Tuberculosis

Anete Trajman, Jonathon R Campbell, Tenzin Kunor, Rovina Ruslami, Farhana Amanullah, Marcel A Behr, Dick Menzies

Lancet 2025; 405: 850–66

Department of Internal Medicine, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil (Prof A Trajman MD PhD); **McGill International TB Centre, Montreal, QC, Canada** (Prof A Trajman, J R Campbell PhD, Prof R Ruslami MD PhD, M A Behr MD, Prof D Menzies MD MSc); **Department of Medicine** (J R Campbell, Prof D Menzies) **and Department of Global and Public Health** (J R Campbell), **McGill University, Montreal, QC, Canada; Respiratory Epidemiology and Clinical Research Unit, Centre for Outcomes Research & Evaluation, Research Institute of the McGill University Health Centre, Montreal, QC, Canada** (J R Campbell); **McGill International TB Centre & WHO Collaborating Centre in TB Research, Montreal Chest Institute, Research Institute of the McGill University Health Centre, Montreal, QC, Canada** (Prof D Menzies); **We Are TB. Madison, WI, USA** (T Kunor MSc); **London School of Hygiene and Tropical Medicine, London, UK** (T Kunor); **Department of Biomedical Sciences, Division of Pharmacology, Faculty of Medicine, Universitas Padjadjaran, Bandung, Indonesia** (Prof R Ruslami); **Boston Children's Network Specialty Physicians, Boston, MA, USA** (F Amanullah FAAP)

Correspondence to:
Prof Dick Menzies, McGill International TB Centre & WHO Collaborating Centre in TB Research, Montreal Chest Institute, Research Institute of the McGill University Health Centre, Montreal H4A 3S5, QC, Canada
dick.menzies@mcgill.ca

Tuberculosis is a leading cause of death globally. Given the airborne transmission of tuberculosis, anybody can be infected, but people in high-incidence settings are more exposed. Risk of progression to disease is higher in the first years after infection, and in people with undernourishment, immunosuppression, or who smoke, drink alcohol, or have diabetes. Although cough, fever, and weight loss are hallmark symptoms, people with tuberculosis can be asymptomatic, so a high index of suspicion is required. Prompt diagnosis can be made by sputum examination (ideally with rapid molecular tests), but chest radiography can be helpful. Most people with disease can be treated with regimens of 6 months or less; longer regimens may be necessary for those with drug resistance. Central to successful treatment is comprehensive, person-centred care including addressing key determinants, such as undernourishment, smoking, and alcohol use, and optimising management of comorbidities, such as diabetes and HIV. Care should continue after treatment ends, as long-term sequelae are common. Prevention relies mostly on treatment with rifamycin-based regimens; current vaccines have limited efficacy. Ongoing research on shorter and safer regimens for infection and disease treatment, and simpler and more accurate diagnostic methods will be key for tuberculosis elimination.

Introduction

This Seminar aims to guide health-care providers in responding appropriately and effectively to their patients' concerns, in identifying those individuals who are at risk or who are affected by tuberculosis, and in promptly initiating rapid and accurate investigations and then offering effective preventive or curative treatment with adequate support, including after the successful completion of treatment.

Tuberculosis pathophysiology and risk factors

Tuberculosis survivor narrative and perspective

> "I was under a lot of stress…trying to figure out how I caught it. How quick can I stop passing it on, 'cause I don't want nobody going through this, what I'm going through."[1]

When a person is diagnosed with tuberculosis, one of their first questions is often, "Why did I get tuberculosis? Why me?" A diagnosis of tuberculosis can be overwhelming, and can lead to feelings of shock, shame, and uncertainty. These feelings must be processed while understanding how this diagnosis will affect one's future and the future of those around them. For some, there is confusion; for others, it might be a relief to have clarity—the cause of the distress might be better understood when accompanied by compassionate and encouraging words of a health-care practitioner and the services to treat the disease. Patients reported that receiving compassionate care from clinicians aided recovery, including an increased sense of responsibility and control over their health.[2]

Search strategy and selection criteria

We searched for publications from Jan 1, 2019, to May 1, 2023 initially, and updated June 10, 2024, in the Cochrane database of systematic reviews, and Cochrane registry of randomised trials, using MESH terms for tuberculosis and Mycobacterium tuberculosis, as well as TB or tuberc* in title or abstract, combined with MESH terms for diagnosis (diagnosis, bacteriology, microbiology, and radiography), treatment (therapeutics, antitubercular agents, and names of specific tuberculosis drugs), and prevention (antibiotic prophylaxis, vaccination, and contact tracing). We used the reference lists of these papers to identify other relevant randomised trials, large-scale cohort studies, and individual patient data meta-analyses.

Considerations for tuberculosis care providers

The development of tuberculosis disease (panel) can be simplified to a few key steps, with risks of occurrence of each step modified by different factors (figure 1). The possibility of inhaling *Mycobacterium tuberculosis* is determined by the concentration of the bacilli in the air breathed and the duration of exposure.[3] Airborne bacterial concentration is higher if the person with tuberculosis has extensive or cavitary pulmonary disease, is sputum-smear positive, or has laryngeal tuberculosis, plus if there are environmental factors that favour accumulation (eg, poorly ventilated indoor environments) over elimination (eg, outdoors or more sunlight).[3,4] Based on these considerations, household and other close contacts of people with pulmonary tuberculosis are at the highest risk of infection.[5–7] However, transmission can also occur in the community[8–11] as many people with pulmonary tuberculosis do not have cough,[12,13] and *M tuberculosis* can be disseminated simply by typical breathing.[14] The proportion attributable to household versus outside is expected to vary according to the epidemiological situation.

Following inhalation of *M tuberculosis*, infection might be established; 50–70% of people exposed to *M tuberculosis* have negative tuberculin skin tests (TSTs) for tuberculosis infection,[6,7] this negative reaction and apparent protection from infection might be under genetic control.[15] Although BCG vaccination was long believed to modify risk of

Panel: Definitions of common tuberculosis-related terms

Tuberculosis disease
Presence of macroscopic pathology caused by *Mycobacterium tuberculosis* complex organisms, including *M tuberculosis* (the majority), *Mycobacterium bovis*, *Mycobacterium orygis*, *Mycobacterium africanum*, or *Mycobacterium caprae*. People might or might not be contagious and might or might not have symptoms. Treatment is given to prevent morbidity and mortality, to reduce transmissibility, and to improve symptoms when present.

Tuberculosis infection
Also referred to as latent tuberculosis infection, or *M tuberculosis* infection. Presence of viable *M tuberculosis* and a host response. People with tuberculosis infection neither have symptoms or physical signs, nor microbiological or macroscopic pathological results consistent with tuberculosis disease. These people are not contagious but are at risk of developing tuberculosis disease.

Tuberculosis preventive treatment
Treatment given to a person with presumed tuberculosis infection to lower the risk of future tuberculosis disease.

Drug-susceptible tuberculosis
Disease due to strains susceptible to all first-line tuberculosis drugs (eg, isoniazid, rifampicin, ethambutol, and pyrazinamide).

Drug-resistant tuberculosis
Disease due to *M tuberculosis* resistant to at least one of the four first-line tuberculosis drugs. Strains resistant to isoniazid but susceptible to rifampicin are isoniazid-monoresistant tuberculosis, those resistant to rifampicin but susceptible to isoniazid are rifampicin-monoresistant tuberculosis, and those resistant to both isoniazid and rifampicin are multidrug-resistant tuberculosis. Multidrug-resistant strains also resistant to a fluoroquinolone are defined as pre-extensively drug-resistant tuberculosis, while extensively drug-resistant tuberculosis is defined as resistance to rifampicin and isoniazid plus fluoroquinolones and either linezolid or bedaquiline.

Extrapulmonary tuberculosis
Although it occurs most frequently in the lungs (pulmonary tuberculosis), tuberculosis disease can occur in any other organ including skin, bones, lymph nodes, pleura, heart, gastrointestinal tract, and CNS. These forms are rarely contagious, but cause considerable difficulty and mortality, especially in children who are also more susceptible to disseminated disease.

developing disease without preventing infection, several studies have shown that BCG-vaccinated contacts are less likely to have positive interferon-γ release assays (IGRAs),[16–18] implying some protection from infection.

The risk of progression from tuberculosis infection to disease is affected by time since infection and host susceptibility (figure 2). The highest risk of disease is in the first year after infection, and decreases thereafter,[4,19,20] as seen in household contacts and in recent migrants from high-incidence countries to low-incidence countries.[21,22] Among contacts, the risk is highest in young children, and lower in adolescents and adults.[22,23] Beyond time and age, risk factors for progression to tuberculosis disease can be conceptualised at an individual level or a public health level. For an individual with a positive TST or IGRA, risk of disease is increased if they have HIV infection, silicosis, end-stage kidney disease requiring dialysis, or are taking immunosuppressive medications (table 1). On the other hand, even though the individual risk associated with undernutrition, smoking, alcohol consumption, and diabetes is not as high, these four conditions have a major effect on public health globally, because they are so common.[38]

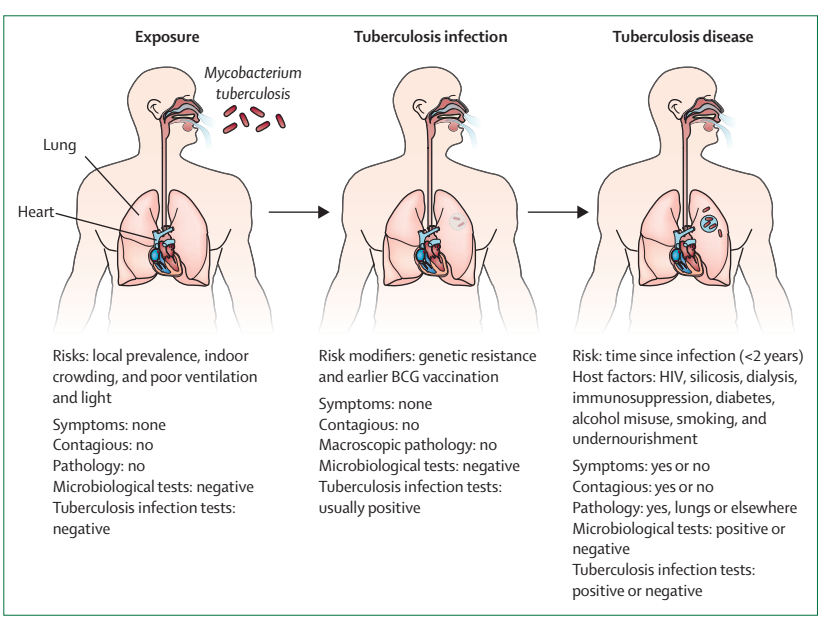

Figure 1: **Risk factors and main clinical charcteristics of tuberculosis infection and disease**
Microbiological tests include smear microscopy, molecular tests, or culture. Tuberculosis infection tests include tuberculin skin tests, tuberculosis-specific skin tests, and interferon-γ release assay.

Epidemiology

Tuberculosis was the leading infectious cause of death worldwide in 2023, with 1·3 million estimated deaths, surpassing both COVID-19 and HIV/AIDS.[38] An estimated 10·6 million people developed tuberculosis, although only 7·5 million were reported to WHO;[38] this gap is largely due to undiagnosed tuberculosis. In total, 1·3 million children were estimated to have tuberculosis disease, of whom more than half (51–58%) were missed.[38]

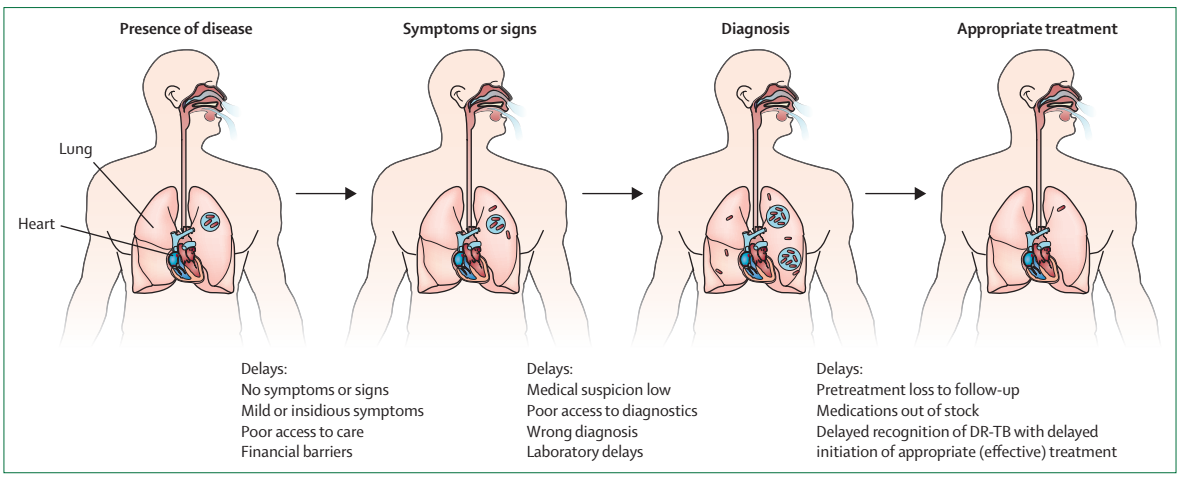

Figure 2: **Tuberculosis cascade of care**
DR-TB=drug-resistant tuberculosis.

