). Conversely, individuals with lower educational attainment, particularly primary and junior high school graduates, were more likely to cite the lengthy vaccination process as their reason for refusal (66.7% and 60.3%, respectively).

In Supplementary Figure S2 (available at https://weekly.chinacdc.cn/), the 503 participants reported a total of 943 responses regarding their previous sources of tetanus prevention information, with the goodness-of-fit test showing statistical significance (χ^2=184.408, *P*<0.001). Medical institutions or healthcare personnel constituted the most frequently cited information source (31.2%). Similarly, for the multiple-choice question about "the most effective way to learn about tetanus prevention" (Supplementary Figure S3, available at https://weekly.chinacdc.cn/), participants provided 1,066 total responses, with the goodness-of-fit test again showing significance (χ^2=217.218, *P*<0.001). Medical institutions or healthcare personnel were again identified as the most effective information source (37.1%).

The final question assessed whether participants would reconsider their decision and accept vaccination after completing the questionnaire. As shown in Table 3, 35% of the 503 participants changed their minds and decided to receive the tetanus vaccine. Notably, primary school graduates demonstrated the lowest rate of decision reversal (7.9%) compared to other educational cohorts. Postgraduates and graduates exhibited the highest rates of reconsideration (63.4% and 50.4%, respectively). The proportion of participants willing to change their decision varied significantly across age groups, with a clear inverse relationship between age and willingness to reconsider. Among participants under 18 years old, 72% ultimately changed their minds, compared to only 5.9% of participants over 65 years old. Furthermore, participants from high-income cities demonstrated

