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Where is tuberculosis transmission happening? Insights from the literature, new tools to study transmission and implications for the elimination of tuberculosis

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Abstract

More than 10 million new cases of tuberculosis (TB) are diagnosed worldwide each year. The majority of these cases occur in low-and middle-income countries where the TB epidemic is predominantly driven by transmission. Efforts to 'end TB' will depend upon our ability to halt ongoing transmission. However, recent studies of new approaches to interrupt transmission have demonstrated inconsistent effects on reducing population-level TB incidence. TB transmission occurs across a wide range of settings, that include households and hospitals, but also community-based settings. While home-based contact investigations and infection control programmes in hospitals and clinics have a successful track record as TB control activities, there is a gap in our knowledge of where, and between whom, community-based transmission of TB occurs. Novel

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tools, including molecular epidemiology, geospatial analyses and ventilation studies, provide hope for improving our under-standing of transmission in countries where the burden of TB is greatest. By integrating these diverse and innovative tools, we can enhance our ability to identify transmission events by documenting the opportunity for transmission—through either an epidemiologic or geospatial connection—alongside genomic evidence for transmission, based upon genetically similar TB strains. A greater understanding of locations and patterns of transmission will translate into meaningful improvements in our current TB control activities by informing targeted, evidence-based public health interventions.

Keywords

epidemiology; molecular epidemiology; public health; tuberculosis

INTRODUCTION

Humans are the sole reservoir for *Mycobacterium tuberculosis* (Mtb), the causative agent of tuberculosis (TB). Therefore, person-to-person transmission is the sole mechanism for propagating the global TB epidemic, which is now responsible for more than 10 million cases each year and 4000 deaths each day. The majority of this burden is borne by individuals living in low-and middle-income countries, where 97% of TB occurs.[1] The World Health Organization has set an ambitious goal to 'end TB' and reduce TB incidence to less than 10 per 100 000 population by 2035. However, this goal will not be achievable without significant innovations in TB control.[2] It is increasingly clear that TB incidence in high-burden countries is driven by transmission, where annual rates of infection can exceed 9% among certain age groups, and rates of reinfection after previously successful treatment can reach 11%.[3–5]

The importance of directly addressing transmission is further underscored by the variable success of latent TB infection (LTBI) treatment campaigns in reducing population-level TB incidence.[6,7] Treatment of LTBI can reduce the number of incident cases resulting from reactivation or from a recent exposure, but will not reduce cases that occur upon subsequent exposure. Thus, while ongoing efforts to reduce the persistent burden of reactivation disease are invaluable, interventions specifically targeted to interrupting transmission are essential if dramatic declines in TB incidence are to be achieved. Yet, our current understanding of transmission dynamics and patterns in high-burden settings remains woefully inadequate.

Historically, transmission has been thought to occur in the context of prolonged, close contact, as would occur among household members or hospitalized patients.[8,9] Attempts to interrupt transmission have traditionally focused on these settings, with interventions such as home-based contact investigations and administrative and environmental controls at hospitals and clinics.[10,11] Yet, epidemiologic investigations in these locations are often unable to identify an individual in the home or hospital as a source of transmission for the majority of cases. In terms of addressing TB control at a broader, community-wide level, there have been calls to expand active case-finding programmes, which aim to decrease the TB burden by identifying undiagnosed cases.[12] However, despite historical success of

population-based interventions including isoniazid preventive therapy and active case-finding, recent trials have yielded mixed results in high-burden settings (Table 1).[13,15–18] These data suggest that more targeted case-finding programmes or location-based environmental or administrative controls might be more effective.

Our ability to design interventions to interrupt trans-mission has been hampered by a gap in our under-standing of where, and between whom, community-based transmission occurs. However, novel tools, including molecular epidemiology, geospatial analyses and ventilation studies, provide hope for improving our understanding of transmission in countries where the burden is greatest. We believe that a better understanding of locations and patterns of transmission can trans-late into meaningful improvements in our current TB control activities by informing targeted, evidence-based public health interventions—and that these targeted interventions to interrupt transmission may be more effective, and more cost-effective, than untargeted, community-wide efforts. A critical step in achieving meaningful reductions in TB incidence will be to close the existing knowledge and implementation gaps around transmission.

EXISTING EVIDENCE FOR LOCATIONS OF TRANSMISSION AND INTERVENTIONS TO INTERRUPT TRANSMISSION

TB transmission is generally categorized as having occurred in one of the following locations: (i) homes;(ii) healthcare and congregate settings, including hospitals, clinics and prisons; and (iii) community-based settings, including workplaces, public transport (e.g. buses and trains) and other congregate locations where transmission may occur between individuals who may or may not know one another.

