

## Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Schwartzman K, Oxlade O, Barr RG, et al. Domestic returns from investment in the control of tuberculosis in other countries. *N Engl J Med* 2005;353:1008-20.

## SUPPLEMENTAL METHODS

### **General outline of model**

We developed a decision analysis model, incorporating multiple Markov processes (TreeAgePro 2005 Health Care release 0.4, TreeAge Software, Williamstown, MA), to estimate the cumulative probability of active tuberculosis (TB), TB-related death, and associated costs among migrants after their entry into the US. A societal perspective was used, meaning that we included costs for governments and health care providers (together considered *direct costs*), and out-of-pocket expenditures, plus lost wages due to time spent for care, plus disability and death for patients and their families (together considered *indirect costs*).

Throughout the 20-year time frame of the analysis, we assumed there would be no change in the number and average age of migrants of each major type entering the US from Mexico (and Haiti and the Dominican Republic in secondary analyses). As shown in Figure S1, at the time of entry, migrants were assumed to be in one of five TB-related health states, and one of three HIV-related health states. The probability (prevalence) of latent tuberculosis infection (LTBI) was the only parameter that differed between the three strategies. With the DOTS expansion strategy, LTBI prevalence declined in migrants – of all types, in proportion to the impact of DOTS on incidence, but prevalence did not change with the radiographic screening/current TB control strategy, or with the tuberculin skin testing (TST) screening strategy.

In the first year after entry, migrants could have one of several outcomes; the probability of each of these outcomes depended on their TB and HIV related health states at entry (Table S1). Clinical outcomes would also vary according to whether the TB-related state was diagnosed and treated. Potential clinical outcomes were the same for HIV infected or uninfected persons, but the probabilities of some outcomes were very different (Table S1). Specifically, for HIV infected

persons there was no chance of spontaneous cure, and 100% mortality from TB disease with MDR strains.

Migrants' health states at the beginning of each subsequent year depended on the events during the preceding year - particularly whether treatment had been successfully completed, or whether new TB or HIV infection had occurred. Since the risk of new TB infection was much lower after entry into the US, the likelihood of development of active TB fell considerably after the first two years in the US – as observed in the US (1), and elsewhere (2;3). Mortality from all other causes among migrants in the US was assumed to be the same as for the US general population (4)

Figure S2 represents a simplified sample decision analysis tree for a migrant who enters the US with recent latent TB infection (acquired within the last two years). After entry the migrant can either die from other (non-TB) causes, remain infected with LTBI, or reactivate to active TB disease. The probability of each of these events was determined from published estimates, summarised in Table S1. If active TB disease develops, this may be diagnosed, or undiagnosed – the probability of which is determined by their migrant status (95% of legal immigrants diagnosed, compared to 90% of undocumented migrants or visitors).

Treatment outcomes were determined by underlying drug sensitivity (the probability of which was taken from published studies of prevalence of drug resistant TB in the countries of origin), compliance and HIV infection. The average probability of cure among defaulters was taken from studies of timing of default and randomised trials of 3, 4, and 5 months of therapy. Co-infection with HIV did not alter probability of diagnosis, nor the treatment outcomes of cure, or relapse. However, mortality among HIV infected persons with active TB was 2.25 times higher during treatment, and was 100% if TB was undiagnosed.

Those who survived the first year re-entered a second Markov process in Year 2. The specific health state in which they began year 2, was the health state in which they ended Year 1. For

example, migrants who survived Year 1 with undiagnosed active TB disease then entered Year 2 in the “active TB disease” state.

### **Detailed definitions and sources of information for migrants**

We developed separate models for three categories of migrants:

- i) Legal Immigrants – this group included all legally accepted permanent residents. This included immigrants who applied and were accepted from overseas, and those who requested adjustment of their status while in the United States. This also included refugees accepted overseas, and persons who sought and were granted asylum after arrival in the US. The number of migrants in this category was taken from Table 2 from reference (5), and the average age for this group of migrants from each country calculated from data in Table 13 from reference (6).
- ii) Undocumented Migrants (previously referred to as “illegal aliens”) – there is little information on the number of undocumented migrants who enter each year and stay long term in the US. We used data from Table Q from reference (5) to obtain the estimated prevalent number from each country in the US in 2002. Based on an assumption they would adjust their status after 5 years, we estimated the number entering per year as the prevalent number divided by 5. We assumed this group would have the same average age as legal immigrants.
- iii) Visitors – this included all short-term visitors such as tourists and individuals visiting friends and relatives, as well as those who enter with temporary visas. This last group includes students, business people and migrant workers. The number of visitors was taken from two federal sources: Table 25 of reference (5), and reference (7). Person years of visitors’ time (shown in all Tables) in the USA was calculated from the total number of entrants each year (7) and average length of stay for different sub-groups (5;7). Inherent in the person-year method is the assumption that the **daily** risk of developing tuberculosis in visitors staying 2 weeks is the same as for a person who stays a full year. The average age for visitors from each country was calculated from data in Table 29 from (5).

There is no published information on the income of visitors. It is likely that a small proportion do work, but likely at temporary jobs and at low wages. Therefore, for this analysis we assumed visitors' income to be nil.

### **Screening of migrants – current practice**

At present in the United States two different screening strategies are employed, depending upon the location of application for permanent residence. If application is made overseas, a chest x-ray (CXR) is done first. If this is abnormal, then sputum smears are done. If the sputum smears are positive, the applicant is treated overseas for active TB - at least until sputum smear-negative. If sputum smears are negative, applicants may be classified as B1 (strong radiographic suspicion of active TB) or B2 (the x-ray is considered compatible with inactive TB), or normal. These individuals are allowed to enter the US. After arrival, immigrants classified as having B1 or B2 chest radiographs are referred to local public health units for active follow-up.

As summarized in Table S2, 10.3% of individuals with B1 designation, and 2.4% of those with B2 designation, are found to have active tuberculosis within the first year after arrival (8). Most likely involve prevalent active cases that are missed by sputum smears - as even after arrival in the United States the great majority of culture-confirmed cases are smear-negative (9). Of those with B1 or B2 CXRs and negative sputum cultures, many will have tuberculin tests; those who are tuberculin positive may be offered treatment for latent tuberculosis. However, tuberculin testing and provision of LTBI therapy is at the discretion of the local public health department; practice and compliance vary considerably. There are no national data on these outcomes, although evaluations of these aspects of the screening programme have been published (10;11).

For individuals who apply to adjust their status to become legal permanent residents from within the United States, the screening procedures are different. They are seen by civil surgeons, who are instructed to perform tuberculin skin testing. If the TST reaction measures 5mm or greater,

then the applicant undergoes a chest x-ray; if this is abnormal, further testing including sputum examinations are done. If the chest x-ray is normal or sputum examinations are negative, then TST-positive individuals are referred to the local public health department. A recent evaluation noted that in approximately 20% of applicants, only a chest x-ray was done--and among those tuberculin tested, approximately 10% of all applicants had positive reactions (12). There are no data on the proportion that are seen at local public health departments, nor the evaluations undertaken, nor the proportion prescribed or completing LTBI therapy.

In total only four legal immigrants who entered the US during 1998-2002 from the three source countries were HIV-positive (CDC, unpublished data) (Table S2). This supports our assumption that the HIV seroprevalence among legal immigrants was nil.

### **Details of tuberculosis control strategies – including screening**

Radiographic screening plus current tuberculosis control strategy: With this strategy, current TB control programmes in the US and Mexico (and Haiti and the Dominican Republic – for secondary analyses) would remain unchanged. This means current levels of case finding, treatment outcomes, incidence of smear positive disease, corresponding annual risk of TB infection as well as prevalence of underlying TB drug resistance and HIV seroprevalence would remain unchanged for the entire 20 year analytic horizon in all three source countries included in this analysis. Therefore the prevalence of latent TB infection, active TB and HIV infection would remain unchanged among migrants from Mexico (and Haiti and the Dominican Republic).

We also assumed that the current levels of DOTS coverage as reported by WHO would remain unchanged. These current levels of DOTS coverage have been achieved with assistance from foreign donors, particularly USAID. Hence consideration of current levels of DOTS coverage implicitly accounts for current levels of US government investment in these three countries. The current levels of foreign donor assistance were not explicitly modelled. This is because the same

expenditures would have been added to all three strategies, making all strategies more expensive, but without changing the differences between them.

When modelling the current radiographic screening strategy, we assumed that ALL applicants would undergo chest radiographic screening as a first step. We also assumed that the 2-3% of individuals with abnormal x-rays suggestive of inactive TB would undergo tuberculin screening and appropriate further evaluation and follow up - including therapy for LTBI, as recommended by the American Thoracic Society (13). This was considered a part of every applicant's evaluation, even though the evaluation and therapy of LTBI is presently performed at a different time, in a different place, and by different providers from the chest radiographic screening.

