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Economic analysis of CDC's culture-based and smear-based tuberculosis instructions for Filipino immigrants

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Abstract

Setting: In 2007, CDC revised its Tuberculosis Technical Instructions for panel physicians who administer mandatory medical examinations of U.S.-bound immigrants. Many U.S.-bound immigrants come from the Philippines, which has high tuberculosis prevalence.

Objective: To quantify economic and health impacts of smear-based versus culture-based tuberculosis screening.

Design: Decision tree modeling compared three Filipino screening programs: (1) 'No Screening', (2) 'Smear-based', and (3) 'Culture-based'. The model incorporated pre-departure tuberculosis screening results from Filipino panel physicians and CDC databases with post-arrival follow-up outcomes. Costs (2013 USD) were examined from societal, immigrant, U.S. public health department and hospitalization perspectives.

Results: With 'No Screening', an annual cohort of 35,722 Filipino immigrants would include an estimated 450 tuberculosis patients with 264 hospitalizations with societal cost of $9.90 million. 'Culture-based' versus 'Smear-based' screening would result in fewer imported cases (80.9 vs. 310.5), hospitalizations (19.7 vs. 68.1), and treatment costs ($1.57 million vs. $4.28 million). Societal screening costs including U.S. follow-up were greater for 'Culture-based" ($5.98 million) than "Smear-based' ($3.38 million). 'Culture-based' requirements increased immigrants' costs by 61% ($1.7 million), but reduced costs for U.S. public health department (22%, $750,000) and hospitalization (70%, $1,020,000) perspectives.

Conclusion: 'Culture-based' screening reduced imported tuberculosis and U.S. costs among Filipino immigrants.

Keywords

costs; cost-effectiveness; screening; immigration

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Introduction

The incidence of tuberculosis in the United States declined from 1992–2014.[1] The 2014 tuberculosis case rates were 1.2 cases per 100,000 for U.S.-born versus 17.6 for foreign-born persons.[2] Reducing tuberculosis in the foreign-born is necessary to achieve the Centers for Disease Control and Prevention's (CDC's) tuberculosis elimination goal.

CDC has regulatory authority (42 CFR, Part 34) to prescribe screening and treatment to prevent U.S. entry by immigrants and refugees with tuberculosis disease. In 2007, CDC revised its Tuberculosis Technical Instructions (TIs) for panel physicians[3] by requiring more rigorous testing. Specifically, pre-departure testing algorithms moved from 'Smear-based' (1991) to 'Culture-based' (2007). Under both 'Smear-based' and 'Culture-based' algorithms, all adult immigrants/refugees receive chest radiographs (CXRs) and those with CXRs or other medical indications suggestive of tuberculosis must provide three sputum samples for acid-fast-bacilli smear and *M. tuberculosis* culture tests. Previously, only sputum smear tests were performed, which limited screening sensitivity.[4–6] For immigrants/refugees ≤14 years, 'Smear-based' TIs required CXRs only for children with specific risk factors in medical histories. 'Culture-based' TIs added latent tuberculosis infection (LBTI) tests, e.g., tuberculin skin tests (TSTs) or interferon gamma release assays (IGRAs), for children in countries with World Health Organization (WHO)-reported tuberculosis incidence ≥20 cases per 100,000 population.[3] Children with positive LTBI results undergo CXRs and more rigorous testing. Refer to Table 1 for full details of all changes that came into effect in 2007.

Immigrants/refugees who test positive for tuberculosis disease cannot enter the United States until they complete treatment according to American Thoracic Society/CDC/Infectious Disease Society of America guidelines and delivered as directly observed therapy.[1, 3] Immigrants with 1) abnormal CXR but negative culture results, 2) positive TST/IGRA results, and/or 3) contacts of tuberculosis patients receive medical classifications on their immigrant visas (e.g., Class B1/B2/B3, Table 1). Notifications to U.S. public health departments (PHDs) are generated for recommended follow-up evaluations for immigrants/refugees with medical classifications within 90 days of U.S. arrival. These follow-up evaluations provide another opportunity to diagnose tuberculosis disease.

The change to 'Culture-based' coincided with a significant increase in cases detected prior to U.S. arrival and decline in tuberculosis case rates among new immigrants.[7, 8] Previous studies have examined the economics of immigrant tuberculosis screening,[9–13] but none have examined CDC's 'Smear-based' and 'Culture-based' protocols using actual surveillance data. The Philippines was chosen because of 1) high tuberculosis prevalence[14] and 2) Filipino-born individuals comprised 12% of foreign-born U.S. tuberculosis patients in 2014[2], and 3) all medical screening for US-bound applicants is performed at just one clinic. The objective of this evaluation is to quantify the costs and benefits of CDC's 'Culture-based' TIs for Filipino immigrants.

Methods

We examined three programs: 1) no tuberculosis screening ('No Screening'), 2) pre-departure ('Smear-based') screening with domestic follow-up, and 3) pre-departure ('Culture-based') screening with follow-up. Two outcome measures were assessed: 1) numbers of imported tuberculosis cases and 2) tuberculosis screening and treatment costs in 2013 U.S. dollars. The total (screening + treatment) cost of each option was evaluated from societal, immigrant, PHD, and U.S. hospitalization perspectives. The U.S. hospitalization perspective was included because insurance coverage/copayment data for newly-arrived Filipino immigrants was unavailable. More details and secondary calculations are available in an online Appendix. This analysis was classified as program evaluation using existing surveillance data and exempted from CDC's Institutional Review Board.

Population

Surveillance data was obtained from two independent sources: CDC's Electronic Data Notification (EDN) System, and Saint Luke's Medical Center Extension Clinic (SLEC) in Manila, Philippines. SLEC maintains a de-identified database of tuberculosis test results for all U.S.-bound Filipino immigrants. CDC's EDN database contains records of results of domestic follow-up exams for Filipinos with tuberculosis notifications.

