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Pediatric tuberculosis immigration screening in high-immigration, low-incidence countries

G. G. Alvarez,* M. Clark,† E. Altpeter,‡ P. Douglas,§ J. Jones,¶ M-C. Paty,# D. L. Posey,** D. Chemtob††

*Divisions of Respirology and Infectious Diseases, The Ottawa Hospital Research Institute, University of Ottawa at The Ottawa Hospital, Ottawa, Ontario, †Department of Pediatrics, Children's Hospital of Eastern Ontario, Ottawa, Ontario, Canada; ‡Swiss Federal Office of Public Health, Bern, Switzerland; §Department of Immigration and Citizenship, Sydney, New South Wales, Australia; ¶Travel and Migrant Health Section for Infections, London, UK; #Direction Générale de la Santé, Sous-direction de Prévention des Risques Infectieux, Paris, France; **Immigrant, Refugee and Migrant Health Branch, Division of Global Migration and Quarantine, Centers for Disease Control and Prevention, Atlanta, Georgia, USA; ††Department of Tuberculosis and AIDS, Public Health Services, Ministry of Health, Jerusalem, Israel

SUMMARY

BACKGROUND: Tuberculosis (TB) screening in migrant children, including immigrants, refugees and asylum seekers, is an ongoing challenge in low TB incidence countries. Many children from high TB incidence countries harbor latent TB infection (LTBI), and some have active TB disease at the point of immigration into host nations. Young children who harbor LTBI have a high risk of progression to TB disease and are at a higher risk than adults of developing disseminated severe forms of TB with significant morbidity and mortality. Many countries have developed immigration TB screening programs to suit the needs of adults, but have not focused much attention on migrant children.

OBJECTIVE: To compare the TB immigration medical examination requirements in children in selected countries with high immigration and low TB incidence rates.

DESIGN: Descriptive study of TB immigration screening programs for systematically selected countries.

RESULTS: Of 18 eligible countries, 16 responded to the written survey and telephone interview.

CONCLUSION: No two countries had the same approach to TB screening among migrant children. The optimal evidenced-based manner in which to screen migrant children requires further research.

KEY WORDS: immigration; screening; tuberculosis; children

LATENT TUBERCULOSIS INFECTION (LTBI) is common among immigrant children from high tuberculosis (TB) incidence countries. A study involving a school-based LTBI screening program in high-risk immigrant children aged 4–18 years in Canada demonstrated a yield of 21% (542/2524) tuberculin skin test (TST) positivity.[1] Another study also involving a school-based LTBI screening program, performed among children aged 12–13 years in Israel, showed significant differences in TST positivity according to the children's country of origin.[2] Lack of formal immigration TB screening in children entering low TB incidence countries may be related to the fact that pediatric pulmonary TB (PTB) is rarely infectious, due to a low bacillary load during active TB disease.[3] It does not, therefore, pose the same public health risk as adult disease.[4] Another reason why formal TB screening is lacking for migrant children may be that children have been shown to represent a small proportion of active TB among all migrants.[5] On the other hand, for countries such as Israel, where more than 80% of TB cases occur among foreign-born patients, and where there is an active case-finding program for all close contacts and active screening for immigrants from sub-Saharan Africa,[6] pediatric TB accounts for 11.7% of all TB cases diagnosed in the country.[7]

Screening migrant children for TB is important, as they have a higher risk of developing active disease due to recent infection. Furthermore, when they develop disease it is more severe, resulting in increased morbidity and mortality compared to adults.[3,8] The younger the child, the higher the risk of developing disease, as it reflects more recent infection. In a study that followed Puerto Rican children for 20 years after positive TST, the major risk factor for developing TB disease among the TST reactors was age. Children aged <4 years had the highest TB rates and the most serious disease.[9] Tools used to screen migrant children

Correspondence to: Gonzalo G Alvarez, Divisions of Respirology and Infectious Diseases, University of Ottawa at The Ottawa Hospital, The Ottawa Health Research Institute, 501 Smyth Road, Ottawa, ON, Canada. Tel: (+1) 613 737 8899. Fax: (+1) 613 737 8537. e-mail: galvarez@ohri.ca

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for TB include: history, physical examination, TST, interferon-gamma release assays (IGRAs), chest radiographs (CXR) and bacteriology. The optimal use of these tools is not fully known in the context of pediatric immigration TB screening programs. The current study presents the immigration TB screening practices among children from selected low TB incidence countries.

