

Spatial and Temporal Variations in Incidence of Tuberculosis in Africa, 1991 to 2005

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Abstract

Objective: To investigate the geographical and temporal distribution of tuberculosis in Africa in order to identify possible high-risk areas.

Design: Time-trend and spatial analyses.

Data sources: World Health Organization Statistical Information System and U.S. Census Bureau International Data Base.

Methods: Time trends in the 15-year study period from 1991 to 2005 were analyzed by Poisson regression models. Global Moran's I and Moran Local Indicators of Spatial Associations were used to test for evidence of global and local spatial clustering, respectively.

Results: Southern, Eastern and Middle Africa experienced an upward trend in the number of reported cases of tuberculosis (TB). The number of Northern African TB cases declined steadily over the 15-year study period. The spatial distribution of TB cases was nonrandom and clustered, with a Moran's I = 0.492 ($p = .001$). Spatial clustering suggested that 25 countries were at increased risk of tuberculosis, and ten countries could be grouped as "hot spots."

Conclusions: The study identified spatial and temporal patterns in tuberculosis distribution, providing a means to quantify explicit tuberculosis risks and laying a foundation to pursue further investigation into the environmental factors responsible for increased disease risk. This information is important in guiding decisions on tuberculosis control strategies.

Background

The World Health Organization (WHO) estimates that the largest number of new tuberculosis (TB) cases in 2005 occurred in the South-East Asia Region, which accounted for 34% of incident

cases globally. However, the estimated incidence rate in sub-Saharan Africa is nearly twice that of the South-East Asia Region, at nearly 350 cases per 100,000 population. It is estimated that 1.6 million deaths resulted from TB in 2005. Both the highest number of deaths and the highest mortality per capita are in the African region (WHO 2003, 2007b). Incidence (cases arising in a given time period) gives an indication of the burden of TB in a population and of the size of the task faced by a national TB control program (WHO 2007a). Incidence and prevalence of tuberculosis can change as the result of changes in transmission (the rate at which people become infected with *Mycobacterium tuberculosis*, the bacterium that causes TB) or changes in the rate at which people infected with *M. tuberculosis* develop the disease (e.g., as a result of changes in nutritional status or of HIV infection).

Millennium Development Goal 6, Target 8 is to “have halted by 2015 and begun to reverse the incidence of malaria and other major diseases” (including TB) (WHO 2007a). The WHO estimates that in 2005 the per-capita incidence of TB was stable or falling in six WHO regions and had peaked worldwide. However, the total number of TB cases was still rising slowly, because the caseload continued to grow in the African, Eastern Mediterranean and South-East Asian regions (Centers for Disease Control and Prevention [CDC] 1993; WHO 2003, 2007b). In common with international initiatives like the Millennium Development Goals (MDGs), numerous interventions have been instituted in Africa aimed at reducing the burden of tuberculosis. The challenge facing the control program is that the disease burden is not homogenous but varies geographically. Minimizing the risk of tuberculosis can be assisted by recognizing its geographical distribution and identifying areas of high risk. Policy makers and researchers often want to know the distribution of a disease incidence by geographical region or associated environmental factors. In addition, the success of any policy or healthcare intervention depends on a broader and accurate understanding of the socio-economic, environmental and cultural factors that determine the occurrence of disease and death (Kandala et al. 2006). The ability to map spatial and temporal variation in disease risk is more important than ever, given the ever-increasing disease burden in Africa (Tanser and Le Sueur 2002). In this regard, mapping and investigating risk variations in tuberculosis is an invaluable tool. Furthermore, mapping the variation in risk can help improve the targeting of scarce resources for public health interventions. With the above issues in mind, the objective of this study was to describe the geographical and temporal distribution of incidence of tuberculosis in Africa in order to identify countries with unusually high rates.

