

Evaluation of Immigrant Tuberculosis Screening in Industrialized Countries

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In industrialized countries, tuberculosis (TB) cases are concentrated among immigrants and driven by reactivation of imported latent TB infection (LTBI). We examined mechanisms used to screen immigrants for TB and LTBI by sending an anonymous, 18-point questionnaire to 31 member countries of the Organisation for Economic Co-operation and Development. Twenty-nine (93.5%) of 31 responded; 25 (86.2%) screened immigrants for active TB. Fewer countries (16/29, 55.2%) screened for LTBI. Marked variations were observed in targeted populations for age (range <5 years of age to all age groups) and TB incidence in countries of origin of immigrants (>20 cases/100,000 population to >500 cases/100,000). LTBI screening was conducted in 11/16 countries by using the tuberculin skin test. Six countries used interferon- γ release assays, primarily to confirm positive tuberculin skin test results. Industrialized countries performed LTBI screening infrequently and policies varied widely. There is an urgent need to define the cost-effectiveness of LTBI screening strategies for immigrants.

Tuberculosis (TB) in industrialized countries has reemerged as a public health concern after decreases in incidence during the 20th century. Over the past 30 years, although industrialized countries have shown country-specific quantitative changes (decrease, stabilization, or increase) in overall TB notifications, they share a similar

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underlying shift in TB epidemiology: decreasing incidence in the native population and an increasing incidence in foreign-born persons (1,2).

This disproportionate epidemiology is driven primarily by interaction of reactivating latent TB infection (LTBI) and high or increasing immigration levels. This interaction is demonstrated by the small proportion of clustered cases among foreign-born persons, which is lower than that among native-born persons, in molecular epidemiology studies from diverse industrialized settings (3). This interaction is also demonstrated by TB acquired before immigration and high or increasing levels of immigration from countries with a high incidence of TB in sub-Saharan Africa, Asia, South America, and northern Africa to industrialized countries that have a low incidence of TB (4,5).

Surveillance data from several industrialized countries show that a high proportion of active TB cases in foreign-born persons occurs in the first 5 years after arrival (new entrants) (6,7). The high level of foreign-born persons with TB in industrialized countries potentially jeopardizes national TB control programs and has reopened the debate about how industrialized, immigrant-receiving countries should screen immigrants (8,9). Although industrialized countries have national policies on immigrant screening, little contemporary comparison (10) of critical elements of these policies has been made.

We conducted an international evaluation of screening practices for TB among immigrants in industrialized countries. We also compared critical elements of national guidance, including whether screening identified cases of active TB or LTBI, which groups were targeted for screening, when screening was conducted, and which screening tools were used.

Methods

Ethics

No patient-specific data or personal identifiers were used. Our study was an analysis of routine data collected as part of service evaluation.

Sampling Frame

All 31 industrialized (high-income) member states, as of 2010, of the Organisation for Economic Co-operation and Development (OECD) (online Technical Appendix Table 1, wwwnc.cdc.gov/EID/pdfs/12-0128-Techapp.pdf) were included in the study (11). These countries have an estimated population of 1.0 billion persons, of whom 109.5 million (10.95%; 95% CI 10.94%–10.95%) are immigrants (12). Six of the top 10 immigrant-receiving countries are industrialized OECD countries (12). In 2009, median TB incidence in these countries was 7.4 cases/100,000 population (interquartile range [IQR] 6.0–10.6 cases/100,000), and a median of 46.9% (IQR 30.1%–65.0%) cases were in foreign-born persons (1,13).

Questionnaire

An 18-point questionnaire (online Technical Appendix Table 2) based on a published evaluation of screening practices in the United Kingdom (14) was formulated to obtain information on immigrant screening practices in each industrialized country. Data were collected during May–December 2010 by abstracting published, publicly available, national immigrant TB screening guidelines or, more frequently, by contacting (by email) persons involved in local TB control programs and screening of immigrants for TB (usually the TB control program director). Replies were received electronically, and nonresponders were emailed 2 reminders. No person-specific data were collected on the questionnaire.

Country-specific Data

Information for 2009 (or the most recent publically available data) on country-specific TB incidence was used. Countries with low and high TB incidence were classified as having <15 cases/100,000 and \geq 15 cases/100,000, respectively, according to national TB reports (15–20). The proportion of cases among foreign-born persons were obtained from the World Health Organization global database (21), and net immigration rates were obtained from the OECD migration database (22).