SLEC provided summary statistics for 5.25 years of screening data from October 2007–December 2012 for U.S.-bound immigrant-applicants. All applicants were evaluated using the 'Culture-based' protocol. Outcome data was subdivided by age and included: tuberculosis patients (Class A), abnormal CXRs but not active tuberculosis (Class B1), normal CXRs but positive TST results (Class B2), contacts of tuberculosis patients (Class B3), or no class (Table 2a). Although SLEC reported results for 231,818 immigrant-applicants, U.S. Department of Homeland Security reported 187,554 new Filipino immigrant arrivals (35,722 per year) over the same period.[15] Thus, some (19%) SLEC-tested immigrant-applicants did not immigrate during the time period.

Follow-up exam results for Filipino immigrants with tuberculosis classifications were extracted from CDC's EDN database for 2010–2012.[16] The EDN system notifies PHDs about immigrants with tuberculosis classifications and stores domestic exam results. This three-year period was the best domestic data available, which overlapped SLEC data.

Results from SLEC and EDN databases were divided into four age-based subgroups; children (≤14 years), adults (15–44 years, 45–64 years, and ≥65 years) to capture heterogeneity in prevalence and differences in child versus adult screening algorithms.

Overseas and domestic screening data

Overseas, SLEC panel physicians diagnosed 2,398 tuberculosis disease cases (80% culture-positive, 17% smear-positive) among 231,818 Filipino immigrant-applicants. The fractions with tuberculosis disease increased with age from 0.05% for children ≤14 years to 2.73% for adults ≥65 years. SLEC reported that 86% of immigrant-applicants diagnosed with tuberculosis disease completed treatment onsite. In addition, 24.8% of immigrants (all ages) received some type of tuberculosis classification (Table 2a).

U.S. follow-up exam results were available for 71.5% of Filipinos with tuberculosis classifications in EDN. Among the remaining 28.5%, 7.8% did not present for U.S. follow-up. Data were unavailable for the remaining 20.7% (Table 2b). We imputed results for immigrants with missing data and assumed that half (10.35%) were screened domestically with outcomes similar to those for whom data were available. Outcomes were aggregated across states and differences across states were not evaluated.

Adults were more likely than children to receive CXRs and sputum testing at domestic follow-up. Across all ages, 72.0% of immigrants undergoing domestic follow-up received CXRs and 39.9% received sputum tests among individuals not diagnosed with active tuberculosis (Table 2b). Active disease diagnoses were more prevalent (1.3%) among immigrants with abnormal CXRs (‘B1’) than with positive TST results (‘B2’, 0.18%) or contacts (‘B3’, 0%).

Tuberculosis period prevalence and hospitalization

Age-specific tuberculosis disease period prevalence rates were estimated from SLEC and EDN follow-up data including the sum of pre-departure patients detected in the Philippines (Class A) and post-arrival patients detected in the United States.

Estimated tuberculosis period prevalence summed over the period between initial screening and domestic follow-up varied by age from 180 to 3,180 (average 1,260) per 100,000 population (Table 2c). The average is three times greater than WHO-reported prevalence,[14] but is based on active screening results for the target population.

U.S. hospitalization rates were estimated by 1) whether patients were passively or actively (i.e. diagnosed at PHD follow-up) detected, and 2) whether diagnosed patients were smear-positive (see appendix). Estimated hospitalization rates ranged from 8.1% (smear negative, active detection) to 66% (smear-positive, passive detection).[14] The smear-positive rate was based on EDN data (10%) for actively-detected patients or CDC’s national surveillance data for passively-detected patients (51%).[2] LTBI prevalence was estimated but only affected the expected numbers and costs of U.S. follow-up examinations (Appendix).[17]

Decision tree model

An age-stratified decision tree model (Appendix, Figure A1) was created in Treeage Pro 2012. The immigrant population was subdivided by age and tuberculosis status: active disease, LTBI, or uninfected (Tables 2a–2c). This population proceeded through each of three screening scenarios: ‘No Screening’, ‘Smear-based’, and ‘Culture-based’. We assumed all patients would be detected within a year so costs were not discounted.

For both ‘Smear-based’ and ‘Culture-based’ scenarios, immigrants started with an examination at SLEC. Estimated and observed test sensitivities (Tables 2a–2c) were used to subdivide tuberculosis cases among 1) patients diagnosed and treated overseas and 2) patients detected domestically after testing negative overseas. Domestic patients would be detected actively at PHDs if immigrants received visa notifications and presented for recommend exams. Patients would be detected passively if immigrants with visa

notifications did not follow-up or among immigrants with false-negative results at SLEC. Estimated test sensitivities were 85% for children (TST)[18] and 98% for adults (CXR)[19–24].

To assess sensitivity of ‘Culture-based’ versus ‘Smear-based’ TIs, we reviewed SLEC data and found that 62% of patients were culture-positive and smear-negative. Thus, ‘Smear-based’ sensitivity would be 38% of ‘Culture-based’; however, prior to implementing ‘Culture-based’, some smear-negative patients were diagnosed clinically.

Relying on self-reported tuberculosis signs and symptoms (‘Smear-based’) instead of TSTs (‘Culture-based’) to identify children needing CXRs probably led to fewer children diagnosed with tuberculosis disease overseas or arriving with ‘B1’ classifications. We assumed that 50% of children diagnosed with tuberculosis disease under ‘Culture-based’ TIs would have self-reported signs and symptoms leading to CXRs under ‘Smear-based’ TIs.

