A spatial analysis of social and economic determinants of tuberculosis in Brazil

Guy Harling*, Marcia C. Castro

Affiliations:

Guy Harling, Department of Social and Behavioral Sciences, Harvard School of Public Health, 677 Huntington Avenue, Boston MA, 02115, USA.
Email: gharling@hsph.harvard.edu.
Tel: +1 617 432 1135.

Marcia C. Castro, Department of Global Health and Population, Harvard School of Public Health, 665 Huntington Avenue, Boston MA, 02115, USA.
Email: mcastro@hsph.harvard.edu

* Corresponding author

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Abstract

We investigated the spatial distribution, and social and economic correlates, of tuberculosis in Brazil between 2002 and 2009 using municipality-level age/sex-standardized tuberculosis notification data. Rates were very strongly spatially autocorrelated, being notably high in urban areas on the eastern seaboard and in the west of the country. Non-spatial ecological regression analyses found higher rates associated with urbanicity, population density, poor economic conditions, household crowding, non-white population and worse health and healthcare indicators. These associations remained in spatial conditional autoregressive models, although the effect of poverty appeared partially confounded by urbanicity, race and spatial autocorrelation, and partially mediated by household crowding. Our analysis highlights both the multiple relationships between socioeconomic factors and tuberculosis in Brazil, and the importance of accounting for spatial factors in analyzing socioeconomic determinants of tuberculosis.

Keywords: Tuberculosis, Brazil, Spatial, Ecological, Social determinants

Introduction

Brazil faces a considerable health burden related to tuberculosis and is designated one of 22 High-Burden Countries by the World Health Organization (WHO). The WHO estimates that there were 83,000 incident tuberculosis cases in Brazil in 2011, an annual incidence rate of 42 cases per 100,000 population (World Health Organization, 2012). Incidence is estimated to have been falling steadily over the past two decades, however while over 90% of estimated cases are detected and reported nationally, treatment success rates remain below the target level needed to eradicate the disease in the near future (IPEA, 2010).

Tuberculosis disease is often associated with demographic and behavioural factors, including age, occupation, alcohol and tobacco consumption, poor nutrition and household crowding (Dye and Floyd, 2006). While these factors are important proximal determinants of tuberculosis, they can be considered to be mediators of more distal individual- and group-level socioeconomic factors, including education, employment and income (Dubos and Dubos, 1992; Gandy and Zumla, 2003; Lonnroth et al., 2009). This view is closely connected to Link and Phelan's conceptualization of social conditions as 'fundamental causes' of ill health (Link and Phelan, 1995). Recently the WHO has begun to promote efforts to address social determinants as an important component of global tuberculosis control (Rasanathan et al., 2011).

Much of the epidemiological tuberculosis literature relies on notified cases. In order for a case to be reported, it is necessary first for an individual to become latently infected, then for them to progress to active disease, and finally for them to be diagnosed by a health professional. Socioeconomic risk factors affect all three of these stages: high population density would be expected to increase the rate of tuberculosis bacillus spread through increased contact between infectious and susceptible individuals; low socioeconomic individuals may have poorer immune defence profiles, making them less able to suppress tuberculosis replication and thus avoid active disease; and poorer individuals are likely to be less able to afford or reach a setting in which they will be diagnosed.

Associations between tuberculosis rates and community socioeconomic structures – including low levels of education, limited social support, high unemployment, poverty and income inequality – have been consistently found in Europe (Bhatti et al., 1995; Parslow et al., 2001; Spence et al., 1993; Tocque et al., 1999), North America (Cantwell et al., 1998; Krieger et al., 2003; Oren et al., 2012), and Hong Kong (Chan-Yeung et al., 2005; Pang et al., 2010). Evidence from ecological and multilevel studies in Brazil, Mexico and South Africa also supports the existence of this relationship in middle-income countries (Alvarez-Hernandez et al., 2010; Harling et al., 2008; Munch et al., 2003; Souza et al., 2000). In lower-income settings, however, evidence is more mixed, with a supporting study from southern India (Shetty et al., 2006), but findings of an inverse gradient in Malawi and Zambia, even after adjusting for HIV status (Boccia et al., 2009; Glynn et al., 2000), and equivocal results in Western Africa (Gustafson et al., 2004; Gustafson et al., 2007; Lienhardt et al., 2005).

Given the infectious nature of tuberculosis, and the geographical autocorrelation of socioeconomic factors, any analysis of the socioeconomic determinants of tuberculosis should at least consider spatial patterning. A number of previous investigations of the spatial distribution of tuberculosis have been conducted in the context of socioeconomic factors, at various levels of aggregation. City-based studies have found tuberculosis to cluster around drinking establishments in peri-urban Cape Town, South Africa (Munch et al., 2003), in high-deprivation areas of Hermosillo, Mexico and Antananarivo City, Madagascar (Alvarez-Hernandez et al., 2010; Randremanana et al., 2009), amongst migrant populations in Beijing, China (Jia et al., 2008; Li et al., 2011), and in areas with high migrant levels in Cologne, Germany (Kistemann et al., 2002).

Regional analyses have found tuberculosis clusters surrounding a homeless shelter in an urban centre in Texas (Moonan et al., 2004), near a tuberculosis treatment centre in India (Tiwari et al., 2006), and in urban and industrial areas of Japan (Onozuka and Hagihara, 2007). National

analyses found clustering around the major urban centres in Portugal (Couceiro et al., 2011; Nunes, 2007), and in the north-west and south-east of Spain (Gomez-Barroso et al., 2009).

Within Brazil, most spatial or socioeconomic analyses of tuberculosis have been conducted at the city or state levels. Aside from a nationwide study of treatment outcomes (Duarte et al., 2009), the only study considering tuberculosis rates nationally appears to be a multilevel study of notification rates in 28 metropolitan regions between 2001 and 2003 (Gonçalves et al., 2009); the authors found both area-level poverty and population density to be positively associated with tuberculosis rates.

At the city level, spatial studies of tuberculosis in various parts of the country have found associations with broad social deprivation indices, low education and asset ownership – both individual and community-wide – and household crowding (Hino et al., 2011; Maciel et al., 2010; Santos et al., 2007; Souza et al., 2007; Souza et al., 2000; Vendramini et al., 2006; Vendramini et al., 2010; Ximenes et al., 2009)

At the state or regional level, studies have found clustering of cases around urban areas (Sales et al., 2010; Vieira et al., 2008) and associations between tuberculosis and both low education and indigenous reserves (Melo et al., 2012; Penna et al., 2009).

Despite all these studies, a comprehensive analysis of sociodemographic and socioeconomic determinants for the entire country is not available. This study addresses this gap in the literature. It uses reported tuberculosis cases in Brazil (2002-2009), at a fine spatial scale, and has two specific objectives. First, it characterizes the spatial pattern of tuberculosis in Brazil; second, it analyses how tuberculosis rates are correlated with social factors, treating existing spatial patterns as a potential confounder of the socioeconomic-tuberculosis relationship. For the second objective, we focus particularly on the role of low community socioeconomic status, given the considerable evidence of an association between low SES and tuberculosis in other locations, at other levels of aggregation, and in non-spatial models.

Methods

We performed a secondary data analysis of Brazilian notification and survey data. All data used were grouped at the *município* (municipality) level, the fifth administrative level in Brazil (the country is divided into macroregions, states, mesoregions, microregions and municipalities). There are currently 26 states and one federal district (Brasília) in the country (see Figure 1). These are divided into 5,565 municipalities (IBGE, 2011).

A geographic map of the municipalities was created using files from the Brazilian Institute of Geography and Statistics (Instituto Brasileiro de Geografia e Estatística; IBGE). All spatial information was projected using WGS 1984 UTM Zone 22S, which is the central longitude Universal Transverse Mercator band in Brazil. Map design and management was conducted in ArcGIS (ESRI; Redlands, CA).

In 2002 there were 5,507 municipalities in Brazil. We excluded the Fernando de Noronha archipelago since it lies 350km from the mainland, and thus had no geographically-contiguous neighbours. There were therefore 5,506 municipalities in the study dataset. For the 58 new municipalities created between 2002 and 2009, we merged data back into the municipality from which they had been carved, in the 40 cases where they had been created from a single municipality. For the 18 municipalities that had been created from territory taken from multiple prior municipalities such a process was not possible, so we excluded case data from such locations. Excluded municipalities accounted for 0.009% of all reported cases in the period; a further 0.15% of cases had no age attached, while 0.53% more had no reporting municipality recorded. In total 0.69% of tuberculosis cases were excluded.

Data Sources

Tuberculosis is a notifiable disease in Brazil, and all notified cases are stored in the Information System for notifiable diseases (Sistema de Informação de Agravos de Notificação: SINAN)

(SINAN). Since notification is passive it is not possible to ascertain whether years in which a municipality reported no cases were due to there being no cases effectively occurring in that period, or due to a failure to report cases. An initial assessment of missingness found that the number of municipalities reporting cases each year was relatively constant, and that very few municipalities consistently reported no cases. We therefore assumed that all zero counts represented a true absence of cases in that year.

We obtained municipality-level data from SINAN, for each year from 2002 to 2009, detailed by age and sex of the patient; age was stratified into ten categories: <1; 1-4; 5-9; 10-14; 15-19; 20-39; 40-59; 60-69; 70-79; and 80+. Age/sex-standardized notification rates were calculated for each municipality based on these age categories, using the national Brazilian population structure as the standard for each year. Population data were estimated by IBGE based on decennial census data and other sources (IBGE, 2013c).

We additionally calculated the average age/sex-standardized tuberculosis rate in each municipality across all eight years. This was done by summing the counts of tuberculosis and the number of person-years in each age-sex strata, and then standardizing the quotient of these two figures to the national average population structure across the eight years.

Population density for each year and municipality were calculated by dividing the population data for each year by the area calculated from the map of municipalities. Proportions of individuals in each municipality from each of the five primary race classifications used in Brazil – White, Brown, Black, Yellow (Asian) and Indigenous – were taken from the 2000 census (IBGE, 2013b). The proportion of individuals living in an urban setting within each municipality was calculated as the mean of the urban proportion at the 2000 and 2010 censuses (IBGE, 2013a).

Municipality-level measures of socioeconomic status (SES) were produced from the 2000 census by the Applied Economic Research Institute (Instituto de Pesquisas Econômicas Aplicadas; IPEA), a government body (IPEA, 2003). Our primary indicator of SES was the headcount extreme poverty level within each municipality, defined as the percentage of

households within the municipality with an income of less than R$75 per month (US$40 at average 2000 exchange rates (US Federal Reserve, 2012)); this equates to 50% of the minimum living wage. This variable was chosen to reflect the experience of those living in the most disadvantaged strata of society, and thus at greatest risk of tuberculosis. We also considered as an alternative measure the mean monthly earned household income (IPEA, 2003). We calculated the average level of household crowding in each municipality as the proportion of households in 2000 with more than two occupants per sleeping room – defined as total number of rooms minus the kitchen and any bathrooms (UN-Habitat, 2003).

Access/availability of health care in each municipality was measured as the number of health facilities participating in the Unified Health System (Sistema Único de Saúde: SUS), which provides healthcare as a right to all Brazilians (IBGE, 2002). We divided the number of SUS facilities in each municipality by its population size in 2002 to arrive at a facility rate per 100,000 inhabitants in that year and also calculated the total number of doctors per 100,000 inhabitants in each municipality in 2002 from the same source. Since individuals diagnosed with AIDS are at significantly increased risk of tuberculosis disease, we measured the number of AIDS cases per 100,000 person-years in the period 2002-09, based on reports to the Ministry of Health (Ministry of Health, 2010). Additionally, low tuberculosis cure rates may contribute to subsequent disease notifications, either through transmission or re-diagnosis of the patient; we therefore included the proportion of tuberculosis cases notified in the study period with cure as an outcome (SINAN).

Data Analysis

We began by measuring non-spatial descriptive statistics for all variables. Next we conducted exploratory spatial data analysis by mapping the distribution of tuberculosis and socioeconomic variables across Brazil. We then used both Global and Local Moran's I statistics to assess if spatial clustering of similar or dissimilar values was present (Anselin, 1995), either for tuberculosis or the independent variables. We defined neighbours using first-order queen's

contiguity, such that only municipalities sharing borders with one-another were considered neighbours. A distance-based approach was considered but rejected as infeasible given the great variability in municipality sizes across the country. Since the local Moran's I uses overlapping populations to study proximal clustering for each municipality, we adjusted the results using the Benjamini–Hochberg–Yekutieli form of the False Discovery Rate method to correct for multiple and dependent tests (Castro and Singer, 2006).

Data analysis and plotting was conducted using R version 3.0 (R Development Core Team, 2005). We conducted regression analysis on the aggregated, average tuberculosis rate across the eight years of available data. Covariates for the analysis were intentionally taken from values in 2000, prior to the beginning of the outcome data, to ensure temporal precedence of the exposures to the outcome. All covariates were mean-centred and scaled by their own standard deviation to improve comparability, interpretability and model convergence.

