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## Transmission of drug-resistant tuberculosis in HIV-endemic settings

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Declaration of interests

We declare no competing interests.

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## Abstract

The emergence and expansion of the multidrug-resistant tuberculosis epidemic is a threat to the global control of tuberculosis. Multidrug-resistant tuberculosis is the result of the selection of resistance-conferring mutations during inadequate antituberculosis treatment. However, HIV has a profound effect on the natural history of tuberculosis, manifesting in an increased rate of disease progression, leading to increased transmission and amplification of multidrug-resistant tuberculosis. Interventions specific to HIV-endemic areas are urgently needed to block tuberculosis transmission. These interventions should include a combination of rapid molecular diagnostics and improved chemotherapy to shorten the duration of infectiousness, implementation of infection control measures, and active screening of multidrug-resistant tuberculosis contacts, with prophylactic regimens for individuals without evidence of disease. Development and improvement of the efficacy of interventions will require a greater understanding of the factors affecting the transmission of multidrug-resistant tuberculosis in HIV-endemic settings, including population-based molecular epidemiology studies. In this Series article, we review what we know about the transmission of multidrug-resistant tuberculosis in settings with high burdens of HIV and define the research priorities required to develop more effective interventions, to diminish ongoing transmission and the amplification of drug resistance.

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## Introduction

Multidrug-resistant tuberculosis originates from the selection of mutations in *Mycobacterium tuberculosis* during first-line antituberculosis treatment, leading to resistance to rifampicin and isoniazid. If inadequately treated, further selection of mutations conferring resistance to fluoroquinolones and second-line injectable agents (amikacin, capreomycin, or kanamycin) results in extensively drug-resistant tuberculosis and eventually resistance to all effective drugs. In addition to de-novo acquisition of resistance (acquired resistance), individuals can become infected with drug-resistant strains as a result of transmission (primary resistance).<sup>1</sup> Acquired resistance can be prevented by ensuring adherence to optimised therapy, whereas the control of primary resistance requires interventions to block transmission.<sup>2</sup>

Understanding the relative importance of acquired and primary resistance is essential for directing tuberculosis control policy, and is particularly important in HIV-endemic settings, where large amounts of primary resistance have been described.<sup>3</sup> HIV infection can affect transmission of drug-resistant tuberculosis in many ways, including the duration and intensity of infectiousness, the characteristics of exposure, and the susceptibility of the population exposed.<sup>4</sup> HIV infection has been proposed to also affect the development of acquired resistance. Conceivably immuno-suppression could alter the in-vivo bacterial mutation rate or factors that promote the selection of resistance-conferring mutations, such as reduction of drug concentrations through malabsorption<sup>4,5</sup> and reduced adherence to complex multidrug therapy.

Analysis of programmatic data that defines primary resistance as a history of no previous tuberculosis treatment has shown the importance of transmission in HIV-endemic settings. Two systematic reviews<sup>6,7</sup> found an epidemiological association between HIV status and multidrug-resistant tuberculosis that was stronger for transmitted multidrug-resistant tuberculosis than acquired multidrug-resistant tuberculosis. However, in another study using data reported to WHO,<sup>8,9</sup> a positive association between HIV infection and multidrug-resistant tuberculosis disease was shown in less than half of the countries examined, indicating that the association between HIV and multidrug-resistant tuberculosis depends on the epidemiological setting. In some HIV-endemic settings (South Africa and Zimbabwe), 75% of all notified multidrug-resistant tuberculosis cases have no previous history of antituberculosis treatment, whereas in others (Zambia) it is less than 30%.<sup>3</sup> Some of this heterogeneity might be due to differences in reporting of tuberculosis cases by control programmes, but modelling of incident multidrug-resistant tuberculosis cases has estimated that, in previously treated individuals, 60% are actually due to transmission, which would normally be classified as acquired resistance.<sup>2</sup> This misclassification is probably due to the high rates of reinfection with multidrug-resistant tuberculosis in countries with very high HIV prevalence, such as Lesotho, eSwatini (formerly Swaziland), and South Africa.<sup>10</sup>

Tackling the multidrug-resistant and extensively drug-resistant tuberculosis epidemic in an HIV-endemic setting will require a more detailed understanding of how HIV affects the transmission dynamics of drug-resistant tuberculosis (figure 1). In this Series article, we provide an overview of drug-resistant tuberculosis transmission in HIV-endemic settings and define research priorities that will inform the design of interventions to block transmission (table). The impetus for this article was derived from a workshop, funded by the National Institutes of Health and South African Medical Research Council, on tuberculosis transmission<sup>11</sup> and has been complemented by a specific literature search. There have been several reviews on drug-resistant tuberculosis;<sup>1,12</sup> however, these excellent reviews do not focus on how HIV affects transmission of drug-resistant tuberculosis.

### **Infectiousness of patients with drug-resistant tuberculosis**

Sputum bacillary burden measured in colony forming units, time to positivity in the mycobacteria growth indicator tube liquid culture system, or Xpert MTB/RIF cycle threshold values<sup>13,14</sup> show that patients with HIV have lower sputum bacillary loads and, therefore, might be less infectious than those without HIV.<sup>13–15</sup> This evidence concurs with the association between HIV seropositivity and negative sputum smears and reduced cavitation. Immunosuppression is thought to result in more rapid progression to symptomatic disease, leading to reduced bacterial load and cavitation at presentation.<sup>16,17</sup> Less is known about drug-resistant tuberculosis and bacterial load, but patients coinfecting with HIV whose treatment for extensively drug-resistant tuberculosis has failed do cause ongoing transmission.<sup>18</sup>

Although bacterial load in sputum is a strong indicator, the quantity of bacteria aerosolised might be a more direct measure of potential infectiousness. The cough aerosol sampling system (CASS) quantifies culturable *M tuberculosis* bacilli contained within aerosolised, inhalable particles using a chamber containing a cascade impactor (a device used for

aerodynamic size analysis of aerosols).<sup>1</sup> Studies in smear-positive patients showed that CASS counts of greater than ten colony forming units correlated with tuberculin skin test conversion in household contacts,<sup>19</sup> and the subsequent development of active tuberculosis disease.<sup>20</sup> Data are scarce for CASS in HIV-positive patients and in those with drug-resistant tuberculosis. A study in Cape Town, South Africa, found that only 10% of cases were extremely infectious (using the threshold of more than ten colony forming units), that HIV seronegativity was associated with CASS positivity, and that twice as many HIV-negative patients were extremely infectious compared with HIV-positive patients (Dheda K, unpublished).