The assumption that under "current conditions," radiographic screening (and not TST screening) would be performed for all legal immigrants was made for a number of reasons. i) Previously published studies have shown that TST screening is much less cost-effective than chest radiographic screening (14). ii) Sensitivity of TST for detection of active TB is, if anything less than with CXR (15). iii) Including TST screening for some, but not all, legal immigrants, and CXR for the others would make the modelling results more difficult to interpret. iv) There is very little published information regarding outcomes and costs of the evaluation, treatment and follow-up of the TST positive adjusters, who are currently seen by US civil surgeons. Including TST screening of legal immigrants as part of the current radiographic screening strategy would have increased the costs, but the effectiveness--in terms of prevention of future cases--could not be predicted, given the absence of data. The primary objective of TST screening of adjusters, and chest radiographic screening of overseas applicants is the detection of prevalent active TB. Therefore, we felt that using chest radiography as the sole screening modality would be less expensive, hence less favourable to the DOTS expansion strategy. Including some TST screening within the radiographic screening strategy, might have resulted in costs and impact closer to the TST strategy, but would not have altered the differences between the TST strategy and the DOTS expansion strategy.

In addition, we considered all costs of radiographic screening to be US costs, even though almost half the legal immigrants undergo this screening overseas. This is because these costs are often borne by family members already in the US, who are their sponsors. As well, it may be argued that cash expenditures just prior to immigration to the US acts to reduce the immigrants' net wealth upon arrival in the US.

The yield of radiographic screening is summarised in Table S2. The prevalence of active TB currently detected in newly arrived immigrants from the 3 source countries is much lower than was assumed for the base case analysis. (We assumed prevalence of active TB = 0.1% for migrants from Mexico, 0.2% for migrants from the Dominican Republic, and 0.3% for migrants from Haiti). The base case assumptions were based on screening studies conducted 20 or more years ago (16-18), or from other countries (19;20). If the prevalence of active TB at the time of entry was over-estimated in our analysis (as it appears to have been), this would inflate the benefits of screening, making DOTS expansion seem less cost-effective. More importantly, this assumption would reduce the apparent advantages of the DOTS expansion strategy, which acts mainly to reduce incident cases after entry due to reactivation of LTBI.

*DOTS expansion strategy:* We assumed this would be in addition to, and would not replace, radiographic screening of legal immigrants. We assumed that in all three countries DOTS would be expanded from the level of coverage in January 2003 (21), to reach 100% of government health facilities by the end of three years. Case detection would increase from WHO estimated levels (22) to 70%, and treatment success (cure and treatment completion) to 85% - the WHO targets (23). Delay in diagnosis, and hospitalization would decrease with DOTS as has been documented elsewhere (24;25). HIV sero-prevalence (26), and underlying drug resistance in the three countries (18;27-29) would not change.

The most important assumption was that DOTS expansion would result in a 6% annual decrease in the incidence of new smear positive TB cases. This would result in corresponding reduction in annual risk of infection (30) and therefore also prevalence of recent and long-standing latent TB infection. This impact of DOTS expansion in Mexico, Haiti and the Dominican Republic was assumed to be the same as reported in Peru because of their similar economic situations(31), health infrastructure, HIV and TB epidemiology - including drug resistance levels. In Peru TB incidence declined by 6% annually for more than a decade after nationwide implementation of DOTS (32). This decline, used for the base case analysis also is midway between two more recent estimates. In China, the annual decline in prevalence of active TB attributable to DOTS was 4.3% (33). Using a well-validated model (34), incidence was predicted to decline by 7.5% annually (35) following achievement of WHO targets of 70% case detection and 85% treatment success.

We ignored the potential impact of the DOTS expansion strategy in reducing prevalent active TB upon entry to the US. This means we assumed the prevalence of active TB among entrants to the US would not change over the full 20 years of analysis – a conservative assumption with respect to potential benefits of the DOTS strategy.

Unfortunately the costs of DOTS implementation in Peru are not available. Therefore, costs for initial expansion in our model were extrapolated from a DOTS expansion project in Ecuador. This project, funded by the Canadian International Development Agency and administered by the Canadian Lung Association is described in detail elsewhere (36). In brief, with an investment of \$3.3 million (US) over three years, DOTS was implemented for 52% of Ecuador's population, or 6.7 million persons. This funding provided for infrastructure, equipment, training, supervision as well as external consultants and administration. By the end of three years, DOTS was initiated in 100% of the Ministry of Health facilities covering 6.7 million persons, case finding had increased, and treatment outcomes had reached WHO targets.

To extrapolate these costs to the three countries analysed, we categorised expenditures as internal i.e. within Ecuador (71% of the total), and international i.e. external (29%). External costs, calculated per new smear positive TB case were extrapolated directly to Haiti, Dominican Republic and Mexico on the basis of the total number of new smear-positive TB cases in each country (22). Internal costs per TB case were extrapolated based on the ratio of per capita annual Gross National Income (GNI) in the country of interest (31) divided by the per capita annual gross national income in Ecuador (31), multiplied by the total number of new smear positive TB cases. This meant costs per TB case were lower in Haiti, but higher in Mexico than in Ecuador. The costs for DOTS expansion based on the Ecuador experience were lower than the funding requested for DOTS expansion in Haiti – in an application to the Global Fund for AIDS, Tuberculosis and Malaria (37), but much higher than actual costs incurred for a massive DOTS expansion project in India (38)- even after accounting for differences in GNI (31) – as shown in Table S3.

Using the same general modeling methods, and the same pathogenetic inputs summarized in table S1, the impact of DOTS expansion in the three countries was estimated. The impact was very substantial. In Mexico, for example, with the current DOTS coverage and programme function, 336,000 TB cases and 147,000 TB deaths are projected over the next 20 years. This mortality is predicted with 70% case detection in DOTS areas and 50% case detection in non DOTS areas, because of the very high mortality of untreated smear positive cases. With the key assumption that DOTS expansion will result in 6% decline in incidence of TB each year, 241,500 TB cases are projected and 94,500 deaths. This means that DOTS expansion in Mexico would prevent 94,500 TB cases and avert 52,500 deaths within that country (data not shown in tabular form).

TST screening strategy: We assumed TST screening would be for all legal immigrants, conducted within the US, and in addition to (not instead of) chest radiographic screening. All immigrants would undergo TST screening; those with a positive TST would undergo a medical evaluation, and

appropriate investigations including repeat CXR, sputum and blood tests. Immigrants with a positive TST would be prescribed 9 months isoniazid (INH), according to US standards (13). The efficacy of 9 months INH would be 90% (39) with drug sensitive LTBI, and 0% with INH resistant LTBI (40). The prevalence of INH-resistant latent TB among migrants would be the same as the prevalence of initial INH resistance among active TB cases in the countries of origin (18;28;29;41).

Since we assumed there would NOT be legal enforcement for TST screening nor INH therapy, immigrants could fail to complete TST testing, not return for reading, not report for medical evaluation, refuse to initiate, or fail to complete INH therapy. And their providers could fail to prescribe INH even when clinically indicated. Therefore, we took the average percentage of dropouts and non-compliance at each step, from published evaluations of large-scale tuberculin screening programmes, which are summarised in Table S4. The probability that LTBI was cured was therefore the product of the probabilities of completing screening, reporting for medical evaluation, prescription of INH by physicians when indicated, acceptance and completion of INH therapy by migrants, and the probability the TB infection was INH sensitive.

### **Tuberculosis pathogenesis, testing and treatment**

Tuberculosis health states: Possible TB-related health states were: 1) no tuberculosis; 2) latent tuberculosis infection (LTBI), which was subdivided into: 2a) recent - meaning acquired within 2 years; and, 2b) long-standing - meaning acquired more than 2 years ago; 3) active tuberculosis; and, 4) healed active tuberculosis (treated, or spontaneously resolved), as shown schematically in Figure S1. Latent and active TB were modelled as drug-sensitive, single-drug resistant, or multi-drug resistant. Key pathogenetic model assumptions regarding reactivation and cure rates for HIV-negative and HIV-positive individuals were based on published cohort studies and randomized trials. These are summarized in Table S1.

Incidence of tuberculosis among migrants is highest in the first two years after entry or re-entry (1;42;43). There is evidence that this is primarily due to recent infection, or re-infection (42;43).