We initially conducted non-spatial bivariate analysis of each covariate using Negative Binomial models. We then continued to multivariable analyses using spatially correlated models with a log link and a lognormal negative binomial variance structure (Clayton and Kaldor, 1987). In all cases the outcome was the total age-standardized count of tuberculosis cases in the municipality across the period and all models included the age-standardized expected count as an offset term. While many municipalities reported no cases in individual years, using pooled data from the whole eight-year period suggested no evidence that zero-inflation was present.

All multivariable regressions were run using an integrated nested Laplace approximation (INLA) method, which mimics a Bayesian Monte Carlo Markov Chain (MCMC) but with significant computational advantages, using the 'INLA' package in R (Rue et al., 2009). The general form of the INLA models was:

$$\text{Observed Age Standardized Tuberculosis Case Count}_{ij} \sim \text{Negative Binomial}(\mu_{ij})$$

$$\text{Log}(\mu_{ij}) = \text{Expected Count}_{ij} + \alpha + \beta \text{X}_{ij} + \gamma\delta_{j} + \lambda \text{W}_{ij}\, u_{ij} + \nu_{ij}$$

$$u_{ij} \sim \text{CARNormal}(0, \tau_u) \qquad \tau_u \sim \text{Gamma}(1, 0.0260)$$

$$\delta_{ij} \sim \text{Normal}(0, \tau_\delta) \qquad \tau_\delta \sim \text{Gamma}(1, 0.0260)$$

$$\nu_{ij} \sim \text{Normal}(0, \tau_\nu) \qquad \tau_\nu \sim \text{Gamma}(1, 0.0260)$$

where i is the municipality, j is the state, X_{ij} are municipality-level covariates, δ_j are indicators for all but one state, to allow for systematic differences by state; and α, β, γ and λ are coefficients to be estimated. Priors for all coefficients were set to improper uniform distributions. The model has two random effects: ν_{ij} are non-spatial municipality-specific random effects, which allow for log-normally distributed overdisperion; u_{ij} are spatial municipality-specific random effects. *CARNormal* refers to an improper conditional autoregressive joint distribution, i.e. one where the conditional distribution of each municipality's random effect u_i is normally distributed with a mean equal to the average of the random effects of its neighbours (Sun et al., 1999; Thomas et al., 2004; Wakefield, 2007). The spatial weights matrix (W_j) was again defined using first-order queen's contiguity, such that each element $w_{ij} = 0$ unless municipalities i and j bordered one-another, in which case $w_{ij} = 1$. The prior distributions assigned to the inverse precision terms τ_u , τ_δ and τ_v are values previously found to allow for reasonable levels of variability to be explored by an MCMC chain (they assume that the residual incidence rate ratios follow a log t distribution with 2 degrees of freedom, with 95% of the distribution falling between 0.5 and 2 (Wakefield, 2007).

We began our multivariable analysis with a model containing only poverty, plus state-level fixed effects and municipality-level spatial and non-spatial random effects. We next added other socio-demographic variables, conceptualizing both urbanicity and race as potential confounders of the poverty-tuberculosis association, and population density as a potential mediator of the urbanicity-tuberculosis relationship. Finally, we considered factors that were potential

mediators of the poverty-tuberculosis relationship, including household crowding, healthcare access and AIDS diagnoses. We considered models containing interactions of each variable with poverty, to allow for the effect of poverty being effect-modified.

Models were compared using the Deviance Information Criteria (DIC), a hierarchical Bayesian version of the Akaike Information Criteria (Spiegelhalter et al., 2002). To measure relative contributions of the random effects in the model we used the spatial variance ratio (SVR), which measures the proportion of all random variance attributable to the spatial random effect.

For the final spatial model containing all covariates (but not their interactions), we generated maps displaying the component of the predicted value for each location associated with each fixed and random variable in the model (i.e. βX_{ij}, $\lambda W_{ij} u_{ij}$, δ_j and ν_{ij}), to investigate spatial patterns of explanatory power.

Results

Between 2002 and 2009, 719,663 cases of tuberculosis disease were reported across Brazil; this includes both pulmonary and extra-pulmonary cases. The annual average age-standardized notification rate was 49.1 cases per 100,000 person-years (HTPY) during the period (Table 1). All but 147 municipalities reported at least one case of tuberculosis in at least one year, although around a quarter of municipalities reported no cases in any given year. Tuberculosis notification rates changed little over the period, with a downward trend from 2003 to 2006 and a subsequent stabilization. This downward trend was largely due to falling rates in those aged 40 and older (Figure 2).

The national age-standardized tuberculosis case rate in this period was 49.1 cases per HTPY. The median municipality reported 24 cases per HTPY, but the distribution was right-skewed such that the mean municipality rate was 29.4 cases per HTPY (Table 2).

There was clear patterning of municipal tuberculosis notification rates across the period (Figure 3). The highest rates in the country are found in coastal cities in the South and Southeastern regions, in the Central-West region along the border with Paraguay, and across much of the North region. The municipality with the highest average notification rate across the eight-year period was Lavínia, located in central São Paulo state, which averaged 413 cases per HTPY.

Spatial exploratory data analysis of these rates revealed significant spatial autocorrelation. The Global Moran's I test found significant ($p<0.0001$) clustering in the data for each individual year (Moran's I ranged from 0.19 to 0.28 with Z-statistics of 24.4 to 34.2), and even stronger clustering for the period as a whole (Moran's I: 0.42, Z-statistic: 52.2).

The Local Moran's I test, after adjustment for multiple comparisons, found significant clustering of tuberculosis rates across the eight-year period (Figure 4 and Supplementary Figure 1). Clusters of high-rate municipalities were present: (i) along the Paraguayan border in Mato Grosso do Sul in the Central-West region; (ii) in and close to Amazonas state in the Northern region; (iii) dotted across Maranhão state in the North-East; and (iv) along the North-Eastern seaboard, particularly in Paraíba, Pernambuco, Alagoas, and Bahia states; and (v) around the metropolises of Rio de Janeiro, São Paulo and Porto Alegre on the southern seaboard.

Around one in three households had an income of less than half the official minimum living wage; the average mean household income per month was a little under R$300 (US$163). Significant household crowding was common in this period, with over one-fifth of households having more than two occupants per potential sleeping room. Nationally, the Brazilian population overwhelmingly reported themselves to be either white (54%) or brown (39%), however there were municipalities in which up to three-quarters of inhabitants report being Indigenous, particularly in the North and Central-West macroregions. There were 47,564 health facilities that participated in the SUS in 2000, one for every 3,846 Brazilians. The number of facilities per 100,000 persons doubled between the 25th and 75th percentile of the municipality distribution. This degree of dispersion was similar for doctors.

The sociodemographic characteristics included in this analysis were spatially patterned (Supplementary Figure 2). Visual patterns were confirmed to be highly significantly clustered based on the Global Moran's I statistic; the location of this clustering varied as shown by Local Moran's I maps for each variable (Supplementary Figure 3).

Bivariate analysis indicated that population density, poverty and urbanicity were associated positively with tuberculosis notification rates (Table 2). Municipalities with higher rates of household crowding also had higher tuberculosis rates. Relative to all-White municipalities, increased proportions of all other race-groups were associated with increased tuberculosis notifications; this effect was largest per standard deviation for the Brown race-group, but per percentage-point increase, the effect was strongest for the Yellow and indigenous populations. Municipalities with more SUS hospitals or with higher rates of medical professionals had lower tuberculosis rates; those with higher AIDS case rates had higher tuberculosis rates.

All multivariable models not containing spatial random effects had large positive spatial autocorrelation in their residuals, and were thus mis-specified; including spatial effects reduced this autocorrelation to negligible levels, indicating that the assumption of independence for the non-spatial residuals was met. (Supplementary Table 1).

In models allowing for spatial autocorrelation, poverty became associated with lower tuberculosis rates in a model containing only State fixed effects (Table 3, model 1). However after adjustment for urbanicity and population density, poverty was once more positively associated with tuberculosis (model 2). Some of this effect appeared to be due to confounding by race (model 3), and the remainder to mediation by household crowding (model 4).

More urban settings were consistently associated with higher tuberculosis rates, as was population density, although its effect may have been mediated by the AIDS case rate. Household crowding, AIDS case rates and tuberculosis cure rates were also all associated with more tuberculosis, although hospital and doctor availability were not significant predictors in multivariable models. Larger proportions of Black, Brown or Indigenous persons were

associated with robustly higher tuberculosis rates. Per standard deviation, the proportion self-identifying as Brown was the strongest predictor of tuberculosis notification rates; however a one percentage-point increase in the proportion of the population self-identifying as Indigenous was associated with a far larger increase in rates than any other race group.

Models containing interaction terms provided somewhat better model fits using the DIC, although few of the interaction terms qualitatively affected the results (Supplementary Table 1). Replacing the proportion of households living below the poverty rate with mean household income at the municipality level did not lead to qualitative changes in any of the findings (results not shown).

Based on model 4 (Table 3), we calculated the predicted contribution to the observed tuberculosis rates (Supplementary Figure 4A) of the non-spatial (Supplementary Figure 4B) and spatial (Supplementary Figure 4C) residuals, as well as the fixed effect covariates (Supplementary Figure 4D). The non-spatial residuals played a negligible role; the spatial effects were positive in the Northeast and much of the North region, and negative in the South and Southeast regions. In contrast the fixed effects contributed positively to rates in the North and some parts of the Central-West, while contributing negatively elsewhere. The breakdown of the fixed effects (Supplementary Figure 5) shows a range of spatial patterns, many contrasting the North and Northeast to the rest of the country.

Finally, given the strongly regional patterns seen in Supplementary Figure 5, we reran model 6 stratified by the five macroregions (Supplementary Table 2). The results did not suggest that parameter estimates diverged strongly for most covariates, although poverty appeared most detrimental in the richest macroregions – the Southeast and Central-West.

Discussion

We conducted univariate and multivariable analyses of tuberculosis notification rates in Brazil at the municipal level. In univariate analysis, we found tuberculosis notification rates to be

strongly spatially clustered, with high rates clustered around cities, especially on the eastern seaboard, and also across the less-densely populated western half of the country. In multivariable analysis, after allowing for spatial dependence, municipal tuberculosis notification rates were associated with higher proportions of black, brown or indigenous persons, greater household crowding, a higher proportion of households living in extreme poverty, a higher proportion of individuals living in urban settings, and greater population density. Almost all the variance in the multivariable models not related to covariates was attributable to spatially correlated random effects.

Many of these associations accord with other studies both in Brazil and elsewhere. Tuberculosis incidence has often been found to be higher in lower-status racial/ethnic groups (Coimbra and Basta, 2007; Hoeppner and Marciniuk, 2000; Miramontes et al., 2013), in more crowded households (Baker et al., 2008; Cantwell et al., 1998; Corbett et al., 2009; Munch et al., 2003; Murray et al., 2011; Souza et al., 2007) and in urban and more densely populated settings (Gonçalves et al., 2009; Liu et al., 2012; Tanrikulu et al., 2008). A positive association between poverty and tuberculosis is in line with much of the existing literature. This includes work in a range of global settings, as well as several studies in Brazil – including both non-spatial national-level analyses (Gonçalves et al., 2009) and city-level spatial analyses (Maciel et al., 2010; Santos et al., 2007; Souza et al., 2000; Vendramini et al., 2006; Vendramini et al., 2010).

The most complex finding of this analysis is the association between municipality-level poverty (or mean income) and tuberculosis. This association varies across regression models, reflecting the interplay between spatial correlation, urbanicity, and poverty (see Supplementary Table 1). In a model with State-level fixed effects, but not population density or spatial autocorrelation, poverty was associated with lower tuberculosis notification rates (HR: 0.95). Allowing for spatial autocorrelation lowered the coefficient (HR: 0.81), but adding urbanicity raised it such that poverty was once again positively associated with tuberculosis (HR: 1.17). The later addition of municipal racial composition led to a further downward shift (HR: 1.06).

The effect of adding urbanicity reflects a classic example of strong negative confounding of poverty and tuberculosis by urbanicity: urban areas are both richer on average, and have higher rates of tuberculosis, making poverty appear protective if urbanicity is not adjusted for. Similarly, spatial confounding occurs when we fail to allow for account for the highly positive spatial autocorrelation of tuberculosis rates: adjusting for spatial autocorrelation removes the effect of unmeasured local characteristics driving high (or low) tuberculosis rates both in each municipality and each municipality's neighbours.

The analysis shows that race also confounds the poverty-tuberculosis relationship in Brazil – with more Black, Brown and Indigenous individuals being associated with higher poverty and higher tuberculosis rates. This finding highlights the role of poverty as a pathway from racial identity to tuberculosis, making poverty a potential target for reducing racial disparities in tuberculosis in the country. Finally, it is notable that tuberculosis was most strongly associated with lower poverty in the two richest macroregions, the Southeast and Central-West (Supplementary Table 2). This effect-modification by macroregions suggests that further analysis at finer geographical scales is likely to yield additional insights.

In addition to the findings relating to poverty, this analysis also presents several other insights in the Brazilian context. First, it provides a clearer picture of the age distribution of tuberculosis in Brazil. The fall in notified incidence across the period of study appears to be a function of a reduction in notifications amongst both older men and women. This stands in contrast to the expectation that tuberculosis control measures will reduce rates faster amongst younger individuals – since new incident cases would fall but reactivation cases amongst the older would not (Chaimowicz, 2001). Unfortunately, this analysis cannot distinguish between changes in notification practices and changes in actual disease incidence, although the differential changes at younger and older ages suggest that a true change may be occurring.

