

SPECIAL ARTICLE

Domestic Returns from Investment in the Control of Tuberculosis in Other Countries

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ABSTRACT

BACKGROUND

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We hypothesized that investments to improve the control of tuberculosis in selected high-incidence countries would prove to be cost saving for the United States by reducing the incidence of the disease among migrants.

METHODS

Using decision analysis, we estimated tuberculosis-related morbidity, mortality, and costs among legal immigrants and refugees, undocumented migrants, and temporary visitors from Mexico after their entry into the United States. We assessed the current strategy of radiographic screening of legal immigrants plus current tuberculosis-control programs alone and with the addition of either U.S.-funded expansion of the strategy of directly observed treatment, short course (DOTS), in Mexico or tuberculin skin testing to screen legal immigrants from Mexico. We also examined tuberculosis-related outcomes among migrants from Haiti and the Dominican Republic using the same three strategies.

RESULTS

As compared with the current strategy, expanding the DOTS program in Mexico at a cost to the United States of \$34.9 million would result in 2591 fewer cases of tuberculosis in the United States, with 349 fewer deaths from the disease and net discounted savings of \$108 million over a 20-year period. Adding tuberculin skin testing to radiographic screening of legal immigrants from Mexico would result in 401 fewer cases of tuberculosis in the United States but would cost an additional \$329 million. Expansion of the DOTS program would remain cost saving even if the initial investment were doubled, if the United States paid for all antituberculosis drugs in Mexico, or if the decline in the incidence of tuberculosis in Mexico was less than projected. A \$9.4 million investment to expand the DOTS program in Haiti and the Dominican Republic would result in net U.S. savings of \$20 million over a 20-year period.

CONCLUSIONS

U.S.-funded efforts to expand the DOTS program in Mexico, Haiti, and the Dominican Republic could reduce tuberculosis-related morbidity and mortality among migrants to the United States, producing net cost savings for the United States.

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ALTHOUGH THE INCIDENCE OF ACTIVE tuberculosis has declined in most high-income countries, the global incidence of the disease continues to increase.¹ Migrants from low-income countries with a high incidence of tuberculosis account for a growing proportion, and often the majority, of these cases.²⁻⁴ Legal immigrants to many high-income countries undergo radiographic screening for tuberculosis.^{5,6} Adjunctive tuberculin skin testing, with treatment of latent tuberculosis infection, has been recommended,⁷ and a recent decision analysis provides support for this approach.⁸ However, the effectiveness of screening is limited by administrative problems of these programs and poor adherence to screening, evaluation, and treatment⁹⁻¹¹; the failure to screen undocumented migrants and visitors, who constitute the majority of entrants to the United States^{12,13}; and reexposure of foreign-born residents who revisit their countries of origin.¹⁴

Implementation of the World Health Organization (WHO) strategy of directly observed treatment, short course (DOTS),¹⁵ can substantially reduce the incidence^{16,17} and prevalence¹⁸ of tuberculosis in countries with a high incidence of the disease. However, because of inadequate funding,¹⁹ global implementation of the DOTS program remains far from complete. One strategy to reduce the incidence of tuberculosis in high-income countries that has received little attention is to strengthen tuberculosis-control programs through the expansion of the DOTS program in key countries that are the source of migrants.

We estimated tuberculosis-related morbidity, mortality, and costs associated with radiographic screening and existing tuberculosis-control programs over a period of 20 years among Mexican-born migrants to the United States. We compared these results with those arising from the addition of either a U.S.-funded expansion of the DOTS program in Mexico or tuberculin skin testing of legal immigrants. We conducted parallel analyses for migrants entering the United States from Haiti and the Dominican Republic.

METHODS

GENERAL DESCRIPTION OF THE MODEL

We devised a decision-analysis model incorporating multiple Markov processes (TreeAgePro 2005 Health Care release 0.4, TreeAge Software) to estimate the cumulative probability of active tubercu-

losis, tuberculosis-related death, and associated costs among migrants to the United States. We used the societal perspective, meaning that direct and indirect costs were included.²⁰ Future expenditures and outcomes were discounted at a rate of 3 percent.²¹ Migrants were categorized as legal immigrants (persons applying for entry from abroad or within the United States, refugees, asylum seekers, and short-term laborers), undocumented migrants, or temporary visitors. Throughout the 20-year period, the number, age, and types of migrants entering the United States annually remained unchanged in this analysis. We considered three source countries: Mexico for the primary analysis and Haiti and the Dominican Republic for secondary analyses. A more detailed description of the structure of the model, underlying assumptions, and variables and additional results are provided in the Supplementary Appendix (available with the full text of this article at www.nejm.org).

TUBERCULOSIS-CONTROL STRATEGIES

We evaluated three strategies of tuberculosis control: the current program of radiographic screening and tuberculosis control in Mexico, radiographic screening plus expansion of the DOTS program in Mexico, and radiographic screening together with tuberculin skin testing. With the use of the current strategy, legal immigrants and refugees would undergo radiographic screening when entering the United States and current outcomes would apply.^{5,9,22,23} Current epidemiologic and tuberculosis-control variables would not change in the United States or in Mexico over a 20-year period in this analysis.

In the second scenario, expansion of the DOTS program would be added to radiographic screening. The U.S. government would pay for all costs of expanding the DOTS program in Mexico in order to achieve WHO benchmarks of 100 percent coverage of the population, a 70 percent rate of case detection, and an 85 percent rate of treatment success¹⁵ within three years. The rates of treatment failure, mortality, and drug resistance would not change during the 20-year period. After the expansion of the DOTS program, the incidence of new, smear-positive cases would decline 6 percent annually,¹⁶ as would the prevalence of latent tuberculosis infection²⁴ among departing migrants.