Another approach to studying the infectiousness of patients with tuberculosis is the human-to-guinea pig transmission model.<sup>21–23</sup> Transmission from patients with tuberculosis was shown to be highly variable, with a minority of patients accounting for most transmission. These studies included patients with drug-resistant tuberculosis and HIV, but were not powered to evaluate the effects of either drug resistance or HIV on infectiousness. A limitation of this approach is that infectiousness can only be measured during the initiation of therapy. However, these studies did highlight the importance of rapid drug susceptibility testing and prompt initiation of effective therapy to prevent ongoing transmission.<sup>10</sup> In a study from Peru,<sup>22</sup> in which all patients had HIV and were treated for drug-susceptible tuberculosis, 98% of transmission events (122 of 125) resulted from nine patients with unsuspected multidrug-resistant tuberculosis who were, therefore, not on effective treatment. Another study,<sup>24</sup> in South Africa, found that inadequately treated extensively drug-resistant tuberculosis cases, of which more than 60% (11 of 17) were HIV-positive, were also transmitters. Further studies could define how rapid diagnostics and individualised treatment regimens are best combined to accelerate the reduction in infectiousness of patients starting therapy, and are crucial for improvement of infection control in health-care settings. Determining whether the most infectious individuals identified in these experimental systems account for transmission at the population level will also be important for control.

Contact investigation studies are another approach to measuring the relative infectiousness of drug-resistant tuberculosis cases. A recent meta-analysis,<sup>25</sup> assessing whether *M tuberculosis* transmission and progression to tuberculosis disease differ between drug-resistant and drug-susceptible tuberculosis, found a greater likelihood of *M tuberculosis* infection in contacts of drug-resistant tuberculosis index patients compared with drug-susceptible tuberculosis index cases, but no difference in risk of tuberculosis disease. This increase in the number of infected contacts of drug-resistant index cases could be due to prolonged duration of infectiousness in drug-resistant tuberculosis as a result of diagnostic delays.<sup>26</sup> Immunosuppressed HIV-positive index cases with drug-susceptible tuberculosis are less likely to transmit to household contacts than HIV-negative cases,<sup>27–31</sup> probably due to aforementioned differences in cavitation and bacillary load.<sup>27,29–31</sup> Contact investigation in rural South Africa<sup>32</sup> has also shown the force of infection in an HIV-endemic setting. It was found that, of 793 contacts of multidrug-resistant tuberculosis index cases, 14 (1.8%) were diagnosed with multidrug-resistant tuberculosis (incidence 1765 of 100 000) and 19 (2.0%) of 973 extensively drug-resistant tuberculosis contacts had extensively drug-resistant

tuberculosis (incidence 1952 of 100 000) within a median of 70 days (IQR 57–89) of index case diagnosis.<sup>32</sup>

Further population-based contact studies from HIV-endemic areas are needed to dissect the relative importance of case infectiousness versus susceptibility of contacts for sustaining drug-resistant tuberculosis transmission. These studies are particularly important in the context of expanding antiretroviral therapy programmes. The effect of antiretroviral therapy on the infectiousness of patients with HIV and tuberculosis coinfections is unknown. Theoretically antiretroviral therapy could increase infectiousness by shifting the clinical manifestation (eg, cavitation) to be more similar to that observed in HIV-negative patients with tuberculosis,<sup>33,34</sup> although this hypothesis has not been confirmed.<sup>31,35</sup> Similarly, antiretroviral therapy reduces the risk of reinfection from tuberculosis at the individual patient level,<sup>36</sup> but its effect on population susceptibility and transmission needs further study.

### **Transmission dynamics and evolution of drug-resistant *M tuberculosis***

Genotyping tools to study the epidemiology of tuberculosis have transformed our understanding of the transmission dynamics of tuberculosis.<sup>37–39</sup> Community-wide genotyping of *M tuberculosis* has confirmed that drug-resistant tuberculosis strains can spread efficiently through person-to-person transmission.<sup>40,41</sup> Molecular epidemiological studies using cluster analysis have found that more than 70% of cases of drug-resistant tuberculosis are generated through transmission in many settings,<sup>40,42</sup> and established that transmission of drug-resistant tuberculosis occurs between close contacts within households,<sup>32,43,44</sup> hospitals,<sup>45,46</sup> and other settings.<sup>1,47</sup> However, some studies have only been able to attribute transmission to close contacts in less than 30% of cases.<sup>38,48–50</sup> In low incidence settings, transmission through casual contact has been shown to occur at diverse sites (eg, restaurants, bars, and shops).<sup>47</sup> Population-based molecular epidemiology studies in populations with a high prevalence of HIV are needed as the susceptibility of individuals with HIV to tuberculosis infection, and their concentration in health-care settings will influence the specific locations of transmission of drug-resistant tuberculosis (figure 1).<sup>51</sup> Furthermore, these studies can determine the roles of highly infectious individuals and transmission from HIV-negative individuals with multidrug-resistant tuberculosis to HIV-positive patients in sustaining multidrug-resistant tuberculosis transmission in an HIV-endemic setting.