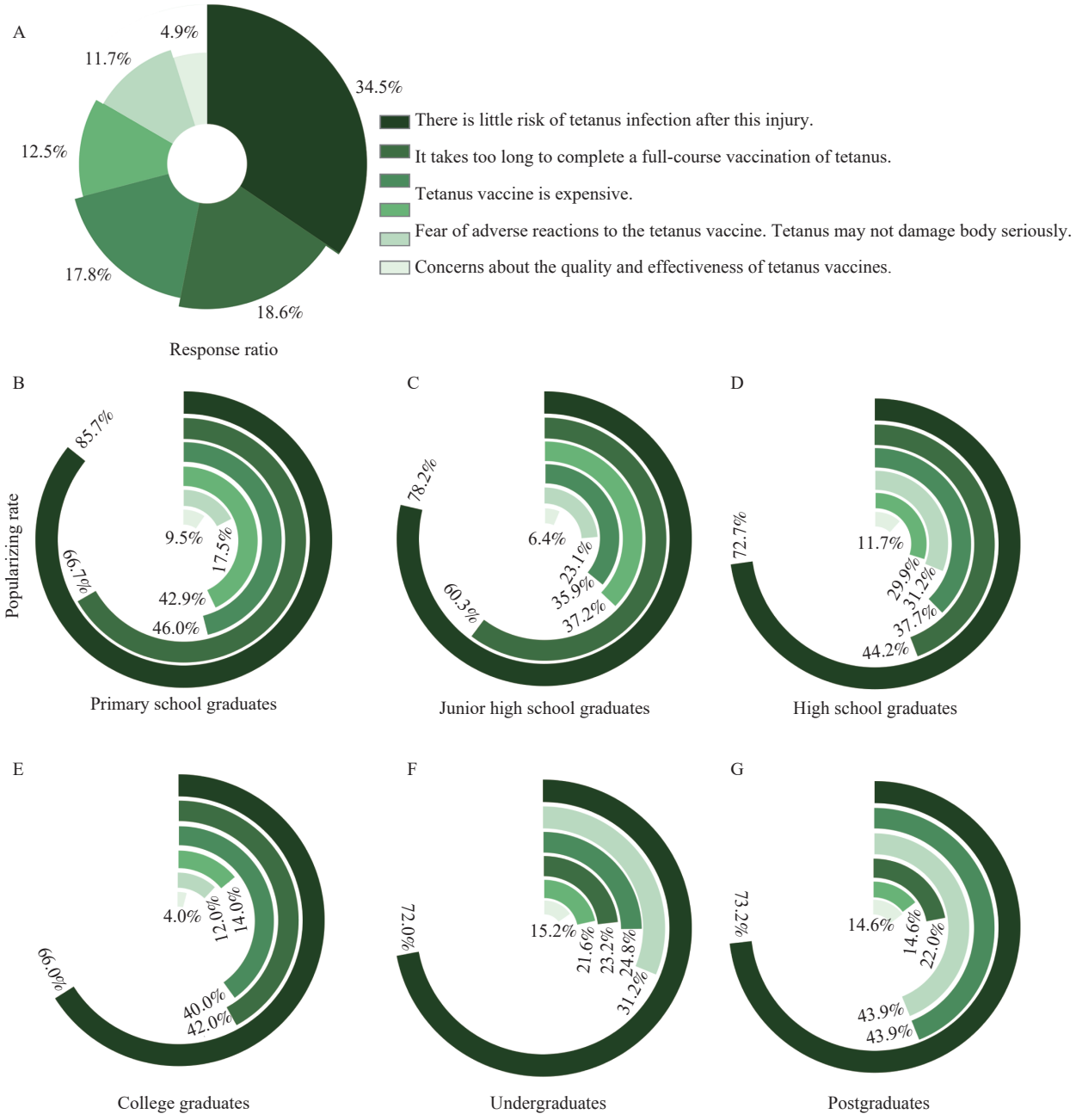

FIGURE 1. Reasons of refusing the tetanus vaccine and educational backgrounds. (A) Response ratio for different reasons of tetanus vaccine refusal among participants. Popularizing rate of tetanus vaccine refusal for different reasons among participants who are (B) primary school graduates, (C) junior high school graduates, (D) high school graduates, (E) college graduates, (F) undergraduates, and (G) postgraduates respectively.

significantly higher rates of decision reversal (44.2%) compared to those from upper-middle income cities (27.4%), a statistically significant difference ($\chi 2$=15.463, P<0.001). Among those who changed their minds, the lowest proportion selected family and friends as effective sources for tetanus information (Supplementary Table S3, available at https://weekly.chinacdc.cn/).

DISCUSSION

Globally, tetanus affects an estimated 1 million individuals annually, resulting in approximately 200,000 deaths, with the highest burden concentrated in Southeast Asia and Africa (*11*). While comprehensive epidemiological data on non-neonatal tetanus in China remain limited, available evidence

TABLE 3. Population of changing decision after completing the questionnaire.

Characteristics	Changing decision			
	Yes, *N* (%)	No, *N* (%)	χ^2	*P*
Education background				
Postgraduates	26 (63.4) *	15 (36.6) *		
Graduates	63 (50.4) *,†	62 (49.6) *,†		
College graduates	12 (24.0) §	38 (76.0) §		
High school graduates	28 (36.4) †, §	49 (63.6) †,§	53.462	<0.001
Junior high school graduates	21 (26.9) §	57 (73.1) §		
Primary school graduates	5 (7.9) ¶	58 (92.1) ¶		
Other	21 (30.4) §	47 (69.6) §		
Sum	176 (35.0)	327 (65.0)		
Age (years)				
11–17	18 (72.0) *	7 (28.0) *		
18–45	126 (48.3) †	135 (51.7) †	76.704	<0.001
46–65	29 (17.5) §	137 (82.5) §		
>65	3 (5.9) ¶	48 (94.1) ¶		
Sum	176 (35.0)	327 (65.0)		
Regional economic level				
High-income cities	100 (44.2) *	126 (55.8) *	15.463	<0.001
Upper-middle-income cities	76 (27.4) †	201 (72.6) †		
Sum	176 (35.0)	327 (65.0)		

Note: For each group, identical superscript markers indicate no statistically significant difference between groups, while different superscript markers denote statistically significant differences between groups.

suggests that tetanus incidence in China substantially exceeds rates observed in the United States and European countries (*12*). Therefore, implementing the 2024 diagnostic and treatment standards for non-neonatal tetanus and accelerating population-wide vaccination initiatives in China represent critical public health priorities.

