



## Review

## Preventive therapy for latent tuberculosis infection—the promise and the challenges

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## SUMMARY

Around one third of the world's population may harbour latent tuberculosis infection (LTBI), an asymptomatic immunological state that confers a heightened risk of subsequently developing tuberculosis (TB). Effectively treating LTBI will be essential if the End TB Strategy is to be realized. This review evaluates the evidence in relation to the effectiveness of preventive antibiotic therapy to treat LTBI due to both drug-susceptible and drug-resistant bacteria. Current national and international preventive therapy guidelines are summarized, as well as ongoing randomized trials evaluating regimens to prevent drug-resistant TB. Populations that may benefit most from screening and treatment for LTBI include close contacts of patients with TB (particularly children under 5 years of age) and individuals with substantial immunological impairment. The risks and benefits of treatment must be carefully balanced for each individual. Electronic decision support tools offer one way in which clinicians can help patients to make informed decisions. Modelling studies indicate that the expanded use of preventive therapy will be essential to achieving substantial reductions in the global TB burden. However, the widespread scale-up of screening and treatment will require careful consideration of cost-effectiveness, while ensuring the drivers of ongoing disease transmission are also addressed.

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## 1. The global significance of latent tuberculosis infection

Tuberculosis (TB) is a leading infectious cause of death and affects nearly ten million people each year.<sup>1</sup> In addition, around one third of the world population – over two billion people – may harbour latent tuberculosis infection (LTBI), as indicated by an immunological reaction to *Mycobacterium tuberculosis*.<sup>2</sup> Asymptomatic individuals with *M. tuberculosis* infection may develop active disease at any time during their lives, representing a substantial hidden reservoir for future disease – independent of global TB control activities focused on limiting transmission.<sup>3</sup>

The antibiotic treatment of high-risk individuals with LTBI to prevent active disease has been a core strategy of TB control programmes in high-income countries for half a century.<sup>4</sup> In these settings, the delivery of preventive therapy has contributed to very low rates of disease, accompanied by early detection and effective

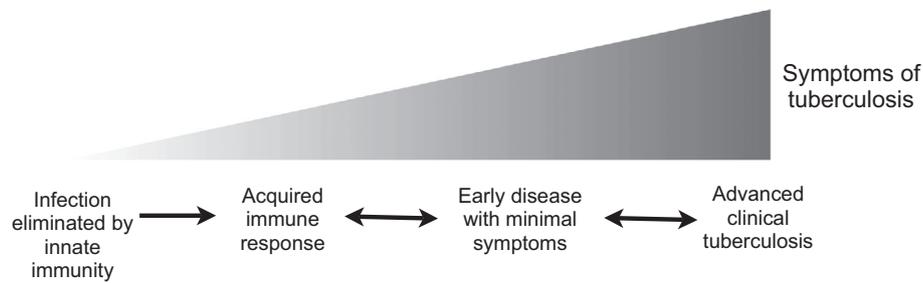
treatment of infectious TB cases.<sup>5</sup> Although the treatment of active TB remains a top priority in endemic settings, this approach alone will not be sufficient to achieve the steep annual reductions in incidence necessary to reach the End TB Strategy targets or TB elimination by 2050 (defined as less than one case per million population).<sup>6</sup> This strategy builds upon the Sustainable Development Goals, and forms the centrepiece of the World Health Organization (WHO) approach to global TB control. Addressing the substantial reservoir of latent infection will ultimately be required.<sup>7</sup> This review explores the rationale for TB preventive therapy and describes the evidence for antibiotic regimens to prevent drug-susceptible and drug-resistant TB. New opportunities for scaling up LTBI therapy as a potential turning point in the battle against TB are highlighted.

## 2. The natural history of tuberculosis infection

*M. tuberculosis* infection was previously considered to lead to one of two binary states (infection versus clinical disease). However, advanced imaging now suggests that TB infection

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**Figure 1.** The spectrum from latent tuberculosis infection to disease.

outcomes represent a spectrum of immunological responses to the infecting mycobacteria.<sup>8</sup> At one end of the spectrum, an individual may completely clear all viable bacteria. At the other end, bacterial replication may result in fulminant active TB (sepsis) (Figure 1). Animal studies have shown that tuberculous lesions may develop, then disappear, without necessarily causing symptoms or progressing to disease.<sup>9</sup> This suggests that disease may arise when the host immune system is no longer able to contain the pathogenic bacteria. In immunocompetent individuals, only a small minority of those with LTBI will develop symptomatic disease. Cohort studies from low-transmission settings indicate that between 5% and 15% of recently infected individuals will suffer from TB during their lifetimes, with the highest risk being among those with recent primary infection (during the past 2 years), demonstrated by tuberculin skin test (TST) conversion.<sup>3,10</sup> Individuals with marked

immunological impairment have a particularly high risk of both early disease progression and disease reactivation at a later stage. Such individuals include people living with HIV, patients with poorly controlled diabetes, and those taking immunosuppressive therapies.<sup>11</sup> Recognized risk factors associated with disease progression are shown in Table 1.

