Epidemics 36 (2021) 100470

Contents lists available at ScienceDirect

Epidemics

journal homepage: www.elsevier.com/locate/epidemics

Geospatial clustering and modelling provide policy guidance to distribute funding for active TB case finding in Ethiopia

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ARTICLE INFO

Keywords:
Geospatial clustering
Mathematical modelling
Tuberculosis
Active TB case finding
Cost-effectiveness analysis

ABSTRACT

Tuberculosis (TB) exhibits considerable spatial heterogeneity, occurring in clusters that may act as hubs of community transmission. We evaluated the impact of an intervention targeting spatial TB hotspots in a rural region of Ethiopia. To evaluate the impact of targeted active case finding (ACF), we used a spatially structured mathematical model that has previously been described. From model equilibrium, we simulated the impact of a hotspot-targeted strategy (HTS) on TB incidence ten years from intervention commencement and the associated cost-effectiveness. HTS was also compared with an untargeted strategy (UTS). We used logistic cost-coverage analysis to estimate cost-effectiveness of interventions. At a community screening coverage level of 95 % in a hotspot region, which corresponds to screening 20 % of the total population, HTS would reduce overall TB incidence by 52 % compared with baseline. For UTS to achieve an equivalent effect, it would be necessary to screen more than 80 % of the total population. Compared to the existing passive case detection strategy, the HTS at a CDR of 75 percent in hotspot regions is expected to avert 1,023 new TB cases over ten years saving USD 170 per averted case. Similarly, at the same CDR, the UTS will detect 1316 cases over the same period saving USD 3 per averted TB case. The incremental-cost effectiveness-ratio (ICER) of UTS compared with HTS is USD 582 per averted case corresponding to 293 more TB cases averted at an additional cost of USD 170,700. Where regional TB program spending was capped at current levels, maximum gains in incidence reduction were seen when the regional budget was shared between hotspots and non-hotspot regions in the ratio of 40% : 60%. Our analysis suggests that a spatially targeted strategy is efficient and cost-saving, with the potential for significant reduction in overall TB burden.

1. Background

Geographic heterogeneity is a defining characteristic in tuberculosis (TB) epidemiology (Shaweno et al., 2018a; Trauer et al., 2018). This means that a small fraction of the population bears the highest burden of disease, while the majority of the population carries a considerably lower burden – raising the possibility that geographically targeted interventions may be particularly effective. However, failure to target resources to these locations has been described as one of the reasons for slow progress in TB incidence reduction (Reid et al., 2019a).

Current TB control programs miss a considerable number of cases, estimated at 36 % in 2017, which poses an important challenge for global TB control (World Health Organisation, 2018). Therefore, active screening will likely be critical to reach the missed cases, although indiscriminate mass screening is expensive and is currently discouraged (World Health Organisation, 2013). Instead, active case finding (ACF) in

Abbreviations: ACF, Active case finding; HTS, hotspot-targeted strategy; UTS, untargeted strategy; TB, tuberculosis; USD, united states dollar; CER, cost-effectiveness ratios; ICER, Incremental cost-effectiveness ratio.

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https://doi.org/10.1016/j.epidem.2021.100470
Received 22 July 2019; Received in revised form 27 January 2020; Accepted 17 May 2021
Available online 19 May 2021

geographical areas with a high disease prevalence is favoured (World Health Organisation, 2013; Theron et al., 2015; World Health Organization, 2015), although the details of how to implement such a strategy are not fully defined. Few studies have evaluated the impact of targeting these locations, and there remains no consensus on how to define a spatial TB hotspot (Shaweno et al., 2018b). A proof of concept study in urban Brazil that evaluated the impact of a hypothetical intervention aimed at reducing time to detection showed that spatial targeting was superior to community-wide approaches (Dowdy et al., 2012). In contrast, results from a study that evaluated the impact of hypothetical vaccine targeting spatial hotspots in India showed modest benefits and the extent of heterogeneity was an important determinant of impact (Shrestha et al., 2016), implying that the effectiveness of spatial targeting was unpredictable and setting-dependent.