None of the ‘Culture-based’ ‘B2’ or ‘B3’ classifications would have occurred under the ‘Smear-based’ TIs, which did not include TSTs for children or contact investigations for immigrant-applicants diagnosed with tuberculosis. For ‘No Screening’, we assumed all patients would be passively-detected after U.S. arrival.

For ‘Culture-based’ and ‘Smear-based’, persons with LTBI or no infection incurred costs of overseas panel exams and additional costs if they received tuberculosis visa classifications and underwent domestic follow-up.

Cost analysis

Overseas immigrant out-of-pocket screening costs were based on direct observation of SLEC during one week in January 2013. SLEC also provided one year of operating data and multiple years of equipment/capital costs. The average cost of the tuberculosis component of the panel exam per immigrant increased from US$34 for ‘Smear-based’ to US$83 for ‘Culture-based’ TIs (Appendix). The 2013 all-inclusive panel exam prices were US$223 for adults and US$183 for children and included U.S. vaccination requirements.

Immigrant-applicant opportunity costs for screening were estimated based on the number of days required to complete screening and treatment if necessary (Table 1). Patient time was valued at daily Filipino gross domestic product (GDP) per capita (purchasing power-adjusted).[25] SLEC provides tuberculosis treatment delivered as directly observed therapy and treatment costs were included in ‘Culture-based’ exam fees. For ‘Smear-based’, Filipino government treatment costs were estimated at $565 inclusive of multidrug resistant cases.[14, 26]

Domestic follow-up costs (Table 2d) were estimated using PHD activities reported to EDN. We estimated PHD staff and diagnostic costs for the PHD perspective. Immigrant transportation and opportunity costs were included in the immigrant perspective.

Tuberculosis societal treatment costs ($7,900 for outpatient-only treatment and $32,000 per inpatient) were estimated from (Appendix)—

- PHD and patient opportunity costs for diagnostics and monthly follow-up,[27]

- PHD costs for contact investigations,[28, 29]
- PHD and patient opportunity costs for drug therapy.[30, 31]
- Average hospitalization costs from 2006–2010[32] adjusted to 2013 USD[33].
- For opportunity costs, we assumed outpatient-only treatment would result in 12.5 days of lost productivity[34]; hospitalized patients would incur additional losses corresponding to average durations of tuberculosis hospitalizations (14.3 days).[32]

Refer to the Appendix and Table 2d to see the distribution of tuberculosis treatment costs across stakeholders/perspectives. The societal perspective was the sum of the other perspectives.

Economic analysis

The societal net costs per imported case and hospitalization averted were calculated based on pairwise comparisons between programs. We subtracted Program A costs from Program B costs for screening and treatment: [$C\_program_A + C\_illness_A - (C\_program_B + C\_illness_B)$] and divided by differences in U.S. cases or hospitalizations ($US\_Cases_B - US\_Cases_A$).

Sensitivity analysis

The potential variation in total costs and averted imported cases was graphed as a function of tuberculosis prevalence among Filipino immigrants. For simplicity, we assumed that LTBI prevalence would vary directly with tuberculosis prevalence, because LTBI prevalence affects the numbers of ‘B1’, ‘B2’, and ‘B3’ classifications and U.S. follow-up costs.

One-way sensitivity analyses of net costs per U.S. case averted were conducted by varying selected parameter estimates across the uncertainty ranges presented in Tables 2c–d (Appendix).

Results

Estimated cases, hospitalizations, and costs (Table 3)

Annual societal costs are greatest for ‘No-Program’ ($9.90 million), which also results in the most imported cases (450.4) and hospitalizations (264.2). ‘Culture-based’ societal costs are slightly less than ‘Smear-based’ ($7.55 million versus $7.67 million), and results in fewer imported cases (80.9 vs. 310.5). Societal costs of pre-departure screening plus U.S. follow-up range from zero for ‘No Screening’ to $3.38 million for ‘Smear-based’ to $5.98 million for ‘Culture-based’. Investment in pre-departure screening reduces societal tuberculosis treatment costs ($9.90 million for ‘No Screening’, $4.28 million for ‘Smear-based’ and $1.57 million for ‘Culture-based’). Treatment savings result from both lower Filipino vs. U.S. treatment costs and reduced probability of U.S. hospitalization for actively versus passively-detected patients.

Breaking societal costs into stakeholder perspectives, immigrants’ annual total (screening + treatment) costs are lowest for ‘No Screening’ ($1.35 million) and highest for ‘Culture-based’ ($4.53 million). This net cost difference is about $3.2 million or about $90 per

immigrant screened. However, U.S. hospitalization costs are much higher for ‘No Screening’ ($5.83 million) compared to ‘Smear-based’ ($1.46 million) or ‘Culture-based’ ($435,000). Thus, screening programs shifts expenditures from U.S. stakeholders to immigrants paying for screening and treatment overseas. Depending on financial and insurance statuses of new Filipino immigrants, U.S. hospitalization costs may accrue to private insurance or to immigrants themselves.

From the PHD perspective, ‘Smear-based’ total costs were $3.31 million including expenditures for treating a large number of U.S. tuberculosis patients ($1.87 million) plus follow-up costs for Class B immigrants ($1.43 million). In comparison, ‘Culture-based’ total costs were $2.56 million and resulted from greater PHD testing costs ($2.07 million), but smaller treatment costs ($488,000). ‘No Screening’ results in only PHD treatment costs ($2.72 million).

Sensitivity analysis

From the societal perspective for U.S.-bound Filipino immigrants, ‘Culture-based’ is cost-saving relative to ‘No Screening’ at period prevalence rates >900 cases per 100,000 all-age population (Figure 1). If Filipino period prevalence drops by 50% relative to baseline, ‘Culture-based’ would have greater net societal costs than ‘Smear-based’; the net societal cost per imported case and hospitalization averted would be $9,000 and $65,000, respectively.