Homes

Soon after Robert Koch's identification of Mtb as the causative agent of TB, it became clear that TB was transmitted between individuals by aerosols and that close contact, as with household members, was associated with a high likelihood of transmission.[19] Several meta-analyses of contact investigations support the elevated risk of TB infection among household contacts, with approximately half of household contacts demonstrating evidence of TB infection.[20–22] While household contact screening is high yield for identifying additional cases of TB infection and disease, a number of recent studies suggest that the proportion of transmission that actually occurs in the household may have been over-estimated in high-burden settings. For example, in one household contact study in South Africa, only 46% of household members had a matching Mtb strain—meaning more than half of these individuals likely acquired their TB infection from someone outside of their household.[23] A similar study in Vietnam, albeit with a small number of household contacts, found that only 17% of household contacts shared the same Mtb strain.[24] A study in Malawi, using population-based whole-genome sequencing (WGS), estimated that only 9.4% of TB transmission occurred between contacts known to one another, although the ascertainment of contacts may have been incomplete.[25] A recent meta-analysis that included 26 studies published from 1929 to 2015 reached similar conclusions.[26] Namely, that residing with a TB case significantly increased the odds of TB infection on an individual level—but household

contact accounted for less than 20% of transmission at the population level. Modelling studies, in conjunction with social mixing and ventilation studies, also suggest that a minority of TB transmission—with estimates ranging from 16% to 30%—occurs in households in high-burden settings such as South Africa and Peru.[3,27–30] Furthermore, a recent study that modelled social-contact behaviour using data from Cape Town, South Africa, determined that transmission from non-repeated casual contact could contribute up to 79% of TB disease.[31]

Nevertheless, home-based contact investigations have a proven record of success for identifying TB infection and disease among household contacts.[12,32] Recent data indicate a prevalence and incidence of TB at least 10-fold greater among household contacts than that in the general population.[33] In another recent study from Vietnam, active case-finding among house-hold contacts significantly increased the identification of incident cases of TB (relative risk: 2.5, 95% CI: 2.0–3.2).[15] Given that the majority of transmission occurs outside the household, the high yield of contact investigations suggests that household contacts may share other risk factors for TB—whether a shared risk of infection from a similar social milieu or shared risk of progression from infection to disease based on mal-nutrition or genetic predisposition. Additional benefits of household contact tracing, beyond the identification of co-prevalent cases of active TB, include the administration of TB preventive treatment, and antiretroviral therapy for HIV-infected individuals. Therefore, house-hold contact investigation remains an essential element of TB control, although these investigations are seldom conducted in resource-limited settings.[34]

Healthcare and congregate settings

Healthcare and congregate settings, which are typically considered to include correctional facilities, barracks and shelters, present yet another high risk for TB transmission.[35–41] In 1940, it was reported that the pro-portion of medical students with a positive tuberculin skin test (TST) increased with each successive year of training.[42] Half a century later, the heightened risk of nosocomial transmission between patients came to the forefront with the rise of the HIV epidemic in the early 1990s and multiple reports of multidrug-resistant (MDR) TB transmission in hospital wards.[37,38,43] More recently, nosocomial transmission was again recognized as a significant driver for a devastating epidemic of extensively drug-resistant (XDR) TB among patients with HIV in South Africa.[44] Healthcare workers have not been spared from these latter waves of nosocomial transmission. A systematic review of over 50 studies identified substantial risk of TB infection among healthcare workers and, in a study from South Africa, healthcare workers had an incidence of MDR and XDR TB more than five times greater than that of the general population.[45,46] Incarcerated persons also have elevated incidence of LTBI and TB, with a series of studies from Brazil indicating that LTBI prevalence among inmates increased by 5% with each year of incarceration, and that 54% of incident cases of TB among non-incarcerated community members could be connected to Mtb strains circulating in local prisons based on shared genotypes.[39,47]

The World Health Organization has advocated for infection control programmes to reduce transmission in healthcare facilities, congregate settings and house-holds.[35] One such programme is the ‘Finding TB cases Actively, Separating safely, and Treating effectively (F-

A-S-T)' strategy, which incorporates early case detection, diagnosis and treatment to reduce the risk and duration of exposure for both patients and health-care workers.[11] Environmental controls, including natural and mechanical ventilation and ultraviolet germicidal irradiation (UVGI), and redesign of health-care facilities to separate potentially infectious individuals from other patients can also reduce the risk of nosocomial transmission.[48–50]

Community-based settings

Given that a minority of transmission occurs among household contacts in high-burden settings, the majority of transmission presumably occurs in a wide range of community-based settings (e.g. marketplaces, houses of worship, public transport, etc.), between casual contacts or individuals not known to one another. Thus, interventions focused on households and nosocomial settings, while important and high yield, will not be sufficient to interrupt the majority of transmission events. Interventions targeted to community-based settings with high rates of transmission, on the other hand, may translate into substantial reductions in TB incidence. However, to date, there have been no studies designed to explicitly confirm the presence or locations of community trans-mission. Rather, the evidence for community-based transmission is garnered primarily from the *lack* of evidence for transmission in homes and hospitals.