The detection gap also includes over 275 000 people with drug-resistant tuberculosis. People living with HIV are at particular risk for tuberculosis disease, and accounted for 6·3% of all incidence of tuberculosis and 13% of tuberculosis-related deaths in 2022.[38] Estimated rates of tuberculosis disease vary widely in different countries, with the highest rates and greatest burden of disease in low-income and middle-income countries. Rates are highest in countries in Africa and southeast Asia, followed by the Western Pacific.[38] In high-income countries, most people who develop tuberculosis disease are migrants; rates in these populations parallel rates in their countries of origin.[39]

The effect of COVID-19 on the epidemiology and clinical aspects of tuberculosis must also be acknowledged. The response to COVID-19 might have reduced tuberculosis transmission due to less person-to-person contact, but also worsened outcomes due to delayed diagnosis and poor access to tuberculosis care.[40] There is great uncertainty regarding the overall effect, which could vary within and between countries.[41]

Clinical presentation, signs and symptoms, and diagnostic investigations

Tuberculosis survivor narrative and perspective

> "At first, I thought I was the only person who had spent months being misdiagnosed—however, when I attended my first *TB* survivor workshop, I learned the unfortunate truth that my experience was not unique. I heard story after story of misdiagnosis and delayed diagnosis."
>
> *Tenzin Kunor (WHO Global Tuberculosis Report Press Conference; Online, Oct 14, 2021).*
>
> "I was very happy because my disease was found before my death."[42]

Delayed or incorrect diagnoses often means unnecessary difficulties for the person with tuberculosis. It also means others, such as household and close contacts, are vulnerable to tuberculosis. Everyone is deserving of accessing diagnostic services and receiving treatment for this curable and preventable disease. One crucial issue is that health-care providers often do not consider tuberculosis when working with patients and, despite best practices established around when to test for tuberculosis, opportunities are too often missed. One key role a practitioner can take is helping the person with tuberculosis better understand what a diagnosis of tuberculosis means, to help make sense of this experience.

Considerations for tuberculosis care providers

Tuberculosis is usually detected in people who seek medical attention because they have symptoms (figure 3). In people with lung involvement, the most common symptom is cough, although systemic symptoms such as fever or weight loss are common. Among children, the only symptoms of tuberculosis might be poor weight gain and lethargy.[43] Symptoms of extrapulmonary tuberculosis reflect the site involved, which can be any organ.[44,45] It is important to be aware that people with pulmonary tuberculosis might be asymptomatic,[8,12,13] and so tuberculosis can be detected on a chest radiograph performed for other reasons; extrapulmonary disease can also be asymptomatic[44,45] (eg, uterine tuberculosis detected as part of an infertility investigation). Children are more prone to extrapulmonary tuberculosis, including disseminated tuberculosis and CNS tuberculosis, which are medical emergencies and need rapid recognition and appropriate referral.[46] It is often stated that assessment for tuberculosis should be initiated only if symptoms have been present for over 2 weeks. However, in people at increased risk of tuberculosis disease (due to recent infection or greater susceptibility), symptoms of any type or duration should prompt health providers to think of tuberculosis.

Time from onset of symptoms to tuberculosis diagnosis ranges from 1 month to 12 months in different settings.[47]

This range reflects the insidious nature of symptoms, plus scarce access to care, so many people defer seeking care (patient delay). Providers often do not think of tuberculosis and so are slow to order appropriate tests (provider delay), and receiving results of these tests could take additional weeks (laboratory delay).[47] Long delays in diagnosis are common for extrapulmonary tuberculosis, for different reasons: in low-incidence settings, these forms are rare and could mimic other diseases; and in high-incidence, low-resource countries, imaging, biopsies, and histopathological examination might not be accessible.

Chest radiography is often the first test ordered for investigation of respiratory symptoms, and although specificity is only 54–60%,[48] this test can help identify the presence of pulmonary disease. One restriction is the need for a specialist to interpret radiographs; this limitation can be overcome with use of computer-aided detection (CAD) algorithms for automatic reading.[49] In people with symptoms, most CAD products have accuracy equivalent to that of experienced radiologists,[48,50] but are less accurate in people who are asymptomatic, older, living with HIV, have a history of previous tuberculosis, or have smear-negative tuberculosis disease.[50] Another restriction is the absence of validated CAD products for children.

In other settings, sputum for microscopy, culture, or molecular testing is the first test. Smear microscopy for acid-fast bacilli is still widely used as it is simple, rapid (results within 1 day), identifies people with more contagious tuberculosis, and can be used to monitor response to treatment. Key limitations are low sensitivity of the test to detect pulmonary tuberculosis disease and the need for more information on drug resistance. Culture in liquid media, followed by phenotypic drug susceptibility testing has long been the reference standard for diagnosis of tuberculosis, but requires complex laboratory infrastructure, and results can take weeks to months for detection and susceptibility testing,[51,52] especially in people with less advanced disease.[51] In addition, drug susceptibility testing is difficult or unreliable for some drugs, notably pyrazinamide.[53]

WHO now recommends that the first test for patients with presumptive pulmonary tuberculosis is a rapid molecular diagnostic test that amplifies *M tuberculosis* nucleic acid.[54] These tests (table 2) provide results within a day, such as microscopy, but have much higher sensitivity, approaching that of culture in pulmonary tuberculosis,[58] and are also useful for diagnosis of extrapulmonary forms.[59] Their use has been associated with improved treatment outcomes, including lower mortality from tuberculosis.[60,61] As a result, these tests are fast replacing acid-fast bacilli smear in many settings, including low-income and middle-income countries.[38]

Young children often do not provide sputum for examination and have paucibacillary disease, making microbiological confirmation challenging. Hence diagnosis of tuberculosis disease in children is best

	Annual risk of tuberculosis for the first 2–3 years after a positive TST or IGRA*	Reference
Very high risk		
People with HIV†	1·7–2·7%	Gupta et al[21] Campbell et al[24]
Child or adolescent (<18 years) tuberculosis contact	2·9–14·6%	Gupta et al[21] Martinez et al[23]
Adult (≥18 years) tuberculosis contact	0·8%–3·7%	Gupta et al[21] Campbell et al[24]
Silicosis	3·7%	Campbell et al[24]
High risk		
Stage 4 or 5 chronic kidney disease with or without dialysis	0·3–1·2%	Campbell et al[24]
Transplant recipients (solid organ or haematopoietic)	0·1–0·7%	Campbell et al[24]
Fibronodular disease	0·2–0·6%	From incidence rates in three longitudinal studies; Grzybowski et al[25,26] Nolan and Elarth[27]
Receiving immunosuppressing drugs (eg, tumour necrosis factor α inhibitors or steroids)‡	0·5%	Campbell et al[24]
Cancer (lung cancer, sarcoma, leukaemia, lymphoma, or gastrointestinal cancer)	0·1–0·4%	Estimated from hazard ratio in a population-based study; Kumar et al[28]
Moderate risk		
Granuloma on chest x-ray	0·1%	From incidence rates in two longitudinal studies; Grzybowski et al[25] Horwitz and colleagues[29]
Diabetes	0·1–0·2%	Estimated from pooled relative risk in observational studies; Jeon and Murray[30]
Undernutrition	0·1%	Estimated from pooled relative risk in observational studies; Franco et al[31]
Heavy alcohol use (≥3 drinks per day)	0·1–0·2%	Estimated from pooled relative risk in observational studies; Lönnroth et al[32]
Heavy tobacco cigarette smoker (≥1 pack per day)	0·1%	Estimated from pooled odds ratios and relative risks in two meta-analyses of observational studies; Lin et al[33] Bates et al[34]
Low risk		
General, adult population with no known risk factor	0·03%	Campbell et al[24]
People with a positive two-step TST booster and no known risk factor	0·02%	Extrapolated from a longitudinal study and a randomised trial; Comstock et al[35] Ferebree SH[36]

TST=tuberculin skin test. IGRA=interferon-γ release assay. *Risks are presented as point estimates for ease of presentation; ranges, when presented, are derived from multiple studies or different tests used (TST or IGRA). Where possible, absolute risks are derived from large systematic reviews; where absolute risks were not available, but relative risks were, we multiplied the general population absolute risk by the relative risk to approximate absolute risk. Risks are expected to diminish after the first 2–3 years, although in settings where frequency of exposure is high, risks might continue to be elevated.[21] †Studies informing this estimate are from the antiretroviral era; proportion receiving antiretroviral therapy in these studies ranged from 40% to 75%. ‡Risk does not appear substantially elevated with low-dose steroids (ie, prednisone), but elevated with moderate or high dose (low dose ≤9 mg/day; medium dose 10–19 mg/day; and high dose ≥20 mg/day).[37]

Table 1: **Risk of tuberculosis disease among different populations with a positive test for tuberculosis infection**

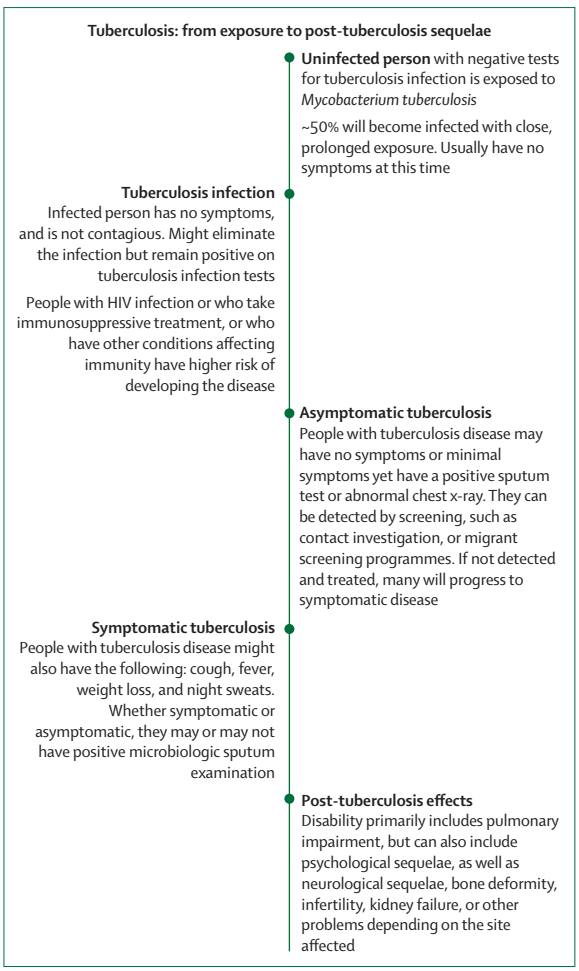

Figure 3: **Progression of tuberculosis infection from initial exposure to post-tuberculosis sequelae**

made using a combination of signs, symptoms, chest radiography findings, and integrated treatment decision algorithms.[62] Induced sputum, gastric lavage, nasopharyngeal aspirate, or stool samples should be tested first with molecular tests and then with culture (although not stool samples) if molecular tests are negative or indicate drug resistance.[54,62]

A decision to test entails a responsibility to provide treatment, should the test be positive. Despite this fundamental principle, approximately 15% of people with a test confirming tuberculosis disease are not started on treatment.[63] Optimisation of health-service delivery to assure adequate follow-up is an obvious solution, but there is also increasing global interest in the development and deployment of affordable point-of-care tests.[64] Tests that do not need sample transportation to a central laboratory, use simple analytic processes, and provide results very rapidly[65] could close the gap between diagnosis and treatment. At present, the lateral flow lipoarabinomannan AlereLAM urine test is the only point-of-care test recommended by WHO, but use is restricted to people living with HIV who have CD4-positive cell counts under 100 per µL, have CD4-positive cell counts under 200 per µL plus symptoms, or are hospitalised.[66,67]

Acute management: treatment, support, and follow-up of people with tuberculosis disease

Tuberculosis survivor narrative and perspective

> "The medication for TB should not cause us harm. I put up with my medication because I want to be cured. I wish someone would have just explained to me what the problem was and the drugs that they were giving me."[68]

Treatment for tuberculosis disease has an immense effect on people's lives in a multitude of ways. It can affect one's physical health with various possible side-effects, such as chronic fatigue, nausea, somatic sensations, or even irreversible disabilities. Providers should be equally mindful of how treatment can affect a person's psychological health. Physical and role functioning, experience with social stigmatisation, isolation, pill burden, and treatment duration are all examples. Shorter treatment options have the possibility to mitigate some of the burden on people with tuberculosis disease, but safety and acceptability of these shorter regimens cannot be forgotten. Quality care in treating people with tuberculosis disease needs more than a biomedical approach. Person-centred care includes integrated psychosocial support care, peer support, and referrals within and beyond the health sector. People might have numerous questions and concerns, which require deep listening, responsiveness, and constant evaluation of regimen appropriateness.