Methods

Data

This study primarily uses data from the WHO statistical information system (WHO 2008b) to describe the temporal and spatial variations in TB incidence in Africa. The data set includes the estimated number of TB cases reported between 1991 and 2005 (expressed as rate per 100,000 population per year). Estimates are based on annual case notifications, on special surveys of the prevalence of infection or disease and on information from death (vital) registration systems. All forms of TB, including cases in people with HIV, were included (WHO 2007a). Estimates of incidence, prevalence and mortality are based on a consultative and analytical process and are published annually (WHO 2008a). Estimates of the incidence of TB for each country are derived using one or more of four approaches, depending on the available data:

1. Incidence = case notifications/proportion of cases detected
2. Incidence = prevalence/duration of condition
3. Incidence = annual risk of TB infection \times blo coefficient
4. Incidence = deaths/proportion of incident cases that die

Available data differ from country to country but include case notifications and death records (from routine surveillance and vital registration) and measures of the prevalence of infection and disease

(from population-based surveys). Further details are available from Corbett and colleagues (2003), Dye and colleagues (1999, 2008) and the WHO (2008a). In addition, total mid year population data from 1991 to 2005 were compiled from the U.S. Census Bureau International Data Base (U.S. Census Bureau) for all African countries ($N = 53$).

Africa Sub-regions

For this study, Africa was divided into five sub-regions based on a combination of geographic, economic and scientific criteria. The sub-regions are Northern Africa, Western Africa, Middle Africa, Eastern Africa and Southern Africa.

Statistical Analyses

Estimation of Time Trend

Temporal patterns were displayed by plotting yearly TB cases against year. Time trends in the 15-year study period from 1991 to 2005 were analyzed by Poisson regression models. Specific counts for each calendar year were used as the unit of observation. Time-on-study was modelled as three different time periods, allowing time effects to be nonlinear. The tertiles were 1991 to 1995 (reference), 1996 to 2000, and 2001 to 2005. Time trend may differ across sub-regions.

The time-trend analysis was done in two steps. In the first approach, the analysis was carried out separately for each country. The Poisson regression procedure fits a model of the following form:

$$\log(tb) = \beta_1(cP_2) + \beta_2(cP_3) + \log(pop) \quad (1)$$

where tb equals number of cases of tuberculosis per year, β_1 and β_2 are trends, cP_2 and cP_3 are time-period (binary 0/1) 1996 to 2000 and 2001 to 2005, respectively, and $\log(pop)$ is an offset term for mid-year population.

In the second model, information on all five sub-regions was pooled into one data set and interaction effects between time trend and regional dummies were calibrated. Percentage changes were calculated using the following formula:

$$\text{Percent Change} = [\exp(\beta_j) - 1] \chi 100 \quad (2)$$

GIS Mapping and Smoothing

For conducting a GIS (geospatial information system)-based analysis on the spatial distribution of TB incidence, the country-level polygon map was obtained, on which the country-level point layer containing information regarding latitudes and longitudes of central points of each county was created. All TB cases were geocoded and matched to the country-level layers of polygon and point by administrative code using the software Stata *smap* routine (Pisati 2004). To alleviate variations of incidence in small populations and areas, annualized average TB cases per 100,000 at each administrative region over the 15-year period were calculated, and spatial rate smoothing was implemented. Based on annualized average incidence, all countries were grouped into four categories: non-endemic area, with annualized average incidence between 54 and 217 per 100,000; low-endemic area, with incidence between 217 and 267 per 100,000; medium-endemic area, with incidence between 267 and 314 per 100,000; and high-endemic area, with incidence greater than 267 per 100,000. The four categories of country were colour coded on maps. To assess the risk of TB in each country, an excess hazard map was produced. The map represents the ratio of the observed incidence for each country over the expected number of cases. A likelihood function was used to test for elevated risk within the country in comparison with risk outside the country. The likelihood function for any given country was proportional to

$$\left(\frac{d}{n}\right) d \left(\frac{[D-d]}{[D-n]}\right) (D-d) I(\cdot) \quad (3)$$

where D is the total number of TB cases, d is the number of TB cases within the country and n is the expected number of TB cases. The indicator function $I()$ is 1 when TB cases in the country are more than expected; otherwise it is 0. The excess risk is a nonspatial measure, which ignores the influence of spatial autocorrelation (Fang et al. 2006).