Genotyping has shown that extensively drug-resistant tuberculosis is spreading in communities and has infiltrated entire geographical regions,<sup>40,42,51</sup> and migration is now likely assisting the spread of drug-resistant tuberculosis across provinces and borders.<sup>52,53</sup> For example between 2011 and 2014, 280 (69%) of 404 patients with extensively drug-resistant tuberculosis (77% were HIV positive) in the KwaZulu-Natal province of South Africa had primary extensively drug-resistant tuberculosis.<sup>40</sup> In addition to de-novo acquisition of drug resistance, genotyping of serial isolates has confirmed that previously treated patients might be reinfected with a new drug-resistant strain.<sup>54–56</sup> Furthermore, the transition from drug-susceptible to drug-resistant tuberculosis might also be explained by superinfection, a scenario associated with HIV.<sup>55</sup> There is a growing body of evidence to

suggest that infection with more than one strain occurs frequently in settings with a high HIV prevalence,<sup>57,58</sup> and, in the case of mixed drug-susceptible and drug-resistant strains, it can interfere with the accurate phenotypic diagnosis of drug resistance.<sup>59</sup>

Studies using whole-genome sequencing (WGS), which has superior resolution relative to traditional genotyping tools, are providing new insights into *M tuberculosis* evolution and transmission. These studies have shown that multidrug-resistant tuberculosis has evolved repeatedly and independently across the globe in response to drug-induced selection pressures,<sup>53</sup> and how clonal expansion of drug-resistant tuberculosis strains caused by ongoing transmission can spread and increase the amount of resistance, particularly in HIV-endemic settings.<sup>46,60</sup> One WGS study<sup>61</sup> showed that HIV coinfection did not affect the infectiousness of people with multidrug-resistant tuberculosis in South America, but further studies using this high resolution approach are needed in HIV-endemic settings.

The use of new analytical methods will enhance WGS studies. The reconstruction of detailed transmission chains was shown in an early study combining WGS and epidemiological data,<sup>47</sup> but it is impeded by the low rate of mutation accumulation in *M tuberculosis* and the highly variable latent stage of infection.<sup>62</sup> Latency is undoubtedly affected by HIV, which increases lifetime risk of progression to active disease after infection.<sup>63</sup> However, the effect of HIV on the *M tuberculosis* mutation rate during human infection is unknown and it could affect the genetic divergence of strains during transmission events. It will, therefore, be important to determine the maximum genetic divergence between isolates collected from patients linked by direct transmission in HIV-endemic settings.<sup>64</sup> One approach is to embrace the uncertainties involved and view transmission events in a probabilistic framework (figure 2).<sup>61,65–67</sup> These models estimate the probability of an individual transmission event on the basis of WGS data and sampling times. They can also adjust for differences in the coverage of WGS at the individual strain level and the total proportion of strains sequenced from a population. The incorporation of methods from viral phylodynamics<sup>68</sup> has also been beneficial. Two independent studies using Bayesian evolutionary methods found that strains responsible for multidrug-resistant and extensively drug-resistant tuberculosis outbreaks in South America<sup>69</sup> and South Africa<sup>60</sup> acquired resistance-conferring mutations over decades. In South Africa the evolution of extensively drug-resistant tuberculosis occurred before the onset of the HIV epidemic,<sup>60</sup> suggesting HIV did not contribute to the initial acquisition of extensively drug-resistant tuberculosis. Instead, it had a key role in subsequently amplifying extensively drug-resistant tuberculosis in this population, by creating a population of immunocompromised individuals that facilitated transmission.

### **Fitness of drug-resistant *M tuberculosis* strains**

Debate as to whether the acquisition of resistance-conferring mutations leads to a clinically relevant fitness cost in *M tuberculosis* is ongoing.<sup>70,71</sup> From a modelling perspective, the fitness cost is an important parameter for predicting the trajectory of the drug-resistant epidemic.<sup>72</sup> Diminished host immunity has been proposed to increase the frequency of the selection and transmission of resistance-conferring mutations that might reduce the fitness of drug-resistant *M tuberculosis* strains in HIV-endemic settings.<sup>73</sup>

Ongoing transmission of drug-resistant strains of *M tuberculosis* suggests fitness costs are not important in a clinical setting,<sup>74</sup> although delayed diagnosis and poor treatment outcomes might facilitate the transmission of low fitness strains. However, in-vitro competition assays have shown fitness differences between strains with and without resistance, albeit in highly artificial in-vitro experiments.<sup>75</sup> Studies into rates of infection or progression to disease in contacts of multidrug-resistant tuberculosis relative to drug-susceptible tuberculosis have yielded variable results, as described previously,<sup>25</sup> and molecular epidemiology studies defining transmission in terms of clustering of strains suggest lower fitness for resistant strains.<sup>76</sup>

The heterogeneity of mutations that confer drug resistance might partly explain the variable results of clinical studies evaluating fitness costs. For example, mutations in *katG* at codon 315 cause resistance by diminishing the activation of the prodrug isoniazid but do not affect catalase-peroxidase activity.<sup>77</sup> By contrast, mutations elsewhere in *katG* not only block drug activation but also lead to loss of enzyme activity, vulnerability to oxidative stress, and a large fitness cost.<sup>78</sup> As a result, more transmission of strains with mutations at codon 315 occurs than strains with other *katG* mutations.<sup>79</sup> Fitness costs can be reduced by the acquisition of compensatory mutations, which also adds to the genetic heterogeneity of drug-resistant strains.<sup>80</sup> To date there is no evidence that HIV infection modifies the fitness of drug-resistant strains.<sup>61,81</sup>

Of note, the genotypic determinants of transmissibility of *M tuberculosis*, be they drug-resistant or drug-susceptible strains, remain poorly understood,<sup>78</sup> and population-based transmission studies that track individual strains with specific mutations are needed from all settings, including areas with a high prevalence of HIV and multidrug-resistant tuberculosis.

## **Interventions to interrupt transmission of drug-resistant tuberculosis**

Prevention of the transmission of drug-resistant tuberculosis in HIV endemic settings requires the effective implementation of a combination of complementary interventions, including rapid diagnosis and effective treatment of individuals with drug-resistant tuberculosis, preventative treatment in those at risk of progression to disease, and good infection control practices in congregate settings.

