The Transmission of *Mycobacterium tuberculosis* in High Burden Settings

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***Unacceptable levels of Mycobacterium tuberculosis (MTB) transmission are observed in high burden settings. Here, we review recent developments in our understanding of airborne MTB transmission. We discuss approaches to measuring MTB transmission in populations and trials. We describe the Wells-Riley Equation, which can be used to evaluate potential interventions and to estimate transmission risk in indoor spaces. A renewed focus on cutting person-to-person transmission in high burden settings is needed. Research priorities include tuberculosis (TB) infection control; the transmission of drug resistant strains; the impact of HIV and antiretroviral therapy (ART) on transmission dynamics; and better understanding where MTB transmission occurs. It is important to consider the context in high burden settings, including the shortage of healthcare workers, when planning research and designing interventions to interrupt MTB transmission.***

**Introduction**

Sustained declines in disease incidence of up to 20% per year are required to meet the targets set out in the World Health Organization (WHO) End-TB Strategy.[1](#_ENREF_1), [2](#_ENREF_2) However, incidence is only estimated to be declining at 1.5% per annum.[3](#_ENREF_3) This 1·5% per annum decline is consistent with model predictions regarding the likely impact of current control strategies,[4](#_ENREF_4) which focus on case detection and treatment completion.[5](#_ENREF_5) Even in areas with good rates of case finding and treatment completion, evidence suggests that transmission remains a problem. Although quality data on active TB in children under the age of 5 years are limited, paediatric cases indicate continuing high levels of transmission.[3](#_ENREF_3), [6](#_ENREF_6), [7](#_ENREF_7) Recent tuberculin surveys in high-prevalence countries estimate annual risks of MTB infection of 0·3-2·2%, [8-12](#_ENREF_8) but exceeding five per cent in some parts of southern Africa.[13](#_ENREF_13), [14](#_ENREF_14) Test reversions (negative tests in people who previously had a positive test) mean such cross sectional surveys may underestimate transmission.[15](#_ENREF_15) Data on MTB transmission derived using molecular typing methods from high burden areas are limited to a small number of research active settings. Nevertheless, these data suggest more disease results from recent transmission than from reactivation of latent TB,[16](#_ENREF_16), [17](#_ENREF_17) particularly in HIV positive people.[18](#_ENREF_18) The rapid rebound in TB incidence following the discontinuation of isoniazid preventive treatment (IPT) in recent Southern African studies also suggests on-going transmission remains important in high burden settings,[19](#_ENREF_19), [20](#_ENREF_20) although models suggest a contribution from reactivation disease, implying IPT may not sterilise.[21](#_ENREF_21), [22](#_ENREF_22)

To achieve the goals of the End-TB strategy,[2](#_ENREF_2) an increased emphasis on reducing person-to-person *Mycobacterium tuberculosis* (MTB) transmission in high burden settings is needed. This review summarises recent research on MTB transmission in these settings. We focus on the biology of airborne MTB transmission, measuring transmission in populations, and modelling transmission using the Wells-Riley approach. We conclude by identifying research priorities. We do not discuss transmission-blocking vaccines nor mixed infections, both the subject of recent review articles.[23](#_ENREF_23), [24](#_ENREF_24) There is no international consensus on TB incidence or prevalence thresholds that constitute ‘high burden’, although a TB incidence of 100 per 100,000 per year has recently been used by the WHO.[25](#_ENREF_25) Most of the studies we refer to in this review were conducted in communities with a TB incidence of 100 per 100,000 per year or more.

**Airborne MTB transmission**

Whilst MTB complex organisms can be spread via unpasteurised milk, direct inoculation and other means, we focus on the predominant route, airborne transmission. The fundamentals of airborne MTB transmission were described by William Frith Wells, Richard Riley, Robert Loudon, Rena Roberts, and others, more than sixty years ago.[26](#_ENREF_26) Progress in basic and clinical sciences has improved our understanding of MTB transmission, which until recently had remained unchanged for over 50 years; although much remains unknown. Figure 1 illustrates the MTB transmission cycle. Interrupting any process in MTB’s natural history will reduce rates of transmission at a population level.