### 3. Testing for LTBI

The diagnosis of LTBI may only be made once active TB has been excluded. For adults, this typically involves symptom screening and chest radiography, followed by bacteriological testing (such as sputum smear, culture, or nucleic acid amplification testing). For children at risk of infection, symptom-based screening alone is generally sufficient to rule out active disease, given the practicality and sensitivity of this approach, as well as the poor specificity and unavailability of chest radiography in many settings.<sup>12</sup>

The two available methods of diagnosing LTBI measure immune sensitization to *M. tuberculosis* proteins. The TST (or ‘Mantoux test’) is an in vivo method of measuring delayed type hypersensitivity to purified protein derivative (PPD) that is injected subcutaneously. This test has been used to diagnose LTBI for more than a century, but is difficult to standardize and is highly operator-dependent. A false-negative test result may occur with inadequate PPD storage, poor administration technique, overwhelming TB disease (e.g., miliary disease in young children), and other causes of immunosuppression such as severe malnutrition, HIV, or following measles infection in children. False-positive results may occur due to bacille Calmette–Guérin (BCG) vaccination, which is most problematic in the first 2 years following vaccination at birth,<sup>13</sup> or following exposure (and especially disease) caused by environmental (non-tuberculous) mycobacteria.<sup>14</sup>

Interferon-gamma release assays (IGRAs) (including the commercially available Quantiferon Gold In-Tube Assay (Cellestis) and T-SPOT.TB (Oxford)) are in vitro diagnostic tests that present TB antigen to whole blood, quantifying interferon-gamma production by sensitized T-cells.<sup>15</sup> The interpretation of IGRAs is based on a calculation that includes subtracting the reading of the negative control tube from that of the TB antigen tube. Test results should always be interpreted in the context of clinical and epidemiological history of potential infection. IGRAs offer increased specificity compared to the TST, as they include antigens rarely found in environmental mycobacteria. However, this method is more costly and technically challenging to implement, particularly in resource-limited settings.

A skin test employing the same antigenic targets as Quantiferon (Culture Filtrate Protein 10 (CFP-10) and Early Secretory Antigenic Target 6 (ESAT-6)) is under development. Early studies suggest sensitivity and specificity similar to the in vitro Quantiferon assay,<sup>16</sup> but without the requirement for expensive laboratory infrastructure. However, it has no internal quality controls and will suffer from the same operator dependency as the TST.

**Table 1**

Predisposing factors associated with progression to active tuberculosis among individuals with latent tuberculosis infection

Risk factor	Risk of developing TB disease compared to those without the risk factor	References
<i>Based on TB exposure</i>		
Close contact with an infectious TB case	16–46	11
Recent migration from a high-prevalence setting	15	3
Chest X-ray with fibronodular abnormalities	6–19	64–66
<i>Based on comorbidities</i>		
<i>High risk</i>		
HIV infection	80–110	67,68
Age <2–3 years <sup>a</sup>	>10	69,70
TNF- $\alpha$ inhibitors	10	71,72
Chronic kidney disease, on dialysis	8	73
Organ transplantation	70–300	74–76
Stem cell transplant	20	76
<i>Intermediate risk</i>		
Age 3–4 years <sup>a</sup>	>3	69,70
Silicosis	1.4–2.5	77,78
Glucocorticoid therapy (oral)	3–8	38,79
Severe underweight	3	80
Poorly controlled diabetes mellitus	1.5–5	81–84
Cigarette smoking <sup>b</sup>	2 <sup>c</sup>	85,86
<i>Low risk</i>		
Glucocorticoid therapy (inhaled)	2.5	87
Diabetes <sup>d</sup>	2	88
<i>Very low risk</i>		
Normal healthy individual with positive TST and no recent TB exposure	1	N/A

TB, tuberculosis; TNF- $\alpha$ , tumour necrosis factor alpha; TST, tuberculin skin test; N/A, not applicable (reference category).

<sup>a</sup> The risk of TB is particularly increased in children <3 years of age.<sup>69</sup>

<sup>b</sup> Data are from settings where community transmission is substantial.

<sup>c</sup> The risk of death due to TB among smokers was 3.0 in a case–control study in India.<sup>89</sup>

<sup>d</sup> Poorly controlled diabetes is associated with a higher risk of disease.<sup>88</sup>

International guidelines recommend that either TST or IGRAs may be used to diagnose LTBI, depending upon local availability and certain patient factors.<sup>17</sup> The TST remains the most widely used test on account of its low cost and relative ease of use.<sup>18</sup> It may also be preferred for very young children and serial testing of healthcare workers.<sup>19</sup> IGRAs may be preferred in some contexts, such as for BCG vaccinated individuals among whom false-positive tests may occur. However, immune responses induced by at-birth BCG vaccination wane fairly rapidly and the chance of a false-positive skin reaction (>10 mm) is unlikely at more than 2 to 5 years post-vaccination.<sup>13</sup> Hence the TST is generally regarded as suitable for older children and adults even if they were vaccinated in infancy.<sup>13,20</sup>

Either TST or IGRA positivity confers an increased risk of disease, and the predictive values of the two tests are equivalent.<sup>21</sup> Neither test reliably differentiates active and latent TB in adults or children. Nonetheless, as these tests identify individuals at an increased risk of disease progression, both may be used to guide clinical decision-making about treatment for LTBI.

