

be misleading or may not apply to important subgroups of patients.<sup>5</sup> In particular, we do not believe that this study convincingly supports the need for all patients to be referred to a cardiologist after myocardial infarction. Generalists alone can often provide compassionate, efficient, and high-quality health care for patients with heart disease who are poor candidates for revascularization.

Paul A. James, M.D.

Arthur J. Hartz, M.D., Ph.D.

Barcey T. Levy, Ph.D., M.D.

University of Iowa  
Iowa City, IA 52242  
paul-james@uiowa.edu

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**THE AUTHORS REPLY:** To assess whether differences in the severity of illness could explain differences in mortality associated with physicians' specialties, we examined three measures of severity that we had previously dichotomized (serum creatinine level) or not included (left ventricular ejection fraction and blood hemoglobin level) when matching patients who did or did not see a cardiologist after discharge. Among patients with renal insufficiency, the mean serum creatinine level was very similar in the two subgroups (3.44 mg per deciliter in those who saw a cardiologist vs. 3.47 mg per deciliter in those who did not;  $P=0.69$ ). Among those with congestive heart failure while hospitalized, the mean ejection

fraction was also similar (40.0 percent vs. 40.6 percent, respectively;  $P=0.21$ ). In the overall matched cohort, the mean hemoglobin level was nearly identical in the two subgroups (13.87 g per deciliter vs. 13.90 g per deciliter, respectively;  $P=0.92$ ). These findings suggest that by incorporating an extensive set of clinical factors when matching patients according to their propensity to see a cardiologist for ambulatory care, we also closely balanced key severity measures that have been shown to affect survival.<sup>1-3</sup>

We agree with James and colleagues that unmeasured socioeconomic factors, such as the level of education or availability of supplemental insurance, may be associated with care by cardiologists and may explain some of the differences in mortality that we observed.<sup>4</sup> However, as we found in a sensitivity analysis, controlling for a plausible unmeasured socioeconomic effect would have reduced but not eliminated the increased mortality among patients who did not see a cardiologist. Therefore, in the absence of randomized trials, we believe that rigorous observational studies can provide useful guidance to patients, physicians, and policymakers about the roles of primary and specialty care for patients with coronary heart disease.

John Z. Ayanian, M.D., M.P.P.

Mary Beth Landrum, Ph.D.

Peter Gaccione, M.A.

Harvard Medical School  
Boston, MA 02115  
ayanian@hcp.med.harvard.edu

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## Management of Latent Tuberculosis Infection in Immigrants

**TO THE EDITOR:** We applaud the rigorous decision analysis by Khan et al. (Dec. 5 issue),<sup>1</sup> who demonstrated the cost effectiveness of screening and treating recent immigrants from countries where tuber-

culosis is prevalent for latent tuberculosis infection. The investigators also attempted to identify the best treatment regimens for latent tuberculosis infection in various populations from developing countries,

on the basis of drug-resistance patterns. However, the differences in direct costs and health benefits among these regimens were relatively small and should be interpreted cautiously. The comparisons were limited, in that the estimates of drug resistance for certain countries (derived from data from the Centers for Disease Control and Prevention [CDC]) were imprecise, the issue of nonadherence under programmatic conditions was not addressed, and the rates and associated costs of adverse events were probably underestimated.

It is important to highlight the recent reports of serious adverse events affecting the liver, some resulting in death, associated with the use of rifampin and pyrazinamide for two months.<sup>2</sup> The CDC now recommends a nine-month regimen of daily isoniazid as the preferred treatment for latent tuberculosis infection, or, as an acceptable alternative, a four-month regimen of daily rifampin. Two months of daily rifampin–pyrazinamide may be considered in selected cases when the completion of longer regimens is unlikely and the patient can be monitored closely. The CDC continues to collect reports of severe liver injury (i.e., injury leading to hospital admission or death) due to any regimen for latent tuberculosis infection (telephone 404-639-8117).

Suzanne M. Marks, M.P.H.

Kashef Ijaz, M.D., M.P.H.

Michael F. Iademarco, M.D., M.P.H.

