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# Quantifying the potential epidemiological impact of a 2-year active case finding for tuberculosis in rural Nepal: a model-based analysis

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## ABSTRACT

**Objectives** Active case finding (ACF) is an important tuberculosis (TB) intervention in high-burden settings. However, empirical evidence garnered from field data has been equivocal about the long-term community-level impact, and more data at a finer geographic scale and data-informed methods to quantify their impact are necessary.

**Methods** Using village development committee (VDC)-level data on TB notification and demography between 2016 and 2017 in four southern districts of Nepal, where ACF activities were implemented as a part of the IMPACT-TB study between 2017 and 2019, we developed VDC-level transmission models of TB and ACF. Using these models and ACF yield data collected in the study, we estimated the potential epidemiological impact of IMPACT-TB ACF and compared its efficiency across VDCs in each district.

**Results** Cases were found in the majority of VDCs during IMPACT-TB ACF, but the number of cases detected within VDCs correlated weakly with historic case notification rates. We projected that this ACF intervention would reduce the TB incidence rate by 14% (12–16) in Chitwan, 8.6% (7.3–9.7) in Dhanusha, 8.3% (7.3–9.2) in Mahottari and 3% (2.5–3.2) in Makwanpur. Over the next 10 years, we projected that this intervention would avert 987 (746–1282), 422 (304–571), 598 (450–782) and 197 (172–240) cases in Chitwan, Dhanusha, Mahottari and Makwanpur, respectively. There was substantial variation in the efficiency of ACF across VDCs: there was up to twofold difference in the number of cases averted in the 10 years per case detected.

**Conclusion** ACF data confirm that TB is widely prevalent, including in VDCs with relatively low reporting rates. Although ACF is a highly efficient component of TB control, its impact can vary substantially at local levels and must be combined with other interventions to alter TB epidemiology significantly.

## STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The modelling analysis incorporates field data on tuberculosis active case finding from a high-burden, low-resource setting.

⇒ The study estimates the epidemiological impact of active case finding at a subnational level, incorporating geographic heterogeneity in notification and active case finding.

⇒ The modelling approach focuses on capturing geographic heterogeneity and makes simplifying assumptions regarding the natural history of tuberculosis.

## INTRODUCTION

Tuberculosis (TB) continues to be a major infectious source of mortality worldwide, with 1.4 million deaths in 2019, most of which occurred in low and middle-income countries.[1] Despite the availability of low-cost and effective cure, many TB patients remain undiagnosed, suffer long diagnostic delays or are lost to follow-up in the diagnostic pathway due to complex multifactorial barriers.[2–5] Active case finding (ACF), designed to find and treat TB cases in the community, is a potentially impactful and cost-effective tool for TB intervention in such settings by reducing the transmission potential of TB cases that are undiagnosed or diagnosed with delay.[6 7]

However, it has proven difficult to develop a quantitative understanding of the longer term impact of ACF in reducing TB transmission. This is highlighted by the fact that while transmission models find significant potential of ACF in reducing transmission,[8–10] the impact observed in controlled trials has been mixed.[11–14] Analyses exploring the impact of ACF on case notification at the national level are unlikely to show large effects because the majority of ACF projects is subnational, and the impact is, therefore, primarily localised. This disconnect may partially be driven by the fact that detailed and informed models are not incorporated early in the planning and design phase of ACF.[14] Incorporating modelling at the onset will help generate *a priori* expectation of the yields and impacts of ACF (thus providing an opportunity for model validation) as well as contribute to optimising the design of ACF (thus potentially improving its yield and impact). Ultimately, if ACF is to be a reliable tool for TB intervention across many settings, there is a need to develop an improved quantitative understanding of ACF—how can data and models be used to design and plan effective ACF, and what are the factors that drive its impact in reducing TB transmission?

In this study, we aimed to develop and validate models of community-level ACF in a low-resource, high-burden setting by embedding the modelling work within an ongoing study of ACF. The IMPACT-TB ACF study was funded by the European Union Horizon 2020 scheme to carry out ACF in four districts in southern Nepal between June 2017 and June 2019 (www.impacttbproject.org).[15 16] Nepal is a low-income country, where TB notification rates have been stagnant for over a decade. After a national prevalence survey conducted in 2018/2019, the WHO revised estimates for TB incidence in Nepal to 245 per 100 000/year (which is approximately 50% greater than the initial WHO estimate).[1] The prevalence survey also revealed that more than half of the incident cases are currently not notified in the national system, suggesting an urgent need to improve detection and treatment throughout the country.

Using available local data on TB and demography, we developed local-level transmission models based on the administrative areas known as village development committees (VDCs), which were in use in Nepal at the time of the IMPACT-TB study. Using data collected during the IMPACT-TB ACF study,[16] we projected the epidemiological impact of ACF and assessed the potential value of optimising ACF by geographic targeting.

## METHODS

### VDC-level TB notification rates in Chitwan, Dhanusha, Mahottari and Makwanpur

We collected and collated data on TB case notifications between 2016 and 2017 in the four districts of Nepal: Chitwan, Dhanusha, Mahottari and Makwanpur, where IMPACT TB ACF efforts were conducted (see online supplemental figure S1). Notification data represented counts of all TB cases reported by the National TB Programme of Nepal. Based on these data, and population denominators from the national census of 2011, we calculated average TB notification rates between 2016 and 2017, at the level of VDC (which were local administrative units used for government administration, from 1990 to 2017, including public health services. The VDC structure was replaced by municipalities in 2017 as part of the federalisation process, which incorporated one or more VDCs into a newly termed municipality).

### VDC-level yields of ACF during IMPACT-TB

IMPACT-TB-ACF was implemented by Birat Nepal Medical Trust (implementation details are described elsewhere [15–17]) using implementation strategies previously shown to be successful in achieving high yields.[18 19] This ACF study screened social contacts (contact investigation implemented by local community health workers) and conducted microscopy camps to detect TB cases across four districts in Nepal for 2 years, from 2017 to 2019. Using data collected on TB cases detected through contact tracing, we estimated the number of TB cases detected in each of the VDCs across four districts. Home address reported and recorded in a written form during the ACF was manually used to assign VDC for each case. Home addresses for cases detected through microscopy camps were not available, and not included in these analyses. In about 5% of identified cases, we were not able to match them to a VDC—we also excluded these cases in our analyses.