Statistical Analysis

Data were analyzed quantitatively, although certain open answers were categorized by investigators. Categorical responses were summarized by using proportions and 95% CIs, and comparisons were made by using the Fisher exact

test. Continuous data were non-normally distributed and summarized as medians and IQRs and compared by using the Mann-Whitney U test. Analyses were performed by using STATA version 12.0 (StataCorp LP, College Station, TX, USA). A p value <0.05 was considered significant.

Results

Response Rate and Profile of Responding Countries

Data were obtained from 29 (93.5%) of 31 industrialized OECD countries (online Technical Appendix Table 1). For these 29 countries in 2009, median TB incidence was 7.6 cases/100,000 (IQR 6.4–10.6), 46.8% (IQR 29.7%–64.6%) of cases were in foreign-born persons, and median net annual number of immigrants was 30,623 (IQR 12,322–77,206). There was no significant difference between responder and nonresponder countries for median TB incidence ($p = 1.00$), median proportion of cases in foreign-born (persons = 0.68), or median net number of immigrants ($p = 0.36$).

Coverage and Extent of Immigrant Screening for Active TB

Twenty-five (86.2%) of 29 countries (95% CI 67.3%–96.0%) had a system for screening immigrants for active TB (Table 1; online Technical Appendix Table 3); this system was compulsory in 19 (76.0%) of 25. Sixteen (64.0%) of 25 screened all legal immigrants and 4 (16.0%) of 25 screened selected legal immigrants. A higher number (24/25, 96.0%; $p = 0.02$) screened refugees/asylum seekers than all legal immigrants. Five (20.0%) of 25 countries restricted screening for active TB to refugees/asylum seekers. Countries that screened immigrants for active TB (either refugees/asylum seekers or legal immigrants) were less likely to have a high incidence of TB (\approx 15 cases/100,000) (50% vs. 95.7%; odds ratio 0.05, 95% CI 0.003–0.59, $p = 0.018$).

Timing of Screening for Active TB

Countries differed in when they screened for active TB (Table 1; Table 2, Appendix, wwwnc.cdc.gov/EID/article/18/8/12-0128-T2.htm); several countries tailored screening according to type of immigrant (refugee/asylum seeker vs. legal immigrant). Nine (36.0%) of 25 countries screened prearrival, 5 (20.0%) of 25 screened at arrival, and 23 (92.0%) of 25 screened postarrival. Of the 23 that screened postarrival, 8 (34.8%) of 23 also screened prearrival and postarrival but reserved screening postarrival mainly for asylum seekers/refugees.

Demographic Characteristics of Immigrants Selected for Active TB Screening

Specific immigrants, in terms of age and country of origin, targeted for active TB screening are shown in Table

Table 1. Screening practices for detecting active TB in immigrants in 29 industrialized OECD countries*

Screen for active TB	No. countries positive/ no. tested (%)
Yes	25/29 (86.2)
Compulsory	19/25 (76.0)
Timing of screening†	
Prearrival	9/25 (36.0)
At arrival	5/25 (20.0)
Postarrival	23/25 (92.0)
Type of immigrants screened	
All legal‡	16/25 (64.0)
Selected legal§	4/25 (16.0)
Refugees/asylum seekers¶	24/25 (96.0)
Selection criteria for immigrants screened	
Age	2/25 (8.0)
All ages	23/25 (92.0)
TB cases/100,000 population in country of origin	6/25 (24.0)
>15	1/6 (16.7)
>40	2/6 (33.3)
>50	2/6 (33.3)
>100	1/6 (16.7)
Region of origin#	19/25 (76.0)
All	5/19 (26.3)
All except EU, North America, Australia, and New Zealand	11/19 (57.9)
Other**	4/19 (21.1)
Screening tools used in children	
Clinical examination	6/25 (24.0)
Clinical examination and TST	8/25 (32.0)
Clinical examination and chest radiograph	0/25 (0.0)
Clinical examination, TST, and chest radiograph	2/25 (8.0)
TST	3/25 (12.0)
TST and chest radiograph	3/25 (12.0)
Chest radiograph	3/25 (12.0)
Screening tools used in adults	
Clinical examination	1/25 (4.0)
Clinical examination and TST	1/25 (4.0)
Clinical examination and chest radiograph	9/25 (36.0)
Clinical examination, TST, and chest radiograph	2/25 (8.0)
TST	1/25 (4.0)
TST and chest radiograph	2/25 (8.0)
Chest radiograph	9/25 (36.0)

*OECD, Organisation for Economic Co-operation and Development; TB, tuberculosis; EU, European Union; TST, tuberculin skin test.

