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Spatial patterns of extensively drug-resistant tuberculosis and associations with sociodemographic factors in Durban, South Africa

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Spatial patterns of extensively drug-resistant tuberculosis and associations with sociodemographic factors in Durban, South Africa

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An abstract of
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Abstract

Spatial patterns of extensively drug-resistant tuberculosis and associations with sociodemographic factors in Durban, South Africa

By Meaghan Peterson

Background: Extensively drug-resistant tuberculosis (XDR-TB) poses profound challenges to tuberculosis control because of few remaining treatment options, leading to poor outcomes and ongoing transmission. Recent data suggest at least 69% of XDR-TB cases are due to transmission of resistant strains in KwaZulu-Natal, South Africa. To further clarify factors driving transmission, we aimed to describe where XDR-TB is occurring in the urban district of eThekwini, in KwaZulu-Natal province, and characterize sociodemographic factors of communities with high XDR-TB case burden.

Methods: We enrolled XDR-TB patients diagnosed from 2011-2014 in KwaZulu-Natal. GPS coordinates for participant homes were recorded and those with home location in eThekwini (Durban) were included for analysis. ArcGIS was used for spatial data analysis and hotspot evaluation (based on population-adjusted incidence) of XDR-TB patients' home locations at the main place level. Sociodemographic features of communities identified as hotspots through spatial analysis were examined using data from the 2011 census. For a subset of participants, we geocoded and mapped non-home congregate locations to compare overall spatial distribution to the distribution of homes alone.

Results: Among 132 enrolled participants, 75 (57%) were female and 87 (66%) lived in urban or suburban locations. Fifteen main places were identified as hotspots for XDR-TB patient homes with $\geq$ 95% confidence. Four spatial mapping methods supported findings of one large cluster northwest of Durban. Communities identified as XDR-TB hotspots had lower educational attainment, higher percentage of school-aged children not attending school, higher unemployment, and higher percentage of homes without flush toilet. We geocoded non-home congregate locations (e.g. workplaces, schools, churches) for 43 (33%) participants. Mapping of these congregate settings showed a shift in case density towards the Durban metro area, largely driven by locations of workplaces.

Conclusions: Distribution of XDR-TB case homes is clustered in our study area and hotspots have more indicators of poverty than non-hotspots. Prevention efforts targeting these communities may be effective in reducing XDR-TB incidence. Additionally, identifying shared congregate settings of XDR-TB cases may be useful in identifying areas to target for efforts to halt community transmission.

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CHAPTER I: LITERATURE REVIEW

Global Tuberculosis Epidemic

Tuberculosis (TB) is an ancient disease believed to have killed more people than any other infectious agent in the history of mankind [2]. Despite the discovery of medicines to cure TB in the mid-20th century, it has persisted as the leading infectious killer worldwide and in 2016 was responsible for over 4,000 deaths each day [1]. TB is caused by *Mycobacterium tuberculosis*, which most commonly affects the lungs and is spread via airborne transmission [3]. In 2016, the World Health Organization (WHO) estimated that 10.4 million people became ill with TB. In the same year, approximately 1.3 million deaths were attributed to TB with an additional 0.4 million among persons with TB and HIV coinfection [1]. It is estimated that one third of the global population is has latent tuberculosis infection (LTBI), but only 5-10% will develop active disease in their lifetime [4]. The burden of TB is disproportionately high in low- and middle-income countries, and five countries (e.g., India, Indonesia, China, the Philippines, and Pakistan) account for over 50% of new cases. The highest population-based incidence rates of TB are estimated in Africa and Southeast Asia, as shown by the WHO map in Figure 1 [1].

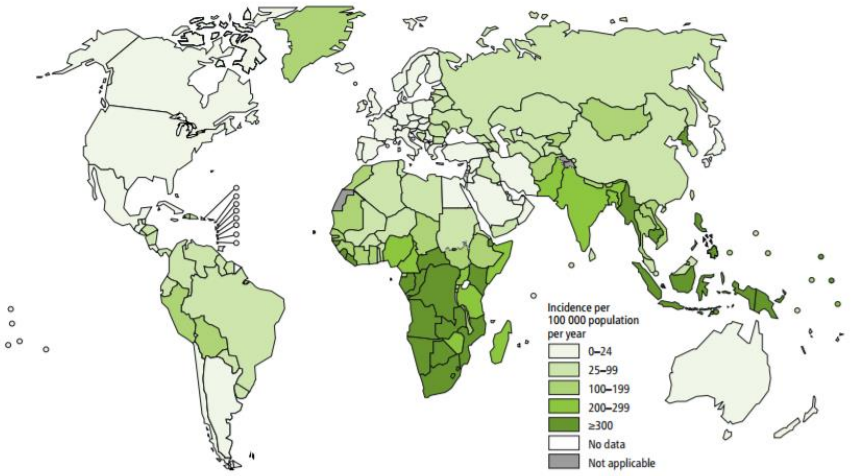
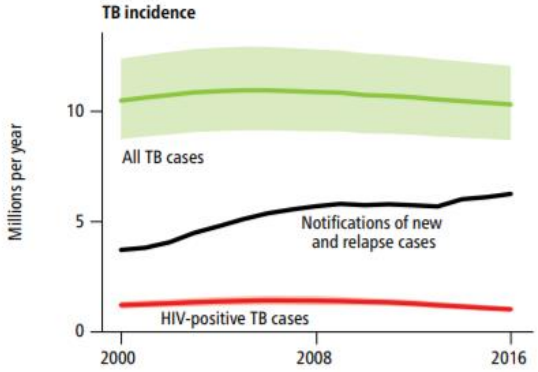


Figure 1. Estimated TB Incidence rates, 2016

Source: WHO, *Global Tuberculosis Report.* 2017 [1].

Worldwide incidence has fallen by an average of 1.5% annually since 2000 (Figure 2); however, this trend has not been observed within many high burden countries where high prevalence of drug resistance and the HIV syndemic impede incidence reduction (Figure 3). Constant or increasing TB incidence in these neglected areas of the world will continue to slow progress towards global elimination, especially considering increasing levels of global connectivity.

Figure 2. Global trends in estimated TB incidence. TB incidence rates are shown in green and incidence rates of HIV-positive TB are shown in red. Shaded areas represent uncertainty intervals. The black lines show notifications of new and relapse cases for comparison with estimates of the total incidence rate.

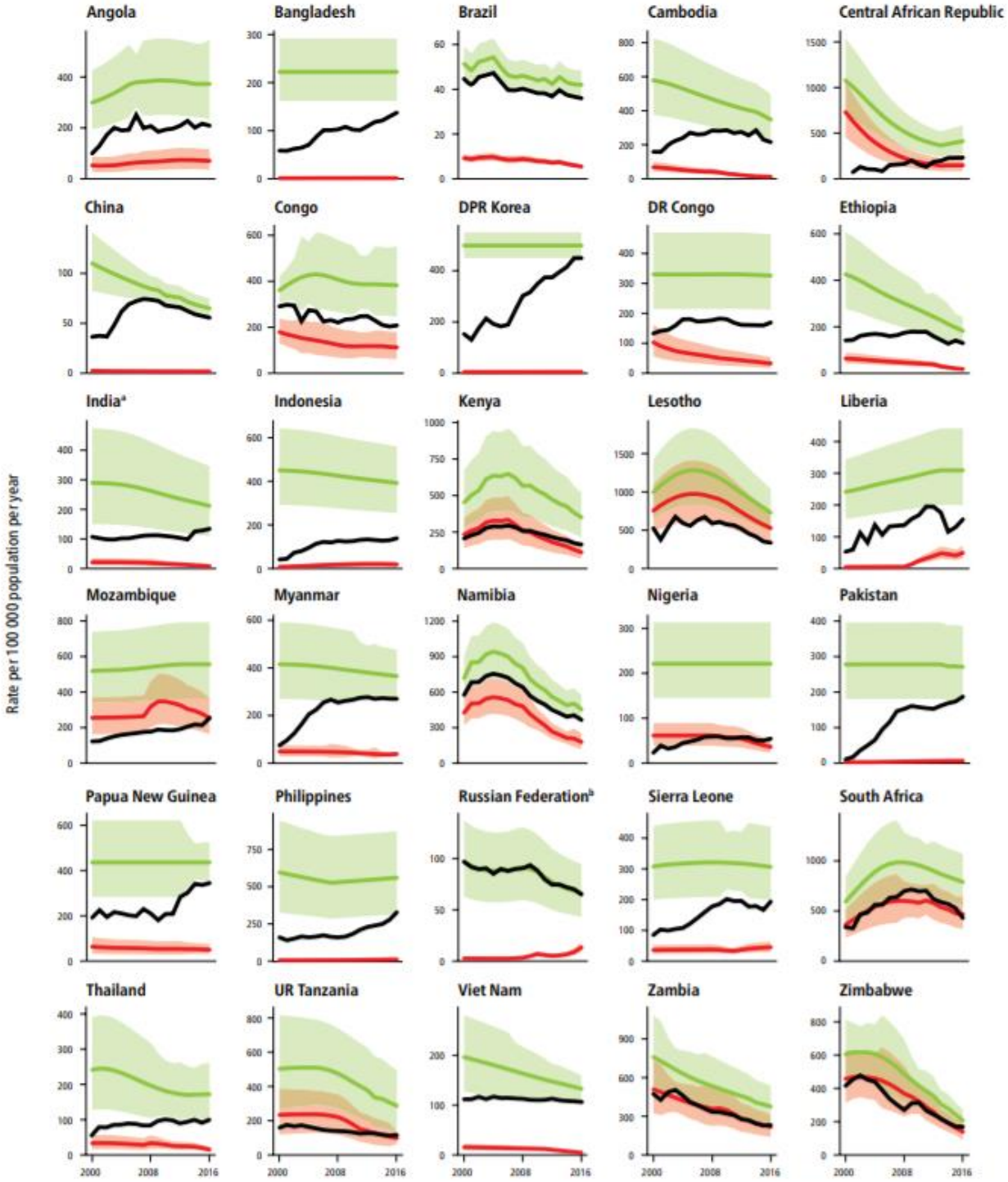


Source: WHO, *Global Tuberculosis Report.* 2017 [1]