### VDC-level transmission model

We developed VDC-level transmission models across all VDCs in each of the four IMPACT TB districts of Nepal: Chitwan (2238.39 $km^2$ with 39 VDCs), Dhanusha (1180 $km^2$ with 102 VDCs), Mahottari (1002 $km^2$ with 77 VDCs) and Makwanpur (2246 $km^2$ with 45 VDCs). This approach of developing VDC-level models allowed us to capture heterogeneity in local TB dynamics and to model interventions implemented at local levels. Each VDC-level model followed a common model structure, a relatively parsimonious compartmental model of the ilk that has been developed previously.[20–22] We calibrated the models to VDC-specific TB prevalence in each of the four districts. TB prevalence was estimated for each of the modelled VDCs using TB case notification data from the VDCs between 2016 and 2017. To ensure that the calibration process remained simple and transparent, we assumed that the population size did not change during the 10-year period we modelled and that there were no secular trends in TB prevalence at baseline. Given that TB incidence has remained fairly constant in Nepal (<1% annual decline in the last decade), this is not an unreasonable assumption to make. A full description of the model, including differential equations describing the model (S1), schematic representation of the model (online supplemental figure S2) and algebraic equations used for calibration process (S2) are included in the supplementary materials.

### Model scenarios

To capture some of the uncertainty around the amount of ongoing TB transmission—the types of data required to quantify the amount of ongoing TB transmission are not yet available for Nepal or similar high-burden urban settings—we modelled three epidemiological scenarios, to reflect the possibility of different levels of TB transmission at the VDC level. See online supplemental table S1[23–29] for parameter values that specify these scenarios.

1. *Baseline* (moderate—transmission), in which we assumed a moderate level of transmission. The percentage of incident cases that resulted due to recent transmission events in this scenario were 68%

(IQR: 64%–72%) in Chitwan, 62% (59%—66%) in Dhanusha, 67% (63%–71%) in Mahottari, and 65% (61%–73%) in Makwanpur, respectively.

2. *Low* (low—transmission), in which we assumed lower levels of transmission. The percentage of incident cases that resulted due to recent transmission events in this scenario were 59% (IQR: 54%–54%) in Chitwan, 52% (48%–56%) in Dhanusha, 58% (53%–63%) in Mahottari and 57% (52%–67%) in Makwanpur, respectively.
3. *High* (High—transmission), in which we assumed a higher rate of transmission. The percentage of incident cases that resulted due to recent transmission events in this scenario were 76% (IQR: 73%–79%) in Chitwan, 72% (69%–74%) in Dhanusha, 75% (72%–78%) in Mahottari and 74% (71%–79%) in Makwanpur, respectively.

### Modelling ACF intervention

We modelled 2-year ACF in all VDC within the four districts. We assumed that all the cases detected during ACF would initiate treatment and would be successfully treated. This is consistent with IMPACT-TB project data on treatment initiation and completion rates for patients diagnosed during ACF, which exceeded 98%. This was implemented in our VDC-level compartmental models as transition of individuals out of active TB compartment, where the number of individuals transitioning out reflected the number of individuals detected in each VDC through ACF.

### Outcomes

The primary outcome was the impact of ACF on the estimated number of TB cases averted within a 10-year period after ACF. We generated these estimates by subtracting the projected number of cases over a 10-year period in model simulations with the intervention from the model simulations without the intervention. Similarly, to estimate the percentage reduction in TB incidence, we compared the TB incidence between the model simulations with and without the intervention. To quantify the efficiency of the ACF, we also estimated the number of cases averted within 10-year period after ACF per case detected via ACF in each of the VDCs across four districts.

### Sensitivity analysis

To explore the sensitivity of the model results to the changes in model parameters, we conducted multivariate uncertainty analyses. We generated 10 000 parameter sets using Latin hypercube sampling, calibrated and simulated the models in each of the VDCs across four districts, estimating the impact of ACF (in terms of number of cases averted in 10 years post ACF). For each model parameter, we compared the simulations corresponding to subsets of parameter values in the top and bottom deciles. The details of this multivariate sensitivity analysis are included in the supplementary materials (S3).

### Patient and public nvolvement

No patients were directly involved in this study.

## RESULTS

### Geographic heterogeneity in TB notification rates

TB notification rates varied between the four districts (figure 1A). Average notification rates per 100 000 per year between 2016 and 2017 were 140 (range: 38–289) in Chitwan, 88 (11–257) in Dhanusha, 125 (7–421) in Mahottari and 166 (0–438) in Makwanpur, respectively (figure 1B). Variability in the TB notification rates within the districts was substantially more pronounced, the VDC-level notification rates varied by more than 10-fold between VDCs (figure 1A). Risk inequality coefficient,[30] a measure of heterogeneity, estimated from the Lorenz curves[31] were between 0.19 in Chitwan and 0.3 in Mahottari (figure 1C).

### Geographic distribution of TB cases detected during ACF

IMPACT-TB ACF activities identified a total of 1176 cases (488 in Chitwan, 270 in Dhanusha, 301 in Mahottari and 117 in Makwanpur) between June 2017 and June 2019. Of those, we were able to match 1043 identified cases (88%) with their corresponding VDC address. These included 462 cases in Chitwan, 230 in Dhanusha, 280 in Mahottari and 71 in Makwanpur. Uptake of ACF activities was substantially delayed in Makwanpur due to the tragic road traffic accident death of the District TB and Leprosy Officer at the start of the project and subsequent disruption to TB activities in the district, which resulted in substantially lower number of cases detected. Cases were detected in the majority of VDCs. Of 263 VDCs across the four districts, cases were detected in 167 (63%). Excluding Makwanpur, where cases were detected in only 10 out of 45 VDCs, cases were detected in 72% of all VDCs in the remaining three districts (figure 2).

We assessed the correlation between the number of cases detected in each of the VDCs and the annual notifications in the corresponding VDC. The degree of correlation varied substantially between the districts: the correlation coefficients were 0.31 in Mahottari, 0.71 in Dhanusha, 0.91 in Makwanpur and 0.97 in Chitwan (figure 3). The correlations were generally much weaker when very large VDCs, with more than 100 case notifications per year on average, were excluded from the analysis. There was one such VDC in each of the four districts, and the correlation coefficients in the remaining VDCs were 0.31 in Mahottari, 0.5 in Chitwan, 0.52 in Dhanusha and 0.85 in Makwanpur. When the notification rates were limited to microbiologically confirmed cases, correlations between cases found during ACF and notification rates of microbiologically confirmed cases did not differ substantially (online supplemental figure S3).