*Figure 1. The MTB transmission cycle.*

*Aerosol generation and inhalation*: Individuals with pulmonary TB aerosolise MTB, placing their contacts at risk of infection (Figure 1). This occurs at a faster rate during speech,[27](#_ENREF_27) singing[28](#_ENREF_28) and, particularly, coughing.[29](#_ENREF_29) Whilst the largest respiratory droplets fall to the ground, rapid evaporation means many droplets attain a sufficiently low mass that they remain suspended in air currents until either inhaled or ventilated out of the room.[30](#_ENREF_30) Important new insights into MTB transmission have come from ‘cough box’ experiments.[31](#_ENREF_31) In these experiments, TB patients were asked to cough ‘as frequently as was comfortable’ for five minutes into a ‘cough aerosol sampling system’. Whilst this may not be physiological, these experiments suggest that most MTB that is aerosolised during coughing is in droplets that are small enough, even without evaporation, to remain suspended in the air.[31](#_ENREF_31) These cough box experiments[31](#_ENREF_31), [32](#_ENREF_32), consistent with studies from guinea pig facilities[33](#_ENREF_33), [34](#_ENREF_34) and molecular epidemiological observations[35-37](#_ENREF_35), suggest that some people with TB may be much more infectious than others. Early animal experiments demonstrated that MTB in smaller droplets more readily produced tubercles in the lung than did MTB in larger droplets, presumably as they escape filtration in the upper airways.[38](#_ENREF_38) The use of surgical masks by TB patients has been shown to reduce transmission to guinea pigs by 56%, suggesting they partially block aerosolisation of the relevant respiratory droplets. [39](#_ENREF_39)

*Establishing infection or disease*: The quantity and characteristics of the inhaled droplet predict clinical outcomes, with early experiments clearly demonstrating that infectious dose predicts risk of progression to disease.[40](#_ENREF_40) In the cough box experiments, the quantity of aerosolised MTB individuals produced predicted infection in household contacts better than smear grade or time to culture positivity.[32](#_ENREF_32) It has recently been proposed that larger droplets, settling in the upper airway, might result in immune memory and a positive test for infection but little risk of progression to disease.[40](#_ENREF_40) That some highly exposed individuals fail to become TST or IGRA positive and the recent discovery of genetic loci that predict TST positivity suggest that it is possible to clear MTB infection without developing an adaptive immune response – so called ‘early clearance’.[41](#_ENREF_41) This process is probably important epidemiologically but, given it leaves no footprint, is difficult to study. There is a growing appreciation, informed by animal studies and advanced imaging techniques, that a binary classification of TB into latent infection and active disease may be too simplistic.[42](#_ENREF_42), [43](#_ENREF_43) Some individuals with positive tests for infection may have cleared the organism,[43](#_ENREF_43) and periods of active replication in ‘latent TB’ have been observed.[42](#_ENREF_42) Pulmonary MTB infection at the more active end of the spectrum is probably necessary for infectiousness.

*Duration of infectiousness*: There is a widely-held view that the infectiousness of patients diminishes sufficiently after two weeks of anti-tuberculous therapy that transmission to contacts is unlikely.[44](#_ENREF_44) Many guidelines rely on proxy measures of infectiousness such as smear status or culture conversion times though it is worth noting that median time to culture conversion amongst patients treated under daily direct observation for drug-susceptible TB in Peru was 37 days.[45](#_ENREF_45) However, the association between sputum smear and culture status of patients on treatment with infectiousness is not straightforward,[46-50](#_ENREF_46) and is likely to be influenced not only by organism viability in respiratory secretions but also by the capacity to generate aerosolised MTB through coughing.[29](#_ENREF_29) Since cough frequency diminishes on treatment,[51](#_ENREF_51) assumptions about infectiousness based upon culture conversion times may overestimate risk. Furthermore, organisms that propagate in culture may not thrive when exposed to a hostile immune system in the alveoli.

Infectiousness can be studied in guinea pig facilities in which the number of animals infected following exposure to air exhausted from isolation rooms containing TB patients is measured. Such experiments show that effective therapy is associated with markedly fewer MTB infections than are seen before treatment is initiated or when isolates are not fully susceptible to the treatment regimen. [34](#_ENREF_34), [50](#_ENREF_50) However, the guinea pigs in these experiments remained exposed to the patients for many weeks. Thus, these experiments have not yet reliably established a time window after which a patient can be considered to be no longer infectious. Most, if not all, household contacts will have been exposed to a much greater risk of infection from the index patient in the pre-treatment period,[52](#_ENREF_52) than will be the case once treatment is initiated. This is due to both a longer duration of exposure and greater infectiousness pre-treatment. This may also hold even for patients with drug-resistant TB, amongst whom culture conversion times will typically be longer.

**Measuring transmission in populations**

Even in the highest burden communities, the prevalence and annual incidence of active TB rarely exceed 2%. This in addition to incomplete surveillance data, particularly in high burden settings, and tests for MTB infection with poor sensitivity and specificity, make the measurement of MTB transmission in populations a challenge and the routine determination of incident TB disease unfeasible.[53](#_ENREF_53) Measuring transmission therefore relies on proxy measures, assumptions and combination approaches. The common tests for MTB infection are summarised in Panel 1. Approaches to measuring TB in populations are summarised in Table 1.

*Panel*: **Diagnostic tests of MTB infection**

• There is no gold standard diagnostic test for MTB infection.