METHODS

Country selection

The following inclusion criteria were applied:

1 Listed in The World Migration 2005 Report, published every 5 years by the International Organization for Migration and United Nations,[10] as the 20 host countries accepting the largest number of international migrants, OR
2 A well-developed immigration TB screening program, as reflected by any publications in the scientific literature, AND
3 A rate of sputum smear-positive PTB of ⩽15 cases per 100 000, as estimated by the World Health Organization (WHO) averaged over the years 2004, 2005 and 2006, as defined by the Canadian TB Standards.[11]

The survey was conducted using a standardized data abstraction sheet completed by each country representative and supplemented by a telephone interview carried out by the primary investigator (GGA) during the months of July and August 2008. Country-specific details were current as of April 2009. Information for the United States is current as of 1 October 2009, as they issued revised TB guidelines on that date.[12]

The present study focused on national guidelines for formal screening of children through immigration screening processes, and not on local programs. Guidelines and policies involving primary care following the immigration process were not studied. The study did not address TB screening of international adoptees. Ethical approval was not required for this questionnaire-based study.

The terms and definitions used are set out in Table 1.

Table 1 Terms and definitions

Term	Definition
Children	Individuals aged 0–17 years
International adoptee	A child from another country who is legally adopted by persons from the host nation
Migrant children	Includes immigrants, refugees, asylum seekers and international adoptees
Latent TB infection	A positive TST or IGRA where there is no evidence of TB disease

TB = tuberculosis; TST = tuberculin skin test; IGRA = interferon gamma release assay.

RESULTS

Participation in the study

Of the 18 countries that were selected and contacted, 16 completed all the requirements, for a response rate of 89%. Although Italy, Japan and Spain participated in the study, they do not have formal TB immigration screening programs and were therefore not included in the analysis. A total of 13 countries were therefore included in the study.

Techniques used for screening migrant children for TB

Initial screening tool used

Although most countries used more than one tool to screen for TB, the initial screening tool varied between countries. Table 2 shows that 8/13 countries used the TST as the initial screening tool, whereas 7/13 used history and physical examination, and Israel and the Netherlands used both the TST and CXR as the initial screening tool.

History and physical examination

Australia, Canada and Germany use only physical examination to screen children, and therefore do not use the TST as part of their formal immigration screening programs (Table 3). They advocate screening high-risk migrant children in the primary care setting with TST. For example, Canada recommends that children aged <15 years who have lived in a country with high TB incidence and who immigrated within the previous 2 years should be screened for LTBI with either a TST or IGRA at the primary care

Table 2 Initial screening tool used by the host country to screen for TB as part of formal immigration TB screening for children

Country	History and physical examination	TST	CXR*	Sputum†
Australia	Yes	No	No	No
Canada	Yes	No	No	No
France	Yes	Yes	No	No
Germany	Yes	No	No	No
Israel	Yes‡	Yes‡	Yes‡	No
Jordan	No	Yes	No	No
The Netherlands	No	Yes	Yes	No
New Zealand	No	No	No	No
Norway	No	Yes	No	No
Sweden	No	Yes	No	No
Switzerland	Yes	No	No	No
United Kingdom	No	Yes	No	No
United States	Yes	Yes§	No	No

* The respective screening program would have to screen all children (0–18 years) with CXR to be considered a yes.
† For microscopy and culture.
‡ Only for immigrants originating from high-incidence countries who applied for permanent residency in Israel.
§ Or IGRA where the 2007 TB TI are in effect.[12]
TB = tuberculosis; TST = tuberculin skin test; CXR = chest radiograph; IGRA = interferon-gamma release assay.

Table 3 History and physical examination used to screen for tuberculosis in migrant children

Country	History and physical examination	Age, years	Comments
Australia	Yes	<16	Screening involves only physical examination
Canada	Yes	<11	Screening involves only physical examination
France	Yes		Age data not obtained
Germany	Yes		Age data not obtained
Israel	Yes	All	As part of the routine active screening for all immigrants from high-incidence countries who applied for residence
Jordan	No		
The Netherlands	No		
New Zealand	Yes	12–18	Children <12 years are not screened
Norway	No		
Sweden	No		
Switzerland	Yes	All*	Symptom-based questionnaire
United Kingdom	Yes	All	Not used in isolation for screening purposes, however, it only applies if the child comes from a high-incidence country and is staying in the UK for >6 months
United States	Yes	All	All children are subjected to a history and physical examination.