### Epidemiological impact of ACF

The projected impact of ACF on TB incidence rates varied between small to moderate across the four districts. Percentage reduction in TB incidence rates in the immediate aftermath of the ACF in Chitwan was 14% (low transmission scenario: 12—high transmission scenario: 16), 8.6% (7.3–9.7); in Dhanusha 8.3% (7.3–9.2) in Mahottari

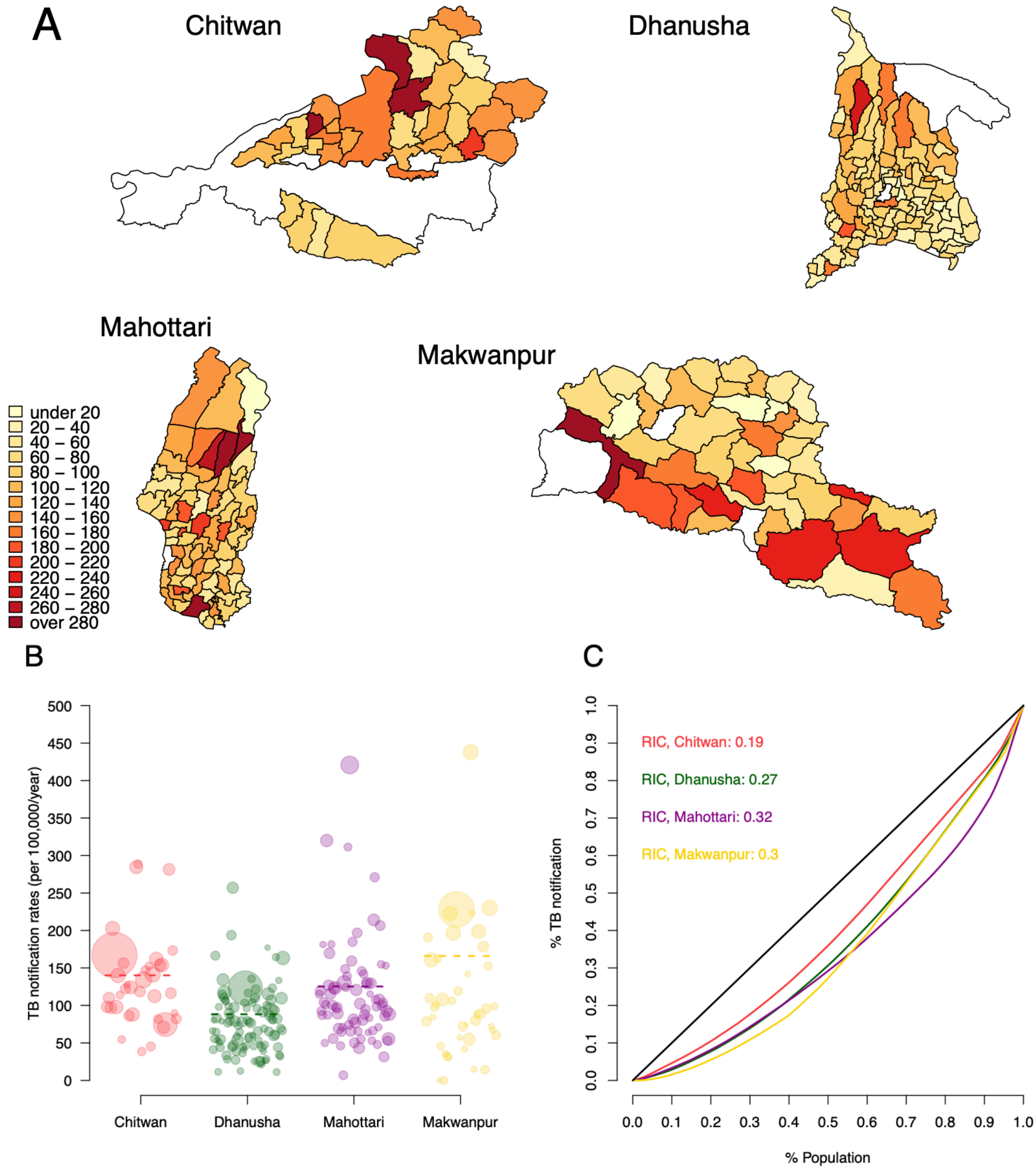


**Figure 1** Geographic heterogeneity in TB notification rates in four districts of Nepal. (A) The choropleth maps show TB case notification rates (per 1 00 000/year averaged at the VDC level between 2016 and 2017) in the four districts: Chitwan, Dhanusha, Mahottari and Makwanpur. (B) TB notification rates in VDCs of each of the four districts. The bubble size represents the VDC population size, and the dashed line shows the weighted average in each district. (C) Shown are Lorenz curves for each of the four districts, with cumulative population on the horizontal axis and cumulative TB notification on the vertical axis. TB, tuberculosis; VDC, village development committee.

and 3% (2.5–3.2) in Makwanpur. The reductions (in the absence of additional changes in TB care) were unlikely to be sustained over time. After 10 years, the reduction in TB incidence across all four districts was below 2% (figure 4). However, these small to moderate reductions in TB incidence rates would nonetheless translate into a substantial number of TB cases that would be averted for the next 10 years: 987 cases (746–1282) in Chitwan, 422 (304–571) in Dhanusha, 598 (450–782) in Mahottari and 197 (172–240) in Makwanpur. A substantial proportion of these impacts were projected to occur in VDCs with low to medium notification rates: for example, more than 50% of the cases averted in Dhanusha and Mahottari were projected to occur in VDCs with notification rates between 50 and 150 per 100 000/year (online supplemental figure S4).