### **Rapid diagnosis and individualised treatment**

Inadequate tuberculosis case detection,<sup>82</sup> and diagnostic delays due to the unavailability of drug-susceptibility testing among those detected,<sup>26,83</sup> perpetuate the transmission cycle of multidrug-resistant tuberculosis. The widespread use of Xpert MTB/RIF, especially in HIV-endemic settings, has transformed case finding for rifampicin-resistant tuberculosis,<sup>83</sup> with a significant reduction in time to initiation of multidrug-resistant tuberculosis treatment.<sup>84</sup> The importance of this advance in diagnostics is that WHO now reports on rifampicin-resistant tuberculosis as a measure of the burden of drug-resistant tuberculosis, but a large proportion of patients who are diagnosed do not end up on treatment.<sup>3,83,84</sup> The duration of infectiousness after initiation of therapy for multidrug-resistant tuberculosis is dependent on the number of active drugs used in the regimen for both HIV-positive and HIV-negative patients,<sup>85</sup> so earlier identification of the full drug-susceptibility profile and individualised

therapy could reduce transmission. This is particularly important in preventing nosocomial transmission in the context of a highly susceptible HIV-positive population and inadequate respiratory isolation.<sup>46</sup>

Given a highly conserved genome and absence of horizontal gene transfer, resistance conferring genes are highly amenable for molecular diagnostics in *M tuberculosis*. The current rapid molecular diagnostic tests for *M tuberculosis* target specific resistance-determining regions<sup>86</sup> or mutations. Currently the sensitivity of these targeted diagnostics is lower for drugs used to treat multidrug-resistant tuberculosis compared with first-line drugs, because of the number of different drug-resistance mutations and our incomplete knowledge of all resistance mechanisms.<sup>87</sup> WGS is an alternative to current molecular diagnostics for determining drug resistance and can potentially identify all genetic correlates of resistance in a single analysis,<sup>88,89</sup> facilitating selection of the most effective regimen.

The optimal use of WGS is reliant on sequencing directly from sputum but acquiring sufficient *M tuberculosis* DNA is a challenge. Attempts to sequence from sputum, bypassing culture-based DNA extraction, are promising.<sup>90</sup> Concordance between Oxford Nanopore Technologies MinION sequencing and WGS from culture has also been reported,<sup>91</sup> indicating the feasibility of rapid individualised treatment based on point-of-care sequencing platforms, but they need further development to cope with the lower bacillary load in patients with HIV. A proportion of phenotypic drug resistance cannot currently be explained genetically.<sup>92,93</sup> The analysis of large phenotypic and genotypic drug resistance datasets, such as ReSeqTB<sup>94</sup> and CRyPTIC,<sup>95</sup> in conjunction with functional genomics studies will define a comprehensive list of all mutations that confer drug resistance. Determination of whether HIV infection modifies the range of mutations that confer drug resistance will also be important, because this could affect the sensitivity of bioinformatic algorithms for predicting resistance from a genome sequence.<sup>96</sup> Evaluation studies will ultimately be needed to determine the effects of rapid WGS genotyping on clinical outcomes and transmission of tuberculosis in HIV-endemic settings.

### **New drug regimens to effectively treat drug-resistant tuberculosis**

Improvement of drug regimens for drug-resistant tuberculosis is important for controlling both the acquisition and transmission of drug-resistant tuberculosis in HIV-endemic settings. Long ineffective or partly effective regimens promote the acquisition of resistance and prolong the duration of infectiousness, leading to ongoing transmission. For example, the median survival of programmatically incurable patients with extensively drug-resistant tuberculosis in South Africa was 19.84 months (IQR 4.16–26.04), despite high mortality,<sup>97</sup> and these patients were highly infectious.<sup>18</sup> Without effective treatment, any control strategy will struggle to reduce onward transmission,<sup>98</sup> especially in settings in which a large reservoir of susceptible, HIV-positive individuals exists.

Until recently, treatment of multidrug-resistant and extensively drug-resistant tuberculosis was long (>18 months), expensive, toxic, difficult to manage, and had suboptimal outcomes in most cohorts,<sup>99</sup> especially in HIV-positive individuals.<sup>100</sup> Additionally, HIV-endemic settings have the added complexity of antiretroviral therapy and multiple drug–drug interactions with tuberculosis chemotherapy.<sup>101</sup> The optimal treatment regimen for



multidrug-resistant or extensively drug-resistant tuberculosis, irrespective of HIV status, is not known,<sup>102</sup> and is rapidly evolving with the introduction of new and repurposed drugs, although access to new drugs remains a problem.<sup>103,104</sup>

The addition of a single new drug to conventional regimens shortens the time to culture conversion, reducing the period of infectiousness,<sup>105,106</sup> with favourable outcomes also observed under programmatic conditions.<sup>107,108</sup> HIV-positive patients with drug-susceptible tuberculosis experience a high early mortality, but those completing standard short course regimens have favourable outcomes. However, guidelines do not recommend specific tuberculosis chemotherapy regimens for patients with HIV and tuberculosis coinfections. Preliminary results from a study combining two new drugs (bedaquiline and pretomanid) with linezolid in a 6-month regimen reported good treatment success in HIV-positive patients with extensively drug-resistant tuberculosis,<sup>109</sup> suggesting universal short regimens for both HIV-positive and HIV-negative patients with drug-resistant tuberculosis are also obtainable.

Paradoxically, some HIV-positive patients with drug-resistant tuberculosis might be particularly responsive to therapy. Individuals that acquire drug-resistant tuberculosis de novo through transmission, and progress rapidly to disease, will not have developed the extensive lung pathology that occurs in chronic HIV-negative cases of tuberculosis, which has been associated with poor drug penetration.<sup>110</sup>

### **Preventive treatment in contacts of patients with drug-resistant tuberculosis**

Reduction of the beneficial effects of rapid diagnostics and treatments on transmission will occur if substantial drug-resistant tuberculosis transmission occurs before identification of disease. Although intensified case finding among HIV-positive individuals identifies a high yield of people with tuberculosis disease in settings with a large burden of tuberculosis,<sup>111</sup> studies provide insufficient evidence that active screening for tuberculosis disease results in individual-level and community-level benefits.<sup>112</sup> Therefore, strategies to prevent progression to disease after exposure to drug-resistant tuberculosis are important, especially in HIV-positive individuals, in whom high rates of progression to disease occur after infection.

