Tuberculosis transmission in HIV-endemic settings 3

Spatially targeted screening to reduce tuberculosis transmission in high-incidence settings

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As the leading infectious cause of death worldwide and the primary proximal cause of death in individuals living with HIV, tuberculosis remains a global concern. Existing tuberculosis control strategies that rely on passive case-finding appear insufficient to achieve targets for reductions in tuberculosis incidence and mortality. Active case-finding strategies aim to detect infectious individuals earlier in their infectious period to reduce onward transmission and improve treatment outcomes. Empirical studies of active case-finding have produced mixed results and determining how to direct active screening to those most at risk remains a topic of intense research. Our systematic review of literature evaluating the effects of geographically targeted tuberculosis screening interventions found three studies in low tuberculosis incidence settings, but none conducted in high tuberculosis incidence countries. We discuss open questions related to the use of spatially targeted approaches for active screening in countries where tuberculosis incidence is highest.

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This is the third in a Series of three papers about tuberculosis transmission in HIV-endemic settings

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Introduction

The annual rate of decline in global tuberculosis incidence is estimated to be 1·9%.[1] This estimate falls short of the 4% annual decline needed to meet the WHO End TB Strategy's 2020 milestone of a 20% reduction in incidence compared with 2015,[1] and the more ambitious target of a 90% reduction by 2035. Increased investment in the development of new tuberculosis diagnostics over the past two decades has brought new products to market,[2,3] but they have not yet been shown to have a substantial epidemiological effect.[4,5] Therefore, finding the best approaches to employing existing tools to reduce the incidence of tuberculosis remains a public health priority.

In countries with high burdens of tuberculosis and among individuals with HIV, most cases of incident tuberculosis arise as a result of recent transmission.[6,7] Thus, efforts to control tuberculosis in these settings depend on reducing transmission, which hypothetically could be achieved through earlier detection and treatment of individuals with active, infectious tuberculosis. Identifying practical approaches to detecting infectious individuals early in their course of disease has proven challenging. A systematic review failed to find conclusive evidence of the improved effectiveness of untargeted active case-finding compared with passive detection.[8] Furthermore, WHO guidance documents[9,10] recommend focusing active screening on individuals with HIV infection, household contacts of a tuberculosis case, and workers exposed to silica, and do not support the adoption of active case-finding in the general population. Active screening can include combinations of symptom interviews, chest radiography, sputum smear, or sputum rapid molecular testing, and is usually done outside of traditional health-care facilities (eg, mobile vans, homes, or shelters).

In addition to using individual-level risk factors to target screening, strategies that target active screening within geographically restricted populations (eg, neighbourhoods or subdistricts) could also be an effective and practical case-finding approach. As the quality and spatial resolution of surveillance systems have improved,[11] marked spatial heterogeneity in the incidence and prevalence of tuberculosis has been documented in various settings,[12–16] frequently approaching ten-fold variation in incidence within a single country. These patterns have motivated enthusiasm for spatially targeted interventions.[17–19] WHO conditionally recommends that "systematic screening for

Key messages

- Modelled analyses show that spatially targeted strategies for tuberculosis screening could help reduce local disease transmission and have beneficial effects outside the targeted areas, but empirical evidence in high-burden settings is lacking
- Issues remaining regarding the effectiveness of targeted strategies include:
  - The effectiveness of active tuberculosis screening in reducing transmission in high-burden settings
  - The degree to which hotspots of tuberculosis disease produce spillover risk for surrounding communities
  - The challenges and costs of implementing spatial targeting in programmatic settings
  - The community acceptability and ethical ramifications of targeting populations for additional screening
- Owing to differences in local transmission dynamics, lessons learned about the effectiveness of spatially targeted strategies from low tuberculosis incidence settings might not be directly applicable to high-incidence settings

active tuberculosis…be considered for geographically defined populations with extremely high levels of undetected tuberculosis (1% prevalence or higher)".[9] In most high-burden regions, recent prevalence surveys are not available; in such settings methods (eg, capture-recapture studies[20]) for identifying geographical areas where tuberculosis is underdiagnosed are still being validated.