Spatial Autocorrelation Analysis

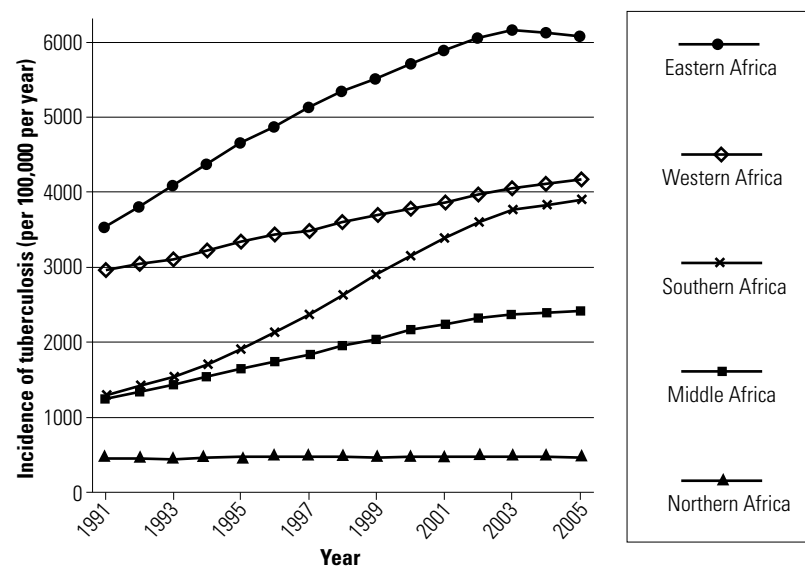
Global and Local Moran's I were used for evidence of global and local spatial clustering, respectively. The index fast becoming the standard tool to examine local autocorrelation is Luc Anselin's LISA (local indicator of spatial association), which can be seen as the local equivalent of Global Moran's I . The spatial weight was determined using first order queen contiguity (i.e., all common points including boundaries and verticals were included in the neighbour definition). LISA values allow for the computation of each location's similarity with its neighbours and also test its significance. Inference for Moran's I was based on a permutation approach in which a reference distribution is calculated for spatially random layouts with the same data as observed. The number of permutation tests was set to 999 and significance level was set as .001.

Results

Temporal variability

Figure 1 depicts the trends of reported cases of tuberculosis in the period 1991 to 2005. Eastern Africa ranked first in absolute upward trend in number of reported cases of TB, followed by Western and Southern Africa. The Northern Africa trend declined during the study period. Poisson regression analyses confirmed a continuous increase in the number of reported cases of TB in all African sub-regions except Northern Africa (Table 1).

Figure 1. Temporal trends in tuberculosis cases, African sub-region, 1991 to 2005



Compared to the reference period (1991 to 1995), incidence risk ratios in the years 1996 to 2000 and 2001 to 2005 were 1.56 (95% CI 1.52 to 1.60) and 2.12 (95% CI 2.07 to 2.18) for Southern Africa, respectively. This equates to a total increase of 55.9% and 112.0% in the number of reported cases of tuberculosis between 1991 and 2000 and 1991 and 2005, respectively. Total increases of

14.9% and 24.5% in the number of reported cases of tuberculosis were found for Eastern and Middle Africa between 1991 and 2005, respectively. The time-trend analysis was not significant for Western Africa. Compared with the reference period (1991 to 1996), incidence risk ratios in the years 1996 to 2000 and 2001 to 2005 were 0.92 (95% CI 0.87 to 0.97) and 0.82 (0.77 to 0.87) for Northern Africa respectively. This equates to a decrease of -8.2% and -17.9% in the number of reported cases of tuberculosis between 1991 and 2000 and between 1991 and 2005, respectively. Table 2 shows the results of time-trend analysis for the pooled cross-regional analysis. As expected, the effect of time trend varied across sub-regions. The cross-region variability in time trend observed is similar to those when the analysis was done separately for each sub-region (Table 1).