Second, our analysis provides a detailed picture of the spatial distribution of tuberculosis in Brazil. Figure 3 shows a clear pattern of higher rates both along land borders with other

countries and in the major coastal cities. Figure 4 shows that many of these areas reflect significant clusters of high-rate municipalities. This analysis does not allow us to determine whether this clustering of rates reflects ongoing disease transmission in these areas, or a historic clustering of infections generating reactivation cases. Research examining the breakdown of cases by these categories, and how they vary by geographic location, is important in determining whether geographically focused prevention efforts may reap large rewards: the greatest impact being likely where most cases are from active transmission.

Third, we show that area-level urbanicity is not merely acting as a proxy for income levels: urbanity remained a predictor of greater tuberculosis rates regardless of the inclusion of spatial dependence, area-level poverty or an interaction term between poverty and urbanicity. Subsequent inclusion of AIDS case rates suggested that the effect of urbanicity may in fact be partially mediated through higher AIDS case rates. Population density appears to predict tuberculosis risk independently of poverty or urbanicity, although it too may be mediated through higher AIDS rates.

Fourth, while higher levels of household crowding were strongly associated with tuberculosis notifications, it was not a mediator of urbanicity or population density, reflected in the lack of effect on these coefficients when household crowding was added to the model. Household crowding did appear to partially mediate the relationship between poverty and tuberculosis, causing the incidence rate ratio to fall from 1.06 to 0.98.

Fifth, the most notable relationship between race and tuberculosis was in areas with high indigenous populations. There is considerable evidence highlighting the heavy burden of tuberculosis amongst the indigenous population – relative both to elsewhere in Brazil (Coimbra and Basta, 2007), and to nearby non-indigenous populations (Croda et al., 2012; Melo et al., 2012). Our findings highlight that this association is not merely a function of where in Brazil the indigenous population lives, or a function of spatial clustering of indigenous persons, but is associated either directly or via some other factor, with increased tuberculosis incidence.

The combination of our findings relating to urbanicity, poverty, crowding, population density and race highlight the complexity of socioeconomic determinants of tuberculosis. There are numerous potential causal pathways running from SES to tuberculosis: race may affect risk via discriminatory practices relating to access to care or economic opportunities; crowding may increase risk through increased exposure to infectious household members; poverty may reduce access to nutritious food. Analysing each SES measure's mediating pathways would be a useful next step.

Brazil has been nationally coordinating its tuberculosis treatment efforts in the recent past, notably including the introduction of Directly Observed Treatment Short-course (DOTS) in 1998 (Kritski and Ruffino-Netto, 2000). The tuberculosis budget has been steadily increased over the past decade, and efforts have been made to improve diagnostics and treatment, facilitated through the Family Health Program (Programa Saúde da Família, PSF) (de Sá et al., 2011; Façanha et al., 2009; Figueiredo et al., 2009; Ignotti et al., 2007). The effect of the PSF appeared to depend on the degree of political and institutional support provided to the program. The number of tuberculosis cases appears to now be declining, meeting the Millennium Development Goal (MDG) of reversing the spread of tuberculosis by 2015, and on track to meet the specific targets of halving tuberculosis prevalence and mortality relative to 1990 levels by that date. However, while detection rates are well above WHO guidelines, treatment cure rates remain well below target; as a result, the longer-term goal of eliminating tuberculosis as a public health problem by 2050 will not be met if current trends continue. Improved treatment support, either at the individual or societal level, may be needed to achieve elimination (Hargreaves et al., 2011).

Strengths and Limitations

The study has several strengths. It is based on almost a decade of data, and includes over 700,000 reported tuberculosis cases with linked demographic and geographic information. Our

methodology explicitly considers the spatial autocorrelation of tuberculosis rates (and of covariate values), which could otherwise have biased any results arising from regression models.

As with any study, however, this analysis also has limitations. First, while notification rates are over 80% of estimated cases in Brazil, it is possible that cases are missing non-randomly from this dataset. In particular, we note that the association between poverty and tuberculosis may suffer from non-differential misclassification error: it is possible that poorer municipalities have lower TB reporting rates (Pinheiro et al., 2012), which would most likely lead to the reported estimates for poverty coefficients being downward-biased. We included healthcare availability as a covariate in our models to account for some of this potential bias. Second, we were not able to include covariates for some traditional tuberculosis risk factors in our models, including alcohol and tobacco consumption and workplace and home exposure to particulate matter. This is a lesser concern if our primary relationship of interest is that between socioeconomic factors and tuberculosis, since most of these missing variables can be conceptualized as pathway mediators, rather than confounders.

Third, as with many spatial analyses, a central area of concern is the unit of aggregation. Since these data are analysed only at the municipal level, our analysis cannot speak to individual-level, or even sub-municipal-level, processes. It may well be the case that the associations seen at this level would not be present at more detailed levels of disaggregation – the issue of modifiable area unit. Ecological study at a level as aggregated as the municipality (mean population ~35,000) may well hide considerable variation in the association between risk factors and tuberculosis within units. Taking the example of poverty, we might worry about low-poverty municipalities which contain high-poverty pockets in which tuberculosis is common, most likely in cities in the south and southeast of the country. Such a hypothesis could be tested were data available at a finer spatial scale, perhaps based in a more limited geographic area such as a single state.

In addition to high-poverty pockets, any small high-risk group that is geographically concentrated within the population is likely to be missed by a study at the municipality level. For example, tuberculosis disease is increasingly prevalent amongst the Bolivian migrant community in the city of São Paulo, which is often undocumented and highly concentrated within certain neighbourhoods (Bermudes, 2012; Da Silva, 2006), and accounts for between 15 and 30 percent of all tuberculosis cases in some areas (Bataiero, 2009; Martinez et al., 2012). Using municipality level data does not allow the quantification of how much of the spatial correlation seen amongst tuberculosis rates is due to within-municipality processes of important disease rate drivers, such as migrant populations.

Conclusions

This study provides a description of the spatial distribution of tuberculosis across Brazil, and begins to explore which risk factors remain associated with notification rates after allowing for spatial autocorrelation. We find that tuberculosis is predicted separately by poverty, urbanicity and population density. As efforts continue to bring tuberculosis under control in Brazil, spatial information can help inform efforts to target ongoing strategies, and risk factor epidemiology provides important information on who remains at risk of infection. Tuberculosis in Brazil continues to be ecologically associated with many of the traditional sociodemographic markers of low social and economic status. Efforts to reach high-risk, low status groups still have the potential to reap benefits.

While this study has begun to explore the national patterns of tuberculosis, there remain several possible extensions to this analysis. First, the great majority of the unexplained variance seen at the municipality level was captured as spatial autocorrelation. This suggests that there remain important spatially correlated variables not captured by our models that might usefully be added to our analysis. Second, a comparative study at multiple levels of aggregation might determine which associations are robust across levels, and which potentially reflect modifiable

areal unit problems. Third, we have merely touched in our analysis on how the effects of social conditions may be mediated through behavioural or biological risk factors that lead to incident tuberculosis. Careful pathway analysis might help find risk factors which are more immediately modifiable than race, income or population density.

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Table 1: Notified cases of tuberculosis in Brazil between 2002 and 2009 [a]

Year	Reporting municipalities [b]	National population (millions)	Crude number of cases notified	Age-Standardized notification rate per 100,000
2002	4,170	174.59	91,234	52.51
2003	4,176	176.84	93,647	53.36
2004	4,133	179.07	91,947	51.85
2005	4,164	184.14	90,387	49.65
2006	4,047	185.45	84,009	45.62
2007	4,065	189.29	85,490	45.85
2008	4,090	189.57	85,167	45.64
2009	4,087	191.43	88,619	47.08
Average	5,359	183.80	88,813	49.07

[a] Excluding cases with no associated geographic or age information, or from the 19 new municipalities excluded from this study (see text for details).

[b] Reporting municipalities are those with non-zero cases in a given year. The figure for the 'Average' row reflects the number of municipalities reporting one or more cases at any point across all eight years.

Table 2: Descriptive statistics and bivariate associations for age/sex-standardized tuberculosis notification rates in Brazilian municipalities

	National	Municipality		
	Mean value	Mean (Range)	IRR [95% CI]	IRR units (1 standard deviation)
Age-standardized TB cases per 100,000	49.12	29.41 (0.00 - 429)		
Area (km^2)		1,579.27 (2.88 - 161,061)		
Population density (per km^2)	21.14	104.90 (0.14 - 13,112)	1.06 [1.04 - 1.08]	567 people
% households in poverty	32.76	46.48 (2.89 - 93.02)	1.19 [1.17 - 1.21]	22.8 percentage points
% individuals in urban area	83.01	61.45 (4.40 - 100)	1.10 [1.08 - 1.12]	22.4 percentage points
Race: % White	53.65	52.54 (0.71 - 100.0)	reference	
Race: % Black	6.20	5.81 (0.00 - 61.72)	2.61 [2.15 - 3.16]	4.85 percentage points
Race: % Yellow	0.45	0.24 (0.00 - 15.01)	1.43 [1.21 - 1.70]	0.58 percentage points
Race: % Brown	38.55	40.10 (0.00 - 98.16)	13.35 [10.88 - 16.39]	23.5 percentage points
Race: % Indigenous	0.44	0.60 (0.00 - 76.31)	3.42 [2.93 - 4.00]	3.24 percentage points
Race: % Undeclared	0.71	0.71 (0.00 - 27.09)	1.38 [1.13 - 1.67]	0.9 percentage points
% households with >2 members per bedroom	21.27	17.70 (2.18 - 86.00)	1.37 [1.35 - 1.39]	11.4 percentage points
SUS Hospitals per 100,000	25.88	0.47 (0.00 - 4.09)	0.85 [0.83 - 0.87]	30.5 facilities
Doctors per 100,000	188.92	0.78 (0.00 - 25.88)	1.00 [0.98 - 1.02]	87.7 doctors
Tuberculosis treatment success rate (%)	68.11	67.46 (0 - 100)	0.99 [0.97 - 1.01]	19.9 percentage points
AIDS cases per 100,000 per year	21.26	8.58 (0.00 - 134.06)	1.15 [1.13 - 1.17]	9.9 cases

IQR: Inter-quartile range. CI: Confidence interval. IRR: Incidence rate ratio. R$: Brazilian Real. SUS: Sistema Único de Saúde (Unified Health System).

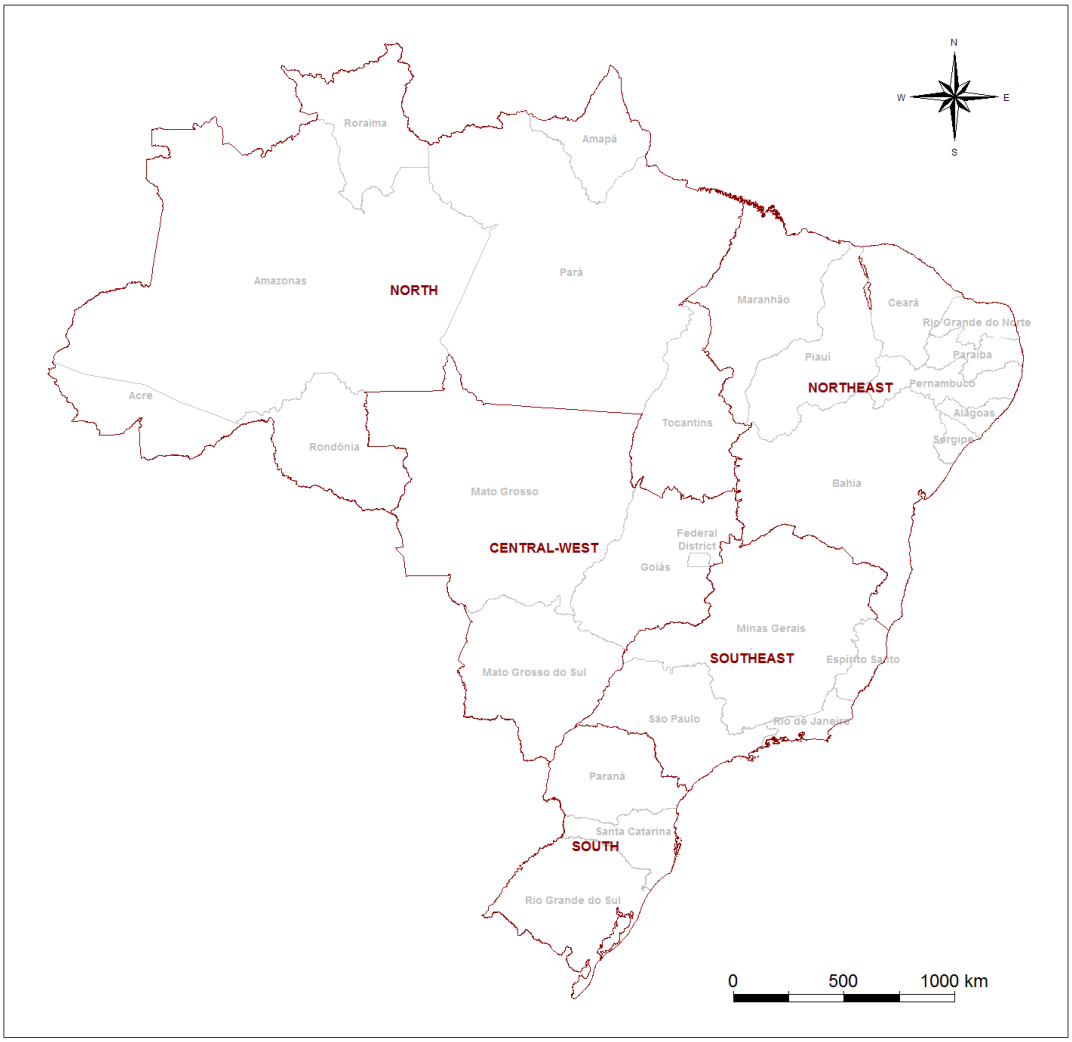
Incidence rate ratios are the proportional change in the tuberculosis rate associated with a one standard-deviation increase in the variable. They were calculated from a series of bivariate non-spatial negative-binomial models with a population offset term (all racial composition variables were entered into a single model).