A population-based genotyping study in China found limited evidence for epidemiologic links among clusters of genotypically related cases, underscoring the dominant role of transmission from casual contact in the community.[51] Likewise, in a recent study of South Africans diagnosed with XDR TB, 15% had evidence for household transmission and an additional 15% had evidence for hospital-based transmission.[52] Among the remaining 70% of individuals without an epidemiologic link, the majority had WGS data suggestive of transmission, with nearly 60% of study participants with an Mtb strain within five single-nucleotide polymorphisms (SNPs) of another participant and nearly 80% within 10 SNPs of another participant.[53] These data, alongside ventilation and social mixing studies suggesting that the majority of rebreathed air and social interactions occur outside of the home, strongly support the hypothesis that much of transmission occurs as a result of casual contact in the community.[3,27–30,52,54,55]

These hypotheses need to be tested in studies that utilize the full breadth of the currently available genomic and geospatial tools. Such studies could also provide an evidence base to guide targeted interventions to interrupt this community-based transmission, just as contact investigations have been successful for addressing transmission in households.

TOOLS TO STUDY TB TRANSMISSION

Historically, annual case notification rates and prevalence surveys of LTBI, particularly among children and adolescents, have also been used to measure transmis-sion.[56,57] While these approaches cannot identify specific transmission events, they provide valuable insight into population-level temporal trends in exposure to infection and can be used to gauge the impact of interventions to decrease transmission. TB transmission in low-burden settings has also been studied using 'shoe-leather' epidemiology to uncover point-source out-breaks, where TB patients are interviewed about people encountered and places visited during their

infectious period. In high-burden settings, household contact surveys have been used to study rates of transmission between index cases and their household contacts.[20,21] However, these approaches have significant shortcomings, in that they presume transmission based upon an epidemiologic connection between two individuals and evidence of TB infection or disease in the contact. The advent of molecular epidemiology and sophisticated tools to characterize ventilation and aerosols, alongside the expansion of geospatial techniques have significantly enhanced our ability to study and understand transmission (Table 2; for a review of existing tools to study transmission, see Kranzer *et al.*, Yates *et al.*, Theron *et al.*[18,57,58]).

Molecular epidemiology: Genotyping to WGS

By characterizing genetic similarities and differences between Mtb strains, molecular epidemiology facilitates the identification of transmission events. Genotyping, which became available in the mid-1980s, identifies genetic biomarkers such as repeated genetic units or insertion sequences that vary between Mtb strains.[59] By identifying related Mtb strains, genotyping has been utilized to determine the likelihood of transmission between individuals.[59–63] In low-burden settings, population-based genotyping in the context of TB out-breaks has allowed for the identification of transmission that occurred not only between named contacts, but also between individuals not known to one another. For example, in two US-based outbreak investigations, genotyping facilitated the identification of epidemiologic links between individuals not known to one another but who frequented the same restaurants, bars or houses of worship.[64,65] While Mtb genotyping has been less utilized in high-burden settings, presumably due to cost and limited laboratory capacity, there are several studies from high-burden settings where genotyping has enhanced our understanding of trans-mission. A study conducted in South Africa utilizing DNA fingerprinting indicated that only 19% of trans-mission was occurring within households.[23] However, in contrast to low-burden settings, where transmission events are relatively isolated and genotypically related cases are often presumed to represent transmission, genotyping may be less sensitive in high-burden set-tings, where TB is endemic and many cases may share a genotype, especially in regions with specific dominant genotypes.

