

EDITORIALS



What Is Thwarting Tuberculosis Prevention in High-Burden Settings?

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The promise of chemoprophylaxis for tuberculosis has yet to be fully realized. Until recently, testing for and treating latent tuberculosis infection have been limited largely to low-burden settings, where active tuberculosis has been under good control. In the United States and several other low-burden countries, treatment of latent tuberculosis infection has been an alternative prevention strategy to early childhood immunization with bacille Calmette–Guérin (BCG). In high-burden settings, vaccination and the treatment of patients with positive smears have been the main public health strategies, with chemoprophylaxis recommended primarily for childhood contacts of patients with active tuberculosis, albeit it has been administered inconsistently. However, the emergence of HIV as the primary factor driving high tuberculosis rates in many parts of the world has led to recommendations by the World Health Organization (WHO) to administer isoniazid preventive therapy in coinfecting adults and children as part of the three I's strategy — the other I's being intensified case finding and infection control.¹ This issue of the *Journal* contains two reports of this application, one (by Madhi et al.²) showing a surprising lack of efficacy of continuous isoniazid as primary prevention among highly vulnerable, very young children of HIV-positive mothers, regardless of HIV status, and the other (by Martinson et al.³) showing efficacy in adults, but no advantage over newer, shorter, intermittent chemoprophylactic regimens designed to facilitate full supervision of therapy.

Even healthy newborns are highly susceptible to tuberculosis infection and progression to disseminated disease, including meningitis. The add-

ed risk of HIV coinfection leads to substantial morbidity and mortality during the first 2 years of life. Although immunization with BCG has been shown to reduce serious extrapulmonary complications, protection is incomplete, as indicated by the rates of illness and death from tuberculosis, despite almost universal vaccine access in high-risk settings. It is in this context that the failure of isoniazid primary chemoprophylaxis to reduce the risk of either tuberculosis or death for 2 years after randomization is especially disappointing. The authors carefully review possible explanations for this failure. In theory, continuous isoniazid treatment at a proper dose, in patients who adhere to the treatment regimen, with appropriate blood levels achieved, should prevent infection and disease from isoniazid-susceptible *Mycobacterium tuberculosis*, even in immunocompromised persons, and this has been shown in other studies.⁴ Among the explanations offered for the lack of protection in the study by Madhi et al., the difficulty of diagnosing tuberculosis in young children, with resulting overdiagnosis on the basis of diagnostic algorithms, seems the most probable source of error, but as noted by the authors, the absence of a difference between treated and untreated bacteriologically proven cases raises doubts about that explanation as well. Whatever the cause of the apparent failure of isoniazid to prevent tuberculosis in this study, one thing is certain: the cases that occurred among these children in their first 2 years of life must have been transmitted recently, most likely from the community.

The study by Martinson et al. is a more conventional comparison of four secondary prophylaxis regimens among persons with tuberculosis

and HIV infection in a high-risk South African setting. Here the new regimens of rifapentine–isoniazid weekly for 3 months, rifampin–isoniazid twice weekly for 3 months, and continuous isoniazid therapy for up to 6 years were compared with 6 months of conventional therapy. On the basis of expected rates of tuberculosis in this population, all four regimens were effective, but rates of active tuberculosis or death were no different with the two new, supervised, rifamycin-containing regimens than with the conventional 6-month isoniazid regimen. However, in a post hoc, as-treated analysis, patients in the continuous-isoniazid group had a 58% lower rate of tuberculosis or death than those receiving the 6-month control regimen of isoniazid, but the rates of tuberculosis in the continuous-isoniazid group markedly increased when therapy was discontinued, which was more common than with the other regimens, probably because of more severe side effects. These findings are consistent with those of the Botswana trial of continuous isoniazid and suggest ongoing transmission and reinfection in this high-prevalence setting, a phenomenon that is likely to compromise the long-term benefit of any chemoprophylactic regimen, regardless of short-term efficacy.⁵

What is thwarting tuberculosis prevention in high-burden settings? There are probably several factors, but a fundamental one, not fully appreciated, is ongoing transmission and reinfection. Although exogenous reinfection can be assumed to have occurred in patients after continuous isoniazid therapy has been stopped, proving reinfection is difficult, because genotyping of initial and subsequent *M. tuberculosis* isolates is rarely possible. **Despite immunization at birth, by early adulthood most young adults in high-risk settings have been exposed to tuberculosis and infected.** Epidemiologic considerations suggest that reinfection routinely occurs in these settings, even in HIV-negative populations.^{6–8} Reinfection has been postulated as an essential pathogenic pathway to lung cavitation and pathogen propagation in populations where there is partial immunity from prior vaccination or tuberculosis infection early in life.^{9,10} If this is true, the long-term benefits of chemoprophylaxis are likely to be limited, and if natural infection is not protective, the development of a more effective vaccine will be challenging.