In the third scenario, tuberculin skin testing would be added to radiographic screening.^{5,8} The tuberculosis-control programs would not change in

Table 1. Modeling Variables and Assumptions.*

Variable	Legal Immigrants†	Undocumented Migrants‡	Temporary Visitors§	Value	Reference or Source
Characteristics of U.S. Entrants from Mexico					
No. entering United States each year	174,201	961,600	633,078		2002 Yearbook of Immigration Statistics, ¹² ITA Office of Travel and Tourism Industries ¹³
Mean age (yr)	29	29¶	35		2002 Yearbook of Immigration Statistics ¹²
Prevalence of latent tuberculosis infection (%)					
Total	6.3	6.3	6.9		Styblo ²⁴
Recent (<2 yr)	0.5	0.5	0.5		
Prevalence of HIV infection (%)	0	0.3	0.3		Joint United Nations Programme on HIV/AIDS ³⁰
Prevalence of underlying multidrug-resistant infection	2.4	2.4	2.4		Granich et al. ³¹
Average income after entry (\$)					
1st yr	14,443	9,027	0		World Bank, ³² Lubotsky, ³³ Green and Worswick, ³⁴ Borjas ³⁵
5th yr	18,054	14,443	0		World Bank, ³² Lubotsky, ³³ Green and Worswick, ³⁴ Borjas ³⁵
Key variables					
Screening legal immigrants					
Radiographic screening					
Sensitivity for active tuberculosis (%)				100	Assumption
Sensitivity for latent tuberculosis infection (%)				11	Nolan and Elarth, ²³ Schwartzman and Menzies, ²⁶ Groth-Peterson et al., ³⁶ Ferebee ³⁷
Cost of screening per person (\$)				16.73	Dasgupta et al. ⁹
Cost of medical evaluation per person if result abnormal (\$)¶				144.36	Dasgupta et al. ⁹
Tuberculin skin testing					
Sensitivity for latent tuberculosis infection (%)				99	WHO ²⁵
Specificity for latent tuberculosis infection (%)				88	Khan et al., ⁸ Schwartzman and Menzies ²⁶
Cost of screening per person (\$)				16.51	Khan et al. ⁸
Cost of medical evaluation per person if test is positive (\$)***				100.44	Dasgupta et al. ⁹

Mexico, nor would relevant variables related to tuberculosis and human immunodeficiency virus (HIV) infection change among migrants. We assumed that tuberculin skin testing would have a sensitivity of 99 percent²⁵ and a specificity of 88 percent.^{8,26} Migrants with a positive test (defined by induration of at least 10 mm) would be prescribed nine months of isoniazid therapy, with an efficacy

of 90 percent for isoniazid-sensitive cases of latent tuberculosis²⁷ and 0 percent for isoniazid-resistant cases²⁸ (Table 1). Overall, only 21 percent of all screened migrants with latent tuberculosis would complete nine months of isoniazid therapy — the average percentage in several large-scale programs that use tuberculin skin testing^{9-11,38,39} (see Table S4 of the Supplementary Appendix).

Table 1. (Continued.)

Variable	Legal Immigrants†	Undocumented Migrants‡	Temporary Visitors§	Value	Reference or Source
Tuberculosis treatment in United States					
Latent tuberculosis infection					
Cost of treatment per person (\$)				281.69	Dasgupta et al. ⁹
Cost of drug-induced hepatitis per person (\$)				9,257	Khan et al. ⁸
Likelihood of person with positive test completing treatment (%)				21	Dasgupta et al., ⁹ British Columbia Center for Disease Control, ¹¹ Blum et al., ³⁸ Catlos et al., ³⁹ Moran-Mendoza, ⁴⁰ Yuan et al., ⁴¹ Lauzardo M: unpublished data
Likelihood of isoniazid-induced hepatitis (%)				1	Kopanoff et al., ⁴² Nolan et al. ⁴³
Likelihood of hospitalization if hepatitis develops (%)				9	Nolan et al. ⁴³
Active tuberculosis					
Likelihood of cure (%)				91.5	CDC ⁴⁴
Direct costs per person (\$)				36,045	Brown et al. ²⁹
Indirect costs per person (\$)				2,262	Questionnaire
Costs associated with expansion of DOTS strategy in Mexico					
DOTS coverage in 2002 in Mexico (%)				70	Lee et al. ⁴⁵
Initial costs of DOTS expansion in Mexico (\$)††				34.9 million	Vaca et al. ⁴⁶
Costs of antituberculosis drugs in Mexico for 20 yr (\$)‡‡				2.8 million	Global Drug Facility ⁴⁷

* Costs are in 2003 U.S. dollars.²⁹ Direct costs were those borne by the U.S. government and health care system for the expansion of the DOTS strategy and tuberculosis-related screening and health care. Indirect costs are out-of-pocket expenditures by patients and their families and lost wages due to death, disability, or provision of care.

† Among legal immigrants, the prevalence of human immunodeficiency virus (HIV) infection is effectively 0, owing to immigration regulations. We assumed that immigrants would visit their country of origin for two weeks every other year, beginning two years after entry.

‡ We assumed that undocumented migrants stay in the United States up to 20 years and visit their country of origin for 2 weeks every other year beginning 5 years after entry. We assumed that the prevalence of seropositivity for HIV and rate of death from HIV were similar to those in the general population of source countries.³⁰

§ The number of person-years in the United States is determined by multiplying the total number of visitors by the average length of stay in days, and then dividing the value by 365. We assumed that the visitors will not work in the United States (no income) or make return visits and that the prevalence of seropositivity for HIV among visitors would be the same as that for undocumented migrants.

¶ We assumed that the mean age and prevalence of latent tuberculosis infection among undocumented migrants are the same as those among legal immigrants.

|| Medical evaluation for abnormal radiographic screening includes an initial clinic visit, a consultation, repeated radiographic screening, tuberculosis skin testing, three sputum smears, blood tests, and follow-up visit (clinic and physician charges).

** Medical evaluation for a positive tuberculin skin test includes an initial clinic visit, consultation, radiographic screening, and blood tests.

