

Extensively drug-resistant tuberculosis hotspots and sociodemographic associations in Durban, South Africa

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ABSTRACT

BACKGROUND: Extensively drug-resistant tuberculosis (XDR-TB) incidence is driven by transmission of resistant strains in KwaZulu-Natal, South Africa. Data suggests cases may be spatially clustered; we therefore sought to identify hotspots and describe these communities.

METHODS: We enrolled XDR-TB patients diagnosed from 2011-2014 in eThekweni. GPS coordinates for participant homes were collected and hotspots were identified based on population-adjusted XDR-TB incidence. Sociodemographic features of hotspots were characterized using census data. For a subset of participants, we mapped XDR-TB case non-home congregate locations and compared to results including only homes.

RESULTS: Among 132 participants, 75 (57%) were female and 87 (66%) lived in urban or suburban locations. Fifteen of 197 census tracts were identified as XDR-TB hotspots with $\geq 95\%$ confidence. Four spatial mapping methods identified one large hotspot in northeastern eThekweni. Hotspot communities had higher percentages of low educational attainment (12% vs 9%), higher unemployment (29.3% vs 20.4%), and lower percentage of homes with flush toilets (36.4% vs 68.9%). Mapping congregate locations, including workplaces, for 43 (33%) participants shifted case density towards Durban.

CONCLUSIONS: In eThekweni, XDR-TB case homes were clustered into hotspots with more indicators of poverty than non-hotspots. Prevention efforts targeting hotspot communities and congregate settings may be effective in reducing community transmission.

Key Words: Tuberculosis, XDR-TB, hotspot, sociodemographic, activity space

INTRODUCTION

Tuberculosis (TB) is the leading cause of infectious disease deaths worldwide and drug-resistant TB is an increasing concern, with an estimated 600,000 cases in 2016.¹ Extensively drug-resistant (XDR) TB involves resistance to the two most potent first-line drugs (isoniazid and rifampin), in addition to a fluoroquinolone and at least one second-line injectable drug.² XDR-TB treatment requires long and costly regimens that are difficult to complete, and treatment success falls from 83% for drug-susceptible TB patients to 30% for XDR-TB patients.^{1,3}

Drug resistance can arise due to improper or incomplete treatment of drug-susceptible TB, referred to as “acquired” drug resistance. However, there is increasing recognition that the majority of drug-resistant TB cases result from direct transmission of an already-resistant strain.⁴⁻⁷ Interventions targeting transmission reduction are therefore critically needed, but gaps remain in our understanding of drivers of transmission at an individual and population level.

Smoking, malnutrition, and indoor air pollution have been shown to increase an individual’s risk for active TB disease,⁸ while overcrowding and poor ventilation increase risk of transmission.⁸⁻¹⁰ These factors are often associated with poverty; indeed, 95% of TB deaths occur in low- and middle-income countries.¹ Addressing these risk factors may improve TB outcomes; one study suggests 80% of TB cases are attributable to modifiable poverty-associated factors.⁸

Recently, Geographic Information Systems (GIS) tools have been recognized for their utility in merging socioeconomic, TB disease burden, and spatial data, allowing for identification and detailed socioeconomic profiling of TB disease “hotspots”.¹¹ Some studies have also

incorporated multiple locations per individual to estimate “activity space”, defined as the space occupied during waking hours, to identify settings where transmission may occur.^{12, 13} Findings have suggested unanticipated associations between TB incidence and factors not traditionally associated with poverty in some instances. These studies demonstrate that TB risk in low-income areas follows complex trends that vary depending on setting, highlighting the need to develop tailored prevention efforts.¹⁴⁻¹⁶

South Africa has among the highest XDR-TB incidence in the world and accounts for almost 20% of all drug-resistant cases in Africa. Within South Africa, nearly half of XDR-TB cases are found in the province of KwaZulu-Natal.¹⁷ Recent data suggests that at least 69% of XDR-TB in KwaZulu-Natal province is caused by person-to-person transmission of XDR-TB strains.⁵ Given these findings, we studied the spatial distribution of XDR-TB in eThekweni, the most populous district of KwaZulu-Natal. We built on previous work by incorporating census data to evaluate sociodemographic characteristics of “hotspots” and examining participant “activity space”. This knowledge could help identify factors influencing community transmission and guide TB control efforts.