• The two widely used diagnostic tests are tuberculin skin tests (TSTs) and interferon-gamma release assays (IGRAs). Positive tests are interpreted as reflecting a prior adaptive immune response to mycobacterial infection.

• Currently it is not possible to detect infections cleared by the innate immune system prior to an adaptive response,[41](#_ENREF_41) nor to distinguish cleared infections that leave a lingering immunological footprint from persistent infection.

• Neither test is able to distinguish between latent infection and disease

*Tuberculin skin test (TST)*

• TSTs involve an intradermal injection of a standardised purified protein derivative (PPD) then measurement of any induration 48-96 hours later.

• Sensitivity and specificity are dependent on the number of millimetres of induration chosen as the cut point and the prevalence of non-specific reactions. [54](#_ENREF_54)

• Non-specific reactions result from infections with environmental mycobacteria. They can also result from prior BCG vaccination though this effect wanes in children vaccinated in infancy.

• Low sensitivity can be seen with advanced age and with immunosuppression as a result of malnutrition or HIV.

• New statistical techniques can suggest appropriate cut points for given distributions of reactions sizes. [55](#_ENREF_55)

• Test reversions do occur and are commoner in young individuals, probably reflecting an initial false positive test. [56](#_ENREF_56)

*Interferon gamma release assay (IGRA)*

• IGRAs involve a blood draw. T cells are then exposed to antigens that are found in MTB but not in BCG nor in most environmental mycobacteria.

• Interferon-gamma released by cells that recognise these antigens is then assayed in the supernatant following incubation (Quantiferon Gold) or by counting the number of interferon gamma producing cells in an ELISPOT assay (T Spot TB).

• IGRAs are a more specific test for MTB infection but there is less precedent for their use in transmission studies. The need for phlebotomy and the high cost of the test are also disadvantages.

• Test reversions are common and the clustering of results around the threshold for positivity means the choice of cut point can substantially affect sensitivity, specificity and prevalence estimates. [15](#_ENREF_15)

*New tools*

• A new and, hopefully, more specific skin test based on similar antigens to those used in IGRAs is now being tested in Phase III trials. [57](#_ENREF_57)

• RNA expression signatures have been developed that may distinguish disease from latent infection, TB from other diseases and that might revert following successful treatment of active TB. [58-60](#_ENREF_58)

• RNA expression signatures need further validation. They may prove useful in research settings but are currently too complex to be used clinically in high burden settings.

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| Tool | What is measured | Advantages | Disadvantages |
| Prevalence of TB infection | Typically measured using TSTs in school going children | Cheap and well established  Infections must have occurred within an individual’s lifetime, hence, in young children, this is a measure of recent infection  Prevalence can be converted into an annualised incidence (‘annual risk of tuberculosis infection’, ARTI)[54](#_ENREF_54)  Repeated surveys or continuous measurement of infection prevalence in the same age group can quantify changes in MTB transmission over time | Does not capture early clearance  Poor sensitivity and specificity, uncertainty regarding cut points plus conversions and reversions can affect estimates in some populations  From a single study, it is not possible to separate age and cohort effects  ‘Styblo’s rule’, which states that there is a fixed relationship between ARTI and the incidence of TB disease, is no longer thought to be valid.[61](#_ENREF_61), [62](#_ENREF_62) WHO no longer recommend single tuberculin surveys. |
| Incidence of TB infection | Testing cohorts for TB infection longitudinally | Older children can be included and inferences still made about recent transmission  An incidence cohort including older children and adults provides more general insights into transmission in the community even if mixing patterns are strongly age assortative | Does not capture early clearance  Requires larger sample or longer duration of follow up than measuring infection prevalence  Losses to follow up may reduce power and bias estimates  Excluding those who are positive at baseline may exclude those at highest risk – a particular problem in older individuals in high burden settings |
| TB notifications | Notifications of TB disease to the national treatment programme | Data are routinely captured  It may be feasible to enhance capacity to diagnose and notify cases of TB for the purposes of research though substantial biases and quality problems inherent to routinely collected data are likely to persist | Serious problems with data quality in most high burden settings  Only captures TB transmission that progresses to disease  Only captures individuals who access a diagnosis and whose diagnosis is notified  May capture individuals who do not have TB – poor specificity is a particular problem where TB diagnosis is primarily based on chest X-ray such as in children |
| Prevalence of TB disease | Typically measured in large surveys using sputum culture with or without pre-screening for symptoms and or with a chest x-ray | Well established  Undiagnosed individuals can be referred for treatment | Substantial and expensive undertaking  Only captures TB transmission that progresses to (pulmonary) disease  It may not be clear whether changes in prevalence are a result of differences in transmission, in progression from infection to disease, or in disease duration  Prevalence surveys are active case finding interventions and will transiently alter local TB epidemiology  Sputum culture has low sensitivity in children |
| Incidence of TB disease | Measured in established cohorts or using two prevalence surveys | Allows changes in incidence to be disaggregated from changes in disease duration | Except in established cohorts in high burden settings, the measurement of incidence requires more than one large prevalence survey – this is rarely feasible  Only captures TB transmission that progresses to (pulmonary) disease  It may not be clear whether differences in prevalence are a result of differences in transmission or in progression from infection to disease |
| Molecular epidemiology (proportion clustered) | The proportion of isolates that have the same strain type usually using RFLP, MIRU-VNTR or WGS \* | Allows inferences to be made about the proportion of TB resulting from reactivation vs. recent infection  Strain typing can disprove or provide evidence to support putative transmission events | Requires advanced laboratory capacity  Only captures transmissions that progress to disease and isolates that are sampled  Biased estimates can be obtained if the sampling fraction is low, if the study is not of sufficient duration or if there is substantial in or out migration |