A series of one-way sensitivity analyses for key parameters is shown in tornado diagrams (Figure A2a–c in Appendix). Parameter estimates with greatest impacts on cost-effectiveness for ‘Culture-based’ versus ‘Smear-based’ are societal treatment costs and relative sensitivity of smear-based versus culture-based sputum testing. Incremental costs per imported case averted remain below $5,100 across one-way analyses. Both screening protocols remain cost-saving across most one-way sensitivity analyses compared to ‘No Screening’ at baseline period prevalence.

Discussion

We found that pre-departure tuberculosis screening and treatment for U.S.-bound Filipino immigrants using either ‘Smear-based’ or ‘Culture-based’ TIs was cost-saving relative to ‘No Screening’ for both societal and U.S. stakeholder perspectives. Transitioning from ‘Smear-based’ to ‘Culture-based’ TIs slightly reduced expected societal and U.S. PHD costs, but greatly reduced imported tuberculosis cases and U.S. hospitalization costs. Tuberculosis treatment is much less expensive in the Philippines and the difference between Filipino and U.S. treatment costs exceed pre-departure screening costs. With lower societal costs and better health outcomes, ‘Culture-based’ TIs are dominant relative to other strategies for Filipino immigrants. Prospective Filipino immigrants, however, must pay more and incur greater opportunity costs for overseas screening and treatment for ‘Culture-based’ TIs. Although immigrant costs increase, immigrants are less likely to arrive ill with tuberculosis.

This evaluation has limitations. In the absence of screening, we assumed that tuberculosis patients diagnosed overseas via active screening would immigrate at the same rate as

persons without disease. However, some patients may self-resolve prior to U.S. treatment-seeking or some immigrants may have become too sick to travel. This evaluation aggregates domestic follow-up data across U.S. states and does not consider interstate heterogeneity in examination practices and costs. We used Medicare reimbursement rates to estimate U.S. diagnostic costs, which are lower than private insurance reimbursement rates. After accounting for higher testing costs and other uncertain parameters in the sensitivity analysis, incremental costs per imported case averted would remain below $5,100 for 'Culture-based' versus other strategies. Finally, we have limited data regarding tuberculosis transmission by recent U.S. immigrants so we omitted domestic transmission from the base case analysis.

This analysis only considered one-year post-arrival and did not attempt to quantify the effect of follow-up exams on LTBI incidence. The appendix (Section 10) provides a description of tuberculosis incidence among Filipinos after U.S. arrival. On average from 2011–2015 there were about 776 cases diagnosed among individuals born in the Philippines, of which about 27% occurred within 5 years of U.S. arrival.[35] CDC and the American Thoracic Society recommend LTBI treatment for new immigrants[36]. PHDs may offer LTBI treatment to immigrants during follow-up exams, and we plan to examine this in a future evaluation. Finally, we only examined the Filipino screening program, and our results are not directly applicable to countries with lower tuberculosis burdens or higher testing costs. We applied a similar model to other immigrating populations in the appendix (Section 11) and generally found cost savings for U.S. public health departments and for U.S. hospitalization and increased costs for prospective immigrants, but not from a societal perspective.

In conclusion, transitioning from 'Smear-based' to 'Culture-based' TIs reduced numbers of imported tuberculosis patients among Filipino immigrants and reduced costs for U.S. taxpayers. This analysis is unique because results are based on actual U.S. and Filipino screening outcomes and detailed cost data for pre-departure screening. This overseas public health initiative results in direct U.S. health and financial benefits. The results of this evaluation can be used to project the impacts of potential future changes to the TIs or expansion of screening requirements to other migrant populations such as students or skilled workers.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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BM, DLP, MSCo, and MSCe contributed to the conception and design of the project. BM, RA, and MR contributed to the acquisition of data. BM, DLP, MSCo, RA, JAP, WZ, MR, and LTW contributed to data analysis and interpretation. BM drafted the manuscript and all co-authors contributed to revise it critically for intellectual content. The authors have no conflicts of interest to declare.