†Numbers do not add up to the total because some countries screened at >1 location.

‡Countries in which all legal immigrants (if they meet screening criteria) are screened (see online Technical appendix, wwwnc.cdc.gov/EID/pdfs/12-0128-Techapp.pdf) for more detailed categorization and definitions.

§Countries in which only selected categories of legal immigrants (if they meet screening criteria) are screened (see online Technical Appendix for more detailed categorization and definitions).

¶Countries in which refugees/asylum seekers are screened (see online Technical Appendix for more detailed categorization and definitions).

#Numbers do not add up to the total because the Czech Republic screened refugees/asylum seekers from all countries but legal immigrants only from selected countries.

**Congo, Czech Republic, Israel, Kenya, Moldova, Mongolia, Nigeria, North Korea, Pakistan, Slovenia, South Korea, Tajikistan, Turkmenistan, Uzbekistan, and Vietnam.

1 and Table 2, Appendix. Twenty-three (92.0%) of 25 countries screened all age groups for active TB.

There was more variability in countries of origin that were targeted for screening. Six (24.0%) of 25 countries determined which immigrants should be screened on the basis of TB incidence in their country of origin. Incidence thresholds at which screening was initiated ranged from >15 cases/100,000 to >100 cases/100,000, although >40 cases/100,000 and >50 cases/100,000 were most commonly used.

Nineteen (76.0%) of 25 countries selected migrants for screening on the basis of the country from which they originated. Immigrants from countries with high incidence of TB were most commonly screened; 11 (57.9%) of 19 countries screened immigrants arriving from any region except for the European Union (EU), North America, Australia, and New Zealand.

Methods of Screening New Immigrants for Active TB

Among countries that screened for active TB, screening methods are shown in Table 1 and online Technical Appendix Table 4, although screening at these locations was reserved. In children and certain adults, such as pregnant women, for whom chest radiography is generally avoided, the most common methods of initial screening for active TB were clinical examination plus tuberculin skin test (TST) and clinical examination alone.

Adults and older children were assessed by using similar methods, although countries differed in the minimum age at which they used chest radiographs to screen for active TB (range birth to >18 years). Overall, screening by clinical examination plus chest radiograph and chest radiograph alone were the most frequent methods of screening adults for active TB.

Coverage and Extent of Immigrant Screening for LTBI

The proportion of industrialized OECD countries that screened immigrants for LTBI is shown in Table 3. Sixteen (55.1%) of 29 countries screened immigrants for LTBI. Of these 16 countries, 11 (73.3%; compulsory in 7 [(63.6%) of 11], 2 (13.3%; compulsory in 0 [0.0%] of 2), and 15 (93.8%, compulsory in 8 [53.3%] of 15) screened for LTBI in all legal migrants, selected legal migrants, and asylum seekers/refugees, respectively (12 countries screened >1 immigrant group) (online Technical Appendix Table 3). There was no difference in TB incidence, proportion of cases among foreign-born persons, and net migration when we compared countries that screened and did not screen for LTBI.

Timing of Screening for LTBI

As with screening for active TB, countries differed in when they screened for LTBI (Table 3), which depended

on the status of the immigrant (Table 4, Appendix, wwwnc.cdc.gov/EID/article/18/9/12-0128-T4.htm). Two (12.5%) of 16 countries screened prearrival and 2 (12.5%) of 16 screened at arrival, although screening was reserved primarily for asylum seekers and refugees. LTBI screening was most frequently conducted postarrival in the host country (16/16, 100%).

Demographic Characteristics of Immigrants Selected for LTBI Screening

Details of which immigrant subgroups were targeted for LTBI screening are shown in Table 3 and online Technical Appendix Table 4. In 16 countries that screened for LTBI and imposed age criteria, persons of a wide range of ages (birth to <40 years of age) were screened. Children and young adults were most commonly targeted for screening although 8 (50.0%) countries imposed no upper age limit for screening.