Despite tetanus vaccine availability across all eight participating hospitals, 26.78% of trauma patients declined vaccination. This study represents the first comprehensive investigation and analysis of tetanus vaccine hesitancy in China. Our findings reveal that individuals exhibiting vaccine hesitancy generally demonstrated poor knowledge regarding tetanus disease and its prevention through vaccination. Unfortunately, because our study design excluded trauma patients who accepted vaccination, comparative analysis of tetanus awareness between hesitant and non-hesitant groups was not possible. Overall, educational attainment positively correlated with greater awareness of tetanus and its vaccine.

Vaccination acceptance involves a complex decision-making process influenced by multiple determinants. Vaccine hesitancy — defined as delayed acceptance or refusal of vaccines despite availability — stems from various factors (*7*–*8*). Several conceptual frameworks categorize vaccine hesitancy determinants, with the "3Cs" model offering particular clarity. First proposed to the WHO in 2011, this model delineates three primary categories: complacency, convenience, and confidence (*7*). In recent years, researchers worldwide have employed the "3Cs" model to analyze factors contributing to vaccine hesitancy among healthcare practitioners and vaccine recipients. Our research identified the predominant reason for tetanus vaccine hesitancy among Chinese trauma patients as the belief that "there is little risk of tetanus infection after this injury," which aligns with the psychological factor of complacency within the "3Cs" framework. Paradoxically, successful immunization programs may engender complacency and ultimately vaccine hesitancy, as individuals weigh perceived vaccination risks against disease risks (*7*). The relative rarity of tetanus in China — attributable to governmental, institutional, and healthcare practitioner efforts — appears to underlie complacency as the leading cause of vaccine hesitancy. Participants with higher educational attainment expressed greater concerns regarding

vaccine side effects, reflecting diminished confidence in vaccine safety. Vaccination duration (convenience) disproportionately influenced vaccination attitudes among individuals with lower educational levels or those residing in upper-middle income cities, potentially reflecting occupational constraints or financial considerations.

Our study further revealed that most participants obtained tetanus prevention information from medical institutions and healthcare professionals, whom they also regarded as the most effective information sources. Consequently, ensuring healthcare providers possess comprehensive knowledge of tetanus vaccine guidelines and effectively communicate this information to the public is paramount. Notably, approximately one-third of initially hesitant participants changed their minds and consented to vaccination by the conclusion of our survey. This finding suggests that healthcare professionals can significantly reduce vaccine hesitancy and increase tetanus vaccination rates through evidence-based education about tetanus and its prevention (such as clarifying that TIG or TAT provides only short-term protection and cannot fully prevent tetanus, whereas complete vaccination confers immunity for at least 5–10 years). Additionally, empathetic, non-judgmental communication — rather than procedural vaccine introduction — proves most effective in building trust and mitigating vaccine hesitancy (*13–14*).

Our findings demonstrate that vaccine hesitancy becomes increasingly entrenched with advancing age, paralleling observations that COVID-19 vaccine hesitancy among elderly Chinese populations exceeds rates in the United States and European countries (*15–17*). With China hosting the world's largest elderly population — many of whom lack fundamental knowledge about tetanus and face higher tetanus-associated mortality — targeted prevention strategies for this vulnerable demographic could substantially reduce the medical and economic burden of this disease.