To account for this phenomenon, we estimated the proportion of migrants who had acquired TB infection less than two years before entry into the US or Canada. This was calculated as:

*[proportion uninfected at (average age of immigration – 2)] times 2[average annual risk of infection (ARI)]*

(The ARI is calculated using the WHO estimated incidence of smear-positive disease (44) and the Styblo formula (30)).

In these migrants the risk of TB reactivation was assumed to be 5% (if HIV-negative) in total during the first two years after entry (45;46). After that, the risk fell to 0.1% annually, the same as those with long-standing LTBI at entry, based on two large cohorts followed prospectively after tuberculin screening (16;47).

Treatment outcomes were taken from US national average outcomes. It was assumed that, once diagnosed, all categories of migrants would receive US standard of care for their tuberculosis and therefore achieve US national average cure rates (48). We assumed that treatment outcomes of transfers-out were equivalent to those of default, based on a California study in which treatment outcomes of transferred patients were much worse than in patients not transferred (49). For individuals who defaulted from therapy we assumed an overall cure rate of 62%. This was based on published studies of timing of default (50), and the following assumptions. For patients who defaulted with two months or less of therapy, cure rate would be 25% which is the same as untreated patients (51). For those who defaulted after three or four months of therapy, risk of relapse and failure is higher, but cure rates are better than in untreated patients – based on randomized trials of regimens of 3 or 4 months duration (52-54). Patients who complete five months or more of therapy were considered to have the same cure rate as those who complete a full course.

LTBI treatment was considered to occur only at initial entry to the US, as the result of radiographic or tuberculin screening as described above. This ignores the small number of

individuals who might be tuberculin tested and receive LTBI therapy as the result of contact investigations. We estimated this number - using the number of cases of active TB reported in the United States among foreign-born individuals and an assumption that each would infect four contacts. Based on this calculation, the annual number of newly infected contacts would be less than 1% of all entrants each year.

The risk of acquiring TB infection in the US in 2002 was assumed to be negligible. The annual risk of TB infection has been declining steadily among US military recruits, from the 1960's (47) until the 1990's (55), when it was less than 0.04% per year. However during return visits to their countries of origin, migrants face the same risk of TB infection as the general population there (56). Low budget travellers from low incidence countries have the same risk of TB infection as the general population of high incidence countries they visit (56). Hence, we assumed that legal immigrants making return visits to their country of origin must have at least the same risk as low budget travellers from low incidence countries.

We assumed the sensitivity of TST to be 99% in HIV negative immigrants (57). TST specificity, as shown in Table 1 (main article), was calculated from the effect of BCG vaccination, non-tuberculous mycobacteria and TB infection in foreign born populations (14;58). Since so few legal immigrants who entered the US between 1998-2002 from the 3 countries had HIV infection – the impact of HIV infection on the sensitivity of TST in the screening of legal immigrants would be negligible, and was ignored.

HIV-related health states: We modelled three HIV-related health states: no HIV infection, early (asymptomatic) infection, and late infection - clinical AIDS. We assumed the prevalence of HIV infection to be zero among legal immigrants, as explained earlier. However, undocumented entrants and visitors were considered to have the same HIV seroprevalence as the general populations of their countries of origin, as estimated by UNAIDS (26).

For entrants with concomitant LTBI and HIV infection, the risk of active TB was determined by the duration of latent TB, and the stage of HIV infection (Table S1). The risk of active TB in persons with long-standing LTBI, and HIV infection has been studied in a number of settings. In many of these studies the states of new or old TB infection and early or late HIV were not clearly distinguished. However, a South African study did address these methodologic problems (59). Therefore the base case estimate is taken from that study. Risk of active disease in persons with long-standing LTBI and late HIV infection was taken from the same study, and is substantially higher.

There is much less information regarding risk of disease following newly acquired TB infection in HIV-infected individuals. We therefore extrapolated from data for HIV-negative persons, in whom the risk of development of active TB following newly acquired TB infection is 10-50 times higher than the risk of reactivation from longstanding LTBI. Patients with early HIV and new TB infection are thus estimated to have a tenfold increase in risk of active disease, relative to persons with early HIV and longstanding LTBI—i.e. a 33% annual risk of disease.

Outbreak reports among groups with late HIV infection describe very high rates of active disease within months of exposure (60-62). Therefore we assumed that 100% of individuals with late HIV infection and new TB infection would develop active TB within one year. We assumed that HIV infection would not affect the likelihood of diagnosis for active TB, nor response to treatment. However, HIV-infected individuals with smear positive active TB were assumed to have a 2.25-fold increase in the risk of death during treatment (63-66), 2.2 times increased risk of death after treatment (67;68), and 100% mortality without treatment.

Risks of progression and survival with early and late HIV infection were obtained from cohort studies in Haiti and Uganda (69;70), because HIV infected undocumented entrants and visitors were assumed to have limited access to HIV care after entry. HIV infection would not affect the sensitivity of the TST strategy, because only HIV-negative legal immigrants undergo TST

screening. We assumed that migrants would not acquire HIV infection within the US, but would have the same risk of infection as the general population, during subsequent return visits to their countries of origin.

## **Costs**

We assumed that all TB-related health care expenditures in the US were made by governments, because the great majority of TB care in the US is publicly funded. Screening costs were also assumed to be borne by governments, as explained earlier.

There is little published information on indirect costs of active TB for patients and their families in high-income countries. Data on disability was therefore taken from studies in low- and middle-income countries (71;72). Patients with active TB would be 50% disabled (productivity loss) from symptom onset until diagnosis, unable to work while hospitalised, and 50% disabled for the remainder of the first two months of treatment(71;73;74). Undiagnosed patients, or those who failed treatment had 50% disability throughout their illness. Productivity loss from death was estimated as annual gross national income per capita (31) times the number of years remaining in the model, with appropriate discounting(75). Hourly wage was the annual gross national income per capita, divided by 2080 hours (40 hours per week for 52 weeks).

To measure out-of-pocket expenditures, and time lost from work for TB patients and their families we adapted a questionnaire originally used to measure the cost of illness in Sub-Saharan Africa (76). This was pre-tested in Montreal, translated into French, Creole, and Spanish, and administered to 50 TB patients and their families in Montreal, New York City, and Miami. This questionnaire estimated lost wages, and out-of-pocket expenditures by TB patients and their families - in the pre-diagnostic period, during hospitalisation if any, and during treatment and follow up. We could find no published report of indirect costs related to tuberculosis screening – so such costs were not included.

## Sensitivity analyses

We conducted extensive sensitivity and threshold analyses, to assess the robustness of our findings to variations in key assumptions. Each parameter was varied, except for those pathogenetic parameters, summarized in Table S1, for which there were estimates from cohorts that were well characterized and properly studied.

For example, we examined the influence of varying rates of decline in tuberculosis incidence following DOTS expansion, and of a doubling in the cost of DOTS expansion. We considered a scenario where the US continues to pay for all TB drugs needed for new and retreatment cases in the countries throughout the 20-year simulation. Although this level of investment may not be sufficient to maintain DOTS, we assumed that the national governments would be motivated by this continued donor investment to support the additional costs of DOTS maintenance such as on-going refresher training, and supervision. Finally, we varied the frequency of return visits to entrants' countries of origin.

We varied the probability of treatment completion for latent TB, which is a key parameter driving the cost-effectiveness of TST screening: we increased adherence to TST testing, reading and medical evaluation by immigrants, prescription of LTBI by practitioners to 100%, and increased the acceptance by patients of INH therapy to 100%, and completion to 78%, as in a previous analysis (77;78). We evaluated favorable and unfavorable scenarios with respect to the specificity of the TST, the baseline prevalence of LTBI and HIV infection, and the probability of INH resistance. Higher specificity of the TST, higher prevalence of LTBI, higher HIV seroprevalence and less INH resistance would make TST screening (and INH therapy for LTBI) more cost effective. The reverse is also true i.e., lower specificity of the TST, lower prevalence of LTBI, lower HIV seroprevalence and more INH resistance would make TST screening less cost effective.

## **SUPPLEMENTAL RESULTS:**

Although the US federal government would be most likely to make foreign investments for DOTS expansion, the majority of the cost reductions would benefit individual US states. Based on the total number of all types of migrants arriving in each state, the estimated reduction in health care costs (ie direct costs) would be \$51 and \$24 million for California and Texas, respectively, as seen in Table S5.

A key sensitivity analysis determined the threshold impact of DOTS expansion on subsequent trends in incidence in Mexico, at which point this strategy would no longer be cost saving. As seen in Figure S3, DOTS expansion would still result in net savings if TB incidence declined by more than 1% annually. This also means that if the incidence of TB declined by 3% or 4% with the radiographic screening/current TB control strategy, and by 5% or 6% with DOTS expansion, then net savings would still result.