In this study, we estimated the impact of spatially targeted active TB contact screening in a remote zone in Ethiopia.

2. Methods

The analysis we present here extends our previous work which explored the implications of spatial heterogeneity for the spatial spread of TB (Shaweno et al., 2018b).

2.1. Overview of past work

In our previous study we used spatial analysis techniques (Shaweno et al., 2017) to identify TB hotspots in Sheka Zone, Ethiopia, which comprised about 22 % of the Zonal population but contained 50 % of notified TB cases. The contribution of hotspots to overall dynamics was determined by dividing the overall study region into three sub-regions based on disease burden and location. These were designated hotspots (statistically significant spatial clusters), non-hotspot regions adjacent to hotspots (having a shared border with hotspots) and remote regions (no shared border) (Shaweno et al., 2018b) *(Supplementary Fig. S 1)*.

We then used a compartmental transmission dynamic TB model which divided the population into five epidemiological compartments depending on TB-related infection or disease progression status, and three geographic patches (Shaweno et al., 2018b) *(Supplementary Fig. S 2)*. The transmission dynamics of TB were assumed to be identical in each spatial subdivision, except that the per capita effective contact rate (β) was calibrated to the local notification rates and the baseline case detection rate.

Mycobacterium tuberculosis (Mtb) transmission within and across regions was captured by constructing models with different contact mixing matrices to represent the strength of interaction within and between regions (Shaweno et al., 2018b). We parameterised the model by considering identical model parameter values across each of the three regions except for case detection rate (CDR) and transmission parameters. The baseline CDR of 65 % was considered in the hotspot region, while a lower CDR of 60 % was applied in the non-hotspot regions, based on our earlier findings. A full list of model parameters used in or estimated from our previous work including the cross-region coupling rate of 4.6 % are provided in the *Supplementary Material, Table S 1*.

2.2. Intervention strategies

We simulated an ACF strategy because the current national TB control program in Ethiopia misses a considerable number of TB cases (World Health Organisation, 2018). We modelled ACF as a community intervention assuming door to door enquiry for chronic cough ($\geq$ 2 weeks) followed by two sputum samples for microscopy (Kebede et al., 2014). Individuals with other TB suggestive symptoms who are unable to produce cough are referred to the nearest health facility for clinical evaluation and chest x-ray.

This community screening intervention (ACF) was conducted under both a spatially targeted strategy (HTS) and a spatially untargeted strategy (UTS). Under HTS, we explored the role of spatially targeted ACF by incrementally increasing CDR in the hotspot region from the baseline value of 65 %, while maintaining the baseline CDR at 60 % in the remaining non-hotspot regions. Under UTS, CDR was increased from the baseline value in all spatial subdivisions. The model was implemented from equilibrium, with outputs of spatially targeted case finding strategy (HTS) compared against the base-case scenario and the spatially untargeted case finding strategy (UTS) (Shaweno et al., 2018b).

The intervention increases TB CDR by reaching the proportion of cases that are missed during their course of illness. Hence, the proportion of cases detected and treated under the intervention is the sum of the baseline CDR (under existing programmatic conditions) and the proportion of missing cases detected by the intervention:

$$\tau_i = p_i(1 - \tau_{0i}) + \tau_{0i}$$

where i may take two values representing spatial hotspots or the overall region, p_i represents the coverage of population screening in the spatial subdivision of interest, τ_i represents the intervention CDR in the subdivision, and τ_{0i} refers to the baseline CDR in the subdivision under the national TB program. The value of p ranges from 0 (no intervention) to 1 (full coverage). The intervention case detection proportion (τ_i) generated in this way was converted to case detection rate (δ_i) to be used in the model (see appendix for details).

Because HTS and UTS operate in regions with different population sizes, direct comparison of the impact of an increase in local screening coverage could be misleading. Hence, to account for differences in efforts of intervention strategies such that impacts are comparable, we used two approaches to estimate the efficiency of intervention strategies. In the first approach, we translated local screening coverage in spatial hotspots into the proportion of entire population reached (total screening coverage) by multiplying local coverage by the proportion of total population in it. In the second approach, we determined efficiency using cost-coverage and cost-effectiveness analysis as described below.