TB remains a public health threat because of shortcomings in detection, poor initiation of treatment, and difficulty in adhering to long treatment regimens. The WHO estimates that only 61% of the estimated incident TB cases were detected in 2016. Of those

detected, not all initiated treatment (data from 2015 cohort suggest that 7% of diagnosed TB cases did not initiate treatment) [1]. Once treatment is initiated, standard course therapy requires 6 months of daily medication that is often associated with adverse drug effects and significant financial burdens [5]. These challenges lead to poor adherence or failure to complete treatment for many patients, and contribute to a global success rate of 83% [1]. Studies have suggested treatment burdens lead to disproportionately higher rates of failure in low income individuals and those with low educational attainment, which contributes to the continuation of TB as a disease of poverty [6-8].

Figure 3. Trends in estimated TB incidence in the 30 high-burden countries, 2000-2016. TB incidence rates are shown in green and incidence rates of HIV-positive TB are shown in red. Shaded areas represent uncertainty intervals. The black lines show notifications of new and relapse cases for comparison with estimates of the total incidence rate.



Source: WHO, *Global Tuberculosis Report.* 2017 [1]

TB epidemics around the world are exacerbated by concurrent HIV epidemics in many countries, especially in the African region which accounts for 75% of TB/HIV cases as suggested in Figure 4 from the WHO 2017 Global Tuberculosis Report [1]. Data suggests HIV-positive patients are at least ten times more likely to develop active tuberculosis disease [9] and have worse treatment outcomes when compared to HIV-negative individuals [10]. As a result, TB incidence and mortality rates are intensified in areas with high HIV burden. Global TB mortality data indicate roughly 22% of TB deaths are HIV/TB co-infected cases, and it is estimated that 43% of TB deaths in Africa are co-infected with HIV [1].

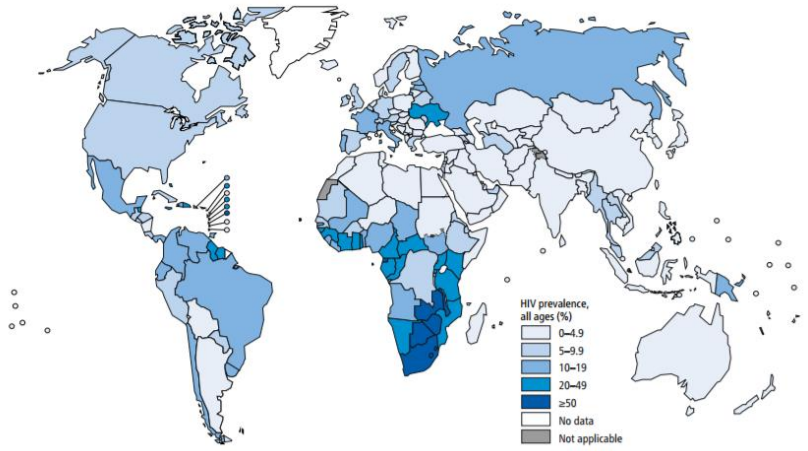


Figure 4. Estimated HIV prevalence in new and relapse TB cases, 2016

Source: WHO, *Global Tuberculosis Report.* 2017 [1]

Drug Resistant Tuberculosis

To prevent the emergence of drug resistance, preferred treatment for TB is comprised of complex multi-drug regimens [2]. Treatment regimens differ for drug-resistant cases compared to drug-susceptible (DS) cases, leading to separate classifications based on the degree of resistance. The most commonly detected mono-drug resistance is to isoniazid, one of the most widely-used TB drugs. Resistance to isoniazid *and* rifampicin,

the two most potent drugs used against drug-susceptible TB, is referred to as multidrug-resistant (MDR) TB. Extensively drug-resistant (XDR) TB denotes resistance to these two drugs plus one fluoroquinolone and at least one of three second-line injectable drugs, the most effective second-line drug classes [11].

The increased challenge to public health associated with drug-resistant TB includes substantially longer, more expensive treatment plans combined with low treatment success [12]. In contrast to six months for drug-susceptible TB treatment, MDR TB and XDR TB usually require treatment lasting at least 24 months (shorter course therapies for MDR are becoming accepted as good alternatives). A review of MDR- and DS-TB treatment costs worldwide found that the average cost to treat MDR is greater than 20 times greater than that of DS-TB [13]. Treatment success also falls from 83% to an average of 54% for MDR and 30% for XDR TB [1]. In addition, possible adverse events associated with drug-resistant treatment are more severe and include hearing loss and renal failure [14]. The complex management of drug-resistant TB is resulting in enormous drains on resources for low- and middle-income countries and catastrophic costs for individuals affected, and the burden of disease is still increasing.

Prevalence and Detection

Though drug resistance has been reported in all countries with TB, many cases are not detected due to limited laboratory capacity and use of drug-susceptibility testing. Only 33% of new TB cases were tested for resistance to rifampicin in 2016 [1]. It is estimated that 5.8% of all TB cases are resistant to at least rifampicin [1]. Data from 2016 estimated

490,000 new cases of MDR, with an additional 110,000 new cases resistant to rifampin alone. These estimates represent an increase from the previous year.

Advances in diagnostic techniques such as the expanded use of the rapid test Xpert MTB/RIF have helped clarify the extent of the drug-resistant (DR) epidemic by detecting resistance during initial diagnosis [15]. Xpert MTB/RIF tests for resistance to rifampicin, and aids in identifying cases that may require additional drug susceptibility testing (DST). The immediacy of this test, which returns results in about four hours, has allowed for progress in tailored treatment and detection and reporting of drug resistance. However, additional DST testing beyond just rifampicin is needed to diagnose XDR TB and is often complicated due to the dearth of laboratories with testing capacity in resource-limited settings. Many physicians report long wait times for DST test results, which can contribute to delays in treatment initiation, worsening of patients' clinical condition, and continued transmission of TB in families and communities.

Etiology of Drug Resistance

Drug resistance can arise in an infected individual due to improper treatment execution, whether from incorrect choice of drugs, treatment duration, or dosage. Improper treatment can also be the result of other scenarios including provider error, patient non-adherence, and unavailability of drugs [11, 16]. These situations introduce selective pressure leading to the survival of bacteria that have developed resistance to the drugs employed. These resistant bacteria strains arise through spontaneous mutations, but only emerge as the dominant strain through selective pressure introduced in treatment. Drug-

resistance in TB is therefore regarded as man-made problem [17]. Resistance resulting from the process described is referred to as *acquired drug resistance*. These resistant strains can then be transmitted, resulting in drug-resistant cases that have not been previously exposed to TB drugs. Cases arising in this way are referred to as *primary* or *transmitted drug-resistant TB* cases [16].

TB in South Africa

The TB epidemic is especially pressing in the African Region (as defined by the WHO) where HIV is most prevalent, and rates of drug resistance are increasing [1]. Outcomes for TB-infected individuals are poor and annual mortality rates for HIV positive as well as HIV negative patients are higher in this region than any other region in the world [1]. In Africa and overall globally, the country with the highest incidence rate of TB is South Africa with an estimated 781 cases per 100,000 people as of 2016 [1]. This estimate translates to 438,000 incident cases in the same year. Although global TB incidence has been steadily decreasing since 2000, incidence in South Africa has risen over the same period. Treatment coverage remains relatively low, and the WHO estimates that only 54% of TB cases are detected and treated. For new and relapse cases started on treatment in 2015, the success rate was 81%. Only 3% of TB patients did not know their HIV status in 2015, and 57% of patients with known status were HIV-positive [1]. 85% of this cohort was on antiretroviral therapy and success was only slightly lower (80%) [1].

TB case rates are not uniform across the country, and a disproportionately high disease burden is born by the east and southeast regions. South Africa is divided into nine

provinces (Figure 5). The highest absolute number of cases are reported in the province of KwaZulu-Natal, with the next highest burden province of Eastern Cape reporting close to half the number of cases (approximately 90,000 cases vs 50,000 cases in 2014) [18]. KwaZulu-Natal has historically also reported the highest incidence rates of TB, but cases have been decreasing since 2011 and the less populated province of Eastern Cape now has the highest incidence rate as of 2015 (692 cases per 100,000 in Eastern Cape compared to 685 per 100,000 in KwaZulu-Natal in 2015) [19]. Despite this, KwaZulu-Natal still has a higher proportion of deaths due to TB than any other province, with 11.2% of all provincial deaths attributable to TB. Treatment success rate in KwaZulu-Natal is 73.8% and the rate of treatment default was 4% as of 2014 [19].