More recently, WGS of Mtb isolates has emerged as a powerful tool to advance our ability to study TB transmission and define outbreaks.[66,67] By accounting for the sequential accumulation of (SNPs), WGS has the potential to reveal microevolution and chains of transmission, not simply clusters of related cases. For example, WGS was used to investigate an extended TB outbreak in Canada and revealed the presence of two genetically distinct Mtb transmission networks, despite identical genotypes, suggesting two concomitant outbreaks rather than a single outbreak (Fig. 1).[68] In Malawi, WGS enabled the reconstruction of transmission networks, estimation of between-patient mutation rates and lineage-specific rates of transmission.[69]

The integration of WGS data with epidemiologic data about individuals' social interactions and movements can provide compelling evidence for transmission events by establishing the opportunity for transmission, based upon an epidemiologic connection, and a closely related Mtb strain. This understanding of where and between whom transmission is occurring can

help inform more directed public health interventions to interrupt future transmission. In order to attain these goals, population-level research that includes WGS is urgently needed in high-burden settings. In addition to enhancing our ability to construct transmission networks, population-level research can also help to address outstanding methodological questions about the interpretation of WGS data, such as the appropriate SNP threshold for identifying transmission, the mutation rate of Mtb in different set-tings, within-host evolution of Mtb and mixed infection with multiple strains.[70–73]

Geospatial analysis

There has also been a dramatic increase in the use of geospatial data and spatial scan statistics to understand disease patterns and transmission over the last several decades.[74] Geospatial data can include a range of data types including: self-report of home residence, administrative data on neighbourhoods and districts, health centre and hospital location data and global positioning system (GPS) coordinates. In the context of TB, geospatial analyses have helped to identify areas of spatial aggregation and 'hotspots' of TB transmission in a number of settings (Fig. 2).[75–81] The sensitivity and resolution of these geospatial analyses depend in large part upon the type of data that is collected. Many studies have mapped TB patients' homes to identify spatial aggregation. These data can then be used to guide interventions or focus further investigation. For example, a targeted, neighbourhood-level intervention in Texas identified individuals with a positive TST residing in higher incidence neighbourhoods and offered them isoniazid preventive therapy—which resulted in dramatic declines in TB in those neighbourhoods for the subsequent decade.[82]

There are several examples of TB outbreaks where individuals were queried about where they spend their time, providing a more comprehensive sense of their 'activity space', which enabled the identification of areas of transmission beyond their primary residence.[83,84] For example, during a TB outbreak investigation in Japan, an activity space analysis identified a major railway station as a likely hotspot for transmission.[84]

Mobile phone data and wearable GPS devices represent another emerging and promising source for geospatial data. These devices have the potential to provide near-continuous information about an individual's movement patterns and interactions with other individuals, with the added advantage of not being subject to recall bias. However, these benefits must be balanced against some of the limitations from these data sources, including signal loss and cellular tower density (for mobile phone data), and battery-life restrictions and not wearing the device (for wearable GPS devices).[85] Also, it is worth noting that structured interviews have been compared to GPS devices or phone records in several studies, and that interviews provide reasonably accurate estimates of locations visited (>70% concordance).[85–87]

An additional challenge in characterizing movement patterns relevant to TB transmission is that individuals are often exposed to TB months to years prior to their development of active disease and then they are often ill for extended periods prior to diagnosis. These delays increase the likelihood that an individual's movement patterns will have changed between when they were infected and diagnosed. Nevertheless, given the increasingly ubiquitous nature of cell phones with geospatial capacity, further research into the potential of these data streams to inform our understanding of TB transmission is warranted. Innovative

studies that incorporate detailed data about individuals' movements with WGS data can greatly enhance our under-standing of where best to intervene to halt ongoing TB transmission.

Social mixing and ventilation studies

Advances in indirect measures of transmission potential are also a significant advance in recent years. For example, studies of social mixing, where the amount of contact between individuals is quantified, demonstrate that casual contact in community locations is quite common in high-burden settings, such as South Africa.[28,29,88] Rates and types of social mixing vary by age and demography—for example, children and young adults are most likely to be infected in schools and workplace contacts increase with adulthood.[3,29] Therefore, the findings of these studies should be viewed as hypothesis-generating for future studies to empirically confirm whether transmission is indeed occurring in community settings such as schools, work-places and public transport. Furthermore, it is likely that social mixing patterns vary across cultures, so it will be essential to characterize these patterns at the local level to direct initial interventions or target further research.

Ventilation studies, with devices that quantify ambient CO_2 levels as a proxy for rebreathed air and trans-mission potential, and new technologies to characterize cough aerosol production also represent new directions to enhance transmission research.[3,55,89] Ventilation studies have recently shown that there are a limited number of air exchanges in many locations where casual contact occurs, such as schools and churches (Fig. 3).[3,30,90] In such spaces, the likelihood of transmission from an infectious person to others is increased, given the high proportion of rebreathed air. It is important to prospectively study transmission rates and rebreathed air to validate whether ambient CO_2 levels are an accurate proxy for transmission potential.