### Projected relative efficiency of ACF

The efficiency of ACF, measured as the projected number of cases averted per treated case, was estimated to be 2.2 in Chitwan, 1.9 in Dhanusha, 2.1 in Mahottari and 2.8 in Makwanpur. Additionally, there was substantial variability in this ratio within the districts, with up to twofold

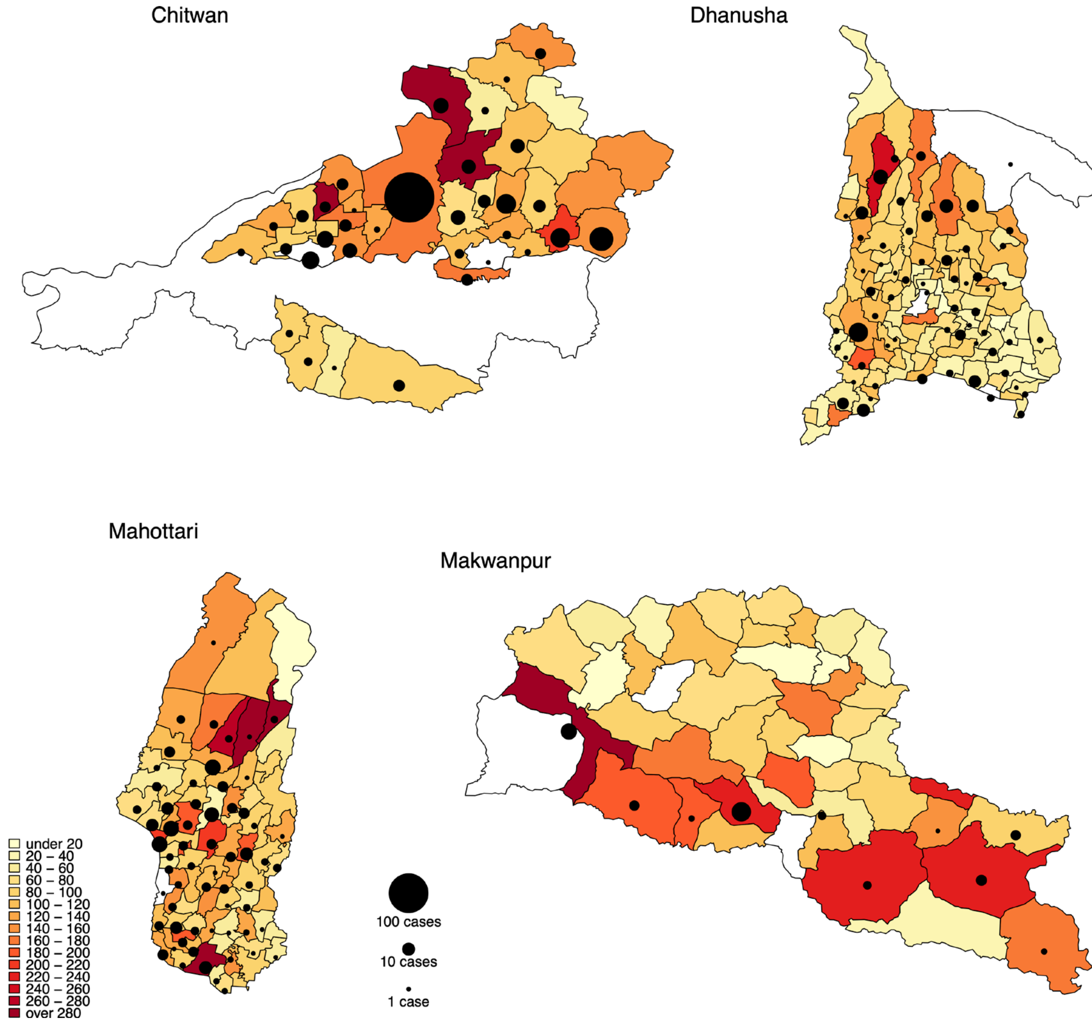


**Figure 2** Cases detected during IMPACT TB active case finding activities in Chitwan, Dhanusha, Mahottari and Makwanpur. The number of TB cases detected in each VDC in the four districts is shown in black bubbles, overlaid on top of the choropleth map of TB notification rates. TB, tuberculosis; VDC, village development committee.

differences in the efficiency of ACF in averting future TB cases within VDCs in each of the four districts (figure 5).

### Sensitivity of model outcomes to natural history parameters

The model results (impact of ACF) were most sensitive to two model parameters that directly specify the overall contribution of recent transmission to TB incidence: the reactivation rate (ie, higher reactivation implies lower recent transmission) and the fraction of recent exposures that progress rapidly to active TB disease (see online supplemental figure S5). The model results were not substantially affected by variation around other model parameters.

## DISCUSSION

In this study, we aimed to estimate the local impact of ACF in four districts of Nepal, namely—Chitwan, Dhanusha, Mahottari and Makwanpur, which represent high-burden, low-resource settings. Our approach involved developing a VDC-level model of ACF using local data on TB notifications as well as data collected during ACF conducted as a component of the IMPACT-TB project (www.impacttb-project.org). Using these data-driven models, we estimated the projected district-level impact of ACF and assessed the potential of optimising ACF by geographic targeting.

There were several important findings resulting from this study. First, relatively modest ACF activity can avert a large number of future TB cases. However, the epidemiological impact of short-term ACF interventions diminishes over time, and ACF activity needs to be sustained long term to have a substantial impact on TB incidence. This modelling analysis suggests that this 2-year case finding through IMPACT TB in the four southern districts of Nepal could avert around two thousand future TB cases. As such, ACF is generally an efficient tool for finding cases and preventing future cases—we estimated that ACF is averting between 1.5 and 3 cases within 10 years per TB case treated during ACF. However, ACF alone is not likely to alter the course of TB epidemiology in these settings unless other aspects of the diagnosis and care cascade are also strengthened.[32] Instead, ACF is one