Centers for Disease Control and Prevention  
Atlanta, GA 30333  
kijaz@cdc.gov

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**TO THE EDITOR:** Khan et al. appropriately emphasize the importance of treating latent tuberculosis infection in persons at high risk, but they probably overstate the potential of shorter treatment regimens. Evidence for the safety and effectiveness of these regimens is more limited than that for preventive treatment with isoniazid. Neither the effectiveness nor the tolerability of a four-month regimen of rifampin has been studied, and the effectiveness of a two-month regimen of rifampin and pyrazinamide has not been studied in persons who are seronegative for the human immunodeficiency virus (HIV). In the only study of a three-month regimen of rifam-

pin, its effectiveness was 46 percent<sup>1</sup>; this estimate was not included in the base-line or sensitivity analyses presented by Khan et al. The sample sizes in studies that assessed the tolerability of longer regimens of rifampin have been small,<sup>2,3</sup> and therefore caution is warranted before such a regimen is recommended for large-scale application.

The authors also do not account for the cost and complexity of screening more than 600,000 immigrants and providing treatment to more than 200,000 per year. Aside from increasing the treatment of latent infection in recent immigrants (whatever regimen is used), we probably cannot eliminate tuberculosis in this country until the disease is better controlled globally. Improving global control measures is cost effective and also serves the interest of tuberculosis control in this country.

Timothy Sterling, M.D.

Johns Hopkins University  
Baltimore, MD 21231

Sonal S. Munsiff, M.D.

Thomas R. Frieden, M.D., M.P.H.

New York City Department of Health and Mental Hygiene  
New York, NY 10013  
smunsiff@health.nyc.gov

1. Hong Kong Chest Service/Tuberculosis Research Centre, Madras/British Medical Research Council. A double-blind placebo-controlled clinical trial of three antituberculosis chemoprophylaxis regimens in patients with silicosis in Hong Kong. *Am Rev Respir Dis* 1992;145:36-41.
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**TO THE EDITOR:** In their cost-effectiveness analysis, Khan and colleagues compared the expected costs and outcomes of screening by tuberculin testing and the treatment of those with a reaction to the costs and outcomes of no screening, instead of analyzing the incremental costs and effects of replacing the current program of screening by chest radiography. A previous analysis suggested that incremental costs would be substantial and the gains limited.<sup>1</sup> Moreover, physicians' adherence in medical evaluations and prescriptions and patients' adherence to screening were assumed to be 100 percent. Patients' adherence to treatment was imputed from expensive clinical trials. However, program evaluations have documented suboptimal adherence, which reduces cost effectiveness, at various steps.<sup>1,2</sup> Since the costs of interventions to promote volun-

tary adherence were not considered, the analysis by Khan and colleagues would be realistic only in the context of legal coercion, which many believe unjust.<sup>3</sup> The public health infrastructure required to coordinate and execute such a massive program was ignored, falsely enhancing cost effectiveness.

Dick Menzies, M.D.

Kevin Schwartzman, M.D., M.P.H.

Montreal Chest Institute  
Montreal, QC H3A 1A3, Canada  
dick.menzies@mcgill.ca

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**TO THE EDITOR:** By excluding consideration of HIV infection in their analysis of the incidence of tuberculosis in immigrants because “persons with HIV infection would be excluded from legal immigration in accordance with current U.S. policy,” Khan et al. miscalculate actual conditions. HIV-infected African expatriates are regularly encountered in New York City. Most have non-B subtypes of HIV type 1 infection, suggesting that their infection was acquired from other Africans,<sup>1</sup> presumably before entry into the United States. Among 60 HIV-infected African expatriate patients seen at a New York City hospital, tuberculosis was the most common opportunistic infection in the 25 whose HIV test was prompted by symptoms of AIDS.<sup>2</sup>

Elizabeth R. Jenny-Avital, M.D.

Albert Einstein College of Medicine  
Bronx, NY 10461  
jennyavita@aol.com

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**THE AUTHORS REPLY:** We share the concern expressed by Marks et al. about the recent reports of hepatotoxicity with rifampin plus pyrazinamide, and we acknowledge that the data on rifampin-based treatment for latent tuberculosis infection are limited,

as noted by Sterling et al. However, the broad use of isoniazid in populations with a high prevalence of resistance is not benign. Treatment of persons with resistant infections needlessly exposes them to the risk of serious adverse reactions, incurs unnecessary costs, and requires a nine-month commitment from which it is unlikely that there will be benefits.<sup>1</sup>

In our analysis, we established benchmark estimates of the effectiveness of each rifampin-based regimen in relation to a landmark clinical trial.<sup>2</sup> Our estimate of the effectiveness of rifampin monotherapy was derived from a study showing the statistical equivalence of three months of rifampin and six months of isoniazid.<sup>3</sup> On the basis of these data, many experts consider the effectiveness of rifampin-based regimens to be approximately equivalent to those based on isoniazid.<sup>4</sup>

