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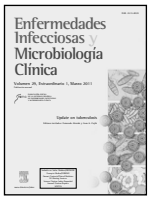

Tuberculosis in special populations

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ABSTRACT

The susceptibility to infection, the pathogenesis and the clinical manifestations of tuberculosis (TB) depend on the immunological status of the host. Immunological status is largely determined by age and comorbidities, but is also affected by other less well known factors. In Spain, most incidental cases of TB arise from the reactivation of remotely acquired latent infections and are favored by the aging of the population and the use of aggressive immunosuppressive therapies. The diagnosis and management of TB in these circumstances is often challenging. On the one hand, the atypical presentation with extrapulmonary involvement may delay diagnosis, and on the other, the toxicity and interactions of the antituberculous drugs frequently make treatment difficult. Immigration from resource-poor, high incidence TB countries, where the social and economic conditions are often suboptimal, adds a new challenge to the control of the disease in Spain. This chapter summarizes our current knowledge of epidemiological, clinical and treatment aspects of TB in particularly susceptible populations.

Palabras clave:
Tuberculosis
Inmunosupresión
Comorbilidad
Inmigración

Tuberculosis en poblaciones especiales

RESUMEN

La susceptibilidad a la infección, patogenia y manifestaciones clínicas de la tuberculosis (TB) dependen de la situación inmunológica del hospedador, lo cual, a su vez, está determinado en gran medida por la edad y las comorbilidades, pero también por otros factores no bien conocidos. La mayor parte de casos nuevos de TB en España tiene su origen en la reactivación de una infección remota latente, y es favorecida por el envejecimiento y las terapias inmunosupresoras agresivas. A menudo, el diagnóstico y tratamiento de la TB en este contexto representan un reto. Las presentaciones atípicas, con afectación extrapulmonar, pueden retrasar el diagnóstico, pero además la toxicidad y las interacciones de los fármacos antituberculosos, a menudo, dificultan el tratamiento. La inmigración de países en vías de desarrollo y alta incidencia de TB, frecuentemente con condiciones sociales y económicas desfavorables, añade un nuevo reto al control de la enfermedad en España. En este capítulo se resume el conocimiento actual acerca de los aspectos epidemiológicos, clínicos y terapéuticos de la TB en poblaciones especialmente susceptibles.

Introduction

The pathogenesis of tuberculosis is closely related to immunity. The host's immune response plays a key role in the proliferation and spread of the tubercle bacilli, and in the tissue damage that is responsible for the clinical manifestations of the disease. Therefore, both the susceptibility of progression to tuberculosis after infection and the degree of dissemination of the primary infection are directly determined by the age and comorbidity of the patient affected[1] (Table 1).

In developed countries, immigrants and refugees born in countries with a high endemicity of tuberculosis make up a significant proportion of incident cases of the disease. As a result, the implementation of adequate policies for rapid detection of active cases and prophylaxis for high risk immigrants is essential in tuberculosis prevention and control.

Tuberculosis in immunosuppressed people

Tuberculosis and human immunodeficiency virus infection

The convergence of the human immunodeficiency virus (HIV) epidemic and tuberculosis has had a considerable impact on morbidity and mortality worldwide. In some areas of sub-Saharan

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Table 1
Risk for developing active tuberculosis relative to a control population[1]

Condition	Relative risk
Silicosis	30
Diabetes mellitus	2-4
Chronic renal failure-hemodialysis	10-25
Jejunoileal by-pass	27-63
Renal transplantation	37
Heart transplantation	20-74
Head and neck cancer	16
HIV infection	20-100

HIV: human immunodeficiency virus.

Africa, annual notification rates of tuberculosis are above 400 cases per 100,000 population, and more than two-thirds of patients are co-infected with HIV.[2]

HIV infection produces cellular immunodeficiency by depleting $CD4^+$ lymphocyte cells and impairing macrophage function, which increases the risk of infection with *M. tuberculosis*, progression to active disease, and reactivation of latent infection (LTBI). The occurrence of multidrug-resistant epidemics among HIV groups reflects the extreme vulnerability of these patients to tuberculosis infection and disease.[3,4] The clinical presentation of tuberculosis in HIV-infected patients varies with the immunological status of the host. Patients with early HIV infection frequently present a "classic" pattern of pulmonary tuberculosis. Conversely, in patients with low CD4 cell counts, extrapulmonary involvement and disseminated disease are frequent even though chest radiographs may be normal.[5,6]