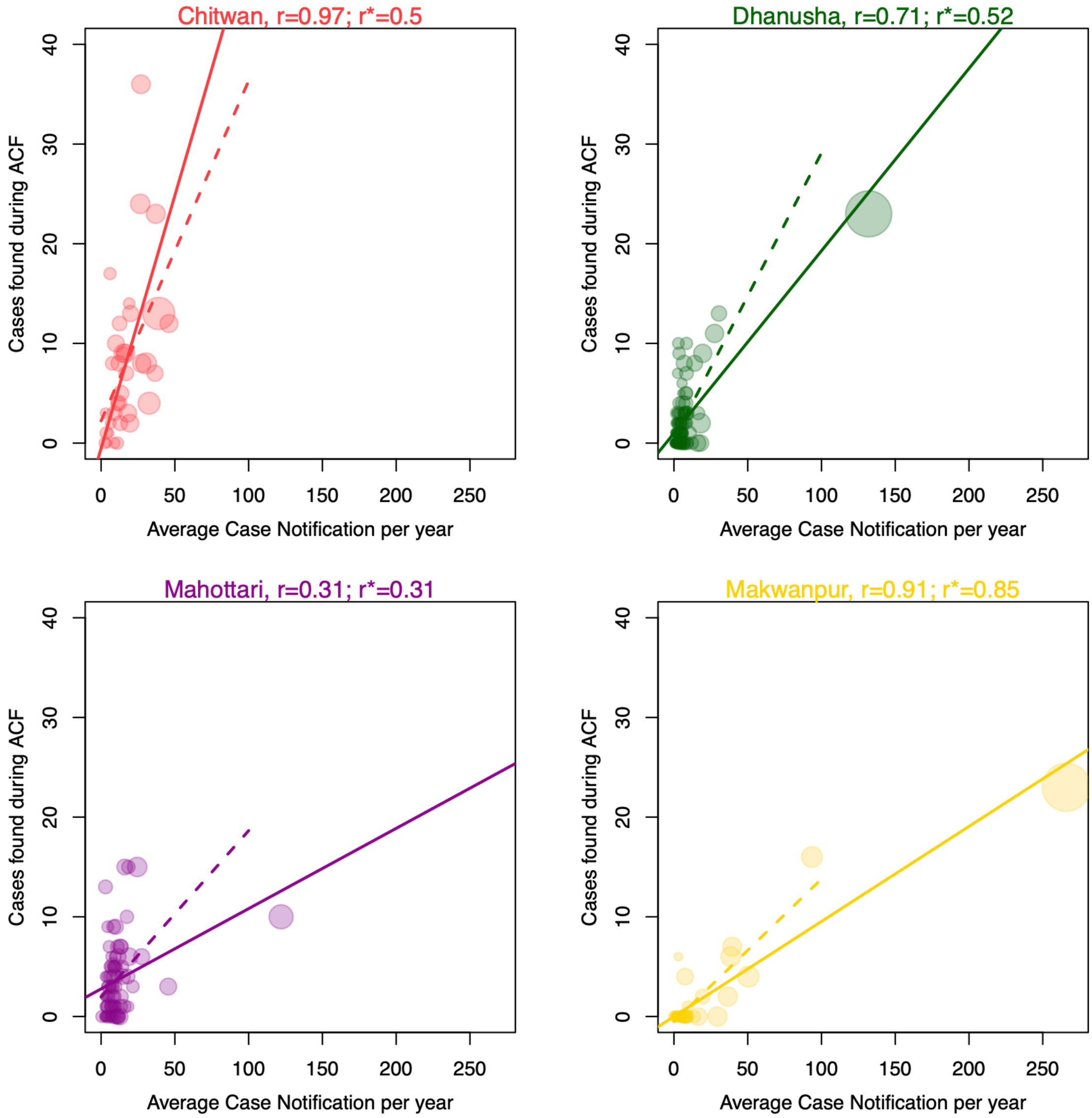


**Figure 3** Correlation between case notification and cases detected with active case finding. Shown is the correlation between notifications (horizontal axis) and the number of cases detected during ACF (vertical axis) in Chitwan, Dhanusha, Mahottari and Makwanpur. Indicated in each panel are (i) correlation coefficient, r, the degree of association between the case notification and the number of cases detected during ACF in the district, (ii) correlation coefficient, r*, when excluding the VDCs with more than 100 average notifications per year. Each district had one such VDC. The solid and dashed lines show the corresponding linear fits. Note for Chitwan, the largest VDC with 314 average annual notifications and 161 detected cases during ACF is not shown on the graph. ACF, active case finding; VDC, village development committee.

essential component of a comprehensive approach to TB elimination. It is crucial that ACF programmes complement, rather than replace, passive case finding backbones of TB diagnosis. Ideally, ACF will be accompanied by a significant strengthening of the passive diagnostic system, including laboratory strengthening and scale-up of molecular diagnostic testing. We estimated that ACF (of the scale that the IMPACT-TB project managed to conduct) is unlikely to reduce TB incidence rates by more than 15%, and this effect is likely to wane over time. Unless case finding efforts can be scaled up and sustained over at least a decade to cover a large portion of the entire communities,[13] it is unlikely to bring a sizeable reduction in TB incidence.

Second, the observed correlations between notification data and ACF yield suggest that notification can help generate reasonable first-degree estimates for where and how many cases are likely to be detected during ACF and in setting realistic local-level detection targets, especially for larger population centres, or when aggregated at district levels, as others have noted.[33] However, we found substantial variability, especially in VDCs with low to medium reporting rates. The fact that ACF detected substantially more cases in these communities (than one would have expected based on local notification rates) may indicate that these communities are under-reporting TB, in line with the findings from the 2018 prevalence survey, which showed TB prevalence to be much higher than previously