#### 4. The rationale for preventive therapy

Preventive therapy is given in order to reduce the risk of progression from LTBI to active disease by killing replicating mycobacteria. This avoids individual morbidity, while potentially also reducing transmission of infection from individuals who would otherwise develop the disease. While treatment for TB typically involves four antibiotics in order to reduce the likelihood of acquired drug resistance, treating LTBI typically uses one or two antibiotics. This assumes that acquired drug resistance is unlikely given the small number of viable bacteria present in LTBI.

The benefits of preventive therapy to individuals infected with drug susceptible bacteria have been demonstrated in a number of randomized clinical trials.<sup>22–27</sup> However, considerations are different in high incidence settings with ongoing TB transmission compared to low incidence settings. In high incidence settings, the protective effect of preventive therapy is transient – given the high likelihood of future re-infection – but has particular value to cover periods of high vulnerability, such as infection in young children or HIV-infected adults.<sup>28,29</sup> In low incidence settings with minimal TB transmission, the protection provided by preventive therapy is more durable (given the limited re-infection risk), but the population benefit is reduced given the low transmission risk posed by TB cases. In both settings, the decision to treat an individual must essentially weigh the potential personal benefits against the risk of drug toxicity. Furthermore, treatment decisions must also consider the likelihood of antibiotic resistance in the source case, as preventive therapy is unlikely to be effective against an organism that is resistant to the chosen antibiotic. The public health value of large-scale community-wide preventive therapy would be most pronounced in settings where high transmission rates can be controlled simultaneously, since a truly durable effect could be achieved when all LTBI and active disease is eliminated at the same time.<sup>30</sup>

#### 5. Evidence for different preventive therapy regimens

##### 5.1. Isoniazid preventive therapy

Isoniazid (INH) is an oral antibiotic with activity against both intracellular and extracellular *M. tuberculosis*. Daily therapy with INH, for between 6 and 12 months, has been the mainstay of LTBI therapy for five decades. Evidence to support this practice includes a series of randomized clinical trials conducted in the mid-twentieth century,<sup>31–35</sup> showing that daily INH to treat LTBI reduced the incidence of TB by 60% to 90%. The findings of a

**Table 2**

Odds of incident tuberculosis among individuals treated for latent tuberculosis infection with selected regimens compared to placebo, reported in a network meta-analysis<sup>a</sup>

Regimen	OR (95% CI)
INH 3–4 months	0.94 (0.53–1.56)
INH 6 months	0.64 (0.48–0.83)
INH 9 months	0.94 (0.40–2.10)
INH 12–72 months	0.52 (0.41–0.66)
RFB–INH	0.28 (0.05–1.49)
RFB–INH (high dose)	0.31 (0.06–1.59)
RPT–INH	0.61 (0.29–1.22)
RIF	0.41 (0.18–0.86)
RIF–INH 1 month	1.07 (0.36–2.79)
RIF–INH 3–4 months	0.52 (0.34–0.79)
RIF–INH–PZA	0.34 (0.18–0.62)
RIF–PZA	0.55 (0.33–0.92)
INH–EMB	0.91 (0.32–2.42)

OR, odds ratio; CI, credible interval; INH, isoniazid; RFB, rifabutin; RPT, rifapentine; RIF, rifampicin; PZA, pyrazinamide; EMB, ethambutol.

<sup>a</sup> Network meta-analysis of 53 studies by Stagg et al.<sup>36</sup>

published meta-analysis of randomised trials of preventive regimens are summarised in Table 2. A meta-analysis of the placebo-controlled studies found the odds of subsequent TB for individuals with LTBI treated with INH were 0.64 (95% credible interval 0.48–0.83) compared with placebo.<sup>36</sup> Although the primary studies upon which current regimens are based used either 6 or 12 months of self-administered therapy, 9-month regimens are also recommended. This strategy is based upon a re-analysis of studies by the US Public Health Service (USPHS), which suggested optimal effectiveness was achieved after 9 months – with potentially less benefit due to decreasing adherence with longer therapies.<sup>37</sup>

Consequently, the WHO recommends either 6 or 9 months of daily INH (9H) as the standard for treatment of LTBI.<sup>21</sup> Other national bodies have made similar recommendations<sup>18,38,39</sup> (Table 3). For people living with HIV infection, 9 months of therapy is generally recommended.

