ZERO TB Initiative

SYNTHESIS OF GUIDELINES ON **TB INFECTION TREATMENT**

A tool for Zero TB coalitions

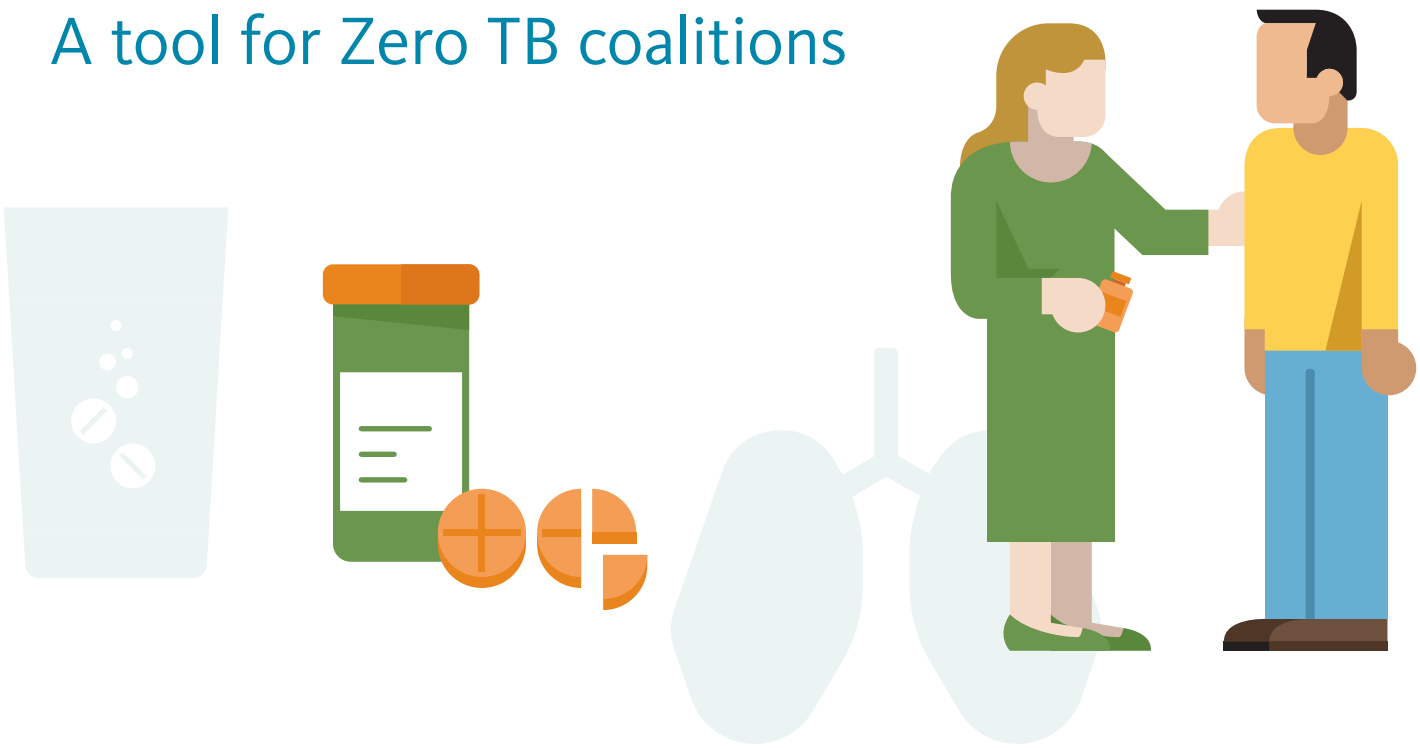

TABLE OF CONTENTS

This handbook was developed by the **Zero TB Initiative**, which advances a comprehensive approach to driving down tuberculosis rates. A comprehensive approach consists of simultaneous use of strategies across a *Search-Treat-Prevent* framework. *Search* entails actively seeking out people who are sick with TB and deploying effective tests to diagnose TB. *Treat* entails ensuring that TB patients receive the correct medications, along with treatment support, for the entirety of their treatment. *Prevent* includes preventing TB disease in those who are already infected with TB by treating their TB infection before it makes them sick. A network of "Zero TB" local coalitions—pursuing a comprehensive approach in each of their settings—are linked to share and disseminate learning. Visit us at **www.zerotbinitiative.org**

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WHY TB INFECTION?

Persons who have **TB infection** and who are not yet sick have TB bacteria in their body, but the bacteria are not multiplying because the immune system is able to control them. However, an estimated 5-10% of people with TB infection will go on to develop **TB disease.** The treatment of TB infection to prevent TB disease is critical to driving down TB rates.[1]

The good news is that we can test for and treat infection in people who have been exposed to TB. Treating infection kills the bacteria and prevents the TB infection from becoming disease and making the person sick. This treatment is routinely used in rich countries, and it has been proven to work well and be safe.

1 Rangaka MX et al. Lancet 2015; 386:2344-53.

1 PURPOSE & APPROACH

We produced this document to help coalitions, activists, and front-line workers advocate for updates to their local and national policy and program guidelines on the management of TB infection. In 2018, the WHO released new guidelines for the treatment and management of TB infection.[2] This presents an opportunity to update guidelines for institutions and programs around the world.

Revising policy and program guidelines can be a lengthy process. We sought to produce a condensed summary of selected national guidelines that can be used as a resource by local coalitions, so that each coalition does not have to repeat this exercise.

The purpose of this document is to summarize guidelines on testing and treating TB infection from selected countries. In this document, we use the term "testing and treatment for TB infection" to refer to the process of (1) administering a test for TB infection, (2) if positive, performing an evaluation to diagnose or rule out TB disease, and (3) if TB disease is ruled out, giving treatment for TB infection.

HOW DID WE CHOOSE THE GUIDELINES TO INCLUDE IN THIS SYNTHESIS?

This document provides a summary of TB infection guidelines and policy updates from a set of countries that we felt could represent a global standard of care. The criteria and rationale that we used to select the countries were:

1 We restricted our review to countries among the top 50 countries with the highest GDP per capita in 2017.[3] We assumed the guidelines in these countries would not be limited by concerns about resource constraints.

2 We restricted our review to countries whose populations include > 10% persons who were born outside the country.[4] The rationale for this choice was countries with a substantial proportion of immigrants are likely to have a substantial number of people affected by TB infection, and therefore are more likely to have developed guidelines around managing TB infection. In contrast, a country where TB infection is a very rare condition might not have needed to develop official guidance for testing and treatment.

3 We initially restricted our review to English-language guidelines, and later included guidelines from additional countries that are home to organizations that provide technical assistance for TB programs in other countries as well as bilateral and multilateral aid, namely France (International Union Against Tuberculosis and Lung Disease), Germany (German Corporation for International Cooperation), and the Netherlands (KNCV).

Based on these criteria, we reviewed guidelines from: Australia, Canada, France, Germany, Ireland, the Netherlands, New Zealand, the United Kingdom, and the United States of America. All but one had a guideline that had been updated since 2010. For comparison, we also reviewed the 2018 World Health Organization guidelines on treating TB infection. A full listing of the guideline documents reviewed can be found in Appendix A.

TABLE 1 COUNTRIES WHOSE GUIDELINES WERE INCLUDED IN THIS SYNTHESIS

Country	Years of publication of documents reviewed
Australia	2017
Canada	2014
France	2003, 2007
Germany	2017
Ireland	2014
The Netherlands	2015, 2017
New Zealand	2010
United Kingdom	2016
United States of America	2000, 2003, 2005, 2018

2 World Health Organization. Latent tuberculosis infection: Updated and consolidated guidelines for programmatic management. 2018.

