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ORIGINAL RESEARCH

Cross-District Transmission of Tuberculosis in a High-Mobility City in China: Implications for Regional Collaboration in Infectious Disease Control

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Objective: This study aims to elucidate the transmission dynamics of tuberculosis in a Chinese city with high population mobility and to identify the associated risk factors.

Methods: We included the data from ten city-level surveillance sites in Shenzhen between 2018 and 2023. Genomic clusters were defined as having a genomic distance of 12 single nucleotide polymorphisms based on whole-genome sequencing. Cross-district clusters were characterized as clusters containing patients from at least two districts, indicating cross-district transmission. Risk factors for clustering were identified using logistic regression.

Results: Of the 2,519 enrolled patients, 263 (10.4%) were grouped into 119 genomic clusters. Notably, 52.1% (62/119) of these clusters were cross-district clusters. We analyzed the data from Shenzhen's 10 districts separately and compared the results with a citywide combined analysis, finding that the combined analysis revealed significantly higher clustering rates across all districts ($P<0.001$). Furthermore, the risk of cross-district transmission was 3.41 times higher (95% CI: 1.49–7.80) among internal migrants than among residents. Multivariable logistic regression analysis identified significant risk factors for TB transmission, including age under 25 years (OR=3.07, 95% CI: 1.17–8.03), age 25–44 years (OR=2.86, 95% CI: 1.13–7.23), and drug-resistant TB (OR=1.57, 95% CI: 1.15–2.13).

Conclusion: Cross-district transmission is a key factor in the spread of tuberculosis in cities with high population mobility. TB control institutions at all levels must transcend regional boundaries and enhance collaboration to achieve more effective tuberculosis control.

Keywords: Mycobacterium tuberculosis, cross-district transmission, whole-genome sequencing, risk factors

Introduction

Tuberculosis (TB) remains a critical global health issue, with 10.6 million cases and 1.3 million deaths reported in 2022.[1] As one of the countries with the highest TB burden, China has achieved a 3.4% annual reduction in TB incidence since 1990 through the implementation of effective prevention and control strategies. In Shenzhen, the TB incidence rate has fallen to a low-to-moderate level, reaching 27.6 per 100,000 individuals in 2023.[2] However, there is still a considerable gap in meeting the World Health Organization's (WHO) target of ending TB.[3] Active case finding is a promising approach, but its success hinges on accurately identifying high-risk populations to allocate resources effectively and enhance intervention outcomes.[4,5]

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The development genomic epidemiology of TB enables detailed mapping of TB transmission networks, analysis of risk factors, and identification of high-risk populations.[6,7] Previous genomic epidemiology studies in rural China indicated that approximately 50% of clustered cases were household contacts and social contacts, suggesting the significance of the screening of close contacts.[8] In urban China, genomic epidemiology studies found a lower proportion of clustered cases with confirmed epidemiological links.[9–11] However, these studies focused on tuberculosis transmission in a single district, often overlooking the potential for cross-district transmission. In urban China, TB transmission chain probably frequently cross multiple districts due to the regular cross-district population movement, which may be rare in rural China.[12] This limitation may result in underestimating the level of recent transmission and missing crucial transmission links, thereby failing to explain how transmission occurs. Given that over 80% of Shenzhen's population is internal migrants, the cross-district transmission of TB is likely to be a significant factor. This highlights the urgent need for a more expansive research in urban areas to comprehensively analyze TB transmission dynamics, thereby facilitating the development of more effective prevention and control strategies.

This study leverages data from ten municipal TB surveillance sites in Shenzhen to address three critical objectives: (1) Characterize clinical and molecular profiles of TB in Shenzhen; (2) Clarify transmission dynamics of TB by mapping transmission chains between districts; (3) Identify high-risk populations associated with recent transmission. By thoroughly capturing cross-district transmission events, this study aspires to establish a robust scientific basis for the development of more precise prevention and control strategies.