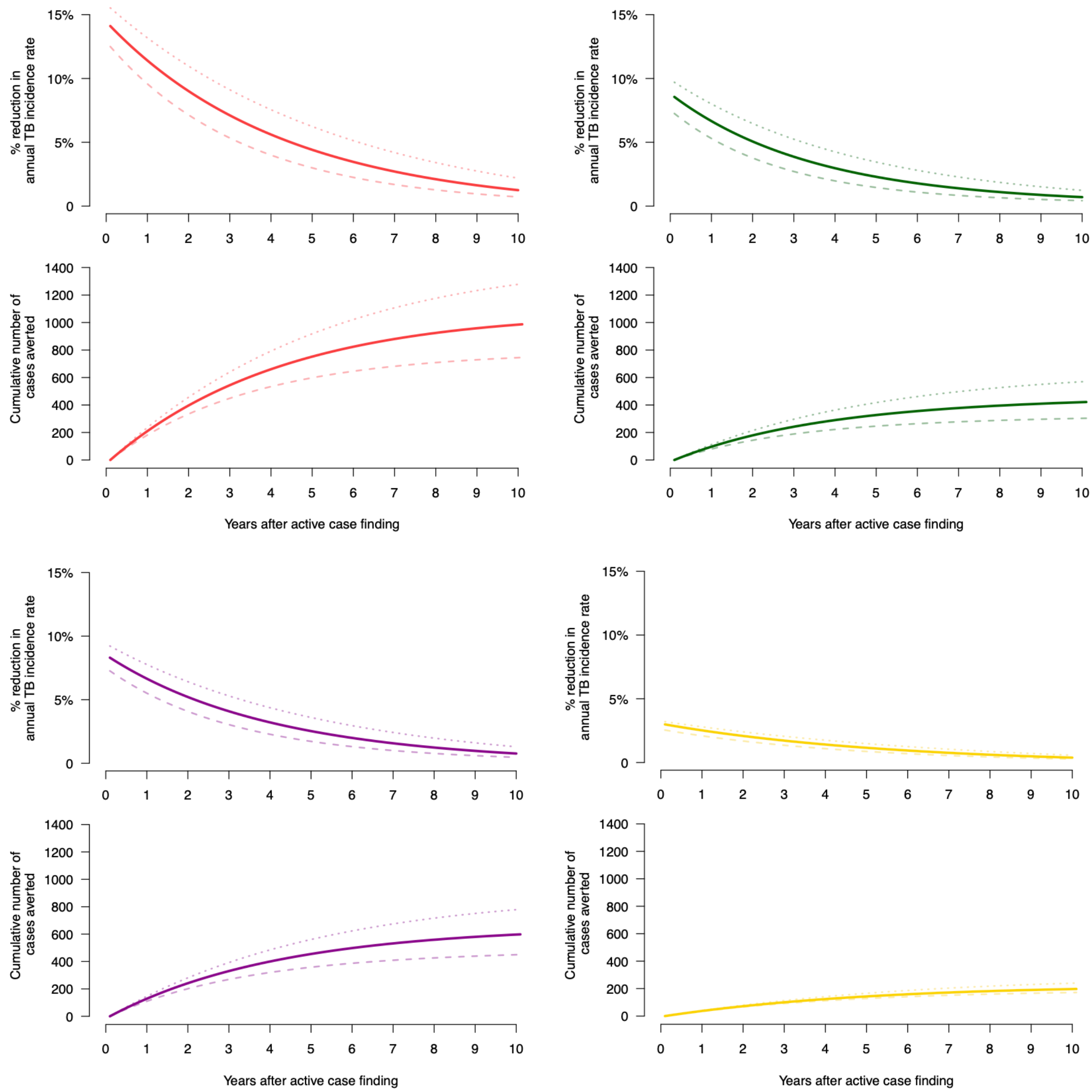


**Figure 4** Projected future impact of active case finding across four districts. Each panel shows (top) projected percentage reductions in annual TB incidence rates and (bottom) projected cumulative cases averted over the 10-year period after the completion of ACF. Red lines correspond to Chitwan, green to Dhanusha, purple to Mahottari and yellow to Makwanpur. Solid lines correspond to baseline scenarios; dashed lines correspond to low transmission scenarios; and dotted lines to high transmission scenarios. ACF, active case finding; TB, tuberculosis.

estimated. Intensified case finding or broader high-risk population screening approaches may be appropriate in VDCs with low notification rates, applying strategies such as the TB SWEEP initiative in Vietnam, and should be trialled to establish effectiveness in detecting undiagnosed TB in these communities.[34]

Finally, the impact of ACF is likely to be heterogeneous at finer local scales, such as at the level of VDCs. This reflects the heterogeneity underlying the transmission risk of TB and the ability to find TB cases during ACF. We estimated that there were more than 10-fold differences in local notification rates within each of the districts, and consequently, there can be up to twofold difference in the efficiency of ACF. In other words, ACF in some VDCs could be two times as impactful as in others. This suggests that being able to tailor interventions locally may help increase the efficiency and impact of ACF[22 35] and optimise cost-effectiveness and access to care; however, notification data alone may not be sufficient to quantify risks accurately.

As with any modelling study, we make several modelling assumptions in this study. First, we used home addresses recorded during ACF to ascertain patients' home VDC. These addresses are likely to have been self-reported by the patients, and the manual process of assigning home addresses to VDCs could have led to misspecification.

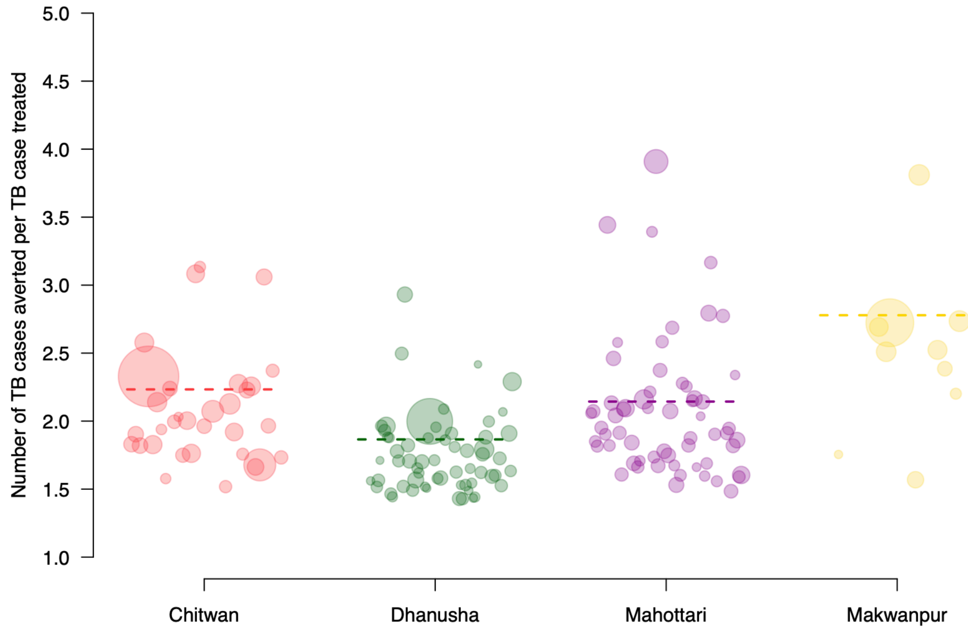


**Figure 5** VDC-level heterogeneity in the efficiency of the projected impact of active case finding. Shown are the projected number of cases averted over a 10-year period after active case finding per TB cases treated through ACF in each VDC, with at least one case detected across all four districts. Each bubble represents a VDC, and the size of the bubble represents the population of the VDC. The dashed horizontal lines represent a weighted average for each district. ACF, active case finding; TB, tuberculosis; VDC, village development committee.

