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## Discussion

The results presented fully explained observed spatial clustering of paediatric TB in the study area. The temporal trend of TB decreased over the study period, and the incidence was shown to have seasonal variation, with more TB observed in the spring. The decline of TB incidence in north-western Ethiopia over the study period might be due to improvements in TB treatment outcomes and TB care overall (Datiko and Lindtjørn, 2009; Dangisso *et al.*, 2015a). According to the World Health Organization (WHO), the TB treatment success rate for new cases increased in Ethiopia from 77% in 2010 to 89% in 2015 (WHO, 2012, 2016). This could be also associated with expansions of directly observed therapy (DOT) and other prevention programmes (MOH, 2008; Dangisso *et al.*, 2015a). The national TB programme report from the Ministry of Health (MOH) showed that the number of hospitals and health centres providing DOT services in the country increased by more than 62% between 2010 and 2013 (MOH, 2013).

The observed seasonal pattern, with a peak observed from March to May (*i.e.*, spring) could be a consequence of high rates of TB transmission during the winter season resulting in active TB developing several weeks or months later (Vynnycky and Fine, 2000; Marais *et al.*, 2004a). This is consistent with previous studies where high rates of TB transmission have occurred during the winter season (Thorpe *et al.*, 2004; Fares, 2011; Willis *et al.*, 2012), which could be due to seasonal variations in food availability and food intake (Roba *et al.*, 2015; Hirvonen *et al.*, 2016), indoor overcrowding (Parrinello *et al.*, 2012) and low exposure to sunlight and its subsequent impact on vitamin D levels (Webb *et al.*, 1988; Sherman *et al.*, 1990; Nnoaham and Clarke, 2008). In addition, during the winter season there are high levels of rainfall and humidity, which may decrease airflow and favour TB transmission. This is supported by our results, whereby high rainfall recorded was associated with increased incidence of TB (Figure 3).

The observed seasonal pattern of TB could be related to migration patterns. In our study, the internal-migrant proportion of the population was associated with TB transmission. The majority of internal migrants are seasonal workers who come from different parts of the country and who are employed in the agricultural sector (Asfaw *et al.*, 2010). These people live, work and eat together in overcrowded living conditions, which may further facilitate TB transmission. Our study identified also urbanisation as a TB risk factor, which is supported by previous studies reporting that TB incidence is associated with urban residence, poor quality housing with overcrowding, lack of water and sanitation (Barnes *et al.*, 2011; Prasad *et al.*, 2016). Indeed, environmental factors that facilitate TB transmission may be more common in urban settings (Lienhardt Christian *et al.*, 2003a, 2003b; Narasimhan *et al.*, 2013).

Furthermore, socioeconomic status has been associated with TB. In districts where a high proportion of the population was illiterate, childhood TB rates were found to be high. This could be due to the fact that lower educational status may lead to a poorer understanding of the transmission of the disease and self-protective measures. It may also be associated with poor living conditions, including household overcrowding and other issues, such as poor access to healthcare. This may suggest that higher educational levels at the community level may reduce TB transmission and incidence. Wealth and levels of educational attainment have been associated with TB across many settings (Harling *et al.*, 2008; Suk *et al.*, 2009).

The present study is the first published study on the spatio-temporal distribution of paediatric TB in Ethiopia. The study included several

**Table 2. Socio-climatic factors associated with tuberculosis in children in north-western Ethiopia in the period 2013-2016.**

