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Heterogeneity of distribution of tuberculosis in Sheka Zone, Ethiopia: drivers and temporal trends

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SUMMARY

OBJECTIVE: To describe the distribution of tuberculosis (TB) and its drivers in Sheka Zone, a geographically remote region of Ethiopia.

METHODS: We collected data on TB patients treated from 2010 to 2014 in the Sheka Zone. Predictors of TB incidence were determined using a multivariate generalised linear regression model.

RESULTS: We found significant spatial autocorrelation of TB incidence by *kebele* (the smallest administrative geographical subdivision in Ethiopia) (Moran's $I = 0.3$, $P < 0.001$). The average TB incidence per *kebele* ranged from 0 to 453 per 100 000 population per year, and was significantly associated with average TB incidence across adjacent *kebeles*, TB incidence in the same *kebele* in the previous year and health facility availability. Each increment in TB incidence by 10/100 000/year in adjacent *kebeles* or in a previous year was associated with an increase in TB incidence of respectively 3.0 and 5.5/100 000/year. Availability of a health centre was associated with an increase in TB incidence of 84.3/100 000.

CONCLUSIONS: TB incidence in rural Ethiopia is highly heterogeneous, showing significant spatial autocorrelation. Both local transmission and access to health care are likely contributors to this pattern. Identification of local hotspots may assist in developing and optimising effective prevention and control strategies.

KEY WORDS: epidemiology; cluster analysis; transmission; tuberculosis

DESPITE CHANGES to public health policy and the adoption of the DOTS strategy some decades ago, Ethiopia has remained a high tuberculosis (TB) burden country.[1] Although about 85% of TB cases in Ethiopia occur in rural and pastoralist areas, the epidemiology of TB in geographically remote regions remains incompletely described.[2] Previously published epidemiological studies on TB in Ethiopia often focus on areas close to major zonal, regional or national capital cities.[3–5] However, a comprehensive understanding of the TB epidemiology in both centrally located and less accessible areas is critical in guiding effective TB control efforts.

Past studies have shown heterogeneity in the spatio-temporal distribution of TB,[6–8] while increased TB rates have been linked to population density,[6,7,9] poverty,[10,11] human immunodeficiency virus (HIV),[12–14] urban residence[15] and social gatherings.[7] Available studies have documented both presence and persistence of high TB rates in some geographical regions of Ethiopia,[6,8] although factors leading to the establishment and perpetuation of these heterogeneities are not fully understood.

In the present study, we aimed to understand the geographical and temporal distribution of TB and explore likely drivers using case records from a cohort of TB patients in a geographically inaccessible zone of Ethiopia.

METHODS

Setting

We collected data on TB patients registered for TB treatment from 2010 to 2014 in Sheka Zone, Southern Nations, Nationalities and Peoples Region (SNNPR), Ethiopia. Sheka Zone is geographically inaccessible (695 km away from the national capital, Addis Ababa, and 970 km from the regional capital, Hawassa) and is thus lacking basic facilities and infrastructure. Census data indicate a zonal population of 199 671 in 2007, projected to have increased to 247 815 in 2014.[16] Sheka Zone is divided into

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three administrative districts, which are further divided into 66 *kebeles,* the smallest geographical administrative units in Ethiopia, typically used as the address of all individuals residing there, with populations ranging from hundreds to thousands; the median *kebele* population in Sheka Zone is 2200. Although Sheka Zone is geographically remote, all *kebeles* in the administrative capitals of each district were treated as urban centres. In urban areas, *kebeles* represent neighbourhoods, while in rural areas they include both habitable and uninhabitable areas (farm lands and forests). The population density of the three districts varies widely: respectively 27.4, 62.9 and 263.0 persons per km^2 in Masha (northern), Andraccha (central) and Yeki (southern).[17]

Sheka Zone is served by 13 health centres, although during the study period only seven had functional laboratories for TB sputum smear microscopy and none had access to X-ray or culture facilities. TB diagnosis and treatment is based on Ethiopia's national TB treatment guidelines,[18] according to which patients with symptoms suggestive of pulmonary TB are considered smear-positive if at least two of three sputum samples are smear-positive. Patients with negative sputum smears who fail to respond to treatment with broad-spectrum antibiotics are considered to have smear-negative pulmonary TB,[19] although the diagnosis of smear-negative and extrapulmonary cases also incorporates clinical judgement.