†† These costs are extrapolated from a DOTS-expansion project in Ecuador and include those related to infrastructure, equipment, materials, personnel, and training.⁴⁶

‡‡ Drug costs are for the treatment of all new smear-positive cases, including retreatment if required during the 20-year period of analysis. Unit prices are from the Global Drug Facility.⁴⁷

PATHOGENESIS, DIAGNOSIS, AND TREATMENT OF TUBERCULOSIS

We included four tuberculosis-related health states: no infection; latent tuberculosis infection, subdivid-

ed into recent infection (acquired within the past two years) and long-standing infection (acquired at least two years ago); active tuberculosis; and healed active tuberculosis (treated or spontaneously re-

solved). Latent and active tuberculosis were modeled as drug-sensitive, resistant to a single drug, or multidrug-resistant. The prevalence of recent and long-standing latent tuberculosis infection reflected migrants' mean age at entry¹² and the annual risk of infection,²⁴ derived from the incidence of smear-positive cases in the source country.⁴⁸ Among HIV-negative migrants with a recent diagnosis of latent tuberculosis infection, we estimated that the infection would become active in 5 percent in the first two years after entry into the United States,⁴⁹ with an annual rate thereafter of 0.1 percent if the chest x-ray film showed no abnormalities^{23,50} and of 0.6 percent if the film showed abnormalities.²³ We also accounted for the possibility that migrants could become infected during return visits to their countries of origin.

We assumed that the outcomes among treated migrants would equal those among U.S.-born persons.² The mortality rate among persons with undiagnosed smear-positive tuberculosis was assumed to be 33 percent annually,⁵¹ and 25 percent of cases were assumed to resolve spontaneously.⁵²

EFFECT OF HIV INFECTION

We modeled three HIV-related health states: uninfected, early infection (asymptomatic), and late infection (clinical acquired immunodeficiency syndrome). The number of HIV-infected legal immigrants entering the United States is negligible, but the prevalence of seropositivity for HIV among undocumented migrants and visitors was assumed to be similar to that in the general population of the source countries.³⁰ For migrants with both tuberculosis and HIV infections, the risk of active tuberculosis depends on the duration of latent tuberculosis and the stage of HIV infection,^{53,54} and the mortality rate is higher, but cure and relapse rates for active tuberculosis are similar to those among HIV-negative migrants^{55,56} (see Table S1 of the Supplementary Appendix).

COSTS

Costs, expressed in 2003 U.S. dollars, were categorized as direct (borne by the U.S. government and health care system for the expansion of the DOTS program and tuberculosis-related screening and health care) or indirect (out-of-pocket expenditures by patients and their families and lost wages due to disability, death, or provision of care). Costs for expansion of the DOTS program, including those related to infrastructure, equipment, materials, per-

sonnel, and training, were derived from a DOTS-expansion project in Ecuador⁴⁶ overseen by the Canadian Lung Association (see the Supplementary Appendix for details). Projected drug expenditures reflected WHO incidence estimates⁴⁸; projected rates of failure, relapse, and defaults requiring retreatment; and drug prices in the Global Drug Facility.⁴⁷

Within the United States, the most important direct cost was \$36,045 for the treatment of active tuberculosis, a value based on a comprehensive, 17-state survey of all payers²⁹ (adjusted for inflation⁵⁷). Productivity losses from premature deaths related to tuberculosis were calculated on the basis of the expected annual income and the number of years remaining in the 20-year simulation. To estimate other indirect costs, we used a standardized questionnaire to interview 50 patients with tuberculosis and their families in Montreal, New York, and Miami. All respondents provided written informed consent, and the survey was approved by the institutional review boards of all participating centers.

SENSITIVITY AND SECONDARY ANALYSES

We changed variables individually and then jointly to assess changes in all outcomes among migrants from Mexico. We also examined the effect of the same three tuberculosis-control strategies among migrants from Haiti and the Dominican Republic.

RESULTS

According to our model, over the 20-year period of analysis, 35.4 million migrants are projected to enter the United States from Mexico. With the current strategy of radiographic screening and the current tuberculosis-control program in Mexico, we estimated that there would be 47,610 cases of tuberculosis and 5245 deaths related to tuberculosis in this population, resulting in direct and indirect costs of \$1.985 billion and \$632 million, respectively (Table 2). If the U.S. government invested \$34.9 million to expand the DOTS program in Mexico without changing screening or control programs in the United States, there would be 2591 fewer cases of tuberculosis and 349 fewer deaths related to tuberculosis in the United States. These numbers reflect the projected reduction in latent tuberculosis infection, particularly recent infection, among newly arrived migrants owing to the reduction in incidence after the expansion of the DOTS program in Mexico.

Table 2. Tuberculosis-Related Morbidity, Mortality, and Costs among Migrants from Mexico after Arrival in the United States with the Three Strategies.*

Variable and Strategy	Legal Immigrants	Undocumented Migrants	Temporary Visitors	Total
Cases of tuberculosis				
Total no. of cases with radiographic screening plus current strategy	5766	34,089	7755	47,610
No. of cases averted with radiographic screening plus expansion of DOTS strategy	322	1,779	490	2,591
No. of cases averted with radiographic screening plus tuberculin skin testing	401	0	0	401
Deaths from tuberculosis				
Total no. of deaths with radiographic screening plus current strategy	392	3,962	891	5,245
No. of deaths prevented with radiographic screening plus expansion of DOTS strategy	33	269	47	349
No. of cases prevented with radiographic screening plus tuberculin skin testing	30	0	0	30
Direct costs (millions of \$)				
Total costs of radiographic screening plus current strategy	263	1,395	327	1,985
Radiographic screening plus expansion of DOTS strategy				
Total costs	286†	1,311	304	1,901
Added costs or net savings	23	(84)	(23)	(84)
Radiographic screening plus tuberculin skin testing				
Total costs	523	1,395	327	2,245
Added costs or net savings	260	0	0	260
Indirect costs (millions of \$)				
Total costs of radiographic screening plus current strategy	129	501	2	632
Radiographic screening plus expansion of DOTS strategy				
Total costs	125	481	2	608
Added costs or net savings	(4)	(20)	0	(24)
Radiographic screening plus tuberculin skin testing				
Total costs	198	501	2	701
Added costs or net savings	69	0	0	69
Total direct and indirect costs (millions of \$)				
Total costs of radiographic screening plus current strategy	392	1,896	329	2,617
Added costs or net savings of radiographic screening plus expansion of DOTS strategy	19	(104)	(23)	(108)
Added costs or net savings of radiographic screening plus tuberculin skin testing	329	0	0	329

* Costs are in millions of 2003 U.S. dollars. Values in parentheses are net savings. Direct costs were those borne by the U.S. government and health care system for the expansion of the DOTS strategy and tuberculosis-related screening and health care. Indirect costs are out-of-pocket expenditures by patients and their families and lost wages due to death, disability, or provision of care.