Materials and Methods

Sample Source

Shenzhen, located at the southern tip of Guangdong Province, is divided into 10 districts. Each district operates a chronic disease control center serving as a tuberculosis surveillance site, tasked with the diagnosis and treatment of TB within its jurisdiction. The Shenzhen Chronic Disease Control Center (CCDC) is responsible for city-wide diagnosis and surveillance of drug-resistant tuberculosis. For high-risk drug-resistant TB patients who consented to receive treatment in Shenzhen, sputum specimens were collected and cultured. Isolates of *Mycobacterium tuberculosis* (*MTB*) obtained from positive cultures were sent to Shenzhen CCDC for drug sensitivity testing (DST) to monitor drug resistance. This study included TB patients 15 years and older who underwent drug resistance surveillance in Shenzhen between January 1, 2018 and June 30, 2023. Strains were excluded if they were duplicates from the same patient, identified as non-tuberculous mycobacteria (NTM), failed re-culture, or exhibited low-quality sequencing data (coverage <95% or depth <20×). Epidemiological data, including age, gender, occupation, and household registration status, were obtained from the China Infectious Disease Surveillance System (CIDSS). This study was approved by the Ethics Committee of the Shenzhen CCDC.

Whole-Genome Sequencing

The isolates were re-cultured and whole genome sequenced. The WGS process and data analysis were performed as previously described.[13] The CTAB method was used to extract strain genomic DNA in a brief manner.[14] The Illumina HiSeq 2500 platform was used to sequence 300-base-pair double-ended DNA libraries constructed for each isolate. The process involved trimming low-quality reads with Sickle and aligning them to the inferred *MTB* ancestral sequences using BWA-MEM. To identify single nucleotide polymorphisms (SNPs), the alignments were processed with SAMtools and Varscan. The SNPs with frequency ≥75% were considered to be fixed. Strains with differences of 12 or fewer SNPs were classified as a genomic cluster, indicating linkage through recent transmission.[15] Clusters that included patients from two or more districts were termed cross-district clusters. The identified SNPs were used to build a phylogenetic tree with SAM-TB,[16] utilizing the maximum likelihood method with 100 bootstraps, and it was visualized through Interactive Tree of Life (https://itol.embl.de/). Strains were grouped into distinct lineages as Liu et al.[17] L2 strains, referred to as the Beijing family, were separated into L2.3, denoting "modern" Beijing, and other sub-lineages regarded as "ancient" Beijing.[18]

Resistance patterns for 17 anti-TB medications were forecasted using SAM-TB, based on mutations linked to resistance.[19] Multidrug-resistant TB (MDR-TB) is characterized by resistance to at least the drugs isoniazid and rifampicin, pre-extreme drug-resistant TB (pre-XDR) refers to MDR strains that are additionally resistant to any fluoroquinolone, and strains classified as XDR are those MDR strains that are resistant to any fluoroquinolone and at least one more group A drug.[20] Strains with mutations associated with resistance to any drugs but not MDR were termed other drug resistant (DR) TB.

Statistical Analysis

For non-normally distributed continuous data, medians and interquartile ranges (IQR) were used, while proportions described categorical variables. The Wilcoxon rank sum test or chi-square test was employed to test differences between groups. Using logistic regression, the odds ratio (OR) and 95% confidence intervals (CI) were calculated for risk factors connected to genomic clustering. In the multivariable analysis, variables with p-values under 0.2 from the univariable analysis were used to compute the adjusted odds ratios (aOR). Statistical significance in the final model was attributed to factors with a p-value less than 0.05. All analyses were carried out in Stata version 14.0.

Results

General Population Characteristics

Between January 2018 and June 2023, there were 4,020 culture-positive strains in the TB laboratory of Shenzhen CCDC. After excluding 1,021 strains from the same patient, 289 strains classified as *NTM*, 90 strains failing re-culture, and 101 strains with low-quality sequencing data, the final analysis included 2,519 patients along with their strains. (Figure 1A). The 2,519 TB patients originated from 10 districts in Shenzhen: Baoan District (940, 37.3%), Longhua District (383, 15.2%), Longgang District (311, 12.3%), Guangming District (213, 8.5%), Nanshan District (208, 8.3%), Luohu District (207, 8.2%), Futian District (147, 5.8%), and Pingshan District (71, 2.8%), Yantian District (24, 1.0%) and Dapeng New District (15, 0.6%) (Figure 1B).