Figure 5. Provinces of South Africa

Source: South African Provinces Map at http://www.mapsopensource.com/south-africa-provinces-map.html [20]

Drug-Resistant TB in South Africa

South Africa also has one of the highest country incidence rates for drug-resistant TB, and accounts for almost 20% of all drug-resistant TB cases in Africa despite comprising only about 5.4% of the continental population [21]. In 2016, the WHO

estimated that 3.4% of new cases and 7.1% of retreatment cases were resistant to at least rifampicin [1].

The seriousness of drug-resistant TB came to attention in South Africa and around the world following a 2005 outbreak of XDR TB among HIV infected individuals in KwaZulu-Natal with almost 100% case mortality [12]. Further epidemiologic research conducted in the wake of this incident suggested the strain of TB responsible for the outbreak had caused transmitted cases of MDR TB in the region over a decade prior to this outbreak. It was found that some isolates of this strain had acquired resistance to up to seven TB drugs in the same period, resulting in strains of XDR TB [22]. This and other similar findings supported the formulation of drug regiments involving more drugs taken concurrently to avoid successively acquired resistances, and drug-susceptibility testing in each patient was advocated for.

Since this time, laboratory capacity for detection of drug resistance has been improving in South Africa. However, 12% of diagnosed TB cases are still not tested for resistance to rifampicin. Additionally, almost 40% of detected MDR/RR TB cases are not further tested for resistance to second-line drugs. This signifies many undetected cases of drug resistant TB in the country that may be treated with ineffective regimens that encourage further development of resistance to drugs. Treatment success rates for the MDR and XDR cohorts in 2014 were 54% and 27%, respectively [1]. These shortcomings in addressing drug resistant cases via detection and treatment result in many individuals that continue to transmit disease in their communities and fuel the epidemic.

Drug-Resistant TB in KwaZulu-Natal

KwaZulu-Natal bears a high burden of drug resistance and in 2010 the province reported the highest number of MDR and the second highest number of XDR TB cases in the country (2,032 and 201, respectively) [19]. A survey of drug resistance in South Africa from 2012-2014 undertaken by the country's National Institute for Communicable Disease showed that 6.4% of retreatment and 1.8% of new cases have MDR TB in this province [23]. This estimate for MDR TB rate among new cases is the same as the WHO estimate for South Africa in 2014, and slightly lower than the WHO estimated retreatment rate of 6.7% among retreatment cases in the country [1]. The highest rates of MDR TB found by the national survey were 4.2% in new cases and 7.6% in retreatment cases, both in the province of Mpumalanga [23]. Though these rates are higher, the population in Mpumalanga is less than half that of KwaZulu-Natal, where higher absolute case numbers persist.

In addition to high numbers of case, KwaZulu-Natal also continued to receive attention for XDR TB due to the international notoriety of the 2005 outbreak and the studies that followed in the province. By the end of 2007, 38% of MDR and 50% of XDR TB reported cases in South Africa were coming from this province [24]. One retrospective study showed a greater than 10-fold increase in MDR TB cases and a greater than 40-fold increase in XDR TB cases from 2001-2007, and also showed that increasing numbers of reported cases may have partially been due simply to improved detection (as opposed to rising incidence) because testing for drug resistance tripled in the province over the same period [24]. Though some findings suggest that increased incidence of XDR TB in KwaZulu-Natal may be partially misleading, estimates for overall drug-resistant TB have

continued to increase. Additionally, the Drug Resistance Survey found that KwaZulu-Natal only screened and confirmed 58.6% of the drug-resistant cases expected in that province; the next lowest province of Free State screened and confirmed 70.3% of what was expected [23]. This figure suggests that many cases of drug resistance are missed here, and current trends of XDR TB in KwaZulu-Natal need to be specifically addressed if the country is to make progress in TB control.

In addition to evidence that many cases are not diagnosed, data also suggests many who are diagnosed are not started on treatment. One 2011 study in KwaZulu-Natal found that only 34% of all MDR TB cases, including XDR TB, were started on treatment following diagnosis [25]. Countrywide data shows higher rates of treatment initiation for detected MDR and XDR TB cases, with 59% and 65% starting treatment following diagnosis [1]. These findings suggest that the gap between diagnosis and treatment initiation is substantial in South Africa, but may be a larger problem in KwaZulu-Natal than in other provinces. This shortcoming results in a higher number of active cases transmitting drug-resistant TB in KwaZulu-Natal and may be responsible for continually high rates of provincial drug-resistance.

A pivotal study aimed to confirm the role of transmitted resistance (vs acquired resistance) in perpetuating the XDR TB epidemic in KwaZulu-Natal by detecting links between cases using genetic comparison of TB strains and social network analysis. XDR TB patients diagnosed between 2011 and 2014 were enrolled and the study found that at least 69% of participants had transmitted XDR TB [16]. This estimate was conservative and likely under-represents the proportion of all XDR TB cases that are due to transmission. Other studies of DR TB in similar settings have supported this important

finding, which has been instrumental in guiding subsequent research in the region. These conclusions suggest that prevention efforts focused at curbing transmission in the community may have more substantial effects in decreasing drug-resistant cases than efforts focusing on improvements to treatment quality or adherence.

KwaZulu-Natal is further divided into ten district municipalities and one metropolitan municipality. The largest city in the province is Durban, located within the metropolitan municipality of eThekwini. As of 2016, eThekwini had a population of 3,702,231 persons and harbored a disproportionately high number of TB cases, though rate of disease was higher in the less populated district of Umzinyathi [18]. Drug resistant incidence in eThekwini is especially high, and roughly 40% of XDR TB cases in the province are found here [26]. Durban is an international city within this high-burden province and represents a threat of more widespread transmission beyond the country of South Africa.

TB Prevention and Risk Factors

Given the difficulty in treatment initiation and completion, effective methods for the prevention of TB cases are crucial. Vaccines are one option that may benefit high-burden settings and those at high-risk. Though there are more than a dozen TB vaccines in clinical trials, only one is currently approved for use in humans and has not demonstrated promising potential for population protection due to variable effectiveness in adults [27]. Isoniazid Preventive Therapy (IPT) given as chemoprophylaxis is an option for prevention therapy and requires medication daily for 6-9 months. IPT has demonstrated considerable

efficacy, and is currently recommended for high-risk groups such as people living with HIV, children in contact with TB patients, and people recently infected with TB but without signs of active disease [28].

Beyond vaccination campaigns, addressing social determinants of disease has also been suggested as an alternative programmatic approach that could benefit communities with high TB burden.[29]. Understanding these determinants can enable programs to address modifiable factors and can also help identify specific populations where targeted approaches would be most effective.

When considering risk factors for TB disease, many intrinsic and extrinsic factors identified in previous research are associated with poverty. Intrinsic or biological risk factors include malnutrition, infection, and immunodeficiency, all of which can increase risk for progression from latent infection to active TB disease [29]. Extrinsic risk factors comprise environmental issues like overcrowding, indoor air pollution, smoking, and poor ventilation [30]. In one analysis of 22 high-burden countries, population attributable fractions (PAFs) were calculated for common risk factors. This analysis suggested the highest percentage of cases could be attributed to malnutrition (34.1%), active smoking (22.7%), and indoor pollution (26.2%) [31]. These results suggest that taken together, these three factors alone account for many cases of TB and targeting them may be a viable public health approach for TB prevention. These estimates highlight the importance of modifiable risk factors, though the authors also emphasize that the mix and relative importance of these risk factors will likely vary depending on geography. Exposure to infected individuals is also a necessary component in acquiring disease, and transmission is therefore driven by TB prevalence in addition to individual and environmental risks factors.

Factors associated with higher risk of developing drug-resistant TB as opposed to drug-susceptible TB have also been examined. A number of studies found that positive HIV status was an independent risk factor for XDR TB compared to MDR and DS TB [32, 33]. A review of 27 articles on risk factors for XDR TB also reported findings of associations between XDR TB and younger age, previous imprisonment, history of prior treatment, and migrant status [33]. Literature on risk factors specific to drug-resistant TB is somewhat limited and no papers reviewed attempt to measure poverty in this cohort, though it has been inferred that some characteristics like prior imprisonment and migrant status may be indicative of lower socioeconomic status.

In general, high levels of poverty and social deprivation were common factors in study areas with high burdens of TB and global data shows over 95% of TB deaths occur in low- and middle-income countries [1]. A strong association between low income level and high burden of TB is supported by numerous studies within high-income countries as well, enforcing the notion that poverty affects risk at the individual and country level [34, 35].