##### 5.2. Rifamycin-based regimens

Rifamycins are a class of oral antibiotics including rifampicin (RIF; also called rifampin), rifabutin, and rifapentine (RPT) that inhibit bacterial RNA synthesis by binding to the DNA-dependent RNA polymerase. This drug class forms the backbone of first-line TB treatment. Rifamycins have been used to treat LTBI either as single agents or in combination with INH.<sup>38</sup>

##### 5.2.1. Daily rifampicin alone for 3–4 months

Four randomized controlled trials have compared 3–4 months of RIF alone with 9 months of INH.<sup>27,42–44</sup> Although none were powered to assess effectiveness, results are promising. Importantly, adherence with the RIF-based regimen appeared better, and the rate of severe adverse events lower, than for INH-based regimens.<sup>45</sup> A network meta-analysis, incorporating data from 53 studies of different preventive therapies, estimated that the odds of incident TB were reduced by 59% with RIF alone compared to placebo (odds ratio 0.41, 95% credible interval 0.18–0.86) (Table 2).<sup>36</sup> However, these analyses only provide indirect evidence of effectiveness. A multi-centre clinical trial comparing 4 months of self-administered RIF to 9 months of daily INH therapy is underway to address this question, with follow-up to be completed in 2017.<sup>46</sup> Nonetheless, a 4-month daily RIF regimen has been widely recommended as an appropriate alternative to INH.<sup>18,21,38,40,47</sup>

##### 5.2.2. Weekly rifapentine/isoniazid for 3 months (3HP)

Twelve doses of weekly directly observed RPT plus INH has been shown to be equivalent to 9 months of INH alone in

**Table 3**  
Current guidelines for the treatment of latent tuberculosis infection<sup>a</sup>

Institution (year)	Recommended treatment for LTBI that is presumed to be drug-susceptible	Recommended treatment for LTBI that is presumed to be MDR
WHO (2014) <sup>21</sup>	6INH or 9INH <sup>b</sup> or 3 months weekly RPT plus INH under DOT or 3–4 months INH + RIF or 3–4 months RIF	Strict clinical observation for 2 years is preferred over provision of preventive therapy. Benefits of preventive therapy may outweigh harm for children <5 years of age. If preventive therapy is given, monitor for acquired drug resistance.
CDC (2000) <sup>38</sup>	9INH daily or twice weekly <sup>c</sup> 6INH daily or twice weekly 4RIF daily <sup>c</sup> 3 months weekly RPT + INH under DOT (If HIV-positive, 9 months is preferred)	Not stated.
UK NICE guidelines (2016) <sup>18</sup>	Close contacts aged <65 years or HIV-positive <sup>d</sup> : either 6INH (with pyridoxine) or 3 months INH + RIF (with pyridoxine) Close contacts aged <35 years for whom hepatotoxicity is a concern: 3 months INH + RIF (with pyridoxine) For people living with HIV and transplant recipients: 6INH (with pyridoxine)	Not stated.
EU Standards for TB Care (2012) <sup>39</sup>	HIV: 6–9 months INH or any new regimen for which evidence becomes available; non-HIV: treatment recommended, but not specified	Clinical monitoring and no preventive therapy.
Canadian TB Standards (2013) <sup>40</sup>	9 months INH (first choice) Alternative regimens: 6INH 3–4 months INH + RIF 3 months weekly INH/RPT under direct observation; intermittent regimens only recommended when daily regimens cannot be used (6–9INH twice weekly; 3 months INH + RIF twice weekly; under direct observation) <sup>e</sup>	INH-R: treat contacts of patients with INH resistance with 4RIF. RIF-R: treat contacts of patients with RIF resistance with 9INH. MDR-TB: 9LFX or 9MOX with close monitoring.

LTBI, latent tuberculosis infection; MDR, multidrug-resistant; WHO, World Health Organization; CDC, US Centers for Disease Control and Prevention; DOT, Directly Observed Therapy; NICE, National Institute for Health and Care Excellence; EU, European Union.

<sup>a</sup> The duration of treatment is indicated by the number of months followed by the drug name (e.g., 6INH is 6 months of isoniazid). Treatment is given daily under self-administered therapy unless otherwise stated. INH, isoniazid; RIF, rifampicin; RPT, rifapentine; LFX, levofloxacin; MOX, moxifloxacin.

<sup>b</sup> The WHO Expert Panel considered 9-INH to be an equivalent treatment option to 6-INH, in the absence of a study directly comparing the two treatment durations. However, it also concluded that optimal protection from INH appeared to be obtained by 9-INH, on the basis of re-analysis of earlier randomised trials.<sup>35</sup>

<sup>c</sup> American Thoracic Society guidelines previously recommended rifampicin with pyrazinamide for 2 months, however this is no longer recommended on account of high rates of hepatotoxicity after implementation.<sup>41</sup>

<sup>d</sup> The UK NICE guidelines recommend preventive therapy be offered to 35–65-year-olds if hepatotoxicity is not a concern.