The mean age of TB patients was 33 years (IQR,26–47). Of these patients, 67.3% (1695/2519) were male, and 87.3% (2199/2519) were internal migrants. Regarding occupational distribution, domestic workers and inactive individuals constituted the largest group (45.1%, 1,135/2,519), followed by laborers (30.0%, 755/2,519). New TB patients accounted for 91.4% (2303/2519). The majority of patients (94.2%, 2,373/2,519) were identified through passive case finding.

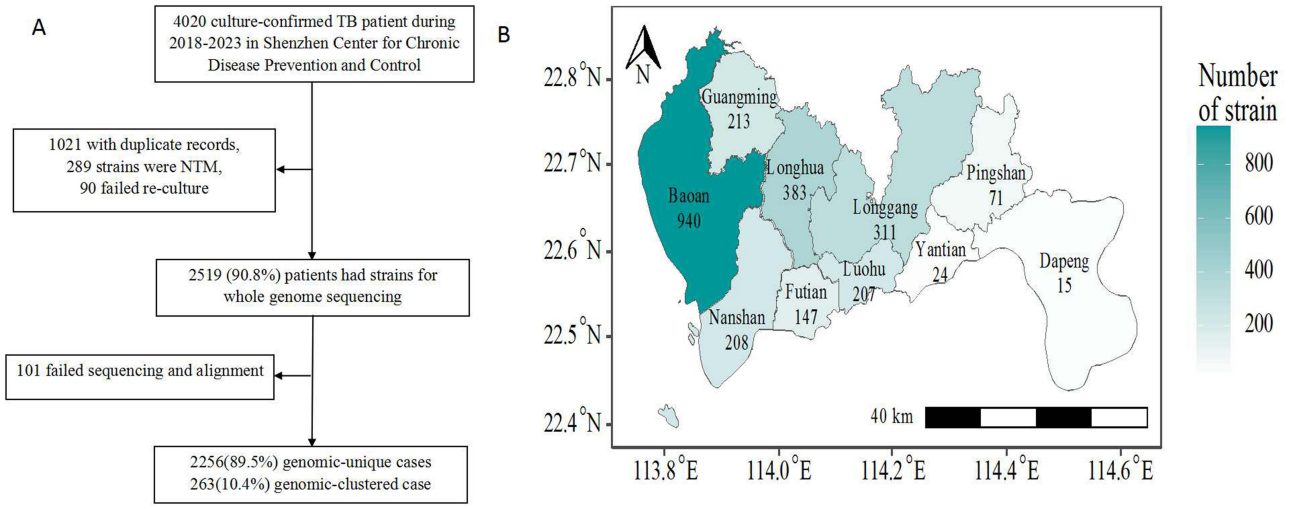

Figure 1 Sample enrollment (**A**) and geographic distribution (**B**) of patients with tuberculosis in Shenzhen, 2018–2023. The colors represents the number of patients.

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Genotyping and Drug Resistance Prediction

Genomic analysis indicated that *MTB* in Shenzhen was predominantly belonged to Beijing family (73.5%, 1851/2519). Among these, 70.7% (1309/1851) belonged to modern Beijing strain, and 29.3% (542/1851) belonged to ancient Beijing strain. The remaining non-Beijing strains included 640 L4 strains, 27 L1 strains, and 1 L3 strain (Figure 2). SAM-TB identified 1772 (70.3%) strains that were susceptible to all anti-TB drugs and 747 (29.7%) strains that were resistant to at least one drug. Of these drug-resistant strains, 262 strains were MDR, 88 were pre-XDR, and one was XDR. Mutations causing resistance to clofazimine and bedaquiline were not identified (Table 1). The highest incidences of drug resistance were observed for isoniazid (17.1%) and rifampicin (15.3%). Among mutations linked to rifampicin resistance, *rpoB_S450L* (46.6%) was the most prevalent, while *katG_S315T* (68.3%) was the dominant mutation linked to isoniazid resistance (Supplementary Table S1).