In this Series paper, we consider the rationale and evidence supporting spatially targeted tuberculosis screening to reduce tuberculosis transmission. Spatial targeting concentrates screening within geographical hotspots of tuberculosis incidence that arise as a result of several different mechanisms (table 1). We review evidence relevant to high-burden countries, many of which also have a high prevalence of HIV, because these settings are where effective strategies are needed most. Although screening household contacts of individuals diagnosed with tuberculosis might be considered a very local form of spatial targeting, contact tracing has been reviewed by others[24,25] and is beyond the scope of this Series paper. In addition to considering the empirical and hypothetical basis for spatially targeted screening, we highlight gaps in knowledge that must be addressed before the effects and benefits of such approaches can be reliably predicted.

Premise of spatially targeted tuberculosis interventions

In many high-incidence settings, a large number of individuals with active tuberculosis will go undiagnosed and untreated. Many individuals who ultimately receive therapy experience substantial delays of months or years before being diagnosed, during which they might transmit infection to others.[26,27] Finding individuals with undiagnosed active tuberculosis and offering them treatment seems to be an attractive approach for reducing prevalence and interrupting transmission. However, a prevalence of active tuberculosis of more than 1% only occurs in countries with the highest burdens,[1] by contrast with pathogens like HIV and malaria, for which prevalence of infection in adults is more than 10% in some countries.[28,29] The low prevalence of tuberculosis challenges case-finding efforts, and might cause health officials in some settings to prioritise activities directed towards diseases with higher prevalence.

One approach to addressing challenges arising from a low prevalence of tuberculosis is to focus screening on subpopulations with disproportionately high prevalence of active disease. The hypothetical benefits of targeted approaches are clear: by identifying subpopulations with a high prevalence of disease, fewer people need to be screened to identify each case, leading to fewer false positive diagnoses and unnecessary treatments.[30] Targeted interventions might also produce local economies of scale, by focusing the use of limited resources in areas in which the burden is most concentrated, by contrast with geographically diffuse, untargeted interventions.

	Supporting evidence	Real-world example
Local transmission	Spatially aggregated risk of tuberculin skin test or interferon γ release assay conversion; spatial aggregation of genotypic clusters	Lima, Peru;[21] concentration of genetically related *Mycobacterium tuberculosis* isolates in a high-incidence area suggests local transmission as a cause of the hotspot
Concentration of risk factors for progression to active disease	Co-localisation of determinants of tuberculosis with hotspots of tuberculosis incidence	Urumqi, China;[22] overlapping high incidence areas of tuberculosis and tuberculosis with HIV co-infection
Migration of individuals from areas with higher risks of infection and disease	Higher tuberculosis incidence in areas where migrants cluster	Shandong province, China;[23] areas of high incidence along major transportation routes

Table 1: **Mechanisms producing spatially aggregated areas of high tuberculosis incidence**

Promise of spatially targeted screening

The potential advantages of strategies that account for marked spatial heterogeneities in tuberculosis burden over strategies that ignore such variability are intuitively compelling. Control programmes for other infectious diseases, including immunisation campaigns, have implemented geographically targeted strategies.[31] But is there empirical evidence to support active screening for tuberculosis?

We conducted a literature search for studies in high-burden settings that used spatial analyses of tuberculosis to guide subsequent screening interventions to lower tuberculosis transmission or prevalence (figure). Articles had to include a spatial analysis of tuberculosis burden (eg, incidence, prevalence, proportion of drug resistance, or proportion of recently transmitted cases) and an intervention that was targeted on the basis of the spatial data. We found just three studies[32–34] that described a geographically targeted screening intervention, each of which was done in low-incidence areas within the USA. We did not identify any such studies done in high tuberculosis incidence settings. Although spatially targeted screening could yet prove to be an effective strategy, little evidence exists of its effect in areas with high burdens of tuberculosis.

In the absence of direct empirical evidence of the effects of targeted screening, modelling has provided some insight into factors that could hypothetically modify the efficacy of spatially targeted screening. Models of transmission dynamics provide a useful framework for estimating the direct effect of spatially targeted screening on screened populations and the indirect effect on transmission. For example, Dowdy and colleagues[35] created a tuberculosis model of Rio de Janeiro, where substantial spatial heterogeneity in tuberculosis notifications exists. They estimated the degree to which three hotspots of tuberculosis incidence contributed to transmission in the city as a whole. Next, they modelled case-finding interventions targeted at the hotspots and found that the benefits of such

targeting in reducing city-wide incidence were dependent on the amount of social mixing between individuals in the hotspot and surrounding areas,[35] which is not typically well measured. In one scenario, within which a hotspot comprised 6% of the city's population, reducing transmission within the hotspot had a similar effect on reducing long-term overall city tuberculosis rates as halving the time to treatment among the remaining 94% of the city's population. Under most modelled assumptions of hotspot-to-community population mixing, screening efforts focused within the hotspots seemed to improve tuberculosis control in the city overall.