Table 1. Measures of MTB transmission in populations.

\* RFLP is restriction fragment length polymorphism. MIRU-VNTR is Mycobacterial Interspersed Repetitive Units – Variable Number of Tandem Repeats. WGS is whole genome sequencing. These are all strain typing techniques.

*Traditional approaches*: Tuberculin surveys in school children are a classical means of estimating MTB transmission at a population level. There is concern that age assortative mixing may mean paediatric infections do not fully reflect MTB transmission between adults.[54](#_ENREF_54), [63](#_ENREF_63), [64](#_ENREF_64) However, repeated TST surveys might still allow estimates of the trend in force of infection over time to be attained. Trend estimates based on tuberculin surveys are fairly robust and not greatly influenced by the proportion of children with BCG scars or the cut point used to define a ‘positive’ test. [62](#_ENREF_62), [65](#_ENREF_65) There is debate about the best approach to measuring MTB transmission in trials of control interventions.[64](#_ENREF_64), [66](#_ENREF_66), [67](#_ENREF_67) Short-term reductions in disease prevalence, for example, are difficult to interpret as prevalence is determined by transmission, progression from infection to disease and disease duration.[64](#_ENREF_64)

*Molecular approaches*: Tools for strain typing MTB include spoligotyping, which has limited resolution; Restriction Fragment Length Polymorphism (RFLP)[68](#_ENREF_68) and Mycobacterial Interspersed Repetitive Units – Variable Number of Tandem Repeats (MIRU-VNTR),[69](#_ENREF_69), [70](#_ENREF_70) both of which have been widely used; and Whole Genome Sequencing (WGS). These molecular epidemiological tools provide evidence for or against potential linkages between two or more cases of active TB and have led to a number of critical insights into MTB transmission.[71](#_ENREF_71) As these techniques require a bacterial isolate, molecular epidemiology, with rare exceptions,[72](#_ENREF_72) only captures infections that have progressed to active TB disease.[73](#_ENREF_73) Molecular epidemiology cannot distinguish changes in transmission intensity from changes in the rate of progression to active TB shortly after infection, for example, resulting from varying levels of immunosuppression. The better resolution of WGS and steep reductions in cost mean it is likely to eventually replace existing strain typing techniques. However, molecular epidemiology using WGS will require an understanding of the rate at which mutations occur. Recent studies suggest that, in active disease, single nucleotide polymorphisms (SNPs) emerge, on average, at half a SNP per genome per year or slower.[37](#_ENREF_37), [74-76](#_ENREF_74) Most of the patients in these studies were on TB treatment and there was considerable variation in the rate at which mutations occurred. Primate studies suggest a similar mutation rate and that the mutation rate may not differ substantially between active and latent infection.[77](#_ENREF_77) However, limited data suggest that, in man, mutations accumulate more slowly during latent infection.[78](#_ENREF_78) Occasional accelerated intra-patient ‘microevolution’ events,[79](#_ENREF_79) and the slow rate at which SNPs accumulate may make inferring chains of transmission from MTB genotypes alone challenging. Probabilistic models that also incorporate epidemiological and clinical data are likely to be needed.[80](#_ENREF_80) With molecular epidemiology using WGS, as with older strain typing techniques, adequate study duration, a high sampling fraction and careful documentation, follow up and reporting is likely to be important.[16](#_ENREF_16), [81-83](#_ENREF_81) However, novel approaches to the analysis of sequence data may allow population level inferences to be made from smaller samples.

*Air sampling:* There is interest in attempting to directly detect aerosolised MTB from room air. This might allow quantification of MTB exposure in putative sites of transmission. A few demonstration studies, using polymerase chain reaction (PCR) on room air filtrate, suggest this may be feasible.[84-86](#_ENREF_84) Whilst PCR detection of MTB DNA does not necessarily mean organisms are viable, it suggests that individual(s) with pulmonary TB have produced bioaerosols in the space. This should be, at least in theory, a reasonable proxy for transmission risk.