Risk Factors for Genomic Clustering

To gauge recent transmission levels, we computed the clustering rate. A total of 263 patients (10.4%, 263/2519) were grouped into 119 genomic clusters, of which 99 clusters containing only 2 patients and 20 clusters containing 3–5 patients (Figure 2). Risk factors for genomic clustering were analyzed (Table 2). Risk factors for recent transmission, as shown by the univariate logistic regression analysis, included age, drug resistance profile, and strain lineage. Further analysis using multivariable logistic regression analysis showed a significant difference in clustering rate among different age groups. Patients under 25 years of age (OR=3.07, 95% CI: 1.17–8.03) and aged 25–44 years (OR=2.86, 95% CI: 1.13–7.23) faced higher clustering risks compared to those aged 65 and above. Moreover, DR-TB was found to be an

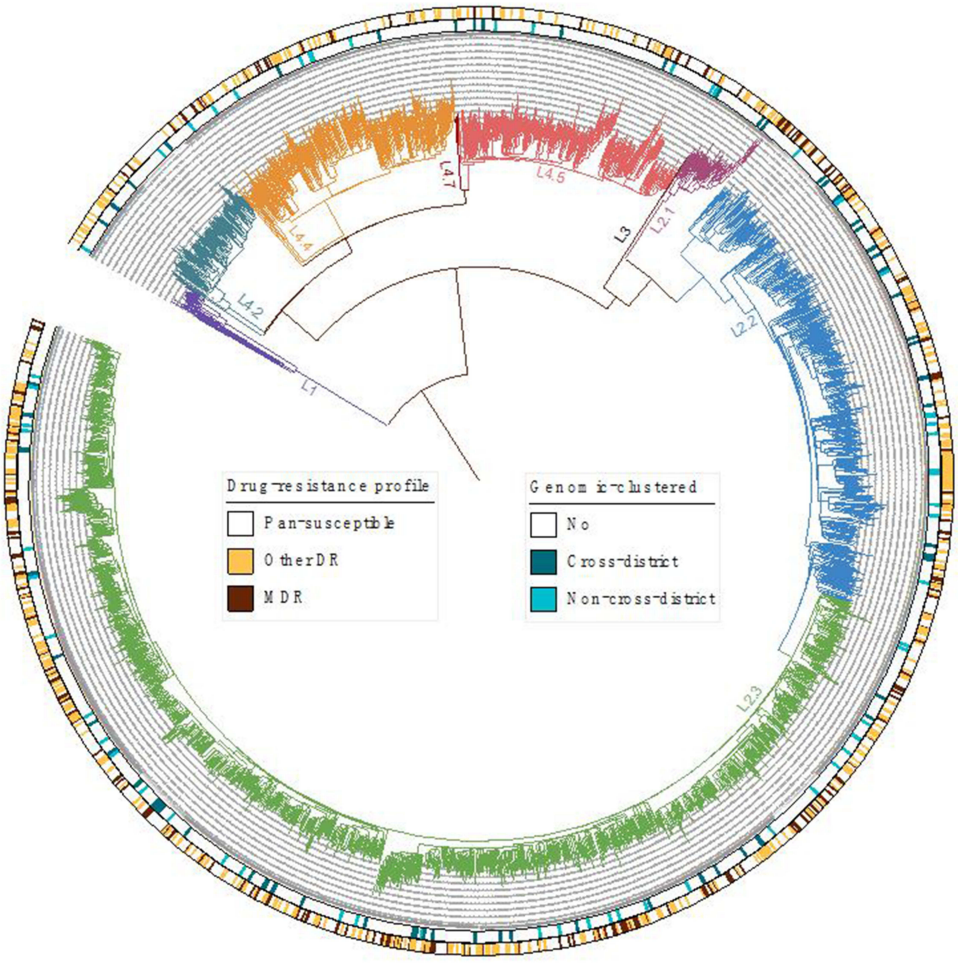

Figure 2 The phylogeny of 2519 Mycobacterium tuberculosis strains isolated in Shenzhen, 2018–2023.