Table 1. Temporal trends in tuberculosis cases by sub-regions in Africa, 1991 to 2005

	Incidence rate ratio (95% CI) / percent change			<i>p</i> -value
	1991–1995	1996–2000	2001–2005	Linear trend
All Africa	1 (reference)	1.16 (1.14–1.17) 15.7	1.23 (1.22–1.24) 22.9	.001
Sub-regions				
Eastern Africa	1 (reference)	1.14 (1.12–1.16) 13.8	1.15 (1.13–1.17) 14.9	.001
Western Africa	1 (reference)	1.01 (0.99–1.03) 1.1	1.00 (0.98–1.02) -0.1	.448
Southern Africa	1 (reference)	1.56 (1.52–1.60) 55.9	2.12 (2.07–2.18) 112.0	.001
Middle Africa	1 (reference)	1.18 (1.15–1.22) 18.1	1.24 (1.21–1.28) 24.5	.001
Northern Africa	1 (reference)	0.92 (0.87–0.97) -8.2	0.82 (0.77–0.87) -17.9	.001

Spatial Distribution of Tuberculosis in Africa

The median annualized average incidence of tuberculosis at the country level was 243.0 (range: 23.4 to 628.5) per 100,000 population per year. Among the 53 countries (excluding the Western Sahara), 14 countries were non-endemic, with annualized average incidence between 54 and 217 per 100,000; 13 were low-endemic, with incidence between 217 and 267 per 100,000; 13 were medium-endemic, with incidence between 267 and 314 per 100,000; and 13 were high-endemic, with incidence greater than 267 per 100,000. The four type areas were displayed in the thematic map as shown in Figure 2. A spatially smoothed percentile map of annualized average incidence was created; smoothed incidence presents a better pattern and shows clearly where the problem is most severe (Figure 2). The incidence of tuberculosis was particularly high in Southern and Eastern Africa but lower in Northern and Western Africa. The excess hazard map showed distribution of the excess risk, which was defined as a ratio of the observed number over the expected number of cases. Countries marked blue had lower incidences than expected, as indicated by excess risk values less than 1. In contrast, countries in red and light yellow had incidences higher than expected, with risk values greater than 1 (Figure 3).

Spatial Autocorrelation of Tuberculosis in Africa

Global spatial autocorrelation analyses for annualized incidence of tuberculosis in Africa from 1991 to 2005 showed that the Moran's I was significant (.001 significance level) for each year (Table 3).

Table 2. Temporal trends in tuberculosis cases: main and interaction effects for Africa sub-regions, 1991 to 2005

Variable	Incidence risk ratio (95% CI)	Percent change
Main effect		
<i>Region</i>		
Northern Africa	1 (reference)	
Eastern Africa	6.33 (6.05, 6.62)***	137.7
Middle Africa	5.79 (5.52, 6.08)***	94.4
Southern Africa	12.90 (12.29, 13.54)***	112.6
Western Africa	5.26 (5.03, 5.51)***	115.3
<i>Time trend</i>		
1991–1995	1 (reference)	
1996–2000	1.03 (0.97, 1.09)	2.7
2001–2005	1.02 (0.96, 1.08)	1.9
Interaction effects		
1996–2000 X Eastern Africa	1.26 (1.19, 1.35)***	7.6
1996–2000 X Middle Africa	1.31 (1.23, 1.41)***	6.6
1996–2000 X Southern Africa	1.63 (1.52, 1.74)***	9.0
1996–2000 X Western Africa	1.12 (1.05, 1.20)***	3.5
2001–2005 X Eastern Africa	1.46 (1.37, 1.55)***	12.4
2001–2005 X Middle Africa	1.61 (1.50, 1.72)***	11.7
2001–2005 X Southern Africa	2.31 (2.16, 2.46)***	15.9
2001–2005 X Western Africa	1.27 (1.19, 1.35)***	7.4