Patients diagnosed with TB are registered in a TB Unit Register for DOTS at their presenting health facility; information on name, *kebele* of residence, age, sex, weight, sputum smear result, TB type, TB category, HIV status, use of chemoprophylactic therapy (cotrimoxazole and isoniazid), antiretroviral treatment (ART) status, anti-tuberculosis treatment regimen, treatment outcome and dates of treatment initiation and treatment outcome are recorded.

Data collection

Data on all TB patients diagnosed and/or treated from 2010 to 2014 at all health centres in the Zone were collected from TB Unit registers by TS, a faculty member of Jimma University, Ethiopia. As patients are entered sequentially in Unit registers, where treatment commencement dates were incomplete we used the midpoint between the start dates of the adjacent registered patients. Data from health centres with power supply were directly entered into EpiData 3.2 (EpiData Association, Odense, Denmark); data from health centres that lacked power supply were transferred to a standardised data entry pro forma and then transferred to EpiData. Where *kebeles* of residence on TB Unit register did not match the names in a shape file, official names known to the Central Statistical Agency (CSA) were used after confirmation from local authorities. Data were analysed using Stata 13.1 (College Station, TX, USA) and ArcMap 10.2.2 (Environmental Systems Research Institute, Redlands, CA, USA).

Polygon shape files for *kebeles* were obtained from the CSA of Ethiopia and used for mapping and area calculations, with aggregate patient-level information then linked to these polygons. The annual projected population based on the 2007 census was used for population density calculation and as the denominator for incidence rate calculations.[20]

Approach to analysis

To obtain an overview of the true geographical distribution of the disease in Sheka Zone, we included only cases of TB diagnosed in residents of the Zone. We calculated attributes of *kebeles,* including overall TB case counts, total population, population density and TB incidence. We evaluated whether the average TB incidence rate per *kebele* over the 5-year period was spatially autocorrelated using global Moran's *I*. Generalised multivariate linear regression (Gaussian family with identity link) was performed to determine predictors of TB incidence. The outcome considered was TB incidence in each *kebele* in each year from 2011 to 2014, with the following predictor variables: health facility availability, population density, average TB incidence rate in adjacent *kebeles* in the same year, TB incidence rate in the previous year in the same *kebele* (including 2010), and proportion of presenting TB cases co-infected with HIV. Analogous models were developed for the outcome of smear-positive TB by year and *kebele,* with the same set of exposure variables. A multivariate model in which all covariates were initially included, but then excluded by backward elimination, is presented. All predictors not significant at $P < 0.05$ were eliminated from the final model, with the variable with the greatest P value dropped first. As we considered that treatment outcomes were less likely to be spatially correlated, we used Pearson's χ^2 to compare among *kebeles*.

The study was approved by the Melbourne University Health Sciences Human Ethics Subcommittee, Melbourne, VIC, Australia, and the Zonal Health Department, Sheka Zone, Masha, Ethiopia.

RESULTS

Patient characteristics

Among 1732 TB patients diagnosed and treated from 2010 to 2014 in all health facilities, 1683 were resident in 55 *kebeles* in Sheka Zone and were included in the final analysis. Virtually all the remaining TB patients ($n = 49$, 2.8%) were from the neighbouring province (Gambella), and were excluded from further analysis.