Table 1 Drug Resistance Profile of Mycobacterium tuberculosis Strains Isolated in Shenzhen Based on Genomic Analysis of Drug-Resistant Mutations

	Clustered (N=263)		Non-Clustered (N=2256)		Total (N=2519)	
	No.	%	No.	%	No.	%
Genetic resistance						
XDR	0	0	8	0.3	8	0.3
Pre-XDR (MDR+FQs)	13	4.9	68	3	81	3.2
MDR	34	12.9	228	10.1	262	10.4
Poly-resistance	0	0	8	0.4	8	0.3
Mono-resistance	45	17.1	253	11.2	298	11.8
Isoniazid monoresistance	15	5.7	56	2.5	71	2.8
Rifampicin monoresistance	13	4.9	86	3.8	99	3.9
Other monoresistance	17	6.5	111	4.9	128	5.1
Pan susceptible	159	60.5	1613	71.5	1772	70.3
First-line drug resistance						
Isoniazid	54	20.5	378	16.8	432	17.1
Rifampin	53	20.2	333	14.8	386	15.3
Ethambutol	17	6.5	145	6.4	162	6.4
Pyrazinamide	13	4.9	107	4.7	120	4.8
Streptomycin	49	18.6	324	14.4	373	14.8
Second-line drug resistance						
Fluoroquinolones	13	4.9	103	4.6	116	4.6
Amikacin	0	0	11	0.5	11	0.4
Capreomycin	0	0	11	0.5	11	0.4
Kanamycin	0	0	16	0.7	16	0.6
Ethionamide	14	5.3	97	4.3	111	4.4
Para-aminosalicylic acid	7	2.7	40	1.8	47	1.9

Table 2 Univariate and Multivariable Logistic Regression of Risk Factors for Genomic Clustering

	Clustered (%)	Non-Clustered (%)	Total (%)	Univariate Regression		Multivariable Regression	
				OR (95% CI)	p Value	aOR (95% CI)	p Value
Total	263 (10.4)	2256 (89.6)	2519				
Sex							
Female	84 (10.2)	740 (89.8)	824 (32.7)	1		-	
Male	179 (10.6)	1516 (89.4)	1695 (67.3)	1.04 (0.79, 1.37)	0.778	-	-
Age							
<25	62 (13.0)	415 (87.0)	477 (18.9)	3.08 (1.21, 7.85)	0.019	3.07 (1.17, 8.03)	0.022
25–44	155 (11.7)	1174 (88.3)	1329 (52.8)	2.72 (1.09, 6.78)	0.032	2.86 (1.13, 7.23)	0.027
45–64	41 (6.8)	564 (93.2)	605 (24.0)	1.50 (0.58, 3.88)	0.406	1.59 (0.61, 4.17)	0.345
≥65	5 (4.6)	103 (95.4)	108 (4.3)	1		1	

(*Continued*)

Table 2 (Continued).