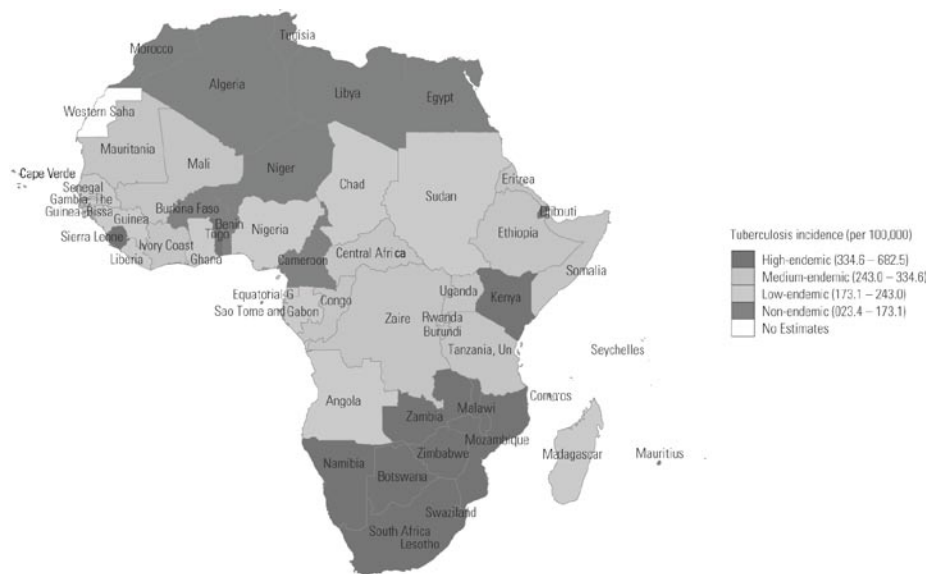
*** $p < .001$.**Table 3. Global spatial autocorrelation analyses for annualized incidence of tuberculosis in Africa, 1991 to 2005**

Year	Moran's I	$E(I)$	p -value
1991	0.304	-0.021	.001
1992	0.343	-0.018	.001
1993	0.379	-0.021	.001
1994	0.426	-0.023	.001
1995	0.469	-0.014	.001
1996	0.507	-0.019	.001
1997	0.528	-0.019	.001

1998	0.538	-0.019	.001
1999	0.525	-0.019	.001
2000	0.512	-0.018	.001
2001	0.495	-0.023	.001
2002	0.480	-0.014	.001
2003	0.458	-0.019	.001
2004	0.428	-0.015	.001
2005	0.380	-0.018	.001

The results of Local Moran's I show statistically significance spatial autocorrelation (Moran's I = 0.492, $p = .001$) (Figure 4). Southern and some parts of Eastern Africa belong to High-high (hot-spot) clusters. These are locations with a higher incidence of tuberculosis with similar neighbours. The locations marked in blue belong to Low-low (cold-spot) clusters. These are countries with a low incidence of tuberculosis with similar neighbours. Madagascar is the only country in a Low-high cluster, potential an outlier. In order words, Madagascar is a country with a low incidence of tuberculosis and with high-incidence neighbours. The other countries marked in white are locations with no statistically significant autocorrelation.

Figure 2. Spatially smoothed percentile map of annualized average incidence of tuberculosis in Africa, 1991 to 2005



No estimates are available for the Western Sahara.