The majority of the patients included were male (57.8%), young to middle-aged adults from urban *kebeles*. Pulmonary TB comprised around three

Table 1 Demographic and clinical characteristics of TB patients, Sheka Zone, Ethiopia, 2010–2014 ($n = 1683$)

Variables	*n* (%)
Sex	
Male	972 (57.8)
Female	711 (42.2)
Residence	
Urban	894 (53.1)
Rural	789 (46.9)
Age, years ($n = 1681$)*	
0–4	28 (1.7)
5–14	150 (8.9)
15–24	504 (30.0)
25–34	519 (30.8)
35–64	430 (25.6)
⩾65	50 (3.0
Type of TB	
Pulmonary, smear-positive	605 (36.0
Pulmonary, smear-negative	643 (38.2
Extra-pulmonary	435 (25.8
TB category	
New	1510 (89.7)
Retreatment	37 (2.2)
Transferred in	136 (8.1)
HIV status ($n = 1669$)*	
Positive	221 (13.1)
Negative	1448 (86.1)

* Variation in totals due to unreported age and HIV status.
TB = tuberculosis; HIV = human immunodeficiency virus.

quarters of all notified TB cases and was evenly split between smear-negative and smear-positive. Most patients did not report past anti-tuberculosis treatment (Table 1).

HIV prevalence among TB patients in the Zone was 13.2% and was comparable for both new and retreatment cases (13.0% vs. 15.0%, $P = 0.7$, two-sample test of proportions). The proportion of smear-positive TB was significantly lower among TB-HIV co-infected patients than among HIV-negative TB patients (28.5% vs. 37.2%, $P = 0.012$, two-sample test of proportions).

Temporal and geospatial distribution

Figure 1 shows choropleth maps of distribution by *kebele* of population, health facilities (overall and with TB laboratory facilities), population density, average TB incidence and child TB incidence. This visually demonstrates the spatial autocorrelation and the higher incidence rates observed in *kebeles* with functional health centres. The distribution of both paediatric TB and overall TB followed similar patterns in the Zone. Average TB incidence rate per *kebele* ranged from 0 to 453/100 000/year (Figure 1). The percentage of *kebeles* with a TB incidence rate of ⩾200/100 000 over the 5-year period was substantial, ranging from 7.6% in 2010 to 18.2% in 2014 (Figure 2).

Overall, TB incidence in Sheka Zone increased from 111 to 151/100 000 over the study period. In this study, both the overall TB incidence and child TB incidence exhibited significant spatial autocorrelation (Moran's $I = 0.28$ overall, 0.34 child, two-sided $P < 0.001$ overall, <0.001 child). Both overall TB incidence and sputum smear-positive TB incidence exhibited significant spatial autocorrelation by *kebele* for each study year except for 2011, with Moran's I ranging from 0.23 to 0.30.

Treatment success (cure plus completion) showed significant difference by *kebele* ($P = 0.001$, Pearson's χ^2 based on Monte Carlo simulation), although an analogous analysis showed no statistically significant difference in treatment outcome by access to diagnosis and treatment ($P = 0.9$, Pearson's χ^2).

Regression analysis

Availability of a health centre, average TB incidence in adjacent *kebeles* and TB incidence in the previous year significantly predicted overall TB incidence in the index *kebele* on both univariate and multivariate regression analysis (Table 2). Although population density appeared significant on univariate analysis, this variable was eliminated from the multivariate model. In the analogous analysis for smear-positive TB incidence, population density as well as all other variables significantly associated with overall TB incidence emerged as significant predictors (results not shown).

Availability of a functional health centre in a *kebele* was associated with an increase of 84/100 000 in TB incidence on multivariate regression, while an increase of 10/100 000 in average TB incidence in adjacent *kebeles* predicted a 3.0/100 000 increment in TB incidence in an index *kebele*. Similarly, an increase of 10 cases/100 000 in a given year predicted 5.5 cases/100 000 in the subsequent year in the same *kebele*. Population density and proportion of TB cases with HIV were not related to TB incidence in the multivariate model. Overall, the model explained 50.6% (adjusted $R^2 = 0.506$) of the variation in the average TB incidence rate.