Table 3: Multivariable spatial regressions for municipal tuberculosis notification rates in Brazil, 2002-09

	Model 1		Model 2		Model 3		Model 4	
Households in extreme poverty (%)	0.805	(0.77 - 0.84)	1.22	(1.16 - 1.29)	1.06	(1.00 - 1.12)	1.02	(0.96 - 1.07)
Individuals living in an urban area (%)			1.31	(1.27 - 1.34)	1.28	(1.24 - 1.31)	1.18	(1.15 - 1.21)
Population Density (log of persons/km^2)			1.07	(1.04 - 1.10)	1.07	(1.04 - 1.10)	0.98	(0.96 - 1.01)
Race (%)								
Black					1.10	(1.07 - 1.12)	1.06	(1.04 - 1.09)
Yellow					1.00	(0.98 - 1.01)	0.99	(0.98 - 1.01)
Brown					1.34	(1.27 - 1.40)	1.25	(1.19 - 1.31)
Indigenous					1.14	(1.12 - 1.16)	1.11	(1.09 - 1.13)
Undeclared					1.02	(1.00 - 1.04)	1.01	(1.00 - 1.03)
Household crowding (persons per bedroom)							1.17	(1.13 - 1.21)
SUS health facilities per capita							1.00	(0.98 - 1.02)
Doctors per capita							0.99	(0.98 - 1.01)
AIDS cases per capita							1.21	(1.19 - 1.24)
Tuberculosis cure rate (%)							1.06	(1.04 - 1.09)
Deviance Information Criterion (DIC)		22,336.7		21,983.6		21,770.2		21,345.3
Spatial Variance		0.342		0.261		0.204		0.140
Municipal-level non-spatial variance		0.004		0.004		0.004		0.003
Spatial Variance ratio		0.988		0.985		0.982		0.977
Global Moran's I of residuals		-0.024		-0.014		-0.013		-0.001
p-value		0.003		0.089		0.109		0.954

Regression coefficients are incidence rate ratios and 95% confidence intervals for a one-standard deviation change in the independent variable.
All independent variables were centered at their mean value and scaled by their standard deviation. Values for standard deviations provided in Table 2.
All models contain fixed effect indicator variables for States.

Figure 1: Administrative levels in Brazil: macroregions, states and the Federal District



Macroregions are titled in upper-case and outlined in dark red. States are titled in lower-case and outlined in pale grey.

Figure 2: Age- and sex-stratified tuberculosis notification rates per 100,000 in Brazil 2002-2009

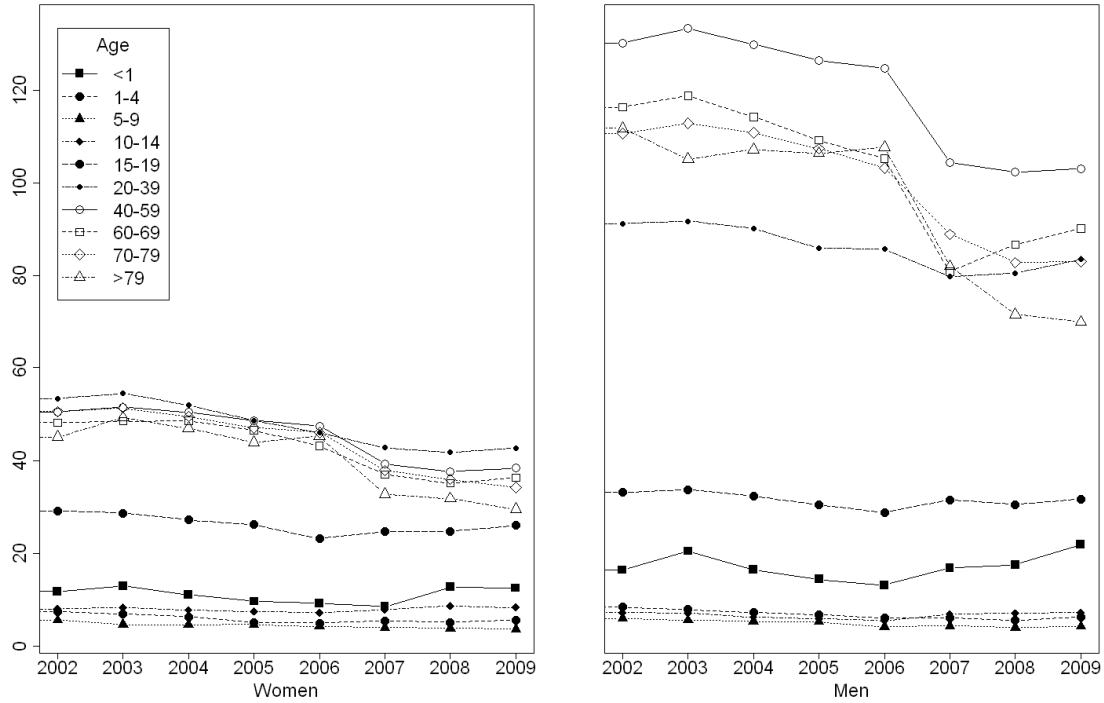
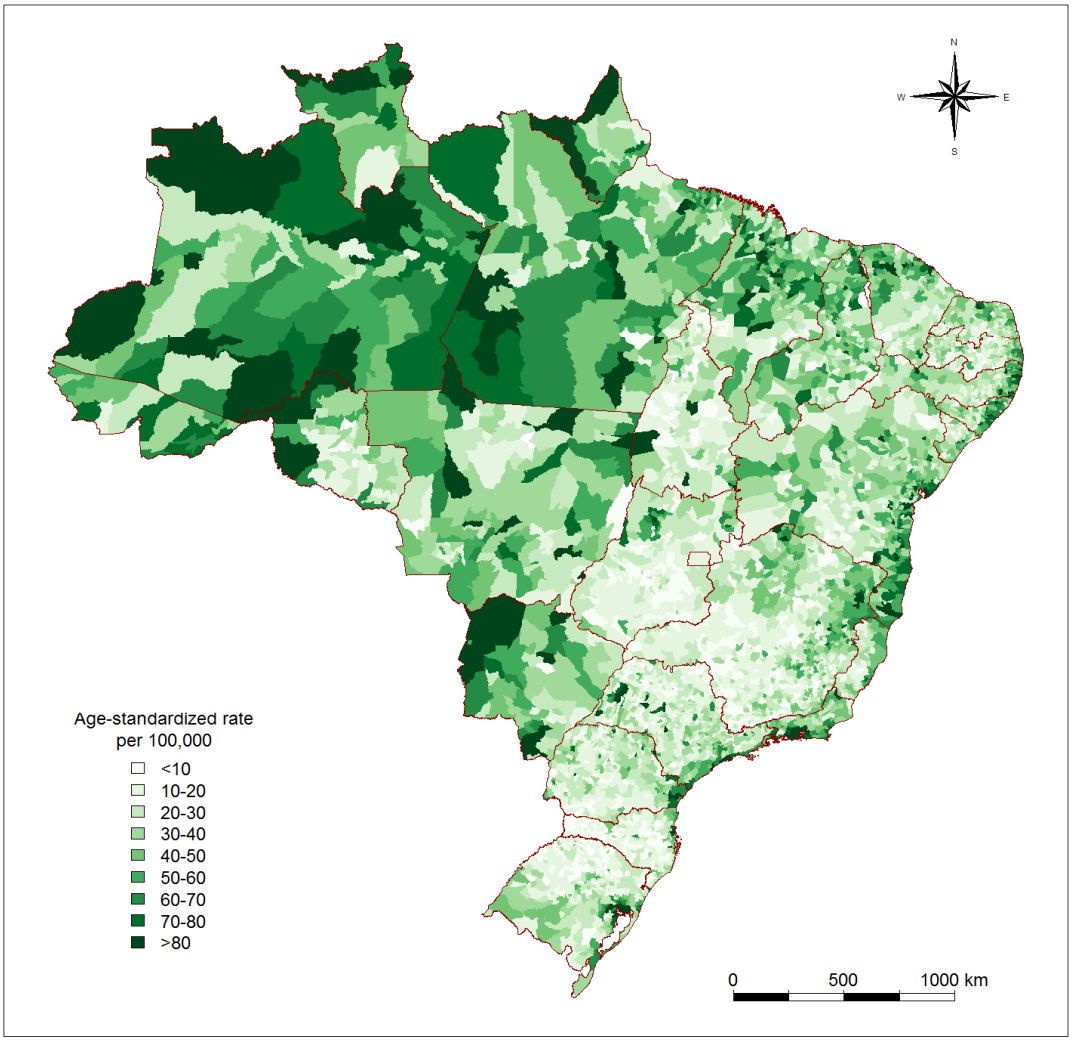
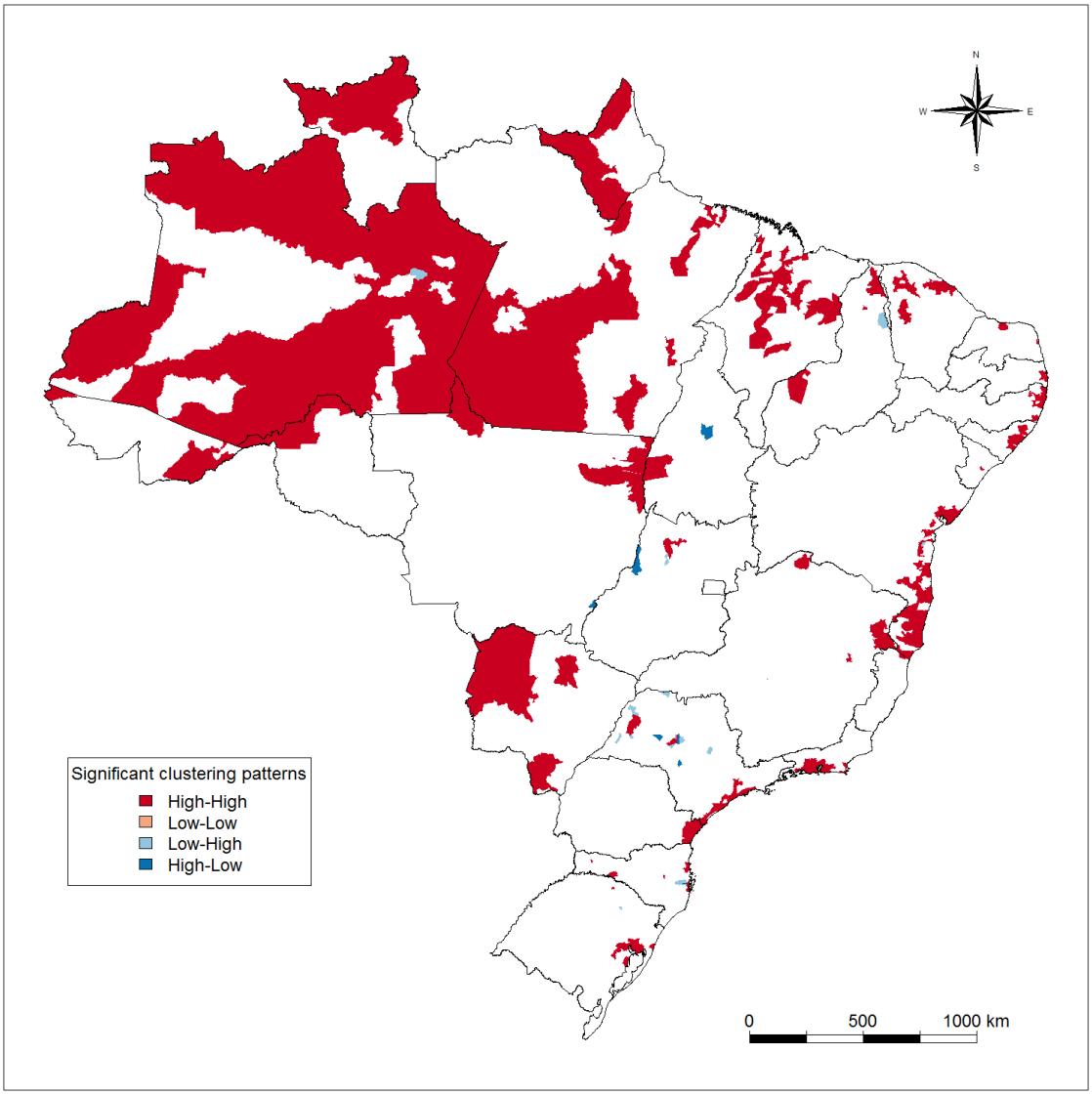


Figure 3: Age- and sex-standardized municipal tuberculosis notification rates per 100,000 in Brazil 2002-2009



Red lines delineate federal state boundaries.