METHODS

Study Population and Setting

We conducted a cross-sectional study of XDR-TB patients diagnosed between 2011 and 2014 in the province of KwaZulu-Natal and focused this analysis on those residing in the eThekweni district. With 3.4 million residents, eThekweni accounts for 33% of the population in KwaZulu-Natal. The district contains the city of Durban, making it a uniquely urban setting

within an otherwise rural province. Approximately 41% of XDR-TB cases in the province reside in eThekweni.¹⁸

Study Variables and Data Sources

We used data from the “Transmission of HIV-Associated XDR-TB in South Africa (TRAX)” study. TRAX cases were identified from the provincial referral laboratory which conducted all diagnostic testing for XDR-TB. We collected global positioning system (GPS) locations of patients’ homes and diagnosing facilities. We interviewed patients to identify locations of congregate settings frequented in the five years prior to XDR-TB diagnosis including work, school, and other social settings. Detailed methods for this study have been published elsewhere.⁵

To examine hotspots in a high-burden urban area, we restricted our analysis to patients with home residences in eThekweni district. The exposure of interest was sociodemographic status at the population level as measured by the 11 indicators identified in South Africa’s Multidimensional Poverty Index, which is used to assess presence and severity of poverty.¹⁹ The index includes household indicators (flush toilet in home, dwelling type, and fuel type for cooking, heating, and lighting), educational indicators (level of education, school attendance for school-aged children), a health indicator (under-five mortality), and an economic indicator (unemployment). Basic demographic information such as sex, age, and race were also examined.

We used the 2011 South Africa census for data on indicators.²⁰ eThekweni district census data and shapefiles defining geographic borders were obtained from Statistics South Africa and included detail to the census units of “main place” and “sub-place”. From largest to smallest, the