DISCUSSION

We found that TB distribution in Sheka Zone, a remote region of Ethiopia, is highly heterogeneous, with incidence ranging widely from 0 to 453/100 000/year, and demonstrating significant spatial autocorrelation. TB incidence was associated with TB incidence in adjacent *kebeles*, TB incidence in the previous year and proximity of health facilities, suggesting roles for intense transmission within 'hotspots' and care access as important potential drivers. While broad demographic and epidemiological parameters reported here, such as proportion of new and retreatment TB, are similar to those observed in previous studies in other Ethiopian contexts, our study presents detailed consideration of geospatial drivers of incidence heterogeneity.[3,21]

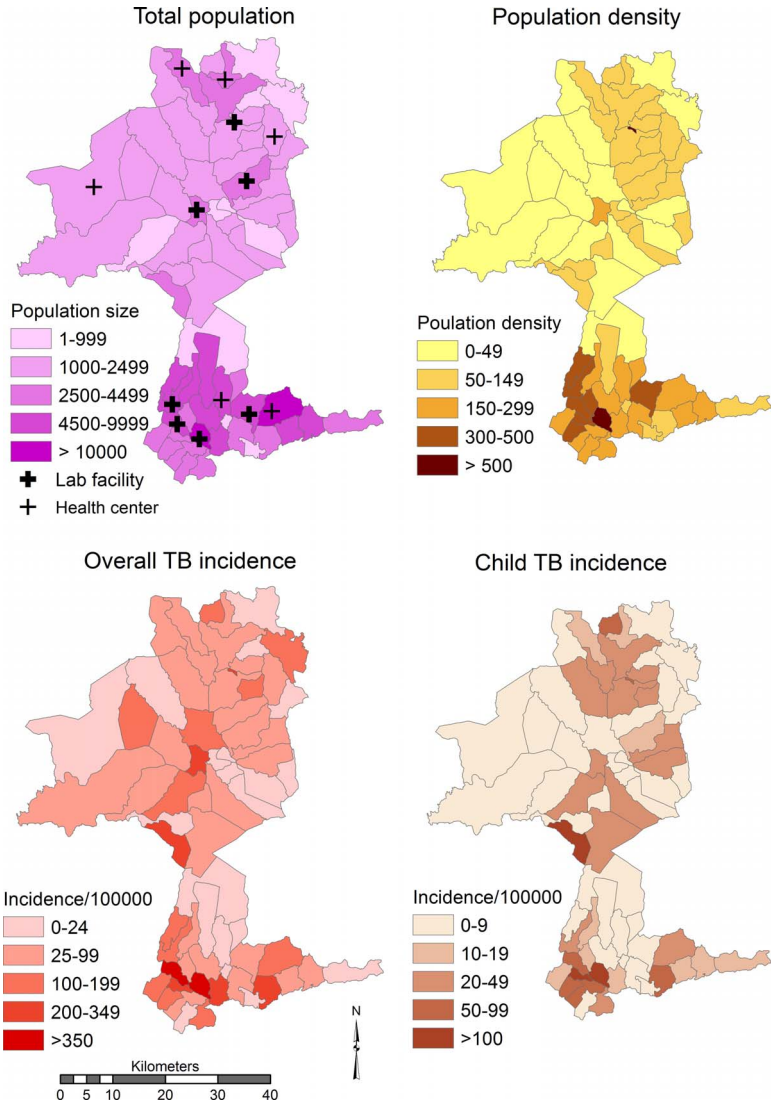

Figure 1 Population, population density, overall TB incidence rate and child TB incidence rate by *kebele*, Sheka Zone, Ethiopia, 2010–2014. Note: 'Lab facility' refers to capacity for performing sputum smear microscopy only. TB = tuberculosis. . This image can be viewed online in colour at http://www.ingentaconnect.com/content/iuatld/ijtld/2017/00000021/00000001/art00015

As in previous studies from Ethiopia,[6] we included only TB cases resident within the study zone, such that our overall incidence estimates are somewhat lower than official notification rates.[21] Linking patients to their place of residence rather than their place of presentation,[21] as in our study, is likely to provide a more accurate picture of the spread of the epidemic, as TB transmission occurs largely within households and communities.[22] Although untraced TB patients treated in the neighbouring zones may lead to underestimation of the true TB incidence rate in the zone, the fact that less than 3% of patients registered at health centres from Sheka Zone reported residence outside of the zone suggests that cross-border notifications are a relatively minor consideration.

