

REVIEW ARTICLE

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THE NATURAL HISTORY OF TUBERCULOSIS BEGINS WITH THE INHALATION of *Mycobacterium tuberculosis* organisms; a period of bacterial replication and dissemination ensues, followed by immunologic containment of viable bacilli. The result of this process is asymptomatic latent tuberculosis infection, which is defined as a state of persistent bacterial viability, immune control, and no evidence of clinically manifested active tuberculosis.¹ Currently, it is not possible to directly diagnose *M. tuberculosis* infection in humans; therefore, latent tuberculosis infection is diagnosed by response to in vivo or in vitro stimulation by *M. tuberculosis* antigens with the use of the tuberculin skin test or interferon- γ release assays (IGRAs). Studies suggest that active tuberculosis will develop in 5 to 15% of persons with latent infection during their lifetimes² (and a higher percentage if the persons are immunocompromised); thus, persons with latent infection serve, according to Osler, as the “seedbeds” of tuberculosis in the community.³ This article will review the pathogenesis, epidemiology, diagnosis, and treatment of latent tuberculosis infection. It will address critical gaps in the understanding of this complex condition and propose the necessary research agenda.

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N Engl J Med 2015;372:2127-35.

DOI: 10.1056/NEJMra1405427

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PATHOGENESIS

After inhalation of *M. tuberculosis*, innate immune responses involving alveolar macrophages and granulocytes begin to combat the infection; in some persons, the bacilli are cleared, whereas in others, infection is established.⁴ Replication of bacilli in macrophages and regional lymph nodes leads to both lymphatic and hematogenous dissemination, with seeding of multiple organs, which may eventually give rise to extrapulmonary disease. Containment of bacilli within macrophages and extracellularly within granulomas limits further replication and controls tissue destruction, resulting in a dynamic balance between pathogen and host. The classic interpretation of this as a binary process with either truly latent *M. tuberculosis* infection or active tuberculosis disease has recently been challenged as an oversimplification. Instead, a spectrum of immunologic responses that are both protective and pathogenic and correlate with a range of bacterial activation has been suggested.⁴ This continuum encompasses a variety of host-microbe interactions, which are characterized by clinical latency when host responses predominate and by disease when bacterial replication exceeds the threshold required to cause symptoms.⁵ Recent evidence suggests that host inflammatory responses, particularly with interleukin-1 β , may actually enhance mycobacterial replication, which illustrates that the double-edged sword of immune responses seen in tuberculosis disease may also be present in latent infection.⁶ In addition, persisting extra-

cellular bacilli may remain active in a biofilm-type of environment and thus evade host defenses; in such cases, the term persistent (rather than latent) infection has been suggested to explain the complexity of the phenomenon.⁷

Animal models such as mice, guinea pigs, rabbits, macaques, and zebrafish have been used to study the pathogenesis and treatment of latent tuberculosis.⁴ A shortcoming of all models, however, is the lack of pathological, clinical, and therapeutic conformity with human infection and disease.⁸ Thus, each model may be used to elucidate some aspects of the human situation — mice, for example, recapitulate human treatment experiences, whereas rabbits display histopathological features that are similar to those in humans — but no model can capture the full spectrum of infection, disease, and treatment.

EPIDEMIOLOGY AND RISK GROUPS

Current tools are insufficient to measure the global prevalence of latent tuberculosis infection, but modeling carried out a decade ago estimated that approximately one third of the world population (>2 billion people) is latently infected with *M. tuberculosis*.⁹ Currently, annual rates of infection range from 4.2% in South Africa¹⁰ and 1.7% in Vietnam¹¹ to 0.03% in the United States.¹² As tuberculosis treatment has expanded in the past 15 years and living conditions have improved worldwide, the annual risk of infection may have declined in many places; the current global burden of latent infection is therefore uncertain and needs to be reassessed.