The high yield of coprevalent tuberculosis within households (2–3%)<sup>113,114</sup> supports the call for all contacts to be actively screened for tuberculosis,<sup>115</sup> regardless of the drug susceptibility of the index case strain. However, in high-burden and especially HIV-endemic settings, second cases within a household might have arisen from transmission in the community and around a quarter of second cases in households exposed to multidrug-resistant tuberculosis are not multidrug-resistant, so drug susceptibility testing is always needed to guide treatment.<sup>116</sup>

The marked toxicity and relatively low effectiveness of conventional treatments for multidrug-resistant tuberculosis suggest measures are needed to prevent progression to active tuberculosis disease among individuals with significant multidrug-resistant tuberculosis exposure, although this might change with the development of newer short course regimens. Preventive therapy with first-line drugs is efficacious in reducing drug-

susceptible tuberculosis but is assumed to have no effect on multidrug-resistant tuberculosis. Three randomised controlled clinical trials (ISRCTN92634082, NCT03568383, and ACTRN12616000215426) are currently investigating the effectiveness of 6 months of daily treatment with levofloxacin or delamanid compared with placebo or isoniazid. Pending the results of these studies, some authorities have advocated the use of preventive therapy with two or three agents for at least 6 months, citing observational data.<sup>117</sup> An alternative approach, supported by WHO,<sup>118</sup> is close monitoring and surveillance of registered contacts of households exposed to multidrug-resistant tuberculosis for 2 years, promoting a focus on early diagnosis and initiation of treatment guided by drug susceptibility testing for the secondary cases that will arise in up to 5% of contacts. This follows the premise of first do no harm, but, given the increased risk of rapid progression to disease after tuberculosis infection in patients with HIV, a more interventional approach is merited. Studies to define the amount of immunosuppression with and without antiretroviral therapy that warrants preventive therapy are needed.

### Infection control

Tuberculosis infection control remains a neglected area of research with well developed theory<sup>119–122</sup> but, with notable exceptions (NCT020732402014), little empiric data. Interventions have thus been recommended largely on the basis of expert opinion. With no robust estimates of potential effects or cost–benefit and competing demands on resources and health-care workers' time, interventions for tuberculosis infection control are inconsistently done in HIV-endemic settings.<sup>123</sup> The tragic consequences are nosocomial *M tuberculosis* transmission<sup>46</sup> and an epidemic of tuberculosis in health-care workers.<sup>124,125</sup> These problems are particularly acute in HIV-endemic settings, in which immunosuppression is prevalent and a large proportion of the population are regularly exposed to health-care facilities.

Interventions in tuberculosis infection control include administrative controls, environmental controls, and the use of personal protective equipment. With little evidence for biological differences in transmission potential,<sup>25</sup> environmental controls and the use of personal protective equipment should have similar effects on the transmission of drug-susceptible and drug-resistant tuberculosis. However, administrative controls that aim to interrupt transmission by facilitating early initiation of effective treatment<sup>126</sup> rely on the ability of health systems to promptly detect drug resistance. The adoption of Gene Xpert will have reduced delays in initiating effective treatment for multidrug-resistant tuberculosis. Challenges remain in making a timely diagnosis of pre-extensively drug-resistant and extensively drug-resistant tuberculosis, and in the early recognition of multidrug-resistant tuberculosis in settings that rely on smear microscopy.

Pending the results of a randomised controlled trial (NCT020732402014) and a proposed single arm study of administrative controls (NCT020732402015), there is a case for implementing many tuberculosis infection control interventions in HIV-endemic settings. For example, modelling suggests low-cost adaptations to the building envelope of primary health-care clinics might result in substantial, and presumably sustainable, reductions in nosocomial *M tuberculosis* transmission.<sup>127</sup> Ideally, these interventions would be

implemented in a phased fashion, allowing robust inference to be made about efficacy. Incidence of *M tuberculosis* infection in health-care workers would, measured longitudinally, be the obvious measure of effect.<sup>128</sup> Definitive randomised controlled trials would also be welcome, particularly for high-cost complex interventions. An example would be ultraviolet germicidal irradiation, a complex but clearly effective technology,<sup>121</sup> and valuable work is ongoing to develop a sustainable approach to implementation.<sup>129</sup>

Most *M tuberculosis* transmission in HIV-endemic settings occurs outside the household,<sup>38,48–50</sup> but there are no robust estimates of the proportion of transmission that occurs in health-care facilities relative to other congregate settings. Data from Cape Town suggest school (for children), workplace (for adults), and public transport might be important sites of *M tuberculosis* transmission.<sup>130</sup> Prisons<sup>131</sup> and mines<sup>132</sup> are also important. It has been argued that taking a tuberculosis infection control approach to interrupting transmission in congregate settings, beyond the health-care sector, could have a substantial effect on transmission.<sup>133,134</sup> Understanding which settings to target, and designing tuberculosis infection control interventions that would be acceptable in community venues, should be research priorities.

### Transmission of drug-resistant tuberculosis in children

The increasing burden of multidrug-resistant and extensively drug-resistant tuberculosis in adults increases the number of children exposed to infectious multidrug-resistant and extensively drug-resistant tuberculosis cases. Because most children develop active disease in the first 12 months following *M tuberculosis* infection,<sup>135</sup> childhood tuberculosis acts as an epidemiological sentinel event for ongoing transmission.<sup>136</sup> However, at present there is no formal global surveillance for multidrug-resistant or extensively drug-resistant tuberculosis in children and reporting to the WHO is inadequate with no age disaggregation of reports.<sup>3</sup>

Most transmission in young children occurs in the household, with up to 60% of children with tuberculosis having a reported household or close contact.<sup>137</sup> Older children are more mobile and have more community contacts with multiple exposures. The household, however, remains important for tuberculosis prevention.<sup>138</sup> Strong predictors of infection relate to the relationship with the child (eg, mother or primary caregiver), nature and quantity of time spent with the index case (eg, sleeping in the same bed or same room, living in the same household, or daily contact), and index case factors (HIV status or degree of smear-positivity).<sup>139</sup> The risk of progression to disease following *M tuberculosis* infection is highest below the age of 5 years, in malnourished children with HIV, and in the first 12 months after exposure.<sup>135</sup>