HIV-related tuberculosis should be treated with a regimen including rifamycin for the full course of therapy. If a rifamycin cannot be given, treatment should be extended to 18-24 months. The rifamycins induce the cytochrome P450-3A (CYP3A) system, increasing the metabolism of most antiretroviral drugs. Rifabutin is a less potent inhibitor than rifampin and may be a reasonable alternative.[7] Table 2 shows the interactions between rifamycins and antiretrovirals and recommended dose adjustments. Although increased rates of recurrence have been reported with the standard regimen of six months in HIV-infected patients, there is insufficient evidence to recommend more prolonged therapy in this setting.[8,9] Regardless of HIV status, patients with cavitation and positive cultures after the first two months of therapy should be treated for nine months.[9] Intermittent treatment with rifampin twice a week or rifapentine weekly is not recommended in HIV patients because of the development of resistance to rifampin, especially in patients with CD4 cell counts less than 100 cells/mm^3.[10,11]

The ideal time to start antiretroviral therapy in HIV-infected patients with tuberculosis when both are diagnosed simultaneously has not been definitively established. Deferring antiretroviral therapy until treatment of tuberculosis has been completed avoids potential drug interactions, overlapping drug toxicities, and paradoxical reactions. However, this strategy is not safe in patients with low CD4 cell counts, in whom delaying treatment may increase mortality due to opportunistic infections and AIDS progression.[12,13] The current ATS/CDC/IDSA guidelines suggest an individualized decision on timing of antiretroviral therapy in patients with CD4 counts below 350 cells/mm^3 and advise delaying antiretroviral therapy for 4–8 weeks if possible.[9]

The paradoxical worsening of symptoms known as the "immune reconstitution inflammatory syndrome" (IRIS) is a frequent complication when antiretroviral therapy is started in patients being treated for active tuberculosis.[14] Immune reconstitution symptoms typically appear in the first days or weeks of treatment and frequently affect patients with low CD4 cell counts.[15] A short course of steroids may be of benefit in these cases. IRIS may also explain the development of tuberculosis in patients with subclinical or latent infection and low CD4 cell counts presenting with clinical symptoms of the disease shortly after initiating antiretroviral therapy.[16]

Table 2
Interactions between rifampin-rifabutin and antiretroviral drugs

Antiretroviral	Rifampin (RIF)	Rifabutin (RFB)
Protease inhibitors (PI)		
Atazanavir		RFB AUC ↑ 2-3 fold
Ritonavir-atazanavir	PI concentrations markedly decreased (>75%): co-administration contraindicated	Decrease RFB to 150 mg/48 h or 3 times a week
Ritonavir-lopinavir		No change in PI dose
Ritonavir-saquinavir		
Ritonavir-fosamprenavir		
Ritonavir-darunavir		
Non-nucleoside reverse transcriptase inhibitors (NNRTI)		
Nevirapine (NVP)	NVP AUC ↓ 37%; NVP dose unchanged; RIF dose unchanged[a]	NVP C_{min} ↓ 16%; RFB AUC ↑ 17%; NVP dose unchanged; RFB unchanged[b]
Efavirenz (EFV)	EFV AUC ↓ 26%; EFV dose unchanged; consider 800 mg/d; RIF dose unchanged	RFB ↓ 38%; EFV dose unchanged; RFB 450-600 mg/d if EFV is not coadministered with a PI
Etravirine (ETR)	ETR concentration markedly decreased: do not coadminister	ETR AUC ↓ 37%; RFB ↓ 17%; no dose adjustment unless PI co-administration
Entry inhibitors		
Enfuvirtide (T20)	No significant interaction: dose unchanged	No significant interaction: dose unchanged
Maraviroc (MVC)	MVC ↓ 78%: Increase MRV dose 600 mg/12 h; RIF dose unchanged	No clinical experience; a significant interaction is unlikely
Integrasa inhibitors		
Raltegravir (RAL)	RAL AUC ↓ 40% and C_{min} ↓ 61% with RAL 400 mg Rifampin with RAL 800 mg BID compared with RAL 400 mg BID alone: RAL AUC ↑ 27% and C_{min} ↓ 53%	Dose: RAL 800 mg BID

[a]Recent issued guidelines recommend do not coadminister. If coadministration is needed, use 600 mg BID. Available at: http://aidsinfo.nih.gov
[b]Standard rifabutin dose: 300 mg/day or 300 mg/48 h.