**The Wells-Riley Equation**

Room ventilation and social contact patterns determine whether others are exposed to MTB that has been aerosolised. The Wells-Riley Equation[87](#_ENREF_87) is used to model the transmission of respiratory pathogens, such as MTB, that are spread by crowd rather than close contact. Transmission risk in a defined space over time *t* is modelled as a Poisson process.

*Probability of transmission = 1 – e –Iqpt/Q*

*I* is the number of infectious individuals present

*q* is the rate at which infectious individuals produce infectious ‘quanta’

*p* is the rate at which susceptible individuals breathe

and *Q* is the rate at which air from the space is exchanged with uncontaminated air (ventilation)

Riley and colleagues defined ‘quanta’ as ‘the number of infectious airborne particles required to infect which may be one or more airborne particles’.[87](#_ENREF_87) This value is often assumed or fitted to data. Various attempts have been made to empirically estimate *q* for TB by venting air exhaled by TB patients over experimental animals. Two sets of experiments in the pre-HIV era estimated quanta production at 0.62-0.82[88](#_ENREF_88) and 1.25[89](#_ENREF_89) per hour using a heterogeneous group of TB patients.[39](#_ENREF_39), [90](#_ENREF_90) More recently, Escombe *et al.* obtained an estimate of 8.2 quanta per hour in a group of HIV positive patients in Lima, Peru.[34](#_ENREF_34) These data disguise huge heterogeneity in infectiousness with the most infectious patients in each study producing 60 and 226 infectious quanta per hour respectively. High rates of quanta production have been measured in patients with advanced multidrug-resistant TB (MDR-TB),[39](#_ENREF_39) and very high rates estimated in outbreaks related to aerosol generating procedures.[91](#_ENREF_91) Interestingly, estimates of *q* obtained by fitting to data from high burden communities are lower than those obtained empirically.[92](#_ENREF_92) This may be because untreated patients in the community are at an earlier stage in their illness than the diagnosed patients used in the animal studies. The Wells-Riley equation has a number of important limitations. Importantly, it assumes air in the space to be fully mixed and does not account for heterogeneity in infectiousness or susceptibility to infection. Adaptations to the equation have been published. One widely used derivative uses instead a ‘rebreathed fraction’ obtained using paired indoor and outdoor carbon dioxide measurements.[93](#_ENREF_93) This avoids the need to measure *Q*, which can be technically challenging. A number of important insights have been derived using the Wells Riley approach. For example, one study suggested that active case finding could not control high levels of MTB transmission in a South African prison if levels of overcrowding and poor ventilation were not also addressed.[94](#_ENREF_94) Another paper, which used the equation to predict settings in which MTB transmission might occur, is described below.[92](#_ENREF_92)

**Research Priorities**

There is much that is not understood about MTB transmission. In the last section of this review, we outline priority areas for future research.

*Infection control*: Approaches to interrupting MTB transmission include active case finding, the provision of isoniazid preventive therapy (IPT) and TB infection control. There have recently been large trials published of active case finding and mass IPT to interrupt MTB transmission. The ZAMSTAR result may be the first empirical data suggesting that active screening for TB disease impacts on TB transmission at a population-level.[66](#_ENREF_66), [95](#_ENREF_95) The Thibela TB trial, conducted in a setting with a very high force of infection, found mass administration of IPT protected individuals whilst on treatment but had no impact on TB incidence in the wider community.[20](#_ENREF_20), [22](#_ENREF_22) TB infection control is conventionally described in three domains – administrative controls (which aim to minimise contamination of shared air by infectious subjects e.g. cough triage, early diagnosis and treatment), environmental controls (which aim to minimise exposure through removal of contaminated air) and personal protection measures (which aim to minimise inhalation of contaminated air e.g. N95 respirators).[96](#_ENREF_96) The FAST approach to TB infection control in congregate settings has recently been promoted and advocates **F**inding TB cases **A**ctively, **S**eparating safely, and **T**reating effectively.[97](#_ENREF_97) A trial of the FAST approach is about to commence in Peru (NCT 02355223) with TST conversion among healthcare workers as an endpoint. However, the lack of a comparator group may limit the strength of the conclusions that can be reached. A review of observational and animal studies concluded that there is strong evidence supporting the role of ventilation as an environmental control in reducing the risk of airborne transmission of MTB.[98](#_ENREF_98) Of the many ways of increasing ventilation, increased mechanical ventilation,[99](#_ENREF_99) natural ventilation through increased window-opening,[100](#_ENREF_100) and wind-driven roof turbines have been investigated specifically as means to reduce MTB infection risk.[101](#_ENREF_101) Natural ventilation has been recommended by the WHO as an effective way to reduce infection.[96](#_ENREF_96) Air disinfection tools, particularly upper room Ultra Violet Germicidal Irradiation (UVGI), have also been studied with UVGI leading to steep reductions in MTB transmission from TB patients to experimental animals [102](#_ENREF_102), [103](#_ENREF_103)