**SUPPLEMENTAL TABLES:**

**Table S1: Summary of assumptions about tuberculosis pathogenesis**

Pathogenetic Factor	Base	Range	Reference
<b>Reactivation from latent TB infection</b>			
<u>Present more than 2 years (“longstanding LTBI”)*</u>			
HIV uninfected	0.1%/ year	0.1% - 0.2%/year	(16;47)
HIV infected – asymptomatic	3.4%/year	3.4% - 8.7%	(59;79;80)
HIV infected – AIDS	33%/year	33% - 67%	(59)
<u>Within 2 years of new TB infection (“recent LTBI”)</u>			
HIV uninfected	5%	2% - 15%	(46;81)
HIV infected – asymptomatic	33%	33% - 100%	Extrapolated
HIV infected – AIDS	100%	50% - 100%	(60;62;82-84)
<u>Within 2 years of a second TB infection (re-infection)</u>			
HIV uninfected – Protective effect 80%	1%		(85;86)*
HIV infected – No protective effect	33% or 100%		Assumption
<b>HIV Uninfected and TB</b>			
<u>Untreated smear positive tuberculosis</u>			
Mortality - 1 year, & 2 years	33%, & 50%		From (87)
Spontaneous remission	25%		(51)
Relapse after spontaneous remission	2.5%/year	1.3% - 2.5%/ year	(51;88)
<u>Treated smear positive tuberculosis:</u>			
Relapse after cure (total over next 2 years)	3.0%	1.5% - 5%	(89-93) (50;52-54)
Cure rate if default (SDR or drug sensitive) **	62.4%		
<u>Effect of drug sensitivity or treatment outcomes</u>			
Relative risk of failure/ if single drug resistant	2.0		(94)
Relative risk of failure/ if multi-drug resistant	10.5		(94)
Relative risk of death/ if single drug resistant	1.0		(94)
Relative risk of death/ if multi-drug resistant	4.5		(94)
If MDR – Probability of cure with treatment	48%	48%-73%	(95;96)
– Probability of death with treatment	12%	12%-26%	(95;96)
<b>HIV Infected and TB</b>			
Average duration of HIV infection – Total	9.8 years	7.3-9.8	(69;70)
- Time spent in HIV asymptomatic state	9.0 years		(69)
Annual risk of progression of asymptomatic HIV to AIDS	7%	7%-9%	(69;70)
Annual risk of death from HIV: HIV asymptomatic state	4.6%		(69)
Annual risk of death from HIV: AIDS	22%		(69)
Effect of prior active TB on relative risk of death from HIV	2.2	(2.2 – 4.0)	(23;67;68)
Effect of HIV infection on relative risk of death during TB treatment (drug sensitive or single drug resistance)	2.25		(63-66)
Relapse after successful TB treatment (cured)	3.1%	3.1% - 6.4%	(97-99)

\* Assume that rate of reactivation from latent TB is the same whether it is more than two years after a first infection, or after re-infection.

\*\* Transfer out considered equivalent to default (49). Overall cure rate if default based on timing of default (from (50)), and cure rates from trials of very short course treatment (52-54).

**Table S2: Active tuberculosis cases detected by immigrant screening abroad—estimated numbers and proportions – between 1998-2002**

	Immigrants to the US from		
	Haiti	Dominican Republic	Mexico
<u>Category B1</u>			
- Total Number identified*	148	140	701
- Proportion with active TB**	.103	.103	.103
- Total Number of TB Cases	15	14	72
<u>Category B2</u>			
- Total Number identified *	769	447	1,092
- Proportion with active TB**	.024	.024	.024
- Total Number of Cases	18	11	26
Total estimated number of TB cases	33	25	98
Total number screened overseas (1998-2000)***	66,294	71,842	323,527
Overall prevalence (%) of active TB	0.05%	0.04%	0.03%
TOTAL Number with HIV infection entering US in 1998-2002*	<b>1</b>	<b>1</b>	<b>2</b>

\* Source: CDC - unpublished data

\*\* Source: Reference (8) – all immigrants and refugees. A second study (9) of refugees only, found higher rates of TB (19.7% for B1, 3.6% for B2).

\*\*\* Source: Tables 3 & 10 from reference (5).

**Table S3: Estimation of total and infrastructure DOTS expansion costs.**

Country (GNI per capita) †	Unit	Population	Annual Smear Positive		DOTS Implementation/Expansion						
			Incidence/ 100,000	Number (per unit)	Costs per			Infrastructure			
					Total (\$)	Person	TB case	Total (\$)	(% of total)	\$ per person	\$ per TB case
Ecuador†† (\$1450)	Health area	104,000	63	65	\$48,102	\$0.46	\$740	\$15,813	(33%)	\$0.15	\$243
China‡ (\$960)	County	400,000	36	144	\$40,000	\$0.10	\$278	\$23,200	(58%)	\$0.06	\$145
India** (\$470)	Country (40%)	436 million	101	440,360	\$50 million	\$0.11	\$114	\$8 million*	(16%)	\$0.02	\$18
Haiti‡‡ (\$440)	Country (all)	8.3 million	147	12,201	\$20 million	\$2.40	\$1,639	\$3.9 million	(20%)	\$0.47	\$320

† GNI: Gross National Income; data from (31)

†† Information from (36)

\* From World Bank Report 1589-N. Includes: “Civil works, laboratory equipment, other goods or equipment, vehicles and project preparation facility”

\*\* Other information from India from (38)

‡ Information from Dr. Dan Chin – WHO office Beijing, personal communication.

‡‡ From (37) application to the Global Fund

**Table S4: Results of large-scale tuberculin skin test screening programmes**

Place (reference)	Years (Reason/Population)	Tuberculin Tested	TST positive	Medical evaluation	LTBI treatment offered	LTBI treatment started	LTBI treatment Completed *		
							completed	% offered	% of LTBI
British Columbia (100)	2002 (All)	19,001	4,292		1,617	814	452	28%	11%
Denver (17)†	1987-88 (immigration Adjusters)	4,840	2,039	1,528	1,029	863	716†	70%	35%
Toronto (101)††	1992-93 (schoolchildren)	720**	162	142	62	56	52††	84%	13%
Seattle (16)	1980-81 (refugees)	9,250	3,300	3,300					
British Columbia (102)	1990-2001 (contacts)	33,146	7,668		4,083	2,600	1,589	39%	21%
Montreal (19)	1996-97 (immigrant applicants ("B2") (Contacts) Total	200	388	353	190		145		
			298	191	66		49		
			113	103	91		57		
			799	647	347		251	72%	31%
USA (103)	1999 (contacts)	55,417‡	12,901			9,018	5,746	64%	37%
Montreal (104)	1987-1991 (Students, workers)	7,669‡‡	782	525	293		140	48%	13%
Florida (105)	2001-2002 (All)					8,350	4,214	50.5%	

\* % of offered - % of subjects who completed at least 6 months of therapy, out of all subjects who were recommended to take INH  
 % of LTBI- the % who completed at least 6 months of INH, out of all subjects initially identified to have LTBI (TST positive) or who would have been identified if they had TST .

\*\* In this study the number tested represented 41% of all those who should have been tested

† Total cost of the program was 209,000 or \$292 per patient completing therapy

†† Total cost of the program was 43,178 or \$830 per patient completing therapy.

‡ This represented 83% of all those who should have been tested.

‡‡ This represented 75% of all who should have been tested.