| District-level variable | Children under 15 years | | | Children under 5 years | | |
|---|---|---|---|---|---|---|
| | Model II[#]: Unstructured RR (95% CrI) | Model III[§]: Structured RR (95% CrI) | Model IV^: Unstructured and structured RR (95% CrI) | Model II[#]: Unstructured RR (95% CrI) | Model III[§]: Structured RR (95% CrI) | Model IV^: Unstructured and structured RR (95% CrI) |
| Female | 1.08 (0.99, 1.17) | 1.08 (0.99, 1.17) | 1.08 (0.99, 1.17) | 1.60 (1.33, 1.92) | 1.60 (1.33, 1.92) | 1.60 (1.33, 1.92) |
| Education status illiterate (%) | 1.47 (1.02, 2.06) | 1.29 (0.86, 1.84) | 1.41 (0.95, 2.02) | 1.19 (0.85, 1.66 ) | 1.09 (0.77, 1.52) | 1.16 (0.81, 1.62) |
| New internal migrant (%) | 1.09 (0.84 1.39) | 1.18 (0.87, 1.55) | 1.13 (0.85, 1.46) | 1.29 (1.01, 1.60 ) | 1.40 (1.07, 1.77) | 1.32 (1.03, 1.67) |
| Use of firewood for cooking (%) | 1.05 (0.84 1.29) | 1.05 (0.76, 1.39) | 1.04 (0.80, 1.32) | 1.03 (0.84, 1.25 ) | 1.06 (0.81, 1.38) | 1.04 (0.82, 1.30) |
| Urban population (%) | 1.85 (1.25, 2.62) | 1.59 (1.03, 2.31) | 1.76 (1.15, 2.58) | 1.58 (1.14, 2.22 ) | 1.40 (0.97, 1.97) | 1.53 (1.06, 2.16) |
| Autumn (Sep-Nov) | 0.74 (0.61, 0.88) | 0.72 (0.58, 0.89) | 0.73 (0.59, 0.88) | 0.86 (0.60, 1.18) | 0.88 (0.60, 1.23) | 0.86 (0.60, 1.20) |
| Summer (Dec-Feb) | 0.46 (0.20, 0.91) | 0.42 (0.18, 0.84) | 0.44 (0.19, 0.90) | 0.41 (0.06, 1.41) | 0.38 (0.05, 1.35) | 0.40 (0.06, 1.43) |
| Spring (Mar-May) | 1.14 (0.91, 1.41) | 1.11 (0.88, 1.38) | 1.13 (0.90, 1.40) | 0.90 (0.55, 1.40) | 0.88 (0.53, 1.38) | 0.89 (0.53, 1.40) |
| Temperature (°C) | 1.34 (1.04, 1.73) | 1.37 (0.99, 1.88) | 1.36 (1.02, 1.82) | 1.20 (0.91, 1.59) | 1.12 (0.81, 1.52) | 1.19 (0.88, 1.59) |
| Rainfall (mm) | 1.50 (1.11, 1.98) | 1.56 (1.15, 2.08) | 1.53 (1.12, 2.03) | 1.68 (0.89, 2.88) | 1.75 (0.90, 3.08) | 1.72 (0.89, 3.03) |
| Temporal pattern (by quarter) | 0.96 (0.95, 0.97) | 0.96 (0.95, 0.97) | 0.96 (0.95, 0.97) | 0.94 (0.92, 0.96) | 0.94 (0.92, 0.96) | 0.94 (0.92, 0.96) |
| Constant | 0.29 (-0.08, 0.67) | 0.35 (0.01, 0.69) | 0.31 (-0.07, 0.67) | 0.30 (-0.32, 0.92) | 0.35 (-0.27, 0.97) | 0.32 (-0.32, 0.96) |
| Variance (unstructured) | 7.05 (2.64, 14.0) | - | 58.14 (2.99, 558.0) | 16.69 (3.6, 53.9) | - | 65.98 (3.91, 552.0) |
| Variance (spatially structured) | - | 1.62 (0.60, 3.25) | 127.40 (0.92, 1056.0) | - | 7.33 (0.8, 21.6) | 176.70 (1.5, 1283.0) |
| DIC | 2839.45 | 2841.81 | 2842.42 | 1379.47 | 1383.14 | 1380.80 |
| DIC (without covariate)° | 2848.30 | - | - | 1383.74 | - | - |

DIC, deviance information criterion; RR, relative risk; CrI, credible interval. °Value obtained from Model I (*i.e.* the model without covariate); [#]model with covariates and unstructured random effects (*i.e.* fixed effects and non-spatial random effects); [§]model with covariates and structured random effects (*i.e.* fixed effects and spatially correlated random effects); ^model with covariates, structured and unstructured random effects (*i.e.* fixed effects, spatially correlated random effects and non-spatial random effects).