2.3. Cost-coverage analysis and cost-effectiveness analysis

The community intervention screening coverage (p_i) in the spatial subdivision of interest was used as an input to a logistic cost-coverage function that linked spending on programmatic interventions to intervention coverage (Trauer et al., 2017). The cost-effectiveness analysis in this study is based on unit costs related to TB service provision collected from the literature in the same study region. Specifically, we considered the cost of TB screening under the intervention (symptom screening, sputum microscopy, and chest x-ray), the cost of passive case detection and the cost of treating each TB patient. Recent estimates from the study region under the current passive case detection scheme indicate that TB patients incur a median of USD 201 total costs before starting anti-TB treatment. This unit cost includes both direct and indirect costs incurred while seeking TB care. The direct costs include medical costs (for consultation, laboratory tests, x-ray, and related services), and non-medical costs (for transportation, accommodation, meals, and related services while seeking care for TB diagnosis and to collect anti-TB drugs). On the other hand, indirect cost captures lost income due to inability to work or lost workdays while traveling to seek care, diagnosis, and treatment for TB (Asres et al., 2018). The average cost of drugs per patient for drug-susceptible TB treatment in Ethiopia is estimated at USD 45 (WHO, 2019). The costing for TB symptom screening (USD 0.3125) is based on time spent by health extension workers (HEWS) for door to door travel at kebele level, considering an average of 30 minutes for symptom screening (Clarke et al., 2006). The time costs were converted to a monetary value based on the monthly income of HEWs in US dollars, taking an average monthly salary of 3000 Ethiopian birr (ETB). The intervention assumes that individuals with symptoms suggestive of TB (chronic cough) will be asked to produce sputum. Smear test will cost an average unit cost of USD 2.5 per TB review in

Ethiopia (in 2018) reflecting the direct costs of TB diagnosis incurred by a TB control program adjusted for inflation (de Cuevas et al., 2016). Individuals unable to produce sputum will be referred to a nearby health facility for chest x-ray, and this will cost about USD 2.5 including travel time (based on the current public hospital fee). After symptom screening, we assume that sputum smear and chest-x-ray are applicable to 6.5 % of the total population (Ethiopian Health and Nutrition Research Institute, 2011).

The cost-coverage relationship is then determined by fixing the saturation (maximum possible coverage of screening) at 60 %, which means that if the intervention is maximally implemented, we would detect 60 % of missing cases which is intended to capture the fact that a substantial proportion of all active cases cannot be detected through the diagnostic algorithm we consider.

We also calculated average cost-effectiveness ratios (CER) for each intervention strategy by comparing cost and impact (reduction in incidence) at a given coverage with the respective values at baseline. The incremental cost-effectiveness ratio (ICER) was calculated as the ratio of the difference in cost to the difference in the number of active TB cases averted between the two interventions (Gray et al., 2011). CER and ICER in this study represent cost per active TB case averted.

Often national TB programs have a fixed budget and it is unclear what proportion of this budget should go to the spatial hotspots in contrast to the non-hotspot regions for a maximum possible impact. To maximise the impact of the available budget, we estimated annual TB funding at approximately USD 65,000 across the study Zone (based on available budget in the Zone, 2018) and identified the optimal resource allocation strategy for this funding envelope. This was achieved by implementing a model such that for every proportion of available budget going to spatial hotspots, the remaining proportion goes to the non-hotspot regions. Similarly, hypothetical annual budget scenarios were considered to define the ideal maximum potential gain of spatially targeted resource allocation.