Considerations for the tuberculosis care providers

People with tuberculosis, including those diagnosed during pregnancy,[69,70] should be treated promptly and followed up monthly for adherence, side-effects, and general support.[71] The standard treatment regimen for drug-susceptible tuberculosis is 6 months of rifampicin and isoniazid, supplemented with pyrazinamide and ethambutol in the first 2 months (2HRZE–4HR).[71] Drugs should be taken daily throughout treatment—although taking doses three times per week during the last 4 months is acceptable,[72] and can be taken with pyridoxine to reduce the risk of isoniazid-induced peripheral neuropathy. Although the standard regimen is efficacious, treatment-related grade 3–4 adverse events occur in approximately 5–10% of participants in clinical trials.[73–75] The most important and potentially life-threatening adverse event is hepatotoxicity, which can be due to pyrazinamide (highest risk), isoniazid, or rifampicin.[76]

People who are pregnant or breastfeeding have been excluded from almost all trials of treatment of tuberculosis disease and tuberculosis infection. Hence, there is scant evidence on which to base

	Sensitivity for tuberculosis diagnosis (sputum, except LAM or CAD)*	Specificity for tuberculosis diagnosis (sputum, except LAM or CAD)*	Drug resistance detected	Sensitivity for drug resistance	Specificity for drug resistance
For initial evaluation in adults, children, PLHIV without a history of previous tuberculosis, or with remote history of tuberculosis (>5 years) testing of sputum samples (except LAM and x-ray)					
Sputum smear microscopy†	0·60 to 0·90[55,56]	0·90 to 0·98	NA	NA	NA
Chest X-ray with or without CAD‡[48]	0·71 to 0·93	0·64 to 0·80	NA	NA	NA
Xpert MTB/Rif	Overall: 0·85 (0·99 in smear-positive samples and 0·61 in smear-negative samples)	0·98	Rifampicin	0·95	0·99
Xpert Ultra[57]	Overall: 0·91 (0·99 in smear-positive samples and 0·78 in smear-negative samples)	0·96	Rifampicin	0·95	0·99
Truenat MTB-Rif Dx	Overall: 0·80 (0·96 in smear-positive samples and 0·46 in smear-negative samples)	0·96	For those in whom Truenat was positive for tuberculosis (two-step test), rifampicin	0·84	0·97
Abott RealTime TB	0·93§	0·98§	Rifampicin	Rifampicin: 0·97§	Rifampicin: 0·99§
Abott RealTime TB RIF/INH	0·93§	0·98§	Rifampicin and isoniazid	Rifampicin: 0·97§; isoniazid: 0·86§	Rifampicin: 0·99§; isoniazid: 0·99§
BD MAX MDR-TB	0·93§	0·98§	Rifampicin and isoniazid	Rifampicin: 0·97§; isoniazid: 0·86§	Rifampicin: 0·99§; isoniazid: 0·99§
Cobas MTB	0·93§	0·98§	Rifampicin	Rifampicin: 0·97§	Rifampicin: 0·99§
Cobas MTB RIF/INH	0·93§	0·98§	Rifampicin and isoniazid	Rifampicin: 0·97§; isoniazid: 0·86§	Rifampicin: 0·99§; isoniazid: 0·99§
FluoroType MTB	0·93§	0·98§	-	-	-
FluoroType MTBDR	0·93§	0·98§	Rifampicin and isoniazid	Rifampicin: 0·97§; isoniazid: 0·86§	Rifampicin: 0·99§; isoniazid: 0·99§
TB-LAMP	0·78	0·98	-	-	-
For initial evaluation of PLHIV of all ages with symptoms and CD4 under 200 per µL or CD4 over 100 per µL without symptoms ‡[1]					
AlereLAM	0·54¶	0·88¶	-	-	-
For resistance detection if initial rifampicin resistance, or exposed to isoniazid-resistant, MD-R or XD-R tuberculosis, presumptive treatment failure, or history of tuberculosis within 5 years					
Culture with phenotypic drug susceptibility tests	Considered the reference (assumed 100%)	..	All	Considered the reference (assumed 100%)	
GenoType MTBDRplus v1 (Hain 1)	Not recommended in smear-negative samples	..	Rifampicin and isoniazid	Rifampicin: 0·97; isoniazid: 0·88	Rifampicin: 0·98; isoniazid: 0·98
GenoType MTBDRplus v2 (Hain 2)	Not recommended in smear-negative samples	..	Rifampicin and isoniazid	Rifampicin: 0·96; isoniazid: 0·95	Rifampicin: 0·98; isoniazid: 0·99
GenoType MTBDRsl for second-line drugs (version 2 available, new data awaited)	Not recommended in smear-negative samples	..	Fluoroquinolones, second-line injectables, and XDR	Fluoroquinolones: 0·86; second-line injectables: 0·77; XDR: 0·71	Fluoroquinolones: 0·99; second-line injectables: 0·99; XDR: 0·99
Genoscholar NTM+MDRTB II (Nipro)	Not recommended in smear-negative samples	..	Rifampicin and isoniazid	Rifampicin: 0·75 to under 0·99; isoniazid: 0·50 to 0·95	Rifampicin: 0·97 to under 0·99; isoniazid: 0·97 to 0·98
Genoscholar PZA-TB II	Not recommended in smear-negative samples	..	Pyrazinamide	0·81‖	0·98‖
Xpert XDR	Not recommended for diagnosis	..	Isoniazid, ethionamide, fluoroquinolones, amikacin, capreomycin, and kanamycin	Isoniazid: 0·94; ethionamide: 0·98; fluoroquinolones: 0·93; amikacin, capreomycin, and kanamycin: 0·94	Isoniazid: 0·98; ethionamide: under 0·99; fluoroquinolone: 0·98; amikacin, capreomycin, and kanamycin: 0·98

LAM=Lipoarabinomannan. CAD=computer-aided detection for interpretation. PLHIV=people living with HIV. NA=not applicable. MDR=multidrug resistant. XDR=extensively drug resistant (the older definition is used here, meaning MDR plus resistance to a fluoroquinolone and a second-line injectable). *In adults with presumptive tuberculosis, compared with culture with phenotypic drug susceptibility tests. For other specific populations (PLHIV or children) or samples (extrapulmonary samples or culture isolates), please refer to reference.[54] For predictive value in settings or populations with different prevalence, also refer to reference.[54] In young children that do not provide sputum, tests should be performed in gastric aspirate, nasopharyngeal aspirate, or stool; †WHO no longer recommends smear microscopy as the initial test, but smear microscopy is still used in many settings, where it might be the only test available; ‡Use of different CAD interpretation thresholds can increase sensitivity but reduce specificity, or vice versa (see text). For use in different clinical situations and populations, and for different software or versions, see reference.[54] Not evaluated in children. Accuracy is lower in PLHIV and previously treated people; §Accuracy for all tests pooled in the systematic review;[54] ¶In PLHIV with symptoms and CD4 cell count under 100 cells per µL. Sensitivity is lower if CD4 count is over 100 cells per µL, and much lower if CD4 is over 200 per µL. Sensitivity is also lower if patient is asymptomatic (see reference[54] for more information); ||Data from tests in isolates, not enough evidence from data in sputum.

Table 2: **Summary of tests for tuberculosis disease diagnosis and drug-resistance detection (accuracy of tests taken from systematic reviews completed for WHO guidelines[54])**

recommendations, although observational studies and programmatic experience have led to acceptance that standard therapy can be given.[71] A 2019 trial of isoniazid preventive treatment among women with HIV who are pregnant or postpartum revealed high rates of severe toxicity including deaths,[77] reinforcing the need to include this group in future trials.[78]

The past 20 years have seen tremendous efforts to shorten drug-susceptible tuberculosis treatment, although given the substantial toxicity of the standard regimen, a regimen that is safer—and not simply shorter—is needed.[79] Three trials consistently showed that 4-month fluoroquinolone-based regimens had inferior efficacy when compared with the standard 6-month regimen.[73,75,80] SimpliciTB, a trial examining a 4-month regimen of bedaquiline, pretomanid, pyrazinamide, and moxifloxacin, also did not show non-inferior efficacy, and raised significant safety concerns.[81] In a trial of 2343 participants, a 4-month regimen of isoniazid, rifapentine, and moxifloxacin, with pyrazinamide for the first 2 months (2HPMZ–2HPM) had non-inferior effectiveness compared with the standard 6-month regimen, but more frequent treatment-related grade 3–4 adverse events (12·9% *vs* 9·8%, respectively).[74] In two subsequent small studies in San Francisco (CA, USA) and New York (NY, USA), 11 (50%) of 22, and 23 (66%) of 35 people did not complete this 4-month regimen, largely because of poor tolerability and safety.[82,83] In the TRUNCATE TB trial, participants received only 2 months of treatment with bedaquiline, linezolid, isoniazid, pyrazinamide, and ethambutol and then were followed up closely for relapse.[84] Recurrence rates were unacceptably high, and toxicity remains a concern, but the trial did show the potential of new tuberculosis drugs for treatment shortening. Other efforts have focused on increasing the dose of rifampicin, as the dose currently recommended (10 mg/kg of bodyweight) might be suboptimal.[85,86] In a recent trial (RIFASHORT), double and triple doses of rifampicin for 4 months did not show non-inferior efficacy;[87] other studies are ongoing. Based on the SHINE-TB trial[88] it is reasonable to give 4 months of a regimen with isoniazid, rifampin, pyrazinamide, and ethambutol, all at standard doses, to children with less severe tuberculosis (smear-negative).

Therapeutic drug monitoring has been used to optimise drug concentrations,[89,90] but the clinical benefits of this approach are not yet confirmed. Risk stratification has been suggested to optimise duration; in post-hoc analyses of three trials,[73,75,80] clinical characteristics were used to classify people into three groups: some could be cured with 4 months, others with 6 months, whereas some required more than 6 months to achieve relapse-free cure.[91] The SHINE-TB trial found that a 4-month regimen (2HRZE–2HR) had non-inferior efficacy compared with the standard 6-month regimen in children aged 3 months to 16 years with non-severe (smear-negative) drug-susceptible tuberculosis.[88] This regimen is now recommended by WHO.[71] In children and adolescents with extrapulmonary tuberculosis, the standard regimen is recommended, although a 6-month intensive regimen (6HRZEto) could be used for those with tuberculosis meningitis.[62]

Treatment of drug-resistant forms of tuberculosis remains a major challenge. In 2022, only 63% of people with disease due to rifampicin-resistant tuberculosis had a successful treatment outcome compared with 88% of people with drug-susceptible tuberculosis.[38] Isoniazid monoresistance is the most common form of drug-resistant *M tuberculosis* but testing for resistance to isoniazid is not available in many settings. Treatment of unrecognised isoniazid monoresistance with the standard 6-month regimen is associated with statistically significant higher rates of failure, disease recurrence, and acquired drug resistance, especially multidrug resistance.[92] WHO recommends a 6-month regimen of rifampicin, pyrazinamide, and ethambutol, plus a fluoroquinolone, based on an individual participant data meta-analysis of observational studies.[93]

The treatment of multidrug-resistant tuberculosis or rifampicin-resistant tuberculosis has been revolutionised with the development of the 6-month all-oral bedaquiline, pretomanid, linezolid, with or without moxifloxacin (BPaL or BPaLM, respectively) regimens. In the TB-PRACTECAL trial, BPaLM was statistically significantly safer, and resulted in a statistically significant higher rate of favourable treatment outcomes than the standard WHO-recommended regimens.[94] Importantly, BPaL appeared as efficacious as BPaLM, making it a good option for fluoroquinolone-resistant tuberculosis. The 6-month BPaL regimen had similar efficacy in the NIX[95] and ZENIX[96] trials, but toxicity was common, particularly peripheral neuropathy, with linezolid doses of 1200 mg/day. From these three studies, it appears that BPaL or BPaLM regimens should now be considered first-line treatment for rifampicin-resistant tuberculosis,[97] but the dose and duration of linezolid to achieve the optimal balance of safety and efficacy is uncertain. The inclusion of patients as young as 14 years in these trials allowed WHO to extend the recommendation to this age group;[97] there is no high-quality evidence on use of these regimens in younger children and pregnant people.[98] The pharmacokinetics and safety of pretomanid in children will be evaluated in the IMPAACT 2034 trial (NCT05586230). Other short, safe, effective options for rifampicin-resistant tuberculosis are being tested in ongoing trials.