Open problems in spatially targeted screening

Despite a reasonable premise in support of spatially targeted tuberculosis screening, the scarcity of empirical evidence of the epidemiological effects suggests the need for caution. A community randomised trial[36] of spatially targeted approaches for malaria control (which was justified in part on promising transmission modelling studies[37]) did not show an effect on overall community malaria prevalence. The authors concluded that there was no significant effect outside the targeted hotspots because "transmission may not primarily occur from hotspots to the surrounding areas". Although the mode of malaria transmission differs from tuberculosis, this example provides an important reminder that we must actually test these spatially targeted tuberculosis strategies to determine their effect. Empirical studies will also inform our understanding of epidemiological mechanisms driving local heterogeneities. In the absence of ambitious randomised studies of spatially targeted tuberculosis screening strategies that can provide definitive evidence of their effect, there remain several tractable questions that, if addressed, will help to identify settings in which they will be most beneficial.

When can we improve tuberculosis control within targeted areas?

Surprisingly, there are few studies that assessed the community level effects of tuberculosis screening; a systematic review in 2013 found only five.[8] The authors concluded that the evidence for screening's effect on reducing community tuberculosis incidence or prevalence was weak. Active screening does increase the number of individuals with tuberculosis found. However, we do not know the proportion of transmission events that can be averted through earlier detection and treatment,[9] because people diagnosed during earlier, less symptomatic stages of disease might be less infectious, but also less likely to initiate and complete therapy.[38]

Studies of active case-finding in high-burden settings illustrate current uncertainty about the effectiveness of community level screening. In Zimbabwe, a cluster randomised trial of active case-finding (DETECTB) showed that screening using mobile vans resulted in an increase in case notifications, leading to a 40% reduction in the prevalence of active tuberculosis by the end of six rounds of screening over 2 years.[39] By contrast, a cluster randomised controlled trial in South Africa and Zambia (ZAMSTAR) found no statistically significant effect of two active case-finding strategies (community-level enhanced tuberculosis case-finding and household level tuberculosis–HIV care) on the prevalence of active tuberculosis.[40] These studies differed in several ways, in terms of both epidemiological setting and the specific approaches used for active case-finding, which makes it difficult to understand what drove these different outcomes. Nevertheless, unless screening interventions can reliably produce detectable reductions in tuberculosis prevalence in high-burden settings, targeting screening to areas of high incidence is unlikely to be successful.

Hotspots of tuberculosis incidence might not necessarily arise as a result of local transmission (table 1). Understanding the degree to which local transmission is responsible for the local concentration of incident tuberculosis is important for estimating the potential epidemiological effects of spatially targeted active screening. A growing number of investigations bring together spatial and pathogen genetic analyses to offer new insights into the importance of local transmission on the generation and maintenance of tuberculosis incidence hotspots (table 2). The increased resolution of whole genome sequencing in determining clusters of recent tuberculosis transmission will help to increase the power of these studies.[46]