Biomarkers

There is great interest and a critical need for an assay of recent TB infection—that could both inform trans-mission research and help to risk-stratify individuals for TB preventive therapy. At present, the TST and interferon-gamma release assays (IGRAs) remain the only established means for gauging whether an individual is infected with TB, yet they are unable to distinguish between remote and recent infection (in the absence of serial testing with conversion to a positive test following a negative test at baseline). This limitation is particularly challenging for understanding trans-mission in high-burden settings where a majority of individuals will have had exposure to TB by adulthood and as a result, chronically positive TST and IGRA.[91] In such settings, recent transmission is often assumed when a close contact has a positive TST or IGRA, but it is equally plausible that the close contact was infected by another index case in the community.

In a recent report from the UK, the presence of TNF-α-only T effector cells was found to distinguish between individuals believed to have acquired TB either recently or remotely, as determined by epidemiologic and clinical data.[92] While this study was relatively small, with only 59 total participants enrolled, and was conducted in a low-burden setting, the prospect of a cellular immune signature capable of reliably identifying recent infection is exciting and

warrants further study in other cohorts and high-burden settings. In another series of recent studies, RNA-based transcriptional sig-natures have been found to predict the risk of developing active TB disease among several household contact cohorts enrolled across Africa.[93,94] While these studies were focused on the risk of progression to active dis-ease and did not explicitly examine whether infection may have been remote or recent, epidemiologic data has long indicated that the risk of progression is inversely associated with the time since infection. In addition, the gene signature did not predict progression to disease among a community-based cohort of South African adolescents. Therefore, it will be worth exploring whether this RNA signature may also be a proxy for recent TB exposure. There are a handful of other reports of immune signatures for various aspects of TB infection that warrant further investigation as potential indicators of recent infection.[95–98] A reliable biomarker of recent transmission would also be helpful for reducing the sample size and duration of trials to evaluate reductions in transmission following the introduction of new interventions.

CONCLUSION

While transmission is driving the global TB epidemic, our current understanding of how to interrupt and pre-vent transmission remains limited.[99] Proven interventions to halt transmission in selected settings, such as household contact investigations and environmental controls to prevent nosocomial transmission, must be more broadly implemented. Yet, true progress towards substantially reducing TB incidence will require additional insights into where, and between whom, TB is transmitted. Recent advances in molecular epidemiology and geospatial analyses have the ability to identify specific locations where the majority of TB transmission is occurring in high-burden settings. Greater understanding of the types of locations where transmission is occurring has the potential to catalyse innovative public health interventions to halt transmission in community settings and bring us meaningfully closer to the goal of ending TB.

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Abbreviations:

IGRA	interferon-gamma release assay
GPS	global positioning system
LTBI	latent TB infection
MDR	multidrug-resistant
Mtb	Mycobacterium tuberculosis
SNP	single-nucleotide polymorphism

TB	tuberculosis
TST	tuberculin skin test
WGS	whole-genome sequencing
XDR	extensively drug-resistant

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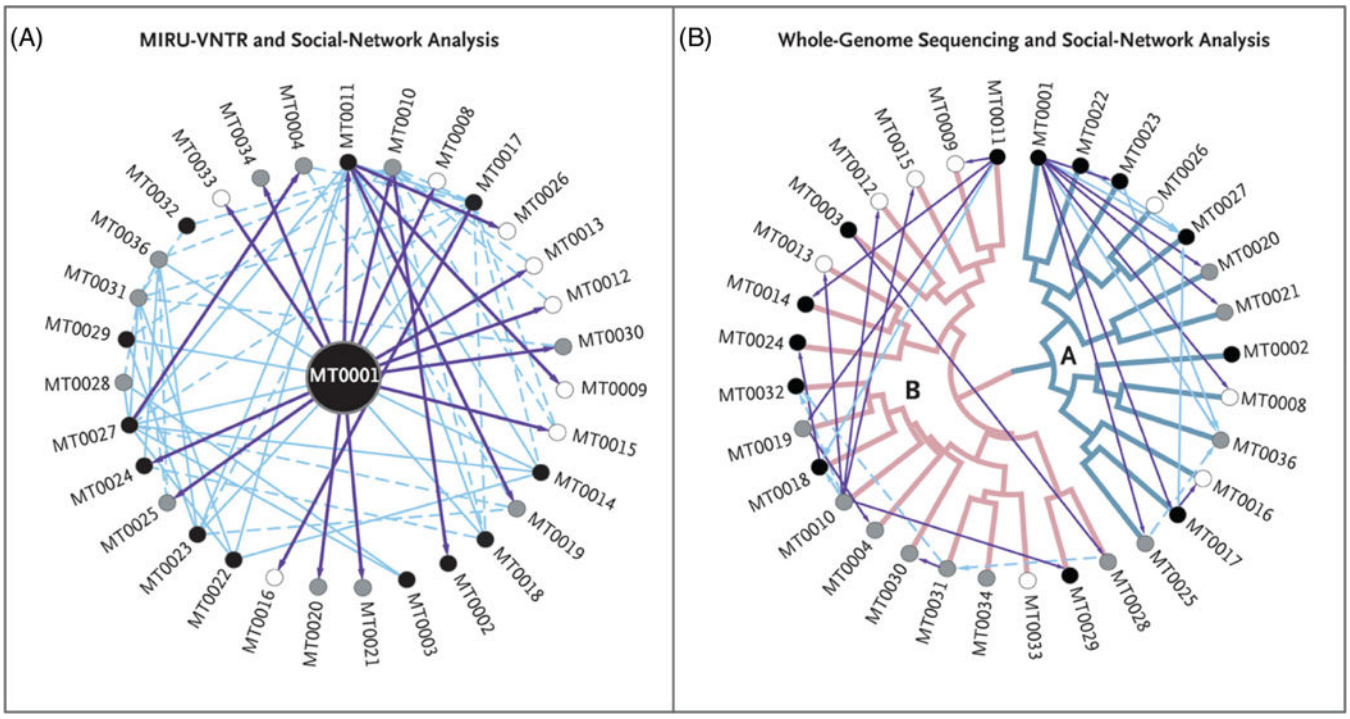