Figure 4: Significant Local Moran's I results for municipal tuberculosis rates



Tuberculosis cases notified between 2002 and 2009. Clustering tests based on municipal-level data. Municipalities shown as significant are those remaining after adjustment for multiple comparisons using the False Discovery Rate method. High-high indicates high rates clustered with neighbouring high rates; low-low, low rates with neighbouring low rates; low-high, low rates with neighbouring high rates; high-low, high rates with neighbouring low rates. Black lines delineate federal state boundaries. A presentation of these same data separately for each macroregion is made in Supplementary Figure 1.

Supplementary material for:

A spatial analysis of social and economic determinants of tuberculosis in Brazil.

Supplementary Table 1: Multivariable spatial regressions for municipal tuberculosis notification rates, all regressions

	1ns		1		2		2i		3		3i		4		4i	
% Households in extreme poverty	0.95	(0.92 - 0.98)	0.81	(0.77 - 0.84)	1.17	(1.11 - 1.23)	1.19	(1.13 - 1.25)	1.22	(1.16 - 1.29)	1.22	(1.16 - 1.29)	1.06	(1.00 - 1.12)	1.07	(1.02 - 1.13)
Individuals living in an urban area (%)					1.34	(1.30 - 1.37)	1.35	(1.31 - 1.38)	1.31	(1.27 - 1.34)	1.32	(1.28 - 1.36)	1.28	(1.24 - 1.31)	1.26	(1.23 - 1.30)
Urbanicity x Poverty							0.96	(0.94 - 0.98)								
Log of Population Density									1.07	(1.04 - 1.10)	1.04	(1.01 - 1.07)	1.07	(1.04 - 1.10)	1.08	(1.05 - 1.10)
Density x Poverty											0.97	(0.95 - 0.99)				
Race (%)																
Black													1.10	(1.07 - 1.12)	1.12	(1.09 - 1.16)
Yellow													1.00	(0.98 - 1.01)	1.00	(0.98 - 1.02)
Brown													1.34	(1.27 - 1.40)	1.32	(1.25 - 1.38)
Indigenous													1.14	(1.12 - 1.16)	1.16	(1.13 - 1.19)
Undeclared													1.02	(1.00 - 1.04)	1.03	(1.00 - 1.05)
Race x Poverty																
Black															0.95	(0.93 - 0.97)
Yellow															0.95	(0.92 - 0.98)
Brown															1.00	(0.98 - 1.02)
Indigenous															0.97	(0.95 - 0.99)
Undeclared															0.99	(0.97 - 1.01)
Deviance Information Criteria (DIC)		24,164.9		22,336.7		21,990.0		21,977.6		21,983.6		21,979.3		21,770.2		21,743.5
Spatial Variance				0.342		0.267		0.266		0.261		0.262		0.204		0.197
Municipal-level non-spatial variance		0.132		0.004		0.004		0.004		0.004		0.004		0.004		0.004
Spatial Variance ratio				0.988		0.986		0.986		0.985		0.985		0.982		0.982
Global Moran's I of residuals		0.434		-0.024		-0.015		-0.016		-0.014		-0.015		-0.013		-0.013
p-value		<0.001		0.003		0.071		0.051		0.089		0.069		0.109		0.100

	5		5i		6		6i		7	
% Households in extreme poverty	0.98	(0.92 - 1.03)	0.99	(0.94 - 1.05)	1.02	(0.96 - 1.07)	1.03	(0.97 - 1.09)	1.03	(0.98 - 1.09)
Individuals living in an urban area (%)	1.25	(1.22 - 1.29)	1.24	(1.20 - 1.27)	1.18	(1.15 - 1.21)	1.18	(1.15 - 1.21)	1.16	(1.13 - 1.20)
Urbanicity x Poverty									1.03	(1.00 - 1.05)
Log of Population Density	1.06	(1.03 - 1.08)	1.05	(1.03 - 1.08)	0.98	(0.96 - 1.01)	0.99	(0.96 - 1.01)	0.98	(0.96 - 1.01)
Density x Poverty									0.99	(0.97 - 1.02)
Race (%)										
Black	1.08	(1.05 - 1.10)	1.07	(1.05 - 1.10)	1.06	(1.04 - 1.09)	1.06	(1.04 - 1.09)	1.07	(1.04 - 1.10)
Yellow	1.00	(0.98 - 1.01)	1.00	(0.98 - 1.02)	0.99	(0.98 - 1.01)	1.00	(0.98 - 1.01)	1.00	(0.98 - 1.02)
Brown	1.26	(1.21 - 1.33)	1.22	(1.16 - 1.28)	1.25	(1.19 - 1.31)	1.24	(1.18 - 1.30)	1.21	(1.15 - 1.27)
Indigenous	1.12	(1.10 - 1.14)	1.11	(1.10 - 1.13)	1.11	(1.09 - 1.13)	1.11	(1.09 - 1.13)	1.10	(1.08 - 1.13)
Undeclared	1.01	(1.00 - 1.03)	1.02	(1.00 - 1.03)	1.01	(1.00 - 1.03)	1.01	(1.00 - 1.03)	1.02	(0.99 - 1.04)
Race x Poverty										
Black									0.98	(0.96 - 1.00)
Yellow									0.99	(0.95 - 1.02)
Brown									1.01	(0.99 - 1.02)
Indigenous									1.00	(0.98 - 1.02)
Undeclared									1.00	(0.98 - 1.02)
Household crowding (persons per bedroom)	1.18	(1.14 - 1.22)	1.25	(1.20 - 1.29)	1.17	(1.13 - 1.21)	1.16	(1.13 - 1.20)	1.22	(1.18 - 1.27)
Crowding x Poverty			0.92	(0.90 - 0.94)					0.94	(0.91 - 0.96)
Number of SUS health facilities					1.00	(0.98 - 1.02)	0.99	(0.97 - 1.02)	0.99	(0.97 - 1.02)
Health facilities x Poverty							1.00	(0.98 - 1.02)	1.00	(0.97 - 1.02)
Doctors per capita					0.99	(0.98 - 1.01)	1.02	(1.00 - 1.04)	1.01	(0.99 - 1.03)
Doctors x Poverty							1.02	(1.01 - 1.04)	1.01	(0.99 - 1.03)
AIDS cases per capita					1.21	(1.19 - 1.24)	1.21	(1.18 - 1.25)	1.18	(1.15 - 1.22)
AIDS cases x Poverty							1.00	(0.98 - 1.02)	0.98	(0.95 - 1.00)
Tuberculosis treatment cure (%)					1.06	(1.04 - 1.09)	1.05	(1.03 - 1.08)	1.05	(1.03 - 1.08)
Tuberculosis cure x Poverty							1.04	(1.02 - 1.06)	1.04	(1.01 - 1.06)
Deviance Information Criteria (DIC)		21,692.1		21,647.5		21,345.3		21,332.6		21,297.0
Spatial Variance		0.194		0.186		0.140		0.137		0.132
Municipal-level non-spatial variance		0.004		0.004		0.003		0.003		0.003
Spatial Variance ratio		0.981		0.981		0.977		0.976		0.976
Global Moran's I of residuals		-0.013		-0.016		-0.001		0.002		0.003
p-value		0.101		0.055		0.954		0.831		0.701

Regression coefficients are incidence rate ratios and 95% confidence intervals for a one-standard deviation change in the independent variable.

All independent variables were centred at their mean value and scaled by their standard deviation. Values for standard deviations provided in Table 2.

All models contain fixed effect indicator variables for States. Models suffixed with 'ns' have no spatial random effects; models suffixed with 'i' include interactions of the newly-added variable with the municipality poverty rate. Model 7 contains interaction terms for all variables; model 8 includes macroregion fixed effects and interactions of these fixed effects with poverty.

For correspondence with Table 3: Models 1,2, 3 and 4 in Table 3 are models 1, 3, 4 and 6 respectively in this Table.

Supplementary Table 2: Comparison of national and macroregion regressions

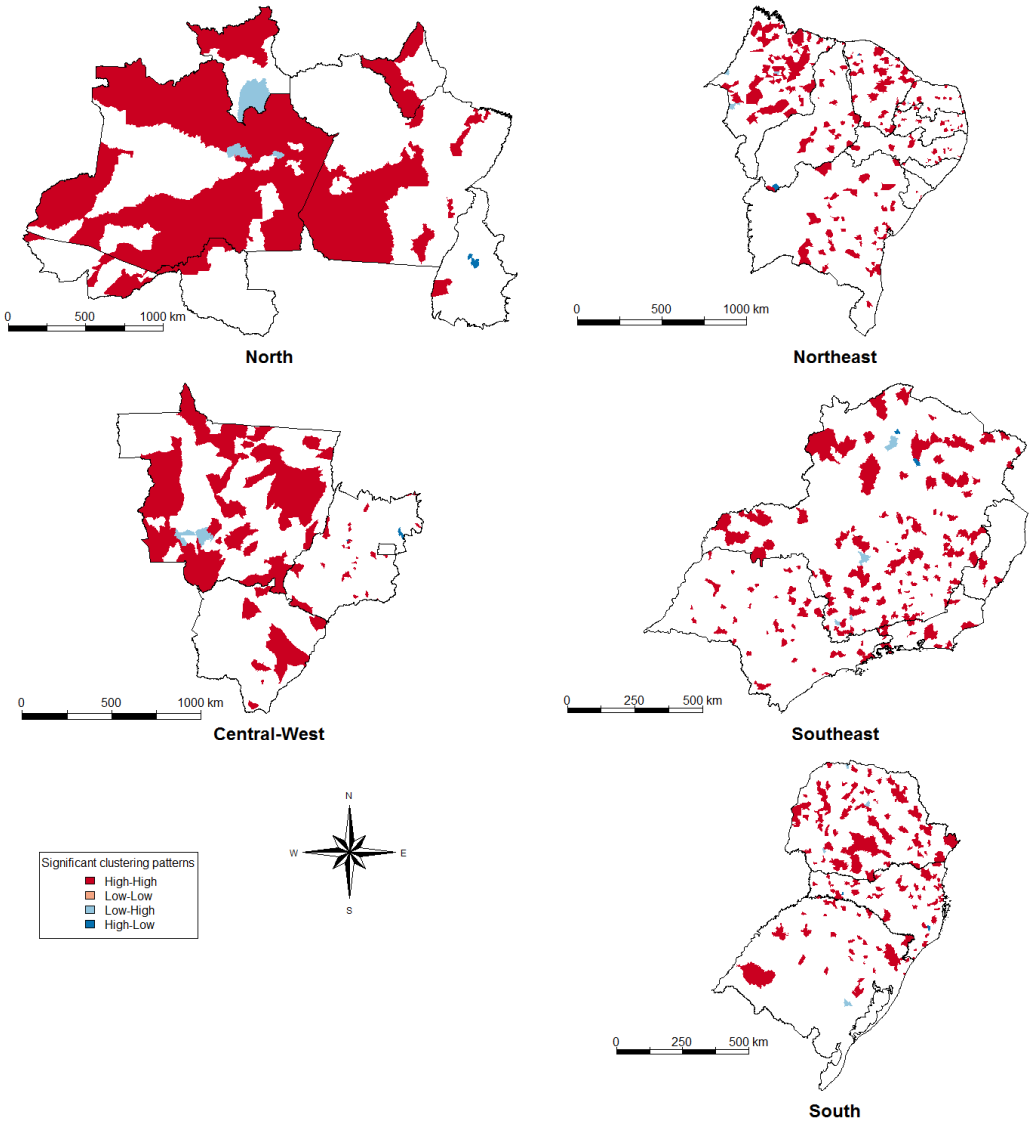
	Brazil		South		South-East		North		North-East		Central-West	
Households in extreme poverty (%)	1.02	(0.96 - 1.07)	0.94	(0.79 - 1.11)	1.29	(1.18 - 1.41)	0.94	(0.80 - 1.10)	1.05	(0.97 - 1.15)	1.38	(1.13 - 1.70)
Individuals living in an urban area (%)	1.18	(1.15 - 1.21)	1.24	(1.16 - 1.33)	1.11	(1.05 - 1.17)	1.18	(1.09 - 1.28)	1.17	(1.13 - 1.22)	1.30	(1.15 - 1.48)
Population Density (log of persons/km^2)	0.98	(0.96 - 1.01)	1.03	(0.96 - 1.10)	1.02	(0.98 - 1.06)	0.92	(0.86 - 0.98)	1.11	(1.07 - 1.16)	0.89	(0.83 - 0.96)
Race (%)												
Black	1.06	(1.04 - 1.09)	1.10	(1.00 - 1.21)	1.08	(1.03 - 1.13)	1.03	(0.96 - 1.11)	1.07	(1.04 - 1.10)	1.04	(0.93 - 1.16)
Yellow	0.99	(0.98 - 1.01)	1.02	(0.99 - 1.05)	1.02	(1.00 - 1.04)	1.02	(0.96 - 1.09)	1.00	(0.94 - 1.06)	0.96	(0.87 - 1.06)
Brown	1.25	(1.19 - 1.31)	1.00	(0.86 - 1.16)	1.29	(1.21 - 1.38)	1.10	(0.94 - 1.29)	1.29	(1.21 - 1.38)	1.13	(0.95 - 1.35)
Indigenous	1.11	(1.09 - 1.13)	0.96	(0.88 - 1.05)	1.14	(1.07 - 1.21)	1.08	(1.05 - 1.11)	1.09	(1.05 - 1.14)	1.15	(1.09 - 1.21)
Undeclared	1.01	(1.00 - 1.03)	1.03	(0.95 - 1.11)	0.99	(0.94 - 1.04)	1.01	(0.97 - 1.05)	1.03	(1.00 - 1.05)	1.01	(0.92 - 1.12)
Household crowding (persons per bedroom)	1.17	(1.13 - 1.21)	1.50	(1.33 - 1.70)	1.26	(1.19 - 1.33)	1.09	(1.03 - 1.15)	1.18	(1.13 - 1.23)	1.28	(1.11 - 1.47)
SUS health facilities per capita	1.00	(0.98 - 1.02)	1.03	(0.97 - 1.10)	0.99	(0.95 - 1.04)	1.02	(0.97 - 1.07)	0.98	(0.95 - 1.02)	0.93	(0.85 - 1.01)
Doctors per capita	0.99	(0.98 - 1.01)	0.89	(0.86 - 0.94)	1.01	(0.99 - 1.03)	0.97	(0.84 - 1.12)	1.00	(0.97 - 1.03)	1.07	(0.98 - 1.16)
AIDS cases per capita	1.21	(1.19 - 1.24)	1.23	(1.20 - 1.27)	1.31	(1.27 - 1.35)	1.23	(1.12 - 1.36)	1.18	(1.12 - 1.25)	1.12	(1.01 - 1.24)
Tuberculosis cure rate (%)	1.06	(1.04 - 1.09)	1.00	(0.95 - 1.05)	1.06	(1.02 - 1.11)	1.15	(1.06 - 1.24)	1.09	(1.05 - 1.13)	1.07	(0.98 - 1.17)
Deviance Information Criteria (DIC)		21,345.3		3,655.2		6,642.0		2,099.2		8,018.7		1,636.6
Spatial Variance		0.140		0.011		0.010		0.028		0.010		0.015
Municipal-level non-spatial variance		0.003		0.010		0.011		0.010		0.009		0.011
State non-spatial variance		0.977		0.512		0.491		0.740		0.531		0.570
Global Moran's I		-0.001		0.182		0.205		-0.002		0.219		0.213
p-value		0.954		<0.001		<0.001		0.995		<0.001		<0.001