2.4. Sensitivity analysis

To account for the extent to which variations in parameter values were related to variations in outcome variable (incidence rate), we carried out a multivariate sensitivity analysis using Latin hypercube sampling (Larson et al., 2005). Sensitivity analysis was done for epidemiological parameters governing transitions between compartments, case detection ratio and population mixing, while keeping the intervention (population screening coverage) constant. These included the within region transmission parameters β_{ii} (β_{11} within hotspots, β_{22} with in adjacent regions and, β_{33} within remote regions), between region coupling parameter (ρ); fast progression rate (ε); stabilisation rate (κ); reactivation rate (ν); and relapse rate (ω). To be able to capture the impact of model parameters on the performance of budget allocation, we sampled intervention coverage that corresponds to the proportion of budget going to spatial hotspots. Plots from these simulations are presented in the *Supplementary Material, Figs. S3-S5)*. The parameter values and their ranges used in the sensitivity analysis are provided in the *Supplementary Material, Table S 1*. The model was coded in Matlab-R2015b.

3. Results

In our previous work, using our baseline parameter values, we estimated TB incidence at 538 cases per 100,000 per year in a hotspot containing one-fifth of the Zone's population, and 110 and 150 cases per 100,000 population per year in adjacent and remote regions respectively. The population-wide prevalence and incidence rates were estimated to be 267 cases per 100,000 and 221 cases per 100,000 population per year, respectively (Shaweno et al., 2018b).

3.1. Impact of intervention strategies on TB epidemiology

HTS resulted in a reduction of overall TB incidence by 52 % with 20 % of the total population reached, which corresponded to achieving a CDR of 95 % in the hotspot region. However, to achieve the same benefit from UTS, the proportion of people that needed to be reached was about four-fold the coverage in the HTS (Fig. 1). Note that if interventions in the hotspot region are maximally implemented, they would cover only 22 % of the entire population, such that the solid lines terminate at 20 %.

While HTS that reached 20 % of the total population (corresponding to a CDR of 95 % in the hotspot region) reduced TB incidence by 78 % in the hotspot region, it reduced incidence by 59 % in the adjacent region and by only 2.7 % in the remote region after 10 years of implementation. However, UTS had the potential for greater impact by extending coverage throughout the region and could reduce TB incidence by more than 74 % in the region at the programmatic coverage value of 95 %.

3.2. Cost-coverage curves

Fig. 2 presents the effect of increased program spending (cost) on intervention coverage, reduction in TB incidence, number of people screened and averted active TB cases under the two intervention strategies - UTS and HTS. The logistic cost-coverage plot (panel A) shows that the HTS (solid line) saturates early compared to the UTS (broken line), which requires considerably more spending to approach saturation because of the greater population to target. The intervention spending associated with specific coverage values from the logistic cost-coverage curves were retrieved and used to calculate the cost-effectiveness ratios as described in the next section.

3.3. Cost-effectiveness analysis

The following plot (Fig. 3) compares the total number of persons under treatment (Panel A), program cost (Panel B), and the total number of prevalent cases (Panel C) between existing passive case detection and passive case detection complemented with ACF (HTS) in spatial hotspots. In HTS, the number of treated cases increases immediately after the launch of intervention and declines thereafter. As a result, compared to the passive only scenario, the cost of treatment increases soon after the intervention launch and declines thereafter following declines in the number of prevalent cases available for detection and treatment. Over ten years, the intervention scenario would reduce TB burden from the baseline prevalence of 268 per 100,000 per year to 186 per 100,000 at a cost of USD 840,000 by treating 65 percent of expected prevalent cases under the intervention (5,100). However, the passive case detection scenario will incur USD 1,015,500 to treat 62 percent (baseline CDR) of expected prevalent cases (6700) under the passive CDR scenario. In line with the above description, Panel D shows the cost per averted case of HTS compared with passive CDR (ICER) measured per year over ten years. The HTS scenario becomes cost saving one year after an intervention begins, with high ICER soon after the start of intervention which then becomes less than 0 afterwards indicating the intervention is cost saving overall (Fig. 3).

Over ten years, the passive case detection scenario at a CDR of 62 percent will incur USD 1, 015,500. However, compared to the passive CDR, the HTS scenario that increases CDR to 75 % in hotspot regions is expected to avert 1,023 new TB cases at a reduced cost of USD 840,000, saving USD 170 per averted case. Similarly, compared to passive CDR, UTS will avert a total of 1,316 new cases at a cost of USD 1,010,700, saving USD 3 per averted case. The incremental-cost effectiveness-ratio (ICER) of UTS compared with HTS is USD 582 per averted case corresponding to 293 more cases averted at an additional cost of USD 170,700.