3 National Accounts Main Aggregates Database, 2017, United Nations Statistics Division. Accessed on 17 Jan 2019.

4 Pew Global (http://www.pewglobal.org/interactives/international-migrants-by-country/)

WHAT INFORMATION DID WE REVIEW IN EACH DOCUMENT?

We reviewed the following key elements in each document:

1. who should be tested and treated for TB infection;
2. how testing for TB infection should be done;
3. which drug regimens should be used for treatment of TB infection; and
4. what laboratory monitoring is recommended during treatment

We considered **consensus** to have been achieved on a specific element if at least six of the nine guidelines made the same recommendation. For groups for which there was consensus to test and treat, this document presents details of the recommendations in **Section 4.**

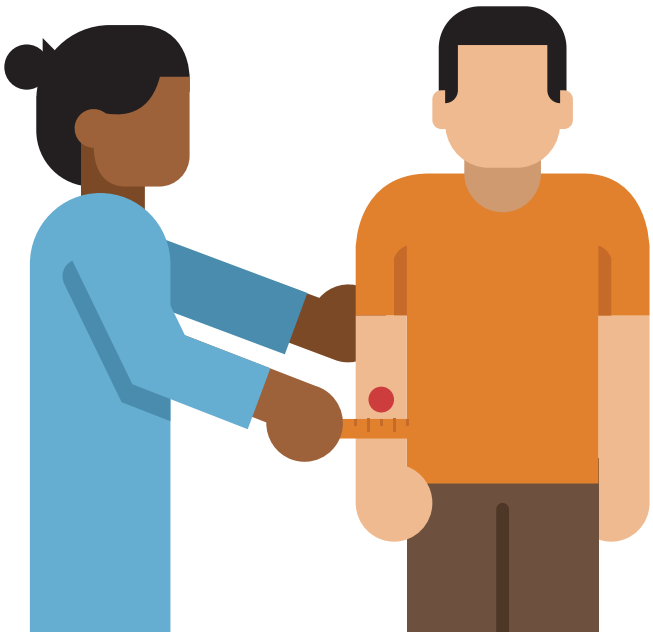
HOW SHOULD THIS DOCUMENT BE USED?

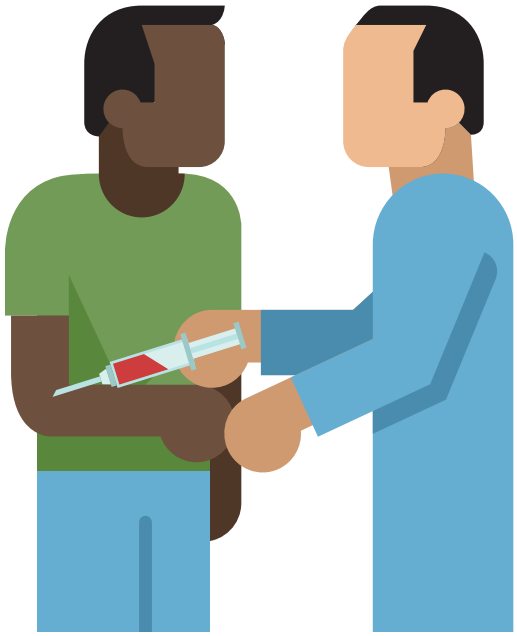
This document is meant to provide a resource for local teams to use as they work to modernize policy and program guidelines on TB infection treatment. When advocating for local guidelines that provide a global standard of care, we felt it would be useful to have an easy-to-access synthesis of the standards of care articulated by high-income countries.

It should be noted that this document is not an implementation guide. The following additional resources are available at **www.zerotbinitiative.org** for teams designing a comprehensive TB program. The second document provides guidance for measuring success and evaluating comprehensiveness at every stage of a comprehensive TB program.

- *An Activist's Guide to Fighting Tuberculosis*
- *A Best-Practice Framework of Program Indicators for Monitoring a Comprehensive Approach to the Tuberculosis Epidemic*

In addition, while this document seeks to briefly summarize key scientific evidence in order to help users understand the context of the guideline recommendations, it does not comprise a comprehensive review of the scientific literature. More in-depth descriptions of the issues surrounding people living with HIV, children exposed to TB, health care workers, migrants, and other vulnerable populations can be found in the Stop TB Partnership's Key Population Briefs (http://www.stoptb.org/resources/publications/acsm_docs.asp).





II

TESTING & TREATMENT OPTIONS

for TB infection

TESTING FOR TB INFECTION

Two types of tests are available to assess TB infection: the tuberculin skin test (TST) and interferon gamma release assay (IGRA) blood tests. Several companies manufacture different IGRA test kits, but this document does not differentiate among them. The TST involves measuring a local cell-mediated reaction to an intradermal injection of purified protein derived from *Mycobacterium tuberculosis* bacteria, typically performed in the forearm. IGRAs operate on the basis that T cells that have been previously exposed to *M. tuberculosis* antigens will release the cytokine interferon gamma when re-exposed to *M. tuberculosis* antigens.

Neither TST nor IGRA is a perfect test. Since both rely on an immune reaction, both can fail to detect TB infection in people with compromised immune systems or who have been very recently infected.[5] The two tests can also give discordant results.[5]

The advantage of the TST is that it requires no laboratory infrastructure to administer. Its disadvantages are that it requires two patient visits to complete (one for test placement and a second to read the result), and that false positive results can occur in people who have received the bacille Calmette-Guerin (BCG) vaccine or who have been exposed to non-tuberculous mycobacteria. The advantages of the IGRA are that only one patient visit is required (to draw a blood sample), and BCG vaccination does not affect the test result. False positive results are possible from a small number of non-tuberculous mycobacteria.[6] The main disadvantage of the IGRA is that it requires laboratory infrastructure. **Table 2** compares the two tests.

WHAT ARE TREATMENT OPTIONS FOR TB INFECTION?

There are currently four established regimen options for the treatment of TB infection that is presumed to be susceptible to isoniazid and/or rifampicin. All four regimens offer

5 Menzies D et al, Ann Intern Med 2007; 146(5):340-54; Sotgiu G et al, J Infect 2019; 79:444-453

6 Hermansen ST et al. PLOS One 2014; 9(4):e93986

7 Rangaka MX et al. Lancet Infect Dis 2012; 12(1):45-55.

TABLE 2 COMPARISON OF TST AND IGRA

Country	TST	IGRA
Sensitivity[5]	~70%	85-95% (varies between test kits)
Specificity in BCG-unvaccinated[5]	> 95%	>90% (varies between test kits)
Specificity in BCG-vaccinated[5]	~55%	>90% (varies between test kits)
Cross-reactivity with BCG	Yes	No
Cross-reactivity with non tuberculous mycobacteria[6]	Yes	Sometimes, depending on mycobacteria species
Incidence rate ratio for progression to TB disease compared to a negative test[7]	1.6	2.1
Number of patient encounters required	2	1
Laboratory required	No	Yes