† Costs of expansion of DOTS strategy were attributed only to legal immigrants in the analysis to facilitate comparison with tuberculin skin testing (which was applied only to legal immigrants). Hence, the direct costs for this group under the strategy of DOTS expansion appear disproportionately higher.

By preventing these cases of tuberculosis, the expanded DOTS program would result in a net reduction in direct (government) spending of \$84 million and a reduction of another \$24 million in indirect costs. Of the cases of tuberculosis averted with the

implementation of the expanded DOTS program, 88 percent would have occurred among undocumented migrants and visitors.

Adding tuberculin skin testing to radiographic screening for legal immigrants and refugees

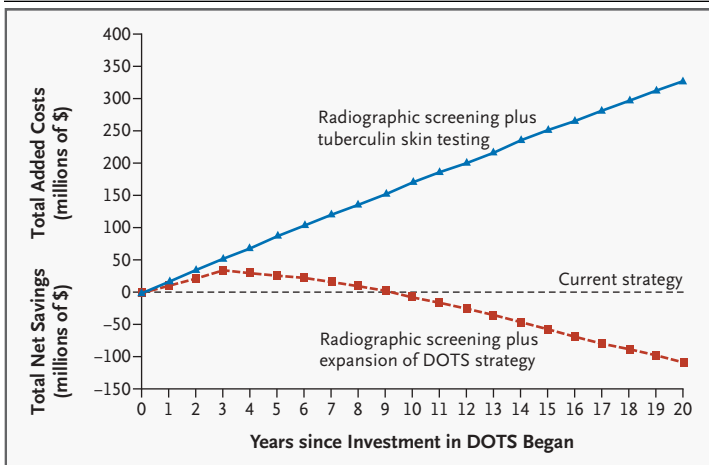


Figure 1. Net Savings or Added Costs of Implementing a Strategy of Radiographic Screening plus Either Expansion of the DOTS Program or Tuberculin Skin Testing over a 20-Year Period among Migrants from Mexico to the United States.

The values are relative to the cost of the current strategy of radiographic screening plus current tuberculosis-control efforts.

would result in 401 fewer cases of tuberculosis but would increase net direct costs by \$260 million, or \$648,379 per additional case averted. Implementing this policy would not affect undocumented migrants and visitors, since they are not screened. With the implementation of the DOTS-expansion strategy, net savings for the United States would begin within 9 years, whereas the implementation of tuberculin skin testing would require progressively greater expenditures over the 20-year period (Fig. 1).

SENSITIVITY ANALYSES

As shown in Table 3, if the expansion of the DOTS program produced a slower-than-expected decline in the incidence of tuberculosis in Mexico, cost savings for the United States would be anticipated unless the rate of decline was less than 1.2 percent annually. Cost savings would be anticipated even if the U.S. government doubled its initial investment for expansion of the DOTS program or paid for antituberculosis drugs for all new and retreated cases in Mexico for all 20 years or if the number of migrants was only 33 percent of current levels. If the number of migrants entering the United States or the prevalence of HIV infection, latent tuberculosis infection, or drug resistance were higher or increased over the 20-year period, savings from expansion of the DOTS program would be even greater (data not shown). Finally, if the frequency

or duration of return visits by legal immigrants and undocumented migrants were doubled, expansion of the DOTS program would avert an additional 249 cases of tuberculosis and save an additional \$5.2 million (data not shown).

In sensitivity analyses, we assumed that 100 percent of migrants completed screening, 100 percent of migrants with positive tuberculin skin tests were evaluated, 100 percent of those with latent infections received treatment, and 78 percent completed nine months of isoniazid therapy. The direct costs of this ideal screening program would be \$187,243 for each additional case of tuberculosis averted in the United States. And, if four additional key variables were also made more favorable, the direct costs of the strategy of radiographic screening plus tuberculin skin testing would be \$240 million to avert 1812 additional cases, equivalent to direct costs of \$132,450 per additional case averted.

SECONDARY ANALYSES INVOLVING HAITI AND THE DOMINICAN REPUBLIC

According to our model, over a 20-year period, nearly 2 million migrants are expected to enter the United States from Haiti and the Dominican Republic, and active tuberculosis will develop in 11,809 of them, resulting in 1288 deaths. These higher rates of morbidity and mortality reflect the higher prevalence of tuberculosis and HIV infection in these countries. As shown in Table 4, a U.S. investment of \$9.4 million to expand the DOTS program in these two countries would result in 590 fewer cases of tuberculosis and net savings of \$20 million in the United States. Adding tuberculin skin testing of legal immigrants would result in 315 fewer cases of tuberculosis in the United States, but at an added total cost of \$128 million.

DISCUSSION

Our comparison of three strategies for the control of tuberculosis among migrants to the United States suggests that U.S. government-funded expansion of the DOTS program in Mexico could result in the lowest net costs to the United States and the greatest reduction in the number of cases of tuberculosis in the United States. This finding was robust in sensitivity analyses. The alternative strategy of adding tuberculin skin testing to current radiographic screening of legal immigrants would have less effect and would substantially increase costs.