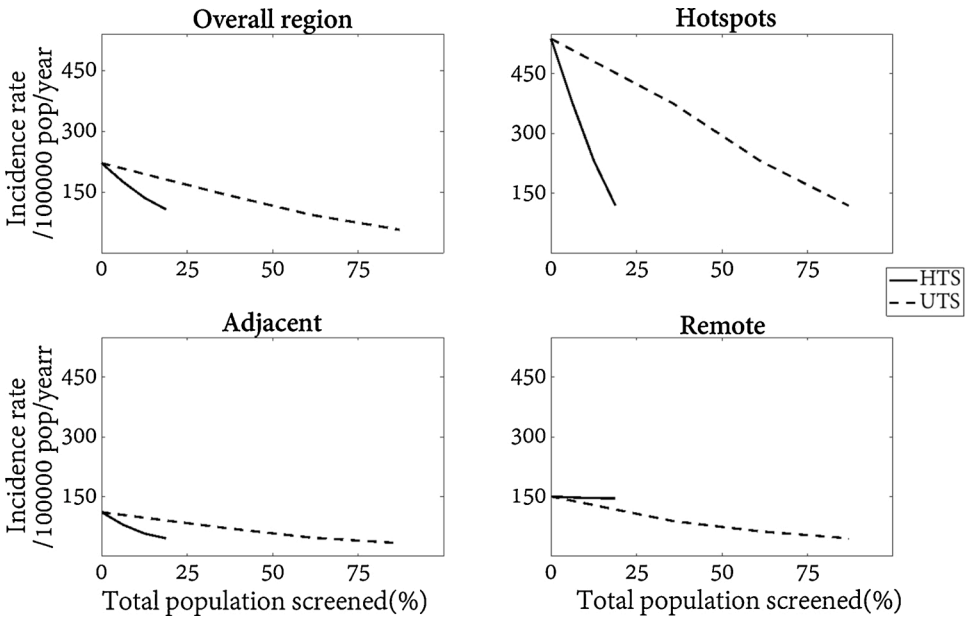

Fig. 1. Proportion of entire population screened under the two intervention strategies and the corresponding reduction in TB incidence for the entire study region, hotspot regions and the two non-hotspot regions (y-axis).

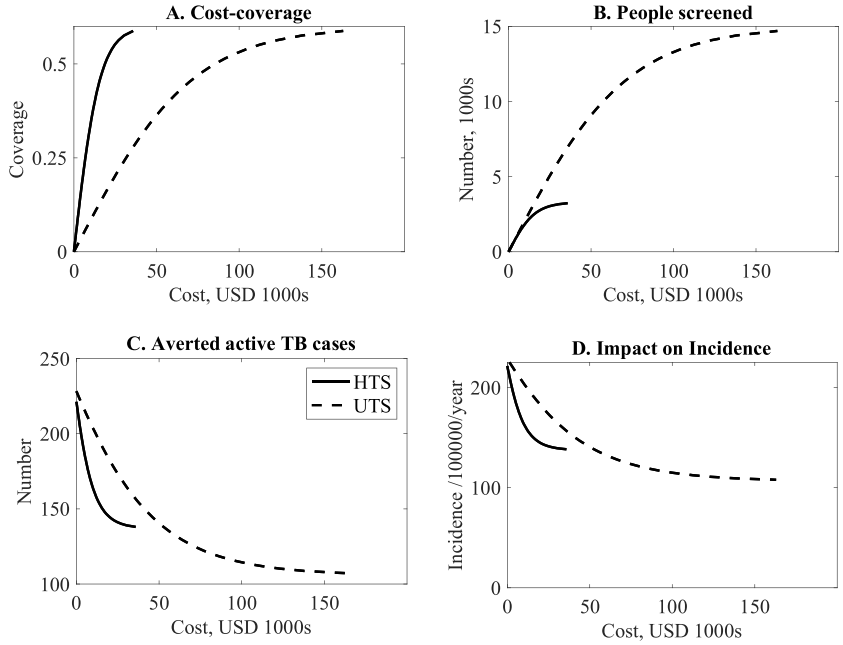

Fig. 2. Impact of program spending: Panel A compares cost-coverage analysis of HTS and UTS. Panels B, C and D show impacts of increased program spending on the number of people reached, averted number of incident TB cases and incidence.