Our analysis evaluated the cost effectiveness of treatment of latent tuberculosis infection in the context of the current health care infrastructure in the United States. Since we recognize that limited medical and public health resources may preclude the targeted screening of all persons at high risk, our analysis was designed to facilitate the most efficient use of available resources. Decisions regarding mass screening and large-scale investment in the public health infrastructure must be considered in the context of current national health care priorities.<sup>5</sup>

The “no intervention” group in our study was not a “no screening” group, as interpreted by Menzies and Schwartzman. Since this group was based on epidemiologic data on tuberculosis in foreign-born persons, it reflects current screening practice for all foreign-born persons in the United States. Among the latter are documented immigrants, who undergo screening by chest radiography, as well as other foreign-born persons who might not have been screened.

We acknowledge that all immigrants with HIV infection might not be identified by the current immigration screening system. Nevertheless, the presence of persons infected with HIV only strengthens the conclusions of our study, since HIV greatly increases the risk of reactivation of latent tuberculosis and thus deepens the benefits of screening.

Finally, we strongly agree that global control of tuberculosis is necessary before its elimination from the United States can realistically be considered. It is our opinion that targeted screening of foreign-born populations at high risk, combined with a strong commitment to global control, is

consistent with the national interests of the United States.

Kamran Khan, M.D., M.P.H.

St. Michael's Hospital  
Toronto, ON M5B 1W8, Canada  
km.khan@utoronto.ca

Peter Muennig, M.D., M.P.H.

City University of New York School of Medicine  
New York, NY 10031

Joshua Graff Zivin, Ph.D.

Columbia University  
New York, NY 10032

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## Treatment of Latent Tuberculosis Infection

**TO THE EDITOR:** I was perturbed by the recommendation of Jasmer et al. (Dec. 5 issue)<sup>1</sup> that an asymptomatic, low risk, 27-year-old schoolteacher with a 17-mm induration on intradermal tuberculin skin test “should not be treated.” The authors state, “One cannot conclude that she has had recent tuberculin conversion, because she has not had a negative tuberculin test within the past two years.” In fact, one might take the opposite tack and state that one cannot conclude that she did not have a tuberculin conversion during the previous two years in the absence of a prior negative tuberculin test. The Centers for Disease Control and Prevention recommend that “persons with no known risk factors for tuberculosis may be considered for treatment of LTBI [latent tuberculosis infection] if their reaction to tuberculin skin test is  $\geq 15$  mm.”<sup>2</sup> One might view this person as being in an intermediate-risk group, since she is in a setting in which she would expose and potentially infect many children and adolescents should she become symptomatic. The authors themselves quote the statement by the Institute of Medicine that “efforts to prevent cases [of tuberculosis] from occurring must be amplified.”<sup>3</sup> Neither financial constraints nor the risk of hepatotoxic effects of isoniazid (a risk that has recently been markedly reduced) should prevent the use of a chemotherapeutic agent whose efficacy has been documented for over 30 years.

Leslie L. Barton, M.D.

University of Arizona School of Medicine  
Tucson, AZ 85724-5073  
llb@peds.arizona.edu

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**TO THE EDITOR:** Jasmer et al. did not mention the administration of isoniazid and rifampin for three months as a choice of treatment. Daily treatment for three months with isoniazid and rifampin has been shown to be highly effective in adults<sup>1</sup> and children<sup>2</sup> who are not infected with the human immunodeficiency virus (HIV). In the United Kingdom, this regimen is currently recommended for the treatment of latent tuberculosis in both adults and children.<sup>3</sup> In addition, three-month regimens of isoniazid and rifampin provided protection against active tuberculosis that was equivalent to the protection provided by a six-month regimen of isoniazid alone or a three-month regimen of isoniazid, rifampin, and pyrazinamide in HIV-positive Ugandan adults.<sup>4</sup>

Philippe Lepage, M.D., Ph.D.

University of Liege  
4000 Liege, Belgium  
philippe.lepage@chrcitadelle.be

1. Hong Kong Chest Service/Tuberculosis Research Centre, Madras/British Medical Research Council. A double-blind placebo-controlled clinical trial of three antituberculosis chemoprophylaxis regimens in patients with silicosis in Hong Kong. *Am Rev Respir Dis* 1992;145:36-41.
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**TO THE EDITOR:** The excellent clinical review of latent *Mycobacterium tuberculosis* infection by Jasmer and coworkers fails to mention, or include in Table 1 of the article, patients treated with anti-tumor-necrosis factor (TNF) monoclonal antibodies, such