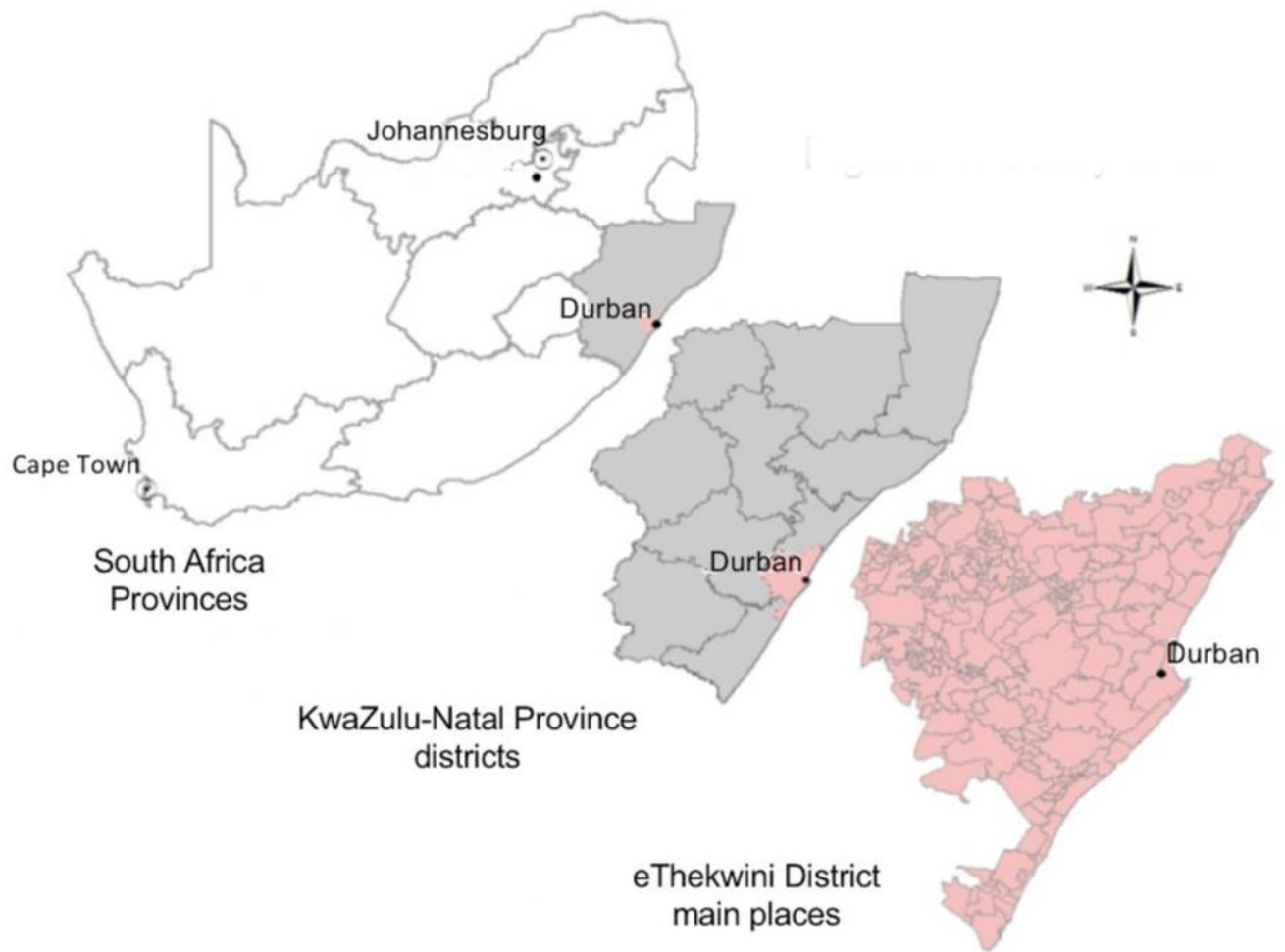


Figure 1.
Study area

census units used in South Africa are: province, district, main place, and sub-place (Figure 1). eThekweni district consists of 197 main places and 394 sub-places.

Data Analysis

The primary outcome of interest was the number of TRAX cases with home residence in a main place census unit. Spatial data was projected using the Universal Transverse Mercator (UTM) 32S projection and analyzed in ArcGIS version 10.5.1 and GeoDa.²¹ Empiric and Spatial Bayes Smoothing (queen contiguity weighting)^{21, 22} were applied to correct for inflated rate calculations due to small populations. ArcGIS was used to calculate incidence rates and create kernel density surfaces. Global Moran's I statistic was calculated, and Local Indicators of Spatial Autocorrelation (LISA) were used to apply this statistic locally for cluster assessment.²³ Getis-Ord $G_i^*(d)$ statistics were also used to evaluate the significance of case clustering. An α value of 0.05 was used to identify main places as hotspots, or areas of significantly higher XDR-TB incidence.

Additional exploratory analyses were performed to estimate activity space^{12, 13} for a subset of participants who reported non-home locations where they spent two or more hours weekly. Patients in this subset were those who provided locations for work, school, and other congregate social settings with enough specificity to be geocoded using ArcGIS and Google Earth. Kernel density surfaces were created incorporating non-home locations and compared to density surfaces generated using home locations alone. We also calculated distance from home to place of work and other congregate locations.

We compared sociodemographic characteristics of XDR-TB patients to the underlying general population using t-tests and chi-square tests. To evaluate sociodemographic features at a population level, census data were merged with shapefiles in ArcGIS and exported to SAS version 9.4. Rates for disease incidence and socioeconomic indicators were calculated with population estimates from the 2011 census. Indicators were examined within hotspot main places identified through spatial analysis and compared to non-hotspot main places using Mann-Whitney tests. An α value of 0.05 was used to determine statistical significance for all tests performed.

Ethical Considerations

Approval for the TRAX study was provided by the institutional review boards of Emory University, Albert Einstein College of Medicine, the University of KwaZulu-Natal and by the Centers for Disease Control and Prevention. All participants provided written informed consent or assent.

RESULTS

Participants

Of the 1,027 XDR-TB patients diagnosed in KwaZulu-Natal between 2011 and 2014, we screened 521 (51%) and enrolled 404 (76% of total screened) in the TRAX study; 132 (33%) resided in eThekwinini and were included in this analysis. Among these participants, 75 (57%) were female and 87 (66%) lived in urban or suburban locations (Table 1). Median age at

Table 1.