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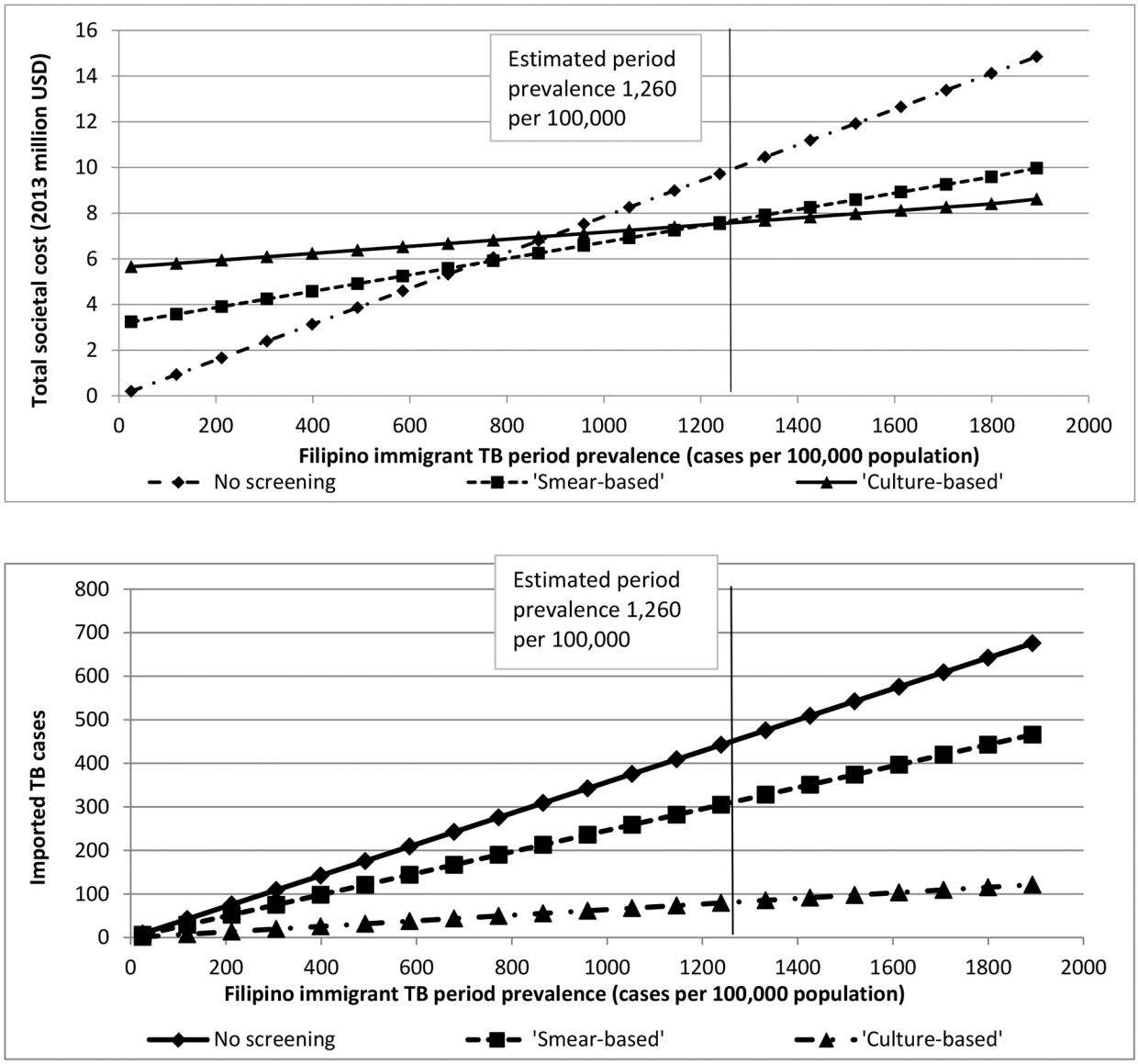

Figure 1.

One-way sensitivity analysis of total societal costs and total imported cases, as functions of tuberculosis disease prevalence among Filipinos

Table 1.

Summary of major differences in testing requirements and applicant time required by notification class between ‘Smear-based’ and ‘Culture-based’ Tuberculosis Technical Instructions (TB TI)

Testing Category	1991 ‘Smear-based’ TB TIs	2007 ‘Culture-based’ TB Tis
Screening of children	Children (aged < 15 years) are examined only if tuberculosis symptoms are reported during medical history/physical exam	In addition to the medical history and physical examination, children aged 2–14 years in countries with a WHO-reported tuberculosis incidence of 20 or more cases per 100,000 receive either a TST or an IGRA test. If positive (≥ 10 mm), these children are examined with a CXR and other examinations for TB disease.
Screening test for persons with abnormal CXRs	3 sputum smear only	3 sputum smear and culture tests with drug susceptibility testing for those with positive cultures
Tuberculosis disease treatment	Directly observed therapy not required	Directly observed therapy provided at a DGMQ-approved treatment site (e.g., SLEC) can reduce waiting time for approval to travel to the United States
Contacts of active patients	Not identified during screening	Identified during screening, evaluated with TST/IGRA, and recommended for follow-up in the United States
Class A	Smear-positive or clinically diagnosed active tuberculosis disease, requiring treatment prior to immigration (Opportunity costs: Individuals cannot travel to United States for at least 6 month while undergoing treatment)	Smear/culture-confirmed or clinically diagnosed active tuberculosis disease, requiring treatment prior to immigration (Opportunity costs: Individuals cannot travel to United States for at least 6 month while undergoing treatment)
Class B1	Smear negative, Abnormal CXR, suspected tuberculosis disease (Opportunity costs: 4 days for adults and children)	Smear/culture negative, Any abnormal CXR or completed TB treatment, same as B1 + B2 under ‘Smear-Based’ TIs (Opportunity costs: 4 days for adults and 5 days for children)
Class B2	Abnormal CXR, suspected inactive tuberculosis (Opportunity costs: 4 days for adults and children)	Latent infection, positive (≥ 10 mm) TST or IGRA test result (primarily for children ages 2–14 years) (Opportunity costs: 3 days for children, not applicable for adults)
Class B3	No classification	Contacts of tuberculosis patients also presenting for overseas exams (Opportunity costs: 3 days for adults and children)

Abbreviations: CXR, chest radiograph; IGRA, Interferon Gamma Release Assay; NA, not applicable; TST, tuberculin skin test; WHO, World Health Organization; TIs, CDC’s Tuberculosis Technical Instructions; DGMQ- Division of Global Migration and Quarantine; SLEC Saint Luke’s Medical Center Extension Clinic

Table 2a.