Several limitations warrant acknowledgment. Our questionnaire lacked comprehensiveness, omitting factors such as participants' physical and economic conditions that may influence vaccine hesitancy. The questionnaire was not a validated scale, precluding reliability and validity analyses. Additionally, all participating hospitals maintaining tetanus vaccine supplies, potentially introducing selection bias. Physicians at these facilities likely possessed superior understanding of tetanus vaccination guidelines and demonstrated greater proactivity in recommending vaccination compared to hospitals without vaccine availability. Furthermore, patients with existing tetanus knowledge may preferentially select hospitals known to provide tetanus vaccines. Consequently, our observed vaccine hesitancy rate may underestimate the true prevalence, suggesting that the national tetanus vaccination landscape may be more concerning than our findings indicate. The exclusion of primary and secondary healthcare institutions introduced additional selection bias. Moreover, our study did not incorporate medical facilities from less economically developed regions, explaining the limited representation of lower-middle and low-income areas in China.

In conclusion, this research underscores the critical importance of enhancing public awareness regarding tetanus and its prevention through vaccination. Addressing complacency, strengthening confidence in vaccine safety, and improving tetanus vaccination accessibility represent essential strategies for mitigating vaccine hesitancy in China. Leveraging medical institutions and healthcare providers as primary information channels may significantly enhance understanding and uptake of tetanus vaccinations. The pronounced resistance to vaccination among older adults necessitates targeted interventions for this demographic. These findings provide valuable insights for governmental and health policymakers to strategically promote tetanus vaccination and reduce vaccine hesitancy rates.

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SUPPLEMENTARY MATERIAL

SUPPLEMENTARY TABLE S1. Questionnaire for patients refusing tetanus vaccine.

Question number	Question	Answer	
1	Hospital		
2	Age		
3	Gender		
4	Education background		
5	The number of tetanus vaccine your doctor recommends.	One	Three
6	Did you know that you may develop tetanus after trauma or animal scratches (bites)?	Yes	No
7	Did you know that TIG or TAT provides only short-term protection and cannot completely prevent tetanus infection?	Yes	No
8	Did you know that the “DTP vaccine” administered during childhood includes tetanus vaccine?	Yes	No
9	After completing the full course of tetanus vaccination, immunity remains effective for at least 5–10 years. Only one booster dose is needed when reinjury occurs more than 5 years after the full-course vaccination. Were you aware of this information?	Yes	No
10	Which of the following are your main reasons for refusing tetanus vaccine? (Multiple choices, sorting)	A. There is little risk of tetanus infection after this injury. B. Tetanus may not damage health seriously. C. Tetanus vaccine is expensive. D. It takes too long to complete a full-course vaccination of tetanus. E. Fear of adverse reactions to the tetanus vaccine. F. Concerns about the quality and effectiveness of tetanus vaccines.	
11	How did you learn about tetanus prevention?	A. Didn’t know tetanus vaccines. B. Mainstream media (TV stations, newspapers, radio, etc.). C. Self-media (WeChat, Tik Tok, etc.). D. Family and friends. E. Schools and other educational institutions. F. Medical institutions or medical personnel.	
12	From your perspective, which is the most effective way to acquire knowledge of tetanus prevention?	A. Mainstream media (TV stations, newspapers, radio, etc.). B. Self-media (WeChat, Tik Tok, etc.). C. Family and friends. D. Schools and other educational institutions. E. Medical institutions or medical personnel.	
13	After completing the questionnaire, do you change your mind to be willing to inject tetanus vaccine?	Yes	No

SUPPLEMENTARY TABLE S2. Knowledge of participants about tetanus disease and tetanus vaccine with different age or regional economic level.