	Clustered (%)	Non-Clustered (%)	Total (%)	Univariate Regression		Multivariable Regression	
				OR (95% CI)	p Value	aOR (95% CI)	p Value
Occupation							
Factory worker	76 (10.1)	679 (89.9)	755 (30.0)	1			
Office worker	27 (11.1)	216 (88.9)	243 (9.7)	1.12 (0.70, 1.78)	0.642	1.18 (0.73, 1.92)	0.499
Public service	25 (10.0)	224 (90.0)	249 (9.9)	1.00 (0.62, 1.61)	0.991	0.91 (0.56, 1.47)	0.692
Student	14 (15.4)	77 (84.6)	91 (3.6)	1.62 (0.88, 3.01)	0.123	1.36 (0.69, 2.68)	0.381
Unemployed	117 (10.3)	1018 (89.7)	1135 (45.1)	1.03 (0.76, 1.39)	0.865	1.07 (0.78, 1.46)	0.684
Unknown	4 (8.7)	42 (91.3)	46 (1.8)	0.85 (0.30, 2.44)	0.764	0.71 (0.24, 2.08)	0.537
History of tuberculosis							
New cases	243 (10.6)	2060 (89.4)	2303 (91.4)	1		-	
Retreated cases	20 (9.3)	196 (90.7)	216 (8.6)	0.87 (0.54, 1.40)	0.553	-	-
Internal migrant							
No	36 (11.3)	284 (88.7)	320 (12.7)	1		-	
Yes	227 (10.3)	1972 (89.7)	2199 (87.3)	0.91 (0.63, 1.32)	0.612	-	-
Diagnosis delay							
<2 weeks	78 (10.4)	670 (89.6)	748 (29.7)	1		-	
2–4 weeks	41 (9.7)	381 (90.3)	422 (16.8)	0.92 (0.62, 1.38)	0.699	-	-
4–8 weeks	57 (9.6)	537 (90.4)	594 (23.6)	0.91 (0.64, 1.31)	0.615	-	-
≥8 weeks	85 (11.6)	650 (88.4)	735 (29.2)	1.12 (0.81, 1.56)	0.484	-	-
Unknown	2 (10.0)	18 (90.0)	20 (0.8)	0.95 (0.22, 4.19)	0.951	-	-
Patient source							
Active case-finding	20 (13.7)	126 (86.3)	146 (5.8)	1		1	
Passive case-finding	243 (10.2)	2130 (89.8)	2373 (94.2)	0.72 (0.44, 1.17)	0.187	0.74 (0.45, 1.23)	0.251
Abnormal chest radiographs							
No	60 (12.7)	413 (87.3)	473 (18.8)	1		1	
Yes	203 (9.9)	1843 (90.1)	2046 (81.2)	0.76 (0.56, 1.03)	0.077	0.89 (0.58, 1.36)	0.582
Sputum smear status							
Negative	144 (10.6)	1215 (89.4)	1359 (54.0)	1		-	
Positive	119 (10.3)	1041 (89.7)	1160 (46.0)	0.96 (0.75, 1.25)	0.783	-	-
Drug resistance profile							
Pan-susceptible	159 (9.0)	1613 (91.0)	1772 (70.3)	1		1	
DR	68 (14.0)	417 (86.0)	485 (19.3)	1.65 (1.22, 2.24)	0.001	1.57 (1.15, 2.13)	0.005
MDR	36 (13.7)	226 (86.3)	262 (10.4)	1.62 (1.10, 2.38)	0.015	1.44 (0.84, 2.46)	0.182
Beijing strain							
No	53 (7.9)	615 (92.1)	668 (26.5)	1		1	
Yes	210 (11.3)	1641 (88.7)	1851 (73.5)	1.48 (1.08, 2.04)	0.014	1.31 (0.95, 1.80)	0.103

independent risk factor for the recent spread of tuberculosis. Patients with DR had a greater likelihood of clustering than those who were pan-susceptible (OR=1.57, 95% CI: 1.15–2.13).

Cross-District Transmission

In order to determine the extent of cross-district transmission in Shenzhen, we separately analyzed the data of Shenzhen's 10 districts and compared the results with citywide together analysis. The together analysis identified 119 clusters, of

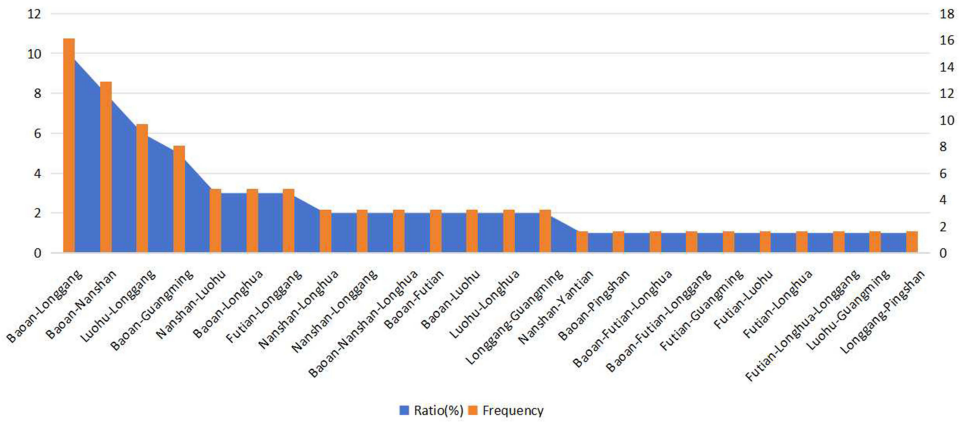

Figure 3 The frequency of clustering between patients from different districts.