St. Luke's Medical Center, Philippines, Extension Clinic screening outcomes by age group, October 2007 through December 2012 (percentages in parentheses) N= 231,818

	Age (yrs.)				
	≤14	**15–45**	**46–65**	**65+**	**Total**
Total screened	44,286	114,633	54,360	18,539	231,818
Class A*	21 (0.047%)	979 (0.85%)	892 (1.64%)	506 (2.73%)	2,398 (1.03%)
Class B1†	402 (0.91%)	7,959 (6.94%)	14,738 (27.11%)	8,498 (45.84%)	31,597 (13.63%)
Class B2‡	22,000 (49.7%)	0	0	0	22,0000 (9.49%)
Class B3§	49 (0.05%)	871 (0.76%)	371 (0.68%)	98 (0.53%)	1,389 (0.60%)

*Class A- tuberculosis disease

†Class B1- abnormal CXR: but negative results from examinations and cultures of sputum specimens; this also includes Class B1–B3 for persons with abnormal CXRs who are also contacts of tuberculosis patients

‡Class B2- Positive TST; this also includes Class B2–B3 for children with positive TSTs who are also contacts of tuberculosis patients

§Class B3- Contacts of tuberculosis patients with normal CXRs

CXR = chest radiograph; TST = tuberculin skin test

Table 2b.

Domestic screening activities by age group (tuberculosis disease screening only); data from CDC's Electronic Disease Notification (EDN) database

Age group	≤14	15–44	45–64	65+	Total
Total number of reported to EDN	10,648	3,902	7,030	4,278	25,858
Fraction that initiated domestic evaluation	67.0%	71.1%	74.7%	75.4%	71.1%
Fraction that did not follow-up	10.5%	7.0%	7.4%	7.5%	8.7%
Fraction for which data are unavailable	22.5%	21.8%	17.9%	17.1%	20.3%
Fraction receiving CXR among those with initiated evaluations (after excluding diagnoses of active tuberculosis)	50.7%	84.3%	87.2%	85.2%	72.0%
Fraction receiving sputum culture/smear among those with initiated evaluations (after excluding diagnoses of active tuberculosis)	7.9%	56.5%	61.8%	63.5%	39.9%
Diagnoses at domestic follow-up *					
Class B1 observations†	155	2,515	4,955	3,053	10,678
Tuberculosis disease	1.9%	2.1%	1.2%	0.9%	1.2%
Class B3 observations‡	5	163	88	19	283
Tuberculosis disease	0	0	0	0	0
Class B2 observations§	6,778	0	0	0	6,778
Tuberculosis disease	0.18%				0.18%

*These data are limited to those with complete evaluations including a final diagnosis reported to EDN. Class B1 includes immigrants with abnormal chest radiographs or other signs/symptoms of tuberculosis and immigrants treated to completion for active tuberculosis. Class B2 includes individuals who test positive to tuberculosis infection based on tuberculin skin tests. Class B3 includes individuals who had been exposed to tuberculosis patients. Note that fractions presented above do not include actively diagnosed cases.

†This category includes persons classified as B1 or B1–B3.

‡For adults (age>15), this category includes those listed as B2, since adults should not receive a TST unless they are a contact of a tuberculosis patient. Thus, for adults, this category includes B2, B2–B3, and B3 classifications. For children, it includes only B3 classifications.

§All children should receive TSTs. Adults only receive TSTs if they are contacts of tuberculosis patients. For children, this includes immigrants with B2 and B2–B3 classifications.

EDN = Electronic Disease Notification; CXR = chest radiograph; CDC = Centers for Disease Control and Prevention; TST = tuberculin skin test.

Table 2c.

Epidemiologic input parameters and uncertainty ranges for decision tree model

Age groups (yrs)	≤14	15–44	45–64	65+	Refs
Annual no. of immigrants screened at SLEC	8,435	21,835	10,354	3,531	SLEC data (2007–12)
Annual no. of Filipino immigrants arriving in United States	6,824	17,665	8,376	2,857	[15]
Prevalence data					
Tuberculosis disease (cases per 100,000 population)	180	1,020	1,990	3,180	SLEC data + U.S. CDC EDN data
Latent tuberculosis (%) *	14	60	67	58	[17]
Smear-positive tuberculosis disease cases at SLEC (%)	17%				SLEC data
Smear-positive tuberculosis disease cases at U.S. follow-up (%)	10%				EDN data
Smear positive tuberculosis among all U.S. patients (2012–2014) †	51%				[2]
Test parameters, uncertainty ranges used in sensitivity analyses included in parentheses					
TST specificity for latent tuberculosis, 2–14 year olds ‡	55% (46%–59%)				EDN data and[18]
TST sensitivity for tuberculosis disease, 2–14 year olds	85% (79%–90%)				[18]
CXR sensitivity, adults	98% (80%–100)%				[19–24]
Fraction of tuberculosis cases diagnosed overseas divided by total diagnosed pre-departure + post-arrival at follow-up exams §	73–87.5% (80%–100)%				Age-specific EDN data and[21]
Sensitivity of ‘Smear-based’ (1991) vs. ‘Culture-based’ (2007) TIs **	38% (20%–60)%				SLEC data and[37]
Hospitalization rates					
Hospitalization: smear positive, passive detection §§	66% (53%−79%)				[13]
Hospitalization: smear negative, passive detection §§	51% (41%−61%)				[13]
Hospitalization: smear positive, active detection §§	35% (28%−42%)				[13]
Hospitalization: smear negative, active detection §§	8.1% (6.5%−9.7%)				[13]
Effectiveness of SLEC tuberculosis treatment	100%				Assumption ††

SLEC- Saint Luke’s Medical Center Extension Clinic in Manila; TST- Tuberculin skin test, TB- tuberculosis, TI- Technical Instructions, CXR- Chest radiograph, EDN- Electronic Disease Notification database.

Additional information regarding parameter assumptions is available in the online Appendix.