<sup>e</sup> In pregnancy, deferral of preventive therapy until 3 months after delivery is recommended unless a very high risk of disease (e.g. HIV or recent infection). INH (with pyridoxine) and RIF considered safe in pregnancy.<sup>40</sup>

preventing disease progression, in an open-label clinical trial conducted in the USA, Canada, Brazil, and Spain.<sup>24</sup> As expected, given the shorter regimen and direct observation, treatment completion was substantially higher in the combination therapy group (82.1% vs. 69.0%). The regimen has also been shown to be equivalent to INH among children aged 2 to 18 years, and among people living with HIV.<sup>25,26</sup>

Toxicity was also less in the shorter regimen, with fewer individuals taking RPT/INH developing drug-related hepatotoxicity in the main study. For people living with HIV, hepatotoxicity was significantly less common for the combined regimen. The weekly RPT/INH regimen has also been shown to be well-tolerated in patients with kidney transplants. A retrospective cohort study found that a higher proportion of patients completed treatment in the RPT/INH group (40/43; 90%) than in the INH group (52/110; 43%) ( $p < 0.001$ ).<sup>48</sup>

While guidelines now recommend the RPT/INH regimen (Table 3), it is unclear whether self-administration of this therapy will achieve similar results to the direct observation undertaken in the published studies.

### 5.2.3. Rifampicin plus isoniazid for 3–4 months

Several randomized studies have compared 3–4 months of daily INH and RIF to daily INH alone. A meta-analysis of five randomized controlled trials in adults found that daily therapy with INH plus RIF for 3 months (3HR) and standard therapy with INH for 6–12 months were equivalent in terms of efficacy, severe side effects, and mortality.<sup>49</sup> Significant heterogeneity was observed among the trials regarding the outcome of severe adverse drug reactions, but a sub-analysis that included only high-quality studies indicated that the two regimens were equally safe. A randomized controlled trial in children <15 years found that 4 months of INH plus RIF (4HR) was at least equivalent to 9H.<sup>50</sup> The 4HR regimen was associated with fewer radiographic abnormalities than 9H (11% vs. 24%). However, no child from either group experienced a clinical episode of active TB.

While it is reasonable to assume that a combination INH and RIF will increase the risk of hepatotoxic side effects compared to INH or RIF alone,<sup>51</sup> this has not been demonstrated clearly. As 4-month daily RIF monotherapy is now being recommended widely (see above), the benefit of adding INH remains unclear. Considering a

potentially increased risk of hepatotoxicity of a combination regimen, this regimen is likely to become increasingly obsolete – except perhaps in children where convenient water dispersible combination tablets are available and in whom toxicity is unlikely.

#### 5.2.4. Other regimens

Several randomized trials have compared a regimen consisting of 2 months RIF and pyrazinamide (2RZ) with regimens comprising 6–12 months of treatment with INH in HIV-infected patients.<sup>52</sup> These trials demonstrated that the two regimens had equivalent efficacy and mortality in patients with LTBI. Based on these findings, the 2RZ regimen was initially recommended for the treatment of LTBI in HIV-positive and HIV-negative patients by the American Thoracic Society in 2000,<sup>38</sup> leading to the widespread use of 2RZ. However, case reports of serious hepatotoxicity and death<sup>53</sup> and the finding of very high rates of severe hepatotoxicity in non-HIV-infected persons in subsequent trials led to a revised recommendation that 2RZ should be used with caution in HIV-infected persons and with extreme caution in non-HIV-infected persons.<sup>41</sup>

## 6. Preventive therapy for drug-resistant *M. tuberculosis*

Contacts of patients with known multidrug-resistant (MDR)-TB have a high risk of infection with a drug-resistant organism.<sup>54,55</sup> Limited evidence is available to inform decision-making about the optimal approach to individuals likely to have MDR-TB. An observational study from the Federated States of Micronesia followed contacts of MDR-TB patients who received preventive therapy with a tailored multi-drug regimen including moxifloxacin with ethambutol (EMB) or ethionamide.<sup>56</sup> No treated contacts developed MDR-TB, while 20% of infected contacts who refused treatment developed the disease. A prospective study in South Africa gave child contacts 6 months of ofloxacin with INH and EMB irrespective of TST status. Just six of 186 (3.2%) children given therapy developed TB – substantially less than historical controls.<sup>57</sup> Another study found that tailored chemoprophylaxis resulted in significantly lower rates of TB compared to those not receiving any therapy.<sup>58</sup> A number of other uncontrolled studies have been conducted,<sup>55,59–61</sup> but to date no randomized controlled trial of preventive therapy following household MDR exposure has been completed. One placebo-controlled study of fluoroquinolones for LTBI among transplant recipients was discontinued early, on account of an excess of musculoskeletal adverse events in those receiving levofloxacin.<sup>62</sup> Corticosteroid use among all participants likely contributed to this increased rate of adverse events.