which 62 (52.1%) contained patients from different districts. Among these cross-district clusters, 5 clusters contained patients from 3 different districts and 57 contained patients from 2 different districts. Notably, 54.8% (144/263) of the 263 clustered cases were part of cross-district clusters. The most frequent cross-district transmission occurred between Bao'an and Longgang districts, representing 16.1% (10/62) of all cross-district transmissions, followed by transmissions between Bao'an and Nanshan districts, which accounted for 12.9% (8/62) (Figure 3). We compared the clustering rates analyzed separately and together (Table 3) and found that together analysis identified significantly higher clustering rates in all districts, except Dapeng District (which had no clustered cases), compared to separate analysis. To comprehend the dynamics of transmission across districts, we studied the share of internal migrants in cross-district clusters. We found that the risk of cross-district transmission was 3.41 times (95% CI:1.49–7.80) higher in internal migrants than in residents, suggesting that internal migrants are likely to be the drivers of cross-district transmission of TB in Shenzhen.

Discussion

It is important to understand the transmission dynamics of TB and its risk factors to develop targeted strategies for prevention and control, including managing outbreaks and preventing the disease from spreading.[8] In this study, we analyzed the recent transmission dynamics of TB in Shenzhen using data collected from citywide TB surveillance sites

Table 3 Separate Clustering Rates and Together Clustering Rates in ten Districts in Shenzhen. Separate Clustering Rate: the Clustering Rates Were Analyzed Based on the Data From 10 Districts in Shenzhen Separately. Together Clustering Rate: the Clustering Rates Were Analyzed Based on the Data From 10 Districts in Shenzhen Together

District	Separate Clustering Rate	Together Clustering Rate	P Value
Baoan	7.6 (71/940)	10.4 (98/940)	0.0295
Longhua	4.7 (18/383)	7.6 (29/383)	0.0977
Longgang	5.5 (17/311)	13.8 (43/311)	0.0004
Guangming	3.8 (8/213)	8.0 (17/213)	0.0636
Nanshan	4.3 (9/208)	12.5 (26/208)	0.0027
Luohu	5.8 (12/207)	12.6 (26/207)	0.0172
Futian	4.1 (6/147)	11.6 (17/147)	0.0169
Pingshan	5.6 (4/71)	8.5 (6/71)	0.5118
Yantian	0 (0/24)	4.2 (1/24)	0.3122
Dapeng	0 (0/15)	0 (0/15)	–
Shenzhen	5.8 (145/2519)	10.4 (263/2519)	<0.001

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between 2018 and 2023. Our results indicate that more than half of the transmission events involved cross-district transmission. Consequently, restricting the analysis to a single district would have excluded a substantial number of transmission events, potentially underestimating the scale and complexity of TB transmission dynamics in Shenzhen.

Population mobility plays a key role in the transmission of infectious diseases, a fact underscored by the COVID-19 pandemic.[21] Despite this, research specifically focusing on the cross - regional spread of TB remains limited. Research in the European Union highlighted that cross-border clusters comprised between 2 and 30 resistant isolates from two to six countries, showing varied RR/MDR-TB transmission patterns in Western and Eastern EU nations.[22] Li et al demonstrated that internal migrants significantly contribute to cross-regional TB transmission in China Shenzhen, where the high mobility of the population often results in cross-regional transmission, pointing to the connection between mobility and transmission. However, this research solely utilized data from the Bao'an and Longhua districts in Shenzhen, without considering cross-district transmission within the city.[23] Given Shenzhen's substantial internal mobility, understanding cross - district TB transmission is key for effective prevention and control.[24] Our study found frequent transmission between Shenzhen's districts, with internal migrants as the main risk factor. This frequent transmission risks underestimating TB levels and challenges identifying and intervening in high - risk groups. In high - mobility regions, lack of cross - district coordination can lead to undetected transmission chains and inefficient resource allocation. Shenzhen's extensive TB spread across districts underscores the importance of surpassing traditional geographic boundaries in TB management. Strengthening resource coordination and district - level collaboration is crucial to address cross - district transmission challenges.