Baseline characteristics of TRAX-enrolled XDR-TB patients in eThekweni, South Africa, compared to underlying population characteristics

Sociodemographic characteristics	TRAX-enrolled XDR patients (n=132)	eThekwini population (n=3,442,670) ¹	<i>p</i> -value
Individual characteristics			
Age ² , median	33.0	26.0	<.001
Female	56.8%	51.7%	0.24
Primary school or less	26.0%	30.0%	0.04
Secondary school or less	58.8%	61.0%	
University or higher	15.3%	9.0%	
Household characteristics			
Flush toilet in home	36.4%	68.9%	<.001
Reside in free-standing home or apartment	87.9%	83.6%	0.19
Electricity in home	88.6%	90.9%	0.37
Annual income <6,000 South African Rand	31.1%	25.6%	<.001
Household size, median	2	3	<.001

¹Population data from 2011 South Africa census

²Age at XDR-TB diagnosis shown for TRAX patients

diagnosis was 33 years (interquartile range [IQR], 29–44). There was no statistically significant difference in spatial distribution for enrolled vs non-enrolled XDR-TB patients based on age ($p=0.52$), sex ($p=0.76$), or facility of diagnosis ($p=0.70$).

Spatial Analysis

The highest number of XDR-TB cases were observed in the eastern part of the district, near the highly populated Durban city centre (Figure 2a). Global Moran's I for XDR-TB incidence rate at the main place level, according to home residence, was 0.87, indicating strong positive spatial autocorrelation (i.e., high values surrounded by similarly high values). The spatial distribution of XDR-TB in eThekweni and unadjusted incidence rates suggested incidence was highest in the northeast part of the district (Figure 2a). Kernel density surfaces based on point locations of cases also revealed high case density in the northeast region (Figure 2b). Population-adjusted kernel density smoothing (Figure 2c) indicated that western eThekweni also had high incidence, though population is sparse in this area.

Getis-Ord-Gi*(d) analysis identified 15 main places as hotspots with $\geq 95\%$ confidence (Figure 2d). The largest identified cluster of contiguous main places was located in the northeast part of the district, suggesting one large hotspot of XDR-TB case homes in this area. LISA analysis (Figure 2e) also demonstrated high-high clustering (i.e., high case areas surrounded by other high case areas) in the northeast region. Three outliers of high incidence surrounded by low incidence were found in the west and southwest regions of the district; however, each of these included only a single case.