* Only asylum seekers are screened with the symptom-based questionnaire.

Table 4 Host countries that used chest radiography to screen for TB in migrant children as part of their immigration screening program

Country	Age CXR requested, years	Indications for CXR
Australia	⩾11	<11 years, CXR if physical examination warrants it
Canada	>11	
France	⩾10	<10 years, if not vaccinated with BCG should have a CXR
Germany	>15	
Israel	All*	
Jordan	>14	
The Netherlands	All	
New Zealand	>11	
Norway	>15	
Sweden†	All	CXR if TST-positive
Switzerland‡	All	TB suspected according to questionnaire
United Kingdom	>11	From high-incidence country, staying in the UK for >6 months and not pregnant
United States	⩾15	CXR if TST or IGRA-positive in those aged 2–14 years, HIV infection, or signs and symptoms of TB where the 2007 TB TI are used[12]

* Only for immigrants originating from high-incidence countries who applied for permanent residency in Israel.
‡ The nurse applies the questionnaire through the parents (see country profile).
† Screens for latent TB as well as active TB, therefore anyone of any age who is TST-positive undergoes CXR.
TB = tuberculosis; CXR = chest radiograph; BCG = bacille Calmette-Guérin; TST = tuberculin skin test; IGRA = interferon-gamma release assay; HIV = human immunodeficiency virus; 2007 TB TI = 2007 Technical Instructions for Tuberculosis Screening and Treatment.

level; however, this does not form part of the formal immigration screening or immigration medical surveillance follow-up process.[4] New Zealand does not screen children aged <12 years with any modality.

CXR

The indication for a CXR as part of the TB screening also varied among countries (Table 4). The age for CXR screening varied from all ages in Israel, Netherlands, Switzerland and Sweden to between 10 and 16 years of age across the remaining countries surveyed. Most countries use CXR screening in children starting at a range of ages from 11 to 16 years.

TST

A total of eight countries surveyed used the TST to screen migrant children (Table 5). The ages of those screened and criteria for a positive test varied. France screens for LTBI in all children aged <15 years. Israel screens children from high-incidence countries (Ethiopia and India) aged <18 years with TST and CXR. Jordan screens children who are not from the United States, Canada or Europe and are aged <14 years with TST. The United States is in the process of implementing new TB guidelines (the 2007 Technical Instructions for Tuberculosis Screening and Treatment [2007 TB TI]),[12] which use TSTs or IGRAs for children aged 2–14 years living in a country in which the WHO-estimated incidence rate of TB is ⩾20/100 000 (the previous guidelines do not require TST). In the United Kingdom, CXR is generally used as the first-line screening tool for anyone travelling from a high-incidence country (>40/100 000) for more than 6 months, but is not used in those aged <11 years. In addition, these children should all be offered TST, as should children aged 11–16 with a normal CXR, and anyone aged 16–35 from sub-Saharan Africa with a normal CXR. TST is only used in the post-entry screening setting. The Netherlands screen children aged <12 years for LTBI when there is no history of bacille Calmette-Guérin (BCG) vaccination. Norway and Sweden test for LTBI in all groups screened, including children.

Interferon-gamma release assays

None of the countries surveyed used IGRAs as part of the TB immigration screening process, except the United States, which allows either TST or IGRA to be used in countries where the 2007 TB TI are in use.[12] Norway is the only country surveyed that uses an IGRA as part of the immigration TB screening program; however, at present it does so only in adults. In Canada, IGRA testing does not form part of the TB immigration screening program.[13]

Table 5 Host countries that used TST screening of migrant children as part of their formal immigration screening program

Country	TST used	Indication for TST	Age, years	Induration considered positive
Australia	No			
Canada	No			
France	Yes		<15	Depending on BCG status, thresholds 5 mm (no BCG) and 10 mm (BCG+)
Germany	No			
Israel	Yes	High-incidence countries	All	⩾10 mm
Jordan	Yes			>10 mm
The Netherlands	Yes		<12*	
New Zealand	No			
Norway	Yes	All	<18	
Sweden	Yes	All	<18	
Switzerland†	Yes	All		
United Kingdom‡	Yes	High-incidence countries	Various age cut-off points‡	>15 mm if prior BCG; >6 mm if no prior BCG
United States	Yes§	Being screened in a country with WHO TB incidence rate ⩾20 per 100 000 where the 2007 TB TI are in use.[12]	2–14	⩾10 mm (CXR needed)