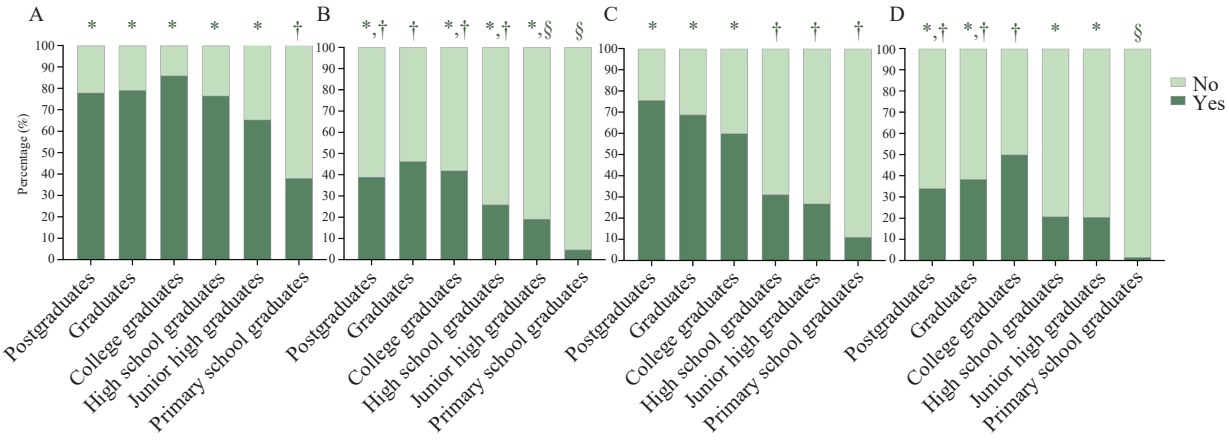
Characteristics	Base lineN	Questions 6–9					
Age (years)		Yes, *N* (%)	χ^2	*P*	No, *N* (%)	χ^2	*P*
11–17	25	1 (4.0) [*]			6 (24.0) [*,†]		
18–45	261	73 (28.0) [†]			32 (12.3) [†]		
46–65	166	24 (14.5) [*]	23.827	<0.001	59 (35.5) [*]	69.895	<0.001
>65	51	3 (5.9) [*]			32 (62.7) [§]		
Sum	503	101(20.1)			129(25.6)		
Regional economic level							
High-income cities	226	50 (22.1)			65 (28.8)		
Upper-middle-income cities	277	51 (18.4)	1.069	0.301	64 (23.1)	2.088	0.148
Sum	503	101 (20.1)			129 (25.6)		

Note: For each group, identical superscript markers indicate no statistically significant difference between groups, while different superscript markers denote statistically significant differences between groups..

SUPPLEMENTARY TABLE S3. Access to tetanus prevention information for those who change their minds.