While a relationship between ventilation rate and TB transmission is clear, there is little empirical evidence on the effectiveness of infection control interventions on transmission reduction, with the majority of studies using animal surrogates or ventilation measurements as a proxy for transmission risk. A notable exception was the Tuberculosis Ultraviolet Shelter Study, which showed that environmental modifications can be safely implemented at scale.[104](#_ENREF_104) Whilst there were too few TST conversions among residents of the shelters to demonstrate an impact on MTB transmission, similar studies in higher burden settings would be valuable in quantifying the impact of TB infection control interventions on transmission to human occupants and, potentially, on transmission in the surrounding community.[105](#_ENREF_105) Implementing environmental controls is not always straightforward.  An increase in indoor levels of outdoor pollution, security concerns, exposure to outdoor hazards such disease vectors, a loss of thermal comfort, energy loss through the exfiltration of conditioned (heated or cooled) indoor air, and higher running and maintenance costs of mechanical systems are side-effects of increased ventilation,[106](#_ENREF_106) and may make such measures unacceptable to occupants. Therefore, the ideal retrofit and design measures employed in a building should account for occupant patterns, numbers, and preferences, the climate and surrounding environment, building geometry, and the materials and budget available. Building simulation tools may be employed to predict the optimal design or retrofit of buildings to maximise ventilation according to specified criteria.[107](#_ENREF_107), [108](#_ENREF_108)An important knowledge gap is whether domestic infection control implemented at diagnosis can mitigate against secondary infections in patients managed in the community. To our knowledge, there have been no trials of such interventions. This is an important question, perhaps in MDR-TB and certainly in extensively drug-resistant TB (XDR-TB), where chemotherapy may not promptly reduce infectiousness and where the consequences of transmission may be severe.

*Drug resistance and transmissibility*: Globally, there were an estimated 480,000 incident cases of MDR-TB in 2013. The proportion of new cases that are infected with MDR-TB is around 3.5% and this has not changed appreciably over the period 2008-13.[3](#_ENREF_3) MDR-TB is disproportionately distributed, with the highest rates seen in Asia and Eastern Europe where, in several countries, a high proportion of MDR-TB cases have no previous history of TB treatment. This suggests high levels of MDR-TB transmission. Projections of the future burden of MDR-TB depend critically on estimates of the reproductive potential of drug-resistant strains.[109](#_ENREF_109), [110](#_ENREF_110) This reproductive potential, which can be quantified as the expected number of secondary cases attributable to a single infectious cases, is the product of several factors: the duration of infectiousness, the rate at which effective respiratory exposures occur, the probability that exposure results in transmission and successful infection, and the probability that such infection progresses to infectious disease.[111](#_ENREF_111) Mutations that confer drug-resistance in MTB may affect several of these factors. For example, the duration of infectiousness will be increased if resistance is not diagnosed and/or effectively treated, and the probability of establishing a successful infection or leading to disease after infection will be decreased if resistance-conferring mutations are biologically costly.[112](#_ENREF_112) *In vitro* experiments (e.g. competitive growth assays which may measure biological fitness) and observational studies (e.g. contact tracing and molecular clustering studies which measure effects of both biological fitness and differences in duration) suggest a wide variety of possible overall relationships between drug-resistance and transmission.[113](#_ENREF_113) Furthermore, even where there are clear biological costs associated with resistance, secondary compensatory mutations may sometimes ameliorate these biological costs.[114](#_ENREF_114), [115](#_ENREF_115) WGS analyses of samples of clinical strains suggest successful transmission of MDR strains in disparate settings such as South Africa[116](#_ENREF_116) and Russia[117](#_ENREF_117). However, a recent household contact study suggested circulating MDR-TB strains in Peru were less likely to infect household contacts than drug sensitive strains.[118](#_ENREF_118) The data on XDR transmission, at least during the time of observation, are also mixed.[116](#_ENREF_116), [119](#_ENREF_119) Given the importance of reproductive potential to projections of the MDR and XDR-TB epidemics, this remains a research priority.