*No prior BCG vaccination will get TST.
†No specific recommendations for TB screening in children.
‡Only screen children with a TST post entry, not prior to or at entry, and they must be staying for >6 months and be from a high-incidence country. All <11 years (no CXR used), those with normal CXR between 11 and 16 years if from high-incidence country and between 16 and 35 if from sub-Saharan Africa.
§Or IGRA.
TST = tuberculin skin test; BCG = bacille Calmette-Guérin; CXR = chest radiograph; WHO = World Health Organization; TB = tuberculosis; IGRA = interferon-gamma release assay; 2007 TB TI = 2007 Technical Instructions for Tuberculosis Screening and Treatment.

Sputum analysis of migrant children

None of the countries surveyed used sputum analysis as a screening tool. However, all used it 'when clinically indicated', with no specified criteria. In the United States, 2007 TB TI children with a TST ⩾ 10 mm or a positive IGRA are required to have a CXR; those with CXR suggestive of TB, signs and symptoms of TB, or human immunodeficiency virus (HIV) infection are required to provide sputum specimens for smear and culture. The system these instructions replace does not require TST, IGRA, cultures, or CXR in children <15 years of age.[12]

BCG immunization offered by host country to migrant children

Most countries surveyed did not offer BCG immunization (Table 6). BCG immunization is offered by Israel, France, the Netherlands and the United Kingdom to migrant children coming from high-burden countries with a negative TST. The age of the child when BCG was offered varied significantly. Israel offers BCG vaccination to high-risk children <5 years of age with TST < 10 mm. The Netherlands offers BCG to asymptomatic children aged <12 years with no history of BCG vaccination, if they have a negative TST. In the United Kingdom, BCG immunization is offered to previously unvaccinated, TST-negative new entrants <16 years of age who were born in or who had lived for a prolonged period (at least 3 months) in a country with an annual TB incidence of ⩾40/100 000. The immunization is not part of the immigration screening done at the three points of screening in the United Kingdom, and is relevant only to local TB control after entering the country.[14]

DISCUSSION

All countries surveyed screened for TB among migrant children. However, the screening programs varied considerably between the countries surveyed in the study.

Tools used for TB screening of migrant children

The initial screening tool is key, as it may affect the yield of detecting TB infection and disease as well as the need for further testing. For example, history and physical examination are often normal in children with active TB disease, thus making the TST a better predictor of TB infection or disease.[15] Eight countries (8/13) used the TST as the first screening

Table 6 Host countries that offered BCG vaccination to migrant children as part of their formal immigration screening program

Country	BCG	Age offered, years	Indications for BCG
Australia	No		
Canada	No		
France	Yes	<15	Negative TST, high-incidence
Germany	No		
Israel	Yes	<5	Negative TST, high-incidence
Jordan	No		
The Netherlands	Yes	<12	Negative TST, high-incidence
New Zealand	No		
Norway	No		
Sweden	No		
Switzerland	Yes		Not part of TB screening program but overall Swiss vaccination recommendations
United Kingdom	Yes	<16	Negative TST, high-incidence
United States	No		

BCG = bacille Calmette-Guérin; TST = tuberculin skin test.

test; however, four (4/13) used history and physical examination as the initial screening tool. Three (3/13) countries used both modalities.

History and physical examination

With regard to history, identifying the country of origin is paramount, given that 22 countries in the world account for 80% of incident TB cases globally.[16] A significant portion of migrant children will have acquired infection or disease in these countries. Israel and Jordan focus their targeted screening on children from high-burden countries; however, they use different criteria for establishing which countries are 'high incidence'. Establishing a TB contact history is essential, as adults with PTB are the main source of childhood TB infection.[17,18]

History and physical examination guidelines need to be explicit so that clinicians can apply the evidence to screening practices. Although most countries screen children with history and physical examination, they do not provide detailed validated approaches. A more detailed approach, including a risk assessment questionnaire history and physical examination specific to pediatric TB, should be used.[19] Validation of these tools in the context of an immigration screening program has not been documented. Other symptom-based approaches have been proposed for the diagnosis of active TB in children. A group from South Africa identified the following three predictors: 1) persistent, non-remittent coughing or wheezing; 2) documented failure to thrive despite deworming and food supplementation (if food security is a concern); and 3) fatigue or reduced playfulness.[20] These three factors had a sensitivity, specificity, and positive predictive value (PPV) of respectively 82%, 90%, and 82% for non-HIV-infected children aged <13 years. Although the sensitivity was quite low in children aged <3 years, the specificity and PPV were both >90%. This approach is designed to address symptom-based approaches in resource-limited settings. Limited resources should not be a significant factor in immigration screening; however, this simple approach could be added to other tests to improve its accuracy. None of the countries surveyed explicitly used the aforementioned detailed history and physical examination approaches to screen children from high-burden countries.