Selection of immigrants for screening of LTBI as determined by TB incidence in the country of origin or by specific countries of origin was conducted in 5 (31.3%) of 16 and 13 (81.3%) of 16 countries, respectively. Selection criteria in the United States and Ireland used TB incidence and country of origin (Table 4, Appendix). The incidence threshold at which immigrants were screened for LTBI ranged from >20 cases/100,000 to >500 cases/100,000. Among 13 countries that screened for LTBI on the basis of specific countries of origin, 5 (38.5%) screened immigrants arriving from countries with a high incidence of TB outside the EU, North America, Australia, and New Zealand, and 5 screened immigrants from all countries.

Methods of Screening Immigrants for LTBI

Screening methods used by 16 industrialized countries that screened immigrants for LTBI are shown in Table 4, Appendix. The most commonly used screening protocol was TST (11/16, 68.8%). Six (37.5%) countries used the interferon-γ release assay (IGRA) when diagnosing LTBI, 3 countries used a stepwise TST plus confirmatory (IGRA) approach, 2 countries advocated single-step IGRA, and 1 country (United Kingdom) recommended TST and confirmatory IGRA (for persons ≤35 years of age) and single-step IGRA (for persons 16–35 years of age).

Discussion

Increased attention is being given to TB among immigrants as a public health issue in industrialized countries (8), which underscores use of our data in determining how to best augment current TB control programs. Our international evaluation of immigrant screening policies among industrialized OECD countries indicated that although screening for active TB is frequently performed, LTBI screening is less common. Moreover, screening

Table 3. Immigrant screening practices for latent TB infection in 16 industrialized OECD countries*

Screen for latent TB	No. positive countries/ no. tested (%)
Yes	16/29 (55.2)
Location of screening	
Prearrival	2/16 (12.5)
At arrival	2/16 (12.5)
Postarrival	16/16 (100.0)
Selection criteria based on age	
No age cutoff†	6/16 (37.5)
Age cutoff values for screening, y	10/16 (62.5)
<5	1/10 (10.0)
<15	2/10 (20.0)
<35	3/10 (30.0)
<40	1/10 (10.0)
Other	3/10 (30.0)
TB incidence in country of origin	
5/16 (31.3)	
TB cases/100,000 population at screening‡§	
>20	1/5 (20.0)
>40	2/5 (40.0)
>50	1/5 (20.0)
>100	1/5 (20.0)
>500	1/5 (20.0)
Specific country of origin§	
13/16 (81.3)	
Countries screened	
All	5/13 (38.5)
All except EU, North America, Australia, and New Zealand	5/13 (38.5)
Other¶	3/13 (23.1)
Screening tools used for LTBI#	
TST	11/16 (68.8)
TST and confirmatory IGRA	4/16 (25.0)
IGRA	3/16 (18.8)

*OECD, Organisation for Economic Co-operation and Development; TB, tuberculosis; EU, European Union; LTBI, latent TB infection; TST, tuberculin skin test; IGRA, interferon-γ release assay.

†All ages screened.

‡Numbers do not add up to the total because certain countries (e.g., Ireland) screened at different incidence thresholds for children and adults.

§Numbers do not add up to the total because certain countries base screening criteria on incidence threshold and country of origin.

¶Ethiopia, sub-Saharan Africa, Asia, Africa, and Eastern Europe.

#Numbers do add up to the total because in some countries (e.g., United Kingdom and United States), >1 screening method is allowed or recommended.

that is performed for active TB and LTBI varies among countries. Our results indicate that heterogeneity exists in screening location, selection criteria for which immigrant subgroups to screen, and screening methods used.

The primary objective of immigrant screening in industrialized countries appears to be to diagnose active TB, either before immigration or soon after arrival in the host country. Although diagnosing and treating infectious TB reduces transmission, data from numerous settings suggest that yields for active TB diagnosed at or around the time of migration are low: 0.35% in recent meta-analyses and lower in UK studies (23–26).