Measurement of Sociodemographic Factors

It has been well established that TB disproportionately affects low- and middle-income countries, but less is known about the spatial and sociodemographic distribution of disease within these countries. Several studies in low-income settings have examined the association between sociodemographic status and TB incidence with varying methods applied to measurement and data collection [36-40]. At an individual level (opposed to

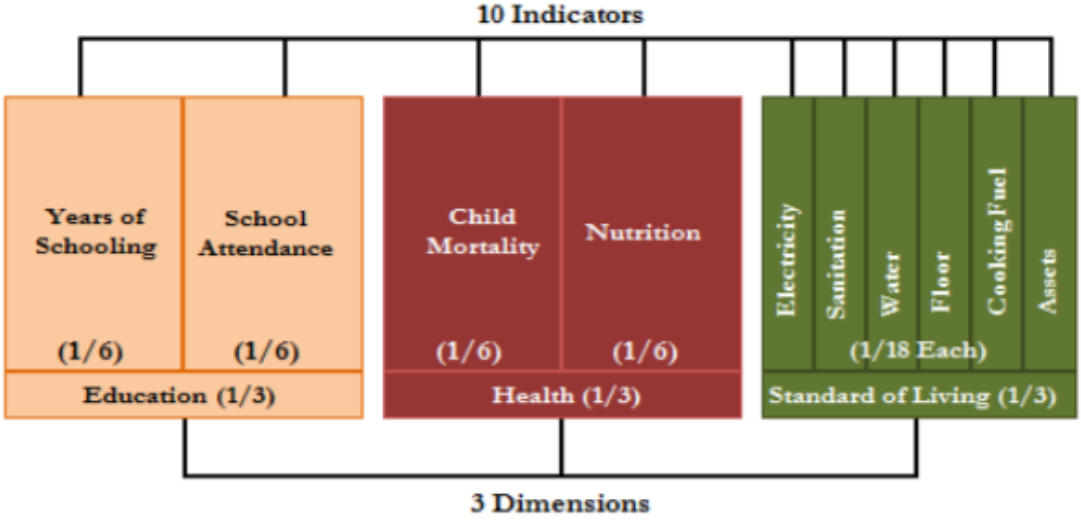
population level), associations between TB and sociodemographic status have been studied using data from TB surveillance programs, death certificates, and study-specific research data [38-40]. Studies at the individual level employ comparisons of TB cases and non-TB-infected controls, highlighting individual characteristics that may contribute to higher risk for TB. Sociodemographic associations are also commonly studied at a population level using data from censuses and national or community surveys [36, 37]. These studies use pre-determined geographic areas such as census units as the unit of analysis and can suggest neighborhood characteristics that increase risk for TB by using aggregate data for these units and making comparisons between units to examine sociodemographic differences.

Studies also differ in their approach to defining sociodemographic status. Many researchers have moved beyond the traditional income-based measure of extreme poverty, which the World Bank defines as living on less than $1.90 USD per day [41]. The United Nations (UN) and other global health leaders have endorsed this shift as a way of capturing a more holistic view of deprivation and standards of living that can affect human health [42]. For studies using pre-existing data, indicators used are limited by the data previously collected. Common variables measured in TB research using pre-existing data include basic demographics (age, gender, race), educational level, population density, and a variety of household deprivation indicators such as access to water, electricity, sanitation, and asset ownership. Well-chosen indicators are especially important in studying poverty, since signs of deprivation often differ depending on place. When possible, studies make use of various indices composed of sets of indicators that have been developed as measures for sociodemographic status and poverty.

Poverty Indices

Different measures used to account for the various factors that play a role in poverty include the Socio-Demographic Index, Poverty Gap Index, Human Poverty Index, and the Multidimensional Poverty Index (MPI) [43]. The MPI is the index currently favored by the UN for holistic measurements of deprivations facing the poor. It was created in 2010 by the Oxford Poverty and Human Development Initiative (OPHI) and the UN to be used in conjunction with income-based measures for a more comprehensive view of poverty that can be disaggregated into individual indicators [42]. Ten individual indicators across three categories contribute to the index. The MPI is calculated using the Alkire-Foster method, taking the proportion of households that are deprived in 33.3% of the predictors and multiplying the result by the average intensity of deprivation among those below the 33.3% line [43]. The OPHI graphic in Figure 6 details the indicators and weights used in calculating the index.

Figure 6. Multi-dimensional Poverty Index (MPI), indicators and weights



Source: Program, U.N.D., *Human Development Report 2016.* 2016 [42].

Though useful, indices like these are at times difficult to calculate using aggregated data as the scores are a product of many factors in an individual household, for which a complete set of variables may not be available. Some general components may also be less relevant in certain areas of the world, contributing to the lack of data. As a result, some studies examining TB associations with poverty use locally developed poverty indices tailored either to specific conditions in the area or to reflect information that has been historically collected in the area. This is useful in examining more nuanced country conditions and for the sake of comparisons over time, though it limits comparisons between countries. The MPI has been used as a model to inform which indicators are used in some country-specific indices like the Mexican Social Deprivation Index (SDI) and the South African Multi-Dimensional Poverty Index (SAMPI) [40, 44].

Findings of Sociodemographic Studies

Sociodemographic factors associated with TB risk vary depending on geographic location. Work done in the United States found that low social capital and higher poverty levels were associated with higher TB rates in a state-level analysis [35]. Studies conducted in high-burden countries have similar overall findings, however there is some variation in findings among different settings. Data support the general conclusion that residing in an urban area and having low socioeconomic status are both independently associated with higher risk for TB disease [36]. However, studies in developing countries make use of different indicators for socioeconomic status, and some findings may challenge common assumptions. For example, one recent study in rural Malawi has suggested some predictors

that are generally associated with higher socioeconomic status—such as working in the cash economy rather than the subsistence economy and having better housing—are associated with higher odds of TB disease [45]. Economic progress may lead to jobs performed indoors and homes that may be more crowded and closed off than traditional homes with open ventilation. These changes would represent a shift to more shared airspace without proper ventilation, thereby increasing the risk for TB transmission and initial infection [45]. Environmental effects may also have unknown implications for risk of progression from latent to active infection. Another study in Cameroon examined 14 indicators of poverty and found level of education, use of modern toilet, and possession of a gas cooker to be better predictors of TB incidence than economic status alone [37]. These conflicting findings suggest that TB distribution in low-income settings may follow more complex trends. Unexpected findings regarding various indicators and their association with TB highlight the need to examine predictors apart from income level in studying disease distribution in low-income settings.

Gaps in Knowledge

While some work has been done to characterize MDR and DS TB cases by their sociodemographic and neighborhood level characteristics, this type of research on XDR has not been well-documented in the literature reviewed. Possible clinical factors increasing risk for XDR TB at the individual level have been assessed, however community-level characteristics have not been examined and these have the potential to influence transmission, which is known to be responsible for a high percentage of XDR TB cases. Additionally, studies conducted in high-burden countries have been able to point

to associations but have not gone much further in assessing the mechanisms for these associations.

Spatial Analysis in Public Health and TB

The use of Geographic Information Systems (GIS) in public health research has been steadily increasing since the early 1990's and the number of studies using spatial models in the study of disease and socio-economic disparities has more than doubled since 2005 [46]. GIS systems are used to store, analyze, and display geographical data and can inform public health decisions for both communicable and non-communicable diseases [47]. Geographic data in public health is primarily available in point or polygon form. Point data represents a single set of geographic coordinates and can represent things like patient home or hospital. Polygon data represents an area contained by defined boundaries and is usually tied to aggregate data of the area contained within these boundaries. Census data is commonly associated with polygon data and is often used in spatial studies due to its abundance and ease of accessibility [48]. In public health, spatial data is most commonly used for distance measurement, spatial aggregation, cluster analysis, spatial smoothing for prediction or interpolation, and spatial regressions [46]. The table below summarizes details of methods that appear regularly in public health infectious disease literature.

Method	Data type	Spatial Resolution	Software	Purpose
Spatial scan statistic	Case-control, case-event, and continuous	Point or polygon	R, SatScan, ClusterSeer	Location of Clusters
Kernel intensity function	Case-control, case-event	Point	R	Smoothed Visualization
Moran's I	Continuous	Point or polygon	GeoDa, ArcGIS, SpaceStat, R	Assessing Spatial Autocorrelation
Generalized additive model	Continuous	Point	R, SPSS, S-PLUS	Assessing Spatial Autocorrelation
Kernel density estimation	Case-event and case-control	Point	Crimestat, ArcGIS	Smoothed Visualization
Getis-Ord Gi*	Case-event and case-control	Point or polygon	ArcGIS	Location of Clusters
Local Indicators of Spatial Association (LISA)	Continuous	Point or polygon	GeoDa, ArcGIS, R	Location of Cluster

Spatial Considerations in Infectious Disease Epidemiology

The use of spatial techniques in infectious disease often focus not only on where the at-risk population is, but where transmission and infection may be occurring. Transmission within communities can be extremely difficult to study and the likely hubs for transmission are different depending on the disease of interest. For example, societal structures may lead to varying time spent at home, in social gathering places, or with other people [49]. Home locations were first examined in studies as a logical representation of an individual's sphere of movement. Home location data is easily collected in most areas of the world, and it was often assumed that individuals spend a large portion of their time

around their place of residence [50]. However, many meaningful contacts occur outside of the home and may be more relevant to study. One study of TB in Tokyo attempted to address this issue by asking study participants to list multiple locations and the amount of waking time spent in each, then using the location where the participant spent the most time as their location for analysis. This study suggested transmission may be occurring in areas surrounding railway station stops[51]. Another approach taken by researchers in Atlanta, Georgia (USA) also collected multiple locations for each participant, and factored all reported locations equally to build polygon areas representative of transmission spheres [52]. This allowed researchers to perform analyses of overlapping area and infer more about where cases may be coming into contact with one another.