HIV-infected people should be screened for LTBI with the TST. Reactors to TST must be thoroughly evaluated, and once active disease has been ruled out preventive chemotherapy must be offered. Although early studies suggested that HIV-seropositive patients with cutaneous anergy had a risk of tuberculosis similar to that of patients with positive TST, nowadays the evidence argues against treating anergic HIV-infected patients.[17] The role of interferon–gamma release assays (IGRA) either in addition to TST or instead of it is still controversial.[18] Daily isoniazid for 9 months remains the treatment of choice for LTBI in HIV-infected patients. Multidrug short-course regimens (rifampin plus pyrazinamide for 2 months, and rifampin plus isoniazid for 3 months) have proved as effective as standard isoniazid treatment in HIV-infected patients.[1,19,20] However, the combination of rifampin and pyrazinamide is no longer recommended due to the unacceptable rate of severe liver toxicity.[21] Rifampin or rifabutin for four months are also good alternatives.

Tuberculosis in transplant recipients

The incidence of tuberculosis in either solid organ or hematopoietic progenitor cell recipients is closely related to the background of tuberculosis infection in the area considered, and it is estimated to be 30 to 100-fold higher than in the general population.[22] A prospective cohort study[23] in Spain found an incidence was 0.48% and an estimated relative risk in relation to the general population of 26.6.

Most cases of tuberculosis in transplant recipients arise from a reactivation of remote infection. Rarely, tuberculosis is transmitted by the transplanted graft. Most cases of tuberculosis develop in the first year after transplantation. Late infections may be related to the treatment of chronic rejection or graft versus host disease in allogenic bone marrow recipients.[23,24]

Treatment of tuberculosis in transplant recipients may be complicated by the potential of drug interactions and toxicity. Rifampin interacts with most immunosuppressive drugs, potentially leading to graft rejection. The experience in renal transplants has been favorable provided that levels of immunosuppressive drugs are carefully monitored.[25] There is no consensus on other solid organ or hematopoietic progenitor cell transplants. Experience with rifabutin, a weaker *cytochrome* P-450 inducer, is scarce. Regimens not containing a rifamycin must be prolonged up to 18-24 months. The Spanish network for transplant related infections (RESITRA) recommends the use of a rifamycin-based regimen in solid organ transplants which develop a severe or disseminated form of tuberculosis or if isoniazid resistance is suspected.[26]

Pre-transplant evaluation of candidates for transplantation should include screening for tuberculosis, and treatment of patients with positive TST and those with evidence of inappropriately treated or untreated past tuberculosis. Treatment of latent infection in candidates for liver transplantation is challenging as the risk of severe liver toxicity is very high in patients with end stage liver disease. Some authors recommend postponing chemoprophylaxis until after transplantation.[26]

Tuberculosis in anti-TNF treated patients

Anti-tumor necrosis factor (TNF) drugs are used in a growing number of immune-mediated inflammatory diseases (IMID). The main drawback of suppressing TNF activity is the blockage of the immune response to infection. Not surprisingly, several opportunistic infections have been reported in association with the use of these agents, such as systemic mycosis and mycobacterial infections.[27] The first descriptions of tuberculosis associated with anti-TNF agents were in patients treated with infliximab, and showed that more than half had extrapulmonary and disseminated infections.[28] Later series found similar features of tuberculosis in other anti-TNF treated patients.[29] After recommendations of screening and chemoprophylaxis for candidates to anti-TNF treatment were issued, the incidence of tuberculosis fell notably.[30] Candidates for anti-TNF therapy and diagnosed with LTBI should receive either isoniazid for nine months or rifampin for four months.[31] There is also some experience with IGRA in patients with IMID for the screening of tuberculosis infection before anti-TNF therapy. The currently available data suggest that these tests perform better than TST in individuals receiving immunosuppressive treatment, but false-negative and indeterminate results also occur.[32,33]

Tuberculosis in the pediatric patients

The burden of childhood tuberculosis has been somewhat neglected in the past. However, of the estimated 8.3 million new tuberculosis cases diagnosed in 2000, 884,019 (11%) were children.[34]