TB incidence observed in a given *kebele* was correlated with the average TB incidence in the neighbouring *kebeles*, likely suggesting community transmission of TB, as has also been demonstrated in Brazil through mathematical modelling.[11] The spatial diffusion of infection across space is well described for other communicable diseases, particularly HIV.[11,23–25] Moreover, the significant spatial autocorrelation observed in our study could also be indicative of contagious spread to neighbouring areas.[6,8,26] In addition, the emergence of population density as a predictor of smear-positive TB incidence suggests that recent local transmission could also be a driver of TB epidemiology.[7]

TB incidence was an important predictor of TB incidence in the subsequent year. This finding highlights the persistence of TB in specific locations, with likely factors including persistent community transmission and durable underlying population vulnerabilities. Moreover, it could also imply that

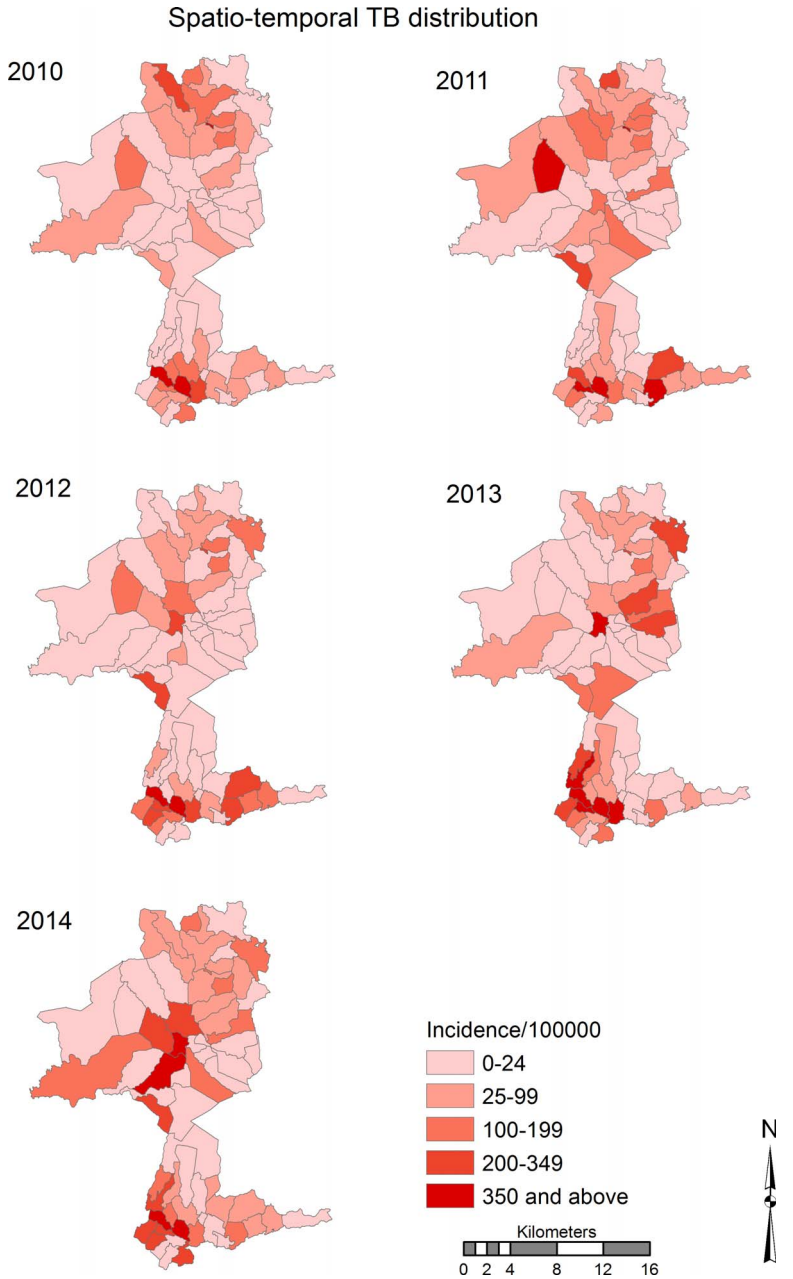

Figure 2 The spatial and temporal trends in rates of tuberculosis by *kebele* in Sheka Zone, Ethiopia, 2010–2014. TB = tuberculosis. This image can be viewed online in colour at http://www.ingentaconnect.com/content/iuatld/ijtld/2017/00000021/00000001/art00015

Table 2 Predictors of TB incidence by *kebele* in Sheka Zone, Ethiopia, 2010–2014

Predictors	Univariate Coefficient (95%CI)	Multivariate Coefficient (95%CI)
Incidence in adjacent *kebeles**	0.61 (0.25 to 0.96)	0.29 (0.12 to 0.47)
Incidence in the previous year*	0.70 (0.56 to 0.84)	0.55 (0.45 to 0.66)
Health centre availability†	170 (60 to 280)	84.3 (34.2 to 134.3)
Population density‡	0.04 (0.01 to 0.07)	§
Proportion of HIV among TB	140 (–170 to 450)	§

* Cases/100 000 population/year.
† Health centre available as compared to unavailable.
‡ Persons/km^2.
§ Eliminated by backwards stepwise regression analysis.
TB = tuberculosis; CI = confidence interval; HIV = human immunodeficiency virus.

the observation of higher numbers of TB cases in a specific year occurs partly as a result of insufficient public health actions in preceding years. This hypothesis is consistent with observations from other areas of high TB persistence in Ethiopia, and further work into correlation of public health activity and disease control will be critical to ensure that targeted strategies are developed towards reducing the TB burden.[6]