TST

The age at which a TST is performed as part of the immigration TB screening varied. More attention should be paid to children aged <2 years from high TB incidence countries, as they harbor a high risk of developing active disease and suffer the greatest consequences from disseminated disease.[8] The induration diameter cut-offs for when a TST is considered positive varied, as they do in clinical and public health practice. In general, the approach should be that the higher the risk of TB the lower the cut-off, and the lower the risk of TB, the higher the cut-off. Most use >5 mm induration for a close contact or immune-compromised child and >10 mm induration for everyone else. However, it has been advocated by some that a ⩽4 mm TST induration in HIV-infected children from a high-incidence country[4] or >15 mm induration in children from low-incidence countries[19] should be considered as a positive TST.

The interpretation of the TST in children who have been vaccinated with BCG poses a challenge, as if BCG is given after infancy or in multiple doses it can result in a false-positive TST.[19] In general, it is accepted that BCG given at birth has little, if any, effect on the TST past the age of 10 years.[21] A recent meta-analysis of 24 studies and data from over 240 000 patients showed that BCG given in infancy results in a false-positive TST in 6% of vaccinated subjects.[22] This figure rose to 40% when the vaccine was given after infancy. Another meta-analysis showed that TST had poor performance as a screening method for vaccinated children aged <2 years, and considerable variation existed in children aged between 2 and 14 years.[23] Age at vaccination is not always easy to obtain. However, a website has been developed for health care professionals to access information on worldwide, country-specific BCG vaccination guidelines.[24] The age at vaccination is provided for most countries. TST results in the BCG-vaccinated child must be interpreted within the context of their risk of infection or disease, and other clinical parameters. United States guidelines stipulate that prior BCG vaccination should not alter the screening requirements or the actions required in the work-up of children being screened for TB, which is supported by the literature.[25]

Interferon-gamma release assays

None of the countries used IGRAs to screen migrant children as part of the TB immigration screening program, except for the United States, which allows either TST or IGRA to be used where TST is required. Research is still ongoing for the use of IGRAs as a screening tool for migrant children entering low TB incidence countries. IGRA testing in children has been challenged by frequent discordance between tests (TST+/IGRA−), and variable sensitivity with active TB, cost and phlebotomy failure have all been reported.[3,13] IGRAs remain an attractive tool, however, for the diagnosis of LTBI, as the test is done on one visit, is less dependent on the interpretation of the operator and can distinguish between BCG-vaccinated and non-vaccinated persons.

CXR

Most children aged <10 years did not receive a CXR in the countries surveyed. This practice is likely a result of adolescent children having a higher incidence of adult-type cavitary TB, which is more easily

identifiable on CXR and associated with a higher risk of transmission. Adolescent children (>10 years) frequently develop sputum smear-positive disease that can be diagnosed using traditional sputum microscopy.[15,26] If a child aged <10 years is to receive a CXR for TB screening, a lateral CXR could also be performed, as it has been shown in one study that lymphadenopathy was only detected on a lateral CXR in 19% of children <10 years with culture-confirmed TB.[27]

Sputum analysis

None of the countries surveyed used sputum as a screening tool for immigration screening, likely because sputum smear microscopy is positive in <10–15% of children with TB, and culture yields are also generally low.[28] It should, however, be noted that a South African study demonstrated that sputum induction was a safe modality with excellent yield and preferable to gastric lavage to obtain specimens for the diagnosis of TB in children.[29] Children identified as high risk for active TB should have sputum samples sent for microscopy and culture and, in the event that they cannot produce sputum, induction or gastric aspirates should be performed.

Role of BCG immunization of immigrant children

Only three of 13 countries offered BCG vaccination as part of the immigration screening process. BCG vaccination reduces the risk of all forms of TB in infants by an average of about 50%, but does not prevent infection.[30] Another meta-analysis found 86% protection against TB meningitis and miliary disease among children.[31] In a study comparing TB screening programs in Europe, only four of 26 countries offered BCG as part of their screening program to uninfected individuals who had not previously received BCG immunization; of these, three restricted BCG to children or young adults.[32] More research is needed to determine the need for vaccinating young children from high-burden countries.