Although most countries in our study screened for active TB, screening was not universal, and countries differed in which immigrants they screened. Among countries that screened for active TB, asylum seekers and refugees were most commonly targeted for screening. Although

these groups are at high risk for having TB infection and disease (because of poor social circumstances, inadequate housing, poor nutrition, and stress of migration), and yields and effects from screening are likely to be higher among them (23), they constitute only 2.1% of all immigrants to industrialized OECD countries and are likely to have a smaller role in TB epidemiology (12). However, a limitation of current national surveillance data is that it does not stratify TB cases among foreign-born persons by immigration status, which makes it impossible to know what proportion of TB cases arise from documented versus undocumented or illegal immigrants.

There was evidence of heterogeneity for specific countries of origin and TB incidence in countries of origin that were selected for active TB screening. Immigrants from countries with high incidence of TB were generally targeted. However, this targeting was partly modulated because free movement of citizens between EU member states indicated that citizens of certain EU nations with a high incidence of TB (particularly where countries based the decision to screen solely on country of origin) were not eligible to be targets for screening when migrating within the EU, although they would be targeted when migrating to countries (mainly non-EU) that based screening policy on TB incidence. In those industrialized countries that used TB incidence as the selection criteria, screening was performed at incidence thresholds from >15 cases/100,000 to >100 cases/100,000.

It is unclear why countries had such different policies although setting the threshold at a higher level may have increased the yield of screening. The specific immigrant subpopulations targeted (either by country of origin or TB incidence in country of origin) may reflect unique migration patterns to each OECD country (5), which may stem from colonial, historic, or linguistic links, financial resources, the current health care system, and infrastructure to deal with immigrants. A possible limitation of current screening protocols is that they may not target immigrants from regions with a high incidence of TB who arrive in industrialized, low-incidence settings, acquire citizenship, and then move to a country with a low incidence of TB (although this group might be small).

Similar variation was observed in screening tools used to diagnose active TB. Younger children were often screened by clinical examination with or without a TST, although making a diagnosis of active TB in children is often difficult when based on such limited evidence (27). Adults and older children were usually screened by chest radiograph, although the lower age limit at which chest radiographs were permissible varied from birth to 18 years of age. The wide range likely reflects reluctance to unnecessarily expose children to radiation and different,

more adult-like patterns of pulmonary disease seen in older children (28).

The prevalence of active TB at entry is small and imported active disease that is detectable among immigrants arriving in their country of destination is not driving the increasing disease incidence seen in foreign-born persons in industrialized OECD countries (24). Moreover, because epidemiologic data suggest a high and increasing proportion of extrapulmonary TB in foreign-born persons, chest radiographs would play a limited role in diagnosis (29,30). This finding would limit screening systems that many industrialized countries currently use for adults. The UK Health Protection Agency has reviewed port health regions and recommended urgent review of continued use of chest radiography as the initial diagnostic test for new entrants (currently underway) (26).

In contrast, TB epidemiology in OECD countries and molecular typing data indicate that reactivation of imported LTBI in the first few years after immigration is driving the increase in foreign-born persons with TB cases (3). Therefore, although screening for active TB is needed, without commensurate targeting of LTBI, screening is unlikely to control TB at a population level. We found that only half of industrialized countries screened immigrants for LTBI, and refugees/asylum seekers were most commonly targeted for screening. This finding indicates that screening legal immigrants for LTBI remains a low-priority TB control measure in industrialized countries, a potential gap that needs to be urgently addressed.

Among countries that screen for LTBI, there was heterogeneity in which immigrant subgroups were screened. For age, children and young adults were most commonly targeted because these groups have the highest risk for progression to active TB and are most likely to benefit from chemoprophylaxis. However, 47% of countries screened all age groups for LTBI, which suggests that in certain countries, older immigrants are given chemoprophylaxis, despite often-cited concerns about hepatotoxicity (31).

Similar variability was seen in which countries of origin of immigrants were targeted for screening. Among industrialized countries that selected immigrants on the basis of TB incidence in the country of origin, the TB incidence screening threshold ranged from >20 cases/100,000 to >500 cases/100,000. This wide variation likely reflects uncertainty about the optimal threshold at which to screen. Setting the incidence threshold too low would result in large numbers of immigrants needing to be screened. Thus, a low threshold would increase costs and likely overwhelm TB screening services, although many immigrants from lower-incidence countries (who have a low prevalence of TB) often do not contribute to TB incidence in industrialized countries. In contrast, if the incidence screening threshold

is set too high, few immigrants would be screened, which means that a large proportion of the immigrant population that has LTBI, and subsequently converts to active TB, would be missed (32).