Public transportation was also considered in one 2013 study in South Africa. Findings here supported the notion that the majority of transmission is occurring outside the home and use of public transportation may be associated with a 2-5% annual risk for TB, representing an elevated risk in the study area [53]. Similarly, another study analyzing DNA fingerprints of TB in the Cape Town area of South Africa found that only 19% of cases were related to household transmission [54].

Transmission has been studied in a variety of ways including modeling based on measured exhaled carbon dioxide as a tracer gas to model respiratory infections. The 2014 study employing this method found that transmission was occurring outside the home in 84% (and within the home in 16%) of cases [55]. While these results suggest that the home itself may not always capture information the place where transmission is occurring, there studies also found significant amounts of transmission do still occur in the home. Though

transmission area may not fully be captured, this does not diminish the utility of studying household location as a way to study populations with elevated risk for TB.

Cluster Detection

In public health studies, GIS is commonly used to describe clusters or hotspots of disease. Clusters have been defined as "foci of particularly high incidence" [56], and more specifically are areas with values that are statistically significantly different enough from expected values to be considered nonrandom (not occurring by chance) [46]. Clusters of high incidence are typically of primary interest, however clusters of low rates can also be meaningful when studying disease [57]. Many different methods have been developed for the quantification of disease clustering. Detected clusters often depend heavily on the scale of measurement used. For example, large areas with dissimilar distribution of qualities within may mask clustering, whereas analysis of small homogenous areas will easily show clusters of interest [57].

Spatial analysis has been used sparsely in TB research, though the last decade has shown an increase in publications that make use of these methods in local areas. Clusters of individual cases or clusters of high incidence areas are commonly tested for and detected [30, 36, 37, 39, 40, 58-61]. The most common statistical tools used in cluster mapping within this body of research are SatScan, Getis-Ord Gi*, and LISA. Once clusters are detected, several studies have gone on to characterize them by sociodemographic features based on census data or surveys [30, 36, 37, 40, 58, 62]. These methods have mostly been applied to aggregate TB data, with a few focused on MDR and no reviewed papers focusing on XDR TB. Low socio-economic status was found to be associated with clusters of high

TB incidence in Madagascar, Malawi and South Africa, however the variables used to characterize socio-economic status were inconsistent [30, 45, 59]. A 2003 study in South Africa used unemployment as an economic measure and found this to be the strongest predictor of TB [59]. In Madagascar, household ownership of tap water was used as the indicator measurement [30]. In Malawi, ownership of household assets such as a television and radio were used to assess this measure [45]. Variability in measurement is based mainly on the availability of data collected in censuses and nationwide surveys. Though this may limit the comparability between studies, it may also get at area specific factors that should be considered when defining poverty and deprivation.

Practical Limitations in GIS

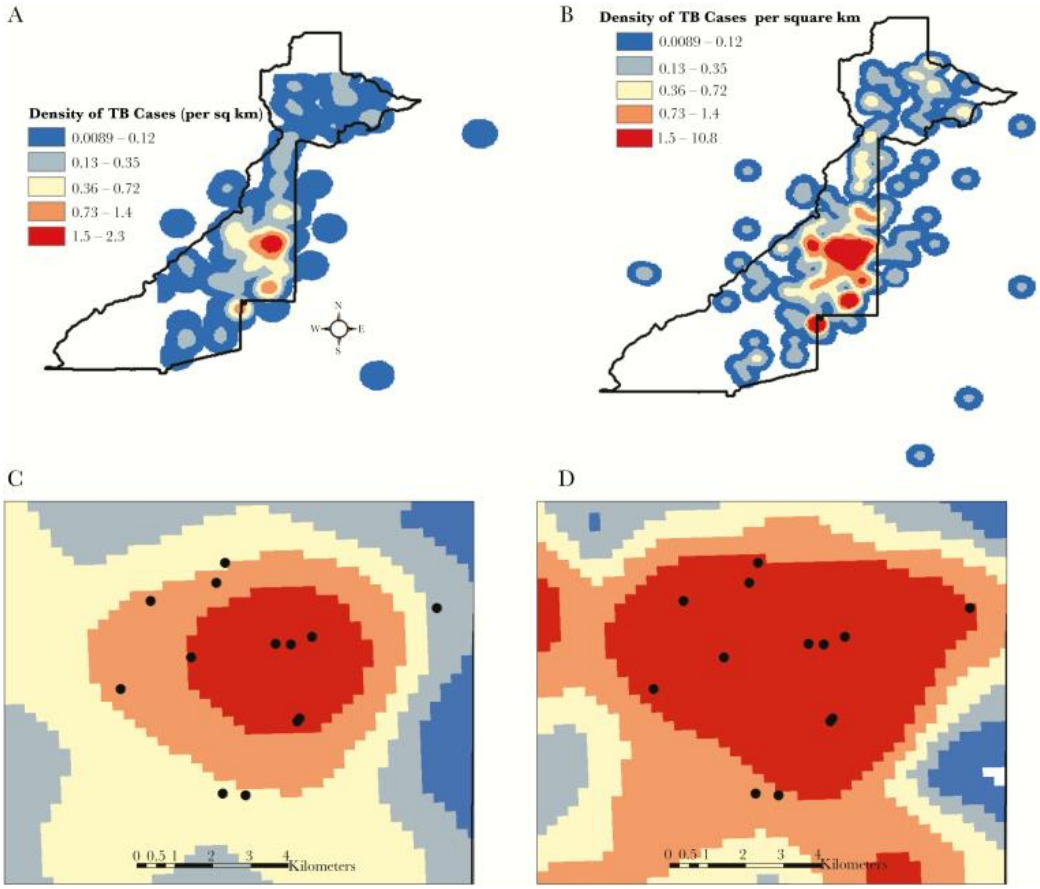
GIS research is associated with some challenges such as technical difficulties with technology, privacy concerns, and discrepancies between area recorded and the desired study area. Human movement studies have highlighted some of the limitations associated with producing spatial data associated with one individual [50]. Though people have regular patterns of travel, capturing the full range of an individual's movement is often unrealistic for research. These issues are complicated because of the heterogeneity that exists among different settings. For example, one study demonstrated people in South Africa spent more time outside of the home and had over twice as many close indoor contacts per day compared to residents in European studies [49, 53, 63]. For this reason, models of movement are often not generalizable to all populations and cultural tendencies should be taken into consideration.

Spatial Findings in TB

Most studies that have tested for the presence of statistically significant clustering of TB in high-burden countries have found evidence to support a clustered distribution pattern for DS TB and MDR TB [30, 36, 39, 61, 64]. Some studies have identified central locations common to a high percentage of the study participants and inferred transmission here. Two examples are a TB treatment clinic in Peru and a local bar in South Africa [38, 64].

TB work attempting to show "activity space" by capturing more than one location for each study participant has produced nuanced results on transmission space suggesting this may be a fruitful direction for future studies. In the Atlanta-based study mentioned above, 50 of the 198 subjects reported three or more addresses and were therefore included in the activity space analysis. From the resulting activity spaces, the researchers were able to make statistically significant conclusions that there was more overlap in activity spaces for isoniazid (INH)-resistant TB cases and for homeless TB cases than INH-susceptible and non-homeless TB cases [52]. They were also able to create kernel density maps based on single location and multiple location data for cases (Figure 5) and found that the larger areas of high TB case density produced by the multiple location data captured more homeless shelters that were believed to be hotspots for transmission [52]. The more comprehensive maps of case movement have the potential to better inform contact investigations and targeting of public health programs.

Figure 6: "Difference in density of tuberculosis (TB) cases when using a single address versus multiple address for each case, Fulton County, Georgia, 2008–2014. (A) Density map (cases/square mile) of TB cases using a single address versus (B) multiple reported addresses; (C) enlarged area of highest TB case density map overlaid with local homeless shelters when using, for each TB case, single address versus (D) multiple addresses" [52]



Source: Worrell, M.C., et al., *Use of Activity Space in a Tuberculosis Outbreak: Bringing Homeless Persons Into Spatial Analyses.* Open Forum Infectious Diseases, 2017. **4**(1): p. ofw280 [52].

Gaps in Knowledge

Mapping projects have been undertaken in TB, however there are very few examining MDR TB and none examining XDR TB in the literature reviewed. The distributions of XDR, MDR, and DS TB have also not been mapped separately in one setting, and it is therefore

unknown if high incidence areas overlap or if each type of TB clusters in distinct settings.

It is also unknown whether the overall spatial distribution (clustered, uniform, random) of the different types of TB differ. Further knowledge about hot spots of XDR disease and whether they coincide with MDR and DS TB could help incentivize synergistic TB programs targeting all types of TB at once and further clarify factors influencing transmission of disease within communities.

Conclusion

In conclusion, the literature is lacking descriptive and spatially analytic information on the XDR TB epidemic. Sociodemographic risk factors for this disease are not well described at the individual or community levels. Spatial behavior of XDR TB has also not been well characterized. There is no evidence to conclude whether XDR TB is clustering in the same places as MDR and DS TB, or whether areas of high burden for these three occupy distinct geographical areas with possibly differing attributes. Though transmission has been identified as a major driver of the XDR TB epidemic in South Africa, more information is needed on where this transmission is occurring to inform possible ways public health programs can intervene.