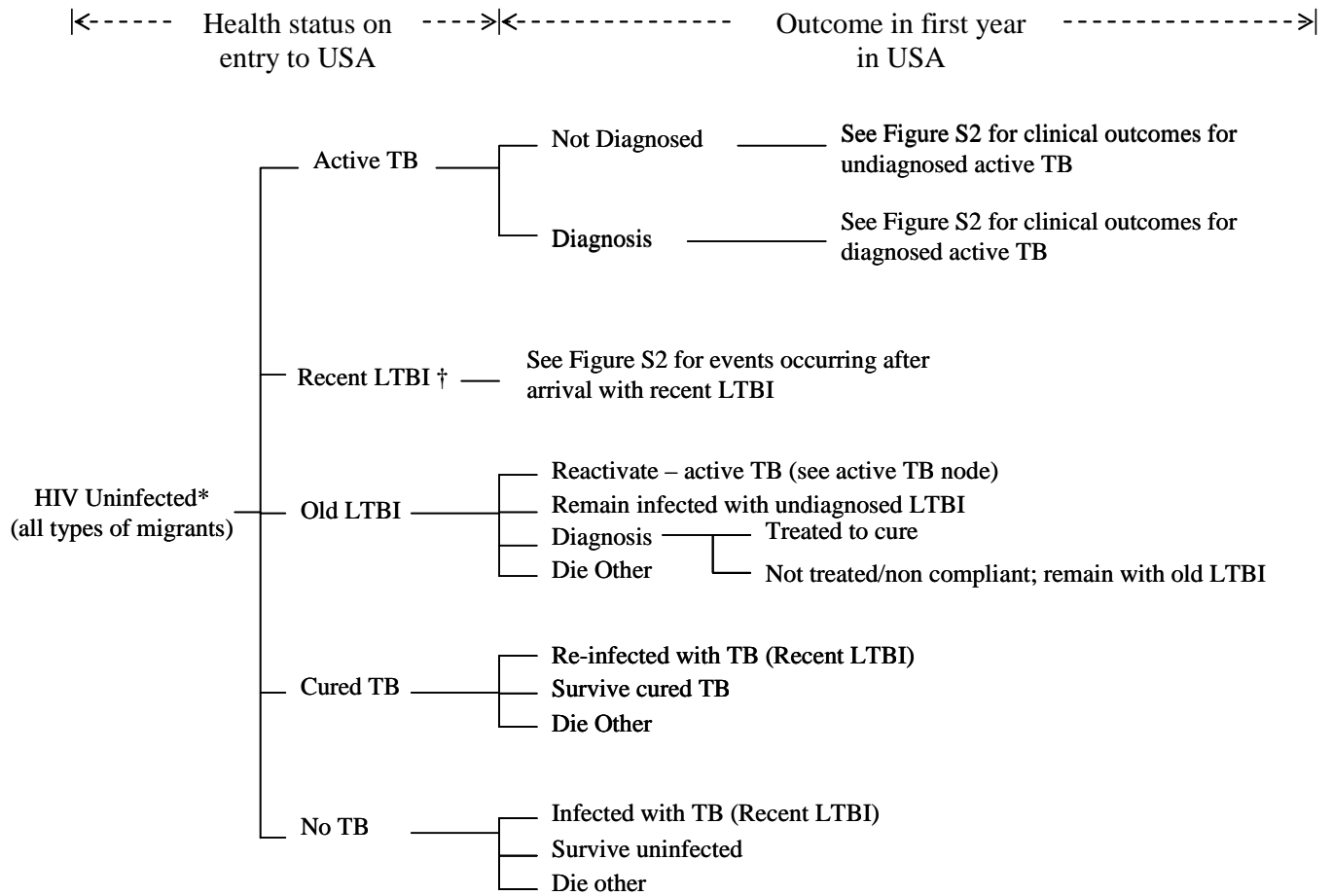
**Table S5: Cases averted and direct savings from DOTS expansion - for 5 US states that receive large numbers of migrants from the 3 source countries** (All costs in US\$ MILLIONS)

	Arizona	California	Florida	New York	Texas	TOTAL
Migrants entering per year (all types)†						
▪ From Mexico	70,193	628,805	30,709	26,323	299,779	1,055,809
▪ From Haiti	32	266	15,920	11,107	119	27,444
▪ From Dominican Republic	34	245	4,730	27,910	272	33,191
▪ <b>TOTAL</b>	70,259	629,316	51,359	65,340	300,170	1,116,444
TB Cases averted over 20 years						
▪ Migrants from Mexico	124	1114	54	47	531	1870
▪ From Haiti	0	2	146	102	1	251
▪ From Dominican Republic	0	1	25	147	1	174
▪ <b>TOTAL</b>	124	1117	225	296	533	2295
Direct, or State government savings with federal DOTS investment *						
▪ Migrants from Mexico	\$5.7	\$51	\$2.4	\$2.1	\$24	\$85.2
▪ From Haiti	\$0.01	\$0.1	\$5.7	\$4.0	\$0.04	\$9.85
▪ From Dominican Republic	\$0.01	\$0.1	\$1.0	\$5.8	\$0.1	\$7.01
▪ <b>TOTAL</b>	\$5.72	\$51.2	\$9.1	\$11.9	\$24.1	\$102.06

† Source: Table PCT 19 from (106), and Tables 2, 25, and Q from (5), and from (7).

\* Assumes that US federal government will make investment but that savings will accrue to the states' at a governmental level

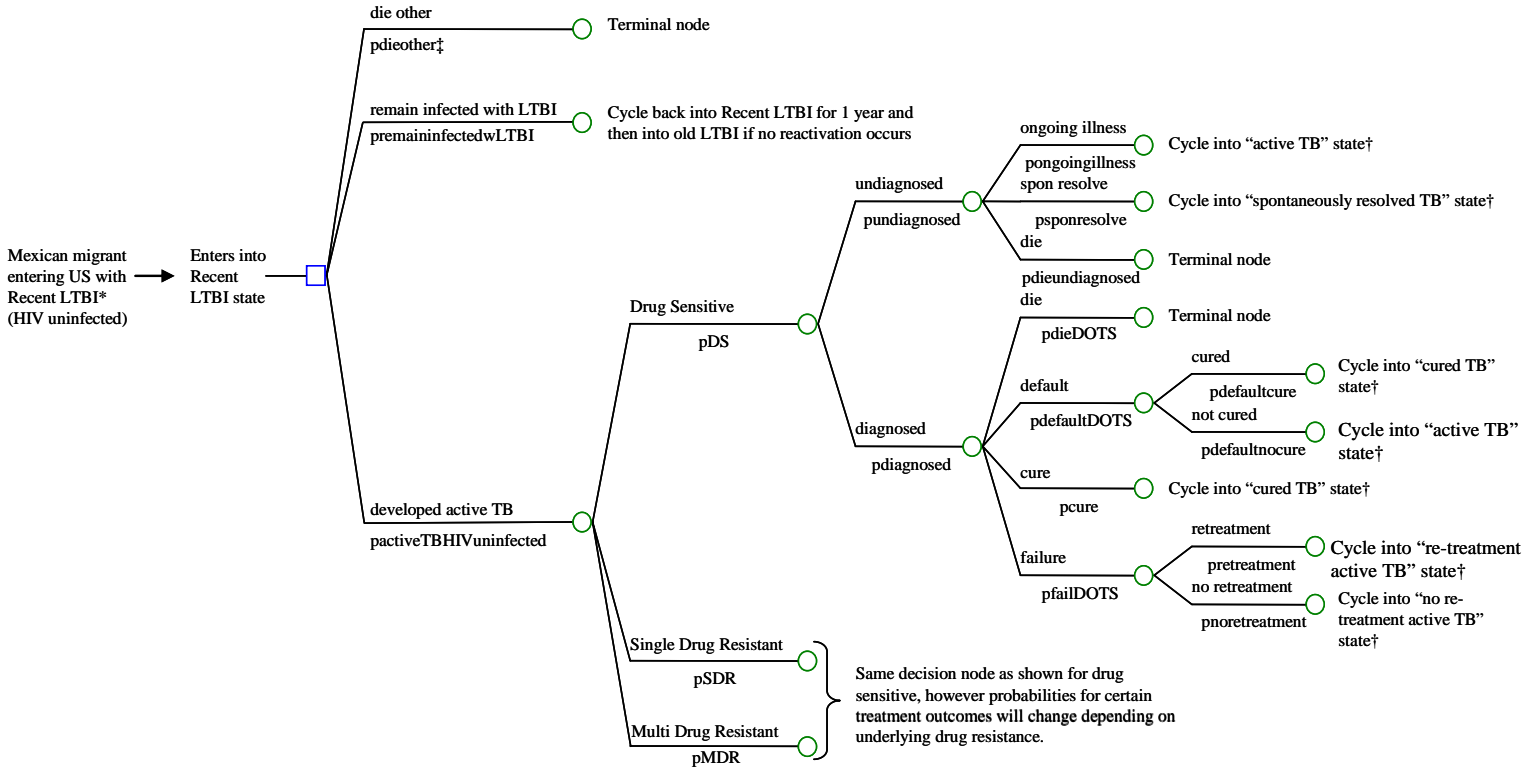
# Figure S1: Modeling migrants' health states on entry to the US



\* Diagram shown for HIV uninfected migrants; certain probabilities and clinical outcomes change for HIV infected individuals

† Migrant can remain a maximum of 2 years in state of “recent LTBI”, then moves to “old LTBI” state.