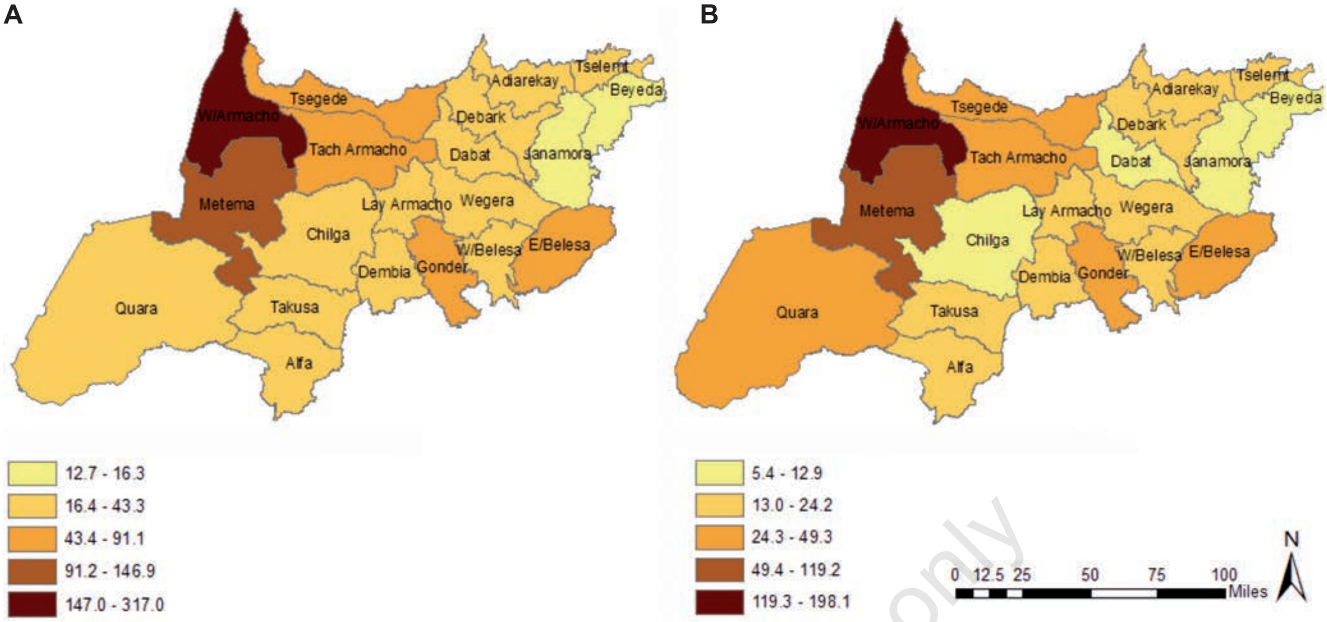


**Figure 2. Paediatric tuberculosis annual incidence rates per 100,000 children in twenty districts of north-western Ethiopia: A) for children under fifteen years; B) for children under five years.**