Despite relatively successful outcomes, the duration and toxicity associated with treatment of multidrug-resistant or extensively drug-resistant tuberculosis in children are clinically significant and exacerbated by HIV infection.<sup>140,141</sup> The exclusion of children from the majority of tuberculosis clinical trials has resulted in a paucity of treatment efficacy data in this population.<sup>142</sup> However, practice-based recommendations covering the use of new and repurposed drugs for paediatric multidrug-resistant tuberculosis, have filled this gap in the interim.<sup>143</sup> The high costs, toxicity, and prolonged hospitalisations associated with treatment

of multidrug-resistant tuberculosis<sup>144</sup> mean research into the management of child contacts should be prioritised. Several cluster randomised community-based trials are ongoing, such as the Tuberculosis Child Multidrug-Resistant Preventive Therapy trial (ISRCTN92634082) in South Africa. This trial is evaluating the use of 6 months of levofloxacin versus placebo in children aged 0–5 years who are household contacts of a confirmed multidrug-resistant tuberculosis index case, which includes children with HIV.

## Conclusions

HIV has a profound effect on the natural history of tuberculosis, manifesting in an increased rate of progression to disease after exposure to tuberculosis, and can lead to increased transmission and the amplification of drug-resistant tuberculosis. Population-based studies are required to tailor interventions to halt transmission of drug-resistant tuberculosis in HIV-endemic settings. These interventions include a combination of new, highly effective regimens and rapid molecular diagnostics for shortening the duration of infectiousness, improved infection control, and active screening of contacts of drug-resistant tuberculosis, with prophylactic regimens for those without evidence of disease. Many of these interventions will benefit from newer classes of drugs, and careful monitoring to prevent the selection of resistance is essential to maintain their lifespan. A reduction in transmission is hard to measure, but would be assisted by improved continuous surveillance of multidrug-resistant and extensively drug-resistant tuberculosis in children and adults, with age and sex disaggregated data,<sup>145,146</sup> as well as the application of new techniques in molecular epidemiology to define more precisely the transmission dynamics of drug-resistant tuberculosis. Hallmarks of tuberculosis epidemiology are its variability among populations and the complex effects of HIV on the transmission of *M tuberculosis*, which emphasise the need for research in HIV-endemic settings to develop appropriate interventions for drug-resistant tuberculosis.

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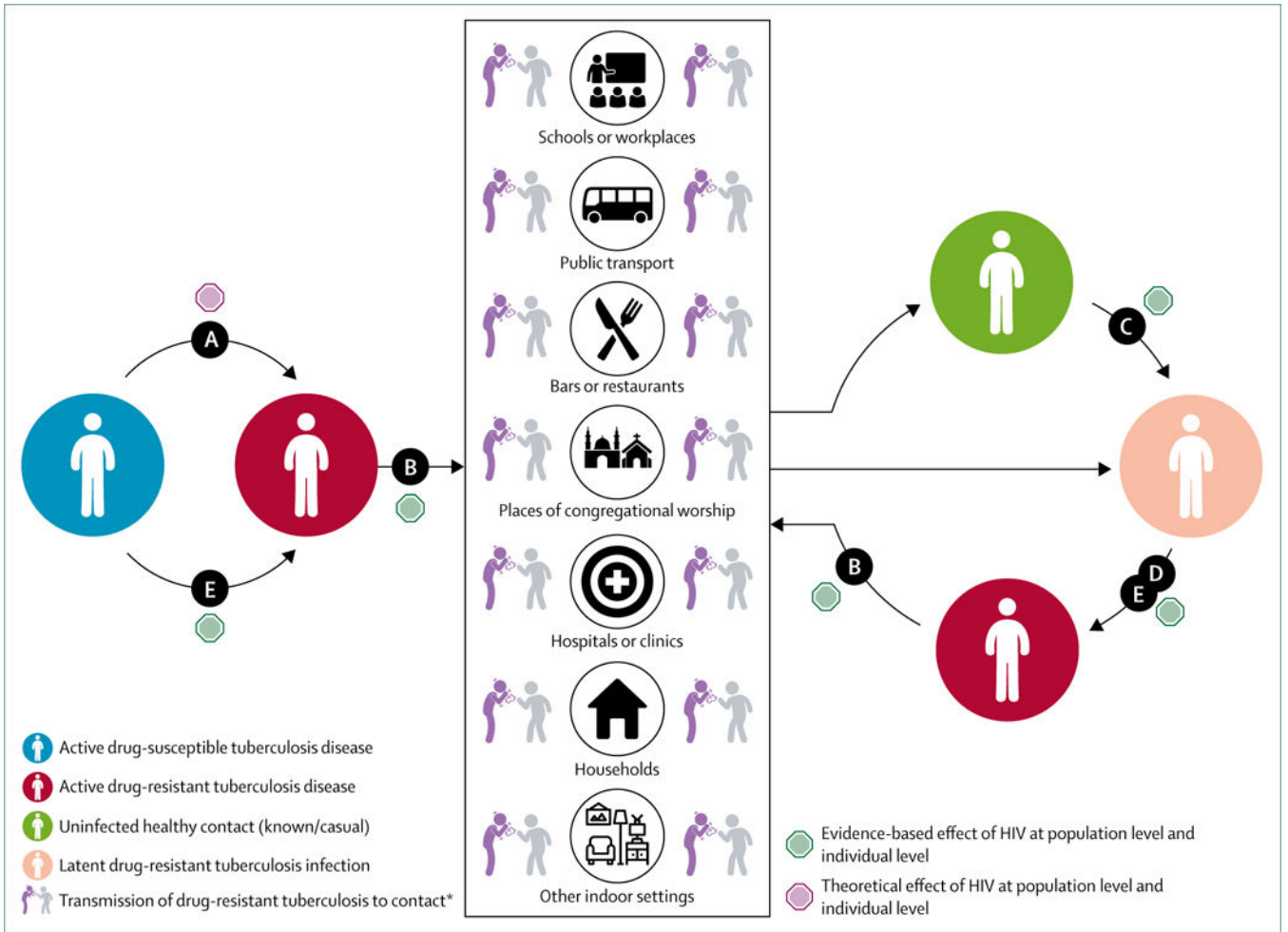
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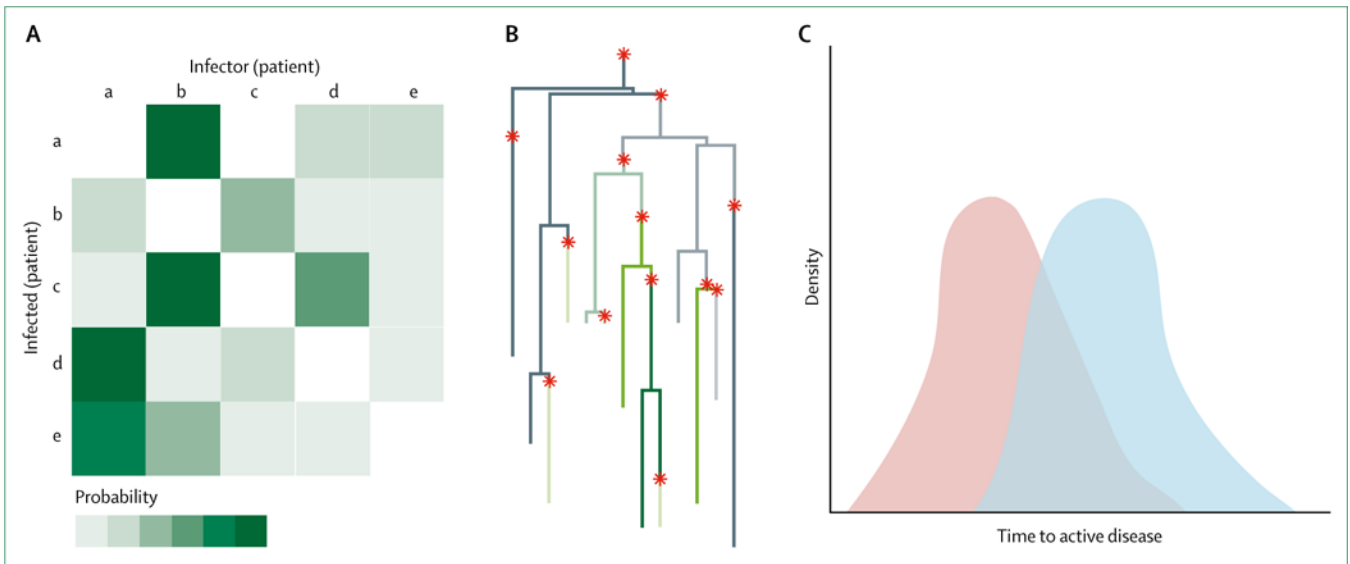
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### Search strategy and selection criteria