TABLE 3 TREATMENT OPTIONS FOR TB INFECTION

Regimen	Total doses	Pills in adult dose	Advantages	Disadvantages
3 months of weekly rifapentine + isoniazid (3HP)	12	9	• Better completion compared to 6-9H • Fewest doses • Low risk of liver damage	• Must consider drug interactions with rifamycins • Rare flu-like side effect • No dosing guidelines for children < 2 years old
3-4 months of daily rifampicin (3-4R)	90-120	2	• Better completion compared to 6-9H • Lowest risk of side effects, including liver damage	• Must consider drug interactions with rifamycins
3-4 months of daily rifampicin + isoniazid (3-4HR)	90-120	3 or 4	• Better completion compared to 6-9H • Pediatric dispersible formulation available	• Must consider drug interactions with rifamycins • Side effect profile similar to isoniazid
6-9 months of daily isoniazid (6-9H)	180-270	1	• Lowest pill burden • No rifamycin drug interactions	• Worse completion than shorter regimens • Highest risk of liver damage

protection by reducing risk of TB disease by at least 60% compared to no treatment.[8] These regimens are commonly abbreviated using a number indicating the number of months of treatment followed by letters indicating the drugs used (H=isoniazid, R=rifampicin, P=rifapentine). **Table 3** compares the four regimens. **Appendix B** summarizes the clinical trial evidence showing that the three shorter regimens have comparable efficacy to the older, longer 6-to-9 months isoniazid treatment. Patients taking shorter regimens are more likely to complete treatment than patients taking 6-9 months of isoniazid.[9] The risk of side effects of the shorter regimens are generally comparable or better than 6-9 months of isoniazid[10] (for more information, see **Appendix B**).

Additional treatment options that are even shorter may be available in the future. A recent clinical trial involving people living with HIV demonstrated that 1 month of daily isoniazid and rifapentine was non-inferior to 9 months of isoniazid.[11]

Many people ask whether treatment of TB infection leads to the creation of drug-resistant TB. While treatment of active TB disease with a single drug can indeed lead to drug resistance, available evidence indicates that treating TB infection after properly ruling out TB disease does not. Across 13 clinical trials comparing a combined ~18,000 people receiving isoniazid for treating TB infection to ~18,000 receiving placebo, there was no statistically significant increase in isoniazid resistance among the people who received isoniazid, either in the individual trials or pooled across all the trials.[12]

For patients exposed to multidrug-resistant (MDR) TB, which is resistant to both isoniazid and rifampicin, the four isoniazid- and rifamycin-based preventive treatments in **Table 3** are assumed to be ineffective. Research around treatment of MDR-TB infection is progressing. In a systematic review and meta-analysis of 21 observational studies (five of which included a comparison group), a 90% (95% confidence interval: 9-99%) reduction was observed in the risk of TB for those who received treatment.[13] The most common regimens used in these observational studies were based on a fluoroquinolone. In addition, there are three ongoing efficacy clinical trials for the treatment of presumed MDR-TB infection (TB CHAMP, V-QUIN, and PHOENIx): two are assessing levofloxacin (a fluoroquinolone), and one is assessing delamanid.

8 Zenner D et al. Ann Intern Med 2017; 167:248-255.
9 Pease C et al. BMC Infect Dis 2017; 17:265.
10 Pease C et al. Pharmacoepidemiol Drug Saf 2018; 27:557-566.
11 Swindells S et al. N Engl J Med 2019; 380:1001-1011.
12 Balcells et al. Emerg Infect Dis 2006; 12(5):744-51.
13 Marks SM et al. Clin Infect Dis 2017;64(12):1670-7.

III WHAT DO THE GUIDELINES SAY?

Table 4 summarizes recommendations and consensus across guidelines. **Section 4** presents more detail. **Consensus** means that at least six of nine country guidelines made the same recommendation.

TABLE 4 SUMMARY OF CONSENSUS AMONG RECOMMENDATIONS FOR TESTING AND TREATING TB INFECTION ACROSS NINE COUNTRY GUIDELINES

Which groups should be tested and offered treatment if infected?	**CONSENSUS** ✔ PLHIV ✔ Contacts (adults and children) ✔ People from countries with high TB burdens ✔ Health care workers when they are first employed ✔ People on immunosuppressive therapy or receiving solid organ transplants **NO CONSENSUS** ✖ Other groups identified varied among the guidelines. Groups mentioned by different guidelines included people with various medical comorbidities, people who inject drugs, people in prisons, and people experiencing homelessness.
Is TST or IGRA preferred for testing?	**NO CONSENSUS** ✖ Eight of the nine country guidelines included both tests, and there was no consensus across the guidelines for preferring one over the other
What regimens are used for treating TB infection?	**CONSENSUS** ✔ All country guidelines recommended multiple regimens as options ✔ 4 months of daily rifampicin, 3-4 months of daily isoniazid and rifampicin, and 6-9 months of daily isoniazid were all recommended by at least six of the nine country guidelines
Should infection be treated if source case is known to have MDR-TB?	**CONSENSUS** ✔ Treatment is an appropriate option ✔ All people exposed to MDR-TB should be monitored for 2 years **NO CONSENSUS** ✖ There is variability in the strength of the recommendation to treat versus actively monitor for 2 years
Which people receiving TB infection treatment need laboratory testing such as liver function tests?	**CONSENSUS** ✔ Children generally do not require laboratory monitoring **NO CONSENSUS** ✖ Recommendations are variable for which adults require laboratory monitoring and the frequency of monitoring

Table 5 shows the infection tests and treatment regimens recommended by each guideline.

TABLE 5 TB INFECTION TESTS AND REGIMENS INCLUDED IN DIFFERENT GUIDELINES

Guideline	Recommended Test	Recommended Regimens				
		HP	R	HR	H	Other
Australia	• TST or IGRA		4R	3HR	6-9H	
Canada	• TST or IGRA • IGRA preferred if BCG vaccination received after infancy or more than once.	3HP	4R	3-4HR	6-9H	
France	• TST		4R	3HR	6-12H	2RZ
Germany	• TST preferred in children < 5 years old • TST or IGRA for children 5-14 years old • IGRA preferred in adults ≥ 15 years old.	3HP	4R	3-4HR	9H	
Ireland	• TST, consider IGRA if positive TST		4R, 6R*	3-4HR	6-9H	
Netherlands	• In general, TST followed by IGRA if TST is positive	3HP	4R	3-4HR	6-9H	
New Zealand	• TST is preferred for some groups and IGRA for others			3-4HR	6-12H	
United Kingdom	• TST is preferred for some groups and IGRA for others			3HR	6H	
United States of America	• TST or IGRA	3HP	4R		6-9H	
World Health Organization	• TST or IGRA	3HP	3-4R	3-4HR	6-9H, 36H†	

* Only for children
† Only for people living with HIV

All country guidelines recommended multiple regimens as options. Often, different preferred regimens were recommended for different types of patients based on risk of toxicity or drug interactions. These specific recommendations are reviewed in the subsequent sections of this document.

IV SPECIAL RECOMMENDATIONS

for risk groups

Certain people have a higher risk of either being infected with TB bacteria or becoming sick with TB disease once infected. Guidelines highlight these groups to provide specific considerations for testing and treating TB infection, as well as to emphasize the importance of testing and treating these groups.