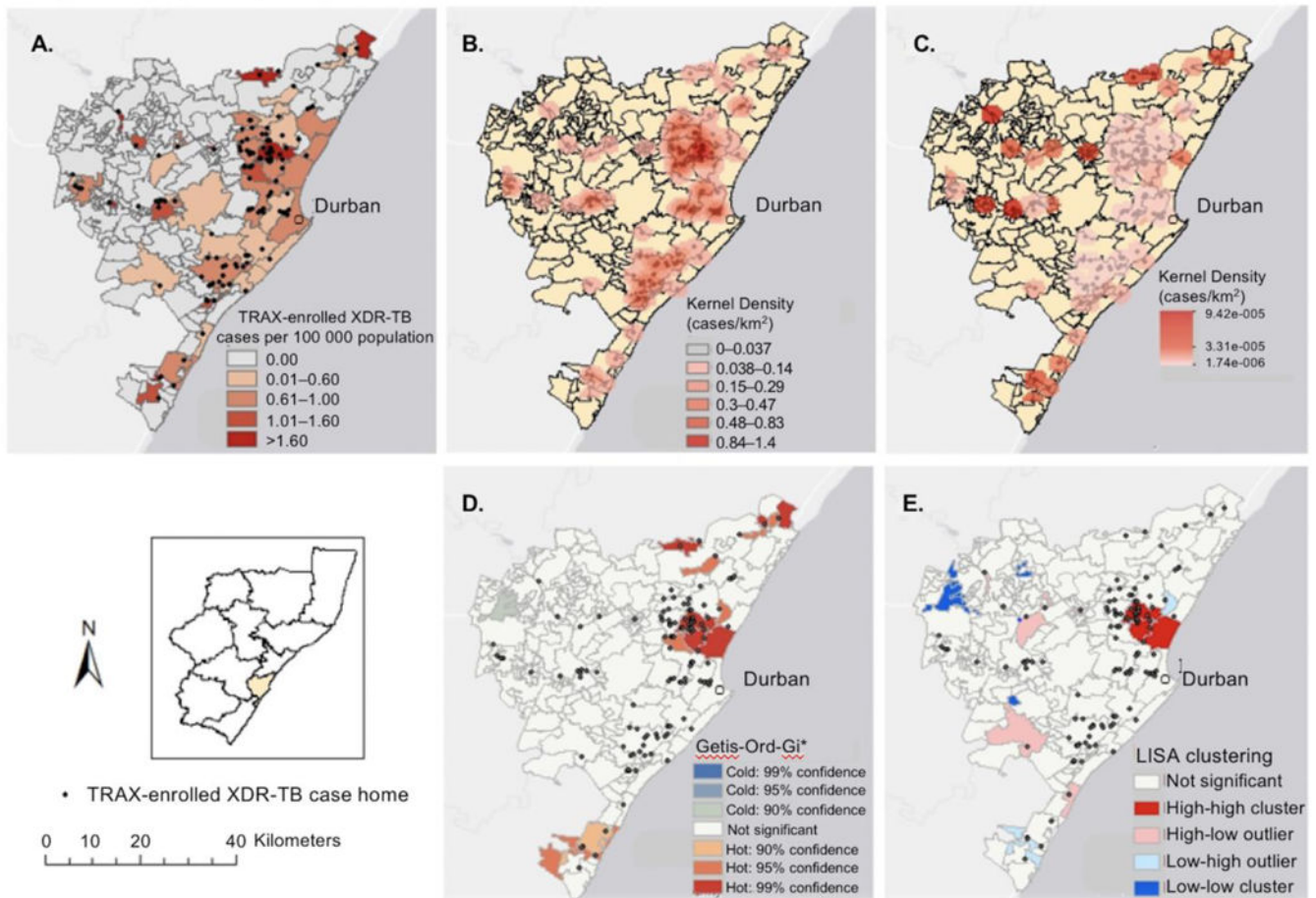


Figure 2. Spatial patterns of TRAX-enrolled XDR-TB case homes in eThekweni, South Africa.

Figure 2A. TRAX-enrolled XDR-TB cases per 100,000 population, at main place level, shows highest study incidence in the northeast region of eThekweni; 2B. Unadjusted kernel density surface of TRAX-enrolled XDR-TB cases shows largest area of high case density in northeast region of eThekweni; 2C. Population-adjusted kernel density surface of TRAX-enrolled XDR-TB cases highlights cases to the west of eThekweni where population is low; 2D. Getis-Ord-Gi* hotspot map census main place unit, shows largest significant hotspot in the northeast region with less significant hotspots in the southern-most region; 2E. Local Indicators of Spatial Autocorrelation (LISA) cluster map, census main place unit, suggests a cluster of high incidence main places (high-high cluster) in the northeast part of the region and a cluster of low incidence (low-low cluster) in the far west; outliers of high and low incidence also detected

Activity Space Analysis

We were able to geolocate specific non-home congregate locations for 43 (33%) of the 132 patients, comprising 40 places of work, two school settings, and nine other congregate settings including churches, casinos, and bar/restaurants. The spatial distribution of homes did not differ among this subset of 43 patients compared to all TRAX patients in eThekweni. A kernel density surface analysis including home, healthcare facility, and non-home locations demonstrated a higher case concentration in the central eastern coast of the district (corresponding to downtown Durban) than was suggested from analysis of home location alone (Figure 3a-c). This shift was driven by a high concentration of work places in the downtown area. Median home-work and home-facility distances were 10.4 and 10.3 kilometers, respectively.

Sociodemographic Factors

At an individual level, participants with XDR-TB were older, fewer had flush toilets in the home, and their annual income was lower than the eThekweni population (p-values all <0.001) (Table 1). Conversely, a higher proportion of XDR-TB participants had a university or higher education (p=0.04). At a population level, persons living in hotspots had statistically significantly lower educational attainment and higher unemployment, under-five mortality, and percentage of school-aged children not attending school than populations in non-hotspot areas (Table 2). Compared to non-hotspot areas, homes in hotspots were less likely to have a flush toilet.

Table 2.

Poverty measures within XDR-TB hotspots and non-hotspots in eThekweni, South Africa, based on general population census characteristics

Indicator Measures for Household	Non-hotspot	Hotspot¹	p-value
Education			
Low educational attainment (15 years old with fewer than 5 years of schooling)	8.7%	12.1%	0.01
School-aged children not attending school	3.6%	9.9%	<0.01
Health			
Mortality under age 5 years	0.3%	0.7%	0.04
Living standards			
Dirty fuel for cooking	27.7%	19.7%	0.82
Dirty fuel for lighting	15.7%	18.3%	0.21
Dirty fuel for heating	40.5%	32.4%	0.93
No source for clean drinking water	26.4%	24.2%	0.98
Informal dwellings (shack/traditional dwelling/caravan/ tent/other)	16.4%	23.6%	0.31
Flush toilet in home	68.9%	36.4%	<0.01
Low asset ownership	14.8%	17.0%	0.10
Economic Activity			
Unemployment	20.4%	29.3%	<0.01