For people with multidrug-resistant tuberculosis or rifampicin-resistant tuberculosis with pretomanid or linezolid intolerance or resistance, additional regimens include a 9–11-month all-oral regimen with bedaquiline, which has been evaluated in programmatic settings.[99] Regimens of 18–20 months, composed of multiple group

	Considerations
Treatment regimen(s)	
Tuberculosis infection	
6–9 months of daily isoniazid	Completion poor due to longer duration. Important and potentially fatal hepatotoxicity. Should be considered second-line treatment.
3 months of once weekly isoniazid and rifapentine	Can be delivered directly observed or self-administered; randomised trial evidence that completion better with directly observed administration. Not for children aged under 2 years. Important toxicity of systemic immune reaction syndrome.
3 months of daily isoniazid and rifampicin	Formulations used are the same as used for tuberculosis disease treatment. This formulation enhances access and feasibility. However, toxicity of isoniazid is combined with drug–drug interactions of rifampicin, and it is no safer than 6–9 months of isoniazid.
4 months of daily rifampicin	Safest of all currently recommended regimens, with rash the most common adverse event. Worse completion than the other rifamycin-containing regimens.
1 month of daily rifapentine and isoniazid	Only recommended for PLHIV as randomised trial only conducted in this population; trials among people without HIV are ongoing.
36 months of daily isoniazid	Only recommended for PLHIV in settings of high tuberculosis transmission. Poor completion and high rates of toxicity.
6 months of daily levofloxacin	For the treatment of contacts of or rifampicin-resistant tuberculosis or multidrug-resistant tuberculosis index patients. Two placebo-controlled trials have assessed levofloxacin in adults and children (ACTRN12616000215426 and ISRCTN92634082). Good safety profile. Efficacy similar to 6 months of isoniazid.
Drug-susceptible pulmonary tuberculosis disease	
2 months of daily isoniazid, rifampicin, pyrazinamide, and ethambutol, followed up by 4 months of daily isoniazid and rifampicin	Standard regimen worldwide. Recommended for all ages and for people who are pregnant (although in some countries pyrazinamide is not recommended for people who are pregnant, or for people older than 70). Considerable toxicity (5–10% of adults will have to stop at least one drug for a severe adverse event), and 3–4% relapse rates.
2 months of daily isoniazid, rifampicin, pyrazinamide, and ethambutol, followed up by 2 months of daily isoniazid and rifampicin	Only recommended for children aged 3 months to 16 years with non-severe smear-negative, probable drug-susceptible tuberculosis. Non-severe defined as respiratory tuberculosis confined to one lobe (opacification of <1 lobe) with no cavities, no signs of miliary tuberculosis, no complex pleural effusion, and no clinically significant airway obstruction or peripheral lymph-node tuberculosis.
2 months of daily isoniazid, rifapentine, moxifloxacin, and pyrazinamide, followed up by 2 months of daily isoniazid, rifapentine, and moxifloxacin	Only recommended for people aged 12 years or over, based on a single non-inferiority trial in adolescents and young adults. Tolerability might be worse than with standard regimen.
Isoniazid-resistant pulmonary tuberculosis disease	
6 months of rifampicin, pyrazinamide, ethambutol, and levofloxacin	Only evidence base is an individual participant data meta-analysis of observational data. Efficacy similar with or without the inclusion of isoniazid; safety data are scarce. One trial to assess regimen with levofloxacin *vs* without levofloxacin ongoing.
Rifampicin and multidrug-resistant pulmonary tuberculosis disease	
6 months of bedaquiline, pretomanid, linezolid, and moxifloxacin	Preferred if fluoroquinolone susceptible. Bedaquiline given daily for 2 weeks, before being switched to three times weekly; all other drugs given daily. Linezolid should be given at a dose of 600 mg but can be reduced to 300 mg or discontinued if toxicity emerges. Approved for children aged 14 years and older. No data for children younger than 14 years or people who are pregnant. Key toxicities with component drugs: bedaquiline, QT prolongation and hepatotoxicity; pretomanid, hepatotoxicity; linezolid, peripheral neuropathy and neutropenia; moxifloxacin, gastrointestinal toxicity and QT prolongation. Shorter and safer than previous standard of care regimens in one trial, but treatment-related grade 3–4 adverse events in up to 20% of people.
6 months of bedaquiline, pretomanid, and linezolid (BPaL)	Preferred if patient is resistant to fluoroquinolone. Dosing and safety information as for bedaquiline, pretomanid, linezolid, and moxifloxacin. Approved for children aged 14 years and older. No data for younger children or people who are pregnant.
9 months of daily levofloxacin or moxifloxacin, clofazimine, ethambutol, and pyrazinamide, supplemented with high-dose isoniazid for the first 4–6 months, bedaquiline in the first 6 months, and either linezolid for the first 2 months or ethionamide for the first 4–6 months	Preferred when pretomanid or linezolid are contraindicated. Bedaquiline given daily for 2 weeks, before being switched to thrice weekly; all other drugs given daily. Linezolid should be given at a dose of 600 mg but can be reduced to 300 mg or discontinued if toxicity emerges. More effective than injectable-containing regimens of similar duration; safety is expected to be better but has not been evaluated.
18–20 months of a 4–5 drug regimen comprising, where possible, all three Group A agents and at least one Group B agent; if only two Group A agents can be used, at least two Group B agents should included; if a four-drug regimen of probably effective drugs cannot be comprised with Group A and B agents, Group C agents should be used.	Use if resistance or contraindications to bedaquiline or to fluoroquinolone and linezolid, and other short regimens cannot be used. The medications and duration of this regimen make it more toxic than shorter regimens. Group A: moxifloxacin or levofloxacin, linezolid, and bedaquiline. Group B: cycloserine or terizidone and clofazimine. Group C: ethambutol, delamanid, pyrazinamide, imipenem-cilastatin or meropenem, amikacin or streptomycin, ethionamide or prothionamide, and p-aminosalicylic acid. Avoid use of any drug for which resistance is detected on drug susceptibility testing.

Table 3: **Treatment regimens for tuberculosis infection and disease**

B and so-called group C drugs, are needed to treat extensively drug-resistant tuberculosis[100] (table 3). Bedaquiline and delamanid can be used in children of all ages as part of longer regimens.[62]

Person-centred care during tuberculosis treatment

For many years, directly observed therapy (DOT) was recommended by WHO to ensure adherence. However, systematic reviews have concluded that end-of-treatment outcomes are not different with DOT than with self-administered therapy,[101–103] with no difference between community-based DOT and clinic-based DOT.[104] In addition to scarce evidence of effectiveness, mandatory DOT does not align with principles of patient-centred care.[105] More flexible methods to support adherence have been introduced, such as the use

of digital health technologies,[106] although their effectiveness has been variable.[106] Other interventions that could improve tuberculosis treatment outcomes plus have broader benefits include enablers, incentives, and other forms of patient support,[107] addressing psychosocial sequelae,[108] conditional cash transfer schemes,[109] food supplements,[110] and other social-protection interventions.[111,112] Providers should assess and intervene on known determinants of tuberculosis, including undernutrition (especially given the prognostic significance[113]), smoking, alcohol, and diabetes.[114] In settings with high tuberculosis burden, WHO recommends family-centred, integrated models of care to deliver diagnostic and treatment services close to the patient's home for children and adolescents with signs and symptoms of, or exposure to, tuberculosis.[115]

Because tuberculosis is highly stigmatised and has major financial consequences, an important role of care providers is education of people with tuberculosis, their families, and communities to reduce stigma,[116] and organisation of social and financial support. This approach is best provided through coordinated care from a multidisciplinary care team.[117] The common practice of isolation (although no longer recommended), the long duration of treatment, and the disability due to disease will together result in missed work or school, with one in four people with tuberculosis losing their jobs altogether.[97,118,119] Together, these factors result in substantial direct (out-of-pocket) and even more substantial indirect costs from lost income.[97,120] For almost half of all people with tuberculosis, these costs will total more than 20% of their annual income (defined as catastrophic costs),[119] and are very important barriers to care engagement. Patient costs are higher for people living with HIV, people with drug-resistant forms of tuberculosis, or when the patient with tuberculosis is the head of the family, but lower when tuberculosis is diagnosed through active case finding such as contact investigation.[97,119]

Tuberculosis prevention

Tuberculosis survivor narrative and perspective

> "The very first stigma I experienced was from a close circle of friends and family members whose reactions were just pure shock. They immediately suggested that I hide my diagnosis… This made me feel really guilty, ashamed of myself for getting tuberculosis, and isolated. I could not stand the idea of bringing stigma to my parents and my family. So, we collectively decided to hide it."[121]

> "My family still supports me whenever I encounter a problem I cannot solve on my own. I think it is almost impossible for people to overcome such health problems morally and psychologically by themselves."[68]

Tuberculosis is a social disease, so tuberculosis is never just one person's experience. Social stigma can come from health-care providers, employers, community members, friends, and family, but it can also be experienced by family and household members. When a person has tuberculosis, their loved ones could be vulnerable to infection and stigma. Chronic disease and multimorbidity might be more common in tuberculosis-affected households because of pre-existing risk factors in addition to the direct and indirect effects of tuberculosis. Engaging household and other close contacts for tuberculosis preventive care should be approached with a family-centred integrated approach. Contact investigation is not simply a surveillance strategy with public health interests, but should instead be seen as an opportunity to extend care to a community impacted by tuberculosis and offer therapies such as tuberculosis preventive treatment (TPT) for family members and close contacts with tuberculosis infection.

Considerations for tuberculosis providers

All close contacts of someone with tuberculosis should be counselled and evaluated in a series of care encounters to identify and initiate therapy for people with tuberculosis disease, and to identify people with tuberculosis infection who will benefit from TPT. Losses and dropouts can occur at each step of this cascade of care.[122] Person-centred care (figure 4) should reduce these losses and enhance the number of people offered TPT.[123,124]

In the first encounter, contacts should be asked about tuberculosis symptoms and, wherever available, tested for tuberculosis infection.[123] Currently, there are two types of tests for tuberculosis infection that measure immune response to *M tuberculosis*: in vivo (cutaneous injection of antigens) and ex vivo (blood-based tests).[123] Mathematical modelling suggests most individuals will clear tuberculosis infection within 10 years,[125] but currently available tests for tuberculosis infection do not distinguish persistence of viable bacilli from cleared infection. Hence, these tests are not useful to verify cure of tuberculosis infection with treatment and should be interpreted considering other epidemiological and clinical information to estimate the risk of disease, and potential benefits of treatment in untreated people. Online decision aids can be useful.[21,126]

In vivo tests are the TST and the tuberculosis-specific skin tests (TBSTs).[127] These tests can be done in clinics or at homes; no laboratory infrastructure is needed. In people with previous BCG vaccination, the TST has lower specificity,[123,128] but this problem is avoided with the recently approved TBST[123,127,128] as these are based on two antigens, ESAT-6 and CFP-10,[129] which are more specific to *M tuberculosis*.

Ex vivo tests or IGRAs are laboratory based. Blood is incubated overnight in tubes containing the same ESAT-6 and CFP-10 antigens, along with negative and positive control tubes, and interferon-γ production is measured, either directly in the supernatant using ELISA techniques, or by counting the lymphocytes producing

interferon-γ. At present, only three blood-based assays are approved by WHO for the diagnosis of tuberculosis infection,[130] although more than a dozen such assays are under development.[130]

There is extensive evidence from trials and observational studies that testing for infection will identify people with positive TST or IGRA who are at highest risk of developing tuberculosis disease,[21,23,24,35,131] and who will benefit from treatment.[132–134] From the same studies, there is consistent evidence of lower risk of tuberculosis disease among those who are TST or IGRA negative, and very little evidence of benefit of tuberculosis preventive therapy. A recent individual participant data meta-analysis with a total of 423 497 close contacts of all ages from 25 cohorts revealed that these contacts benefited from TPT when they were TST or IGRA positive (relative risk among treated *vs* untreated 0·17, 95% CI 0·14–0·20), but not if they were TST or IGRA negative (relative risk 0·99, 95% CI 0·67–1·44). However, among the subgroup of children younger than 5 years, TPT was beneficial even if they were TST or IGRA negative.[134,135]

Tests for tuberculosis infection, including the TST or TBST, require training and quality control, as with any test in clinical medicine, and these tests—as well as tests to exclude disease—can be inaccurate or difficult to interpret, especially in young children. Testing could also create barriers or cause substantial delays in initiating TPT. Recognising these barriers, WHO recommends that testing for tuberculosis before offering TPT is preferred, but is not essential; therefore, in settings where these tests are not available, this should not be a barrier to initiating TPT in individuals at highest risk.[136] Providers should refer to their country's recommendations and consider availability of testing when evaluating contacts.

When the tuberculosis infection test result is obtained, usually 48–72 h later, symptoms can be re-evaluated. In people with a positive tuberculosis infection test, before prescribing TPT, a chest radiograph or rapid molecular test should be obtained to rule out tuberculosis disease. Sensitivity of symptom screen is adequate to detect tuberculosis disease in people living with HIV not on antiretroviral therapy,[137] and in children younger than 5 years,[138] but sensitivity is only 53% in people living with HIV on antiretroviral therapy[66] and similarly low in people without HIV.[12,139] Hence, additional testing is necessary to avoid misdiagnosis and inadvertent monotherapy of tuberculosis. Given the speed at which tuberculosis disease can develop in contacts, especially young children and people living with HIV, it is imperative (and should be possible) that the entire investigation is completed and TPT started within 1–2 weeks.

For decades, the only TPT regimen used was isoniazid for 6–12 months. In multiple randomised trials, this regimen was shown to prevent tuberculosis disease, when given to people with evidence of tuberculosis infection. However, adherence and completion of isoniazid is poor and severe, even fatal, adverse events can occur, particularly hepatotoxicity.