- **People living with HIV**
- **Close contacts**
- **Health care workers**
- **Migrants**
- **People with medical co-morbidities**

PEOPLE LIVING WITH HIV

SCIENTIFIC BACKGROUND

People living with HIV have weakened immune systems. This makes them more likely to progress from TB infection to TB disease. Across sub-Saharan African countries, which have the highest burden of HIV globally, people living with HIV have 5 to 20 times the risk of falling sick with TB disease compared to people without HIV.[14]

Across five randomized controlled trials of people living with HIV who had positive TST results, treatment of latent TB infection reduced the risk of TB by 52% (95% confidence interval 29-82%).[15] The benefit for people living with HIV who have negative tests for TB infection is less clear. Because tests for TB infection rely on immune responses, people living with HIV can have false negative results.[5] Most trials to date, which have mostly been conducted among people not receiving antiretroviral therapy, have suggested no statistically significant benefit of treating TB infection in this group.[16] However, a large trial in South Africa of 12 months of isoniazid for people who were receiving antiretroviral therapy showed greater benefit for people with negative TST or IGRA results compared to those with positive tests.[16] In settings with high TB incidence, long-term isoniazid preventive therapy has been shown to offer greater protection than a single course of isoniazid.[17]

Drug-drug interactions occur between rifamycins and certain medications. While this has led to hesitation in using rifamycin-based regimens for TB infection treatment in people taking antiretroviral therapy, the most recent evidence suggests that neither rifampicin nor rifapentine compromises the effectiveness of efavirenz or dolutegravir at standard doses.[18, 19, 20] Research is ongoing in this area.

CONSENSUS AMONG GUIDELINES

People living with HIV should be tested and treated for TB infection.

WHAT DO THE GUIDELINES SAY?

All nine country guidelines recommended treating people living with HIV. Isoniazid-based regimens were frequently preferred for this group, likely given concerns over drug interactions with antiretroviral therapy.

14 Corbett EL et al. Lancet 2006; 367(9514):926037.
15 Ayele HT et al. PLOS One 2015; 10(11):e0142290.
16 Rangaka MX et al. Lancet 2015; 384(9944):682-690.
17 Samandari T et al. Lancet 2011; 377(9777):1588-98.
18 Dooley KE et al. J Acquir Immune Defic Syndr 2013; 62(1):21-27.
19 Podany AT et al. Clin Infect Dis 2015;61(8):1322-7.
20 Cerrone M et al. Clin Infect Dis 2019;68(4):446-452.

TABLE 6 SPECIAL RECOMMENDATIONS FOR TESTING AND TREATMENT OF TB INFECTION FOR PEOPLE WITH HIV

in addition to general recommendations in Table 5

Guideline	Eligibility	Special considerations regarding testing	Special considerations regarding treatment
Australia	All		6-9H is preferred for adults. 3HR is an alternative for children.
Canada	All	• TST preferred. • IGRA may be considered as an additional test if TST is negative	9H is preferred
France	All	• Testing is not a requirement for treatment	
Germany	All	• Treatment should be given irrespective of infection test result.	
Ireland	All	• IGRA may be considered if false negative TST is suspected • Treatment can be given irrespective of TST result.	
Netherlands	All	• Use both TST and IGRA	9H, 4HR, or 3HP is preferred
New Zealand	All	• IGRA is preferred	9H is preferred
United Kingdom	All	• For adults with a CD4 < 200 both TST and IGRA should be used concurrently. • For adults with a CD4 ≥ 200, consider IGRA alone or TST and IGRA concurrently.	6H is preferred
United States of America	All	• Annual testing is recommended if person has ongoing risk for TB exposure	9H or 3HP is preferred
World Health Organization	All	• Testing is not a requirement for treatment	Adults and adolescents in countries with high TB incidence should be offered long-term treatment (36H)

CLOSE CONTACTS

CONSENSUS AMONG GUIDELINES

Close contacts of people with known TB disease should be tested and treated for TB infection.

SCIENTIFIC BACKGROUND

Because TB is passed through the air, the people with the highest risk of infection are those that spend extended time in close contact with someone with infectious TB. These individuals are called "close contacts." Although there is no consensus definition for the amount or type of exposure that defines a close contact, this group often include family members, close friends, and some co-workers.

Without TB infection treatment, a person has the highest risk of developing TB disease within the first 1–2 years after being infected.[21] While the risk is higher for young children, adults still have substantial risk. A meta-analysis of published reports of contact investigations in low- and middle-income countries found that on average, 10% of child contacts < 5 years old, 8% of child contacts 5-14 years old, and 3% of adult contacts were diagnosed with TB at the time of the contact investigation.[22] Overall, around 3% of contacts (combining all age groups) were diagnosed with TB at the time of the contact investigation, and an additional 1.5% of contacts who did not have TB at the time of the contact investigation developed TB within one year.

The efficacy of TB infection treatment for avoiding these incident TB cases from developing is well established. Large placebo-controlled trials of isoniazid for TB prevention in household contacts of TB patients showed that treatment reduced the risk of TB by 50-80%.[23] More recently, in an observational study conducted in the United States and Canada, 0.2% of contacts who received treatment for TB infection developed TB over the next four years, compared to 9.8% of contacts who did not receive treatment.[24]

WHAT DO THE GUIDELINES SAY?

All nine country guidelines recommended testing and treating both child and adult close contacts of people with TB disease. All nine guidelines also recommended that once TB disease is ruled out, young child contacts should be started immediately on treatment for TB infection, even if their test for infection is negative.

Six of the nine country guidelines included a recommendation to treat contacts exposed to MDR-TB. The strength of the recommendations to treat versus monitor were variable across guidelines. In addition, the recommendations for treatment regimens were variable. Four of the nine guidelines recommended fluoroquinolone-based regimens.

CONSENSUS FOR CONTACTS EXPOSED TO MDR-TB

Treatment for TB infection is a valid option, and all MDR-TB contacts should be monitored for 2 years regardless of whether they are treated.

21 Ferebee SH. Adv Tuberc Res 1970; 17:28-106.

22 Fox GJ et al. Eur Respir J 2013; 41(1):140-156.

23 Smieja M et al. Cochrane Database of Systematic Reviews 1999; 1:CD001363.

24 Reichler MR et al. Clin Infect Dis 2019; doi10.1093/cid/ciz438.

TABLE 7 SPECIAL RECOMMENDATIONS FOR TESTING AND TREATMENT OF TB INFECTION FOR CONTACTS OF PEOPLE WITH ACTIVE TB DISEASE

in addition to general recommendations in Table 5

Guideline	Eligibility	Special considerations regarding testing and treatment
Australia	All	• Children < 5 years old can be treated regardless of test result. • For all ages, if initial test is negative, the test should be repeated 8-12 weeks after last exposure
Canada	All	• Children < 5 with negative infection test should start treatment. Test should be repeated 8 weeks after last exposure; if second test is negative, treatment can be stopped.
France	All	• Children with negative infection test should start treatment. Test should be repeated 3 months later; if second test is negative, treatment can be stopped.
Germany	All	• Children < 5 should start treatment regardless of test result. • For adults with a negative infection test, treatment should be initiated until 8 weeks after last exposure. Test should then be repeated; if second test is negative, treatment can be stopped.
Ireland	All	• Children < 5 with negative infection test should start treatment. Test should be repeated 8 weeks after last exposure; if second test is negative, treatment can be stopped. • Infants should be given isoniazid until three months of age, when a TST should be performed.
Netherlands	All	• Children < 5 with negative infection test should start treatment. Test should be repeated 8 weeks after last exposure; if second test is negative, treatment can be stopped.
New Zealand	All	• TST preferred for child contacts ≤ 7 years old. • TST or IGRA, or IGRA following a TST positive test for contacts > 7 years old. • IGRA preferred in BCG-vaccinated people. • Children < 5 with negative infection test should start treatment. Test should be repeated 8 weeks after last exposure.
United Kingdom	People up to 65 years old	• Children < 2 years old with negative infection test should start treatment. Test should be repeated 6 weeks later. • 6H is preferred for neonates • 3HR and 6H are both recommended for people up to 65 years with no hepatotoxicity risk • 3HR is preferred for people < 35 years old with hepatotoxicity risk • No treatment is recommended for people 35-65 years old with hepatotoxicity risk
United States of America	All	• Children < 5 years old with negative infection test should start treatment. Test should be repeated 8-12 weeks later; if second test is negative, treatment can be stopped.
World Health Organization	All	• For child household contacts < 5 years old, testing is not a requirement for treatment. • For children ≥ 5, adolescents, and adults from high-incidence countries who are household contacts, testing is not a requirement for treatment.