Second, we do not model the movement of TB cases and transmission of cases across VDC borders. We would expect a substantial mixing of people, especially in the urban centres of these districts. We also expect migration of individuals, especially from rural VDCs to urban areas. Both of these can have important implications for the epidemiology of TB.[36] However, the mixing and movements of individuals at these scales are hard to quantify, especially in a low-resource setting like Nepal. By only considering local transmission dynamics, we may be underestimating the impact of ACF in some of the VDCs. Third, we have attributed heterogeneity in TB notification to differences in transmission rates. However, many VDC-level factors can be driving these differences, including differences in socioeconomic demographic factors (eg, size of the elderly population, lower socioeconomic conditions), the prevalence of other risk factors (eg, prevalence of smoking, alcohol consumption, diabetes), strength and proximity of healthcare facilities (eg, time/cost of getting to the closest microscopy centre).[37–39] Fourth, we have used a relatively simple natural history model, which does not capture heterogeneity in TB disease (eg, subclinical TB, smear positive and negative TB), demographic heterogeneity (eg, risk of TB and latent TB infection [LTBI] by sex and age) and long-term resolution and reactivation of LTBI. LTBI prevalence, and more generally, the proportion of incident cases resulting from reactivation, is an important determinant of how impactful ACF will be. However, data informing these critical factors are currently lacking and is a limitation of this approach. Finally, we have assumed that cases found through ACF represent average prevalent TB cases in these communities. However, ACF could be finding cases that are disproportionately less likely to seek healthcare (eg, elderly) or cases that are at an early presymptomatic stage before they begin transmitting.[40 41] In such a scenario, our projections are likely to be underestimates since individuals found through ACF could be contributing to transmission more than an average TB case. Conversely, it is also conceivable that most cases detected through ACF would either have sought diagnosis in the near future (ie, ACF only shortened their infectious duration by a small amount) or are likely to self-resolve[42] (without contributing significantly to transmission). In this instance, our projections are likely to be overestimates.

In summary, this work suggests that incorporating primary data from ACF can improve models TB in these high-burden settings by capturing some of the under-reporting that is not reflected in standard notification data and potentially help optimise ACF by identifying geographic areas where ACF may have a disproportionately larger impact. Data collected during ACF suggest that TB is widely prevalent in these communities, corroborating the national prevalence survey findings, and concerted efforts to detect TB are likely to be successful in finding TB cases. Our modelling analyses suggest that ACF is likely to be a highly efficient and cost-effective tool for TB control in these local communities. However, limited duration ACF, which only captures a small fraction of prevalent TB cases, is not likely to have a course-altering population-level pact on local TB epidemiology if other factors contributing to the TB burden and transmission, including health system-related factors are not addressed. The END-TB strategy goals for progress towards TB elimination require comprehensive, system-based approaches incorporating FIND-TREAT-PREVENT strategies to cure every case and protect vulnerable groups from exposure.

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**Contributors** SS contributed to planning and conceptualisation of the project, modelling, data analysis, and manuscript writing. GM contributed to data acquisition, collation, analysis, and manuscript writing. MH contributed to data collation, analysis, and manuscript writing. RD, SS, AS, NPS, MK, SG: contributed to data acquisition, and manuscript writing. MC contributed to planning and conceptualisation of the project, and manuscript writing. All authors read and approved the manuscript. SS accepts full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

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**Competing interests** None declared.

**Patient and public involvement** Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication** Not applicable.

**Ethics approval** We did not seek IRB approval for this modeLling study because it only used secondary de-identified data collected as part of the parent study. The ethical approvals for the parent study were received from the Liverpool School of Tropical Medicine (LSTM) [N 17-019] and the Nepal Health Research Council [149/2017].

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**Data availability statement** Data are available upon reasonable request. Data and model codes are shared at the following repository: https://doi.org/10.5281/zenodo.8092803