Figure S2: Sample decision analysis tree for Mexican migrants who enter the US with recently acquired latent tuberculosis infection

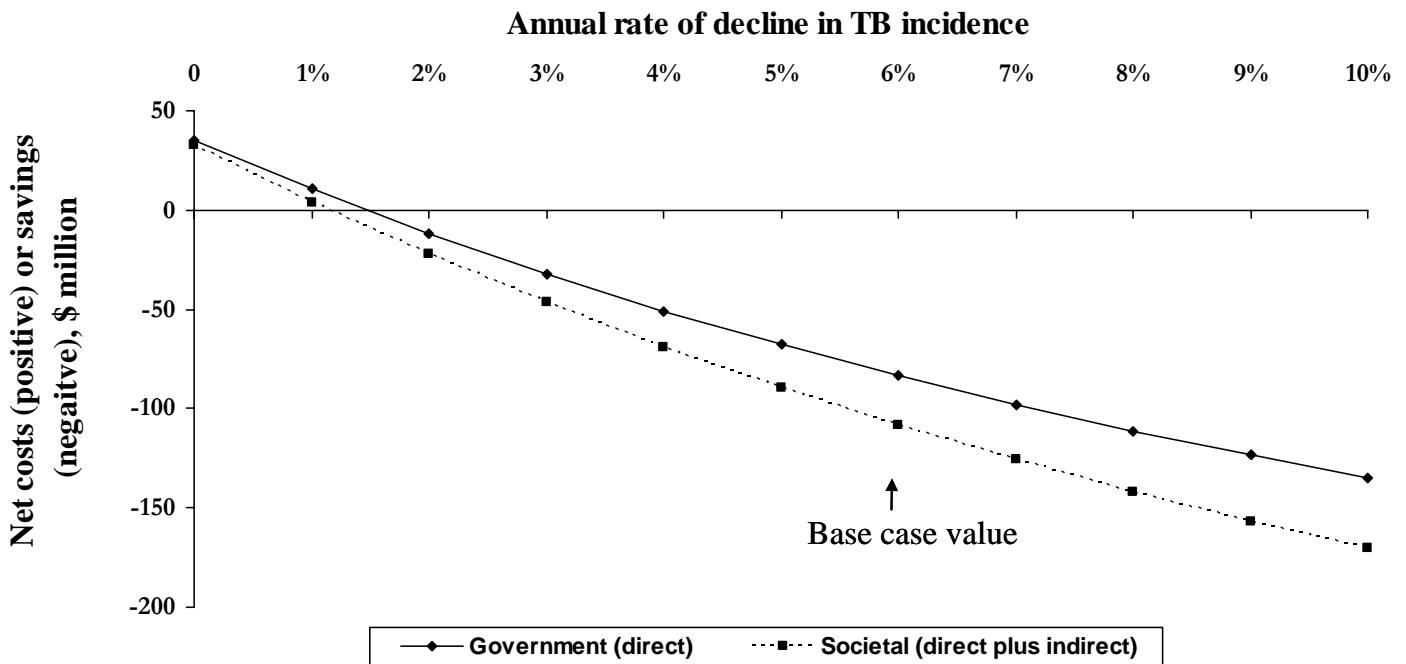


\* Probability of having Recent LTBI will fall over time as DOTS expansion occurs in Mexico, and remains unchanged in other strategies

‡ the letter “p” refers to probability. For example pdieother = probability of dieing from other cause.

† states that are entered in subsequent cycles are not shown in figure

Figure S3 – Government (direct), and societal (direct plus indirect) savings in the US, with varying annual decline in TB incidence after DOTS expansion in Mexico



## REFERENCE LIST

- (1) Zuber PLF, McKenna MT, Binkin NJ, Onorato IM, Castro KG. Long-term risk of tuberculosis among foreign-born persons in the United States. *JAMA* 1997; 278(4):304-307.
- (2) Marks G, Bai J, Simpson S, Sullivan E, Stewart G. Incidence of Tuberculosis among a Cohort of Tuberculin-Positive Refugees in Australia. *Am J Respir Crit Care Med* 2000; 162:1851-1854.
- (3) Wobeser W, Yuan L, Naus M, Corey P, Edelson J, Heywood N et al. Expanding the epidemiologic profile: risk factors for active tuberculosis in people immigrating to Ontario. *CMAJ J* 2000; 163(7):823-828.
- (4) Lopez AD, Salomon J, Ahmad O, Murray CJL, Mafat D. Life Tables for 191 Countries: Data, Methods and Results. 2000. Geneva, World Health Organization (GPE Discussion Paper Series: No.9).
- (5) 2002 Yearbook of Immigration Statistics - October 2003. Homeland Security, editor. 2003. Office of Immigration Statistics.
- (6) U.S.Department of Justice Immigration and Naturalization Service. 2000 Statistical Yearbook of the Immigration and Naturalization Service.  
<http://uscis.gov/graphics/shared/aboutus/statistics/Yearbook2000.pdf>. 2000.
- (7) ITA Office of Travel & Tourism Industries. "Information on inbound travel to the US". 2004. Access date: April 15, 2004., <http://tinet.ita.doc.gov/outreachpages/index.html#inbound>.
- (8) 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; 23:1226-1232.
- (9) Thorpe LE, Laserson K, Cookson S, Mills W, Field K, Koppaka VR et al. Infectious tuberculosis among newly arrived refugees in the United States. *N Engl J Med* 2004; 350(20):2105-2106.
- (10) Zuber PLF, Binkin NJ, Ignacio AC, Marshall KL, Tribble SP, Tipple MA et al. Tuberculosis screening for immigrants and refugees. Diagnostic outcomes in the State of Hawaii. *Am J Respir Crit Care Med* 1996; 154:151-155.
- (11) 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; 158:1037-1041.
- (12) Saraiya M, Cookson ST, Tribble P, Silk B, Cass R, Poonja S et al. Tuberculosis screening among foreign-born persons applying for permanent US residence. *Am J Public Health* 2002; 92(5):826-829.
- (13) American Thoracic Society. Targeted tuberculin testing and treatment of latent tuberculosis infection. *Am J Respir Crit Care Med* 2000; 161:S221-S247.
- (14) Schwartzman K, Menzies D. Tuberculosis screening of immigrants to low-prevalence countries. A cost-effectiveness analysis. *Am J Respir Crit Care Med* 2000; 161:780-789.

- (15) Menzies D. The tuberculin skin test. In: Reichman L, Hershfield E, editors. Tuberculosis, a comprehensive international approach. New York: Dekker M, 2000.
- (16) Nolan CM, Elarth AM. Tuberculosis in a Cohort of Southeast Asian Refugees: A five-year surveillance study. *Am Rev Respir Dis* 1988; 137:805-809.
- (17) 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; 103:1670-1674.
- (18) Pitchenik AE, Russell BW, Cleary T, Pejovic I, Cole C, Snider DJr. The prevalence of tuberculosis and drug resistance among Haitians. *N Eng J Med* 1982; 307(3):162-165.
- (19) 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 Resp Crit Care Med* 2000; 162(6):2079-2086.
- (20) Cauthen GM, Snider DE, Onorato IM. Boosting of tuberculin sensitivity among Southeast Asian refugees. *Am J Respir Crit Care Med* 1994; 149:1597-1600.
- (21) Lee JW, Espinal M, Jaramillo E. Report of site visit to evaluate DOTS expansion in Latin America. World Health Organization, 2002.
- (22) World Health Organization. Global Tuberculosis Control: Surveillance, Planning, Financing. WHO Report 2003. 2003. Geneva, Switzerland.
- (23) World Health Organization. Treatment of Tuberculosis: Guidelines for National Programmes. Second Edition. 1997. Geneva.
- (24) Floyd K, Skeva J, Nyirenda T, Gausi F, Salaniponi F. Cost and cost-effectiveness of increased community and primary care facility involvement in tuberculosis care in Lilongwe District, Malawi. *Int J Tuberc Lung Dis* 2003; 7(9 Suppl 1):S29-S37.
- (25) Floyd K, Wilkinson D, Gilks C. Comparison of cost effectiveness of directly observed treatment (DOT) and conventionally delivered treatment for tuberculosis: experience from rural South Africa. *BMJ* 1997; 315(7120):1407-1411.
- (26) UNAIDS. Joint United Nations Programme on HIV/ AIDS. 2002. <http://www.unaids.org/EN/default.asp#>.
- (27) Scalcini M, Carré G, Jean-Baptiste M, Hershfield E, Parker S, Wolfe J et al. Antituberculosis drug resistance in Central Haiti. *Am Rev Respir Dis* 1990; 142:508-511.
- (28) Espinal MA, Laszlo A, Simonsen L, Boulahbal F, Kim SJ, Reniero A et al. Global trends in resistance to antituberculosis drugs. World Health Organization-International Union against Tuberculosis and Lung Disease Working Group on Anti-Tuberculosis Drug Resistance Surveillance. *N Engl J Med* 2001; 344(17):1294-1303.
- (29) Granich RM, Balandrano S, Santaella AJ, Binkin NJ, Castro KG, Marquez-Fiol A et al. Survey of Drug Resistance of *Mycobacterium tuberculosis* in 3 Mexican States, 1997. *Arch Intern Med* 2000; 160:639-644.