3.4. Budget allocation to spatial hotspots

We also explored the relation between cost and its impact on TB incidence using various assumed budget envelopes: USD 10,000, USD 20,000, USD 35,000, USD 50, 000 and USD80,000. Using these envelopes, the relation between the proportion of budget going to spatial hotspots and impact (reduction in incidence) is not linear, particularly for budget envelopes greater than USD 10,000. In general, for larger budget envelopes (USD 50,000, USD65,000 and USD80,000) the maximum gains were seen when the regional budget was shared between hotspots and non-hotspot regions in the ratio of 40% to 60%. Using these budget envelopes, when the proportion of the budget allocated to hotspot exceeded 50 %, population incidence rises markedly (Fig. 4). With a lower budget envelope maximum gains are seen when all or larger proportion of the envelope goes to hotspots (where there are larger number of TB cases-incidence rate of 540/100,000 per year. As the budget envelope increases, the proportion of general population screened increases, consequently increasing the cost per averted case (CER). In contrast, at lower budget envelope schemes, the maximum gains are observed when all the budget is directed to spatial hotspots, hence lower CERs (Fig. 4).

3.5. Sensitivity analysis

Sensitivity analysis showed that the estimated reduction in incidence was highly sensitive to the impact of hotspot targeting. As expected, the

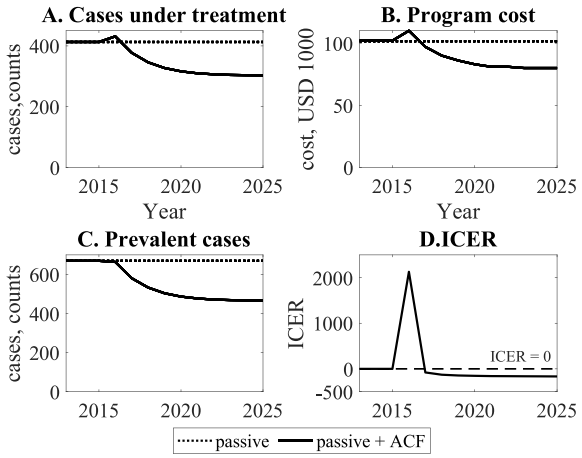

Fig. 3. Comparison of passive case detection with active case detection based on the number of cases detected, cost, overall prevalent cases and ICER.

estimated incidence was linearly correlated with parameters governing TB transmissions (β's and ρ), and with parameters governing disease progression (fast progression rate, and reactivation rates (ν)) (Fig. 5). However, the association between budget allocation and incidence is not linear for our target budget envelope as well as other budget envelopes exceeding USD 50,000. TB incidence decreases with increasing proportion of budget going to spatial hotspots, with maximum reduction in TB incidence observed when 40 percent or less of the target budget goes to spatial hotspots and the remaining proportion to no-spatial hotspots (Fig. 4, Supplementary Figs. S3, S4, S5).

4. Discussion

Using a spatially structured mathematical model, we found that targeting spatial hotspots is efficient compared with spatially untargeted intervention up to a ceiling of around 20 % overall coverage of the population. Compared with the UTS, HTS was predicted to be more efficient and cost-effective under most scenarios. Our results suggest that to obtain comparable reductions in TB incidence from HTS and UTS, the required coverage of the UTS intervention was about four-fold that of HTS before approaching saturation in hotspots. While less efficient, this strategy has the advantage of allowing further scale-up to reach a greater proportion of the population and could achieve a theoretical impact of a 60 % reduction in TB incidence if 87 % of the population were reached. However, it should be remembered that this level of coverage in ACF is much higher than current levels and has not been described to date.