The DOTS strategy is a cost-effective method of

Table 3. Added Costs or Net Savings in Sensitivity Analyses of the Two Alternative Strategies for Tuberculosis Control among Migrants from Mexico.*

Assumptions That Were Changed	No. of Cases of Tuberculosis Averted	Change in Direct Costs	Change in Indirect Costs	Change in Total Costs
<i>millions of dollars</i>				
Expansion of DOTS strategy vs. current strategy				
Base case (no change in assumptions)	2591	(84)	(24)	(108)
Initial investment for DOTS doubled	2591	(49)	(25)	(74)
U.S. government also pays all drug costs over 20-yr period	2591	(80)	(26)	(106)
Annual decline in incidence is 4%	1909	(51)	(18)	(69)
Annual decline in incidence is 3%	1518	(32)	(15)	(47)
Annual decline in incidence is 2%	1048	(12)	(11)	(22)
Annual decline in incidence is 1.2%	658	6	(7)	(1)
Three variables made less favorable†	1444	(26)	(14)	(40)
No. of migrants entering the United States from Mexico declines to 50% of current levels	1296	(24)	(12)	(37)
No. of migrants entering the United States from Mexico declines to 33% of current levels	864	(5)	(8)	(13)
Addition of tuberculin skin testing to radiographic screening vs. current strategy				
Base case (no change in assumptions)	401	260	69	329
78% of legal immigrants with latent tuberculosis infection complete 9 mo of isoniazid therapy	1411	264	64	328
Five variables made less favorable‡	305	510	101	611
Five variables made more favorable§	1812	240	56	296

* Costs are in millions of 2003 U.S. dollars. Values in parentheses represent net savings realized by the expansion of the DOTS strategy or the addition of tuberculin skin testing to the current strategy. Because of rounding, subcategories may not add up to the total.

† We assumed that there was a 3 percent annual decline in the incidence of tuberculosis with the use of the DOTS strategy, long-term residents made no return visits to their country of origin, and the U.S. government would pay for all drug costs in Mexico over the full 20 years, as well as for the costs of the initial DOTS expansion.

‡ We assumed that tuberculin skin testing had a specificity of 65 percent and that 21 percent of those with latent tuberculosis infection completed nine months of isoniazid therapy. We also assumed that in Mexico, the underlying prevalence of resistance to isoniazid was 50 percent higher than current estimates, the prevalence of latent tuberculosis infection was 50 percent lower than current estimates, and the prevalence of seropositivity for HIV was 50 percent lower than current estimates.

§ We assumed that tuberculin skin testing had a specificity of 90 percent and that 78 percent of those with latent tuberculosis infection completed nine months of isoniazid therapy. We also assumed that in Mexico, the prevalence of resistance to isoniazid therapy was 50 percent lower than current estimates, the prevalence of latent tuberculosis infection was 25 percent higher than current estimates, and the prevalence of seropositivity for HIV was 25 percent higher than current estimates.

controlling tuberculosis in low-income countries⁶¹ that has reduced the mortality,^{62,63} prevalence,¹⁸ and incidence¹⁶ of tuberculosis in several countries with a large burden of disease. Despite these demonstrated benefits, global implementation of the DOTS program remains hampered by insufficient funding. Our analysis demonstrates the potential

domestic economic and public health gains afforded by U.S. underwriting of expansion of the DOTS program in three nearby countries. These domestic gains would complement the humanitarian, economic, and public health benefits from improved control of tuberculosis abroad.

A recent analysis predicted that the implemen-

Table 4. Analysis of the U.S. Government's Investing in Expansion of DOTS Strategy in Haiti and Dominican Republic.*

Variable	Haiti	Dominican Republic	Total†	Reference
Key model variables				
No. of migrants entering United States each year				
Legal immigrants (screened)‡	18,701	19,387	38,088	2002 Yearbook of Immigration Statistics ¹²
Undocumented migrants and temporary visitors (unscreened)§	21,448	36,734	58,182	2002 Yearbook of Immigration Statistics, ¹² ITA Office of Travel and Tourism Industries ¹³
Annual incidence of new smear-positive cases of tuberculosis in 2001 (no./100,000)	138	59		WHO ⁵⁸
Prevalence of latent tuberculosis infection among 30-year-old migrants (%)				
Total	50.8	24.3		Styblo ²⁴
Recent (<2 yr)	2.3	1.5		
Prevalence of underlying multidrug resistance (%)	0.1	6.6		Pitchenik et al., ⁵⁹ Espinal et al. ⁶⁰
Prevalence of HIV infection (%)	4.5	2.5		United Nations Joint Programme on HIV/AIDS ³⁰
DOTS coverage beginning of 2002 (%)	37	25		Lee et al. ⁴⁵
Cost of initial expansion of DOTS strategy (millions of \$)¶	4.2	5.2	9.4	Vaca et al. ⁴⁶
Costs of antituberculosis drugs over 20 yr (millions of \$)‖	1.8	0.9	2.7	Global Drug Facility ⁴⁷
Key model findings				
No. of cases of tuberculosis in United States				
Radiographic screening plus current strategy	7,349	4,460	11,809	
No. of cases prevented with radiographic screening plus expansion of DOTS strategy	342	248	590	
No. of cases prevented with radiographic screening plus tuberculin skin testing	213	102	315	

tation of tuberculin skin testing of immigrants to the United States from various parts of the world, with treatment of latent infection tailored to regional patterns of drug resistance, would result in cost savings.⁸ Our findings regarding the implementation of tuberculin skin testing are at variance with this analysis for several reasons. We focused on Mexico because of its geographic proximity and the high numbers of Mexicans who migrate to the United States. The cost-effectiveness of tuberculin skin testing of migrants from countries such as Mexico, with an intermediate incidence of tuberculosis, will be less than that among migrants from countries with a higher incidence and therefore a higher prevalence of latent tuberculosis infection.²⁶ We also accounted for the anticipated failures of providers and patients to comply with recommendations for screening and therapy for latent infection. These operational problems have substantially re-

duced the impact of several large-scale screening programs.^{9-11,23,38,39}

There remains uncertainty regarding several key assumptions in our analysis, particularly the assumption that the incidence of tuberculosis would decline 6 percent annually within the migrants' source countries after the expansion of the DOTS program. This rate of decline was documented in Peru after the countrywide implementation of the DOTS program¹⁶ and falls midway between the 4.3 percent annual decline in prevalence attributable to the implementation of the DOTS program in China¹⁸ and the projected 7.5 percent reduction in the annual incidence in countries meeting DOTS targets.¹⁷ However, the epidemiologic effect in Mexico of the expansion of the DOTS program from 70 percent to 100 percent coverage of the population might be lower than the effect of expanding coverage from the very low levels that existed in Peru

Table 4. (Continued.)