HEALTH CARE WORKERS

SCIENTIFIC RATIONALE

TB has long been recognized as an occupational hazard for health care workers. Higher rates of TB disease and infection have been documented consistently among health care workers compared to the general population in low- and middle-income countries.[25] When people with TB come into a health center, they frequently do not yet know they are sick with TB; this can put health care workers at risk for contracting TB from these untreated patients. Prompt diagnosis and effective treatment of people with TB, as well as good infection control in health care facilities, are critical to preventing transmission of TB among patients and health care workers in health facilities.[26] Interventions to improve infection control have been shown to reduce the risk of TB disease and infection in health care workers in both low-burden and high-burden settings.[27]

Modeling studies have suggested that in settings of low TB incidence, testing and treating TB infection in health care workers is beneficial and cost-effective.[28] In contrast, the role of testing and treating TB infection in heath care workers in high-burden settings has not been well established, as the impact of a single treatment for TB infection in the context of repeated occupational exposures to TB is unclear. It is possible that guidance can be drawn from evolving evidence around protecting people living with HIV in high-burden settings, who are likewise subject to repeated exposures and are at high risk of developing disease. For example, lifelong isoniazid preventive therapy has been suggested for HIV-infected health care workers in high-TB-burden settings.[29] In addition, the idea of periodic TB infection treatment is currently being assessed in the WHIP3TB trial, which compares a single course of 3HP with repeated courses of 3HP given once a year to people living with HIV.[30] It is possible that similar strategies could be adopted for health care workers, implemented in conjunction with improvements to infection control and TB diagnosis.

25 Joshi R et al. PLoS Med 2006; 3(12):e494.
26 Von Delft et al. Int J Infect Dis 2015;37:147-151.
27 Schmidt B et al. BMC Public Health 2018; 18:661.
28 Diel R et al. Pharmacoeconomics 2015; 33(8):783-809.

CONSENSUS AMONG GUIDELINES

New health care employees should be tested and treated when they are first hired.

WHAT DO THE GUIDELINES SAY?

Seven of the nine guidelines recommended testing and treatment for either all or some new employees. In addition, five of the nine guidelines recommended periodic testing for employees with higher risk of occupational TB exposure because of their specific responsibilities.

29 Baker BJ. Int J Tuberc Lung Dis 2018; 22(4):356.
30 https://clinicaltrials.gov/ct2/show/record/NCT02980016

TABLE 8 SPECIAL RECOMMENDATIONS FOR TESTING AND TREATMENT OF TB INFECTION FOR HEALTH CARE WORKERS

in addition to general recommendations in Table 5

Guideline	Eligibility	Special considerations regarding testing and treatment
Australia	• New employees who were born or worked in a country with higher TB incidence • New employees who are likely to encounter TB patients in the future • New employees with known past history of TB exposure • Repeated testing depending on risk	TST is preferred
Canada	• New employees + annual testing depending on risk	TST is preferred
France	• New employees + repeated testing depending on risk	
Germany	• Those in pneumonology and those in contact with TB patients or specimens	
Ireland	• New employees	
Netherlands	*No recommendations*	*No recommendations*
New Zealand	• New employees + repeated testing depending on risk	IGRA preferred
United Kingdom	Three groups of new employees: **a** those from high-incidence countries **b** those not from high-incidence countries who have not received the BCG vaccine **c** those who have had contact with patients in a setting where TB is highly prevalent	Different tests are recommended for each group: **a** TST **b** TST followed by IGRA **c** IGRA Different treatment regimens are recommended based on age and hepatotoxicity risk: • 3HR and 6H are both recommended for people up to 65 years with no hepatotoxicity risk • 3HR is preferred for people <35 years old with hepatotoxicity risk • No treatment is recommended for people 35-65 years old with hepatotoxicity risk
United States of America	• New employees + repeated testing depending on risk	
World Health Organization	• May consider in low incidence settings	

MIGRANTS

SCIENTIFIC RATIONALE

Four of the five countries that most contribute to the population of international migrants have high burdens of TB: Bangladesh, China, India, and Russia.[31] While most international migration is to high-income countries, around one third of international migrants live in low- and middle-income countries.[31] In addition to international migrants, large numbers of people migrate within their home country seeking economic opportunity or fleeing unrest. Migrants—both international and domestic—often have a higher risk of TB than the non-migrant population either because they come from a place with a higher TB burden or because they face barriers to accessing health care in the place where they reside.[32]

WHAT DO THE GUIDELINES SAY?

Six of the nine guidelines specified that this recommendation applied to immigrants from countries with high burdens of TB. Four of the nine guidelines included age eligibility criteria for testing and treating immigrants.

CONSENSUS AMONG GUIDELINES

People immigrating from high-incidence countries should be tested and treated for TB infection.

31 United Nations, Department of Economic and Social Affairs, Population Division (2017). International Migration Report 2017. (ST/EST/SER.A/404)

32 Stop TB Partnership (2016). Key populations brief: mobile populations.

TABLE 9 SPECIAL RECOMMENDATIONS FOR TESTING AND TREATMENT OF TB INFECTION FOR MIGRANTS

in addition to general recommendations in Table 5

Guideline	Eligibility	Special considerations regarding testing and treatment
Australia	• Those from any country with a history of TB contact within the last 2 years • Those from high-incidence countries who are < 35 years old • Those from high-incidence countries who are ≥ 35 years old and have additional risk factors	
Canada	• Foreign-born children up to 20 years old • Refugees up to 50 years old from high-incidence countries	
France	*No recommendations*	*No recommendations*
Germany	• Those from high-incidence countries	
Ireland	• Those from high-incidence countries up to 55 years old	• Treatment recommended for all those < 35 years old • Treatment recommended for those 35-55 years old if directly observed therapy is available
Netherlands	*No recommendations*	*No recommendations*
New Zealand	• Refugees < 16 years old • Adults from high-incidence countries who have a known history of exposure to an infectious case within the preceding two years	• TST preferred for children < 7 years old • TST or IGRA, or IGRA following a positive TST, for refugee children 8-15 years old. • IGRA preferred in BCG-vaccinated children.
United Kingdom	• Those from high-incidence countries who present to health care services	• IGRA preferred • 3HR and 6H are both recommended for people up to 65 years with no hepatotoxicity risk • 3HR is preferred for people < 35 years old with hepatotoxicity risk • No treatment is recommended for people 35-65 years old with hepatotoxicity risk
United States of America	• Those from high-incidence countries	• IGRA preferred if BCG-vaccinated
World Health Organization	• May consider testing immigrants from high incidence settings moving to low incidence settings	

PEOPLE WITH MEDICAL CO-MORBIDITIES

SCIENTIFIC RATIONALE

Certain medical conditions or treatments can increase a person's risk for developing TB disease once infected. Conditions or treatments that impair the immune system can increase the risk of developing TB disease based on an infection acquired in the past, which was previously contained by the immune system. A few examples of such conditions are:

- Immunosuppressive treatments for autoimmune disorders have been shown to increase the risk of developing TB. In clinical trials, patients receiving TNF-α antagonists for conditions such as rheumatoid arthritis had twice the risk of developing TB as patients in the control arms.[33]

- Patients receiving organ transplants are a special category of immune-suppressed individuals. They are given immunosuppressive therapy to prevent rejection of the transplanted organ. In addition, a special consideration unique to organ transplant recipients is that they can develop TB because of an infection in the transplanted organ.[34]

- Diabetes, particularly if uncontrolled, can impair the immune system. Cohort studies from low-TB incidence settings show significantly higher TB risk among people with diabetes, suggesting that this impairment increases the risk of disease progression from previously acquired infection.[35]

Silicosis is another important condition that increases the risk of TB. Inhalation of silica dust can cause scarring or damaging of the lungs, and can increase the risk of TB by threefold.[36] This is a particular concern in places that have both high TB burdens and large mining industries, as people who work in mining-related industries often have long-term exposure to silica dust. People who work in ceramic industries and construction may also have this exposure.

33 Zhang Z et al. BMJ Open 2017;7(3):e012567.

34 Epstein DJ and Subramanian AK. Infect Dis Clin North Am 2018; 32(3):703-718.

35 Hayashi S and Chandramohan D. Trop Med Int Health 2018; 23(10):1058-1070.

36 Rees D and Murray J. Int J Tuberc Lung Dis 2007; 11(5):474-484.

CONSENSUS AMONG GUIDELINES

People receiving immunosuppressive therapy or solid organ transplant should be tested and treated for TB infection.

WHAT DO THE GUIDELINES SAY?

Eight of the nine country guidelines recommended testing and treatment of TB infection for patients receiving immunosuppressive therapy (e.g. TNF-α antagonists, corticosteroids). Seven guidelines recommended testing and treatment of TB infection for patients receiving solid organ transplants.

Several other medical conditions were commonly mentioned as reasons to test and treat individuals for TB infection. However, there was no consensus reached, as different medical conditions were included in different guidelines. Specific conditions for which testing and treatment of TB infection were recommended are shown in **Table 10**.

TABLE 10 MEDICAL CONDITIONS OR TREATMENTS THAT CONSTITUTE REASONS FOR TESTING AND TREATING TB INFECTION

Guideline	Immunosuppressive treatments*	Solid organ transplant	Diabetes	Kidney disease	Malnutrition	Fibrotic lesions in lungs *potentially indicative of previous untreated TB*	Silicosis	Gastrectomy, bypass, malabsorption	Hematologic malignancies
Australia	✔	✔							
Canada	✔	✔	✔	✔	✔	✔	✔		✔
France	✔	✔							
Germany	✔	✔	✔	✔			✔		✔
Ireland	✔				✔				
Netherlands	✔	✔			✔				
New Zealand	✔	✔	✔	✔			✔	✔	
United Kingdom									
United States of America	✔	✔	✔	✔	✔	✔	✔	✔	✔
World Health Organization	✔	✔		✔			✔		

* Examples of immunosuppressive treatments are anti-tumor necrosis factor α therapy, long term oral corticosteroids, and some cancer chemotherapies

V RECOMMENDATIONS FOR LABORATORY MONITORING

SCIENTIFIC RATIONALE

Historically, isoniazid was the drug most commonly used for treating TB infection. Isoniazid has long been known to be a hepatotoxic drug (i.e. one that can cause damage to the liver). One of the early trials to systematically assess isoniazid-induced hepatitis found that 0.5% of people taking 12 months of isoniazid developed drug-induced hepatitis (i.e. hepatitis attributable to the isoniazid); in comparison, the risk of TB was reduced from 1.4% to 0.4%, so substantially more TB cases were prevented than hepatitis cases caused.[37] To avoid the possibility of isoniazid-induced hepatitis, it is possible to conduct liver function tests before and during treatment so that treatment can be stopped preemptively if there is evidence of abnormal liver function. However, because certain groups of people are at much higher risk for hepatotoxicity than others, a risk-stratified approach can help avoid unnecessary testing, which can be costly and present a barrier to care. For example, a surveillance study in Canada found that only 0.1% of people up to 35 years old who were taking treatment for TB infection were admitted to the hospital because of a side effect related to the liver, compared to 2.6% of people over 65 years old.[38] In addition to age, chronic liver disease from causes such as excess alcohol use may also increase the risk of drug-induced hepatitis.[39]

Of note, hepatotoxicity is less of a problem with 3-4R and 3HP compared to 6 or 9 months of isoniazid.[10] **Appendix B** contains additional information on side effects of the shorter regimens compared to isoniazid. Shifting away from regimens that require long-term isoniazid exposure can help reduce the requirement for liver function testing for the majority of people receiving treatment.

37 International Union Against Tuberculosis Committee on Prophylaxis. Bull World Health Organ 1982; 60(4):555-564.

38 Smith BM. CMAJ 2011; 183(3):E173-179.

39 Kopanoff DE et al. Am Rev Respir Dis 1978;117(6):991-1001.

CONSENSUS AMONG GUIDELINES

Child contacts do not need laboratory monitoring either prior to the initiation of treatment for TB infection or during treatment.

WHAT DO THE GUIDELINES SAY?

Six of the nine country guidelines indicated that baseline laboratory tests were necessary only for adults or people with risk factors for hepatotoxicity that generally apply only to adults (e.g. alcohol use, pregnancy). Therefore, children general would not require laboratory tests under these guidelines.

No consensus existed on which adults require monitoring, what monitoring tests should be done, or with what frequency. The most common recommendation was that some form of monitoring—often liver function testing—should be done for adults over the age of 35 and for persons with risk factors for hepatotoxicity. However, there was no consensus on how pre-treatment test results should be acted upon, how frequently testing should be done during treatment, or what test results should lead to discontinuation of treatment. A summary of the monitoring recommendations across guidelines can be found in **Table 11**.