This study was undertaken to further characterize the XDR TB epidemic in a subset of cases from 2011-2014 in eThekwini, KwaZulu-Natal, South Africa. Increased XDR incidence and poor treatment outcomes in this region have been well documented. However, spatial data on where these cases are occurring has not been thoroughly analyzed. This study aims to assess the distribution of XDR for clustering, and to describe the sociodemographic characteristics of high-burden areas in eThekwini to shed light on possible associations with risk for XDR TB.

CHAPTER II: MANUSCRIPT

Spatial patterns of extensively drug-resistant tuberculosis and associations with sociodemographic factors in Durban, South Africa

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Introduction

Tuberculosis (TB) is the leading cause of infectious disease deaths worldwide and is responsible for over 4,000 deaths each day [1]. Drug-resistant tuberculosis is an increasing concern, with an estimated 600,000 cases in 2016 [1]. Multidrug-resistant (MDR) TB is defined as resistance to rifampin and isoniazid, the two most powerful drugs used against TB [65]. The most severe category of resistance is extensively drug-resistant (XDR) TB, which is MDR TB with further resistance to a fluoroquinolone and at least one second-line injectable drug [11]. Treatment of XDR TB requires long and costly treatment regimens that are difficult to complete, and global success falls from 83% for drug-susceptible TB patients to 30% for XDR TB patients [1, 66]. Efforts to prevent XDR TB from occurring are therefore critical for patients and public health programs.

Drug resistance has been known to arise due to improper or incomplete treatment of drug-susceptible TB, referred to as “acquired” drug resistance. However, it is increasingly recognized that a majority of individuals with drug-resistant TB developed it

from person-to-person direct transmission of an already resistant strain, referred to as "primary" or "transmitted" drug resistance [67]. This suggests prevention efforts may be best targeted towards factors that would halt transmission, leading to an increased need to further characterize disease patterns in communities and factors driving transmission at an individual and population level.

In countries with a high burden of TB, factors such as smoking, malnutrition, and indoor air pollution have been shown to increase individual risk for active disease [31], while overcrowding and poor ventilation increase risk of transmission [30]. These factors are often associated with poverty, and 95% of TB deaths occur in low- and middle-income countries [1]. Studies in high-income countries also support a strong association between TB disease and low-socioeconomic status, enforcing the notion that poverty increases risk at the individual and country level [34, 35]. Addressing these factors may improve TB outcomes; one study suggests 80% of TB cases are attributable to modifiable poverty-associated factors [31].

Recently, Geographic Information Systems (GIS) tools have been recognized for their utility in merging socioeconomic, TB disease burden, and spatial data, allowing for more detailed socioeconomic profiles of high-burden TB areas and identification of disease "hotspots". Some studies have also incorporated multiple locations per individual to estimate "activity space" and identify areas of high transmission risk [51, 52]. These approaches have suggested significant heterogeneity in TB epidemics around the world

and in underlying population-level socioeconomic factors. Unanticipated findings of associations between TB and measures not traditionally associated with poverty such as cash industry jobs (vs sustenance), developed housing, and gas cooker use have been suggested in various locations [45]. These findings suggest TB risk in low-income settings follow complex trends that may vary depending on setting, highlighting the need to tailor targeted efforts by location.

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 all XDR TB is found in the province of KwaZulu-Natal [18]. Recent data suggests that approximately 69% of XDR TB in KwaZulu-Natal province is caused by direct person-to-person transmission of XDR TB strains [16]. Since transmission is driving the XDR TB epidemic, there is a need to examine where cases are in the community. Further knowledge about “hotspots” of disease and whether they are associated with sociodemographic indicators could help target TB programs and further clarify factors influencing community transmission. Therefore, we studied the spatial distribution of XDR TB in KwaZulu-Natal and utilized census data to evaluate sociodemographic characteristics of areas designated as “hotspots”.

Methods

Study Population and Setting

We conducted a cross-sectional study of XDR TB patients diagnosed between 2011 and 2014 in the district of eThekwini, South Africa, and examined sociodemographic factors of communities where they reside. eThekwini is in the province of KwaZulu-Natal, which harbors roughly half of all XDR TB cases in South Africa despite the province comprising less than 20% of the country population [24]. Though eThekwini is the smallest of 11 districts in KwaZulu-Natal, it accounts for 33% of the provincial population and approximately 41% of XDR TB cases in the province are found here [26]. eThekwini has a population of 3.4 million people and contains the city of Durban, characterizing it as a uniquely urban setting in relation to other districts in the generally rural province of KwaZulu-Natal.

Study Variables and Data Sources

We used data from the "Transmission of HIV-Associated XDR TB in South Africa (TRAX)" study but restricted our analysis to patients with home GPS in eThekwini district to examine hotspots in this high burden urban area. Patients in KwaZulu-Natal with newly diagnosed XDR TB between the years 2011 and 2014 were recruited for TRAX. Cases were identified from the provincial referral laboratory which conducted all diagnostic testing for XDR TB.

Clinical and sociodemographic information was obtained through structured interviews with participants. Information on congregate settings including work, school, and social

settings was also obtained during participant interviews. GPS coordinates of home location for each participant were recorded through home visits and plotted using ArcGIS software. Geospatial data was also obtained for facilities diagnosing XDR TB. Detailed methods for this study have been published elsewhere [16].

The exposure of interest was sociodemographic status at the population level as measured by indicators identified in South Africa's Multidimensional Poverty Index, which is used in assessing the presence and severity of poverty in the country-specific context. These included household indicators (flush toilet in home, type of dwelling, and fuel used for cooking, heating, and lighting), educational indicators (highest 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 at the main place level.

To obtain this population-level information, we used data from the 2011 South Africa census. The census was conducted by Statistics South Africa (Stats SA). eThekwini district census data were exported by Stats SA and included detail to the census unit of "main place" and "sub place". From smallest to largest, the census units used in South Africa are: sub-place, main place, district, and province (Figure 1). eThekwini district consists of 197 main places and 394 sub places. Shapefiles defining geographic borders in ArcGIS were provided by Stats SA.

Data Analysis

The primary outcome of interest was home location of XDR TB cases and the number of TRAX cases reporting their home residence within a particular census unit. Spatial data was analyzed in ArcGIS version 10.5.1 and GeoDa. Raw incidence rates were calculated in ArcGIS. Empiric and Spatial Bayes Smoothing [68] were applied in GeoDa to correct for inflated rate calculations in census units with small populations. Queen contiguity weighting of neighbors was used for spatial smoothing methods. Raw and population-adjusted kernel density surfaces were created in ArcGIS to visualize incidence and incidence rates across the district. Global Moran's I statistic was calculated to assess for the presence and magnitude of spatial autocorrelation in the distribution of cases, and Local Indicators of Spatial Autocorrelation (LISA) were used to apply this statistic locally for cluster assessment. Getis-Ord Gi* statistics were also used to evaluate the significance of case clustering. An α value of 0.05 was used to classify main places as hotspots for XDR TB disease.

Additional analyses were performed to estimate activity space [51, 52] for a subset of participants who reported non-home locations in which they spent $\geq$2 hours per week. Reported locations for work, school, and other congregate social settings were geocoded using ArcGIS version 10.5.1. When necessary, addresses were located using Google Earth and plotted in ArcGIS using latitude and longitude coordinates. Shapefiles were projected to the UTM 32S projection for analyses. Kernel density surfaces were created incorporating all locations to visualize potential areas of transmission and results were compared to density surfaces generated using home locations alone. Among cases with

available data, we also calculated distance from home to place of work and other congregate locations.

We compared sociodemographic characteristics of XDR TB participants from TRAX and the underlying general population using basic descriptive statistics, t-tests, and chi-square tests. To evaluate sociodemographic associations at a population level, census data were merged with shapefiles in ArcGIS version 10.5.1 and exported to SAS version 9.4. Rates for disease incidence and socioeconomic indictors 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, and the University of KwaZulu-Natal and by the Centers for Disease Control and Prevention. All participants provided written informed consent or assent, when appropriate.

Results

Participants

Among 404 participants enrolled in the TRAX study, 132 (33%) resided in eThekwini 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 diagnosis was 33 years (interquartile range [IQR], 29–44). The spatial distribution of enrolled patients did not differ significantly from the distribution of all XDR TB patients in eThekwini based on facility of diagnosis.

Spatial Analysis

The highest number of XDR TB cases were observed in the eastern part of the district, near the highly populated Durban central business district (Figure 2a). Global Moran's I for XDR TB incidence rate at the main place level was 0.87, indicating strong positive spatial autocorrelation at the main place level. Spatial distribution of XDR TB in eThekwini and raw incidence rates as estimated by our study population suggest rates are highest in the northeast part of the district (Figure 2a). Empiric and Spatial Bayes Smoothing produced similar patterns but suggested main place incidence rates in the far north and south of the district may have been artificially inflated by small population sizes. Kernel density surfaces based on point locations of cases show high case density to the northwest of Durban (Figure 2b). Population-adjusted kernel density smoothing (Figure 2c) found that western eThekwini appeared to have a high incidence of cases, though population is sparse in this area.