Variable	Haiti	Dominican Republic	Total†	Reference
Costs in United States (millions of \$)				
Direct costs				
Total costs of radiographic screening plus current strategy	278	171	449	
Added costs or net savings of radiographic screening plus expansion of DOTS strategy	(9)	(5)	(14)	
Added costs or net savings of radiographic screening plus tuberculin skin testing	64	45	109	
Indirect costs				
Total costs of radiographic screening plus current strategy	106	61	167	
Added costs or net savings of radiographic screening plus expansion of DOTS strategy	(4)	(2)	(6)	
Added costs or net savings of radiographic screening plus tuberculin skin testing	10	9	19	
Total direct and indirect costs				
Total costs of radiographic screening plus current strategy	384	232	616	
Added costs or net savings of radiographic screening plus expansion of DOTS strategy	(13)	(7)	(20)	
Added costs or net savings of radiographic screening plus tuberculin skin testing	74	54	128	

* Costs are in millions of 2003 U.S. dollars. Values in parentheses represent net savings.

† Because of rounding, subcategories may not add up to the total.

‡ The same assumptions hold as listed in Table 1 for legal immigrants from Mexico.

§ The same assumptions hold as listed in Table 1 for undocumented migrants and visitors from Mexico, and the same method was used to calculate the number of person-years of visitors in the United States.

¶ Costs are extrapolated from a DOTS-expansion project in Ecuador and include those related to infrastructure, equipment, materials, personnel, and training.⁴⁶

|| Drug costs are based on estimates of new and retreated cases over a period of 20 years and unit prices listed by the Global Drug Facility.⁴⁷

before the DOTS program was implemented or might be lower than assumed because the incidence in Mexico is already declining. However, in a threshold analysis, expansion of the DOTS program in Mexico would remain cost saving for the United States as long as the annual decline in the incidence after the expansion of the program was at least 1.2 percentage points greater than the decline expected in the absence of changes in the tuberculosis-control strategy.

Other important limitations of our analyses were our assumption that the patterns of migration would remain constant and our estimates of the number of undocumented migrants in the United States. If the number of migrants decreases in future years, then the savings afforded by the DOTS

program would decrease, although this strategy would remain cost saving even if migration fell to a third of current levels. Conversely, if the number of migrants increases, expansion of the DOTS program would produce greater savings. Because of the large number and epidemiologic importance of undocumented migrants, inaccurate estimation of their numbers will affect overall projections. However, even if this group were excluded from our analysis, expansion of the DOTS program in Mexico would still result in net savings for the United States.

It may have been unrealistic to assume that the prevalence of seropositivity for HIV would not change for 20 years in the three source countries or among persons leaving these countries. However, in sensitivity analyses, expansion of the DOTS pro-

gram would yield greater cost savings if the prevalence of seropositivity for HIV was higher, because only undocumented migrants or visitors enter the United States with both tuberculosis and HIV infection. Enhanced screening would have no effect on these groups, since they are not screened, whereas expansion of the DOTS program would reduce the prevalence of latent tuberculosis infection among all migrants, including those with HIV infection.

We did not model the secondary spread of tuberculosis within the United States. However, the inclusion of secondary cases would further favor expansion of the DOTS program, because of the greater reduction in cases in the United States among all types of migrants with the implementation of this strategy.

The true costs of expanding the DOTS program are also uncertain, although costs similar to the ones we used have been documented in India.⁶³ We used Ecuadorian cost data because of the similarity of socioeconomic conditions, health, and infrastructure in Ecuador⁴⁶ to those in Mexico and the Dominican Republic. The applicability of these data to Haiti is less certain, given the possible need for increased infrastructure. Yet, the actual infrastructure-related costs of expanding the DOTS program in India⁶³ (which has income levels very similar to those in Haiti³¹) were lower than the costs we estimated for Haiti. Moreover, in sensitivity analyses, the finding of net U.S. savings with expansion of the DOTS program was robust even with substantial increases in the costs of initial expansion.

Our analysis had a number of strengths. We considered all types of migrants, including undocumented migrants and visitors, who constitute the vast majority of entrants to the United States.^{12,13} We also considered the effect of recent infection

and return visits to migrants' countries of origin, since the latter variable accounts for 20 percent of cases of tuberculosis among foreign-born permanent residents.¹⁴ Most values in the model were derived from cohort studies or randomized trials, reducing uncertainty. We estimated direct and indirect costs in an effort to determine the total costs to society of tuberculosis. Ultimately, the DOTS-expansion strategy remained the most effective and economical approach in multiple sensitivity analyses. Findings were similar for migrants from Haiti and the Dominican Republic, despite differences from Mexico in the current infrastructure of the DOTS program, DOTS coverage, and the epidemiologic characteristics of tuberculosis and HIV infection. This suggests the findings are potentially applicable to migrants from other countries and possibly also for other high-income countries that receive large numbers of migrants.

We conclude that U.S. government's underwriting of the expansion of the DOTS strategy in Mexico, the Dominican Republic, and Haiti is the most effective long-term approach to reducing tuberculosis-related morbidity and mortality among migrants from those countries and would produce net savings in the United States. These projected domestic benefits should encourage the governments of developed countries to provide substantial and sustained funding for the control of tuberculosis abroad.