* Age-specific LTBI prevalence was estimated using a 1997 population-based Filipino survey[17] and an assumption that LTBI rates declined by the same 20% reported for Philippines’ tuberculosis prevalence during 1997–2013.[14]

† According to the U.S. surveillance data[2], from 2012 through 2014, there were 7,704 smear-positive patients, 6,680 smear-negative patients, and 2,147 patients with missing or unperformed smear testing. Using these numbers, 7,704/(7,704 + 6,680) =54% smear positive among patients with known smear test results; 7,704/(7,704+6,680+2,134) = 47% smear positive among all patients including those with missing results. The midpoint, 51%, was used as a best estimate considering that tuberculosis with missing smear test results may be less likely to be smear-positive.

‡ TST specificity was estimated based on the difference between the fraction of patients with positive TST results from testing at SLEC minus the expected prevalence of latent tuberculosis infection in the Filipino ≤14 population. The provided range is based on the work of Sun et al.[18] for a population with BCG vaccination. Among the diagnoses at U.S. follow-up exams, about 40% of children with B2 tuberculosis classifications had diagnoses of ‘No exposure or infection’ (37%) or ‘Exposed but not infected (3%).

[§] This probability was estimated based on the number of patients diagnosed overseas divided by the number of patients diagnosed overseas + patients diagnosed in the United States after an abnormal CXR overseas (class B1). Separate rates were calculated for each age group. Rates were lower for children. (Appendix).

[**] Since the previous 'Smear-based' technical instructions were already in place in 2007, these changes represent the effect of the change from the 'Smear-based' to the 'Culture-based' protocols and not the difference between screening and no screening. The screening process for adults began with CXRs for both the 'Smear-based' and 'Culture-based' protocols. Thus, for adults, the biggest change is the difference in sensitivity for sputum culture + smear vs. smear-only. We estimated the impact of the change to the overseas screening protocol by dividing the number of culture-positive/smear-negative cases diagnosed at SLEC relative to the total number of pulmonary tuberculosis cases diagnosed (62%) under the 'Culture-based' protocol. However, prior to the change to the culture-based protocol in 2007, SLEC frequently made clinical diagnoses in addition to cases detected via positive sputum smear results. Thus, this assumption may overstate the change in sensitivity in moving from the 'Smear-based' protocol to the 'Culture-based' protocol. An evaluation performed at the time of the transition found that in the 6 months (January to June 2017) prior to the implementation of the 'Culture-based' protocol, SLEC diagnosed 192 pulmonary tuberculosis cases among 27,425 Filipino immigrant-applicants (0.7%). The cases diagnosed under the 'Smear-based' protocol included 121 smear-positive cases and 71 clinically diagnosed cases (37% of total). In comparison, after implementation of the 'Culture-based' protocol, 244 cases were diagnosed among 21,173 immigrant applicants (1.2%) from October 2007 through March 2008.[37] Comparing the case detection rates across these two periods would suggest that the sensitivity of the 'Smear-based' protocol may have been as high as 60% of the rate detected under the 'Culture-based' protocol if we account for clinically diagnosed cases in comparison to the 38% sensitivity estimate based on the fraction of culture-positive, smear-negative cases currently being diagnosed. If this higher sensitivity is used, the expected change in cases diagnosed for 'Smear-based' vs. 'Culture-based' protocol would be 150 cases instead of the 230 estimated in the baseline analysis.

[††] Treatment effectiveness is assumed to be 100% for immigrants that receive visas because immigrants are either treated at the panel physician with directly observed therapy and evaluated with follow-up CXR and culture testing or must be re-evaluated by panel physicians at least one year after diagnosis if immigrants elect not to be treated by panel physicians.

[§§] The uncertainty ranges used for hospitalization rates were varied by +/− 20% to account for uncertainty in hospitalization probabilities. The base case estimates were previously reported by Porco et al. for California.[13]

Table 2d.

Estimated cost inputs for U.S. tuberculosis treatment and screening (2013 USD)

	Societal costs	Health Department cost *	U.S. hospital-ization	Patient opportunity costs	Patient out-of-pocket costs	Filipino govt. *
U.S. outpatient-only tuberculosis treatment per patient †	8,000 (4,200 – 23,000)	6,200 (2,700 – 10,700)	0	1,700 (1,500 – 11,000)	130 (26 – 1,200)	0
U.S. tuberculosis treatment cost per patient for those requiring hospitalization †,‡	32,000 (25,000 – 54,000)	6,200 (2,700 – 10,700)	22,000 (18,000 – 29,000)	3,700 (3,500 – 13,000)	130 (26 – 1,200)	0
Domestic follow-up, sputum sampling §	510 (370 – 1,400)	480 (340 – 1,300)	0	18 (12 – 87)	12	0
Domestic follow-up, CXR and no sputum sampling **	190 (80 – 510)	180 (70 – 470)	0	9 (6 – 44)	3	0
Domestic follow-up, no CXR or sputum sampling ††	150 (40 – 320)	140 (30 – 270)	0	9 (6 – 44)	3	0
Overseas tuberculosis patient treated in the Philippines ‡‡	1,850	0	0	1,170	18 ***	565

CXR- Chest radiograph

Ranges are based on differences between public sector and private sector pricing for visits, diagnostic tests, and drugs, but also depend on different assumptions around the amount of time required for diagnosis/treatment, the opportunity cost of patient time, and how DOT is implemented by health departments. More detail available in online Appendix

* We assumed that most patients would have drug-susceptible tuberculosis and would receive 2 months of initial therapy with isoniazid, rifampin, pyrazinamide, and ethambutol, followed by 4 months of isoniazid and rifampin. Multidrug resistant tuberculosis (MDR-TB) patients in our base-case analysis accounted for an estimated 1.7% of the culture-positive patients diagnosed at SLEC. Patients with MDR tuberculosis diagnosed at SLEC among U.S.-bound immigrants are treated by the Filipino national tuberculosis control program and not at SLEC. Outpatient treatment costs including medication for MDR-TB were calculated using cost estimates from U.S.[38] and Filipino studies[26] (appendix). See Appendix for details.