Three randomized trials of preventive therapy for MDR-TB are underway or in preparation. The V-QUIN Trial is comparing levofloxacin to placebo among infected contacts of MDR-TB in Vietnam. TB CHAMP provides children under the age of 5 years in South Africa with either levofloxacin or placebo. The PHOENIX study in Africa, South America, and Asia will compare delamanid and INH to INH alone. However, the results of these three studies will not be available until after 2020.

In the meantime, current guidelines regarding the treatment of MDR infection differ considerably. The WHO recommends periodic screening of infected contacts for at least 2 years after exposure.<sup>21</sup> Another consensus expert statement recommends using fluoroquinolones in MDR-TB-infected contacts, based upon the drug resistance profile of the presumptive source case. The United States Centers for Disease Control and Prevention (CDC) and European guidelines offer alternatives of periodic screening or preventive therapy.<sup>38,39,63</sup> Even if preventive antibiotics are given, until clear evidence of effectiveness is available, where possible all infected contacts of patients with MDR-TB should be followed up for at least 2 years – the highest risk period.

## 7. Selecting populations for which preventive therapy may be considered

In deciding whether to recommend preventive therapy, clinicians must weigh the likely benefits and risks of treatment. Once active TB has been ruled out, the benefits of therapy can be assessed by considering (1) the likelihood that the diagnostic test result for LTBI (TST or IGRA) is a true-positive (as discussed above), and (2) the risk that an individual will subsequently progress to disease.

The risk of disease progression is greatest close to the time of infection, with the majority of disease progression occurring within the first 2 to 3 years after exposure.<sup>11</sup> For this reason, recent contacts of infectious individuals and migrants arriving from endemic areas within the preceding 2 years are often considered at a high risk. Other epidemiological factors affecting the likelihood of disease progression are summarized in Table 1.

The decision regarding whether to initiate preventive therapy must also take into account the potential toxicity of therapy, which requires consideration of the patient's age and comorbidities.

## 8. Recommendations for TB contacts

Close contacts of patients with infectious drug-susceptible TB are a priority population for whom LTBI testing and treatment should be applied, given their high likelihood of early disease progression. Child contacts of patients with TB are a priority group for screening and treatment.<sup>21</sup> Those under 5 years of age have a particularly increased risk of severe forms of disease. Exclusion of active disease on the basis of a symptom screen has been shown to be a reliable method for excluding prevalent TB, prior to commencing therapy.<sup>12</sup> On account of the logistical barriers introduced when using the TST in resource-limited settings, and the excellent tolerability of preventive therapy in children, empirical treatment may be appropriate for young children with significant recent exposure.<sup>90</sup> Effective treatment regimens for children include the same antibiotics as for adult LTBI, with dose adjustment for weight.

The highest priority group of contacts for whom WHO recommends treatment are children under 5 years of age and people living with HIV, given their susceptibility to develop severe disease.<sup>21</sup> However, these guidelines have recognized the importance of extending preventive therapy to all infected contacts, regardless of age or comorbidities, where feasible.

## 9. Recommendations for recently arrived migrants

The majority of TB in low-prevalence settings often occurs among newly arrived migrants from endemic areas. In order to substantially reduce TB in these settings, it will be necessary to prevent infected migrants from developing TB disease. Pre-migration screening of migrants for active TB is undertaken in many settings, including the USA, Europe, Australia, and Canada. However, until recently, screening for LTBI has not been recommended. The CDC have recently concluded that screening of individuals from selected high-prevalence countries for LTBI was likely to provide a moderate net economic benefit where feasible.<sup>91</sup> In the UK, screening new arrivals aged <35 years from countries with a TB incidence of 150/100 000 is implemented.<sup>92</sup>

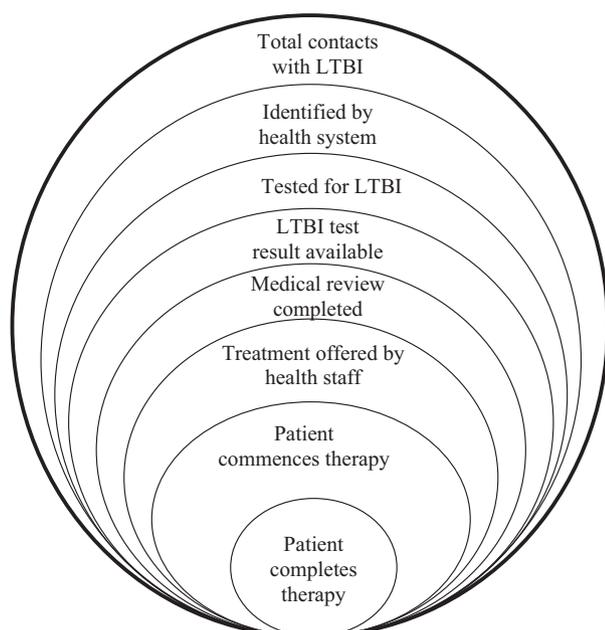
Such policies are based upon an assumption that toxicity of treatment will be relatively small in comparison to the long-term individual and population-wide benefits. They reflect the growing momentum towards widespread testing and treatment for LTBI in resource-rich countries, in recognition that the bulk of local transmission occurs among recent migrants.<sup>93</sup>

Defining the costs and benefits of this approach is important, in order to ensure the efficient use of health resources. A recent modelling study showed that screening high-risk migrants entering the USA was likely cost-saving for those originating from high and medium prevalence settings.<sup>94</sup> While routine migrant screening for LTBI may be too costly for implementation in all countries, this strategy may provide a pathway to further reducing TB in settings where prevalence is already low.