Persons with untreated tuberculosis of the respiratory tract are the source of transmission in essentially all new cases of tuberculosis infection, and up to one third of their household contacts become infected.² Factors associated with an increased risk of infection in a household contact include severe disease in the index patient, long periods of exposure to the index patient, and poor ventilation and poor exposure to ultraviolet light during proximity to the index patient. Reactivation of latent tuberculosis infection accounts for the majority of new tuberculosis cases, especially in countries in which the incidence of tuberculosis is low.¹³

The likelihood of progression of latent infection to active clinical tuberculosis disease is determined

by bacterial, host, and environmental factors. It has been postulated that there are differences in the ability of various strains of *M. tuberculosis* to cause disease, but little clinical or epidemiologic data support this theory. The initial bacterial load, inferred by the severity of disease in an index case and the closeness of the contact, is directly associated with the risk of development of the disease. Disease develops at a higher rate among infants and very young children who have latent infection than among older children with latent infection; after a child reaches approximately 5 years of age, age appears to have little correlation with the risk of disease.²

Suppression of cellular immunity by human immunodeficiency virus (HIV) infection,¹⁴ tumor necrosis factor α inhibitors,¹⁵ glucocorticoids,¹⁶ and organ¹⁷ or hematologic¹⁸ transplantation increases the risk of progression of latent infection substantially. End-stage renal disease confers an increased likelihood of progression to active tuberculosis.¹⁹ Silicosis and exposure to silica dust are also associated with increased rates of progression, and the combination of HIV and silicosis in South African miners has contributed to an explosive epidemic of tuberculosis in this population.²⁰ Other risk groups that should be considered for management of latent tuberculosis infection on the basis of a high prevalence or an increased risk of active tuberculosis disease include prisoners,²¹ illicit-drug users,²² homeless adults,²³ recent immigrants from countries that have a high tuberculosis burden,²⁴ the elderly,²⁵ health care workers and medical students,²⁶ patients with diabetes,²⁷ and persons with recent conversion of a negative tuberculin skin test to a positive test.²⁶ Table 1 presents the range of published data on the risk of active tuberculosis and the prevalence of latent infection in selected high-risk groups.

DIAGNOSIS

There are no perfect methods for the diagnosis of latent tuberculosis infection. The tuberculin skin test and the IGRAs indirectly measure tuberculosis infection by detecting memory T-cell response, which reveals only the presence of host sensitization to *M. tuberculosis* antigens.⁸ The tests are generally considered to be acceptable but imperfect.²⁸

The tuberculin skin test is widely used and inexpensive, but it has poor specificity in popu-

Table 1. Incidence of Active Tuberculosis and Prevalence of Latent Tuberculosis Infection in Selected High-Risk Groups, According to Published Studies.*

High-Risk Group	Incidence of Active Tuberculosis <i>median rate per 1000 population (range)</i>	Prevalence of Latent Tuberculosis Infection†		
		QuantiFERON-TB Gold In-Tube	T-SPOT.TB	Tuberculin Skin Test
		<i>median percentage (range)</i>		
Persons with HIV infection	16.2 (12.4–28.0)	14.5 (2.7–21.5)	11.3 (4.3–67.6)	19.2 (2.1–54.8)
Adult contacts of persons with tuberculosis	0.6‡	21.1 (6.6–55.1)	48.0 (29.6–59.6)	26.3 (1.8–82.7)
Patients receiving tumor necrosis factor blockers	1.4‡§	11.8 (4.0–22.3)	20.0 (12.9–25.0)	18.6 (11.3–68.2)
Patients undergoing hemodialysis	26.6 (1.3–52.0)	33.4 (17.4–44.2)	43.6 (23.3–58.2)	21.9 (2.6–42.1)
Patients undergoing organ transplantation	5.1‡	21.9 (16.4–23.5)	29.5 (20.5–38.5)	7.7 (4.4–21.9)
Patients with silicosis	32.1‡	46.6‡	61.0‡	—
Prisoners	2.6 (0.03–9.8)	—	—	45.5 (23.1–87.6)
Health care workers	1.3 (0.4–4.1)	14.1 (0.9–76.7)	5.2 (3.5–28.7)	29.5 (1.4–97.6)
Immigrants from countries with a high tuberculosis burden	3.6 (1.3–41.2)	30.2 (9.8–53.8)	17.0 (9.0–24.9)	39.7 (17.8–55.4)
Homeless persons	2.2 (0.1–4.3)	53.8 (18.6–75.9)	—	45.6 (20.5–79.8)
Illicit-drug users	6.0‡	63.0 (1.4–66.4)	45.8 (34.1–57.5)	85.0 (0.3–86.7)
Elderly persons	—	16.3‡	—	31.7‡