We searched for studies published in English only from database inception until Dec 1, 2017 in PubMed, Embase, and Scopus. We searched PubMed using the terms ((tuberculosis[MeSH Terms]) AND ((drug resistance[MeSH Terms]) OR multidrug resistance[MeSH Terms])) AND ((disease transmission, infectious[MeSH Terms]) OR “transmission”[MeSH Subheading]), Embase using the terms (Mycobacterium tuberculosis complex/ or extensively drug resistant tuberculosis/ or exp multidrug resistant tuberculosis/ or Mycobacterium tuberculosis/ or exp drug resistant tuberculosis/ or tuberculosis/) AND (exp drug resistance/ or drug resistan\*.mp) AND (exp disease transmission/), and Scopus using the terms KEY(tuberculosis OR phthisis) OR (TITLE-ABS-KEY(“Multidrug Resistant” OR “drug resist\*”)) AND KEY(transmission). We included papers from these searches, those suggested by all authors, and reviewed papers that were not specific to HIV-endemic settings but were informative about transmission.



**Figure 1: Overview of the transmission dynamics of drug-resistant tuberculosis and the effects of HIV (evidence-based or theoretical) at each step of the cycle**  
 (A) Acquired resistance (due to suboptimal adherence, decreased drug concentrations, or drug-drug interactions). (B) Transmission of drug-resistant *M tuberculosis*. (C) Establishment of drug-resistant *M tuberculosis* infection. (D) Progression from recently acquired or latent infection to active disease. (E) Superinfection or reinfection with drug-resistant *M tuberculosis*. \*Contact can be an uninfected healthy contact, contact with latent infection (drug-susceptible or drug-resistant tuberculosis), or contact with active disease (drug-susceptible or drug-resistant tuberculosis).



**Figure 2: New approaches for studying the transmission dynamics of drug-resistant tuberculosis** (A) A hypothetical heat map illustrating the probability of all possible infector-infected associations estimated. The method used to generate this heat map (TransPairs) estimates the probability and direction of transmission occurring between all possible pairs of patients based on a timed phylogenetic tree. In the example presented here there are five patients (a, b, c, d, e) who can either be an infector or an infected patient relative to the other patients. Patient b is the most likely infector of patients a and c, whereas patient a probably infected patient d. Patient e was most likely infected by patient a, but could also have been infected by patient b. In this group of patients, b is identified as the index case, with no high-probability infector identified for this case.<sup>61</sup> (B) Transmission modelling output can also be represented phylogenetically as high-likelihood transmission chains (TransPhylo). Stars show predicted transmission events followed by a change in branch colour, indicating transmission from one patient to the next. Importantly, TransPhylo can also infer unsampled cases, but performs best if the sampling density is high.<sup>65</sup> (C) The time of infection for each patient is among the parameters estimated by TransPhylo. The time difference between estimated infection time and the time of diagnosis can serve as an estimate of the speed of disease progression. The plot illustrates a scenario where a hypothetical factor used to stratify patients into two groups (represented by the pink and purple graphs) affects the speed of disease progression.

**Table:**

Knowledge gaps in our understanding of transmission of drug-resistant tuberculosis in an HIV-endemic setting.