- (30) Styblo K. The relationship between the risk of tuberculosis infection and the risk of developing infectious tuberculosis. *Bull Int Union Tuberc* 1985; 60(3-4):117-119.
- (31) World Bank Website. <http://www.worldbank.org/data/countrydata/countrydata.html>. 2004. Access date: April 15, 2004.
- (32) Suarez PG, Watt CJ, Alarcon E, Portocarrero J, Zavala D, Canales R et al. The Dynamics of Tuberculosis in Response to 10 Years of Intensive Control Effort in Peru. *J Infect Dis* 2001; 184:473-478.
- (33) The effect of tuberculosis control in China. *Lancet* 2004; 364(9432):417-422.
- (34) Dye C, Garnett GP, Sleeman K, Williams BG. Prospects for worldwide tuberculosis control under the WHO DOTS strategy. Directly observed short-course therapy. *Lancet* 1998; 352(9144):1886-1891.
- (35) Elzinga G, Raviglione MC, Maher D. Scale up: meeting targets in global tuberculosis control. *Lancet* 2004; 363(9411):814-819.
- (36) Vaca J, Peralta H, Gresely L, Cordova R, Kuffo D, Romero E et al. DOTS Implementation in a Middle Income Country - Development and Evaluation of a Novel Approach. *Int J Tuberc Lung Dis* 2005; 9(5):521-27.
- (37) Deas J. Haiti's Response to Tuberculosis and Malaria. Application to the Global Fund to Fight AIDS Tuberculosis and Malaria, editor. 2002.
- (38) Khatri GA, Frieden TR. Controlling Tuberculosis in India. *N Engl J Med* 2002; 347(18):1420-1425.
- (39) Comstock GM. How much isoniazid is needed for prevention of tuberculosis in immunocompetent adults. *Int J Tuberc Lung Dis* 1999; 3(10):847-850.
- (40) Nolan CM, Aitken ML, Elarth AM, Anderson KM, Miller WT. Active tuberculosis after isoniazid chemoprophylaxis of Southeast Asian refugees. *Am Rev Respir Dis* 1986; 133:431-436.
- (41) Espinal MA, Baez J, Soriano G, Garcia V, Laszlo A, Reingold AL et al. Drug-resistant tuberculosis in the Dominican Republic: results of a nationwide survey. *Int J Tuberc Lung Dis* 1998; 2(6):490-498.
- (42) Ormerod LP, Green RM, Gray S. Are there still effects on Indian Subcontinent ethnic tuberculosis of return visits?: a longitudinal study 1978-97. *J Infect* 2001; 43(2):132-134.
- (43) McCarthy OR. Interval between entry or re-entry to Britain and notification of tuberculosis among Asians in London. *Br J Dis Chest* 1984; 78:248-53.
- (44) World Health Organization. Global Tuberculosis Control: Surveillance, Planning, Financing: Annex 4: Regional Profile for the Americas: notification, detection and DOTS coverage, 2000. 1-13-2004. Geneva, Switzerland, <http://www.who.int/gtb/publications/globrep02/Excel/02Annex4AMR.xls>.
- (45) Sutherland I. Recent studies in the epidemiology of tuberculosis, based on the risk of being infected with tubercle bacilli. *Adv Tuberc Res* 1976; 19:1-63.

- (46) Sutherland I. The evolution of clinical tuberculosis in adolescents. *Tuberc* 1966; 47:308.
- (47) Comstock GW, Edwards LB, Livesay VT. Tuberculosis morbidity in the US Navy: its distribution and decline. *Am Rev Respir Dis* 1974; 110:572-580.
- (48) Centers for Disease Control (CDC). Reported tuberculosis in the United States, 2000. Atlanta: U.S. Department of Health and Human Services, 2000.
- (49) Cummings KC, Mohle-Boetani J, Royce SE, Chin DP. Movement of tuberculosis patients and the failure to complete antituberculosis treatment. *Am J Respir Crit Care Med* 1998; 157(4 Pt 1):1249-1252.
- (50) Chee CBE, Boudville IC, Chan SP, Zee YK, Wang YT. Patient and disease characteristics, and outcome of treatment defaulters from the Singapore TB control unit - a one-year retrospective survey. *Int J Tuberc Lung Dis* 2000; 4(6):496-503.
- (51) Grzybowski S, Enarson DA. The fate of cases of pulmonary tuberculosis under various treatment programmes. *Bull Int Union Tuberc* 1978; 53(2):70-74.
- (52) Parthasarathy R, Prabhakar R, Somasundaram PR. A controlled clinical trial of 3- and 5- month regimens in the treatment of sputum-positive pulmonary tuberculosis in South India. *Am Rev Respir Dis* 1986; 134:27-33.
- (53) East African/ British Medical Research Councils Study. Controlled clinical trial of five short-course (4-month) chemotherapy regimens in pulmonary tuberculosis: Second report of the 4th study. *Am Rev Respir Dis* 1981; 123:165-170.
- (54) Singapore Tuberculosis Service/British Medical Research Council. Long-term Follow-up of a clinical trial of six-month and four-month regimens of chemotherapy in the treatment of pulmonary tuberculosis. *Am Rev Respir Dis* 1986; 133:779-783.
- (55) Cross ER, Hyams KC. Tuberculin skin testing in US Navy and Marine Corps personnel and recruits, 1980-1986. *Am J Public Health* 1990; 80:435-438.
- (56) Cobelens FG, van Deutekom H, Draayer-Jansen IW, Schepp-Beelen AC, van Gerven PJ, Kessel RP et al. Risk of Infection with *Mycobacterium tuberculosis* in travellers to areas of high tuberculosis endemicity. *Lancet* 2000; 356:461-465.
- (57) World Health Organization, Tuberculosis Research Centre. Further studies of geographic variation in naturally acquired tuberculin sensitivity. *Bull World Health Organ* 1955; 22:63-83.
- (58) Menzies RI, Vissandjee B, Amyot D. Factors associated with tuberculin reactivity among the foreign-born in Montreal. *Am Rev Respir Dis* 1992; 146:752-756.
- (59) Wood R, Maartens G, Lombard CJ. Risk factors for developing tuberculosis in HIV-1 - Infected adults from communities with low or very high incidence of tuberculosis. *J Acquir Immune Defic Syndr* 2000; 23:75-80.
- (60) Edlin BR, Tokars JI, Grieco MH, Crawford JT, Williams J, Sordillo EM et al. An outbreak of multi-drug resistant tuberculosis among hospitalized patients with the acquired immunodeficiency syndrome. *New Engl J Med* 1992; 326(23):1514-1521.

- (61) Fischl MA, Daikos GL, Uttamchandani RB, Poblete R, Moreno JN, Reyes RR et al. Clinical presentation and outcome of patients with HIV infection and tuberculosis caused by multiple-drug resistant bacilli. *Ann Intern Med* 1992; 117:184-190.
- (62) Daley CL, Small PM, Schecter GF, Schoolnik GK, McAdam RA, Jacobs WR et al. An outbreak of tuberculosis with accelerated progression among persons infected with the human immunodeficiency virus. *New Engl J Med* 1992; 326(4):231-235.
- (63) 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; 159:733-740.
- (64) Malkin JE, Prazuck T, Simonnet F, Yameogo M, Rochereau A, Ayerour J et al. Tuberculosis and human immunodeficiency virus infection in West Burkina Faso: clinical presentation and clinical evolution. *Int J Tuberc Lung Dis* 1997; 1(1):68-74.
- (65) Desvarieux M, Hyppolite PR, Johnson WD, Pape JW. A novel approach to directly observed therapy for tuberculosis in an HIV-endemic area. *Am J Public Health* 2001; 91(1):138-141.
- (66) Chaisson RE, Clermont HC, Hole EA, Cantave M, Johnson MP, Atkinson J et al. Six-month supervised intermittent tuberculosis therapy in Haitian patients with and without HIV infection. *Am J Respir Crit Care Med* 1996; 154:1034-1038.
- (67) Whalen C, Horsburgh CR, Hom D, Lahart C, Simberkoff M, Ellner J. Accelerated course of human immunodeficiency virus infection after tuberculosis. *Am J Respir Crit Care Med* 1995; 151:129-135.
- (68) Connolly C, Reid, Davies G, Sturm W, McAdam K, Wilkinson D. Relapse and mortality among HIV-infected and uninfected patients with tuberculosis successfully treated with twice weekly directly observed therapy in rural South Africa. *AIDS* 1999; 13:1543-1547.
- (69) Morgan D, Mahe C, Mayanja B, Okongo JM, Lubega R, Whitworth JA. HIV-1 infection in rural Africa: is there a difference in median time to AIDS and survival compared with that in industrialized countries? *AIDS* 2002; 16(4):597-603.
- (70) Deschamps MM, Fitzgerald DW, Pape JW, Johnson WD. HIV Infection in Haiti: Natural History and Disease Progression. *AIDS* 2000; 14:2515-2521.
- (71) Sherman LF, Fujiwara PI, Cook SV, Bazerman LB, Frieden TR. Patient and health care system delays in the diagnosis and treatment of tuberculosis. *Int J Tuberc Lung Dis* 1999; 3(12):1088-1095.
- (72) Lonroth K, Thuong LM, Linh PD, Diwan VK. Delay and discontinuity - a survey of TB patients' search of a diagnosis in a diversified health care system. *Int J Tuberc Lung Dis* 1999; 3(11):992-1000.
- (73) Yamasaki-Nakagawa M, Ozasa K, Yamada N, Osuga K, Shimouchi A, Ishikawa N et al. Gender difference in delays to diagnosis and health care seeking behaviour in a rural area of Nepal. *Int J Tuberc Lung Dis* 2001; 5(1):24-31.
- (74) Wandwalo ER, Mørkve O. Delay in tuberculosis case-finding and treatment in Mwanza, Tanzania. *Int J Tuberc Lung Dis* 2000; 4(2):133-138.