* Data are from studies in countries with a low incidence of tuberculosis (<1 per 1000 population). The search for the incidence of active tuberculosis covered the period from January 1, 2004, to August 30, 2014, and data were restricted to articles published in English. The search for the prevalence of latent tuberculosis covered the period from January 1, 2009, to August 30, 2014, and data were restricted to articles published in English, Spanish, or French. The list of included studies and specific values for each risk group are provided in Tables S1 and S2, respectively, in the Supplementary Appendix. Dashes denote no data.

† The QuantiFERON-TB Gold In-Tube assay (Cellestis) and the T-SPOT.TB assay (Oxford Immunotec) are interferon- γ release assays. In response to the tuberculin skin test, indurations that measured at least 5 mm in diameter were used to compute prevalence.

‡ Data are from a single study.

§ Patients received treatment with infliximab.

lations vaccinated with bacille Calmette–Guérin (BCG), is subject to cross-reactivity with environmental nontuberculosis mycobacteria, and has poor sensitivity in immunocompromised persons.⁸ There are also logistic drawbacks, including the need for a return visit in 2 to 5 days to read the amount of induration, since self-reading is associated with a high error rate.²⁸ Furthermore, there is a worldwide shortage of tuberculin, attributed to market forces.

IGRAs (the QuantiFERON-TB Gold In-Tube assay [Cellestis] and the T-SPOT.TB assay [Oxford Immunotec]) measure in vitro responses of T cells or peripheral-blood mononuclear cells to *M. tuberculosis* antigens that are not found in BCG and most nontuberculous mycobacteria, and thus specificity for *M. tuberculosis* is higher than with the

tuberculin skin test.²⁸ However, recent studies involving serially tested health care workers in the United States have shown that false conversions (from a negative to a false positive result) and reversions (from a positive to a false negative result) are more common with IGRAs than with tuberculin skin tests.²⁶ In addition, IGRAs are more costly and require more work in the laboratory.

The ability of tuberculin skin tests and IGRAs to identify persons at the highest risk of progressing to active tuberculosis (i.e., the positive and negative predictive values) is poor. Neither test can reliably predict future disease among persons with positive tests, and strong positive tests do not suggest a higher risk. In one meta-analysis, the pooled positive predictive value for progression

to active tuberculosis was 2.7% (95% confidence interval [CI], 2.3 to 3.2) for IGRAs and 1.5% (95% CI, 1.2 to 1.7) for the tuberculin skin test.²⁹ A meta-analysis of only longitudinal studies of IGRAs, with a median follow-up of 4 years, showed a moderate association between positive tests and subsequent tuberculosis (pooled, unadjusted incidence ratio, 2.10 [95% CI, 1.42 to 3.08]).³⁰ In a 2-year prospective study in the United Kingdom involving adult contacts of persons with active tuberculosis, a positive IGRA was associated with a significantly higher risk of the development of tuberculosis except among contacts older than 35 years of age.³¹ The comparative performance of the tuberculin skin test and IGRAs varies between high-incidence countries and low-incidence countries, possibly because of the effects of BCG vaccination and reinfection.^{28,30}