Both the risk of tuberculosis in young chil-

dren and the risk of reinfection when chemoprophylaxis ends in adults point to the need for **better control of transmission in the community and in congregate settings, such as clinics, hospitals, and prisons. This can best be achieved by intensified case finding, rapid diagnosis, and prompt institution of effective therapy — fully supervised and based on rapid drug-susceptibility testing.** The feasibility and effectiveness of intensified case finding in the community have been shown.¹¹ The Xpert MTB/RIF technology recently endorsed by the WHO will provide an opportunity to screen patients with cough and other risk factors, to establish a precise diagnosis within hours, and to institute effective treatment within days, assuming that treatment programs are in place.¹² The impact of effective treatment of tuberculosis transmission is both rapid and profound, preceding sputum-smear and culture conversion, and is the cornerstone of tuberculosis infection control.¹³ In the near future, it should not be necessary, as it often is today, to wait for weeks or months to diagnose tuberculosis or identify drug resistance, during which time transmission continues. Unless the force of transmission can be reduced by intensified case finding and the use of new rapid diagnostics, resulting in more effective treatment, durable benefits from prevention strategies, either chemoprophylaxis or immunization, are likely to be elusive.

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

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The Lost Decade of Nesiritide

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The concept of the “lost decade” is typically attributed to the Japanese economy in the 1990s, when there was exceptionally little or weak economic growth, amid unprofitable zombie firms and liquidity traps.¹ With the financial collapse in the United States in 2008, some economists have forecast the potential for a similar circumstance in this country.² But there are other places to find lost decades.

Unfortunately, the “lost decade” can now also be applied to the deficient clinical development of certain pharmaceutical agents. In this issue of the *Journal*, O'Connor and colleagues³ report the results of a large, randomized, placebo-controlled trial of nesiritide, a biologic drug that was approved by the Food and Drug Administration (FDA) in 2001 for the relief of dyspnea in patients with acute heart failure. The results of the study involving 7141 patients showed a lack of efficacy for the clinical end point — rehospitalization for heart failure or death from any cause. There was also no significant reduction of self-reported dyspnea at 6 and 24 hours after treatment, on the basis of criteria that were prospectively defined. However, nesiritide led to a significant excess of hypotension, a near doubling, irrespective of whether it was symptomatic or asymptomatic. The primary conclusion of the authors was that “nesiritide cannot be recommended for routine use in the broad population of patients with acute heart failure.”³ Indeed, a thorough review of the multiplicity of subgroups that are described in the article does not identify any type of patient who would benefit from nesiritide.³

The FDA reviewed nesiritide for commercial approval in 1999, but it determined there were insufficient data. In 2001, Vasodilatation in the

Management of Acute Congestive Heart Failure (ClinicalTrials.gov number, NCT00270374), a new trial involving 498 patients that compared nesiritide with placebo or intravenous nitroglycerin, showed improvement in self-reported dyspnea at 3 hours after drug administration, even though nearly two thirds of the patients had not received diuretics and the dose of nitroglycerin was not appropriately titrated.⁴ Nonetheless, shortly thereafter, the FDA granted approval of nesiritide for the relief of dyspnea in acutely decompensated heart failure. This approval led to aggressive marketing of the drug beyond its marginal intended indication to the fostering of outpatient “tune-up” clinics where patients with chronic heart failure would come for weekly intravenous injections of nesiritide — an off-label and non-validated approach.⁴

In a Perspective article in the *Journal* in 2005, I wrote that “nesiritide was approved on the basis of a single trial in which surrogate end points were assessed 3 hours after administration” and that “nesiritide has not yet met the minimal criteria for safety and efficacy.”⁴ From FDA approval of the drug to the publication of the findings of the current trial, it has taken a full decade to learn the truth about nesiritide's lack of efficacy in acute heart failure.

The term “fuzzy logic” has generally been relegated to a branch of mathematics, but this concept can now be figuratively applied to the clinical development of a drug. Over the course of decades of clinical research, physicians have learned on too many occasions that a drug's effect on surrogate end points may not be representative of clinical outcomes. Previous examples of such end points in cardiovascular medicine include premature ventricular contractions with