- (75) Weinstein MC, Siegel JE, Gold MR, Kamlet MS, Russell LB. Recommendations of the Panel on Cost-Effectiveness in Health and medicine. *JAMA* 1996; 276(15):1253-1258.
- (76) Ainsworth M, Koda G, Lwihula G, Mujinja P, Over M, Semali I. Measuring the Impact of Fatal Adult Illness in Sub-Saharan Africa - An Annotated Household Questionnaire. 1992. Washington, DC, The World Bank. LSMS Living Standards Measurements Study Working Paper No.90.
- (77) Institute of Medicine (US). Ending neglect: the elimination of tuberculosis in the United States. Washington: National Academy Press 2000.
- (78) 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(23):1850-1859.
- (79) Whalen CC, Johnson JL, Okwera A, Hom DL, Huebner R, Mugenyi P et al. A trial of three regimens to prevent tuberculosis in Ugandan adults infected with the human immunodeficiency virus. Uganda-Case Western Reserve University Research Collaboration. *N Engl J Med* 1997; 337(12):801-808.
- (80) Guelar A, Gatell JM, Verdejo J, Podzamczek D, Lozano L, Aznar E et al. A prospective study of the risk of tuberculosis among HIV-infected patients. *AIDS* 1993; 7:1345-1349.
- (81) Grzybowski S, Barnett GD, Styblo K. Contacts of cases of active pulmonary tuberculosis. *Bull IUAT* 1975; 50:90-106.
- (82) Beck-Sague C, Dooley SW, Hutton MD, Otten J, Breedan A, Crawford JT et al. Hospital outbreak of multi-drug resistant *Mycobacterium tuberculosis* infections: Factors in transmission to staff and HIV-infected patients. *JAMA* 1992; 268:1280-1286.
- (83) Fischl MA, Uttamchandani RB, Daikos L, Poblete RB, Moreno JN, Reyes RR et al. An outbreak of tuberculosis caused by multiple-drug resistant tubercle bacilli among patients with HIV infection. *Ann Intern Med* 1992; 117:177-183.
- (84) Small P, Shafer R, Hopewell P. Exogenous reinfection with multidrug-resistant *Mycobacterium tuberculosis* in patients with advanced HIV infection. *N Engl J Med* 1993; 328:1137-1144.
- (85) Menzies D. Issues in the management of contacts of patients with active pulmonary tuberculosis. *Can J Public Health* 1997; 88(3):197-201.
- (86) Stead WW. Management of health care workers after inadvertent exposure to tuberculosis: A guide for use of preventive therapy. *Ann Intern Med* 1995; 122:906-912.
- (87) Rieder HL. Epidemiologic basis of tuberculosis control. First Edition, 1-162. 1999. Paris, France, International Union Against Tuberculosis and Lung Disease.
- (88) Horwitz O. Public health aspects of relapsing tuberculosis. *Am Rev Respir Dis* 1969; 99:183-193.
- (89) Cohn DL, Catlin BJ, Peterson KL, Judson FN, Sbarbaro JA. A 62-dose, 6-month therapy for pulmonary and extrapulmonary tuberculosis. A twice-weekly, directly observed, and cost-effective regimen. *Ann Intern Med* 1990; 112(6):407-415.

- (90) Results at 5 years of a controlled comparison of a 6-month and a standard 18-month regimen of chemotherapy for pulmonary tuberculosis. *Am Rev Respir Dis* 1977; 116(1):3-8.
- (91) Somner AR. Short-course chemotherapy in pulmonary tuberculosis. A controlled trial by the British Thoracic Association (third report). *Lancet* 1980; 1(8179):1182-1183.
- (92) Controlled clinical trial comparing a 6-month and a 12-month regimen in the treatment of pulmonary tuberculosis in the Algerian Sahara. Algerian working group/British Medical Research Council cooperative study. *Am Rev Respir Dis* 1984; 129(6):921-928.
- (93) Benator D, Bhattacharya M, Bozeman L, Burman W, Cantazaro A, Chaisson R et al. Rifapentine and isoniazid once a week versus rifampicin and isoniazid twice a week for treatment of drug-susceptible pulmonary tuberculosis in HIV-negative patients: a randomised clinical trial. *Lancet* 2002; 360(9332):528-534.
- (94) Espinal MA, Kim SJ, Suarez PG, Kam KM, Khomenko AG, Migliori GB et al. Standard short-course chemotherapy for drug-resistant tuberculosis: treatment outcomes in 6 countries. *JAMA* 2000; 283(19):2537-2545.
- (95) Suarez PG, Floyd K, Portocarrero J, Alarcon E, Rapiti E, Ramos G et al. Feasibility and cost-effectiveness of standardised second-line drug treatment for chronic tuberculosis patients: a national cohort study in Peru. *Lancet* 2002; 359(9322):1980-1989.
- (96) Mitnick C, Bayona J, Palacios E, Shin S, Furin J, Alcantara F et al. Community-based therapy for multidrug-resistant tuberculosis in Lima, Peru. *N Engl J Med* 2003; 348(2):119-128.
- (97) Johnson JL, Okwera A, Vjecha MJ, Byekwaso F, Nakibali J, Nyole S et al. Risk factors for relapse in human immunodeficiency virus type 1 infected adults with pulmonary tuberculosis. *Int J Tuberc Lung Dis* 1997; 1(5):446-453.
- (98) 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(9294):1687-1693.
- (99) Pulido F, Peña JM, Rubio R, Moreno S, González J, Guijarro C et al. Relapse of tuberculosis after treatment in human immunodeficiency virus-infected patients. *Arch Intern Med* 1997; 157:227-231.
- (100) BC Center for Disease Control. Annual Report Tuberculosis Control in 2002. 2003. Vancouver, BC Ministry of Health.
- (101) Yuan L, Richardson E, Kendall PRW. Evaluation of a tuberculosis screening program for high-risk students in Toronto schools. *C.MAJ* 1995; 153(7):925-932.
- (102) Onofre Moran-Mendoza A. The value of the tuberculin skin test size in predicting the development of tuberculosis in contacts of active cases. Department of Health Care and Epidemiology, University of British Columbia, 2004.
- (103) 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* 7[12], S384-S390. 2003.

- (104) Adhikari N, Menzies R. Community-based tuberculin screening in Montreal: A cost-outcome description. *Am J Public Health* 1995; 85(6):786-790.
- (105) Lauzardo M. LTBI treatment completion rates in Florida in 2001-2002 (Unpublished Report). 2004. Florida, Florida State Health Department.
- (106) US Census 2000. PCT 19. Place of Birth for the Foreign-born Population. Available on-line at [http://factfinder.census.gov/servlet/CTGeoSearchByListServlet?ds\\_name=DEC\\_2000\\_SF3\\_U&\\_lang=en&\\_ts=142349219781](http://factfinder.census.gov/servlet/CTGeoSearchByListServlet?ds_name=DEC_2000_SF3_U&_lang=en&_ts=142349219781) Accessed 3/11/2004.