Figure 1.

Putative transmission networks constructed from genotyping data versus whole-genome data for 32 patients. Genotyping data from analyses of mycobacterial interspersed repetitive unit–variable number tandem repeats (MIRU-VNTRs) were used in panel (A), and whole-genome data were used in panel (B). Each panel shows patients (identified by case number) represented by circles coloured according to smear status and clinical presentation as an index of infectivity: Black circles indicate smear-positive pulmonary disease, grey circles smear-positive miliary disease or smear-negative pulmonary disease and white circles indicate smear-negative extrapulmonary disease. The cases are connected by arrows on the basis of reported social relationships representing plausible transmission attributable to a single case (purple arrows) or multiple potential sources of transmission (light blue lines), with dashed arrows indicating moderately infective patients and solid lines highly infective patients. The network in panel (B), with cases shown according to tuberculosis lineage (A in blude and B in pink), provides a more accurate picture of transmission, with transmission restricted to each lineage, facilitating epidemiologic interpretation of the underlying social-network data and revealing the role of the second and third source cases (MT0010 and MT0011) (Adapted from Gardy *et al.*,[68] with permission).

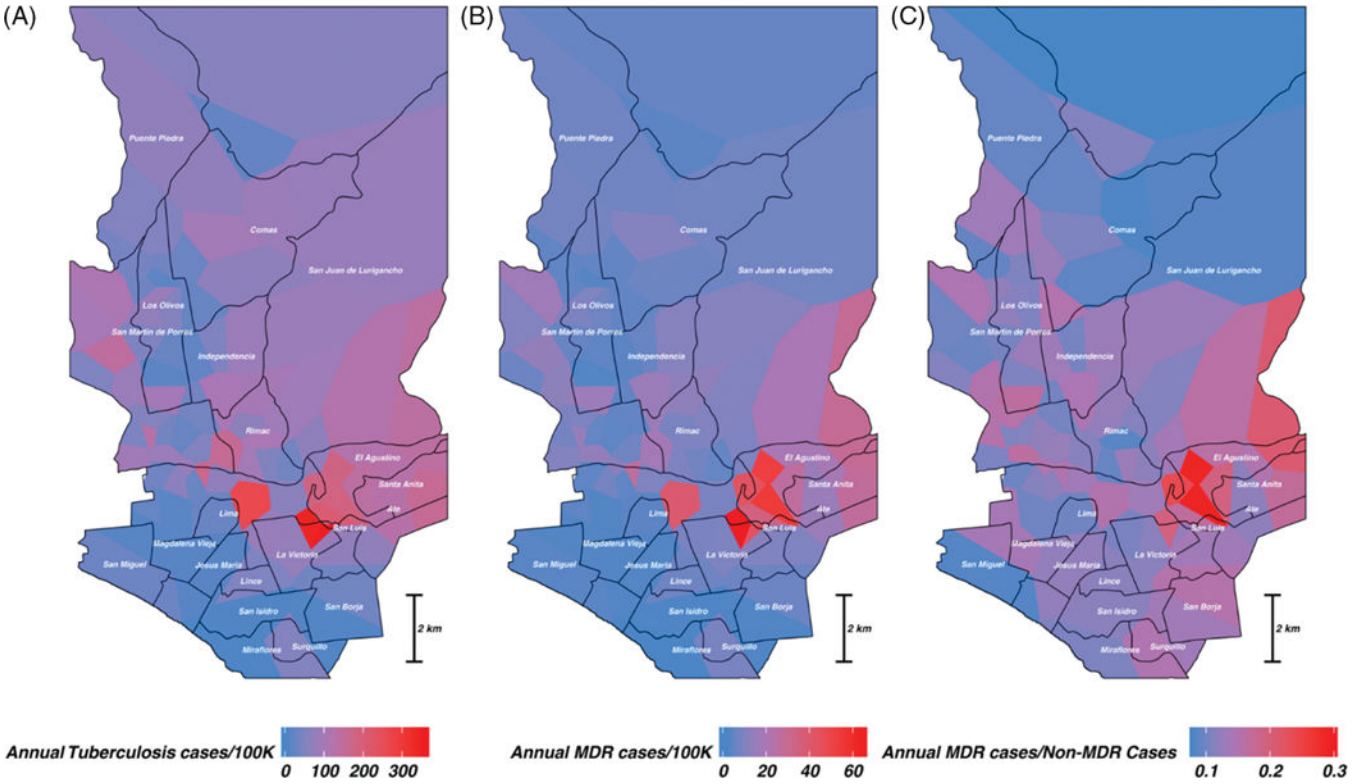

Figure 2.

Health centre-level risks of tuberculosis (TB). Annual per-100 K rates of drug-sensitive and drug-resistant TB (A) and multidrug-resistant (MDR) TB (B) by health centre catchment area. (C) Ratio of the per-capita rate of MDR to non-MDR cases by health centre. Health centre catchment areas are represented by polygons, with polygon fill colour indicating the TB or MDR TB rate in cases/100 K population. The boundaries of administrative districts of Lima are overlaid in black and labelled in white (Adapted from Zelner *et al.*,[75] with permission).