Getis-Ord-Gi* analysis classified 15 main places as hotspots with ≥ 95% confidence (Figure 2d). The largest identified cluster of contingent 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) shows high-high clustering (i.e., high case areas surrounded by other high case areas) in the northeast region; these findings are consistent with findings from the Getis-Ord-Gi* analysis and kernel density visualization of risk. Outliers of high incidence surrounded by low incidence were found in the west and southwest regions of the district, suggesting these cases may be of interest due to their isolation, though they often represent only a single case.

Activity Space Analysis

We were able to locate non-home congregate locations given for 43 (33%) of the 132 patients in eThekwini. Locations geocoded included 40 places of work, two school settings, and nine other congregate settings. The spatial distribution of homes did not differ among this subset of 43 patients compared to all TRAX patients in eThekwini. Kernel density surface creation suggested a higher case concentration is located in the central part of the eastern coast of the district (which corresponds to the Durban downtown area) 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 and a population-level, sociodemographic factors associated with poverty were found to be associated with higher burden or risk of XDR TB. Individual case characteristics demonstrated that XDR TB cases enrolled in our study were statistically significantly older, fewer had a flush toilet in the home, and annual income was lower than the eThekwini population (Table 1). Conversely, a significantly higher proportion of study participants had a university or higher education and a smaller household size.

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 (Table 2). Hotspots also had homes that were less likely to have a flush toilet, and a higher percentage of their population was employed in domestic servant work (according to census 2011 data).

Discussion

KwaZulu-Natal province bears approximately 50% of South Africa's XDR TB burden [15], and despite substantial advances in diagnosis and treatment of TB over the past decade, an ongoing cycle of transmission is perpetuating the epidemic [10]. We sought to identify whether XDR TB cases are geographically clustered and what sociodemographic factors may be influencing risk in the urban district of eThekwini, which accounts for 41% of KwaZulu-Natal cases [14]. We found that XDR TB is not uniformly distributed; clusters of XDR TB case residences were detected to the northeast part of eThekwini district. Compared to other neighborhoods, those with geographic clustering 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 and will require a multisectoral response aimed at not only improving XDR TB diagnosis and treatment, but also addressing underlying social determinants of health.

Homes of XDR TB cases demonstrated clustering within eThekwini. Detection of clustered distribution is consistent with studies of TB and MDR TB using home location in similarly high burden settings [30, 36, 39, 61, 64]. This finding suggests that neighborhood-level factors are influencing risk in certain areas. One strength of our approach was that our conclusions about the spatial distribution of disease were reinforced by performing analyses at multiple levels of granularity, using 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 [57]. Our study was able to examine trends at varying levels of South African census units as data was available at the sub and main place levels. For the purposes of data visualization and incidence comparison, data were aggregated to main place levels. However, availability of sub place data made it possible to more closely examine areas of interest and to focus in on the highly populated areas of the Durban metro.

We examined neighborhood-level sociodemographic characteristics of XDR TB clustered neighborhoods and found that residents in these areas had more indicators of poverty than in non-cluster neighborhoods. This is consistent with other research that has found associations between poverty and MDR TB [36, 37, 45]. Previous studies examining risk factors for XDR TB have suggested that positive HIV status and failure of previous TB treatment may increase risk of XDR- compared to MDR- and drug-susceptible TB [32]. In addition to examining individual characteristics of our patient population, our study took a population-level approach to assessing the communities XDR TB patients are living in. We found that on an individual level and on a neighborhood level, poverty is associated with XDR TB or being in an XDR TB hotspot. These findings may aid in targeting of neighborhoods for increased interventions such as education, screening, and clinic outreach. It is important to note that these analyses were based on home location and clusters detected may not represent the actual locations where transmission occurred. However, clustering of home locations may suggest several plausible mechanisms including higher biologic susceptibility to active TB infection due to environmental living conditions, variable access to quality diagnostic testing, or differing levels of motivation to seek care among distinct neighborhood-level groups [69, 70].

Though these data may aid in case finding and suggest neighborhood-level factors that increase risk, the use of home location may overlook transmission hotspots. One study analyzing DNA fingerprints of tuberculosis cases in Cape Town suggested that only 19% of cases were due to transmission between household members [41]. To examine other areas of movement for our participants, we performed an analysis including work and

congregate settings on a subset of cases for whom data were available. We found strong evidence of a shift in high density clustering towards the Durban downtown area. This shift was driven mostly by work place locations, as many eThekwini residents appear to travel long distances from their homes in the direction of downtown Durban for work. 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. Previous studies attempting to use movement information to infer transmission sphere in TB have been able to implicate community locations such as local drinking spots and homeless shelters [40, 52].

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. XDR TB cases may additionally be under-reported countrywide due to limited use of second-line drug susceptibility testing; estimates from 2016 suggest that 40% of MDR TB cases 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 regards to home location and sociodemographic characteristics, there was no statistically significant difference in spatial distribution for enrolled vs non-enrolled XDR TB patients based on facility of diagnosis.

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 [50]. A more comprehensive log of individual case movement would be useful in further assessing where transmission is occurring in eThekwini. This information could help focus efforts to break transmission chains, however there are difficulties associated with collecting reliable human movement data such as cost, reluctance of participants, and technical issues with GPS [50]. Though missing movement data limits study of transmission, our ability to draw conclusions based on place of residence was strong due to our study's methodology of exact GPS coordinate collection for home locations as opposed to alternative methods such as self-report or area level aggregation.

Transmission is driving the XDR TB epidemic in KwaZulu-Natal, South Africa. Knowledge of transmission patterns, areas of high risk, and sociodemographic factors associated with risk can help to target prevention efforts within hardest hit communities. We have shown that XDR TB case homes demonstrate a clustered distribution and that clusters are associated with low education attainment and school attendance, high unemployment, and lack of in home flush-toilets at the neighborhood level in eThekwini, South Africa. Our data also point to additional congregate areas where cases move, such as workplaces outside the home in the downtown Durban area. Further work

characterizing more complete range of movement among XDR TB cases is needed to determine where transmission is occurring.

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TABLES

Table 1. Baseline characteristics of TRAX-enrolled XDR TB patients in eThekwini, South Africa, compared to underlying population characteristics

Sociodemographic characteristics	**TRAX-enrolled XDR patients (n=132)**	**eThekwini population (n=3,442,670)[1]**	***p-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 ZAR	31.1%	25.6%	**<.001**
Household size, median	2	3	**<.001**

[1]Population data from 2011 South Africa census
[2]Age at XDR TB diagnosis shown for TRAX patients

Table 2. Poverty measures within XDR TB hotspots and non-hotspots in eThekwini, South Africa, based on general population census characteristics

	eThekwini Population		
Indicator Measures for Household	**Non-hotspot**	**Hotspot[1]**	***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**
Employed as servants	0.4%	0.5%	**0.02**

[1]Hotspots identified at main place level with ≥95% confidence using ARCGIS Getis-ORD Gi*
[2]Dirty fuel defined as paraffin, wood, coal, or animal dung

FIGURES

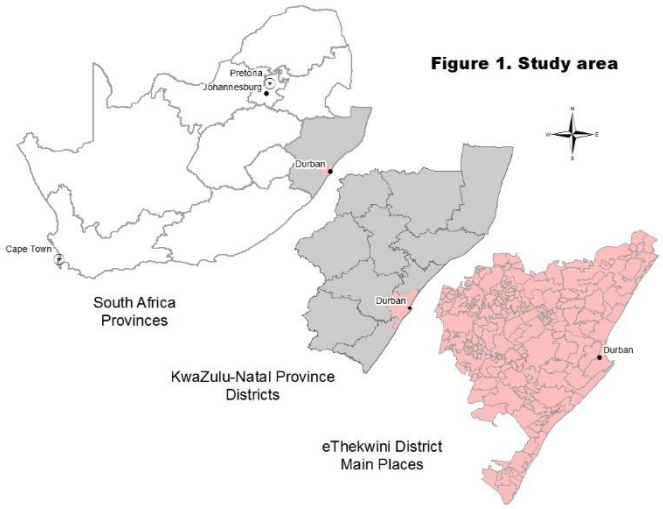

Figure 2. Spatial patterns of TRAX-enrolled XDR-TB case homes in eThekwini, South Africa