† These costs include diagnostics, medications, contact investigations, directly observed therapy, and follow-up visits (see appendix for details).

‡ Average hospitalization costs from 2006–2010 National Inpatient Sample data (primary diagnosis ICD-9 code 011, pulmonary tuberculosis)[32] and adjusted to 2013 USD using the Consumer Price Index for Medical Care[33]. We assumed that no patients were re-hospitalized after discharge.

§ We estimated that this exam requires 2 hours of nurse time, 1 hour of doctor time, a CXR, and 3 sputum samples/smears/cultures. It requires four visits by the immigrants.

** We estimate that this exam requires 1 hour of nurse time, 0.5 hours of doctor time, and a CXR. It requires one visit by the immigrants.

†† We estimate that this exam requires 1 hour of nurse time and 0.5 hours of doctor time. It requires one visit by the immigrants.

[##]The additional cost for patients treated by the panel physician is just the opportunity cost ($1,170), since the initial panel exam fee includes the cost of treatment for those who are diagnosed and treated by the panel physician in the Philippines. For MDR cases, patients out-of-pocket costs would be about $1,100,[26] but only 1.7% of patients were expected to have MDR TB, resulting in a weighted average cost of $18 per patient. For patients treated under the 'Smear-based' TIs, there is an additional cost of $565 for the Filipino national tuberculosis control program, since SLEC did not provide DOT under the 'Smear-based' TIs. This includes $500 per non-MDR TB patient (98.3%) and $4,300 per MDR TB patient (1.7%). For the 'Culture-based' TIs, only the cost per MDR TB cases (1.7%) are included as a separate cost in the analysis. The flat fee charged by SLEC includes the cost of treatment if necessary.

[***]The overseas out-of-pocket cost is estimated to be zero for individuals treated by panel physicians, in part because directly observed therapy (DOT) costs are included in the panel physician fees paid by all visa applicants. Thus, there is no additional out-of-pocket cost to pay for treatment for patients with drug-susceptible tuberculosis. They may have incurred additional out-of-pocket costs to receive DOT at the panel physician's office. However, we do not have data to quantify these costs. Instead, we estimated opportunity costs based on 50% of PPP-adjusted GDP per capita for the entire period of treatment to capture the costs associated with treatment. An estimate of out-of-pocket costs for multidrug resistant tuberculosis treatment in the Philippines is available and was used for the 1.7% of cases expected to be resistant.

Table 3.

Estimated program costs, treatment costs, and U.S. health outcomes under the 'Smear-based' TIs, 'Culture-based' TIs, and in the absence of screening programs, (2013 USD)

	No screening overseas or domestic	1991 'Smear-based' TB TIs	2007 'Culture-based' TB TIs
Overseas and domestic screening			
Immigrant perspective (out of pocket)	$0	$1,244,000	$3,004,000
Immigrant perspective (opportunity cost)	$0	$708,000	$909,000
PHD perspective	$0	$1,431,000	$2,067,000
Total (societal perspective)	*$0*	*$3,383,000*	*$5,980,000*
Treatment cost (including diagnostic costs for cases treated in United States)			
Immigrant perspective (out of pocket)	$56,000	$39,000	$10,000
Immigrant perspective (opportunity cost)	$1,292,000	$831,000	$632,000
PHD perspective	$2,718,000	$1,874,000	$488,000
U.S. Hospitalization perspective	$5,832,000	$1,459,000	$435,000
Filipino govt. cost *	0	$82,000	$31,000
Total (societal perspective)	*$9,898,000*	*$4,285,000*	*$1,596,000*
Sum of screening and treatment			
Immigrant perspective (out of pocket)	$56,000	$1,283,000	$3,014,000
Immigrant perspective (opportunity cost)	$1,292,000	$1,539,000	$1,541,000
PHD perspective	$2,718,000	$3,305,000	$2,555,000
U.S. Hospitalization perspective	$5,832,000	$1,459,000	$435,000
Filipino govt. *	$0	$82,000	$31,000
Total (societal perspective)	*$9,898,000*	*$7,668,000*	*$7,576,000*
Health outcomes			
No. of cases diagnosed overseas	0	139.9	369.5
No. of cases detected at US PHDs (active detection)	0	242.5	58.0
No. of cases passively detected in United States	450.4	68.1	22.9
No. of hospitalizations in US †	264.2	66.1	19.7
Economic outcomes ‡	'Smear-based' TI vs. No Screening	'Culture-based' TI vs. No Screening	'Culture-based' TI vs. 'Smear-based' TI
Net societal cost savings	$2,230,000	$2,322,000	$92,000
No. of imported cases averted	139.9	369.5	229.6
No. of imported hospitalizations averted	198.4	244.5	46.4

TB= tuberculosis; TIs= Technical Instructions; PHD= public health department

* The total societal cost estimate includes an additional $580 per case treated for the 1991 'Smear-based' TIs. The cost of treatment for the 2007 'Culture-based' TIs is included in the cost to immigrants, except for MDR-TB cases $5,400).

† Note that hospitalization in the United States depend on whether patients are actively or passively diagnosed. As a result, the probability of hospitalization is much higher under 'No Screening' compared to 'Smear-based' or 'Culture-based'.

‡† The ‘No Screening’ Scenario has both higher costs and more cases occurring in the United States than either the ‘Smear-based’ or ‘Culture-based’ TI scenarios. The ‘Culture-based’ TI screening alternative has lower net societal costs and better U.S. health outcomes and dominates the ‘Smear-based’ TIs. Thus, net societal cost per imported case or hospitalization averted cannot be calculated for the base-case outcomes.