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## REFERENCES

1 WHO. Global tuberculosis report 2020. 2020.
2 Subbaraman R, Nathavitharana RR, Satyanarayana S, *et al*. The tuberculosis cascade of care in India's public sector: a systematic review and meta-analysis. *PLoS Med* 2016;13:e1002149.
3 Sreeramareddy CT, Qin ZZ, Satyanarayana S, *et al*. Delays in diagnosis and treatment of pulmonary tuberculosis in India: a systematic review. *Int J Tuberc Lung Dis* 2014;18:255–66.
4 Choudhari M, Jha N, Yadav DK, *et al*. Factors associated with patient delay in diagnosis of pulmonary tuberculosis in a district. *J Nepal Health Res Counc* 2013.
5 Bronner Murrison L, Ananthakrishnan R, Swaminathan A, *et al*. How do patients access the private sector in Chennai, India? An evaluation of delays in tuberculosis diagnosis. *Int J Tuberc Lung Dis* 2016;20:544–51.
6 Golub JE, Mohan CI, Comstock GW, *et al*. Active case finding of tuberculosis: historical perspective and future prospects. *Int J Tuberc Lung Dis* 2005;9:1183–203.
7 Kranzer K, Afnan-Holmes H, Tomlin K, *et al*. The benefits to communities and individuals of screening for active tuberculosis disease: a systematic review [state of the art series. *Int J Tuberc Lung Dis* 2013;17:432–46.
8 Murray CJL, Salomon JA. Expanding the WHO tuberculosis control strategy: rethinking the role of active case-finding [The Pittsfield Lecture]. *Int J Tuberc Lung Dis* 1998;2:S9–15.
9 Azman AS, Golub JE, Dowdy DW. How much is tuberculosis screening worth? Estimating the value of active case finding for tuberculosis in South Africa, China, and India. *BMC Med* 2014;12:216.
10 Dowdy DW, Lotia I, Azman AS, *et al*. Population-level impact of active tuberculosis case finding in an Asian Megacity. *PLoS One* 2013;8:e77517.
11 Ayles H, Muyoyeta M, Du Toit E, *et al*. Effect of household and community interventions on the burden of tuberculosis in Southern Africa: the ZAMSTAR community-randomised trial. *Lancet* 2013;382:1183–94.
12 Corbett EL, Bandason T, Duong T, *et al*. Comparison of two active case-finding strategies for community-based diagnosis of symptomatic smear-positive tuberculosis and control of infectious tuberculosis in Harare, Zimbabwe (DETECTB): a cluster-randomised trial. *Lancet* 2010;376:1244–53.
13 Marks GB, Nguyen NV, Nguyen PTB, *et al*. Community-wide screening for tuberculosis in a high-prevalence setting. *N Engl J Med* 2019;381:1347–57.
14 Burke RM, Nliwasa M, Feasey HRA, *et al*. Community-based active case-finding interventions for tuberculosis: a systematic review. *Lancet Public Health* 2021;6:e283–99.
15 Gurung SC, Dixit K, Rai B, *et al*. The role of active case finding in reducing patient incurred catastrophic costs for tuberculosis in Nepal. *Infect Dis Poverty* 2019;8:99:99.:.
16 Gurung SC, Rai B, Dixit K, *et al*. How to reduce household costs for people with tuberculosis: a longitudinal costing survey in Nepal. *Health Policy Plan* 2021;36:594–605.
17 Gurung SC, Dixit K, Rai B, *et al*. Comparative yield of tuberculosis during active case finding using Genexpert or smear microscopy for diagnostic testing in Nepal: a cross-sectional study. *Trop Med Infect Dis* 2021;6:50.
18 Khanal S, Baral S, Shrestha P, *et al*. Yield of intensified tuberculosis case-finding activities using Xpert Extregistered MTB/RIF among risk groups in Nepal. *Public Health Action* 2016;6:136–41.
19 Joshi B, Chinnakali P, Shrestha A, *et al*. Impact of intensified case-finding strategies on childhood TB case registration in Nepal. *Public Health Action* 2015;5:93–8.
20 Shrestha S, Knight GM, Fofana M, *et al*. Drivers and Trajectories of resistance to new first-line drug regimens for tuberculosis. *Open Forum Infect Dis* 2014;1:ofu073.
21 Blower SM, Small PM, Hopewell PC. Control strategies for tuberculosis epidemics: new models for old problems. *Science* 1996;273:497–500.
22 Shrestha S, Reja M, Gomes I, *et al*. Quantifying geographic heterogeneity in TB incidence and the potential impact of geographically targeted interventions in South and North city corporations of Dhaka, Bangladesh: a model-based study. *Epidemiol Infect* 2021;149:e106.
23 Dye C, Garnett GP, Sleeman K, *et al*. Prospects for worldwide tuberculosis control under the {WHO DOTS} strategy. *The Lancet* 1998;352:1886–91.
24 Vynnycky E, Fine PE. The natural history of tuberculosis: the implications of age-dependent risks of disease and the role of Reinfection. *Epidemiol Infect* 1997;119:183–201.
25 Horsburgh CR, O'Donnell M, Chamblee S, *et al*. Revisiting rates of reactivation tuberculosis: {A} population-based approach. *Am J Respir Crit Care Med* 2010;182:420–5.
26 Sutherland I. Recent studies in the epidemiology of tuberculosis, based on the risk of being infected with Tubercle Bacilli. *Adv Tuberc Res* 1976;19:1–63.

27 Vynnycky E, Fine PE. The annual risk of infection with Mycobacterium tuberculosis in England and Wales since 1901. *Int J Tuberc Lung Dis* 1997;1:389–96.
28 Basu S, Orenstein E, Galvani AP. The theoretical influence of immunity between strain groups on the progression of drug-resistant tuberculosis epidemics. *J Infect Dis* 2008;198:1502–13.
29 Andrews JR, Noubary F, Walensky RP, *et al*. Risk of progression to active tuberculosis following Reinfection with Mycobacterium tuberculosis. *Clin Infect Dis* 2012;54:784–91.
30 Gomes MGM, Oliveira JF, Bertolde A, *et al*. Introducing risk inequality Metrics in tuberculosis policy development. *Nat Commun* 2019;10:2480:2480.:.
31 Lorenz MO. Methods of measuring the concentration of wealth. *Publ Am Stat Assoc* 1905;9:209.
32 Shrestha S, Kendall EA, Chang R, *et al*. Achieving a "step change" in the tuberculosis epidemic through comprehensive community-wide intervention: a model-based analysis. *BMC Med* 2021;19:244.
33 Robsky KO, Kitonsa PJ, Mukiibi J, *et al*. Spatial distribution of people diagnosed with tuberculosis through routine and active case finding: a community-based study in Kampala, Uganda. *Infect Dis Poverty* 2020;9:73.
34 Creswell J, Khan A, Bakker MI, *et al*. The TB REACH initiative: supporting TB elimination efforts in the Asia-Pacific. *Trop Med Infect Dis* 2020;5:164.
35 Shaweno D, Trauer JM, Doan TN, *et al*. Geospatial clustering and Modelling provide policy guidance to distribute funding for active TB case finding in Ethiopia. *Epidemics* 2021;36.
36 Dowdy DW, Golub JE, Chaisson RE, *et al*. Heterogeneity in tuberculosis transmission and the role of geographic Hotspots in Propagating epidemics. *Proc Natl Acad Sci U S A* 2012;109:9557–62.
37 Shaweno D, Shaweno T, Trauer JM, *et al*. Heterogeneity of distribution of tuberculosis in Sheka zone, Ethiopia: drivers and temporal trends. *Int J Tuberc Lung Dis* 2017;21:79–85.
38 Trauer JM, Dodd PJ, Gomes MGM, *et al*. The importance of heterogeneity to the epidemiology of tuberculosis. *Clin Infect Dis* 2019;69:159–66.
39 Lönnroth K, Jaramillo E, Williams BG, *et al*. Drivers of tuberculosis epidemics: the role of risk factors and social determinants. *Soc Sci Med* 2009;68:2240–6.
40 Frascella B, Richards AS, Sossen B, *et al*. Subclinical tuberculosis disease - a review and analysis of prevalence surveys to inform definitions, burden, associations and screening methodology. *Clin Infect Dis* 2021;73:e830–41.
41 Kendall EA, Shrestha S, Dowdy DW. The Epidemiological importance of Subclinical tuberculosis. A critical reappraisal. *Am J Respir Crit Care Med* 2021;203:168–74.
42 Ragonnet R, Flegg JA, Brilleman SL, *et al*. Revisiting the natural history of pulmonary tuberculosis: A Bayesian estimation of natural recovery and mortality rates. *Clin Infect Dis* 2021;73:e88–96.