Most cases of pediatric tuberculosis are acquired through inhalation of bacilli from a person with active tuberculosis. Rarely, transplacental infection may occur after acute primary or miliary tuberculosis during pregnancy. Neonatal infection may very occasionally be acquired by fetal aspiration or ingestion of infected amniotic fluid. The risk of developing active tuberculosis in children varies with age: infants in the first year of life have the highest risk (40-50%), and also the most severe forms (10 to 20% miliary tuberculosis or meningitis). The risk of progression is still high in children infected up to the fifth year of life, and then falls between 5 and 10 years of age.

Primary lung disease may be asymptomatic and may resolve spontaneously. The classic form of primary lung disease is a parenchymal infiltrate with hilar lymphadenopathy. Progression of primary tuberculosis leads to lung consolidation, lymph node enlargement with bronchial obstruction, and pleural disease.[35] Common symptoms of pulmonary tuberculosis in children include chronic cough, prolonged fever and weight loss or failure to thrive.[36] Complications related to massive lymph node enlargement are more frequent in children under five years of age. Lung cavitation is rare in the under-tens. Peripheral lymphatic tuberculosis and meningitis are the most common forms of extrapulmonary disease. Microbiologic confirmation of tuberculosis in children is hampered by the difficulty of obtaining appropriate respiratory secretions.[35] Sputum smears are positive in less than 20% of cases, and culture confirmation is achieved in less than half of these. The yield of 3 consecutive early morning gastric aspirates is higher than bronchoalveolar lavage in the diagnosis of pulmonary pediatric tuberculosis.[37] Nasopharyngeal aspiration and induced sputum with hypertonic saline aerosol are good alternatives.[38]

A six-month regimen of isoniazid and rifampin with pyrazinamide during the initial phase is effective in most forms of pulmonary or extrapulmonary disease. In meningeal and disseminated tuberculosis, as well as in HIV-infected children, treatment should be extended to 9-12 months.[9] Ethambutol is contraindicated in children less than 13 years, in whom ophthalmological monitoring may not be sufficient to exclude optical neuropathy. However, in the experience reported with 15-20 mg/kg daily doses in young children, optical toxicity is exceptional.[39]

Children are high priority targets of preventive chemotherapy after contact with active tuberculosis. Household exposure must be treated as infection from the first moment onwards, as tuberculin response may be delayed for up to 3 months. Treatment may be stopped if the second TST remains negative. In immunosuppressed children TST is not sensitive enough to rule out infection, and therefore chemotherapy must be completed for the whole nine-month course despite the lack of conversion. Isoniazid is well tolerated, and severe liver toxicity is extremely rare. As in adults, rifampin is the alternative of choice in intolerant children or after contact with isoniazid resistant strains.[40]

Tuberculosis in pregnancy and breastfeeding

The stress and the physiological changes experienced in pregnancy create a state of cellular immunodeficiency that may facilitate the development of tuberculosis.[41] In the early 20th century, after a publication that reported a less favorable course of tuberculosis in pregnant than in non-pregnant women, therapeutic interruption of the pregnancy was recommended. Nowadays, it is clear that if anti-tuberculosis treatment is started early, the outcome is the same as in non-pregnant women.[42,43]

Diagnosis may be delayed because certain manifestations of pregnancy, such as asthenia, tachycardia and anemia, and manifestations of tuberculosis may confuse clinicians. Diagnosis of tuberculosis infection relies on TST, which is valid in pregnancy and is safe for the woman and fetus. New diagnostic blood tests (IGRA) can be used, but they have not been evaluated in pregnant women. Chest x-ray can be performed safely by shielding the abdomen, as fetal exposure is below 0.3 mrads.[44]