Computed tomography might prove to be a promising complementary imaging method to chest radiography in distinguishing latent tuberculosis infection from active disease.³² Although currently no standard immunodiagnostic biomarkers have been identified to measure latent tuberculosis infection, there is a growing landscape of chemokines, tumor necrosis factor, interleukins, growth factors, and soluble receptors under development that could improve diagnostic capacity.³³

TREATMENT

The aim of the treatment of latent tuberculosis infection is the prevention of progression to active clinical disease. Isoniazid administered daily for 6 to 12 months has been the mainstay of treatment, with efficacy ranging from 60 to 90%.^{34,35} Reanalysis and modeling of the U.S. Public Health Service isoniazid trials of the 1950s and 1960s showed that the benefit of isoniazid increases progressively when it is administered for up to 9 or 10 months and stabilizes thereafter.^{2,36} As a consequence, in the absence of controlled, clinical trials comparing isoniazid with placebo, the 9-month isoniazid regimen has been recommended as adequate treatment. However, a meta-analysis of 11 isoniazid trials involving 73,375 HIV-uninfected persons showed that, as compared with placebo, the risk of progression to active tuberculosis at 6 months (relative risk, 0.44; 95% CI, 0.27 to 0.73) is similar to that at 12 months (relative risk, 0.38; 95% CI, 0.28 to 0.50).³⁷

Isoniazid was associated with a reduction in the incidence of tuberculosis among persons with HIV who were receiving antiretroviral therapy, and one study showed the benefit of isoniazid in patients with negative tuberculin skin tests or IGRAs who were also receiving antiretroviral therapy.³⁸ A recent study from Uganda showed a high rate of conversion from a negative tuberculin skin test to a positive tuberculin skin test (30 cases per 100 person-years) among persons with HIV during the first 6 months of antiretroviral therapy.³⁹ In geographic areas known for a high rate of transmission of tuberculosis, the protective effect of isoniazid against tuberculosis among people with HIV wanes over time, and continuous protection is maintained through a lifetime duration of treatment for tuberculosis.⁴⁰ The World Health Organization recommends that HIV-infected persons in countries with high rates of transmission of tuberculosis receive at least 36 months of isoniazid as a proxy for lifelong treatment. In Brazil, a country with low rates of transmission of tuberculosis, isoniazid therapy for 6 months has been shown to have long-term protective benefits in HIV-infected adults.⁴¹

Other effective regimens are daily rifampin for 3 or 4 months, daily isoniazid and rifampin for 3 months, and isoniazid (900 mg) and rifapentine (900 mg) once weekly for 12 weeks.⁴² A regimen of rifampin and pyrazinamide that was initially shown to be effective in people with HIV infection was found to cause severe liver injury in HIV-uninfected people⁴³; thus, it is no longer recommended. In a multicenter, randomized clinical trial, a regimen of daily rifampin for 4 months was associated with fewer serious adverse events and better adherence and was more cost-effective than a 9-month regimen of isoniazid.⁴⁴ Regimens containing rifampin should be considered for persons who are likely to have been exposed to an isoniazid-resistant strain of *M. tuberculosis*.

In one study, the efficacy of a once-weekly, directly observed isoniazid–rifapentine regimen for 3 months was similar to that of a 9-month, self-administered regimen of isoniazid alone and was associated with higher treatment-completion rates (82.1% vs. 69.0%) and less hepatotoxicity (0.4% vs. 2.7%), although permanent discontinuation of the regimen due to side effects was more frequent with the isoniazid–rifapentine regimen (4.9% vs. 3.7%).⁴⁵ Similar results were ob-