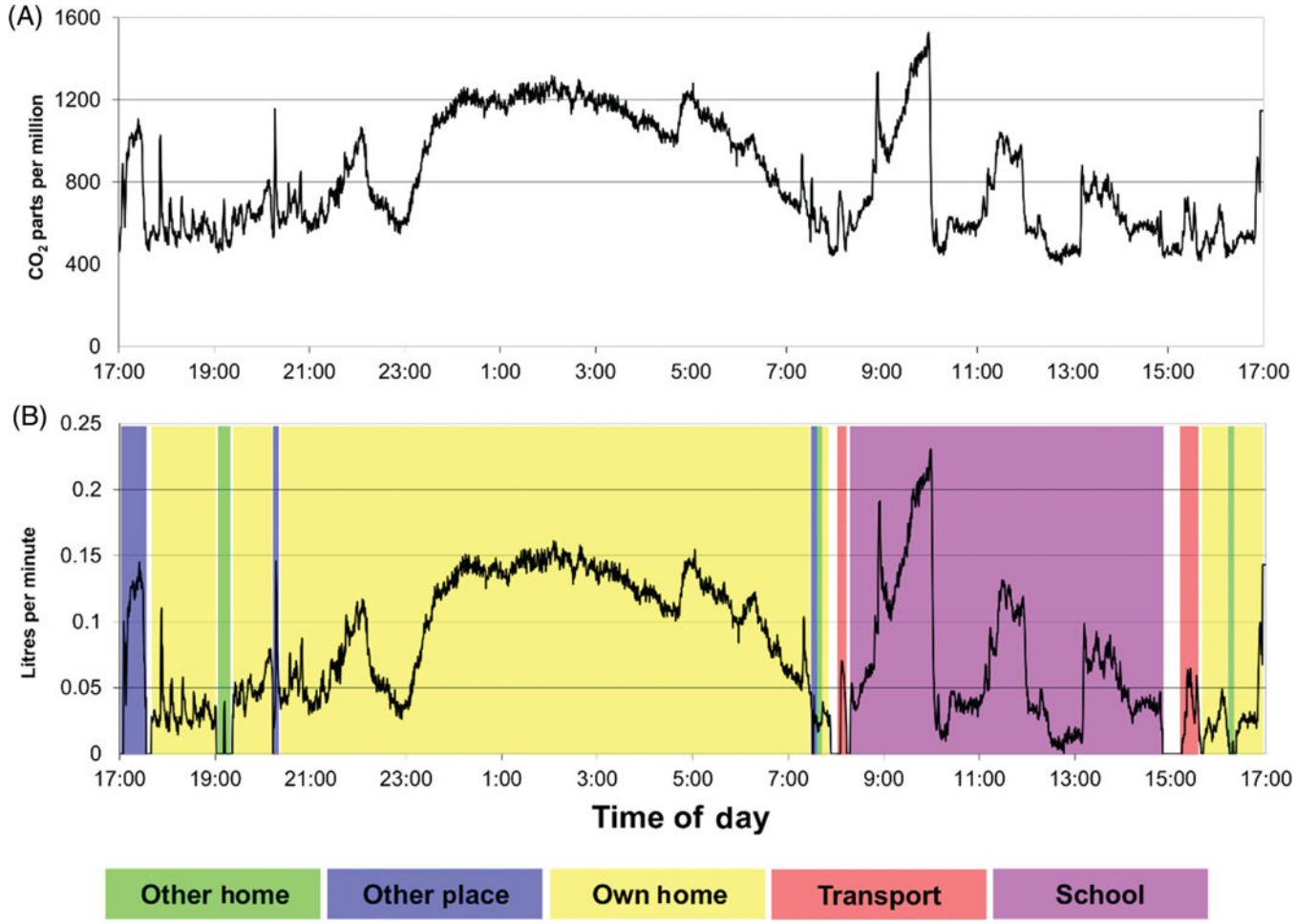

Figure 3.

(A) Ambient parts per million of CO_2 recorded at minute intervals by the logging device carried by a subject during a 24-h period. (B) Litres per minute of rebreathed air with additional allocation to specific locations. Litres per minute of rebreathed air were calculated for a 24-h period (transformation from ambient CO_2 levels in Fig. 2A) and additionally allocated to specific locations using diary and global positioning system (GPS) information. The volume of rebreathed shared air is represented by the area under the curve for each location visited and the daily rebreathed volume is the sum of all volumes at all locations visited (Adapted from Wood *et al.*,[55] with permission).

Table 1

TB interventions intended to achieve a population-level impact

Intervention	Study setting and year	Outcomes
IPT	Tunisia, urban slums, 1963	25.8% Reduction in TB case rates
	Greenland, villages, 1966	31.3% Reduction in cumulative case rates
	Alaska (USA), villages, 1967	59.3% Reduction in cumulative case rates
	Brazil, HIV clinics, 2013	27% Reduction in TB incidence
Active/enhanced case-finding	Oregon (USA), homeless shelters, 1986	87% Reduction in case notification rate
	Cambodia, national survey, 2002	62% Reduction in case notification rate
	Harare (Zimbabwe), suburbs, 2005	41% Reduction in TB prevalence
	Zambia, South Africa, rural communities, 2006	No significant reductions in TB prevalence or infection incidence
	Vietnam, districts, 2018	39% Reduction in TB incidence
Active/enhanced case-finding + IPT	Brazil, urban slums, 2010	15% Reduction in TB incidence
	South Africa, gold mines, 2011	No significant reduction in TB incidence