Treatment for active tuberculosis in pregnant women should be started promptly since its delay has been associated with hazard for mother and fetus. The preferred regimen includes rifampin, isoniazid and ethambutol for two months, followed by rifampin and isoniazid for seven additional months. Pirazynamide is not recommended because its effect on the fetus is unknown.[9] However, no theratogenic effects have been reported; the WHO recommends it, and in fact its use is widespread in many countries. Streptomycin should not be used because of its interference with the aural development of the fetus. Due to the potential harmful effects on the fetus and the unknown risks of second-line drugs, terminating pregnancy or suspending treatment during pregnancy is frequently advised in pregnant women who require treatment with these drugs.[42] A recent retrospective study of pregnant women treated with second-line drugs for multidrug-resistant tuberculosis (MDR-TB) showed similar birth outcomes to those of healthy women and no congenital defects in newborns.[45] This experience indicates that the benefits of treating MDR-TB probably outweigh the risk for mother and fetus. Therefore, after receiving counselling concerning the potential risks, women should have the option to continue treatment without termination of pregnancy.[45]

Breastfeeding is not contraindicated in women treated with first-line antituberculous drugs. Isoniazid, rifampin, ethambutol, and pyrazinamide are considered safe for breastfeeding because the levels of these drugs achieved in breast milk are too low to produce toxicity in the baby.[46,47] Fluoroquinolones are not recommended during breastfeeding.[9]

Tuberculosis in the frail population

Tuberculosis in the elderly

Incidence of tuberculosis is higher in the elderly, due to the increased prevalence of the infection and the higher rates of reactivation as a result of impairment of T-cell mediated immune response with aging. Other age-associated factors, such as malignancy and chronic diseases, also contribute to the greater risk of reactivation of latent infection.[48] In addition, nursing home residents have a two to four-fold higher incidence of tuberculosis, due not only to reactivation but also to an increased transmission in this clustering environment.[49,50]

Around 75% of elderly persons with tuberculosis present pulmonary involvement, and the clinical features are similar to those found in younger persons.[51] However, tuberculosis may present atypically: unexplained low-grade fever, fatigue, reduction in daily living activities, anemia and liver function test abnormalities being the predominant manifestations.[52] Respiratory sample collection may be limited by the difficulty of obtaining sputum from old people. In addition, the sensitivity of TST wanes with aging. Radiographic findings do not differ significantly from those in younger people, except for the lower proportion of cavitation.[52]

Current standard treatment for tuberculosis is also recommended for older people. While also applicable to young patients, two main issues are of particular relevance in the elderly: the greater risk of drug toxicities, and the risk of interactions with other drugs, since these patients are more likely to be taking other medications.[53,54] Particularly, an increased risk of hepatic toxicity from isoniazid with aging has been found.[48,55] Preventive treatment may also be indicated in elderly people.[1] Prevention of tuberculosis in long-term care facilities requires each unit to apply an appropriate prevention and control program in order to protect residents and staff.[56]

Tuberculosis and end-stage renal disease

Patients with end-stage renal disease (ESRD) undergoing hemodialysis are at increased risk of developing tuberculosis.[57] Diagnosis may be challenging due to false-negative TST results, more frequent extrapulmonary involvement and on occasion the non-specificity of symptoms, which may be attributable to uremia or other infections.

Since some antituberculous medications are cleared by the kidney, drug-dosing adjustment is required, which complicates treatment of tuberculosis in these patients.[9] Furthermore, some antituberculosis drugs are removed by haemodialysis.[58] Rifampin and isoniazid are metabolized by the liver, so dosing adjustment is not necessary in ESRD.[9] Pyrazinamide, which is metabolized by the liver but whose metabolites are cleared by the kidneys, and ethambutol which is 80% cleared by the kidneys, may accumulate in case of renal insufficiency and require adjustment.[9] Although isoniazid, pyrazinamide and ethambutol are removed by haemodialysis, only in the case of pyrazinamide is the dialysis significant. So, if pyrazinamide is given after dialysis, a supplementary dose is not necessary. Rifampin is not dialyzable and does not require dosing-adjustment.[9] Renal clearance of fluoroquinolones varies from drug to drug. Of the two most commonly used for tuberculosis treatment, levofloxacin is mainly cleared by kidneys; moxifloxacin undergoes hepatic metabolism, and the urinary excretion of the unchanged drug only accounts for 19-22% of the given dose.[59] Antituberculosis aminoglycosides (streptomycin, kanamycin and amikacin) and capreomycin are excreted by kidneys, and require dosing-adjustment in patients with renal insufficiency.[9] Table 3 shows the dosing adjustment for the commonest antituberculosis agents in patients with renal function impairment.