Over the past 20 years, several shorter rifamycin-containing regimens have been recommended by WHO[136] and other agencies[140] (table 3). All have been shown to have non-inferior efficacy to the longer monoisoniazid regimens, but better completion. Of these regimens, 3 months of isoniazid and rifampicin is attractive as the formulations used for TPT are the same as those used for tuberculosis disease. However, this regimen is not safer

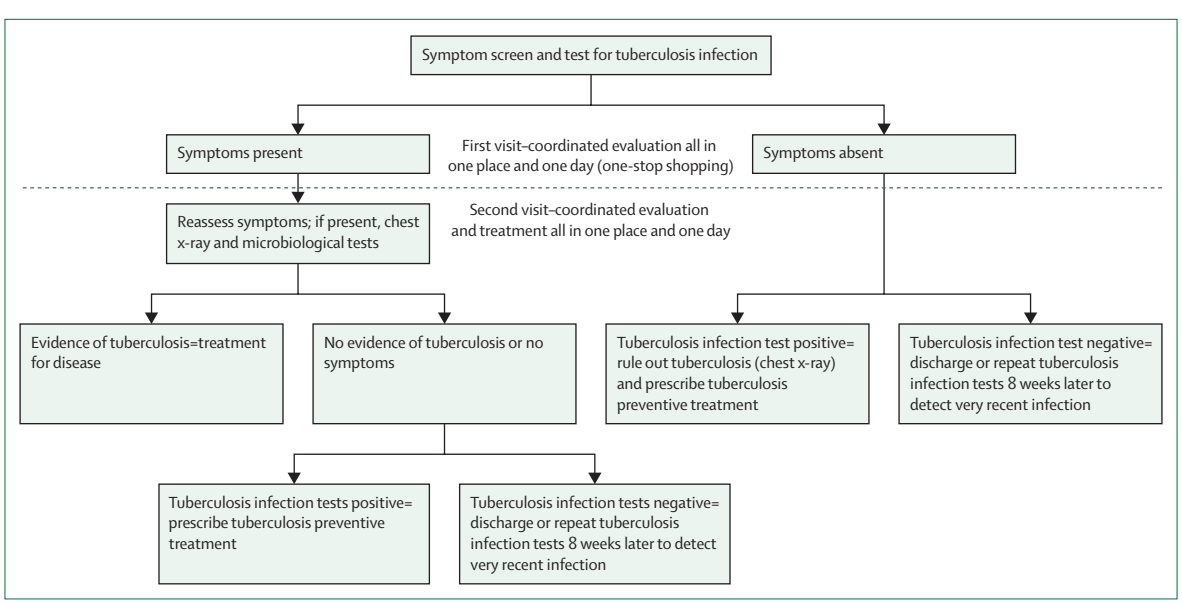

Figure 4: **Person-centred integrated algorithm for contact evaluation**

than 6 months of isoniazid, and completion has not been consistently better.[141] A 12-dose regimen of isoniazid and rifapentine given once per week for 3 months is being scaled up in many countries; this regimen is approved for children aged 2 years and older.[136] This regimen has excellent efficacy,[142] but is associated with hypersensitivity reactions,[143] which can be common in some populations,[144,145] and sometimes severe.[143,146] 4 months of daily rifampicin has the lowest rates of severe adverse events of all currently recommended TPT regimens[146,147] and can be used in children of all ages,[148] but completion is lower than with the 3 months weekly isoniazid and rifapentine regimen.[149] A regimen of 1 month isoniazid plus rifapentine given daily had superior completion, and non-inferior efficacy among people living with HIV;[150] evaluation of safety and tolerability in people without HIV infection, children, and other populations is ongoing. For contacts of multidrug-resistant tuberculosis or rifampicin-resistant tuberculosis, a trial in children in South Africa and a trial among adults in Viet Nam, both published in 2024,[151–154] have concluded that 6 months levofloxacin reduces the risk of subsequent disease by 50–60%.

Antiretroviral therapy for people living with HIV[155] and nutritional support for close contacts in settings with high rates of undernourishment have also been shown to lower the risk of tuberculosis disease.[156] BCG vaccination reduces the risk of infection, progression to disease, and mortality from tuberculosis in children if given in the first month of life, but the effect is insufficient[157] and the duration of protection is still controversial, probably waning with age.[16,18] Cash transfers can improve TPT completion[158] and should be considered.

Long-term management, follow up, and outcomes

Tuberculosis survivor narrative and perspective

Personal account from We Are Tuberculosis support space meeting (May 15, 2023):

> "When I finished treatment, all my pills came to an abrupt stop, and I wondered, 'what next? How do I take care of myself now?'"

Survivors of tuberculosis, especially after experiencing a physically, socially, and psychologically challenging treatment process, grapple with the difference between being cured of tuberculosis and feeling healed. Post treatment, survivors might wonder, "When will I feel like myself again?", "Will these side effects go away?", "How often do I need to get a check-up?", and "Am I more vulnerable to other illnesses and conditions now that I've had tuberculosis?" Providers should consider how tuberculosis and its treatment has created new or exacerbated pre-existing hardships. Insight from survivors could strengthen understanding of the long-term effects, how to minimise them, and improve recovery. More efforts are needed to holistically treat people with tuberculosis with genuine care, dignity, and respect.

Considerations for tuberculosis providers

Typically, tuberculosis disease has been considered a curable illness, with little consideration of the long-term effects for those who have been cured. Hence, for most people treated for tuberculosis, care abruptly ends at treatment completion.[159] This termination of care results in neglect of the long-term clinical, psychological, social, and economic sequelae of tuberculosis on survivors.[160,161] Given that tuberculosis survivors now number over 155 million globally,[162] the burden of these sequelae is estimated to be similar to the burden associated with the acute phase of tuberculosis disease.[163]

In a meta-analysis, 27 083 tuberculosis survivors had a standardised mortality ratio of 3·8 (95% CI 3·0–4·7) after successful tuberculosis treatment, compared with controls, with their most common causes of death being cardiovascular disease and cancer.[164] In a meta-analysis of 41 014 primarily adult survivors of pulmonary tuberculosis, 59% had abnormal spirometry compared with 5% of controls.[165] In the subset of survivors with such assessments, nearly 25% reported breathlessness (Medical Research Council breathlessness or dyspnoea scale 3–5) and 6-min walk distance was 79% of predicted, suggesting potential effects on functional ability.[165] As many as two-thirds of children and adolescents surviving pulmonary tuberculosis could develop respiratory impairment and children developing tuberculosis in their first 5 years of life are about twice as likely to have difficulties with wheezing and coughing when compared with those without tuberculosis.[166,167] Tuberculosis survivors are also substantially more likely to develop lung cancer, chronic obstructive pulmonary disease, aspergillomas, and bronchiectasis.[161,165,168]

Tuberculous meningitis and CNS tuberculosis might result in lasting neurological abnormalities including cognitive impairment, cerebral palsy, seizures, or blindness, in up to half of children and adolescents,[166] and one-quarter to one-third of adults.[169] Musculoskeletal tuberculosis in adults and children might lead to lasting sequelae, such as bone deformities and chronic pain, and tuberculosis affecting the spine can lead to kyphosis and even paraplegia.[166,170]

People diagnosed with tuberculosis also face numerous social stressors, such as stigma, loss of income, isolation in the early stages of treatment, and absence of social support. In a prospective study in Malawi, schoolchildren had frequent interruptions in schooling during treatment and for 1 year thereafter, while adult survivors earned and worked less after than before their tuberculosis diagnosis.[171] Approximately 20% of tuberculosis survivors also report mental health disorders that persist after treatment.[172]

Recent clinical practice guidelines for post-tuberculosis lung disease[108] recommend assessing every person completing tuberculosis treatment for post-tuberculosis lung disease as soon as possible after treatment ends. This evaluation could include some of the following

assessments: clinical status (symptoms); health status (quality of life, Patient Health Questionnaire [PHQ-9]); exercise capacity (Medical Research Council dyspnoea scale, 6-min walk test); lung imaging (chest radiograph); and lung function (spirometry).[108] Recommendations for pulmonary rehabilitation suggest treatment should include aerobic activities, use of airway clearing techniques, and nutritional support, for which there is good evidence of benefit,[108,173] and also provide comprehensive health education programmes covering smoking cessation and other topics.[174] Other approaches, such as inspiratory muscle training, could be considered.[174]

Controversies, uncertainties, and outstanding research questions

As with many areas of clinical medicine, in tuberculosis the greatest areas of uncertainty are also the most controversial; fortunately, they are also the most active areas of research. Diagnosis of tuberculosis disease is slow, expensive, and inaccessible in many settings. Ongoing research is testing alternative samples such as saliva, breath-based and swab-based specimens,[175] and use of artificial intelligence algorithms to interpret recorded cough sounds.[176] Whole-genome sequencing detects *M tuberculosis*, plus mutations responsible for resistance,[177] but is costly and requires complex infrastructure, hampering implementation where it is needed most.[178] Targeted next-generation sequencing, is promising as it is performed directly on clinical samples, and amplifies specific DNA sequences to detect tuberculosis, and resistance at lower cost.[179]

Treatment of drug-susceptible tuberculosis disease remains stuck at 6 months for most patients, despite many treatment-shortening trials, which have involved giving higher doses of anti-tuberculosis drugs, or a greater number of these drugs, including new anti-tuberculosis drugs. To date, these trials have shown a trade-off between shorter versus safer or better tolerated.[79] New drugs that permit treatment shortening and are also safe and well tolerated are needed; many are in the pipeline.[180] Treatment of drug-resistant tuberculosis has leapt forward in the past decade with the development of all-oral, 6-month regimens that are effective and safer than previous regimens. Further treatment shortening will also depend upon new drugs.

Tuberculosis prevention remains a major challenge, given the absence of an effective vaccine, poor diagnostics, and lengthy plus potentially toxic preventive treatment. A phase 3 study[181] has been initiated to test a new vaccine that had 50% efficacy for prevention of tuberculosis disease in IGRA-positive adults in a phase 2 trial.[182] Candidate vaccines for preventing tuberculosis infection, disease, or recurrence are being tested,[183] or are in the pipeline.[184,185] Current tests for tuberculosis infection are unsatisfactory, as very few with a positive test (TST or IGRA) will ever develop disease, leading to controversy as to whether these tests are needed. However imperfect, currently available tests do identify people at higher risk for tuberculosis disease, and also those who will benefit from preventive therapy. Improved tests that would identify people with highest risk for tuberculosis disease, by improving identification of people who will derive maximal benefit from preventive therapy, would be a major advance. Development of such tests is still in the early stages. In the absence of better tests, the pressing need is to develop and evaluate safer and better tolerated tuberculosis preventive regimens of 1–2 months duration.

The need for continued patient care for tuberculosis-related disability after successful treatment of tuberculosis disease has only recently been recognised. Better understanding of who is at risk for these sequelae, and why, plus how to prevent or mitigate them, possibly by modulating host response, will inform future therapeutic trials.

Conclusion

Tuberculosis continues to be a major challenge for all who confront it. For people with tuberculosis, challenges include being diagnosed quickly to reduce disease progression, and being treated with an effective, safe, and well tolerated treatment that is easy to complete. For care providers, challenges include thinking about tuberculosis, and initiating testing that is rapid, yet accurate, then selecting the shortest, safest, and most effective treatment. A key provider role is to educate people with tuberculosis and their families to reduce shame, stigma, confusion, and fear, and to organise adequate treatment support to ensure full adherence with the selected regimen. The challenges for tuberculosis programmes include prevention of disease through strategies to address social determinants, and detection and treatment of tuberculosis infection, and to reduce transmission, morbidity, and mortality through improved detection and treatment of tuberculosis disease. For researchers, development and application of new tools for diagnosis, treatment, and prevention, based on improved understanding of the biological mechanisms of infection and disease, pose the biggest challenges. Progress over the past decade leads us to be optimistic that these challenges can be overcome, and tuberculosis ultimately eliminated.

Contributors

All authors contributed equally to the conceptualisation, method, visualisation, and writing of the original draft, and subsequent review and editing.

Declaration of interests

DM, MAB, and JRC report funding from peer-reviewed funding agencies for operating grants for tuberculosis research: Canadian Institutes of Health Research (DM, MAB, and JRC); Fonds de Recherche en Santé de Québec (JRC); and TB Trials Consortium (DM and MAB). AT is supported by the Brazilian Ministry of Science, Technology and Innovation (CNPq 301794/2022–7). DM is supported by a Canada Research Chair Tier 1. JRC reports salary support from Fonds de

Recherche en Santé de Québec. All other authors declare no competing interests.

Acknowledgments

Figures 1 and 2 adapted from Furin et al.[186] Figure 3 created with Canva. Table 1 adapted from Campbell et al,[187] by permission of the authors.

References

1 Hansel NN, Wu AW, Chang B, Diette GB. Quality of life in tuberculosis: patient and provider perspectives. *Qual Life Res* 2004; **13:** 639–52.

2 Sinclair S, Norris JM, McConnell SJ, et al. Compassion: a scoping review of the healthcare literature. *BMC Palliat Care* 2016; **15:** 6.

3 Reichler MR, Khan A, Yuan Y, et al. Duration of exposure among close contacts of patients with infectious tuberculosis and risk of latent tuberculosis infection. *Clin Infect Dis* 2020; **71:** 1627–34.

4 Reichler MR, Khan A, Sterling TR, et al. Risk and timing of tuberculosis among close contacts of persons with infectious tuberculosis. *J Infect Dis* 2018; **218:** 1000–08.

5 Fox GJ, Dobler CC, Marks GB. Active case finding in contacts of people with tuberculosis. *Cochrane Database Syst Rev* 2011; **2011:** CD008477.

6 Fox GJ, Barry SE, Britton WJ, Marks GB. Contact investigation for tuberculosis: a systematic review and meta-analysis. *Eur Respir J* 2013; **41:** 140–56.

7 Morrison J, Pai M, Hopewell PC. Tuberculosis and latent tuberculosis infection in close contacts of people with pulmonary tuberculosis in low-income and middle-income countries: a systematic review and meta-analysis. *Lancet Infect Dis* 2008; **8:** 359–68.