Adapted from Churchyard *et al.,*[13] with the addition of data from Okada et al.[14] and Fox *et al.,*[15] with permission IPT, Isoniazid preventive therapy; TB, tuberculosis.

Table 2

Novel tools to study TB transmission

Tool	Applications	Challenges	Research needs
Molecular epidemiology and WGS	Identification of clusters of related cases and chains of transmission, including between individuals not known to one another	Unclear SNP threshold for determining likelihood of transmission	Large-scale WGS studies to better understand Mtb transmission networks on a population level
Geospatial analysis	Identification of spatial 'hotspots' of high transmission areas	Logistical obstacles to collecting comprehensive patient-level data	Validation of various types of geospatial data, for example home residence versus daily movement patterns; individual recall versus mobile phone or wearable GPS data
Social mixing and ventilation studies	Documentation of social interactions associated with transmission and quantification of rebreathed air in congregate settings	Social mixing studies difficult given variable latency of TB; technology to directly measure aerosolized Mtb and compare to ambient CO_2	Characterization of social mixing and ventilation patterns in congregate settings across different cultures and environments
Biomarkers	Biological assay of recent exposure and infection	Research in early stages; cost and technical challenges for immune-based diagnostics	Replication and validation of immune-based signatures for recent infection in multiple populations and settings

GPS, global positioning system; Mtb, *Mycobacterium tuberculosis*; SNP, single-nucleotide polymorphism; TB, tuberculosis; WGS, whole-genome sequencing.