Discussion

Temporal Variability

The number of reported cases of tuberculosis increased yearly in Africa. Trends varied markedly among African sub-regions. The study found a total increase of 112.0%, 24.5% and 14.9% in the number of reported cases of tuberculosis between 1991 and 2005 for Southern, Middle and Eastern

Africa respectively. Tuberculosis cases in Northern Africa declined steadily over the study period. Possible explanations for the reported temporal trends are that they are due mainly to changes in the distribution of causal factors, changes in diagnostic or registration practices, or just chance. Another explanation could be the HIV/AIDS epidemic. That the HIV/AIDS epidemic may have fuelled the current high levels of tuberculosis disease in sub-Saharan Africa has been established in the literature (Corbet et al. 2003; Evans et al 2004; Lawn, Bekker et al. 2006; Lawn et al. 2002; Lawn, Myer et al. 2006). HIV infection is a potential risk factor for tuberculosis (Corbet et al. 2003). Not only does HIV increase the risk of reactivating latent *M. tuberculosis* (MTB) infection (Bucher et al. 1999); it also increases the risk of rapid tuberculosis progression soon after infection or re-infection with MTB (Daley et al. 1992; Shafer et al. 1995). A TB-control strategy based on the directly observed treatment, short-course (DOTS) strategy has failed to contain the African TB epidemic, primarily because of the effects of the HIV epidemic in the region (Lawn, Bekker et al. 2006).

Figure 3. Excess hazard map of annualized average incidence of tuberculosis in Africa, 1991 to 2005



No estimates are available for the Western Sahara.

Spatial Variability

In the study, exploratory spatial data analysis and spatial cluster analysis of tuberculosis were conducted at country level in Africa. Tuberculosis cases were mapped from different aspects such as crude incidence, excess risk and spatially smoothed incidence. In addition, the study evaluated spatial patterns and highlighted geographic areas with a significantly high incidence of tuberculosis in Africa. Spatial empirical Bayesian smoothing of disease rates was chosen because it utilizes three kinds of information to estimate an area's disease rate: (1) the observed disease events in an area, (2) prior information on the variability of disease rates in the overall map, and (3) information on the disease rates in an area's neighbours, since geographically close areas tend to have similar rates of disease (Tobler 1970). Moran's I is a weighted correlation coefficient used to detect departures from

spatial randomness (Moran 1950). Departures from randomness indicate spatial patterns such as clusters. The statistic may identify other kinds of patterns such as geographic trend. The Moran's I statistic is a measure of autocorrelation, similar in interpretation to the Pearson's Product Moment correlation statistic for independent samples in that both statistics range between -1.0 and 1.0, depending on the degree and direction of correlation (Anselin 1995; Ord and Getis 1995).

The study showed that the spatial distribution of tuberculosis in Africa was nonrandom and clustered with a Moran's I of 0.492 ($p = .001$) from 1991 through 2005. Through exploratory spatial analyses, the study was able to pinpoint geographic areas with higher risk and to assess temporal variability of the risk areas, thus providing a working hypothesis on risk of tuberculosis and environmental exposures. Geographic areas with higher cases of tuberculosis need further epidemiologic investigation for potential relationships between lifetime environmental exposures and risk of tuberculosis.

Figure 4. Local Indicator of Spatial Association (LISA) cluster map for annualized average incidence of tuberculosis in Africa, 1991 to 2005



No estimates are available for the Western Sahara

Conclusions

This study has shown the presence of hot spots of tuberculosis in Africa, providing more information on priority areas for public health planning and resource allocation for preventing tuberculosis. The study has also demonstrated that using existing health data, GIS and GIS-based spatial statistical techniques could provide an opportunity to clarify and quantify the health burden from tuberculosis within highly endemic areas and also lay a foundation to pursue further investigation into the environmental factors responsible for increased disease risk. To implement specific and geographically appropriate risk-reduction programs, the use of such spatial analysis tools should become an integral component in the epidemiological description and risk assessment of tuberculosis.

Competing Interests

None

Authors' Contributions

OAU conceived the study, extracted the data, did the analyses and interpretation, and wrote the first draft of the manuscript.

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