8 Frascella B, Richards AS, Sossen B, et al. Subclinical tuberculosis disease–a review and analysis of prevalence surveys to inform definitions, burden, associations, and screening methodology. *Clin Infect Dis* 2021; **73:** e830–41.

9 Kendall E, Shrestha S, Dowdy D. The epidemiological importance of subclinical tuberculosis. a critical reappraisal. *Am J Respir Crit Care Med* 2021; **203:** 168–74.

10 Verver S, Warren RM, Munch Z, et al. Proportion of tuberculosis transmission that takes place in households in a high-incidence area. *Lancet* 2004; **363:** 212–14.

11 Buu TN, van Soolingen D, Huyen MN, et al. Tuberculosis acquired outside of households, rural Vietnam. *Emerg Infect Dis* 2010; **16:** 1466–68.

12 Stuck L, Klinkenberg E, Abdelgadir Ali N, et al. Prevalence of subclinical pulmonary tuberculosis in adults in community settings: an individual participant data meta-analysis. *Lancet Infect Dis* 2024; **24:** 726–36.

13 Hamada Y, Quartagno M, Law I, et al. Association of diabetes, smoking, and alcohol use with subclinical-to-symptomatic spectrum of tuberculosis in 16 countries: an individual participant data meta-analysis of national tuberculosis prevalence surveys. *eClinicalMedicine* 2023; **63:** 102191.

14 Dinkele R, Gessner S, McKerry A, et al. Aerosolization of *mycobacterium tuberculosis* by tidal breathing. *Am J Respir Crit Care Med* 2022; **206:** 206–16.

15 Cobat A, Gallant CJ, Simkin L, et al. Two loci control tuberculin skin test reactivity in an area hyperendemic for tuberculosis. *J Exp Med* 2009; **206:** 2583–91.

16 Lalvani A, Seshadri C. Understanding How BCG vaccine protects against mycobacterium tuberculosis infection: lessons from household contact studies. *J Infect Dis* 2020; **221:** 1229–31.

17 Soysal A, Millington K, Bakir M, et al. Effect of BCG vaccination on risk of mycobacterium tuberculosis infection in children with household tuberculosis contact: a prospective community-based study. *Lancet* 2005; **366:** 1443–51.

18 Katelaris A, Jackson C, Southern J, et al. Effectiveness of BCG vaccination against Mycobacterium tuberculosis infection in adults: a cross-sectional analysis of a UK-based cohort. *J Infect Dis* 2020; **221:** 146–55.

19 Menzies NA, Swartwood N, Testa C, et al. Time since infection and risks of future disease for individuals with mycobacterium tuberculosis infection in the United States. *Epidemiology* 2021; **32:** 70–78.

20 Behr MA, Edelstein PH, Ramakrishnan L. Revisiting the timetable of tuberculosis. *BMJ* 2018; **362:** k2738.

21 Gupta R, Calderwood C, Yavlinsky A, et al. Discovery and validation of a personalized risk predictor for incident tuberculosis in low transmission settings. *Nat Med* 2020; **26:** 1941–49.

22 Trauer JM, Moyo N, Tay EL, et al. Risk of active tuberculosis in the five years following infection . . . 15%? *Chest* 2016; **149:** 516–25.

23 Martinez L, Cords O, Horsburgh C, Andrews J. The risk of tuberculosis in children after close exposure: a systematic review and individual-participant meta-analysis. *Lancet* 2020; **395:** 973–84.

24 Campbell JR, Winters N, Menzies D. Absolute risk of tuberculosis among untreated populations with a positive tuberculin skin test or interferon-gamma release assay result: systematic review and meta-analysis. *BMJ* 2020; **368:** m549.

25 Grzybowski S, Fishaut H, Rowe J, Brown A. Tuberculosis among patients with various radiologic abnormalities, followed by the chest clinic service. *Am Rev Respir Dis* 1971; **104:** 605–08.

26 Grzybowski S, McKinnon N, Tuters L, Pinkus G, Philipps R. Reactivations in inactive pulmonary tuberculosis. *Am Rev Respir Dis* 1966; **93:** 352–361.

27 Nolan C, Elarth A. Tuberculosis in a cohort of Southeast Asian refugees. A five-year surveillance study. *Am Rev Respir Dis* 1988; **137:** 805–09.

28 Kumar D, Ronald L, Romanowski K, et al. Risk of active tuberculosis in migrants diagnosed with cancer: a retrospective cohort study in British Columbia, Canada. *BMJ Open* 2021; **11:** e037827.

29 Horwitz O, Wilbek E, Erickson PA. Epidemiological basis of tuberculosis eradication. 10. Longitudinal studies on the risk of tuberculosis in the general population of a low-prevalence area. *Bull World Health Organ* 1969; **41:** 95–113.

30 Jeon CY, Murray MB. Diabetes mellitus increases the risk of active tuberculosis: a systematic review of 13 observational studies. *PLoS Med* 2008; **5:** e152.

31 Franco JV, Bongaerts B, Metzendorf MI, et al. Undernutrition as a risk factor for tuberculosis disease. *Cochrane Database Syst Rev* 2024; **6:** CD015890.

32 Lönnroth K, Williams BG, Stadlin S, Jaramillo E, Dye C. Alcohol use as a risk factor for tuberculosis - a systematic review. *BMC Public Health* 2008; **8:** 289.

33 Lin HH, Murray M, Cohen T, Colijn C, Ezzati M. Effects of smoking and solid-fuel use on COPD, lung cancer, and tuberculosis in China: a time-based, multiple risk factor, modelling study. *Lancet* 2008; **372:** 1473–83.

34 Bates MN, Khalakdina A, Pai M, Chang L, Lessa F, Smith KR. Risk of tuberculosis from exposure to tobacco smoke: a systematic review and meta-analysis. *Arch Intern Med* 2007; **167:** 335–42.

35 Comstock G, Edwards L, Livesay V. Tuberculosis morbidity in the U.S. Navy: its distribution and decline. *Am Rev Respir Dis* 1974; **110:** 572–80.

36 Ferebee SH. Controlled chemoprophylaxis trials in tuberculosis. A general review. *Bibl Tuberc* 1970; **26:** 28–106.

37 Brode S, Jamieson F, Ng R, et al. Increased risk of mycobacterial infections associated with anti-rheumatic medications. *Thorax* 2015; **70:** 677–82.

38 WHO. Global Tuberculosis Report 2023. World Health Organization, 2023. https://www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2023 (accessed Feb 13, 2025).

39 Enarson D, Ashley MJ, Grzybowski S. Tuberculosis in immigrants to Canada. A study of present-day patterns in relation to immigration trends and birthplace. *Am Rev Respir Dis* 1979; **119:** 11–18.

40 Vadlamudi N, Basham C, Johnston J, et al. The association of Sars-cov-2 infection and tuberculosis disease with unfavorable treatment outcomes: a systematic review. *Value Health* 2023; **26** (suppl): S34.

41 Dowdy DW. Has the COVID-19 pandemic increased tuberculosis mortality? *Lancet Infect Dis* 2022; **22:** 165–66.

42 Tulloch O, Theobald S, Morishita F, et al. Patient and community experiences of tuberculosis diagnosis and care within a community-based intervention in Ethiopia: a qualitative study. *BMC Public Health* 2015; **15:** 187.

43 Cruz AT, Starke JR. Clinical manifestations of tuberculosis in children. *Paediatr Respir Rev* 2007; **8:** 107–17.

44 Golden MP, Vikram HR. Extrapulmonary tuberculosis: an overview. *Am Fam Physician* 2005; **72:** 1761–68.

45 Baykan AH, Sayiner HS, Aydin E, Koc M, Inan I, Erturk SM. Extrapulmonary tuberculosıs: an old but resurgent problem. *Insights Imaging* 2022; **13:** 39.

46 Jaganath D, Beaudry J, Salazar-Austin N. Tuberculosis in children. *Infect Dis Clin North Am* 2022; **36:** 49–71.

47 Getnet F, Demissie M, Assefa N, Mengistie B, Worku A. Delay in diagnosis of pulmonary tuberculosis in low- and middle-income settings: systematic review and meta-analysis. *BMC Pulm Med* 2017; **17:** 202.

48 Tavaziva G, Harris M, Abidi SK, et al. Chest x-ray analysis with deep learning-based software as a triage test for pulmonary tuberculosis: an individual patient data meta-analysis of diagnostic accuracy. *Clin Infect Dis* 2022; **74:** 1390–400.

49 WHO. Rapid communication on systematic screening for tuberculosis. World Health Organization, 2020. https://www.who.int/publications/i/item/9789240016552 (accessed Feb 13, 2025).

50 Geric C, Qin Z, Denkinger C, et al. The rise of artificial intelligence reading of chest X-rays for enhanced tuberculosis diagnosis and elimination. *Int J Tuberc Lung Dis* 2023; **27:** 367–72.

51 Bowness R, Boeree M, Aarnoutse R, et al. The relationship between Mycobacterium tuberculosis MGIT time to positivity and CFU in sputum samples demonstrates changing bacterial phenotypes potentially reflecting the impact of chemotherapy on critical sub-populations. *J Antimicrob Chemother* 2015; **70:** 448–55.

52 Elsaghier A. Auditing smear microscopy results according to time to detection using the BACTEC™ MGIT™ tuberculosis system. *Int J Tuberc Lung Dis* 2015; **19:** 1076–77.

53 Köser CU, Cirillo DM, Miotto P. How to optimally combine genotypic and phenotypic drug susceptibility testing methods for pyrazinamide. *Antimicrob Agents Chemother* 2020; **64:** e01003-20.

54 WHO. WHO consolidated guidelines on tuberculosis: module 3: diagnosis: rapid diagnostics for tuberculosis detection, 2021 update. World Health Organization, 2021. https://www.who.int/publications/i/item/9789240029415 (accessed Feb 13, 2025).

55 Steingart KR, Henry M, Ng V, et al. Fluorescence versus conventional sputum smear microscopy for tuberculosis: a systematic review. *Lancet Infect Dis* 2006; **6:** 570–81.

56 Steingart KR, Ng V, Henry M, et al. Sputum processing methods to improve the sensitivity of smear microscopy for tuberculosis: a systematic review. *Lancet Infect Dis* 2006; **6:** 664–74.

57 Zifodya JS, Kreniske JS, Schiller I, et al. Xpert Ultra versus Xpert MTB/RIF for pulmonary tuberculosis and rifampicin resistance in adults with presumptive pulmonary tuberculosis. *Cochrane Database Syst Rev* 2021; **2:** CD009593.

58 Xie Y, Eichberg C, Hapeela N, et al. Xpert MTB/RIF Ultra versus mycobacterial growth indicator tube liquid culture for detection of Mycobacterium tuberculosis in symptomatic adults: a diagnostic accuracy study. *Lancet Microbe* 2024; **5:** e520–28.

59 Denkinger CM, Schumacher SG, Boehme CC, Dendukuri N, Pai M, Steingart KR. Xpert MTB/RIF assay for the diagnosis of extrapulmonary tuberculosis: a systematic review and meta-analysis. *Eur Respir J* 2014; **44:** 435–46.

60 Lee J, Garg T, Lee J, et al. Impact of molecular diagnostic tests on diagnostic and treatment delays in tuberculosis: a systematic review and meta-analysis. *BMC Infect Dis* 2022; **22:** 940.

61 Di Tanna G, Khaki A, Theron G, et al. Effect of Xpert MTB/RIF on clinical outcomes in routine care settings: individual patient data meta-analysis. *Lancet Glob Health* 2019; **7:** e191–99.

62 WHO. WHO consolidated guidelines on tuberculosis: module 5: management of tuberculosis in children and adolescents. World Health Organization, 2022. https://www.who.int/publications/i/item/9789240046764 (accessed Feb 13, 2025).

63 MacPherson P, Houben R, Glynn J, Corbett E, Kranzer K. Pre-treatment loss to follow-up in tuberculosis patients in low- and lower-middle-income countries and high-burden countries: a systematic review and meta-analysis. *Bull World Health Organ* 2014; **92:** 126–38.

64 WHO. High priority target product profiles for new tuberculosis diagnostics: report of a consensus meeting, 28–29 April 2014, Geneva, Switzerland. World Health Organization, 2014. https://www.who.int/publications/i/item/WHO-HTM-TB-2014.18 (accessed Feb 13, 2025).

65 Nichols J. Point of care testing. *Clin Lab Med* 2007; **27:** 893–908.

66 WHO. WHO consolidated guidelines on tuberculosis: module 2: screening: systematic screening for tuberculosis disease. World Health Organization, 2021. https://www.who.int/publications/i/item/9789240022676 (accessed Feb 13, 2025).

67 Bjerrum S, Broger T, Székely R, et al. Diagnostic accuracy of a novel and rapid lipoarabinomannan test for diagnosing tuberculosis among people with human immunodeficiency virus. *Open Forum Infect Dis* 2019; **7:** ofz530.

68 Almeida A, Adjuntsov M, Bushura W, et al. Hear us! Accounts of people treated with injectables for drug-resistant tuberculosis. *Public Health Action* 2021; **11:** 146–54.

69 Mathad JS, Gupta A. Tuberculosis in pregnant and postpartum women: epidemiology, management, and research gaps. *Clin Infect Dis* 2012; **55:** 1532–49.

70 Sobhy S, Babiker Z, Zamora J, Khan KS, Kunst H. Maternal and perinatal mortality and morbidity associated with tuberculosis during pregnancy and the postpartum period: a systematic review and meta-analysis. *BJOG* 2017; **124:** 727–33.