Tuberculosis and liver disease

Treatment of tuberculosis in patients with chronic liver disease is complicated by the increased hepatotoxicity of antituberculosis drugs, the potentially harmful consequences of toxicity in patients with marginal liver function reserve and, finally, the difficulty of monitoring drug-related alterations in liver tests.[9] In addition, the high incidence of alcohol use may lead to poor compliance and treatment failure. The first line antituberculosis agents rifampin, isoniazid and pyrazinamide may produce hepatotoxicity, but they should be used whenever possible. Careful assessment of hepatic disease and expert consultation is advisable in treating these patients with drugs or regimens other than the standard ones.[9]

Tuberculosis and immigration

The increase in immigration during the last decade has slowed the steady fall in the incidence of tuberculosis in Spain. The proportion of foreign-born subjects among tuberculosis patients has increased consistently since the late 1990s, reaching figures as high as 67% in some areas.[60,61]

Table 3
Recommended dosing adjustment of antituberculosis agents in adult patients with impaired renal function (creatinine clearance <30 ml/min) or receiving hemodialysis[a]

Drug	Dosing adjustment
Rifampin	Not required
Isoniazid	Not required
Pyrazinamide	25-35 mg/Kg 3 times per week
Ethambutol	15-25 mg/Kg 3 times per week
Streptomycin	12-15 mg/Kg two or 3 times per week[b]
Kanamycin	12-15 mg/Kg two or 3 times per week[b]
Amikacin	12-15 mg/Kg two or 3 times per week[b]
Capreomycin	12-15 mg/Kg two or 3 times per week[b]
Levofloxacin	750 mg 3 times a week
Moxifloxacin	Not required
Ethionamide	Not required
p-Aminosalicylic acid	Not required
Cycloserine	500 mg 3 times per week
Linezolid	Not required[c]

[a]Treatment should be taken after the dialysis session.
[b]Dose and interval according to the American Thoracic Society Guidelines.
[c]Recommended dose: 600 mg per dose once daily. Two primary metabolites may accumulate in patients with renal insufficiency, whose clinical significance is largely unknown.

It has commonly been assumed that tuberculosis in immigrants results from the reactivation of latent infection acquired in their country of origin.[62-64] However, data from two molecular epidemiology studies in Spain, in which 29% and 33% respectively of isolates from immigrant patients were clustered, suggest that recent transmission also plays a significant role in the development of tuberculosis in immigrants in our country.[60,65] Most cases of tuberculosis in immigrants occur within two or 3 years of arrival.[66,67] However, the risk not only persists beyond this point but its incidence remains higher than in the native-born population for more than five years.[68,69] Clinical and radiographic characteristics do not differ substantially from those of Spanish-born patients, except for a younger age at diagnosis.[67,70] Some authors reported a higher proportion of extrapulmonary involvement than in native-born patients.[70]

Most immigrants to Spain come from Latin American and African countries with higher rates of resistant tuberculosis.[71] Although the resistance of *M. tuberculosis* in Spain has not increased substantially in recent years, rates of resistance in immigrants are higher than in Spanish-born people.[3,66,70,72,73] In a study conducted in Madrid the rate of resistance to any first-line antituberculous drug was 33% in immigrants who had no prior treatment, compared with 10.7% among all patients with tuberculosis.[72]

Treatment for tuberculosis in immigrants should not differ from that of native-born patients, and all isolates should be tested for susceptibility to first-line antituberculous drugs. Early diagnosis and treatment are the two best preventive and control measures. Diagnosis of tuberculosis should be coupled with detection and treatment of secondarily infected people. Treatment of active disease and infection in the immigrant population presents significant challenges to tuberculosis control measures: several studies have found lower rates of treatment completion, including preventive treatment, among immigrants than in native-born people.[74,75]

How to screen people from areas with high tuberculosis rates who migrate to developed countries is a matter of debate. Strategies including chest radiograph screening and TST to detect cases of active tuberculosis have little (if any) public health impact and are not cost-effective.[76] On the other hand, detection of LTBI using the TST, and universal treatment of those with positive results is limited by the low positive predictive value of the test, low rates of treatment completion, and toxicity. Nowadays, early diagnosis and treatment of active tuberculosis cases and detection of subjects with latent infection at risk of progression seems to be the most reasonable strategy for tuberculosis control.

Conflict of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties. No writing assistance was utilized in the production of this manuscript.

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