The observed TB incidence is also closely linked to the proximity of functional health facilities capable of diagnosing TB. Although significant heterogeneity was observed in the outcomes reported by individual health centres, *kebeles* with functional health centres consistently reported higher TB incidence than those without. This finding highlights inequalities in TB case detection as a function of distribution of health facilities, and implies a need to account for the potential role of access, especially when notification data are the main source of information for the National TB Control Program planning. Priority setting and resource allocation based solely on notification data, without accounting for issues of access, could mask true incidence in areas with poor access, and could even fuel community transmission by diverting attention and resources to the wrong places. In this study, trends in TB incidence were found to change over the study period. These changing trends could be related to four (31%) health centres that were equipped to provide TB sputum smear testing during the study period,[27] and to the community TB programme that was introduced in 2013. However, rather than public health responses leading to a decline in disease burden, the increasing number of presentations over a period during which health care services were expanded is also consistent with access to care uncovering a greater number of cases.

Geographic access to health care poses an immense challenge for early presentation and adherence to care, as most rural *kebeles* have no road network and many are located more than 2 h walking distance from health facilities.[28,29] As travel from almost all rural *kebeles* is on foot, TB patients from rural *kebeles* of Northern Ethiopia have reported travelling for 2–10 h for initial diagnosis and treatment.[29]

As mycobacterial culture is not part of standard of care in Ethiopia, the possibility of missing sputum smear-negative patients who would be diagnosed as culture-positive cases if laboratory facilities were available is unavoidable. The absence of culture and drug susceptibility testing in this setting means that no consideration of multidrug-resistant TB has been possible in this present study. However, the ratio of smear-negative to smear-positive TB in our study is comparable with the ratio of smear-negative, culture-positive cases to smear-positive TB from a population-based survey in Ethiopia.[30] Our data set is therefore likely to be consistent with patterns observed broadly across the country. In the absence of sputum culture, it is also impossible to comment on the extent to which drug resistance is driving transmission in this area.