Regression coefficients are incidence rate ratios and 95% confidence intervals for a one-standard deviation change in the independent variable.

All independent variables were centred at their mean value and scaled by their standard deviation. Values for standard deviations provided in Table 2.

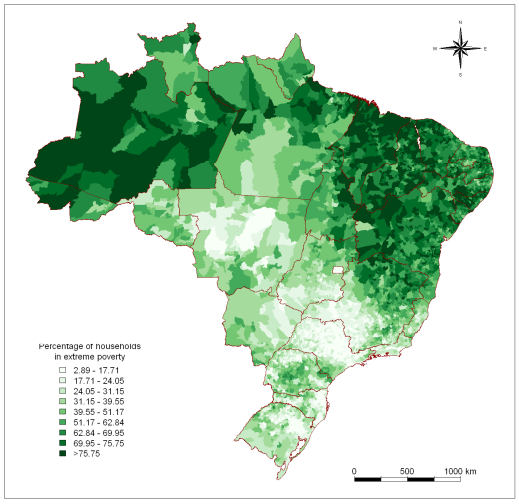
All models contain fixed effect indicator variables for States.

Supplementary Figure 1: Significant Local Moran's I results for municipal tuberculosis rates, by macroregion

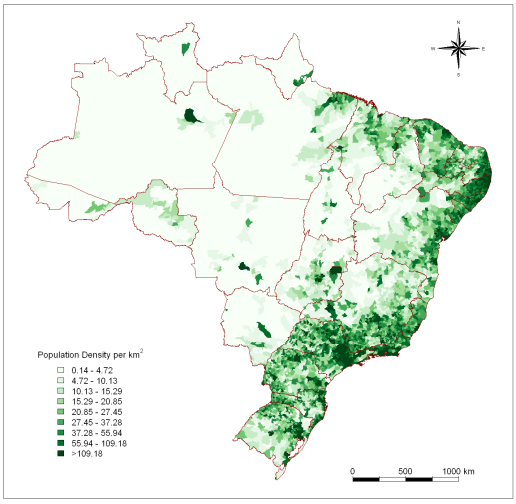


Tuberculosis cases notified between 2002 and 2009. Clustering tests based on municipal-level data. Municipalities shown as significant are those remaining after adjustment for multiple comparisons using the False Discovery Rate method. High-high indicates high rates clustered with neighbouring high rates; low-low, low rates with neighbouring low rates; low-high, low rates with neighbouring high rates; high-low, high rates with neighbouring low rates. Black lines delineate federal state boundaries. A presentation of these same data for the whole country in a single figure is made in Figure 4.

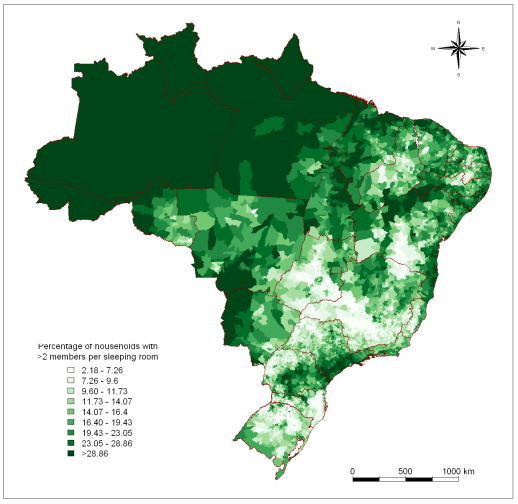
Supplementary Figure 2: **Spatial distribution of social and demographic covariates**



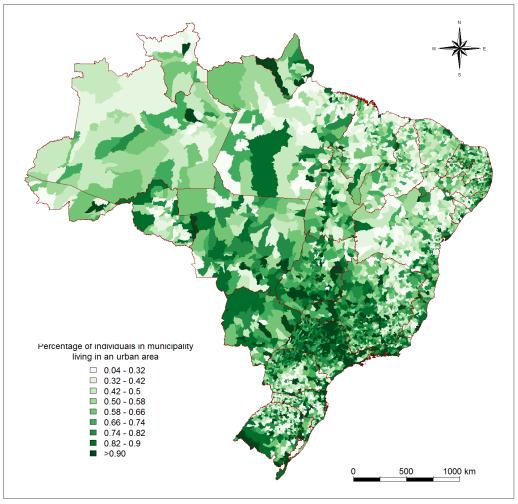
A



B



C



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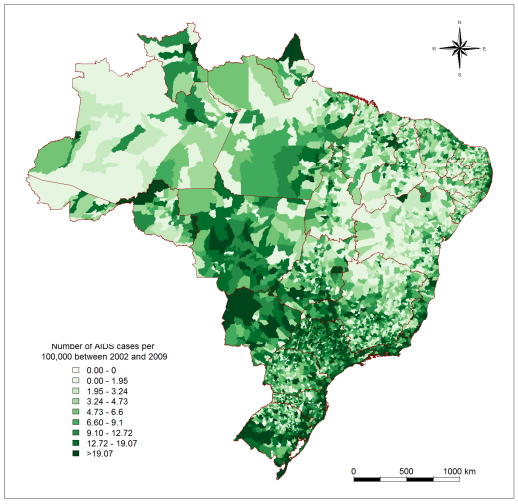

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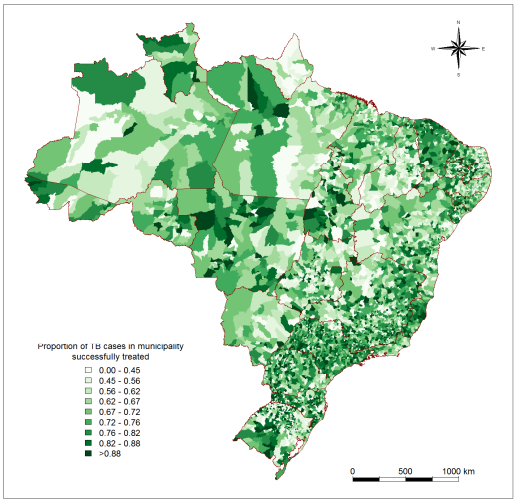
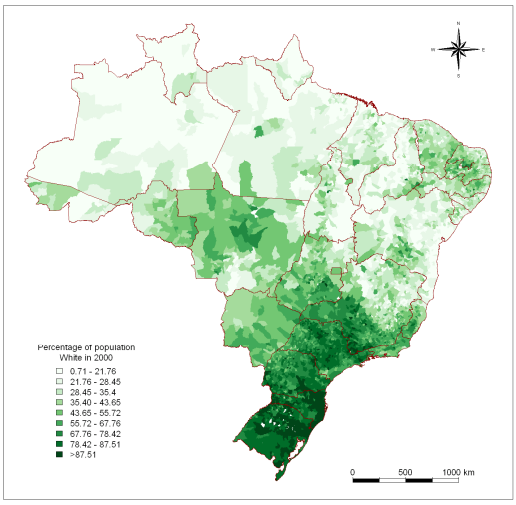
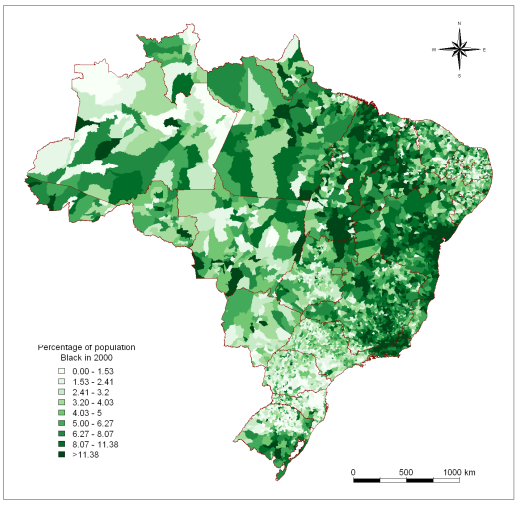


F

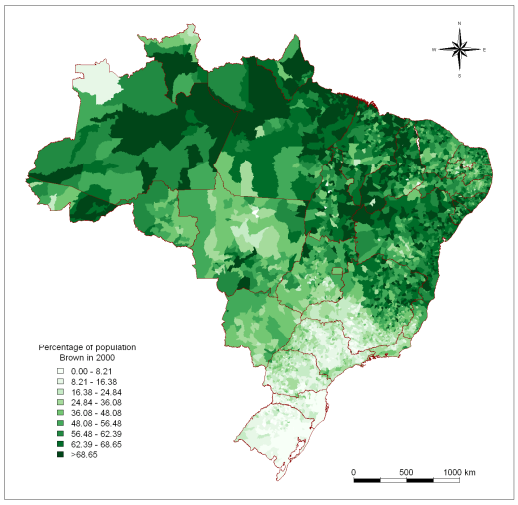
J


Percentage of population
White in 2000
0.71 - 21.76
21.76 - 28.45
28.45 - 35.4
35.40 - 43.65
43.65 - 55.72
55.72 - 67.76
67.76 - 78.42
78.42 - 87.51
>87.51
0
500
1000 km

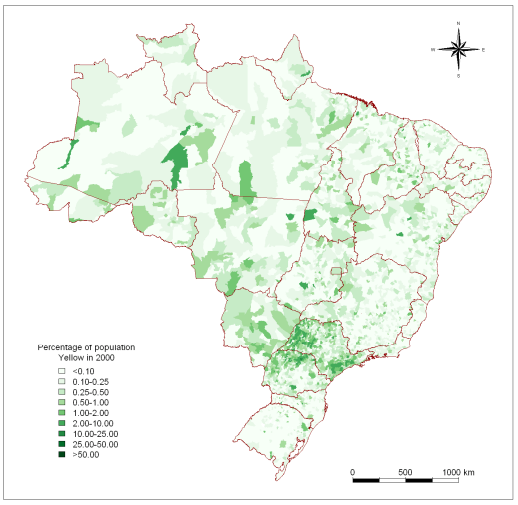
G


Percentage of population
Black in 2000
0.00 - 1.53
1.53 - 2.41
2.41 - 3.2
3.20 - 4.03
4.03 - 5
5.00 - 6.27
6.27 - 8.07
8.07 - 11.38
>11.38
0
500
1000 km