served in a study involving 1058 children 2 to 17 years of age; however, hepatotoxic effects attributed to treatment were not observed in either study group.⁴⁶ A follow-up study involving 208 HIV-infected persons showed that the 3-month isoniazid–rifampentine regimen was as effective as the 9-month isoniazid regimen and was associated with a higher treatment-completion rate (89% vs. 64%).⁴⁷ The weekly isoniazid–rifampentine regimen was also evaluated in 1148 South African adults who had HIV infection and a positive tuberculin skin test and were not receiving antiretroviral therapy; the efficacy of that regimen was shown to be similar to a 6-month isoniazid regimen.⁴⁸ Recent studies of interactions between rifampentine, with or without isoniazid, and efavirenz showed that coadministration of efavirenz for the treatment of HIV infection did not result in reduced efavirenz exposure that could jeopardize antiviral activity.⁴⁹ A fixed-dose combination of rifampentine (300 mg) and isoniazid (300 mg) is expected to be marketed soon in tablet form, which will facilitate treatment. The 3-month isoniazid–rifampentine regimen may be a cost-effective alternative to the 9-month isoniazid regimen, particularly if the cost of rifampentine decreases and the treatment is self-administered.⁵⁰ Currently, the 3-month isoniazid–rifampentine regimen is not recommended for children younger than 2 years of age, persons with HIV infection who are receiving antiretroviral therapy, and women who are pregnant.

A few small studies have explored treatment of latent tuberculosis infection in contacts (both children and adults) of persons with multidrug-resistant tuberculosis on the basis of the results of drug-susceptibility testing of the source patient.^{51,52} However, evidence is lacking on the best treatment approach. Rather, strict observation and monitoring for at least 2 years for the development of active tuberculosis disease are the preferred clinical measures.

CLINICAL EVALUATION AND MONITORING

The clinical management of latent tuberculosis infection starts with tuberculin skin testing, IGRAs, or both and careful clinical and radiologic evaluation to rule out active tuberculosis disease. Persons receiving treatment should be educated about the potential toxic effects of the medica-

tions and counseled to stop treatment and seek attention if signs or symptoms such as jaundice, abdominal pain, severe nausea, or fever develop. Hepatotoxicity and clinical hepatitis are serious adverse events associated with drugs that are currently used for the treatment of tuberculosis (Table 2). Unfortunately, there is a paucity of data on the role of baseline tests and the reasonable frequency of visits to monitor adverse events. The role of the tests and the frequency of visits should be defined on the basis of the clinical indications and social profile of the person being treated, as well as the capacity of clinical services. Initial screening with liver-function tests and regular measurement of liver function afterward could facilitate clinical management. Persons with underlying liver disease, those receiving antiretroviral therapy, women who are pregnant or post partum, alcohol abusers, or persons who are receiving long-term treatment with potentially hepatotoxic medications should be given priority for regular liver-enzyme monitoring.

Clinical management of latent tuberculosis infection should also address such concomitant risk factors as illicit-drug use, alcohol abuse, and smoking through opioid-substitution treatment and counseling about alcohol and smoking cessation, respectively. Table 2 summarizes the common drug interactions associated with latent tuberculosis infection treatment that warrant attention.

Acceptance of and adherence to the full course of latent tuberculosis treatment must be encouraged. In a study conducted in the United States and Canada, 17% of persons who were offered treatment for latent infection refused it.⁵³ Treatment completion varies widely (from 19% to 96%), and the reasons for noncompletion need to be fully assessed.⁵⁴ The use of various incentives to promote treatment initiation and adherence, depending on the specific need of the person being treated, should be considered. Peer education, counseling, people-friendly services, and properly trained service providers boost confidence and may improve adherence to treatment.⁵⁵

GUIDELINES AND PROGRAMMATIC APPROACH

The underlying epidemiology of tuberculosis in various risk groups, the availability of resources, and the cost-effectiveness of interventions should

Table 2. Regimens for Latent Tuberculosis Treatment, According to Pooled Efficacy, Risk of Hepatotoxicity, Adverse Events, and Drug Interactions.