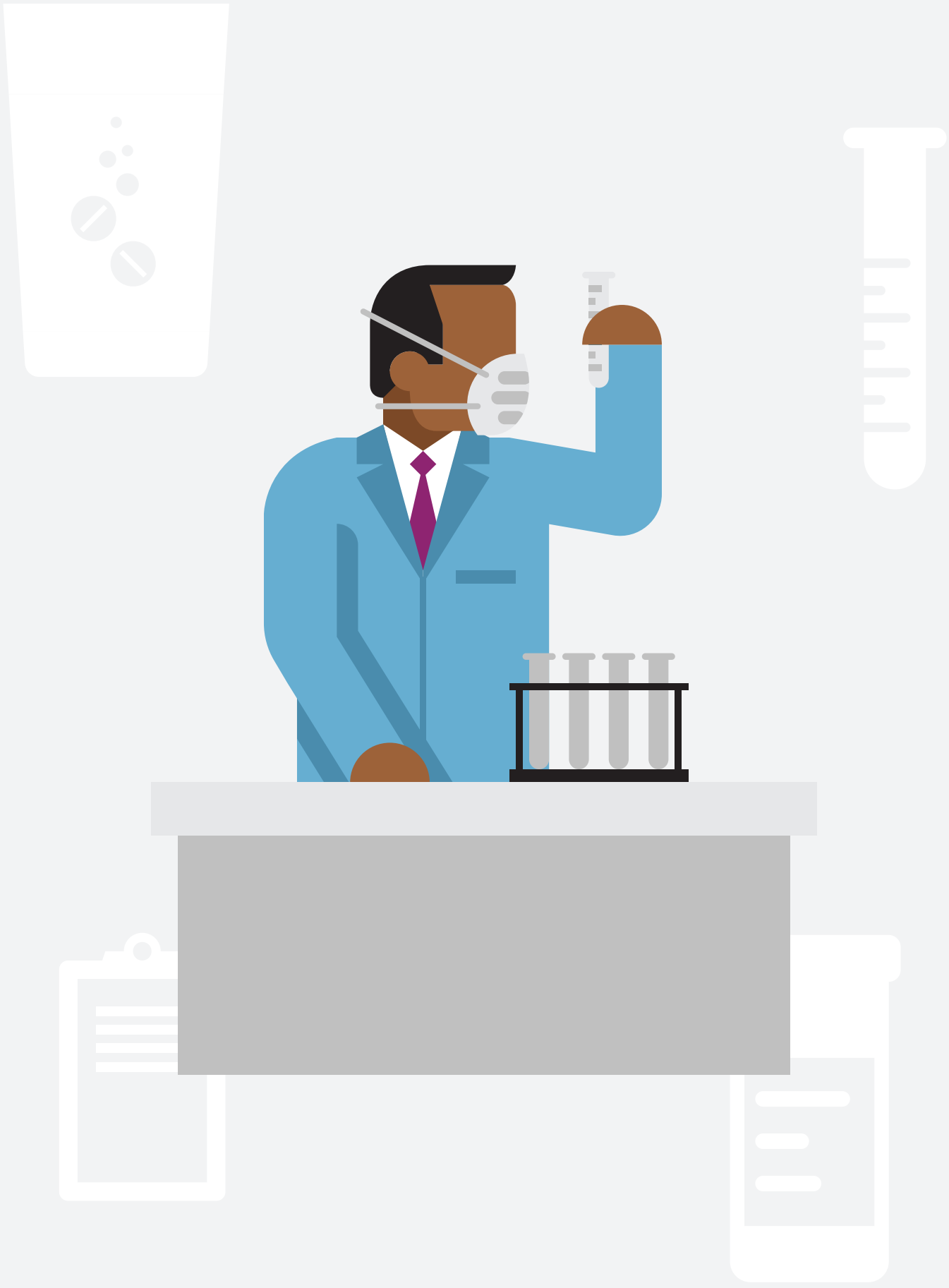


TABLE 11 LABORATORY MONITORING RECOMMENDATIONS FOR PEOPLE UNDERGOING TREATMENT FOR TB INFECTION

Guideline	People for whom laboratory monitoring is recommended	Risk factors for hepatotoxicity	Tests used for monitoring	Frequency of monitoring for those who require it	When to stop TB infection treatment
Australia	Adults ≥35 years old and people with risk factors for hepatotoxicity	• Regular alcohol use • History of liver disease	• Liver function tests	Monthly for at least 3 months	**No symptoms:** Transaminases > 5 times the upper limit of normal **Symptoms:** Transaminases > 3 times the upper limit of normal
Canada	Adults > 35 years old and people with risk factors for hepatotoxicity	• Daily alcohol consumption • Current cirrhosis, chronic active hepatitis, hepatitis C, hepatitis B with abnormal transaminase • History of drug-induced hepatitis • Pregnant or first 3 months post-partum • On treatment with other hepatotoxic medications	• Bilirubin • Transaminases	**Age < 35 if there is a concern for liver disease:** baseline, repeat as needed **Age 35-50:** baseline, after 1 month, every second month as needed, and at end of therapy **Age > 50 or with risk factors:** baseline and monthly	**No symptoms:** Transaminases > 5 times the upper limit of normal **Symptoms:** Transaminases > 3 times the upper limit of normal
France	Everyone	• N/A	• Transaminases	Twice monthly in first month; repeat as needed if elevated	Transaminases > 6 times the upper limit of normal (reassess risks and benefits if > 3 times the upper limit of normal)
Germany	Children	• N/A	• Bilirubin • Transaminases • GGT • Blood count • Creatinine	Baseline, after 2 weeks, and after 4-6 weeks; repeat as needed (frequency not specified)	Not specified
Ireland	Adults > 35 years old and people with risk factors for hepatotoxicity	• History of heavy alcohol consumption • History of liver disease • History of hepatitis • Pregnant or 2-3 months post-partum • Injecting drug users • On treatment with other hepatotoxic medications • HIV infection	• Liver function tests • If rifampicin-based regimen: full blood count and platelets	Baseline; monthly if baseline is abnormal or risk factors present during clinical monitoring	**No symptoms:** Transaminases ≥ 5 times the upper limit of normal **Symptoms:** Transaminases ≥ 3 times the upper limit of normal

Guideline	People for whom laboratory monitoring is recommended	Risk factors for hepatotoxicity	Tests used for monitoring	Frequency of monitoring for those who require it	When to stop TB infection treatment
Netherlands	Adults > 35 years old and people with risk factors for hepatotoxicity	• Alcohol use • Liver disease • Pregnant or post-partum • HIV infection	• Liver function tests	Baseline, then biweekly or monthly for certain risk groups	**No symptoms:** Transaminases >5 times the upper limit of normal **Symptoms:** Transaminases ≥3 times the upper limit of normal
New Zealand	Adults	• N/A	• ALT; if elevated, then full liver function tests • Creatinine • Haematology	**No risk factors:** Baseline, at 1 month, then every two months **Risk factors:** At least monthly	**No Symptoms:** Transaminases > 5 times the upper limit of normal **Symptoms:** Transaminases ≥ 3 times the upper limit of normal. ALP or GGT > 2 times the upper limit of normal. **Jaundice:** Stop all hepatotoxic drugs immediately
United Kingdom	All	• N/A	• Unclear	Not specified	Not specified
United States of America	People with risk factors for hepatotoxicity	• Regular alcohol consumption • History of liver disease or at risk for chronic liver disease • Pregnant or up to 3 months post-partum • HIV infection	• Liver function tests	Baseline; repeat if baseline is abnormal or risk factors present (frequency not specified)	**No symptoms:** Transaminases > 5 times the upper limit of normal **Symptoms:** Transaminases > 3 times the upper limit of normal
World Health Organization	Adults > 35 years old and people with risk factors for hepatotoxicity	• Regular alcohol consumption • History of liver disease or chronic liver disease • Pregnant or up to 3 months post-partum • HIV infection	• Liver function tests	Baseline; repeat if baseline is abnormal (frequency not specified)	Not specified

Abbreviations: ALT = alanine transaminase, GGT = gamma glutamyl transferase, ALP = alkaline phosphatase

ABBREVIATIONS

Abbreviation	Definition
3HP	3 months of weekly rifapentine + isoniazid
3-4HR	3–4 months of daily rifampicin + isoniazid
3-4R	3–4 months of daily rifampicin
6H	6 months of daily isoniazid
9H	9 months of daily isoniazid
12H	12 months of daily isoniazid
BCG	bacille Calmette-Guerin
IGRA	interferon gamma release assay
TB	tuberculosis
TST	tuberculin skin test

APPENDIX A

GUIDELINE DOCUMENTS REVIEWED

AUSTRALIA

Stock, David, and the National Tuberculosis Advisory Committee, National Position Statement for the Management of Latent Tuberculosis Infection. 2017.