However, given ethical concerns raised by policies of preventive treatment based upon relatively non-specific tests for LTBI, and potential for migrants to be re-infected during return visits to their countries of origin, this solution is unlikely to be sufficient to eliminate TB in low-prevalence settings.<sup>95</sup> Ultimately, aggressively lowering the prevalence of TB in high-burden source countries will be essential if TB elimination is to be realized in low-prevalence countries with substantial migrant populations.

## 10. Recommendations for immunocompromised patients

The risk of TB reactivation is increased in people with immunosuppressive conditions such as chronic renal failure,<sup>73</sup> poorly controlled diabetes mellitus,<sup>81</sup> or treatment with tumour necrosis factor (TNF) inhibitors.<sup>96</sup> These medical risk factors have to be taken into account when assessing the risk–benefit balance of an individual patient with LTBI. Decision analysis modelling has shown that the vast majority of immunocompromised patients with LTBI will benefit from LTBI treatment.<sup>21,97</sup> However, the decision to screen those with immunosuppressive conditions must consider a range of additional factors. The true incidence of LTBI in the specific population, and the accuracy of LTBI tests (especially the proportion of false-negative results of TSTs and IGRAs) will have a major impact on the costs and benefits of a screening programme. International guidelines for screening high-risk groups are summarized in Table 3.



**Figure 2.** The ‘cascade of care’ for contacts exposed to *Mycobacterium tuberculosis*. Each circle represents a proportion of the overall population (thick line), with the smaller circles corresponding to successive steps in the treatment cascade, from identification to treatment completion. At each step of the cascade, individuals may fail to progress. This may result in a small proportion of eligible individuals actually benefiting from preventive therapy.

## 11. Addressing the barriers to LTBI screening

In spite of evidence that preventive therapies are effective, and recent WHO recommendations to expand their use, substantial gaps exist between policy and practice.<sup>98</sup> This limits the potential impact of preventive therapies.

Potential barriers to the uptake of LTBI testing and treatment include reluctance of providers to prescribe LTBI treatment (for example because of fear of facilitating the development of drug resistance with monotherapy,<sup>99</sup> or because the health providers are not convinced that the benefits of LTBI treatment outweigh the potential risk from adverse effects<sup>100,101</sup>), reluctance of people with LTBI to undergo a prolonged course of treatment for an asymptomatic condition that may never progress to active TB disease, lack of trained and experienced medical staff, and lack of availability of single drugs in some low- and middle-income countries in which only combination therapy for treatment of active TB is readily available.

Close contacts of patients with TB are a well-recognized group that is likely to benefit from preventive therapy. Yet a considerable proportion of contacts miss out on the opportunity to receive treatment. A recent meta-analysis of 58 studies including 748 572 people identified substantial rates of drop-out at each step of work-up for LTBI treatment.<sup>98</sup> Figure 2 illustrates the ‘cascade of care’ between the time at which contacts are infected and treatment completion, indicating how just a small proportion of eligible individuals may actually benefit from the therapy. Even in high-income countries, the proportion of eligible patients who complete LTBI treatment is often small.<sup>102</sup> Unfortunately, the gap between the total number of contacts with LTBI and the number completing treatment is rarely, if ever, measured by TB programmes. In order to achieve optimal individual and population benefit from preventive therapy, health systems can develop strategies to address each step of the cascade.

## 12. Optimizing preventive therapy adherence

Once high-risk individuals with LTBI have been identified, TB control programmes must support patients to achieve optimal adherence, and appropriately manage adverse events.<sup>103</sup> The range of available adherence support strategies includes face-to-face direct observation of therapy (DOT – a recommended part of the 3HP regimen), regular patient review throughout treatment, mobile phone-based methods (including two-way SMS and staff phone contact),<sup>104</sup> and even video DOT. Appropriate management of toxicity is not only important for reducing the harms associated with preventive therapy, but also in allowing staff to improve adherence by managing the events appropriately.