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REFERENCES

1. Corbett EL, Watt CJ, Walker N, et al. The growing burden of tuberculosis: global trends and interactions with the HIV epidemic. *Arch Intern Med* 2003;163:1009-21.
2. Reported tuberculosis in the United States, 2002. Atlanta: Centers for Disease Control and Prevention, 2003. (Accessed August 22, 2005, at <http://www.cdc.gov/nchstp/tb/surv/surv2002/default.htm>.)
3. Ellis E, Sauvé L, Phipers M, Sheardown C, Allegakone M. Tuberculosis statistics 2003. Ottawa: Public Health Agency of Canada, 2004. (Accessed August 11, 2005, at <http://www.phac-aspc.gc.ca/publicat/tbcan02/index.html>.)
4. Reported tuberculosis in the United States, 2001—tuberculosis case rates: United States, 2001. Atlanta: Centers for Disease Control and Prevention, 2001. (Accessed August 11, 2005, at <http://www.cdc.gov/nchstp/tb/surv/surv2001/default.htm>.)
5. Binkin NJ, Zuber PLF, Wells CD, Tipple MA, Castro KG. Overseas screening for tuberculosis in immigrants and refugees to the United States: current status. *Clin Infect Dis* 1996;23:1226-32.
6. Coker RJ, Bell A, Pitman R, Hayward A, Watson J. Screening programmes for tuberculosis in new entrants across Europe. *Int J Tuberc Lung Dis* 2004;8:1022-6.
7. Geiter L, ed. Ending neglect: the elimination of tuberculosis in the United States. Washington, D.C.: National Academies Press, 2000.
8. Khan K, Muennig P, Behta M, Zivin JG. Global drug-resistance patterns and the management of latent tuberculosis infection in immigrants to the United States. *N Engl J Med* 2002;347:1850-9.
9. Dasgupta K, Schwartzman K, Marchand R, Tannenbaum TN, Brassard P, Menzies D. Comparison of cost-effectiveness of tuberculosis screening of close contacts and foreign-born populations. *Am J Respir Crit Care Med* 2000;162:2079-86.