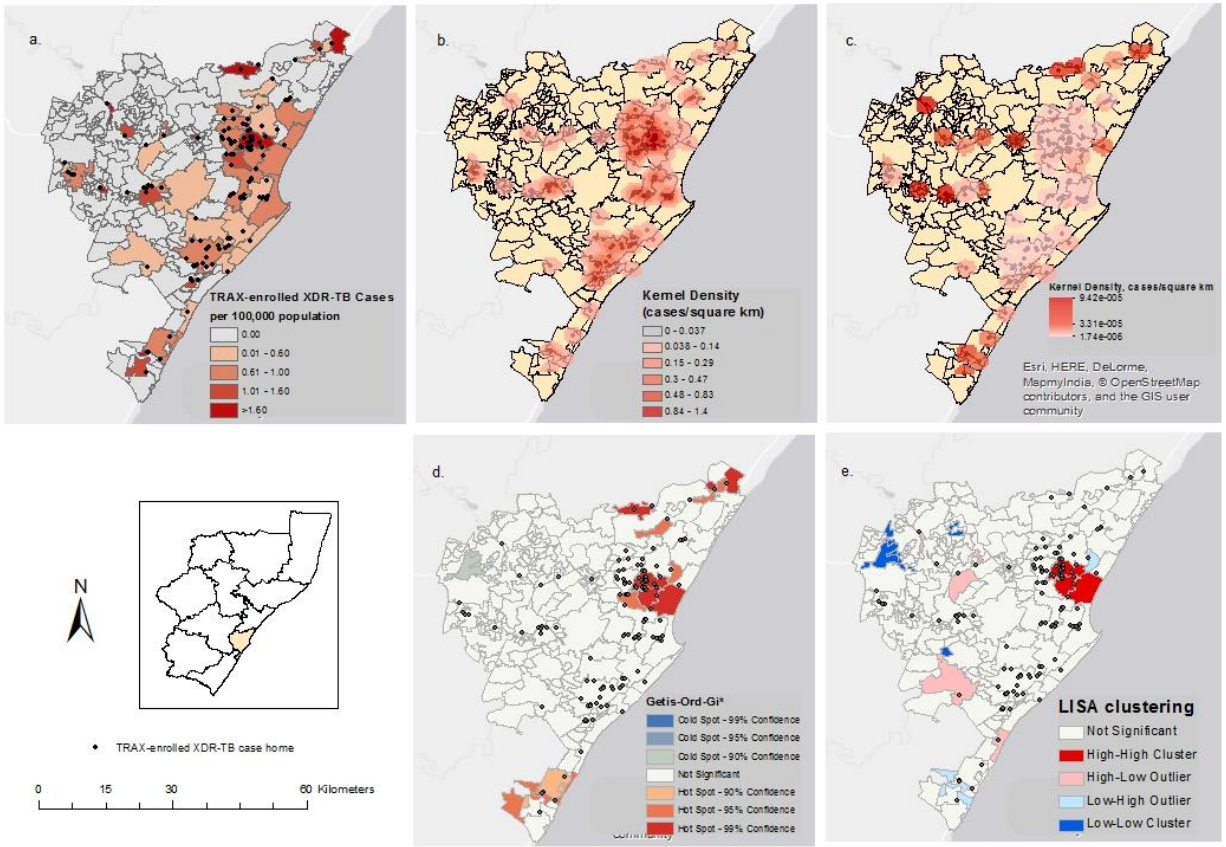

Figure 2a. TRAX-enrolled XDR-TB cases per 100,000 population, at main place level, shows highest study incidence in the northeast region of eThekwini; 2b. Unadjusted kernel density surface of TRAX-enrolled XDR-TB cases shows largest area of high case density in northeast region of eThekwini; 2c.Population-adjusted kernel density surface of TRAX-enrolled XDR-TB cases highlights cases to the west of eThekwini where population is low; 2d. Getis-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

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

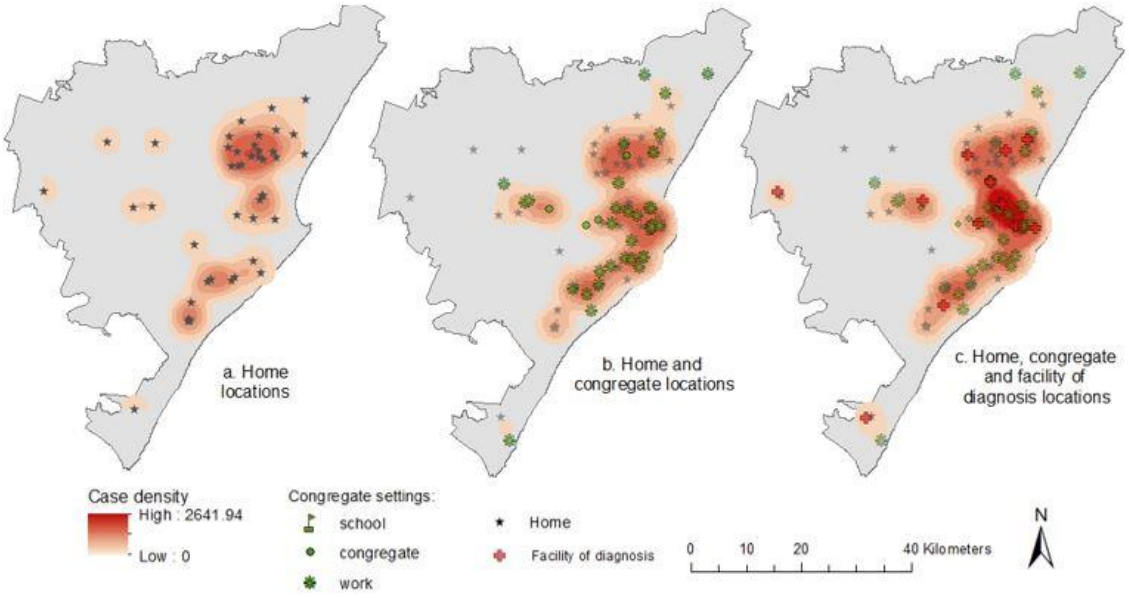

Figure 3a. Kernel density surface of TRAX-enrolled XDR-TB case homes; 3b. Kernel density surface of TRAX-enrolled XDR-TB case homes and congregate locations; 3c. Kernel density surface of TRAX-enrolled XDR-TB case homes, congregate settings, and facilities of diagnosis

CHAPTER III: PUBLIC HEALTH IMPLICATIONS

This study indicates that in Durban, South Africa, XDR TB disproportionately affects individuals living in neighborhoods where poverty levels are high. With persistently high levels of drug resistance in this region and minimal success in treatment efforts, further work to clarify the reasons behind increased risk in certain geographic areas may be critical in identifying modifiable factors for targeted interventions in the areas indicated.

Through this analysis, we found significant clustering or "hotspots" based on XDR TB cases' homes in Durban, at the main place level. It is important to note that hotspot neighborhoods identified in this study do not necessarily correspond to hotspots where transmission is occurring, as previous work suggests only a small fraction of TB transmission may occur in or near the household [54]. Instead, these hotspots represent neighborhoods where residential status appears to confer some additional risk for XDR TB. This increase in risk may be viewed as two separate but related risks; one is the potential increase in risk due to increased susceptibility for infection and progression to active TB infection. This increased risk has been attributed to poverty-related factors such as malnutrition, compromised immune status, exposure to air pollutants through smoking or indoor air pollution, and HIV infection [29]. The other is increased risk of transmission of disease, which may be associated with overcrowding and the use of mass transport, such as small buses commonly used in the Durban area.

The risk factors mentioned are not exclusive risk factors for XDR TB (compared to drug-susceptible [DS] TB) and it is possible that XDR TB hotspots are simply mirroring

overall TB distribution trends. However, there is some reason to believe that these neighborhoods have higher risk for XDR TB alone. In this study, unemployment was higher in hotspots vs non-hotspots, which may lead to many residents experiencing job insecurity, more frequent movement, and fear of stigma. These factors may make XDR TB treatment adherence and completion difficult to achieve, leading to higher treatment failure; previous failure of TB treatment and migrant status are both known risk factors for development of drug resistance [32, 33].

Based on current data, is it unclear which mechanism (increased risk of infection, progression or transmission) may be most responsible for increased incidence of XDR TB disease in identified hotspots; it is also unclear whether these hotspots align with hotspots of DS TB or MDR TB. Future studies examining detailed environmental and sociodemographic characteristics of individuals with XDR TB may be appropriate to help elucidate risk factors responsible for neighborhood-level trends. Additionally, future studies should investigate the spatial distributions of DS TB and MDR TB alongside that of XDR TB to determine whether different factors may be influencing development of each.

Because analysis of home locations may not represent the site of transmission, we attempted to identify other potential transmission areas by investigating XDR TB cases' *activity space*. This sub-analysis indicated that many cases travel to the Durban central business district. This may suggest high rates of transmission are occurring here since the activity space of some otherwise unrelated-seeming cases appears to overlap most

heavily in this location. Identification of likely transmission areas through activity space analyses can thus be useful in targeting prevention efforts aimed to halt transmission. However, in the case of our study area, movement to the Durban central business district is likely not unique to our patient population as the general population also probably follows similar movement patterns. Our finding that XDR TB cases tend to come from similar communities (homes clustered in "hotspots") may demonstrate the working of the previously mentioned neighborhood-level factors that are increasing susceptibility among these individuals. This may suggest that though transmission is driving the current XDR TB epidemic, neighborhood-level factors like poverty are ultimately driving risk for transmission upstream.

These findings support the need for interventions targeting poverty-associated risk factors or further study of transmission areas in this region. Future studies aiming to identify transmission hotspots will need to collect more comprehensive data on human movement using reliable methods of spatial data collection such as direct GPS measurements or identification of named locations on a map (rather than providing business names or descriptions of locations that are difficult to map). If programs are able to locate areas where realistic interventions are possible, this may be a promising route in decreasing XDR TB incidence in KwaZulu-Natal. However, until underlying sociodemographic risk factors are addressed, certain groups and neighborhoods will likely still be at increased risk.