## 13. Decision aids to optimize the impact of preventive therapy

Studies have examined whether translating guidelines on LTBI treatment and screening into an electronic decision support (EDS) tool improves guideline-consistent decision-making. An EDS tool to assist clinicians in applying USA LTBI treatment guidelines led to substantially improved compliance with the guidelines in theoretical case scenarios (95.8% vs. 56.6%,  $P < 0.001$ ).<sup>105</sup>

A particular challenge for clinicians who treat LTBI is the emphasis that guidelines place upon evaluation of individualized risk prior to recommending therapy. Medical practitioners are expected to balance their patients’ individual risks and benefits prior to making a treatment recommendation. Quantifying overall appropriateness of therapy can be challenging in situations where the risk of disease progression is moderately increased (e.g., patients with diabetes or cancer). In these settings, EDS can provide valuable guidance for individual patient decision-making.<sup>97</sup> A

Canadian group developed a web-based calculator that estimates the personalized risk of individuals with LTBI developing TB and predicts the risk of drug-induced hepatitis when receiving INH.<sup>106</sup> Another recent study showed how decision analysis can provide treatment recommendations.<sup>107</sup> It is highly likely that the importance of EDS will expand in future as more health care providers (including those involved in primary care) are enlisted to deliver expanded LTBI treatment programmes.

#### 14. Future promise of preventive therapy

With the adoption of the End TB Strategy in 2015, policymakers have begun to recognize the importance of scaling up preventive therapy. Modelling studies indicate that the treatment of active disease will be insufficient to reduce TB incidence at the rate required to eliminate TB by 2050.<sup>108</sup> Hence, expanded treatment of LTBI will be essential to realizing this vision.

##### 14.1. Community-wide preventive therapy

The Bethel study of community-wide preventive therapy in rural Alaskan communities between 1958 and 1964 provides a prototype for the delivery of widespread treatment for LTBI.<sup>35</sup> The TST prevalence in participating communities exceeded 80%, and the annual risk of infection was 8% – indicating high rates of transmission. Daily self-administered INH or placebo was given for up to 12 months to 3047 and 3017 people, respectively (83% of the total population). The effect on TB incidence in this remote population was dramatic and rapid. A 60% reduction in the cumulative TB incidence was observed. Greater effects were seen among those with a TST of  $\geq 10$  mm. Toxicity due to the therapy was not reported. Nonetheless, the magnitude of the effect seen in this study, if sustained, is consistent with that required for TB elimination. New short-course preventive regimens promise to make community-wide treatment for LTBI more feasible. However, before community-wide screening and treatment can be achieved, further research is required to identify the populations most likely to benefit.

##### 14.2. Expanding testing and treatment of high-risk populations

Expanded access to preventive therapy is likely to be of greatest benefit to those in settings where the risk of TB acquisition and reactivation is substantial – including close contacts, health care workers, mine workers, homeless populations, and prisoners.<sup>21</sup> Decisions about which populations should be tested should be informed by research that examines the long-term benefits of treatment. For example, although miners in South Africa have high rates of LTBI and progression to disease, no sustained benefit was seen when preventive therapy was used.<sup>28</sup> Although a transient decrease in incidence was observed, the risk of disease quickly returned to the baseline following treatment – most likely owing to the high rates of ongoing transmission in these communities. This study provides an important lesson – showing that expanded use of mass treatment for LTBI may be futile if ongoing community transmission is not addressed concurrently.

##### 14.3. New diagnostics for LTBI

Diagnostic advances promise to improve the ability of clinicians to predict which high-risk individuals will progress to develop disease. A recent study conducted in several African countries identified a characteristic biomarker signature associated with subsequent TB.<sup>109</sup> These promising findings may allow more targeted treatment for LTBI, potentially minimizing the number of individuals who need to be treated unnecessarily.

##### 14.4. New treatment regimens

New treatment regimens are also needed to reduce the toxicity and improve the effectiveness of LTBI therapies. In particular, as described above, further research is required to evaluate the most effective regimens that will prevent TB among infected contacts of MDR-TB patients.<sup>110</sup> Ideal preventive regimens should require a short and effective treatment that is non-toxic, delivered in the community, and avoids acquired drug resistance in those with undetected early disease.

#### 15. Ethical dimensions of TB prevention

Administering preventive therapy to whole populations carries important ethical challenges. In particular, while individuals themselves benefit from a reduction in the future risk of TB, benefits also flow to communities at decreased risk of transmission after treatment completion. Individuals at higher risk of adverse effects from treatment may, however, suffer greater potential harm in order to achieve an equivalent personal and communal benefit. Ethically appropriate public health policy requires proportionate balance between these potentially conflicting priorities.

Stigma is another potential impact of routine screening for LTBI, which otherwise is an asymptomatic condition.<sup>111</sup> The significant majority of individuals with a positive TST or IGRAs will never develop TB – with the diagnosis potentially causing anxiety and prejudice. Hence, screening strategies must be accompanied by appropriate individual and community education to avoid unintended harm for tested individuals.

#### 16. Conclusions

Prevention of TB remains a key component of a comprehensive control strategy in both high and low prevalence settings.<sup>7</sup> Recent advances in diagnostics and treatment offer substantial hope that more effective and efficient treatment programmes can be implemented at scale. However, more research is required to improve the precision with which TB risk can be determined, and to identify less toxic and more feasible treatment strategies. Greater engagement with community members will be critical to ensuring that any eradication programme is ethical and avoids unnecessary stigmatization.

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