¹Hotspots identified at main place level with 95% confidence using ARCGIS Getis-Ord Gi*(d)

²Dirty fuel defined as paraffin, wood, coal, or animal dung

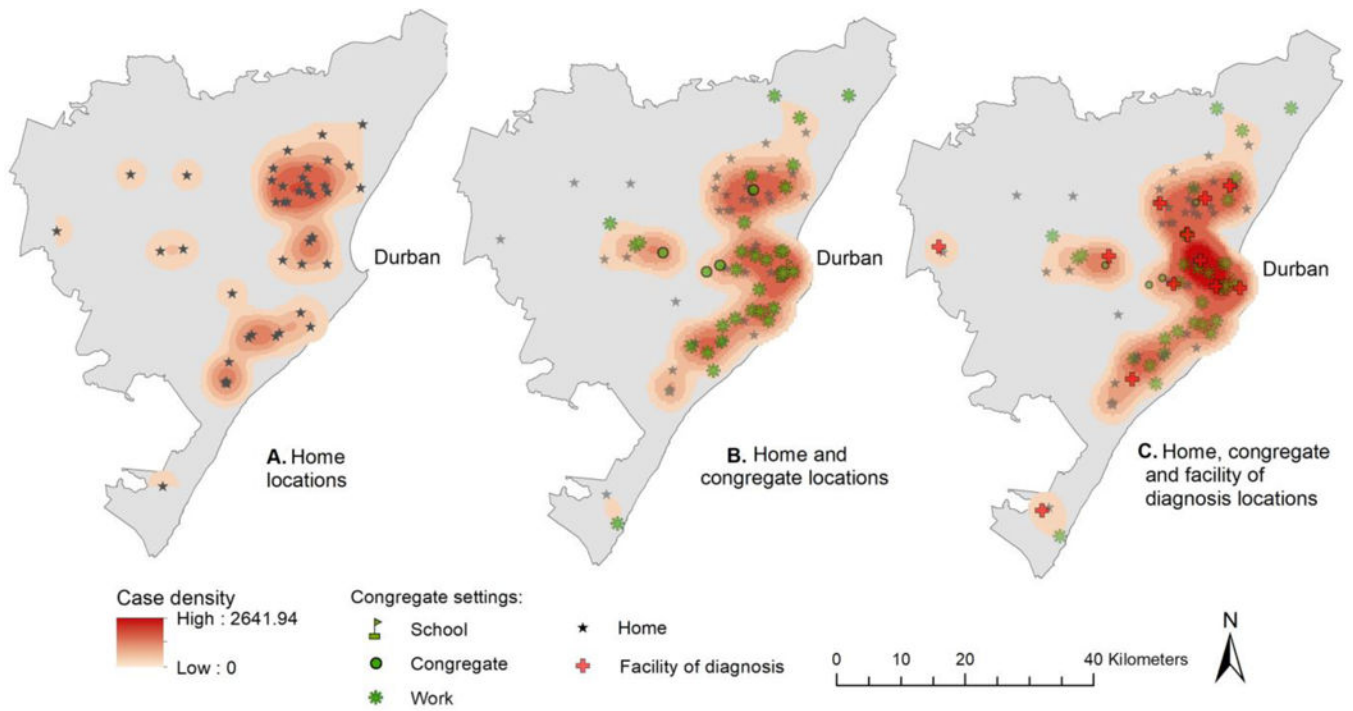


Figure 3. Case density of TRAX-enrolled XDR-TB cases in eThekweni with home, congregated, and facility of diagnosis.

Figure 3A. Kernel density surface of TRAX-enrolled XDR-TB case homes; 3B. Kernel density surface of TRAX-enrolled XDR-TB case homes and congregated locations; 3C. Kernel density surface of TRAX-enrolled XDR-TB case homes, congregated settings, and facilities of diagnosis

DISCUSSION

KwaZulu-Natal province bears approximately half of South Africa's XDR-TB burden¹⁷ and, despite substantial advances in diagnosis and treatment of TB over the past decade, an ongoing cycle of transmission is perpetuating the epidemic.⁵ We found that XDR-TB is not uniformly distributed in the urban center of KwaZulu-Natal, and that a hotspot of XDR-TB case residences exists in the northeast part of eThekweni district. Hotspot neighborhoods had lower educational attainment, higher unemployment rates, and homes that were less likely to have a flush toilet. Public health interventions to halt the XDR-TB epidemic may be more effective if high incidence neighborhoods are targeted. Our data suggests these efforts will require a multifaceted response aimed at not only improving XDR-TB diagnosis and treatment, but also addressing underlying social determinants of health.