The impact of spatially-targeted ACF is primarily confined to regions in close proximity to the hotspots, suggesting that spatial targeting would be effective in rural-remote settings such as the ones we studied here. The impact of hotspot targeting that resulted in significant reduction in the overall TB incidence as well as incidence in the proximal regions reflects significant transmission from hotspots to the other regions. However, given that the fitted cross coupling rate is low (4.6 %), the impact of spatial targeting in reducing the overall incidence of TB primarily reflects the disproportionate burden of TB in hotspot regions, which is 3–4 times the disease burden in remote and adjacent regions. Consistent with this explanation, passive CDR and entire population screening in a hotspot region lead to saturation of effect and an incidence rate that remains above 110 cases per 100,000 population. This implies that spatial targeting alone would not achieve disease elimination, as a considerable burden of transmission persists in non-hotspot regions (Shaweno et al., 2018b).

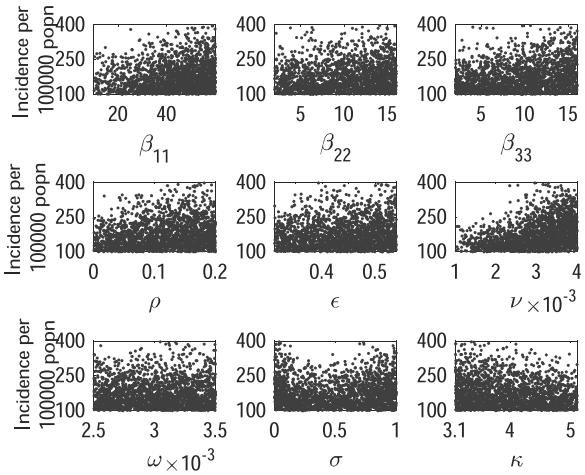

Fig. 5. Sensitivity of impact of intervention to variations in selected model parameters (κ -stabilisation rate, ν - reactivation rate, ω - relapse rate,σ - CDR corresponding to proportion of budget going hotspots, ρ - coupling parameter, ε - fast progression rate, βs – within region per-capita effective contact rates).

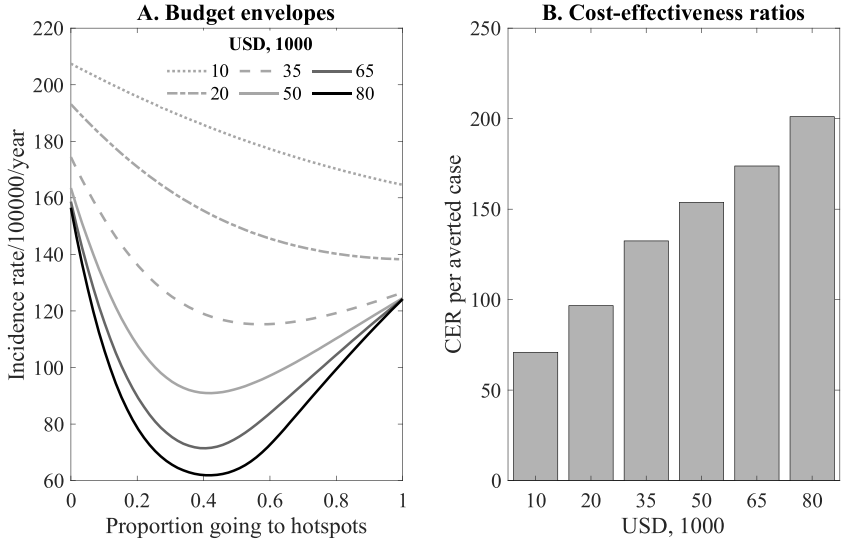

Fig. 4. Impact of geographic funding allocation on population TB incidence under six budget envelope scenarios.