CONCLUSIONS

Most of the countries surveyed have well-developed imaging and laboratory approaches to pediatric TB screening; however, further research to improve screening should focus on the pediatric-specific TB history and physical examination, which could be more precise and based on validated clinical models. CXRs should be performed in adolescent children aged >10 years, as they more often present with adult-type disease compared to younger children. TST is an important tool for screening children for both latent and active disease. More research is needed to determine the need for vaccinating young children (<2 years) from high TB burden countries entering low-incidence countries. The use of IGRAs in the migrant pediatric population also requires further investigation.

Although pediatric TB may not be of immediate public health importance due to its paucibacillary nature, thus making it rarely infectious,[4] individual morbidity and mortality is such that targeted TB screening in high-risk children from high-incidence countries should form part of all immigration TB screening programs. Considerable variation exists, however, between pediatric immigration TB screening programs in low TB incidence countries, and the optimal manner in which to screen requires further research.

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RÉSUMÉ

CONTEXTE : Le dépistage de la tuberculose (TB) chez les enfants migrants (y compris les immigrants, les réfugiés, les demandeurs d'asile et les adoptés internationaux) constitue un défi permanent dans les pays à faible incidence de TB. Un grand nombre d'enfants provenant de pays à incidence élevée de TB sont atteints d'une infection tuberculeuse latente (LTBI), et certains d'entre eux souffrent d'une maladie tuberculeuse active au moment de l'immigration dans leurs nations hôtes. Chez les jeunes enfants atteints de LTBI, le risque de progression vers la maladie TB est élevé et il est plus élevé par comparaison avec les adultes en ce qui concerne le développement de formes graves disséminées de TB comportant une morbidité et une mortalité significatives. Dans beaucoup de pays, des programmes de dépistage de la TB lors de l'immigration ont été élaborés pour répondre aux besoins chez les adultes sans se focaliser beaucoup sur les enfants migrants.

OBJECTIF : Comparer les exigences de l'examen médical d'immigration pour la TB chez les enfants dans certains pays sélectionnés où les taux d'immigration sont élevés et les taux d'incidence de la TB faibles.

SCHÉMA : On a entrepris une étude descriptive des programmes de dépistage de la TB lors de l'immigration dans certains pays systématiquement sélectionnés.

RÉSULTATS : Au total, 16 des 18 pays éligibles ont répondu à l'enquête écrite et à l'interview téléphonique.

CONCLUSION : Il n'y a pas deux pays qui aient la même approche du dépistage de la TB parmi les enfants migrants. Des recherches complémentaires s'imposent pour déterminer la façon de mener le dépistage chez les enfants migrants d'une manière optimale basée sur les évidences.

RESUMEN

MARCO DE REFERENCIA: La detección sistemática de la tuberculosis (TB) en los niños inmigrantes, los refugiados y los que buscan asilo político constituye una dificultad permanente en los países con baja incidencia de TB. Muchos niños que provienen de países con altas tasas de TB albergan la infección tuberculosa latente (LTBI) y algunos padecen la forma activa de TB en el momento de su llegada como inmigrantes al país que los acoge. Los niños pequeños que son portadores de la LTBI presentan un alto riesgo de progresión hacia la TB activa y

su riesgo es mayor que en los adultos de padecer una forma de TB grave, con morbilidad y mortalidad considerables. En muchos países, los programas establecidos de detección sistemática de la TB en los inmigrantes se ajustan a la situación de los adultos, pero prestan poca atención a los niños.

OBJETIVO: Comparar los exámenes médicos exigidos en el estudio de la TB de los niños inmigrantes en determinados países donde se observa una alta tasa de inmigración y baja incidencia de TB.

MÉTODOS: Estudio descriptivo de los programas de detección de la TB en inmigrantes, en países escogidos sistemáticamente.

RESULTADOS: De los 18 países que cumplían con los criterios definidos, 16 respondieron al cuestionario escrito y las entrevistas telefónicas.

CONCLUSIÓN: No se encontraron dos países que aplicaran la misma estrategia de detección sistemática de la TB en los niños inmigrantes. Se precisa más investigación acerca la mejor estrategia, basada en pruebas científicas, para el estudio de los niños de las poblaciones migratorias.