10. Jereb J, Etkind SC, Joglar OT, Moore M, Taylor Z. Tuberculosis contact investigations: outcomes in selected areas of the United States, 1999. *Int J Tuberc Lung Dis* 2003;7(Suppl 3):S384-S390.
11. British Columbia Center for Disease Control. Annual report: tuberculosis control in 2002. Vancouver, Canada: British Columbia Ministry of Health, 2003.
12. Office of Immigration Statistics. 2002 Yearbook of immigration statistics — October 2003. Washington, D.C.: Department of Homeland Security, 2003.
13. ITA Office of Travel and Tourism Industries. Information on inbound travel to the US. (Accessed August 11, 2005, at <http://tinet.ita.doc.gov/outreachpages/index.html#inbound>.)
14. McCarthy OR. Asian immigrant tuberculosis — the effect of visiting Asia. *Br J Dis Chest* 1984;78:248-53.
15. Treatment of tuberculosis: guidelines for national programmes. 2nd ed. Geneva: World Health Organization, 1997.
16. Suarez PG, Watt CJ, Alarcon E, et al. The dynamics of tuberculosis in response to 10 years of intensive control effort in Peru. *J Infect Dis* 2001;184:473-8.
17. Elzinga G, Raviglione MC, Maher D. Scale up: meeting targets in global tuberculosis control. *Lancet* 2004;363:814-9.
18. China Tuberculosis Control Collaboration. The effect of tuberculosis control in China. *Lancet* 2004;364:417-22.
19. Floyd K, Blanc L, Raviglione M, Lee JW. Resources required for global tuberculosis control. *Science* 2002;295:2040-1.
20. Drummond MF, Stoddart GL, Torrance GW. Methods for the economic evaluation of health care programmes. Oxford, England: Oxford University Press, 1987.
21. Weinstein MC, Siegel JE, Gold MR, Kamlet MS, Russell LB. Recommendations of the Panel on Cost-Effectiveness in Health and Medicine. *JAMA* 1996;276:1253-8.
22. Zuber PLF, Binkin NJ, Ignacio AC, et al. Tuberculosis screening for immigrants and refugees: diagnostic outcomes in the State of Hawaii. *Am J Respir Crit Care Med* 1996;154:151-5.
23. Nolan CM, Elarth AM. Tuberculosis in a cohort of Southeast Asian refugees: a five-year surveillance study. *Am Rev Respir Dis* 1988;137:805-9.
24. Styblo K. The relationship between the risk of tuberculosis infection and the risk of developing infectious tuberculosis. *Bull Int Union Tuberc* 1985;60:117-9.
25. Further studies of geographic variation in naturally acquired tuberculin sensitivity. *Bull World Health Organ* 1955;12:63-83.
26. Schwartzman K, Menzies D. Tuberculosis screening of immigrants to low-prevalence countries: a cost-effectiveness analysis. *Am J Respir Crit Care Med* 2000;161:780-9.
27. Comstock GW. How much isoniazid is needed for prevention of tuberculosis among immunocompetent adults? *Int J Tuberc Lung Dis* 1999;3:847-50.
28. Nolan CM, Aitken ML, Elarth AM, Anderson KM, Miller WT. Active tuberculosis after isoniazid chemoprophylaxis of Southeast Asian refugees. *Am Rev Respir Dis* 1986;133:431-6.
29. Brown RE, Miller B, Taylor WR, et al. Health-care expenditures for tuberculosis in the United States. *Arch Intern Med* 1995;155:1595-600.
30. UNAIDS home page. Joint United Nations Programme on HIV/AIDS. (Accessed August 11, 2005, at <http://www.unaids.org/EN/default.asp#>.)
31. Granich RM, Balandrano S, Santaella AJ, et al. Survey of drug resistance of *Mycobacterium tuberculosis* in 3 Mexican states, 1997. *Arch Intern Med* 2000;160:639-44.
32. World Bank home page: data by country. (Accessed August 11, 2005, at <http://www.worldbank.org/data/countrydata/countrydata.html>.)
33. Lubotsky D. The effect of changes in the U.S. wage structure on recent immigrants' earnings. Princeton, N.J.: Research Program in Development Studies, Woodrow Wilson School of Public and International Affairs, 2001.
34. Green DA, Worswick C. Immigrant earnings profiles in the presence of human capital investment: measuring cohort and macro effects. Vancouver, Canada: University of British Columbia, 2003.
35. Borjas G. The economic analysis of immigration. In: Ashenfelter OC, ed. *Handbook of labor economics*. New York: Elsevier, 1999:1697-760.
36. Groth-Peterson E, Knudsen J, Wilbek E. Epidemiological basis of tuberculosis eradication in an advanced country. *Bull World Health Organ* 1959;21:5-49.
37. Ferebee SH. Controlled chemoprophylaxis trials in tuberculosis: a general review. *Bibl Tuberc* 1970;26:28-106.
38. Blum RN, Polish LB, Tapy JM, Catlin BJ, Cohn DL. Results of screening for tuberculosis in foreign-born persons applying for adjustment of immigration status. *Chest* 1993;103:1670-4.
39. Catlos EK, Cantwell MF, Bhatia G, Gedin S, Lewis J, Mohle-Boetani JC. Public health interventions to encourage TB class A/B1/B2 immigrants to present for TB screening. *Am J Respir Crit Care Med* 1998;158:1037-41.
40. Moran-Mendoza AO. The value of the tuberculin skin test size in predicting the development of tuberculosis in contacts of active cases. Vancouver, Canada: University of British Columbia, 2004.
41. Yuan L, Richardson E, Kendall PRW. Evaluation of a tuberculosis screening program for high-risk students in Toronto schools. *CMAJ* 1995;153:925-32.
42. Kopanoff DE, Snider DE Jr, Caras GJ. Isoniazid-related hepatitis: a U.S. Public Health Service cooperative surveillance study. *Am Rev Respir Dis* 1978;117:991-1001.
43. Nolan CM, Goldberg SV, Buskin SE. Hepatotoxicity associated with isoniazid preventive therapy: a 7-year survey from a public health tuberculosis clinic. *JAMA* 1999;281:1014-8.
44. Reported tuberculosis in the United States, 2000. Atlanta: Centers for Disease Control and Prevention, 2000. (Accessed August 11, 2005, at <http://www.cdc.gov/nchstp/tb/surv/surv2000/default.htm>.)
45. Lee JW, Espinal M, Jaramillo E. Report of site visit to evaluate DOTS expansion in Latin America. Geneva: World Health Organization, 2002.
46. Vaca J, Peralta H, Gresely L, et al. DOTS implementation in a middle-income country: development and evaluation of a novel approach. *Int J Tuberc Lung Dis* 2005;9:521-7.
47. Global Drug Facility. First-line tuberculosis drugs and formulations currently supplied/to be supplied by the global TB drug facility. Geneva: World Health Organization. (Accessed August 11, 2005, at http://www.stoptb.org/gdf/drugsupply/drugs_available.asp.)
48. Global tuberculosis control: surveillance, planning, financing. Geneva: World Health Organization, 2003. (Accessed August 11, 2005, at <http://www.who.int/docstore/gtb/publications/globrep03/>.)
49. Sutherland I. The evolution of clinical tuberculosis in adolescents. *Tubercle* 1966;47:308.
50. Comstock GW, Edwards LB, Livesay VT. Tuberculosis morbidity in the U.S. Navy: its distribution and decline. *Am Rev Respir Dis* 1974;110:572-80.
51. Rieder HL. Epidemiologic basis of tuberculosis control. Paris: International Union Against Tuberculosis and Lung Disease, 1999.
52. Grzybowski S, Enarson DA. Results in pulmonary tuberculosis patients under various treatment conditions. *Bull Int Union Tuberc* 1978;53:70-5. (In French.)
53. Whalen CC, Johnson JL, Okwera A, et al. A trial of three regimens to prevent tuberculosis in Ugandan adults infected with the human immunodeficiency virus. *N Engl J Med* 1997;337:801-8.
54. Wood R, Maartens G, Lombard CJ. Risk factors for developing tuberculosis in HIV-1-infected adults from communities with a low or very high incidence of tuberculosis. *J Acquir Immune Defic Syndr* 2000;23:75-80.
55. Murray J, Sonnenberg P, Shearer SC, Godfrey-Faussett P. Human immunodeficiency virus and outcome of treatment for new and recurrent pulmonary tuberculosis in African patients. *Am J Respir Crit Care Med* 1999;159:733-40.
56. Sonnenberg P, Murray J, Glynn JR, Shearer S, Kambashi B, Godfrey-Faussett P. HIV-1 and recurrence, relapse, and reinfection of tuberculosis after cure: a cohort study in South African mineworkers. *Lancet* 2001;358:1687-93. [Erratum, *Lancet* 2002;359:2120.]

57. Consumer price index. Washington, D.C.: Department of Labor, Bureau of Labor Statistics. (Accessed August 11, 2005, at <http://www.stats.bls.gov>.)
58. Global tuberculosis control: surveillance, planning, financing. Annex 4. Regional profile for the Americas: notification, detection and DOTS coverage, 2001. Geneva: World Health Organization, 2003. (Accessed August 11, 2005, at http://www.who.int/docstore/gtb/publications/globrep03/pdf/rep_sections/4_page_143-180.pdf.)
59. Pitchenik AE, Russell BW, Cleary T, Pejovic I, Cole C, Snider DE Jr. The prevalence of tuberculosis and drug resistance among Haitians. *N Engl J Med* 1982;307:162-5.
60. Espinal MA, Baez J, Soriano G, et al. Drug-resistant tuberculosis in the Dominican Republic: results of a nationwide survey. *Int J Tuberc Lung Dis* 1998;2:490-8.
61. Murray CJL, Styblo K, Rouillon A. Tuberculosis in developing countries: burden, intervention and cost. *Bull Int Union Tuberc Lung Dis* 1990;65:6-24.
62. Dye C, Fengzeng Z, Scheele S, Williams B. Evaluating the impact of tuberculosis control: number of deaths prevented by short-course chemotherapy in China. *Int J Epidemiol* 2000;29:558-64.
63. Khatri GR, Frieden TR. Controlling tuberculosis in India. *N Engl J Med* 2002;347:1420-5.

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