ACF could yield considerable gains when targeted to population at increased risk of developing active TB including household contacts of patients with active TB (Fox et al., 2018), areas with high HIV prevalence (Corbett et al., 2010) and people in congregate settings (eg. prison) (Reid et al., 2019b). Although geographic heterogeneity in TB risk has been documented well (Shaweno et al., 2018a), evidence has been lacking on the epidemiologic and economic impact of spatially targeted ACF and hence remained unimplemented. The study we presented here shows, like other high TB risk groups explored in previous studies (Reid et al., 2019a; Fox et al., 2018; Corbett et al., 2010), geographically targeted ACF would provide considerable gains in TB control.

The potential effectiveness of spatially targeted ACF is a consequence of two main phenomena. First, current passive approaches to case detection rely on the index case seeking health care and so miss many people with TB. Health care seeking behaviour usually occurs in advanced stages of clinically apparent disease and so may have limited impact on transmission (Getnet et al., 2017). Conversely, indiscriminate population-wide screening could produce high levels of coverage at a markedly increased cost and so may not be feasible (Dobler, 2016). This provides a rationale for considering spatially-targeted ACF. Moreover, spatially-targeted ACF could be feasible because routinely collected data and the techniques we propose could be used to identify the hotspots (Shaweno et al., 2017).

Our study suggested that when the available budget is limited, the intervention impact increases with increasing budget allocation to hotspots. However, at budget envelopes that correspond to currently available in the study region, maximum gains in incidence reductions were observed when budget is shared between the regions in the ratio of 40% to 60%. In contrast, at budget envelopes that are up to one-third of the current budget, maximum reduction in overall TB burden consistently occurs when all the available budget is allocated to hotspots. However, this raises equity concerns as spatial targeting has considerable impact locally, in adjacent regions as well as in the overall population, but little or no impact on the remote region of the zone. Such equity concerns could be offset by improving passive case detection across the entire zone (Trauer et al., 2018).

With the intervention, as the incidence of TB declines, the number of people found with chronic cough could decline and so would the number undergoing smear microscopy test. Therefore, the expected cost of active case finding could decline. However, we do not specifically account for this phenomenon because the prevalence of TB among population with a chronic cough is very low (1.8 %), (Kebede et al., 2014; Ethiopian Health and Nutrition Research Institute, 2011) the vast majority (>98 %) of individuals with chronic cough have no TB and the fraction of individuals with chronic cough is unlikely to diminish substantially as the intervention proceeds.

Although we predict that spatial targeting could be effective in a high burden setting, we may not have fully captured the mechanism leading to spatial clustering in TB incidence, which may result from intense localised transmission or aggregation of cases among groups of individuals sharing risk factors for progression (Verma et al., 2014; Haase et al., 2007). However, others have also argued that concentration of disease in high burden settings is mainly driven by localised transmission (Floyd et al., 2018) and hence our study assumes transmission to be the predominant mechanism driving TB epidemiology. An improved understanding of drivers of spatial heterogeneity in TB incidence would be useful to inform targeted control interventions and hence data that describe the extent to which transmission accounts for the local TB epidemiology through the use of genotypic methods would further assist in the design of intervention studies.

5. Conclusions

In summary, our analysis suggests that spatial hotspot target strategy is efficient and cost-saving with the potential for significant reduction in overall TB burden.

Authors contributions

DS wrote the initial code, TND, JMT and ESM added additional lines of code. DS drafted the initial study concept and ESM, JTD and JMT refined this further. DS wrote the initial draft of the manuscript, and all authors provided input into revisions and approved the final draft and submission for publication.

Ethics approval and consent to participate

We collected data used in this study after obtaining ethical approval from the University of Melbourne Health Sciences Human Ethics Subcommittee (Ethics ID-1544898) and the Zonal Health Department of Sheka Zone, Ethiopia.

Funding

No specific funding was received for this study. Debebe Shaweno is the recipient of the Melbourne International Research Scholarship and Melbourne International Fee Remission Scholarship. James Trauer is a recipient of an Early Career Fellowship from the NHMRC (APP1142638).

Declaration of Competing Interest

The authors report no declarations of interest.

Acknowledgements

The authors thank Sheka Zone Health Department, Ethiopia, and all health centres for permission to access the data.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.epidem.2021.100470.

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