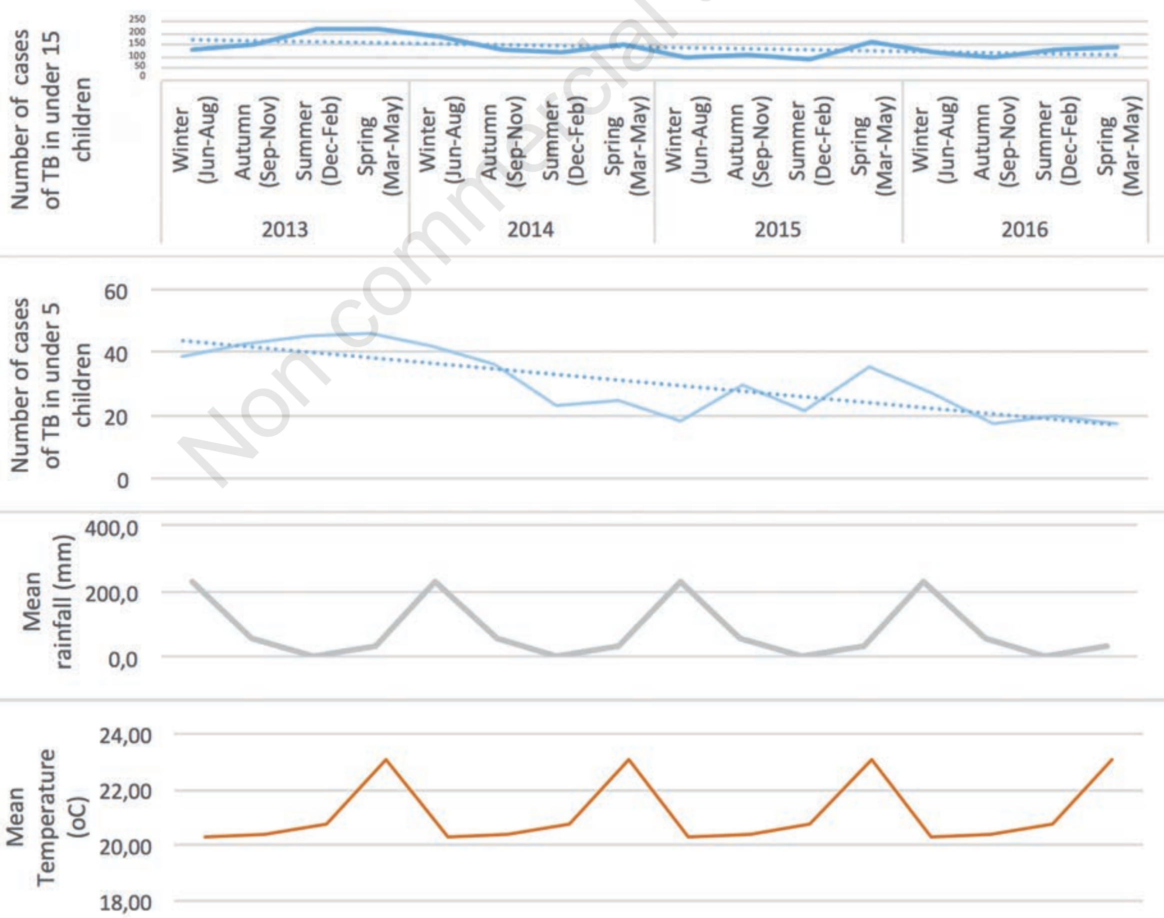


**Figure 3. Tuberculosis diagnoses in children under fifteen years and in children under five years compared to temperature and rainfall in north-western Ethiopia by quarter over the period 2013-2016.**

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ecological variables that were associated with rates of TB, but all environmental variables plausibly associated with TB were not included. For instance, temperature and rainfall are not the only climatic factors that may be associated with TB transmission, other important meteorological variables such as hours of sunshine, wind speed and atmospheric pressure may also be associated (Rao *et al.*, 2016). However, since north-western Ethiopia is located in a tropical region, some climatic factors, such as hours of exposure to sunshine, are relatively homogenous in the study area. Additionally, it should be acknowledged that TB transmission is multi-factorial and heavily influenced by socio-economic factors, many of which we did not examine.

Given that this was an area-level analysis, it is important to acknowledge the ecological fallacy, whereby associations at one level of aggregation cannot be assumed to hold true at other levels, including for individual people in the study area. Under-detection and under reporting of paediatric TB are a potential limitation of the study, and the exact burden of TB among children in north-western Ethiopia is not be known. Finally, we have not incorporated some other important clinical risk factors into the analysis such as HIV infection, a potent risk factor for TB.