The research discovered that the percentage of clustered cases differed notably among age groups, with individuals under 25 and those aged 25–44 showing much higher clustering risks than those over 65. This indicates that young and middle-aged people frequently transmit the disease, whereas TB in older adults is probably due to endogenous reactivation, aligning with findings from Shanghai.[25] This pattern is likely due to the increased social and work activities of young and middle-aged people, who frequently act as the main income providers. Enhancing focused monitoring and educational programs for this demographic is essential to boost awareness of TB prevention and treatment. Additionally, implementing tailored control measures could help mitigate TB transmission in this population. The investigation revealed a significant clustering risk for DR-TB cases in Shenzhen, with drug-resistant TB cases showing a 1.57-fold higher risk of clustering from recent transmission than pan-susceptible cases. This is consistent with earlier research showing that patients resistant to drugs tend to form clusters.[26–29] Drug resistance makes treatment more difficult, frequently resulting in longer periods of infection and higher rates of transmission. Improving diagnostic, therapeutic, and management approaches for patients with drug-resistant TB is crucial to reduce transmission.

In China, the majority of *MTB* strains belong to the Beijing family, which also accounted for over 70% of strains in Shenzhen. Prior studies have demonstrated that Beijing strains exhibit specific traits, including the ability to evade the protective effects of the BCG vaccine, thereby facilitating its effective transmission and contributing significantly to its widespread distribution.[30] Differences in lineage distribution emphasize the necessity of adopting region-specific approaches in TB control programs. Research in Central Asia identified a significant link between Beijing strains and the spread of MDR-TB.[31] Our research consistently found that Beijing strains are an independent risk factor for recent transmission, which is in agreement with other studies from China.[17,32] Rifampicin and isoniazid, as commonly used first-line anti-TB drugs, exhibited the highest risk of developing resistance.[33] In this study, isoniazid resistance observed in 17.1% of cases and rifampicin resistance in 15.3%. These rates are notably higher than those for other drugs, consistent with findings by Wang et al.[34] Also, no gene mutations associated with resistance to clofazimine or bedaquiline were detected in this study. This finding differs from the results reported by Zhang[35] and Karmakar,[36] potentially due to the limited use of these two new drugs in China to date.

This study preliminarily investigated the frequency of cross-district transmission in Shenzhen. However, due to the inability to obtain culture-positive strains from all TB patients in Shenzhen for WGS, the sample representativeness in this study is limited, and the clustering rate is likely underestimated. Despite these limitations, our findings underscore that cross-regional transmission is a critical issue meriting further investigation, with important implications for the development and refinement of public health policies. To more accurately characterize this transmission dynamics, future studies should aim to incorporate a larger and more representative sample, employ rigorous data analysis methodologies,

and potentially develop transmission models. Such efforts would provide robust scientific evidence to enhance our understanding of TB transmission dynamics in regions with high population mobility and inform targeted public health interventions.

In conclusion, this study analyzed the recent transmission level, risk factors, and cross-district transmission of TB in Shenzhen based on data from citywide surveillance sites. Cross-district transmission constitutes a key driver of tuberculosis spread in mobile populations. Our findings advocate for cross-jurisdictional collaboration among TB control institutions to optimize disease containment strategies.

Ethics Approval Statement

This study was approved by the Ethics Committee of the Shenzhen CCDC (SZCCC-2024-009-01-PJ). Our study complies with the Declaration of Helsinki.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors have declared that they have no conflicts of interest in this work.

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