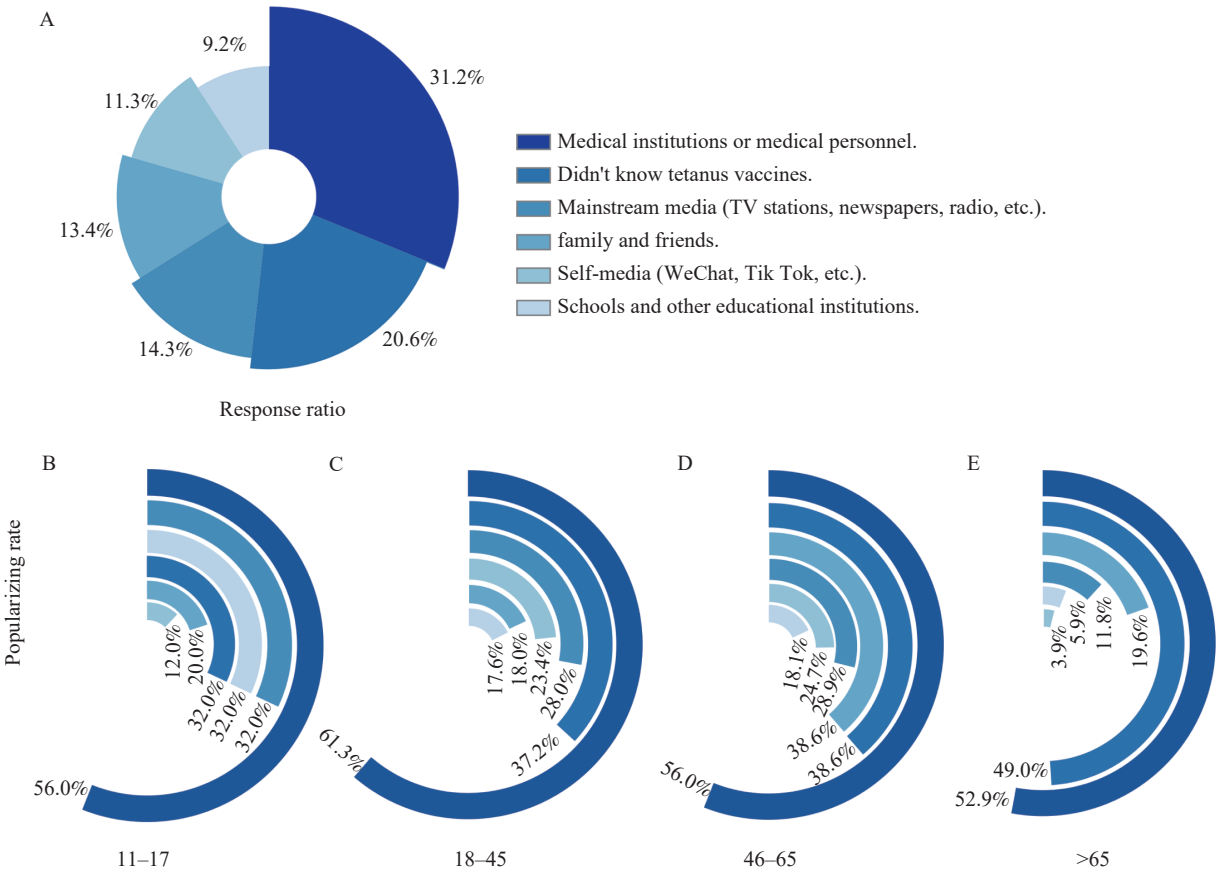
Access to tetanus prevention information	Changing decision		χ^2	*P*
	Yes N (%)	No N (%)		
Previous sources				
Didn't know tetanus vaccines.	59 (30.4) [*,†,§,¶]	135 (69.6) [*,†,§,¶]		
Mainstream media	47 (34.8) [§,¶,**]	88 (65.2) [§,¶,**]		
Self-media	39 (36.4) [†,¶,**]	68 (63.6) [†,¶,**]		
Family and friends.	28 (22.2) [*]	98 (77.8) [*]	19.941	<0.001
Schools and other educational institutions.	26 (29.9) [*,†,§,¶]	61 (70.1) [*,†,§,¶]		
Medical institutions or medical personnel.	126 (42.9) [**]	168 (57.1) [**]		
The most effective way in their mind				
Mainstream media	73 (32.7) [*,†]	150 (67.3) [*,†]		
Self-media	56 (33.9) [*,†]	109 (66.1) [*,†]	25.409	<0.001
Family and friends.	23 (15.8) [§]	123 (84.2) [§]		
Schools and other educational institutions.	38 (27.9) [†]	98 (72.1) [†]		
Medical institutions or medical personnel.	150 (37.9) [*]	246 (62.1) [*]		

Note: For each group, identical superscript markers indicate no statistically significant difference between groups, while different superscript markers denote statistically significant differences between groups.