Drug Regimen	Dosage	Efficacy vs. Placebo*	Efficacy vs. 6 Mo of Isoniazid*	Hepatotoxicity vs. 6 Mo of Isoniazid*	Adverse Events
<i>odds ratio (95% confidence interval)</i>					
Isoniazid alone for 6 mo or 9 mo	Adults, 5 mg/kg; children, 10 mg/kg (maximum, 300 mg)	6-mo regimen, 0.61 (0.48–0.77); 9-mo regimen, 0.39 (0.19–0.83)	Not applicable for 6-mo regimen, and not available for 9-mo regimen	Not applicable for 6-mo regimen, and not available for 9-mo regimen	Drug-induced liver injury, nausea, vomiting, abdominal pain, rash, peripheral neuropathy, dizziness, drowsiness, and seizure
Rifampin alone for 3 to 4 mo	Adults, 10 mg/kg; children, 10 mg/kg (maximum if <45 kg, 450 mg; maximum if ≥45 kg, 600 mg)	0.48 (0.26–0.87)	0.78 (0.41–1.46)	0.03 (0.00–0.48)	Influenza-like syndrome, rash, drug-induced liver injury, anorexia, nausea, abdominal pain, neutropenia, thrombocytopenia, and renal reactions (e.g., acute tubular necrosis and interstitial nephritis)
Isoniazid plus rifampin for 3 to 4 mo	Adults, 10 mg/kg; children, 10 mg/kg (maximum if <45 kg, 450 mg; maximum if ≥45 kg, 600 mg)	0.52 (0.33–0.84)	0.89 (0.65–1.23)	0.89 (0.52–1.55)	Influenza-like syndrome, rash, drug-induced liver injury, anorexia, nausea, abdominal pain, neutropenia, thrombocytopenia, and renal reactions (e.g., acute tubular necrosis and interstitial nephritis)
Weekly rifapentine plus isoniazid for 3 mo	Adults and children: rifapentine, 15–30 mg/kg (maximum, 900 mg)‡; isoniazid, 15 mg/kg (maximum, 900 mg)	Not available	0.44 (0.18–1.07)§	0.16 (0.10–0.27)§	Hypersensitivity reactions, petechial rash, drug-induced liver injury, anorexia, nausea, abdominal pain, and hypotensive reactions

* Data on efficacy and hepatotoxicity are from Stagg et al.⁴²

† The Food and Drug Administration recommends increasing the daily dose of efavirenz to 800 mg when it is coadministered with rifampin, but clinical outcomes and patient pharmacokinetic data do not support this recommendation.

‡ The following incremental adjustments are required for persons weighing less than 50 kg: 10.0 to 14.0 kg, 300 mg; 14.1 to 25.0 kg, 450 mg; 25.1 to 32.0 kg, 600 mg; and 32.1 to 49.9 kg, 750 mg.

§ The comparison is with 9 months of isoniazid.

guide the programmatic approach to latent tuberculosis infection. For example, in countries that are resource-constrained and have a high prevalence and transmission rate of tuberculosis, priority should be given to risk groups with the highest likelihood of active tuberculosis (e.g., persons with HIV and children younger than 5 years of age who are contacts of persons with active tuberculosis). Clinicians need to consult and follow international and national guidelines. However, recommendations contained in national guidelines from countries with a low incidence of tuberculosis differ in the selection of risk groups and

tests as well as in treatment options (Table S3 in the Supplementary Appendix, available with the full text of this article at NEJM.org).

Simplified, evidence-based clinical algorithms⁵⁶ will be useful, as evidenced by the scaling-up of tuberculosis prophylaxis among persons with HIV.⁵⁷ Recording and reporting tools with indicators must constitute a monitoring system for any large-scale implementation program. It would also be crucial to monitor the development of clinical tuberculosis disease during and after the completion of treatment and evaluate the quality and effectiveness of such a program.