	Potential effects
<b>Transmission</b>	
What degree of genetic difference (threshold) should be used to define transmission clusters?	Differentiating ongoing transmission from endemic drug-resistant tuberculosis; enhanced accuracy of molecular epidemiological studies of drug-resistant tuberculosis
Does real-time spatial-geographical mapping inform the control of drug-resistant tuberculosis?	Determine the role of geographic information systems as a tool to target interventions to reduce drug-resistant tuberculosis transmission
Where does transmission of drug-resistant tuberculosis occur in an HIV-endemic setting?	Targeting interventions to transmission hot spots; guide the implementation of infection control strategies
Do patients who generate highly infectious aerosols (super-spreaders) contribute disproportionately to transmission?	Intensified contact tracing for index cases who are super-spreaders
What proportion of transmission is attributable to HIV-negative index cases in an HIV-endemic setting?	Identify target population for interventions; determine the importance of active case finding to reduce transmission at a population level
Is the infectiousness of the index case more important than the susceptibility of HIV-positive contacts in determining transmission?	Determine the relative importance of active case finding and initiation of antiretroviral therapy in the control of drug-resistant tuberculosis transmission
How do HIV infection and antiretroviral therapy modify the infectiousness of drug-resistant tuberculosis?	Projecting the impact of increasing use of antiretroviral therapy on the drug-resistant tuberculosis epidemic; contact tracing strategies for HIV-positive index cases and contacts
How important is migration in propagating the spread of drug-resistant tuberculosis?	Identify migrant populations for active case finding; design of strategies to maintain drug-resistant tuberculosis patients on appropriate treatment in highly mobile populations
<b>Evolution</b>	
What are the clinically selected mutations causing resistance to new or repurposed drugs?	Adaption of genetic based diagnostics for the diagnosis of resistance to new drug regimens
What factors (host and pathogen) influence the emergence of resistance to new and repurposed drugs?	Protecting the efficacy of new drug regimens; identifying risk factors for the emergence of resistance
Does HIV coinfection affect the mutation rate of <i>Mycobacterium tuberculosis</i> ?	Enhanced accuracy of defining transmission chains using molecular epidemiology
Does HIV infection promote acquired resistance, as well as increase susceptibility to infection?	Understanding whether HIV-positive individuals require modification to drug treatment, including preventive therapy
<b>Fitness</b>	
Are drug-resistant <i>M tuberculosis</i> strains less fit in an HIV-endemic setting?	Modelling the trajectory of the drug-resistant tuberculosis epidemic
How important are compensatory mutations in maintaining fitness?	Modelling the trajectory of the drug-resistant tuberculosis epidemic; identification of new targets for drug development; interpreting the relevance of drug resistance-associated mutations
How does the emergence of resistance to new and repurposed drugs affect bacterial fitness?	Insight into the amplification of resistance through transmission
Is HIV permissive for the selection and transmission of low-fitness drug resistance-conferring mutations?	Development of genetics-based diagnostics for drug-resistant tuberculosis
Are genetic diagnostics leading to the selection of <i>M tuberculosis</i> strains with undetected mutations?	Utility and lifespan of molecular diagnostic assays
<b>Diagnostics</b>	
Is the current implementation of rapid diagnostics reducing transmission of drug-resistant tuberculosis?	Assessing the impact of diagnostic tests on drug-resistant tuberculosis at the population level; identification of diagnostic algorithms that maximally reduce transmission
What is the full repertoire of drug resistance-conferring mutations?	Design of new high sensitivity genetic diagnostics; maximise the utility of whole-genome sequencing to comprehensively diagnose drug-resistant tuberculosis



	Potential effects
How common and what is the clinical consequence of heteroresistance?	Insight into the sensitivity of current and new diagnostics; identification of risk factors facilitating the emergence of drug resistance; improve the selection of drugs to treat patients with drug-resistant tuberculosis
What is the clinical impact of rapid whole-genome sequencing-based diagnosis of drug-resistant tuberculosis?	Feasibility and clinical relevance of whole-genome sequencing for diagnosing drug-resistant tuberculosis
<b>Treatment</b>	
What is the optimal treatment regimen for patients with multidrug-resistant or extensively drug-resistant tuberculosis and should HIV-positive patients have different treatment regimens?	Define minimal duration and composition of treatment for drug-resistant tuberculosis; determine whether new short course drug-resistant tuberculosis regimens are also appropriate for HIV-positive patients
How much do new short treatment regimens for drug-resistant tuberculosis reduce transmission?	Determine if active case finding as well as new treatments are required to control drug-resistant tuberculosis
What is an efficacious and safe regimen for chemoprophylaxis of drug-resistant tuberculosis contacts?	Evidence for treating drug-resistant tuberculosis contacts with second-line drugs
<b>Contacts</b>	
What are the outcomes of drug-resistant tuberculosis contacts who are monitored rather than treated?	Optimum strategy for managing contacts of drug-resistant tuberculosis
What is the best algorithm for contact tracing of index cases of drug-resistant tuberculosis?	Feasibility of contact tracing in high burden drug-resistant tuberculosis and HIV-endemic settings; strategies for identifying and targeted screening of contacts of highly infectious drug-resistant tuberculosis patients
What is the impact of implementing tuberculosis infection control measures on reducing nosocomial transmission?	Identification of specific measures to protect health-care workers and patients
<b>Infection control</b>	
What tuberculosis infection control measures should be used in congregate settings other than health-care settings?	Interruption of transmission in settings potentially driving the drug-resistant tuberculosis epidemic (mines, prisons etc)
What are the most cost-effective tuberculosis infection control measures?	More widespread and targeted implementation of tuberculosis infection control
<b>Children</b>	
How many children are infected with drug-resistant tuberculosis globally?	Accurate age disaggregated surveillance of drug-resistant tuberculosis in children
Where are children being infected outside of the household?	Targeting of contact tracing and tuberculosis infection control measures
What is an efficacious and safe regimen for chemoprophylaxis of drug-resistant tuberculosis contacts?	Evidence for treating drug-resistant tuberculosis childhood contacts with second-line drugs
Are new short course treatments for drug-resistant tuberculosis also effective in children?	Implementation of new safe highly effective regimens in children

The knowledge gaps and their potential impact on the development of interventions to control transmission were collated from discussions held among participants at a workshop on tuberculosis transmission held in Cape Town, South Africa. Additional information was provided by the listed authors, who contributed according to their area of expertise.