One strength of our analysis was the use of multiple geospatial methodologies with both raw and spatially smoothed data. Though there was slight variation in detected clusters in more rural geographic areas with small populations, the spatial clustering observed northeast of the district was consistent, regardless of the method applied. Spatial studies are often limited by data aggregation, which can mask nuanced trends when areas with distinct characteristics are aggregated together.²⁴ For the purposes of data visualization and incidence comparison, data were aggregated to main place levels for this study; however, availability of sub-place data made it possible to examine trends at various levels of aggregation.

Geographical clustering has also been reported in studies of drug susceptible and MDR-TB,^{9, 16, 25-27} and suggests that neighborhood-level factors may influence risk of XDR-TB. We found that residents in hotspot areas had more individual-level indicators of poverty than in non-hotspot neighborhoods. This finding is consistent with other research that has found associations

between poverty and MDR-TB.¹⁴⁻¹⁶ Neighborhood indicators of poverty were also associated with being a hotspot. These findings may help target neighborhoods for increased interventions such as education, screening, and clinic outreach—even if these neighborhoods may not represent the actual locations where transmission occurred. Clustering of home locations may suggest several plausible mechanisms including higher susceptibility to active TB infection due to environmental living conditions, variable access to quality diagnostic testing, or differing levels of motivation to seek care.^{28, 29}

To examine potential transmission settings outside of homes, we analyzed non-home locations for a subset of participants. These analyses revealed a density shift towards the Durban downtown area, which was largely driven by work place locations. Though the subset for this analysis was small, the findings suggest the need for more comprehensive spatial information in examining possible areas where transmission is occurring. These findings are in line with previous research suggesting more transmission of TB may occur in non-home locations than in homes. Previous studies that systematically collected data to infer an activity space for TB patients have been able to implicate community locations such as local drinking spots and homeless shelters.^{13, 25} One study analyzing DNA fingerprints of TB cases in Cape Town found that only 19% of cases were due to transmission between household members; additional non-home locations were not analyzed.³⁰

Our analysis of XDR-TB clustering was limited to cases that were enrolled in the TRAX study and may have provided more robust models if geographic and sociodemographic information was known for all diagnosed XDR-TB cases to eliminate the possibility of selection bias. Additionally, XDR-TB may be under-reported due to limited use of second-line drug susceptibility testing; estimates from 2016 suggest that 40% of MDR-TB cases in South Africa

are not tested for further resistance.¹ These undetected cases may contribute to differing cluster detection, especially if patients visiting certain facilities are systematically untested and unreported. Though data were not available to assess the representativeness of our sample in regard to home location and sociodemographic characteristics,

Another limitation of this study was the scarcity of geographic movement information available for TRAX participants outside the home. While we were able to geocode work and congregate setting for a subset of participants, data was not collected with this purpose in mind and activity space could not be estimated for the majority of participants. Recent data examining human movement have demonstrated that there are often numerous hubs for infectious disease transmission outside of the home.³¹ A more comprehensive log of individual case movement would be useful in further assessing where transmission is occurring in eThekweni. Nevertheless, our use of exact GPS coordinate collection for home locations, as opposed to alternative methods such as self-report or neighborhood-level aggregation, enhances the strength of our conclusions.

Direct transmission of resistant strains is driving the XDR-TB epidemic in KwaZulu-Natal, South Africa.⁵ Knowledge of geographic hotspots and sociodemographic factors associated with risk can help to target prevention efforts within the hardest-hit communities. We have shown that homes of XDR-TB cases are spatially clustered and that these clusters are associated with multiple indicators of poverty. Our data also point to congregate settings where cases spend time, including workplaces in the downtown Durban area. Further research characterizing a more complete range of movement among XDR-TB cases is needed to determine where transmission is occurring and to target prevention efforts.

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DISCLAIMER

The findings and conclusions in this manuscript are those of the authors and do not necessarily represent the official position of the US Centers for Disease Control and Prevention nor the US

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