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WORLD HEALTH ORGANIZATION

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APPENDIX B

KEY RESULTS FROM RANDOMIZED CONTROLLED TRIALS

of short preventive therapy regimens

3 MONTHS WEEKLY ISONIAZID AND RIFAPENTINE (3HP) COMPARED TO 9 MONTHS DAILY ISONIAZID (9H)

ADULTS

The PREVENT-TB randomized controlled trial included 7731 adults mostly from USA and Canada, with smaller numbers from Brazil and Spain. The trial was a non-inferiority trial to test whether 3HP was at least as effective as 9H. Comparing safety was a secondary objective, with treatment discontinuation due to side effects as the main outcome of interest.[40]

Type of endpoint	Measurement	3HP	9H	Conclusion
Efficacy	TB cases per 100 patient-years among all eligible patients	0.07	0.16	3HP was non-inferior to 9H
	TB cases per 100 patient-years among patients with good adherence	0.05	0.13	3HP was non-inferior to 9H
Treatment completion	Percentage of patients who completed treatment	82.1%	69.0%	Significantly more patients completed 3HP compared to 9H
Safety	Percentage of patients who had any side effect related to treatment	8.2%	5.5%	Significantly more patients receiving 3HP had side effects related to the study drug compared to those receiving 9H
	Percentage of patients who stopped treatment because of a side effect	4.9%	3.7%	Significantly more patients receiving 3HP stopped treatment because of side effects

CHILDREN

The PREVENT-TB pediatric randomized controlled trial included 905 children 2–17 years old, mostly from the USA and Canada, with smaller numbers from Brazil, Spain, and Hong Kong. The primary objective of the trial was to compare safety between the two regimens, with treatment discontinuation due to side effects as the main outcome of interest.[41]

Type of endpoint	Measurement	3HP	9H	Conclusion
Efficacy	TB cases per 100 patient-years among all eligible patients	0.00	0.27	3HP was non-inferior to 9H
Treatment completion	Percentage of patients who completed treatment	88.1%	80.9%	Significantly more patients completed 3HP compared to 9H
Safety	Percentage of patients who had any side effect related to treatment	1.2%	2.6%	No significant difference between the two groups
	Percentage of patients who stopped treatment because of a side effect	1.7%	0.5%	No significant difference between the two groups

40 Sterling et al. N Engl J Med 2011; 365(23):2155

41 Villarino et al. JAMA 2015; 169(3):247

4 MONTHS OF DAILY RIFAMPICIN (4R) COMPARED TO 9 MONTHS OF DAILY ISONIAZID (9H)

ADULTS

This randomized controlled trial included 6012 adults from Australia, Benin, Brazil, Canada, Ghana, Guinea, Indonesia, Saudi Arabia, and South Korea. The trial was a non-inferiority trial to test whether 4R was at least as effective as 9H. Comparing safety was a secondary objective, with treatment discontinuation because of grade 3-5 adverse events related to the study drug as the outcome of interest; grade 3-5 adverse events are those that are severe or life-threatening, causing hospitalization or limiting a person's ability to take care of him/herself.[42]

Type of endpoint	Measurement	4R	9H	Conclusion
Efficacy	TB cases per 100 patient-years among all eligible patients	0.10	0.11	4R was non-inferior to 9H
	TB cases per 100 patient-years among patients with good adherence	0.09	0.11	4R was non-inferior to 9H
Treatment completion	Percentage of patients who completed treatment	78.8%	63.2%	Significantly more patients completed 4R compared to 9H
Safety	Percentage of patients who had any side effect related to treatment	2.8%	5.8%	Significantly more patients receiving 9H had side effects related to the study drug compared to those receiving 4R
	Percentage of patients who stopped treatment because of a grade 3-5 adverse event related to treatment	0.8%	2.1%	Significantly more patients receiving 9H stopped treatment because of side effects

CHILDREN

This randomized controlled trial included 829 children 0–17 years old from Australia, Benin, Brazil, Canada, Ghana, Guinea, Indonesia. The trial was a non-inferiority trial to compare the safety of 4R and 9H. The outcome of interest was treatment discontinuation due to side effects.[43]

Type of endpoint	Measurement	4R	9H	Conclusion
Efficacy	TB cases per 100 patient-years among all eligible patients	0.00	0.37	4R was non-inferior to 9H
Treatment completion	Percentage of patients who completed treatment	86.5%	77.1%	Significantly more patients completed 4R compared to 9H
Safety	Percentage of patients who stopped treatment because of a side effect related to treatment	0.0%	0.0%	No significant difference between the two groups

42 Menzies et al. N Engl J Med 2018; 379(5):440

43 Menzies et al. N Eng J Med 2018; 379(5):454

3 MONTHS OF DAILY ISONIAZID AND RIFAMPICIN (3HR) COMPARED TO 6 OR 9 MONTHS OF DAILY ISONIAZID (6H OR 9H)

ADULTS

The efficacy of the 3HR regimen was established relatively early with several smaller trials rather than a single multi-site trial. Trials conducted in Hong Kong, Spain, and Uganda are summarized in a systematic review and meta-analysis.[44] Across five trials, 972 adults received 3HR and 954 received 6 to 12 months of isoniazid, with most receiving 6H. Pooled results from the meta-analysis are shown here.

Type of endpoint	Measurement	3HR	6H	Conclusion
Efficacy	Percentage of patients who developed TB, pooled across 5 trials	4.2%	4.1%	3HR was non-inferior to 6H
Safety	Percentage of patients who stopped treatment because of side effects, pooled across 2 high-quality trials	2.9%	2.3%	No significant difference between groups

CHILDREN

A two-stage randomized controlled non-inferiority trial of 926 children 0-14 years old was conducted in Greece. In the first stage, 9 months of daily isoniazid (9H) was compared to 4 months of daily rifampicin and isoniazid (4HR), and in the second stage, 4HR was compared to 3 months of daily rifampicin and isoniazid (3HR). Outcomes of interest with development of TB, adherence (measured based on attendance at follow-up visits and urine testing for drug concentration), and occurrence of serious drug-related side effects. In the second stage, no significant difference in outcomes was detected between 4HR and 3HR; in this table, results for 9H and 3HR are shown.[45]

Type of endpoint	Measurement	3HR	9H	Conclusion
Efficacy	Percentage of patients who developed TB	0.0%	0.0%	3HR was non-inferior to 9H
Treatment completion	Percentage of patients who attended all visits and who had all urine drug tests positive for medications	89.5%	65.5%	Significantly more patients receiving 3HR achieved this level of adherence compared to those receiving 9H
Safety	Percentage of patients with serious drug-related side effects	0.0%	0.0%	No significant difference between groups

44 Ena and Valls. Clin Infect Dis 2005; 40:670

45 Spyridis et al. Clin Infect Dis 2007; 45(6):715

APPENDIX C

GUIDELINE EDITORIAL COMMITTEES

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https://www1.health.gov.au/internet/main/publishing.nsf/Content/cdna-ntac-members.htm

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CANADA

Canadian Tuberculosis Standards 7th Edition: 2014—Contributors

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GERMANY

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https://pneumologie.de/fileadmin/user_upload/2017-06_Tuberkulose.compressed.pdf

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NETHERLANDS

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NEW ZEALAND

Guidelines for Tuberculosis Control in New Zealand 2010

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SYNTHESIS OF GUIDELINES ON **TB INFECTION TREATMENT**

A tool for Zero TB coalitions

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