71 WHO. WHO consolidated guidelines on tuberculosis: module 4: treatment: drug-susceptible tuberculosis treatment. World Health Organization, 2022. https://www.who.int/publications/i/item/9789240048126 (accessed Feb 13, 2025).

72 Johnston JC, Campbell JR, Menzies D. Effect of intermittency on treatment outcomes in pulmonary tuberculosis: an updated systematic review and meta-analysis. *Clin Infect Dis* 2017; **64:** 1211–20.

73 Gillespie SH, Crook AM, McHugh TD, et al. Four-month moxifloxacin-based regimens for drug-sensitive tuberculosis. *N Engl J Med* 2014; **371:** 1577–87.

74 Dorman S, Nahid P, Kurbatova E, et al. Four-month rifapentine regimens with or without moxifloxacin for tuberculosis. *New Eng J Med* 2021; **384:** 1705–18.

75 Jindani A, Harrison TS, Nunn AJ, et al. High-dose rifapentine with moxifloxacin for pulmonary tuberculosis. *N Engl J Med* 2014; **371:** 1599–608.

76 Johnston J, Cooper R, Menzies D. Chapter 5: treatment of tuberculosis disease. In: Menzies D, ed. Canadian tuberculosis standards, 8th edn. Canadian Thoracic Society, 2022: 66–76.

77 Gupta A, Montepiedra G, Aaron L, et al. Isoniazid preventive therapy in HIV-infected pregnant and postpartum women. *N Engl J Med* 2019; **381:** 1333–46.

78 Gupta A, Mathad JS, Abdel-Rahman SM, et al. Toward earlier inclusion of pregnant and postpartum women in tuberculosis drug trials: consensus statements from an international expert panel. *Clin Infect Dis* 2016; **62:** 761–69.

79 Burman W, Rucsineanu O, Horsburgh CR, Johnston J, Dorman SE, Menzies D. Research on the treatment of rifampin-susceptible tuberculosis-time for a new approach. *PLoS Med* 2024; **21:** e1004438.

80 Merle CS, Fielding K, Sow OB, et al. A four-month gatifloxacin-containing regimen for treating tuberculosis. *N Engl J Med* 2014; **371:** 1588–98.

81 Cevik M, Thompson LC, Upton C, et al. Bedaquiline-pretomanid-moxifloxacin-pyrazinamide for drug-sensitive and drug-resistant pulmonary tuberculosis treatment: a phase 2c, open-label, multicentre, partially randomised controlled trial. *Lancet Infect Dis* 2024; **24:** 1003–14.

82 Louie JK, Agraz-Lara R, Velásquez GE, Phillips A, Szumowski JD. Experience with four-month rifapentine and moxifloxacin-based tuberculosis treatment in San Francisco. *Open Forum Infect Dis* 2024; **11:** ofae178.

83 Galvis ME, Gao G, Salerno MM, et al. Tuberculosis treatment with four-month rifapentine-moxifloxacin regimen in New York City Health Department clinics. *Int J Tuber Lung Dis* (in press).

84 Paton NI, Cousins C, Suresh C, et al. Treatment strategy for rifampin-susceptible tuberculosis. *N Engl J Med* 2023; **388:** 873–87.

85 Onorato L, Gentile V, Russo A, et al. Standard versus high dose of rifampicin in the treatment of pulmonary tuberculosis: a systematic review and meta-analysis. *Clin Microbiol Infect* 2021; **27:** 830–37.

86 Stott K, Pertinez H, Sturkenboom M, et al. Pharmacokinetics of rifampicin in adult tuberculosis patients and healthy volunteers: a systematic review and meta-analysis. *J Antimicrob Chemother* 2018; **73:** 2305–13.

87 Jindani A, Atwine D, Grint D, et al. Four-month high-dose rifampicin regimens for pulmonary tuberculosis. *NEJM Evidence* 2023; **2:** EVIDoa2300054.

88 Turkova A, Wills G, Wobudeya E, et al. Shorter treatment for nonsevere tuberculosis in African and Indian children. *N Engl J Med* 2022; **386:** 911–22.

89 Mota L, Al-Efraij K, Campbell J, Cook V, Marra F, Johnston J. Therapeutic drug monitoring in anti-tuberculosis treatment: a systematic review and meta-analysis. *Int J Tuberc Lung Dis* 2016; **20:** 819–26.

90 Märtson AG, Burch G, Ghimire S, Alffenaar JC, Peloquin CA. Therapeutic drug monitoring in patients with tuberculosis and concurrent medical problems. *Expert Opin Drug Metab Toxicol* 2021; **17:** 23–39.

91 Imperial MZ, Nahid P, Phillips PPJ, et al. A patient-level pooled analysis of treatment-shortening regimens for drug-susceptible pulmonary tuberculosis. *Nat Med* 2018; **24:** 1708–15.

92 Gegia M, Winters N, Benedetti A, van Soolingen D, Menzies D. Treatment of isoniazid-resistant tuberculosis with first-line drugs: a systematic review and meta-analysis. *Lancet Infect Dis* 2017; **17:** 223–34.

93 Fregonese F, Ahuja SD, Akkerman OW, et al. Comparison of different treatments for isoniazid-resistant tuberculosis: an individual patient data meta-analysis. *Lancet Respir Med* 2018; **6:** 265–75.

94 Nyang'wa BT, Berry C, Kazounis E, et al. A 24-week, all-oral regimen for rifampin-resistant tuberculosis. *N Engl J Med* 2022; **387:** 2331–43.

95 Conradie F, Diacon AH, Ngubane N, et al. Treatment of highly drug-resistant pulmonary tuberculosis. *N Engl J Med* 2020; **382:** 893–902.

96 Conradie F, Bagdasaryan TR, Borisov S, et al. Bedaquiline-pretomanid-linezolid regimens for drug-resistant tuberculosis. *N Engl J Med* 2022; **387:** 810–23.

97 WHO. National surveys of costs faced by tuberculosis patients and their households 2015–2021. World Health Organization, 2023. https://www.who.int/publications/i/item/9789240065536 (accessed Feb 13, 2025).

98 Garcia-Prats AJ, Hoddinott G, Howell P, et al. Children deserve simple, short, safe, and effective treatment for rifampicin-resistant tuberculosis. *Lancet Infect Dis* 2023; **23:** 778–80.

99 Ndjeka N, Campbell JR, Meintjes G, et al. Treatment outcomes 24 months after initiating short, all-oral bedaquiline-containing or injectable-containing rifampicin-resistant tuberculosis treatment regimens in South Africa: a retrospective cohort study. *Lancet Infect Dis* 2022; **22:** 1042–51.

100 WHO. WHO consolidated guidelines on tuberculosis. Module 4: treatment - drug-resistant tuberculosis treatment, 2022 update. World Health Organization, 2022. https://www.who.int/publications/i/item/9789240063129 (accessed Feb 13, 2025).

101 Karumbi J, Garner P. Directly observed therapy for treating tuberculosis. *Cochrane Database Syst Rev* 2015; **5:** CD003343.

102 Tian J, Lu Z, Bachmann M, Song F. Effectiveness of directly observed treatment of tuberculosis: a systematic review of controlled studies. *Int J Tuberc Lung Dis* 2014; **18:** 1092–98.

103 McKay B, Castellanos M, Ebell M, Whalen C, Handel A. An attempt to reproduce a previous meta-analysis and a new analysis regarding the impact of directly observed therapy on tuberculosis treatment outcomes. *PloS One* 2019; **14:** e0217219.

104 Zhang H, Ehiri J, Yang H, Tang S, Li Y. Impact of community-based DOT on tuberculosis treatment outcomes: a systematic review and meta-analysis. *PloS One* 2016; **11:** e0147744.

105 Khachadourian V, Truzyan N, Harutyunyan A, et al. People-centred care versus clinic-based DOT for continuation phase tuberculosis treatment in Armenia: a cluster randomized trial. *BMC Pulm Med* 2020; **20:** 105.

106 Ngwatu B, Nsengiyumva N, Oxlade O, et al. The impact of digital health technologies on tuberculosis treatment: a systematic review. *Eur Respir J* 2018; **51:** 1701596.

107 Alipanah N, Jarlsberg L, Miller C, et al. Adherence interventions and outcomes of tuberculosis treatment: a systematic review and meta-analysis of trials and observational studies. *PLoS Med* 2018; **15:** e1002595.

108 Migliori G, Marx F, Ambrosino N, et al. Clinical standards for the assessment, management and rehabilitation of post-tuberculosis lung disease. *Int J Tuberc Lung Dis* 2021; **25:** 797–813.

109 Richterman A, Steer-Massaro J, Jarolimova J, Luong Nguyen L, Werdenberg J, Ivers L. Cash interventions to improve clinical outcomes for pulmonary tuberculosis: systematic review and meta-analysis. *Bull World Health Organ* 2018; **96:** 471–83.

110 Wagnew F, Gray D, Tsheten T, Kelly M, Clements A, Alene K. Effectiveness of nutritional support to improve treatment adherence in patients with tuberculosis: a systematic review. *Nutr Rev* 2023; **82:** 1216–25.

111 Andrade K, Nery J, Souza R, Pereira S. Effects of social protection on tuberculosis treatment outcomes in low or middle-income and in high-burden countries: systematic review and meta-analysis. *Cad Saude Publica* 2018; **34:** e00153116.

112 WHO, ILO. Guidance on social protection for people affected by tuberculosis. World Health Organization and International Labour Organization, 2024. https://www.who.int/publications/i/item/9789240089327 (accessed Feb 13, 2025).

113 Sinha P, Ponnuraja C, Gupte N, et al. Impact of undernutrition on tuberculosis treatment outcomes in India: a multicenter, prospective, cohort analysis. *Clin Infect Dis* 2023; **76:** 1483–91.

114 Kyaw NTT, Kumar AMV, Harries AD, et al. Synergy between low BMI and hyperglycemia at baseline increases tuberculosis incidence among people living with HIV. *AIDS* 2022; **36:** 117–25.

115 WHO. Module 5: roadmap towards ending tuberculosis in children and adolescents, 3rd edn. World Health Organization, 2023. https://www.who.int/publications/i/item/9789240084254 (accessed Feb 13, 2025).

116 Nuttall C, Fuady A, Nuttall H, Dixit K, Mansyur M, Wingfield T. Interventions pathways to reduce tuberculosis-related stigma: a literature review and conceptual framework. *Infect Dis Poverty* 2022; **11:** 101.

117 Marley G, Zou X, Nie J, et al. Improving cascade outcomes for active TB: a global systematic review and meta-analysis of TB interventions. *PLoS Med* 2023; **20:** e100409.

118 Addo J, Pearce D, Metcalf M, et al. Living with tuberculosis: a qualitative study of patients' experiences with disease and treatment. *BMC Public Health* 2022; **22:** 1717.

119 Ghazy R, El Saeh H, Abdulaziz S, et al. A systematic review and meta-analysis of the catastrophic costs incurred by tuberculosis patients. *Sci Rep* 2022; **12:** 558.

120 Sinha P, Carwile M, Bhargava A, et al. How much do Indians pay for tuberculosis treatment? A cost analysis. *Public Health Action* 2020; **10:** 110–17.

121 GFAN. Interview with Handaa Enkh-Amgalan, author of Stigmatized: A Mongolian Girl's Journey from Stigma & Illness to Empowerment, and GFAN speaker. Global Fund Advocates Network, Aug 10, 2021. https://globalfundadvocatesnetwork.org/interview-with-handaa-enkh-amgalan-author-of-stigmatized-a-mongolian-girls-journey-from-stigma-illness-to-empowerment-and-gfan-speaker/ (accessed Feb 13, 2025).

122 Alsdurf H, Hill P, Matteelli A, Getahun H, Menzies D. The cascade of care in diagnosis and treatment of latent tuberculosis infection: a systematic review and meta-analysis. *Lancet Infect Dis* 2016; **16:** 1269–78.

123 WHO. WHO operational handbook on tuberculosis: module 3: diagnosis: tests for tuberculosis infection. World Health Organization, 2022. https://www.who.int/publications/i/item/9789240058347 (accessed Feb 13, 2025).

124 Oxlade O, Benedetti A, Adjobimey M, et al. Effectiveness and cost-effectiveness of a health systems intervention for latent tuberculosis infection management (ACT4): a cluster-randomised trial. *Lancet Public Health* 2021; **6:** e272–82.

125 Emery J, Richards A, Dale K, et al. Self-clearance of Mycobacterium tuberculosis infection: implications for lifetime risk and population at-risk of tuberculosis disease. *Proc Biol Sci* 2021; **288:** 20201635 .

126 Menzies D, Gardiner G, Farhat M, Greenaway C, Pai M. Thinking in three dimensions: a web-based algorithm to aid the interpretation of tuberculin skin test results. *Int J Tuberc Lung Dis* 2008; **12:** 498–505.

127 WHO. Rapid communication: tuberculosis antigen-based skin tests for the diagnosis of tuberculosis infection. World Health Organization, 2022. https://www.who.int/publications/i/item/WHO-UCN-TB-2022.1 (accessed Feb 13, 2025).