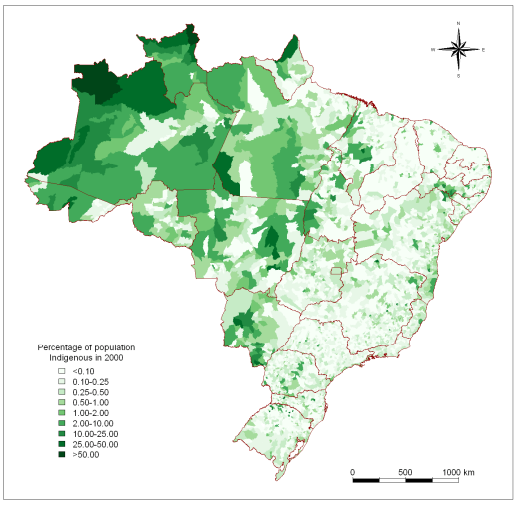
H


Percentage of population
Brown in 2000
0.00 - 8.21
8.21 - 16.38
16.38 - 24.84
24.84 - 36.08
36.08 - 48.08
48.08 - 56.48
56.48 - 62.39
62.39 - 68.65
>68.65
0
500
1000 km

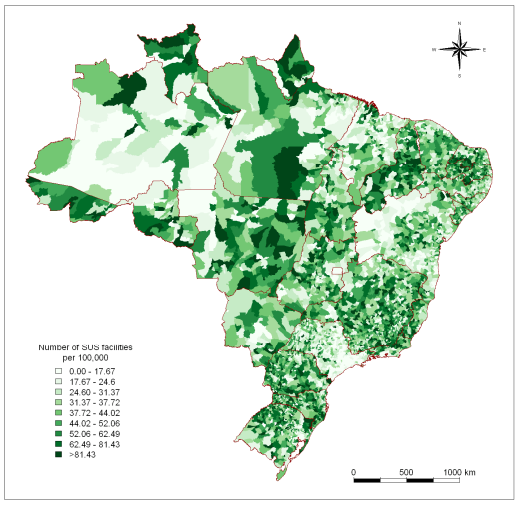
J


Percentage of population
Yellow in 2000
<0.10
0.10-0.25
0.25-0.50
0.50-1.00
1.00-2.00
2.00-10.00
10.00-25.00
25.00-50.00
>50.00
0
500
1000 km

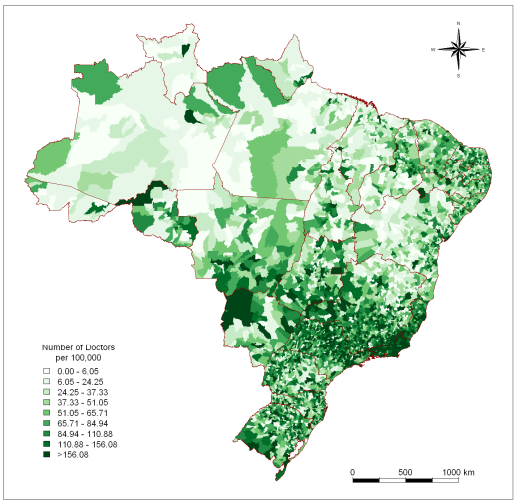
K


Percentage of population
Indigenous in 2000
<0.10
0.10-0.25
0.25-0.50
0.50-1.00
1.00-2.00
2.00-10.00
10.00-25.00
25.00-50.00
>50.00
0
500
1000 km

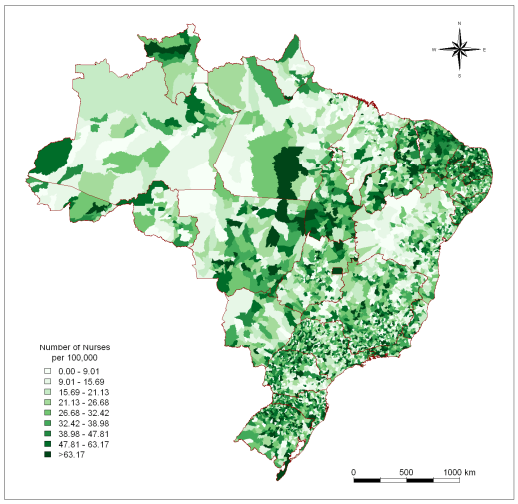
L


Number of SUS facilities
per 100,000
0.00 - 17.67
17.67 - 24.6
24.60 - 31.37
31.37 - 37.72
37.72 - 44.02
44.02 - 52.06
52.06 - 62.49
62.49 - 81.43
>81.43
0
500
1000 km

M



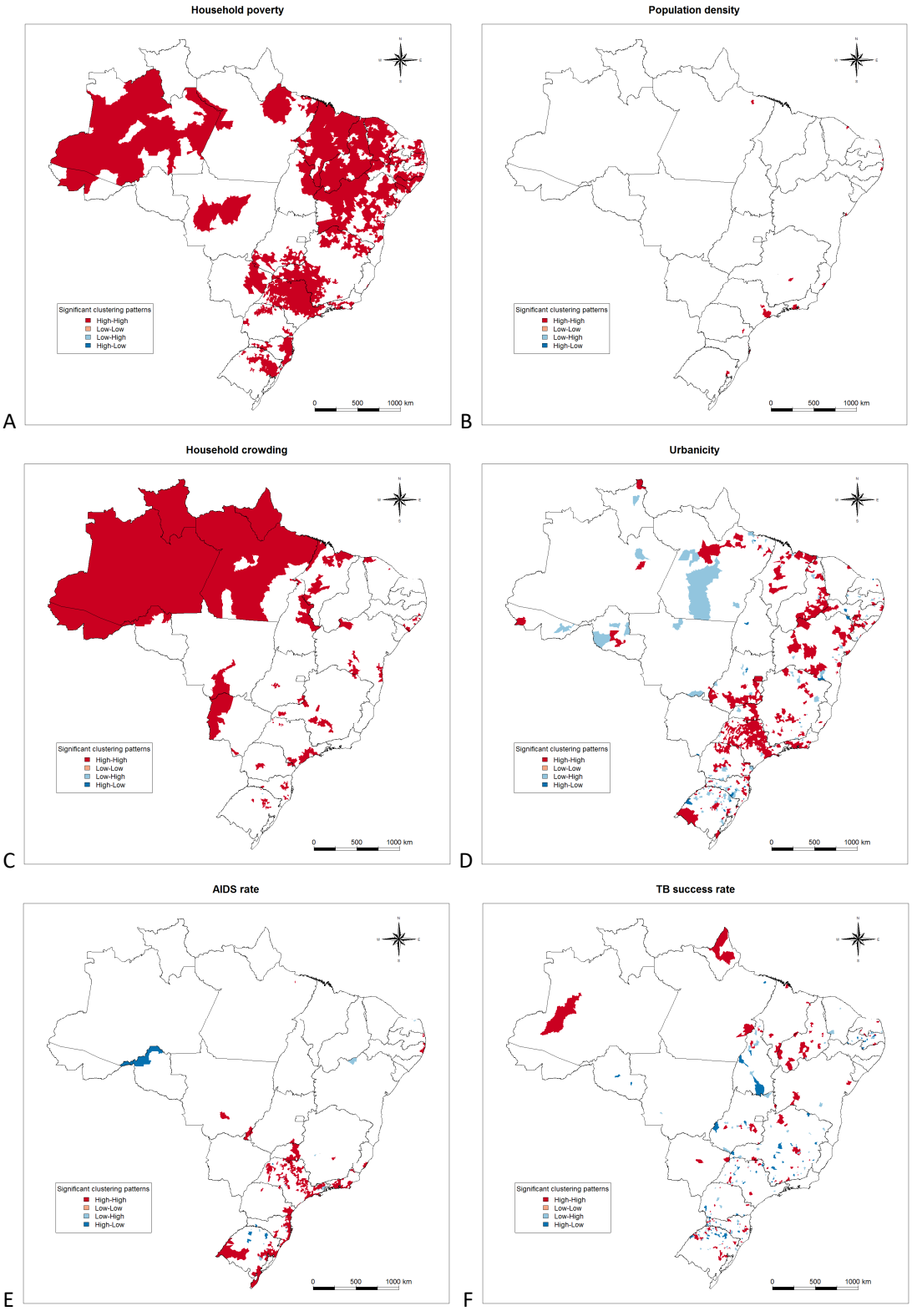
N



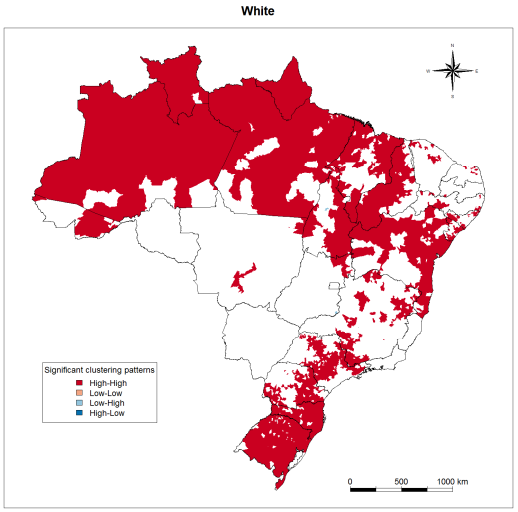
P

Red lines delineate federal state boundaries.

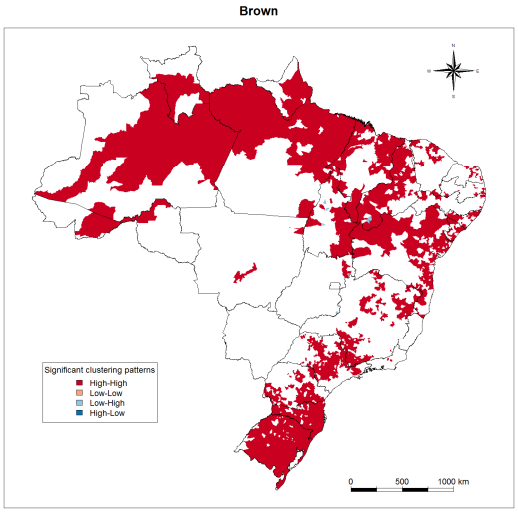
Supplementary Figure 3: Significant Local Moran's I results for social and demographic variables, after adjustment for multiple comparisons using the False Discovery Rate method



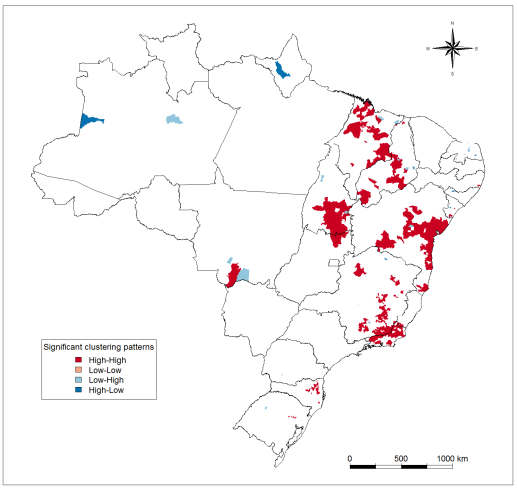
G


White
Significant clustering patterns
High-High
Low-Low
Low-High
High-Low
0
500
1000 km

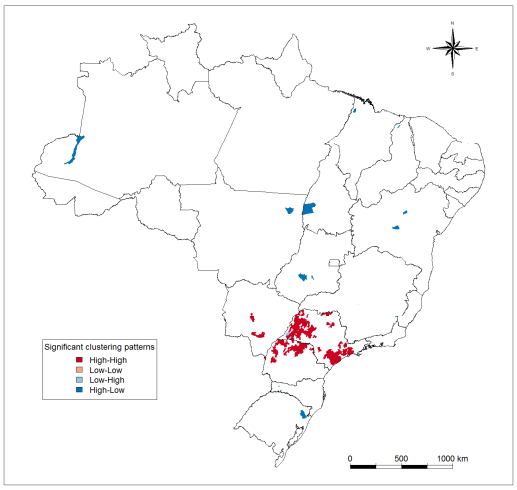
H


Brown
Significant clustering patterns
High-High
Low-Low
Low-High
High-Low
0
500
1000 km

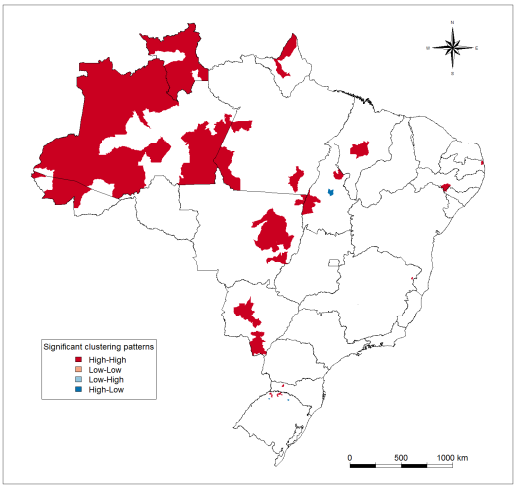
J


Black
Significant clustering patterns
High-High
Low-Low
Low-High
High-Low
0
500
1000 km