Common Drugs That Could Interact with the Regimen		
Antiretroviral Agents	Opioids and Immunosuppressants	Other
Efavirenz (efavirenz levels may increase in slow metabolizers of both drugs)	None	Carbamazepine, benzodiazepines metabolized by oxidation (e.g., triazolam), acetaminophen, valproate, serotonergic antidepressants, disulfiram, warfarin, and theophylline
Efavirenz [†] ; dolutegravir (dolutegravir dose should be increased to 50 mg every 12 hr); rifampin should not be administered with any protease inhibitor (regardless of ritonavir boosting), rilpivirine, elvitegravir, or maraviroc	Methadone (methadone dosage may need to be increased 50%); cyclosporine; glucocorticoids	Mefloquine, azole antifungal agents, clarithromycin, erythromycin, doxycycline, atovaquone, chloramphenicol, hormone-replacement therapy, warfarin, cyclosporine, glucocorticoids, anticonvulsant drugs, cardiovascular agents (e.g., digoxin), theophylline, sulfonyleurea hypoglycemic agents, hypolipidemic agents, nortriptyline, haloperidol, quetiapine, benzodiazepines, zolpidem, and buspirone
Efavirenz [†] ; dolutegravir (dolutegravir dose should be increased to 50 mg every 12 hr); isoniazid plus rifampin should not be administered with any protease inhibitor (regardless of ritonavir boosting), rilpivirine, elvitegravir, or maraviroc	Methadone (methadone dosage may need to be increased 50%); cyclosporine; glucocorticoids	Mefloquine, azole antifungal agents, clarithromycin, erythromycin, doxycycline, atovaquone, chloramphenicol, hormone-replacement therapy, warfarin, cyclosporine, glucocorticoids, anticonvulsant drugs, cardiovascular agents (e.g., digoxin), theophylline, sulfonyleurea hypoglycemic agents, hypolipidemic agents, nortriptyline, haloperidol, quetiapine, benzodiazepines, zolpidem, and buspirone
Rifapentine plus isoniazid should not be administered with any protease inhibitors, any integrase inhibitors, or maraviroc; early studies show nonsignificant interactions with dolutegravir, emtricitabine, and tenofovir	Methadone (methadone dosage may need to be increased 50%); cyclosporine; glucocorticoids	Mefloquine, azole antifungal agents, clarithromycin, erythromycin, doxycycline, atovaquone, chloramphenicol, hormone-replacement therapy, warfarin, cyclosporine, glucocorticoids, anticonvulsant drugs, cardiovascular agents (e.g., digoxin), theophylline, sulfonyleurea hypoglycemic agents, hypolipidemic agents, nortriptyline, haloperidol, quetiapine, benzodiazepines, zolpidem, and buspirone

RESEARCH PRIORITIES

Better understanding of the pathogenesis of latent tuberculosis infection is a critical research priority, as is the development of biomarkers and diagnostic tests with improved performance and predictive values. Reliable animal models that simulate pathogenesis and treatment response in humans will facilitate the development of biomarkers, new treatments, and potentially therapeutic vaccines. The availability of new drugs and regimens that can be administered for a shorter duration and with fewer adverse events is imperative to allow larger-scale implementation. Trials

should be performed to define the benefits and harms of treatment for latent tuberculosis infection in patients with diabetes, in alcohol abusers and tobacco smokers, and in contacts of persons with multidrug-resistant tuberculosis. Innovative research synergies between public and private funders are required to overcome market shortcomings. The development of better diagnostic tests, preventive therapies, and vaccines for tuberculosis will confer enormous public benefit.

The diagnosis and treatment of latent tuberculosis infection are crucial when tuberculosis control — in particular, elimination — is being pursued. Modeling shows that if 8% of persons

with latent tuberculosis could be permanently protected each year, the global incidence in 2050 would be 14 times as low as the incidence in 2013, with no other intervention needed.⁵⁸ The incomplete understanding of the pathogenesis of latent tuberculosis infection and the lack of an ideal test and treatment regimen require intensified research efforts and cooperation across disciplines. The market potential for a new test or treatment for this public health problem, which could affect one

third of the world population, should motivate the corporate sector to invest in research. Reassessment of the global burden and better understanding of the magnitude of latent tuberculosis infection should inform both clinical and public health measures.

Dr. Chaisson reports receiving consulting fees from Merck. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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