The most cost-effective policy option is likely to be to target at an intermediate incidence that balances, most cost-effectively, the numbers of immigrants being screened (and therefore associated costs) against prevalence of LTBI in the immigrant population (33). However, in many OECD countries, making cost-effective policy decisions about immigrant screening for LTBI is hampered by gaps in evidence in several areas, including which immigrant groups to screen (depending on TB incidence/country of origin), which screening methods to use, and which location is best for screening. This policy may partly explain variability in screening models adopted by OECD countries. These gaps could be appropriately addressed by obtaining prospective, multicenter data on prevalence of LTBI in immigrants and assessing performance of screening tools and outcomes of screening in different locations. This policy would enable investigators to calculate yields and relative cost-effectiveness of screening at different incidence thresholds (as was conducted recently in the United Kingdom [33]), for different screening tools and in different locations, thereby enabling countries to formulate country-specific, evidence-based, immigrant screening policies.

LTBI screening methods also varied widely. The most commonly used screening method was TST. Although TST is widely used and inexpensive, it has poor specificity in *Mycobacterium bovis* BCG-vaccinated populations (e.g., immigrants arriving in industrialized countries), poor sensitivity in immunocompromised persons, and logistic drawbacks, including the need for a return visit and trained staff (34). Although data suggest that IGRAs have higher specificity and sensitivity than TST (34), their use was limited to 40% of industrialized countries as a confirmatory test for a positive TST result and increasingly as a single-step test to replace TST. This finding may reflect recent evidence that suggests that IGRAs are cost-effective and, if results are positive, can predict progression to active TB (35,36). However, the predictive power of IGRA for progression to active TB does not appear to be higher than that of TST (37). Empirical data are needed for relative performance of these tests in immigrant populations so that contemporary health economic analyses can conclude which screening modality is most cost-effective. Given the pivotal need for predictive power in improving cost-effectiveness of testing for LTBI (33), a more powerfully prognostic test would transform the cost-benefit equation for LTBI screening.

A major factor when considering the potential effect of screening for and treating LTBI is that suboptimal

completion rates for chemoprophylactic regimens adversely affect efficacy of screening programs, thereby underscoring the need for adopting a patient-centered approach and new, faster-acting, drugs for LTBI (38). Given these potential drawbacks, an alternative approach, depending on patient preference and risk perception, could be to follow-up persons with LTBI for clinical signs over a defined period to rapidly identify and treat those with infections that become active. This approach is used in parts of the United Kingdom and the Netherlands (39).

Our study builds on previous research, which focused on fewer industrialized countries (40) and was conducted some years ago. However, it failed to capture recent changes in guidance (40), did not specifically focus on LTBI, and failed to identify the critical elements of immigrant screening programs, such as which immigrants were selected for screening (10,40).

Our study had several limitations. Information was gathered through a questionnaire with potential for recall/responder bias, although this limitation was minimized by clarifying ambiguous responses of responders or cross-referencing against national guidelines. In addition, our study only captured what screening is currently recommended, and thus presents an idealized situation of how screening should be conducted, which may be different from actual practice at the local level (14). Only a detailed assessment of national practice can determine the extent to which national guidance is followed.

TB in industrialized countries primarily occurs in foreign-born persons. Current immigrant screening policies in these countries focus primarily on identifying active TB. Although the contribution of active TB at the time of immigration is crucial, data from 2 large contemporary meta-analyses suggest that the prevalence of active disease in immigrants arriving from countries with a high incidence of TB remains relatively low (0.35%) (23,24), making cost-effectiveness and value of the current screening strategies uncertain. In contrast, epidemiologic data suggest that LTBI reactivation in immigrants plays a central role in determining national TB incidence. However, LTBI screening is paradoxically limited, and there is no consensus on which immigrants to screen and how to screen.

Addressing these issues is critical to effective TB control in industrialized countries, as is identification and treatment of persons with LTBI, and where control measures should be targeted while remaining vigilant about timely diagnosis and treatment for active disease. To address this problem effectively, robust evidence-based data are urgently needed to develop affordable, effective, and cost-effective policies on which immigrant subgroups to screen (33). Such policies will need to be developed in the context of nation-specific economic considerations,

including resource availability and the funds policy makers are willing to spend to control the incidence of active TB.

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