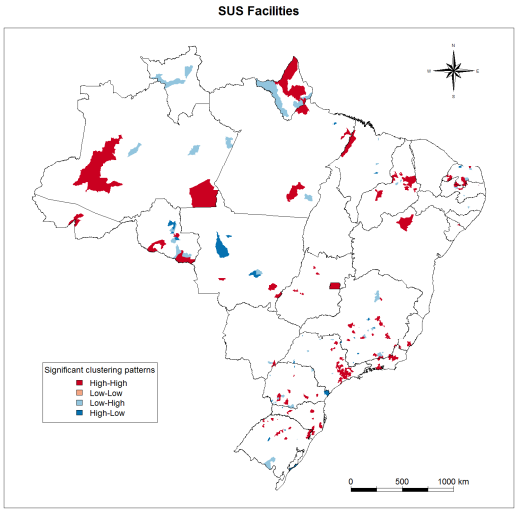
K


Yellow
Significant clustering patterns
High-High
Low-Low
Low-High
High-Low
0
500
1000 km

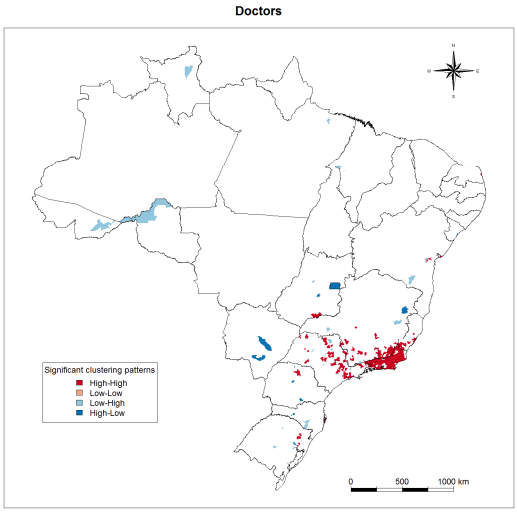
L


Indigenous
Significant clustering patterns
High-High
Low-Low
Low-High
High-Low
0
500
1000 km

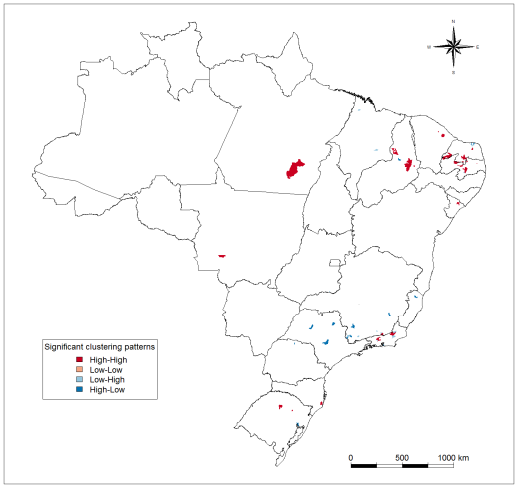
M



N



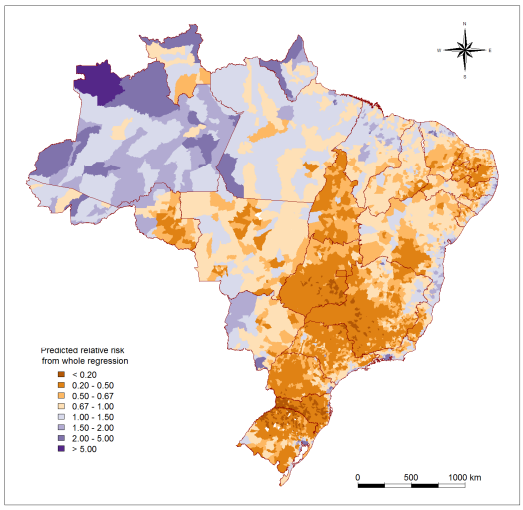
P



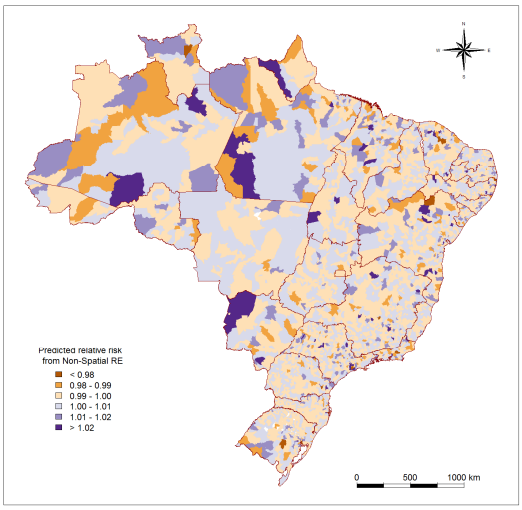
Note: Clustering tests based on municipal-level data. High-high indicates high rates clustered with neighbouring high rates; low-low, low rates with neighbouring low rates; low-high, low rates with neighbouring high rates; high-low, high rates with neighbouring low rates.

Black lines delineate federal state boundaries.

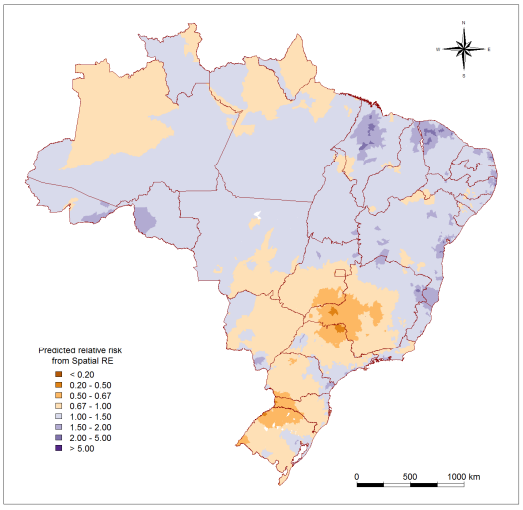
Supplementary Figure 4: Predicted relative risks for tuberculosis rates based on parameter estimates



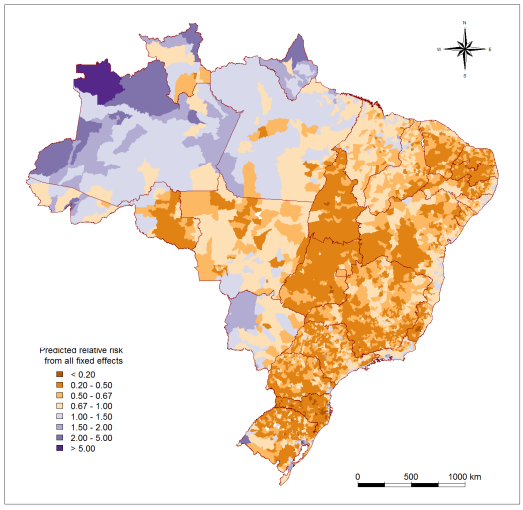
A



B



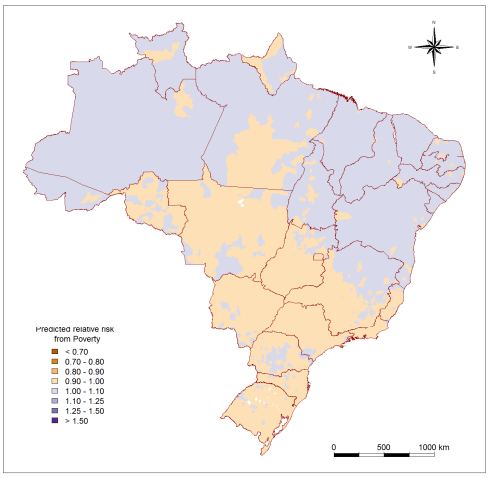
C



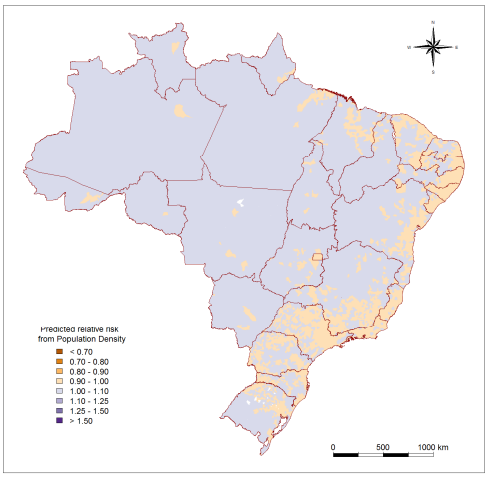
D

All results based on model 4 in Table 3. The reference category for all figures is the value of the mean municipality. 3A shows the prediction based on both fixed and random components of the model; 3B and 3C show respectively the non-spatial and spatial random effects; 3D shows the fixed effects alone.

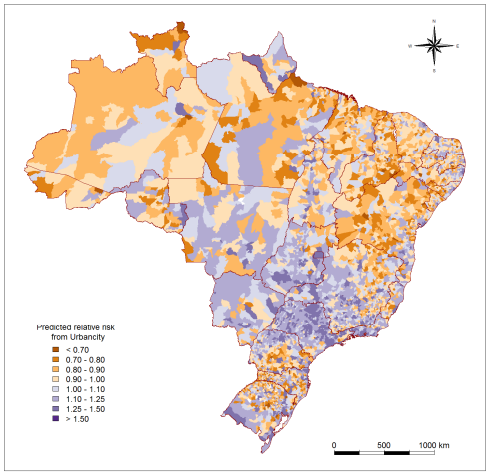
Supplementary Figure 5: Predicted relative risks for tuberculosis rates based on covariate values & parameter estimates



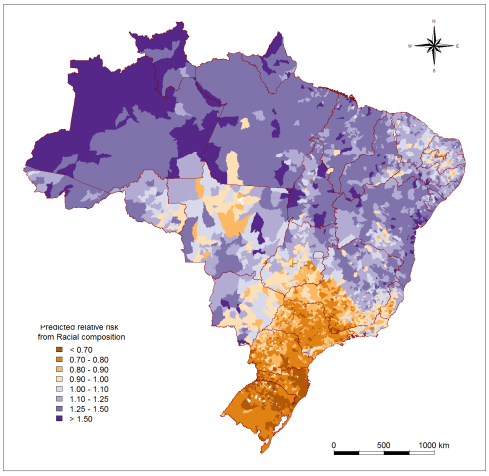
A



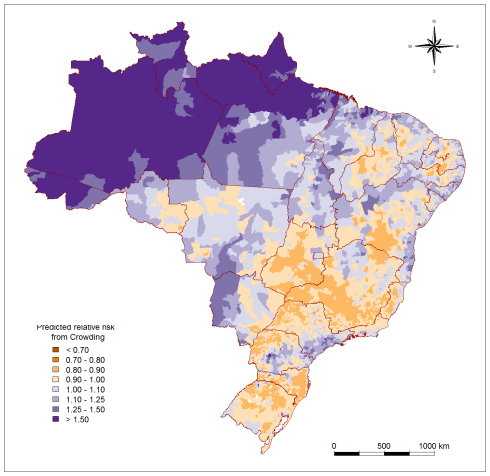
B



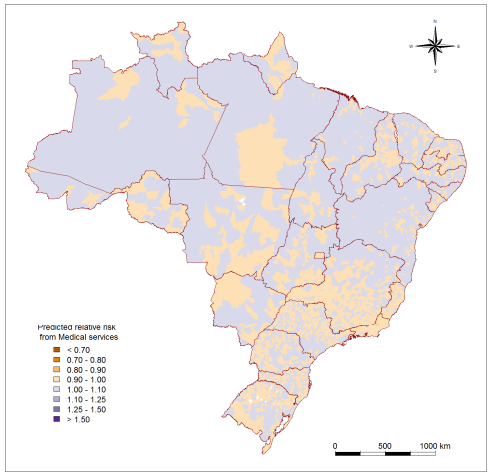
C



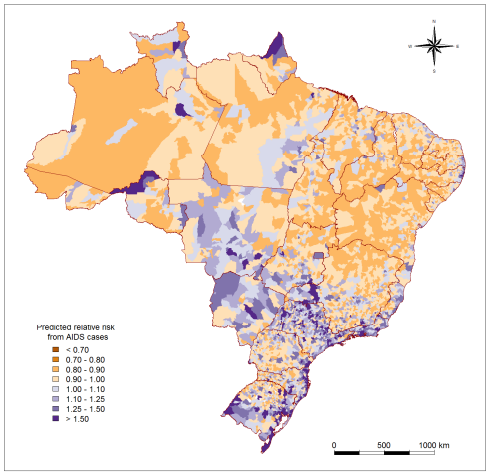
D



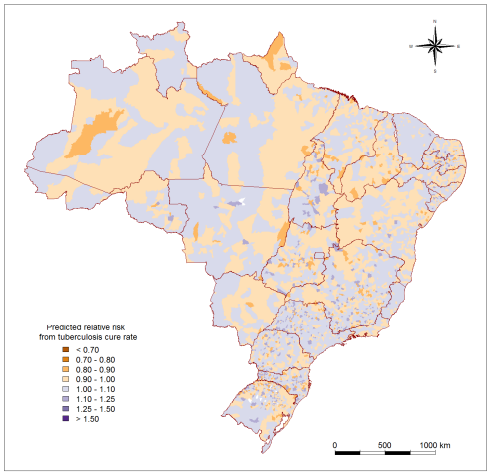
E



F



G



H

Note: All results based on model 4 in Table 3. For the State FE figure, the reference category is São Paulo; for all other figures the reference is the value of the mean municipality. Red lines delineate federal state boundaries.