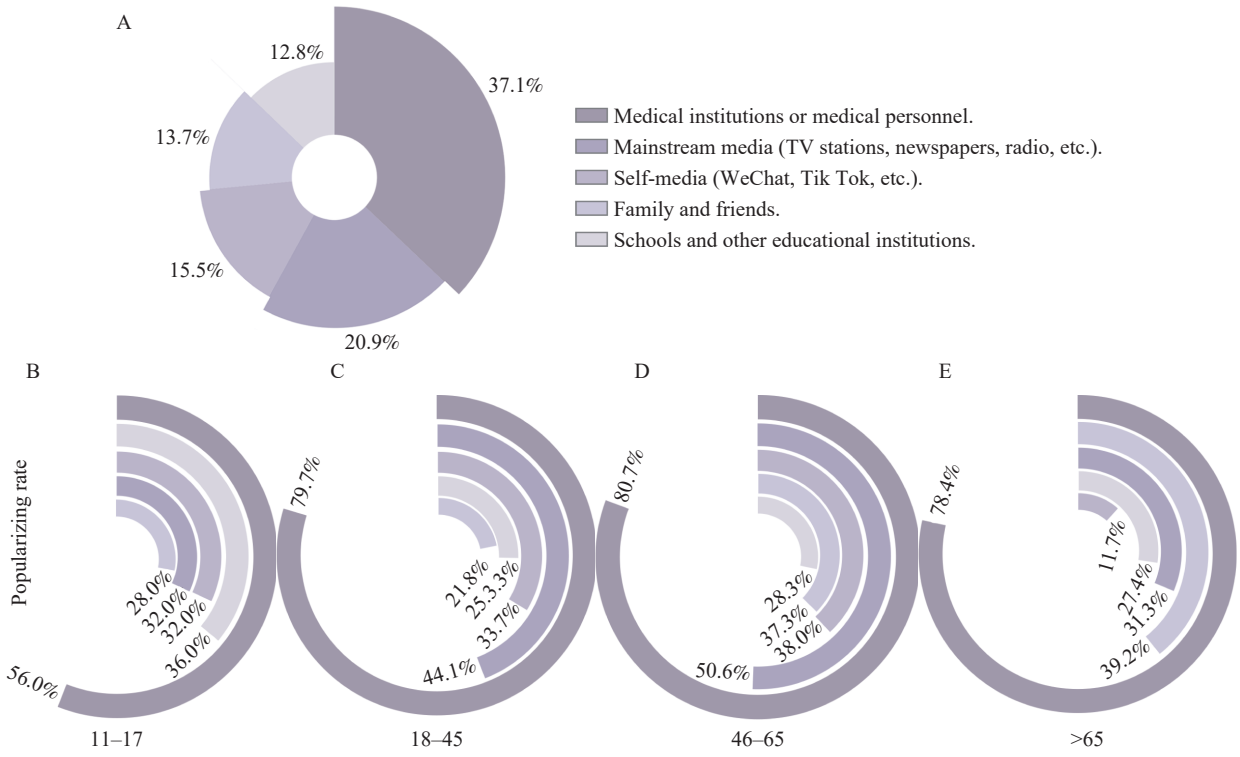
SUPPLEMENTARY FIGURE S1. The proportion of awareness regarding tetanus and tetanus vaccine-related issues in relation to educational level. (A) Perceptions of Question 6 among people with different educational backgrounds. (B) Perceptions of Question 7 among people with different educational backgrounds. (C) Perceptions of Question 8 among people with different educational backgrounds. (D) Perceptions of Question 9 among people with different educational backgrounds.

Note: For each question, if the same markers appears at top of columns, there is no statistically significant difference between the groups; if the markers at top of columns are different, it indicates a statistically significant difference between the groups.



SUPPLEMENTARY FIGURE S2. Previous channels for obtaining information about tetanus prevention.

A: Response ratio for different information sources of tetanus prevention among participants. B-E: Popularizing rate for different information sources of tetanus prevention among different ages' participants.



SUPPLEMENTARY FIGURE S3. The most effective media of acquiring knowledge about tetanus prevention for respondents. (A) Response ratio for the most effective media of acquiring tetanus prevention knowledge among participants. Popularizing rate for the most effective media of acquiring tetanus prevention knowledge among participants of age (B) 11–17; (C) 18–45; (D) 46–65; (E) >65 groups.

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