*Antiretroviral therapy and MTB transmission*: Our understanding of the effects of HIV on MTB transmission remains limited.[73](#_ENREF_73) Some data suggest that HIV positive people with TB disease make a small contribution to MTB transmission. The arrival of HIV in Tanzania was associated with an increase in TB incidence but a decline in annual risk of TB infection measured in a series of tuberculin surveys.[65](#_ENREF_65) The arrival of HIV in South Africa was associated with a marked increase in TB incidence in HIV positive but not HIV negative miners.[120](#_ENREF_120) This finding was substantiated in a prospective cohort study in business employees in Harare.[121](#_ENREF_121) These studies were conducted before antiretroviral therapy was widely available. Household contact studies suggest transmission to household contacts is lower when the index case has more advanced HIV related immunosuppression.[122](#_ENREF_122) Molecular epidemiology suggests that, in a South African township, HIV negative people are more likely to be the index cases in strain clusters than HIV positive people.[17](#_ENREF_17), [123](#_ENREF_123) However, a study in Malawi using WGS found no association between HIV status or receipt of ART and the probability of being linked to secondary cases.[76](#_ENREF_76) Recent empirical data support the importance of timely ART initiation in reducing TB incidence.[124](#_ENREF_124), [125](#_ENREF_125) There are several potential explanations for these observations. HIV positive people are more likely to have smear negative or extrapulmonary disease, which are less infectious. Shorter disease duration[126](#_ENREF_126) due to faster progression to death or treatment may limit opportunity to transmit, as might reduced social contact as a result of greater morbidity. However, whilst people in HIV care may have their TB diagnosed faster, healthcare facilities may be important sites of transmission.

Current WHO guidelines include provision of ART to all adults living with HIV when their CD4 cell count falls to 500 cells/mm³ and to all HIV-infected people with active TB disease, irrespective of CD4 cell count.[127](#_ENREF_127) ART reduces TB disease incidence rates in HIV cohorts by approximately two-thirds.[128-130](#_ENREF_128) Short-term reductions in population level TB disease rates have also been observed in communities in South Africa and Malawi where ART has been scaled up rapidly.[131](#_ENREF_131), [132](#_ENREF_132) This may be largely explained by reduced progression from infection to disease rather than by reductions in transmission. However, the longer-term impact of ART on population–level TB disease burden and the impact on MTB infection incidence are uncertain. ART certainly affects longevity, levels of contact with healthcare services and susceptibility to TB disease. It may also affect TB disease duration and phenotype, including the presence of cavities, smear positivity,[133](#_ENREF_133), [134](#_ENREF_134) the relative frequency of extra-pulmonary disease, all of which might affect infectiousness. Furthermore, reduced morbidity as a result of ART might result in increased levels of social contact. An influential modelling study estimating the impact of the roll-out of annual HIV testing and immediate ART on TB disease incidence in nine African countries predicted a 21% (range: 10%–31%) reduction in the cumulative AIDS-related TB disease incidence over the first five years, and a 48% (range: 37%–55%) reduction in the incidence of TB disease at five years.[135](#_ENREF_135)  A multi-model analysis over 2014-2033, estimated that increasing ART coverage to 80% of those with CD4 count<350 could reduce TB incidence by 8-14% and, if ART was provided to all HIV infected individuals (at current levels of access), incidence could be reduced by 6-30%.[136](#_ENREF_136) However, a more recent modelling study suggested that the longer-term impact of expanded ART access was less certain.[137](#_ENREF_137) Whilst TB incidence should initially decline, the model predicted that, if good adherence and immunologic responses to ART are not sustained, and combined with effective HIV preventive interventions, we could see increases in TB disease incidence in the future despite high levels of ART coverage.[137](#_ENREF_137)Following publication of the START[138](#_ENREF_138) and ANRS TEMPRANO[139](#_ENREF_139) trials, it is likely that more people will be initiated on ART at higher CD4 counts. Given the substantial impact – either positive or negative - that this may have on TB in HIV endemic settings, the impact of HIV and ART on transmission dynamics should be a focus of research.

*Locating MTB transmission*: Historically, households have been considered a major focus of MTB transmission. However, three molecular epidemiology studies from Sub Saharan Africa,[17](#_ENREF_17), [140](#_ENREF_140), [141](#_ENREF_141) and one from rural Vietnam,[142](#_ENREF_142) all suggest that most transmission occurs between rather than within households. In these high burden settings, this likely reflects a high transmission risk outside the home rather than a reduction in the risk of transmission to household contacts. Other evidence also suggests that, overall, most transmission may occur outside the household,[143](#_ENREF_143), [144](#_ENREF_144) but studies suggest this is age dependent with young children more likely to have been infected by a household member.[145-147](#_ENREF_145)  It is likely that transmission in indoor congregate settings is important in high burden settings. For example, time working in public transport is strongly associated with TST positivity in Lima, Peru.[148](#_ENREF_148) Understanding which settings are important should be a research priority, as this would allow infection control and active case finding interventions to be better targeted.[105](#_ENREF_105)