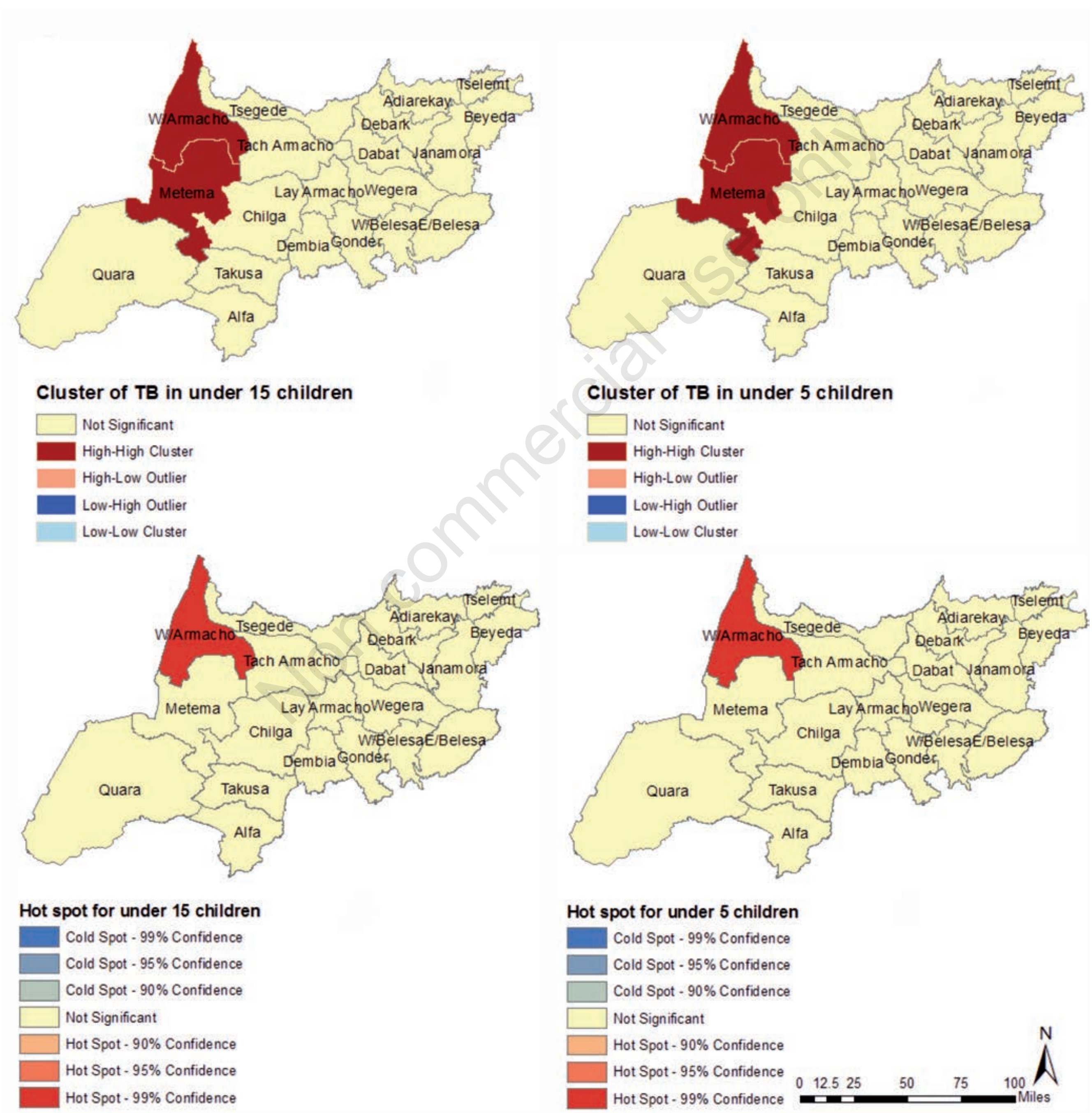




**Figure 4. Spatial clusters tuberculosis incidence rate and hot spots for children in north-western Ethiopia in the period 2013-2016.**



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## Conclusions

We found that paediatric TB was spatiotemporally clustered in north-western Ethiopia and that clustering was associated with several socio-climatic factors, including urbanisation, internal migration, educational status, rainfall, and temperature. The identification of paediatric TB clustering can help to identify TB transmission hotspots. Using this information, decision-makers may want to implement focused interventions for the control and prevention of TB in high-transmission districts.

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