CONCLUSIONS

TB incidence in rural Ethiopia is highly heterogeneous and demonstrates significant spatial autocorrelation. Transmission within and between *kebeles*, as well as proximity to health care, are likely drivers of these patterns. Identification of local TB hotspots may assist in developing more effective locally targeted strategies, and will be critical for ensuring that limited resources for TB control efforts are optimally engaged in this high-burden setting. The likely under-reporting of TB cases in areas remote from health facilities implies a potentially important role for pro-active interventions, such as active case finding, and highlights the importance of more objective approaches to estimating total burden, such as prevalence surveys.

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Conflicts of interest: none declared.

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RESUME

OBJECTIF : Décrire la distribution de la tuberculose (TB) et ses moteurs dans la Sheka Zone, une région géographiquement isolée d'Ethiopie.

MÉTHODE : Nous avons recueilli des données relatives aux patients TB traités entre 2010 et 2014 dans la Sheka Zone. Les facteurs de prédiction de l'incidence de la TB ont été déterminés grâce à un modèle de régression linéaire multivarié généralisé.

RÉSULTATS : Nous avons trouvé une autocorrélation spatiale significative de l'incidence de la TB par *kebele* (la plus petite subdivision géographique administrative en Ethiopie) (Moran's $I = 0{,}3$; $P < 0{,}001$). L'incidence moyenne de la TB par *kebele* allait de 0 à 453 par 100 000 personnes par année et était significativement associée à l'incidence moyenne de la TB dans les *kebeles* adjacents, à l'incidence de la TB dans le même *kebele* pendant l'année précédente et à la disponibilité des structures de santé. Toute augmentation de l'incidence de la TB de 10/100 000 personnes/an dans les *kebeles* adjacents ou dans une année précédente était associée à une augmentation de l'incidence de la TB de 3,0 et 5,5/100 000/année, respectivement. La disponibilité d'un centre de santé a été associée avec une augmentation de l'incidence de la TB de 84,3/100 000.

CONCLUSION : L'incidence de la TB dans l'Ethiopie rurale est très hétérogène et montre une autocorrélation spatiale significative. Ce profil est probablement lié à la fois à la transmission locale et à l'accès aux soins de santé. L'identification de points chauds locaux pourrait contribuer à élaborer et à optimiser des stratégies efficaces de prévention et de lutte.

RESUMEN

OBJECTIVO: Describir la distribución de la tuberculosis (TB) y los factores que favorecen la aparición de la enfermedad en la zona Sheka, una región geográficamente apartada de Etiopía.

MÉTODOS: Se recogieron datos sobre los pacientes con TB del 2010 al 2014 en la zona Sheka. Se definieron las variables independientes de la incidencia de TB mediante un modelo de regresión lineal generalizada multivariante.

RESULTADOS: Se observó una autocorrelación espacial significativa de la incidencia de TB por *kebele,* que es la subdivisión geográfica administrativa más pequeña en Etiopía (índice de Moran = 0,3; $P < 0{,}001$). La incidencia promedio de TB por *kebele* osciló entre 0 y 453 por 100 000 habitantes por año y se observó una asociación significativa con la incidencia promedio en los *kebeles* adyacentes, la incidencia de TB en el mismo *kebele* en el año anterior y la disponibilidad de establecimientos de salud. Cada incremento en la incidencia de TB de 10/100 000/año en los *kebeles* adyacentes se asoció con un aumento de la incidencia de 3,0 casos/100 000 en un *kebele* de referencia y un aumento equivalente en 1 año pronosticó un incremento de 5,5 casos/100 000 el año siguiente en un mismo *kebele*. La disponibilidad de un centro de atención de salud se asoció con un aumento de la incidencia de TB de 84,3/100 000.

CONCLUSIÓN: La incidencia de TB en las regiones rurales de Etiopía es muy heterogénea y exhibe una sólida autocorrelación espacial. La transmisión local y también el acceso a un centro de salud favorecen esta distribución. El reconocimiento de importantes focos de transmisión puede contribuir a elaborar estrategias eficaces de prevención y control y a optimizarlas.