The Wells-Riley equation, and its variants, has been used to estimate MTB transmission risk by location. Many studies adopting these approaches have estimated ventilation or likely exposure to exhaled bioaerosols based on carbon dioxide (CO2) levels. These methods have recently been applied to study transmission in a Cape Town township. Data were collected on carbon dioxide (CO2) concentrations in multiple settings visited by 63 adolescents. It was estimated that 93% of total exposure to ‘rebreathed air’ occurred in a few locations: own home, visited homes, public transport, work or school.[149](#_ENREF_149) The same research group used a modified Wells-Riley equation, CO2 measurements and social contact pattern data to estimate the proportion of overall MTB transmission by location. They found that, in the same Cape Town township, 50% of incident infections among 15-19 year olds may take place in school, that workplaces are important places for adult transmission and that household and public transport may be important sites of transmission between age groups.[92](#_ENREF_92) These inferences are potentially useful but the studies were small. The conclusions may be context-specific and assume TB disease prevalence is the same in each location within an age and sex group, which is probably not the case.  Similar studies need to be undertaken on larger scales and in more settings, ideally combined with location specific estimates of TB prevalence. In many settings, there are substantial spatial and temporal variations in CO2 concentrations. The Cape Town studies did not obtain contemporaneous CO2 measurements from directly outside the buildings studied.[92](#_ENREF_92), [149](#_ENREF_149) Whilst this may be reasonable in Cape Town, where strong winds blowing off two oceans may limit local spatial and temporal variations in CO2, it would not be reasonable elsewhere.

Health facilities, particularly in HIV endemic areas, are an important setting in which infectious TB patients mix with susceptible persons. TB patients attend healthcare facilities prior to diagnosis, when presenting with TB symptoms, and during the course of TB treatment. Delays in recognition, diagnosis and isolation of infectious cases augment the risk of nosocomial transmission from unsuspected index cases. Overcrowded outpatient clinics and Emergency Departments congregate vulnerable subjects in settings where the likelihood of exposure to patients with infectious TB is relatively high. In one Emergency Department study in Lima, Peru, IGRA conversion was observed in 30% of healthcare workers during a 12 month period compared to 0% of hospital security and domestic personnel;[150](#_ENREF_150) remarkably one third of patients identified with TB in the study were attending the hospital for an apparently unrelated reason (trauma, pregnancy etc.) highlighting the importance of the unrecognized risk. Nosocomial transmission played an important role in the Tugela Ferry extensively drug resistant tuberculosis XDR-TB outbreak.[151](#_ENREF_151) Future research should attempt to quantify the proportion of MTB transmission in high burden settings that occurs within healthcare facilities.

Spatial heterogeneity in the incidence of TB and drug-resistant TB is evident in analyses of programmatically collected data and has been well documented in many studies,[152](#_ENREF_152), [153](#_ENREF_153) raising the possibility that targeted interventions may be effective. At this time, however, the mechanisms driving such heterogeneity are not completely understood; for example, localized transmission and or aggregation of individuals sharing risk factors for infection or progression may combine to generate such patterns of disease. A better understanding of this spatial heterogeneity might usefully inform targeted TB control interventions. The spatial extent of TB transmission networks in these settings is not known. Better data on the geographical extent of social contacts relevant for TB transmission could provide important data in designing intervention studies and it would be helpful to see research addressing this question.

**Conclusions**

Addressing MTB transmission is critical to achieving TB control in high burden settings. Repeated surveys measuring TB infection in the same community, including young adults, offer a feasible measure of TB transmission that might be used in trials in high burden settings. The wider use of such measures would allow the impact of interventions on transmission to be disaggregated from any impact on rates of progression to disease or disease duration. TB infection control is an important and neglected area of research. Given most infection control interventions use simple existing technology, they could be widely and rapidly implemented if studies demonstrated a substantial impact on MTB transmission – this is low hanging fruit. To understand how MTB transmission dynamics are likely to evolve, we need more research on the transmissibility of drug resistant MTB and on the impact of HIV, including the initiation of ART at higher CD4 counts. Better understanding where MTB transmission occurs outside the household should also be a research priority. This could allow case finding and infection control interventions to be better targeted. The coming years will likely see innovative and exciting research on MTB transmission in high burden settings. When designing studies, researchers should be mindful of the context in high burden settings. Priority should be given to the development and evaluation of TB control strategies that place minimal additional demands on poor patients and overstretched healthcare systems,[105](#_ENREF_105) or that involve elements of social protection or health system strengthening.

**SUPPLEMENTARY MATERIALS**

This review was written following the M.tb Transmission meeting, held in London in November 2014. Slides and videos of the presentations at this meeting can be found at http://tb.lshtm.ac.uk/mtb-transmission-2014-presentation-slides-videos.

**AUTHOR CONTRIBUTIONS**

TAY, PYK, GMK, JGT, RGW, TC, FGC, DAJM and IA drafted sections of the manuscript. All authors commented on and edited the manuscript. TAY, PYK and IA prepared the final draft. All authors approved the final version of the manuscript prior to submission.

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