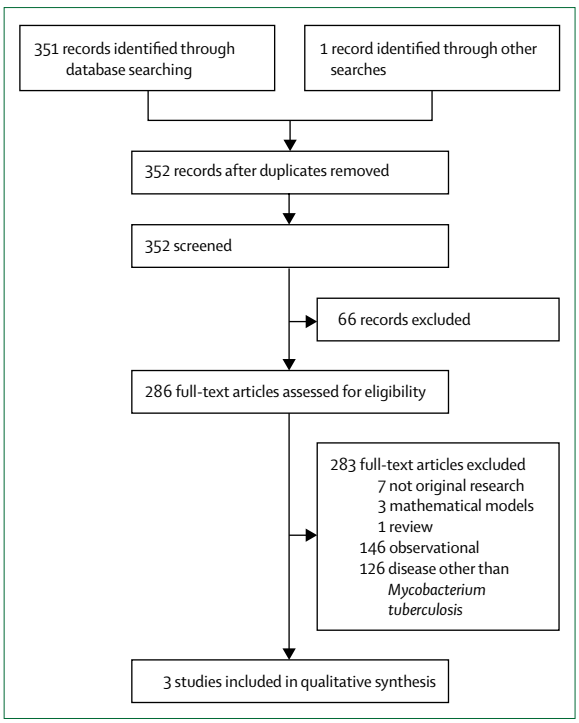

Figure: **Flow diagram of the selection of studies for systematic review**

	Spatial data	Pathogen genetic data	Conclusion
All people with culture-positive tuberculosis in a mid-sized city in Brazil[41]	Household location	IS6110 RFLP	Most transmission observed outside the household, but within locations <2000 m away
All people diagnosed with tuberculosis in 12 of the 43 districts of metropolitan Lima, Peru[23]	Household location	24-loci MIRU-VNTR	Location was an equally strong risk factor for multidrug-resistant tuberculosis as history of prior tuberculosis treatment
All people with culture-positive tuberculosis in two urban communities in South Africa[42]	Household location	IS6110 RFLP	Within a very high tuberculosis incidence community there was extensive transmission outside the household but within the community
All people diagnosed with tuberculosis in a rural town in eastern Uganda[43]	Household, health-care, work, and social locations	Spoligotyping	Transmission likely at health-care and social venues
Most people diagnosed with tuberculosis in 14 Inuit communities in Canada[44]	Community location	Whole genome sequencing	Transmission more common within each community than between communities with limited contact
All people with culture-positive tuberculosis in a suburb of Shanghai[45]	Household location	12-loci MIRU-VNTR and whole genome sequencing for strains within MIRU clusters	Spatial proximity positively associated with genomic similarity among strains within a MIRU cluster, consistent with local transmission

RFLP=restriction fragment length polymorphism. MIRU-VNTR=mycobacterial interspersed repetitive units–variable numbers of tandem repeats. Spoligotyping=spacer oligonucleotide typing.

Table 2: **Examples of study settings using spatial and pathogen genetic data to understand local transmission in populations**

Spatially targeted interventions could still be effective even in incidence hotspots not driven by transmission, such as those arising from migration or aggregation of vulnerable hosts. The intervention strategies employed might differ depending on the mechanism driving the hotspot. For example, an incidence hotspot resulting from a concentration of risk factors for progression to active disease (eg, malnutrition or HIV) might benefit more from detection and treatment of latent tuberculosis infection than an incidence hotspot resulting from local transmission.

Will improvements in local control achieved through targeted screening affect the surrounding areas?

If targeted screening in high-burden areas is successful in lowering incidence locally, do benefits in the hotspot also accrue to individuals living outside the area? Transmission dynamic models[35] suggest that targeted screening on high incidence hotspots is more effective at lowering community-wide tuberculosis incidence when tuberculosis transmission spills over from hotspots to surrounding areas. Increasingly, pathogen genotyping[21,47] and social network and mobility data[48] have been used to understand the transmission of disease across spatial gradients.

Several studies have documented how hotspots may serve as transmission sources for tuberculosis in the wider community. For example, using spatial and pathogen genetic data from Lima, Peru, Zelner and colleagues[21] identified patterns of disease that were consistent with transmission of multidrug-resistant tuberculosis from a hotspot to surrounding areas of the city. In Brazil, Sacchi and colleagues[47] found that epidemiological and pathogen genotypic links suggested that increased tuberculosis transmission occurred within prisons, and extended into the communities surrounding the prison. Such data provide evidence that spillover from hotspots to the broader community occurs, but the extent to which this spillover occurs on a population level will influence the effects spatially targeted case detection has on tuberculosis incidence in the community. Understanding the genetic relatedness of tuberculosis isolates from within geographical hotspots and between isolates from those hotspots and lower burden areas could inform better estimates of the probable effects of targeted interventions. New approaches to characterising transmission events on the basis of whole genome sequencing data could yield additional insights into these patterns.[49]

Is spatially targeted screening practical?

Spatially targeted screening strategies will be possible only if surveillance systems can reliably identify areas where tuberculosis incidence is most intense, and distinguish true variability in incidence from variability in population density, tuberculosis detection, or reporting. Improvements in tuberculosis surveillance systems are needed to increase the effectiveness of interventions,[50] yet many high-burden countries have struggled to implement high-quality tuberculosis surveillance systems.[51] If quality of surveillance is poor or variable within a country, routine tuberculosis notification might not adequately identify true spatial clusters of tuberculosis, because those individuals most affected by tuberculosis often have the least access to tuberculosis services.[52] Furthermore, even with increasingly cheap and accessible tools for production, processing, and analysis of spatial data,[11] local expertise might need to be developed to ensure data quality and reliable analysis and interpretation.

