The effectiveness of isoniazid (INH) monotherapy for the treatment of Mycobacterium tuberculosis infection to prevent active tuberculosis (TB) was first seen in a U.S. Public Health Service trial in 1962 (1). After that sentinel trial, over 20 randomized trials with more than 100 000 participants have shown a 25% to 90% reduction in active TB with 6 to 12 months of INH therapy compared with no treatment or placebo (1). In 1970, the regimen with optimal efficacy, 12 months of INH, was recommended as standard therapy for latent TB infection by the American Thoracic Society (2). Subsequently, a large Eastern European trial of older persons with fibrotic lung lesions showed that 6 months of INH had similar effectiveness to 12 months of INH because of better treatment completion rates (3). As a result, 6 months of INH was recommended by many authoritative agencies, including the World Health Organization. When a post hoc analysis of randomized trials in the Eskimo population of Alaska showed that 9 months of INH offered optimal effectiveness, this regimen became the standard in North America (4). However, completion rates under program conditions are very low for both 6 and 9 months of INH, and INH-associated hepatotoxicity, which can be fatal, is a major concern (4).

As a result, there has been an active search over the past 20 years for shorter and safer regimens. At least 30 studies have assessed various regimens. The safest and most effective have been 3 to 4 months of INH and rifampin (RMP), 3 to 4 months of RMP alone, and 3 months of once-weekly INH and rifapentine (RPT). These new regimens were compared with 6 or 9 months of INH in most studies and placebo or no treatment in a few.

However, few studies have compared these short-course regimens with each other. Hence, if one study shows that regimen A is better than 9 months of INH, but another shows that regimen B is better, the unanswered question of greatest interest to the clinician remains: “Is A better than B?” This type of question can be answered using Bayesian network meta-analysis, which is also known as mixed-treatment comparison analysis. This relatively underused method, which has been available for more than a decade, allows the comparison of A versus B when no trials directly compare them. The resultant estimates cannot replace evidence from direct comparisons in trials. However, given the many options for the treatment of M. tuberculosis infection, this method takes advantage of all of the published evidence to provide a reasonable estimate (best guess) of the results expected from a direct comparison of A versus B.

In this issue, Stagg and colleagues (5) have addressed this important question. Of the several alternative regimens for treatment of M. tuberculosis infection, which regimen provides the optimal balance of efficacy and tolerability? They used a network meta-analysis to compare 15 regimens assessed in 53 studies with a total of 133 992 participants. Forty-five of these studies reported outcomes of active TB, and 25 reported hepatotoxicity. Each of the 15 regimens was compared with each other and with no treatment or placebo. They were ranked according to relative effectiveness in preventing active TB and causing hepatotoxicity. In some cases, these rankings were counterintuitive. For example, the placebo regimens had the worst ranking for hepatotoxicity because of high rates of hepatic events in the placebo groups of a few trials.

Despite this unusual result, the analysis provides 2 useful and important messages. First, a great deal of evidence has accumulated over the past 2 decades. Thirty-three studies with 10 300 patients who took shorter regimens containing rifamycin (without pyrazinamide [PZA]) have shown convincingly that these regimens are at least as effective as, and are safer than, 6 or 9 months of INH. Surely, it is time to get a move on—away from INH as our primary therapy and toward regimens containing rifamycin. The advantages are considerable for patients who would benefit from greater safety and better protection against TB and TB programs in which shorter duration should result in reduced workload and potentially lower costs.

The second message about which specific rifamycin-containing regimen to choose is less clear. The 2 regimens that ranked the highest for TB prevention were combinations of INH and rifampin. However, both were evaluated in very small trials in which the effectiveness was not significantly better than the comparator and toxicity was not reported. The third most efficacious regimen was a combination of INH, RMP, and PZA. This regimen ranked eighth in hepatotoxicity and has largely been abandoned after the high rates of hepatotoxicity reported with 2 months of RMP and PZA (6). Rifampin alone for 3 or 4 months had the best combined rankings in this study; it was the fourth-best regimen for TB prevention and the best for hepatotoxicity (that is, least toxicity). However, the estimate of efficacy comes from a single study of 3 months of RMP (7). An ongoing trial comparing the efficacy and effectiveness of 4 months of RMP with 9 months of INH should provide important additional evidence. Stagg and colleagues also found that 3 to 4 months of INH and RMP ranked fairly well; it was the sixth-best regimen for TB prevention and ranked fourth for hepatotoxicity. However, in a different meta-analysis of 5 trials, the toxicity of 3 to 4 months of INH and RMP was no better than that of 6 to 9 months of INH (8), which implies that there may not be
any safety advantage with the former regimen. Surprisingly, 3 months of INH and RPT ranked eighth for TB prevention and third for hepatotoxicity, yet this regimen had excellent effectiveness and low hepatotoxicity in HIV-infected and uninfected persons in 2 trials (9, 10). However, all doses were given under direct observation in these trials; this may be impractical in many settings and add substantially to costs. Trials are under way to evaluate 3 months of self-administered INH and RPT therapy.

Further trials are needed to clarify which of these short-course regimens offer the greatest advantages for patients and programs and under what conditions. Nevertheless, we believe that the TB control community should get a move on—it’s time to switch our focus to rifamycin-containing short-course treatment of M. tuberculosis infection.

Dick Menzies, MD, MSc
Montreal Chest Institute, McGill University
Montreal, Quebec, Canada

Timothy R. Sterling, MD
Vanderbilt University School of Medicine
Nashville, Tennessee

Disclosures: Disclosures can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M14-1719.

Requests for Single Reprints: Dick Menzies, MD, MSc, Respiratory Epidemiology and Clinical Research Unit, Montreal Chest Institute, 3650 Saint Urbain, Room K1.24, Montreal, Quebec H2X 2P4, Canada; e-mail, dick.menzies@mcgill.ca.

Current author addresses are available at www.annals.org.

This article was published online first at www.annals.org on 12 August 2014.

References
4. Targeted tuberculin testing and treatment of latent tuberculosis infection. This official statement of the American Thoracic Society was adopted by the ATS Board of Directors, July 1999. This is a Joint Statement of the American Thoracic Society (ATS) and the Centers for Disease Control and Prevention (CDC). This statement was endorsed by the Council of the Infectious Diseases Society of America. (IDSA), September 1999, and the sections of this statement. Am J Respir Crit Care Med. 2000;161:5221-47. [PMID: 10764341]

Current Author Addresses: Dr. Menzies: Respiratory Epidemiology and Clinical Research Unit, Montreal Chest Institute, 3650 Saint Urbain, Room K1.24, Montreal, Quebec H2X 2P4, Canada.

Dr. Sterling: Vanderbilt University School of Medicine, 1161 21st Avenue, Nashville, TN 37232.