128 WHO. WHO consolidated guidelines on tuberculosis: module 3: diagnosis: tests for tuberculosis infection. World Health Organization, 2022. https://www.who.int/publications/i/item/9789240056084 (accessed Feb 13, 2025).

129 Ruhwald M, Aggerbeck H, Gallardo RV, et al. Safety and efficacy of the C-Tb skin test to diagnose Mycobacterium tuberculosis infection, compared with an interferon γ release assay and the tuberculin skin test: a phase 3, double-blind, randomised, controlled trial. *Lancet Respir Med* 2017; **5:** 259–68.

130 WHO. Use of alternative interferon-gamma release assays for the diagnosis of tuberculosis infection - WHO Policy Statement. World Health Organization, 2022. https://www.who.int/publications/i/item/9789240042346 (accessed Feb 13, 2025).

131 Comstock GW, Livesay VT, Woolpert SF. The prognosis of a positive tuberculin reaction in childhood and adolescence. *Am J Epidemiol* 1974; **99:** 131–38.

132 Akolo C, Adetifa I, Shepperd S, Volmink J. Treatment of latent tuberculosis infection in HIV infected persons. *Cochrane Database Syst Rev* 2010; **2010:** CD000171.

133 Samandari T, Agizew T, Nyirenda S, et al. A randomized placebo-controlled trial of 6 versus 36 months isoniazid tuberculosis preventive therapy for HIV-infected adults in Botswana. *Lancet* 2011; **377:** 1588–98.

134 Martinez L, Seddon JA, Horsburgh CR, et al. Effectiveness of preventive treatment among different age groups and Mycobacterium tuberculosis infection status: a systematic review and individual-participant data meta-analysis of contact tracing studies. *Lancet Respir Med* 2024; **12:** 633–41.

135 Ortiz-Brizuela E, Apriani L, Mukherjee T, et al. Assessing the diagnostic performance of new commercial interferon-γ release assays for Mycobacterium tuberculosis infection: a systematic review and meta-analysis. *Clin Infect Dis* 2023; **76:** 1989–99.

136 WHO. WHO consolidated guidelines on tuberculosis. Module 1: prevention - tuberculosis preventive treatment, 2nd edn. World Health Organization, 2024. https://www.who.int/publications/i/item/9789240096196 (accessed Feb 13, 2025).

137 Getahun H, Kittikraisak W, Heilig CM, et al. Development of a standardized screening rule for tuberculosis in people living with HIV in resource-constrained settings: individual participant data meta-analysis of observational studies. *PLoS Med* 2011; **8:** e1000391.

138 Marais BJ, Gie RP, Obihara CC, Hesseling AC, Schaaf HS, Beyers N. Well defined symptoms are of value in the diagnosis of childhood pulmonary tuberculosis. *Arch Dis Child* 2005; **90:** 1162–65.

139 WHO. Latent tuberculosis infection: updated and consolidated guidelines for programmatic management. World Health Organization, 2018. https://www.who.int/publications/i/item/9789241550239 (accessed Feb 13, 2025).

140 Sterling T, Njie G, Zenner D, et al. Guidelines for the treatment of latent tuberculosis infection: recommendations from the National Tuberculosis Controllers Association and CDC, 2020. *MMWR Recomm Rep* 2020; **69:** 1–11.

141 Ena J, Valls V. Short-course therapy with rifampin plus isoniazid, compared with standard therapy with isoniazid, for latent tuberculosis infection: a meta-analysis. *Clin Infect Dis* 2005; **40:** 670–76.

142 Sterling TR, Villarino ME, Borisov AS, et al. Three months of rifapentine and isoniazid for latent tuberculosis infection. *N Engl J Med* 2011; **365:** 2155–66.

143 Sterling TR, Moro RN, Borisov AS, et al. Flu-like and other systemic drug reactions among persons receiving weekly rifapentine plus isoniazid or daily isoniazid for treatment of latent tuberculosis infection in the PREVENT tuberculosis study. *Clin Infect Dis* 2015; **61:** 527–35.

144 Gao L, Zhang H, Xin H, et al. Short-course regimens of rifapentine plus isoniazid to treat latent tuberculosis infection in older Chinese patients: a randomised controlled study. *Eur Respir J* 2018; **52:** 1801470.

145 Huang HL, Huang WC, Lin KD, et al. Completion rate and safety of programmatic screening and treatment for latent tuberculosis infection in elderly patients with poorly controlled diabetic mellitus: a prospective multicenter study. *Clin Infect Dis* 2021; **73:** e1252–60.

146 Melnychuk L, Perlman-Arrow S, Bastos M, Menzies D. A systematic review and meta-analysis of tuberculous preventative therapy adverse events. *Clin Infect Dis* 2023; **77:** 287–94.

147 Zenner D, Beer N, Harris R, Lipman M, Stagg H, van der Werf M. Treatment of latent tuberculosis infection: an updated network meta-analysis. *Ann Intern Med* 2017; **167:** 248–55.

148 Diallo T, Adjobimey M, Ruslami R, et al. Safety and side effects of rifampin versus isoniazid in children. *N Engl J Med* 2018; **379:** 454–63.

149 Winters N, Belknap R, Benedetti A, et al. Completion, safety, and efficacy of tuberculosis preventive treatment regimens containing rifampicin or rifapentine: an individual patient data network meta-analysis. *Lancet Respir Med* 2023; **11:** 782–90.

150 Swindells S, Ramchandani R, Gupta A, et al. One month of rifapentine plus isoniazid to prevent HIV-related tuberculosis. *N Engl J Med* 2019; **380:** 1001–11.

151 Seddon JA, Garcia-Prats AJ, Purchase SE, et al. Levofloxacin versus placebo for the prevention of tuberculosis disease in child contacts of multidrug-resistant tuberculosis: study protocol for a phase III cluster randomised controlled trial (TB-CHAMP). *Trials* 2018; **19:** 693.

152 Hesseling AC, Purchase SE, Martinson NA, et al. Levofloxacin preventive treatment in children exposed to MDR tuberculosis. *N Engl J Med* 2024; **391:** 2315–26.

153 Fox GJ, Nhung NV, Cam Binh N, et al. Levofloxacin for the prevention of multidrug-resistant tuberculosis in Vietnam. *N Engl J Med* 2024; **391:** 2304–14.

154 Fox GJ, Nguyen CB, Nguyen TA, et al. Levofloxacin versus placebo for the treatment of latent tuberculosis among contacts of patients with multidrug-resistant tuberculosis (the VQUIN MDR trial): a protocol for a randomised controlled trial. *BMJ Open* 2020; **10:** e033945.

155 Danel C, Moh R, Gabillard D, et al. A trial of early antiretrovirals and isoniazid preventive therapy in Africa. *N Engl J Med* 2015; **373:** 808–22.

156 Bhargava A, Bhargava M, Meher A, et al. Nutritional supplementation to prevent tuberculosis incidence in household-contacts of patients with pulmonary tuberculosis: Results from the RATIONS, a field-based open-label cluster randomised controlled trial in Jharkhand, India. *Lancet* 2023; **402:** 627–40.

157 Hatherill M, Cobelens F. Infant BCG vaccination is beneficial, but not sufficient. *Lancet Glob Health* 2022; **10:** e1220–21.

158 Wingfield T, Tovar MA, Huff D, et al. A randomized controlled study of socioeconomic support to enhance tuberculosis prevention and treatment, Peru. *Bull World Health Organ* 2017; **95:** 270–80.

159 Allwood B, van der Zalm M, Amaral A, et al. Post-tuberculosis lung health: perspectives from the First International Symposium. *Int J Tuberc Lung Dis* 2020; **24:** 820–28.

160 Nightingale R, Carlin F, Meghji J, et al. Post-tuberculosis health and wellbeing. *Int J Tuberc Lung Dis* 2023; **27:** 248–83.

161 Allwood B, Byrne A, Meghji J, Rachow A, van der Zalm M, Schoch O. Post-tuberculosis lung disease: clinical review of an under-recognised global challenge. *Respiration* 2021; **100:** 751–63.

162 Dodd PJ, Yuen CM, Jayasooriya SM, van der Zalm MM, Seddon JA. Quantifying the global number of tuberculosis survivors: a modelling study. *Lancet Infect Dis* 2021; **21:** 984–92.

163 Menzies N, Quaife M, Allwood B, et al. Lifetime burden of disease due to incident tuberculosis: a global reappraisal including post-tuberculosis sequelae. *Lancet Glob Health* 2021; **9:** e1679–87.

164 Romanowski K, Baumann B, Basham CA, Ahmad Khan F, Fox GJ, Johnston JC. Long-term all-cause mortality in people treated for tuberculosis: a systematic review and meta-analysis. *Lancet Infect Dis* 2019; **19:** 1129–37.

165 Taylor J, Bastos M, Lachapelle-Chisholm S, Mayo N, Johnston J, Menzies D. Residual respiratory disability after successful treatment of pulmonary tuberculosis: a systematic review and meta-analysis. *EClinicalMedicine* 2023; **59:** 101979.

166 Igbokwe V, Ruby L, Sultanli A, Bélard S. Post-tuberculosis sequelae in children and adolescents: a systematic review. *Lancet Infect Dis* 2023; **23:** e138–50.

167 Martinez L, Gray D, Botha M, et al. The long-term impact of early-life tuberculosis disease on child health: a prospective birth cohort study. *Am J Respir Crit Care Med* 2023; **207:** 1080–88.

168 Byrne A, Marais B, Mitnick C, Lecca L, Marks G. Tuberculosis and chronic respiratory disease: a systematic review. *Int J Infect Dis* 2015; **32:** 138–46.

169 Stadelman A, Ellis J, Samuels T, et al. Treatment outcomes in adult tuberculous meningitis: a systematic review and meta-analysis. *Open Forum Infect Dis* 2020; **7:** ofaa257.

170 Garg R, Somvanshi D. Spinal tuberculosis: a review. *J Spinal Cord Med* 2011; **34:** 440–54.

171 Meghji J, Gregorius S, Madan J, et al. The long-term effect of pulmonary tuberculosis on income and employment in a low income, urban setting. *Thorax* 2021; **76:** 387–95.

172 Alene K, Wangdi K, Colquhoun S, et al. Tuberculosis related disability: a systematic review and meta-analysis. *BMC Med* 2021; **19:** 203.

173 Hilleboe HE, Kiefer NC. Rehabilitation and aftercare in tuberculosis. *Public Health Rep* 1946; **61:** 285–94.

174 Spruit M, Singh S, Garvey C, et al. An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation. *Am J Respir Crit Care Med* 2013; **188:** e13–64.

175 Nathavitharana R, Garcia-Basteiro A, Ruhwald M, Cobelens F, Theron G. Reimagining the status quo: how close are we to rapid sputum-free tuberculosis diagnostics for all? *EBioMedicine* 2022; **78:** 103939.

176 Pahar M, Klopper M, Reeve B, Warren R, Theron G, Niesler T. Automatic cough classification for tuberculosis screening in a real-world environment. *Physiol Meas* 2021; **42:** 105014.

177 Pankhurst LJ, Del Ojo Elias C, Votintseva A, et al. Rapid, comprehensive, and affordable mycobacterial diagnosis with whole-genome sequencing: a prospective study. *Lancet Respir Med* 2016; **4:** 49–58.

178 Meehan C, Goig G, Kohl T, et al. Whole genome sequencing of Mycobacterium tuberculosis: current standards and open issues. *Nat Rev Microbiol* 2019; **17:** 533–45.

179 Bonnet I, Enouf V, Morel F, et al. A comprehensive evaluation of GeneLEAD VIII DNA platform combined to Deeplex Myc-tuberculosis(®) assay to detect in 8 days drug resistance to 13 antituberculous drugs and transmission of mycobacterium tuberculosis complex directly from clinical samples. *Front Cell Infect Microbiol* 2021; **11:** 707244.

180 McKenna L. TAG's 2023 pipeline report: tuberculosis treatment. Treatment Action Group. 2023. https://www.treatmentactiongroup.org/resources/pipeline-report/2023-pipeline-report/ (accessed Feb 13, 2025).

181 Tozer L. Promising tuberculosis vaccine gets US$550-million shot in the arm. Nature News, June 29, 2023. https://www.nature.com/articles/d41586-023-02171-x

182 Tait DR, Hatherill M, Van Der Meeren O, et al. Final analysis of a trial of M72/AS01$_E$ vaccine to prevent tuberculosis. *N Engl J Med* 2019; **381:** 2429–39.

183 Nemes E, Geldenhuys H, Rozot V, et al. Prevention of M. tuberculosis infection with H4:IC31 vaccine or BCG revaccination. *N Engl J Med* 2018; **379:** 138–49.

184 Satti I, Meyer J, Harris S, et al. Safety and immunogenicity of a candidate tuberculosis vaccine MVA85A delivered by aerosol in BCG-vaccinated healthy adults: a phase 1, double-blind, randomised controlled trial. *Lancet Infect Dis* 2014; **14:** 939–46.

185 McShane H. Insights and challenges in tuberculosis vaccine development. *Lancet Respir Med* 2019; **7:** 810–19.

186 Furin J, Cox H, Pai M. Tuberculosis. *Lancet* 2019; **393:** 1642–56.

187 Campbell JR, Pease C, Daley P, Pai M, Menzies D. Chapter 4: diagnosis of tuberculosis infection. *Can J Resp Crit Care Sleep Med* 2022 **6** (supp1): 49–65.