Additionally, the financial costs of targeted screening interventions are uncertain. Hotspot identification might require improvements in routine surveillance or periodic surveys. Furthermore, targeted screening could decrease costs by focusing efforts on high-yield areas; or it could increase costs, if identifying and operating in hotspots is expensive because of transient populations, weak infrastructure, and few local health-care facilities from which to operate. Studies in challenging high-burden settings,[53,54] such as Cambodia and South Africa, have shown specific non-geographically targeted active case-finding strategies to be cost-effective. A more generalised understanding of the costs associated with spatially targeted interventions will be crucial to understanding whether these approaches are a good investment.

Health-care systems must be robust enough to properly manage additional cases discovered through active screening. Without the capacity to definitively diagnose and treat individuals who screen as positive for tuberculosis, the resources used in finding these additional cases will be wasted.

When is spatially targeted screening culturally acceptable?

Targeting of screening to specific communities might expose subpopulations to stigma and related social and economic costs.[55] Alternatively, this targeting might galvanise communities at risk to take actions that could facilitate better disease control, as Moonan and colleagues found when targeting high-risk neighbourhoods in Texas.[32]

Active case-finding measures that reach out into the community will require substantial local support to succeed. Therefore, we must better understand how targeting of case-finding to specific geographical areas is likely to be viewed and what approaches are most likely to be acceptable to target populations.

Beyond the desire to optimise tuberculosis screening to gain the most benefit from available resources, spatially targeted screening could address issues of equity. Tuberculosis is often associated with barriers to care, including poverty, malnutrition, and poor housing, as well as other risk factors such as HIV;[52] many of these factors are often spatially concentrated.[14,56,57] By preferentially delivering screening services to areas where the burden of tuberculosis is highest, the needs of disadvantaged populations could be better addressed.

Conclusion

Analysis of surveillance data has revealed large geographical variation in tuberculosis incidence in many settings, including those with high HIV prevalence. Although empirical evidence is sparse, models suggest that disease control strategies that preferentially target tuberculosis incidence hotspots could improve local control and create indirect reductions in prevalence in the surrounding community by reducing transmission spillover. Important questions need to be answered regarding the effectiveness of active screening needed to lower levels of tuberculosis transmission in hotspots, and the degree to which the benefit of local control will spread into surrounding areas. The feasibility of spatially targeted screening under programmatic conditions remains to be determined.

Although we are optimistic about the role of active case-finding and spatially targeted screening in accelerating tuberculosis control in high-burden countries, we also recognise the need to invest in research to determine where, when, and how these strategies should be used. Ultimately, interventional trials of spatially targeted screening would be the definitive way to address many of the questions we raise here. In the short term, investing in smaller studies that use spatial and pathogen genetic data to understand local transmission dynamics and to estimate the costs and community acceptability of these interventions would move the field forward. We believe that spatially targeted screening can be an important component of new strategies to accelerate reductions in tuberculosis incidence, and modest investments in research could rapidly improve our ability to identify areas where this targeting will be most effective.

Search strategy and selection criteria

We searched multiple databases for articles published from database inception to Aug 1, 2017. We searched PubMed with the terms ("Tuberculosis"[Mesh]) AND (("Spatial Analysis"[Mesh]) OR ("Geographic Information Systems"[Mesh])), Embase with the terms ((geographic information system/ OR exp spatial analysis/) AND exp tuberculosis/), Scopus with the terms ("Geographic Information System*" OR "Global Positioning System*" OR "Spatial Analysis*") AND ("Tuberculosis" OR "Koch's disease" OR "Koch disease" OR "kochs disease"), and Web of Science with the terms ("Geographic Information System*" OR "Global Positioning System*" OR "Spatial Analys*") AND (Tuberculosis OR "Koch's disease" OR "Koch disease" OR "kochs disease"). We reviewed articles resulting from these searches and relevant references cited in those articles. We reviewed 352 abstracts, and included original peer-reviewed publications in English, Spanish, and Portuguese.

Contributors

PGTC did the literature searches. PGTC and TC compiled the first draft with input from all authors. All authors were involved in conceiving the overall structure of the review and critically revising drafts.

Declaration of interests

We declare no competing interests.

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