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Childhood tuberculosis in the United States: shifting the focus to prevention

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SUMMARY

In the last century, the United States has transitioned from a high to a low tuberculosis (TB) incidence country. A major factor in this decline has been the emphasis on identification and treatment of patients with tuberculous infection. While identification, testing, and preventive therapy pose challenges, recent developments in childhood TB offer more options for effective strategies that are acceptable to both children and their families. These include screening and testing in non-traditional settings, use of more specific assays (interferon-gamma release assays) for testing, and implementation of shorter-course preventive regimens.

KEY WORDS: directly observed preventive therapy; isoniazid/rifapentine; tuberculous infection

THE INCIDENCE OF TUBERCULOSIS (TB) in the United States has declined from 90 to 3 per 100 000 population in the last 60 years, with 5–6% of cases occurring in children.[1] The decline was spurred largely by active surveillance, which enabled earlier identification of TB-infected persons, widespread testing for tuberculous infection, and initiation of preventive therapy. As almost two thirds of cases occur in foreign-born adults,[1] strategies to reduce incidence further must address TB prior to arrival in the United States and emphasize TB prevention. The latter is particularly true for young children aged <5 years, for whom the risk of rapid progression to disease is higher than for adults.

ASPECT OF INTEREST

Therapy for tuberculous infection is effective and well tolerated in children. That it 'works' is not in doubt, rather considerations center on screening, testing, and treatment. It is unclear how to best operationalize a strategy that relies on the administration of 1) very long antibiotic courses to 2) asymptomatic children whose care givers may not understand the benefit of therapy or may doubt the diagnosis (especially in bacille Calmette Guérin-immunized children diagnosed with the tuberculin skin test [TST]), and who may not have 3) an established medical provider to conduct screening. Even in low-incidence, high-income countries, these challenges are difficult to surmount, and a recent study found that up to three quarters of childhood TB cases in the United States were potentially preventable.[2] The last decade has seen changes in strategies to combat each of these obstacles: respectively shorter-course preventive regimens, interferon gamma release assays (IGRAs), and screening in non-traditional settings (Table 1).

DISCUSSION

Screening

As TB rates declined, the United States moved from using universal TST among children for tuberculous infection to targeted testing by screening for risk factors and only testing at-risk children in 2000.[4] The attempt to reduce false-positive TSTs and identify persons who would most benefit from preventive therapy was well-intentioned, but had the unintended consequence that children simply went unscreened. Although this situation was most acute among children who lacked access to care, a recent study indicated that even among children with established primary care providers, screening questions were not always asked or, if positive, were not followed by TST placement and/or interpretation.[5] Screening immigrant children adds another level of complexity. Since 2009, children aged 2–14 years emigrating from high-burden countries have required a TST or IGRA prior to arrival in the United States.[6] Before this, children were unscreened for either tuberculous infection or TB disease. The new policy provides an opportunity to identify cases of disease and initiate therapy prior to arrival. However, gaps remain in the initiation of therapy for tuberculous infection after arrival in the

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Table 1 Obstacles and opportunities in identification, diagnosis, and treatment of tuberculous infection

Category	Obstacle	Opportunity
Identification	Screening for risk factors assumes children have a primary care provider	Screen for risk factors in non-traditional settings (e.g., schools, health fairs)
	Immigrant children aged <15 years previously not tested for tuberculous infection or TB disease prior to arrival	US immigration guidelines changed in 2009, now testing children aged 2–14 years using TST or IGRA
	Validated risk factor questionnaire does not include parental foreign birth	While this is a risk factor for disease, the role of parental foreign birth in increasing the risk of infection in children is less clear
Diagnosis	Concern about false-positive TST results in BCG recipients	IGRAs are more specific than the TST
	Children fail to return in 48–72 h for TST interpretation	IGRAs require only one face-to-face encounter for diagnosis
	Relative lack of knowledge about IGRA performance in children aged <2 years as compared with older children	TST continues to be recommended for this age group; more information is needed, as this is the population in which a positive TST may reflect cross-reaction with the BCG vaccine. More recent data suggest that indeterminate results are infrequent in young children.[3]
	Inability to detect reinfection	Reinfection occurs more often in high-burden settings, but can also occur after travel to endemic regions. Prior treatment for infection may not prevent reinfection. Some experts currently treat young children (<5 years) who have been treated for tuberculous infection and are re-exposed with another course of preventive therapy, but this is based on expert opinion, not controlled trials
Treatment	Parental reluctance to give medication	Parental education on benefits and risks of therapy; infection therapy cannot be mandated by public health officials
	Community providers underemphasizing the importance of treatment, especially for window prophylaxis for exposed children	Education of providers by public health providers and maintaining open lines of communication
	Poor adherence	DOT,* ESAT, shorter-course regimens
	Accessibility of medications	DOT,* ESAT
	Family's ability to navigate the health care system	DOT,* ESAT
	Lack of child-friendly formulations	Several organizations, including the TB Alliance, are focusing on development of dispersible and other child-friendly formulations of first- and second-line medications
Policy	Need for cost-benefit analyses comparing different preventive regimens	Can focus on feasibility, cost, and safety of different regimens in the United States in addition to how to extend these programs to countries that send the most immigrants to the United States

* Requires the presence of an adult (parent/guardian or care giver approved by the parent/guardian) before medication can be administered by the health department.
TB = tuberculosis; TST = tuberculin skin test; IGRA = interferon gamma release assay; BCG = bacille Calmette-Guérin; DOT = directly-observed therapy; ESAT = enhanced self-administered therapy.

United States, and delays in the initiation of preventive therapy may reduce adherence. Screening for risk factors and testing for infection in non-traditional settings (schools, mobile clinics) has been shown to be feasible and successful in identifying groups that otherwise would not have received preventive therapy for tuberculous infection.[7]

Testing: interferon gamma release assays

There are few data on the acceptability of preventive therapy by families depending on how infection was diagnosed in their children. However, by reducing false positivity and using a test that is more associated with risk of progression to disease than the TST, IGRAs can delineate a cohort of children who would most benefit from preventive therapy. This may not seem important in a low-incidence, resource-rich country, where preventive therapy is theoretically available to all who need it. However, preventive therapy for tuberculous infection is not free in all states, and even when available, poor adherence reduces effectiveness. IGRAs could potentially be used to stratify resources to optimize medication delivery to the children who would derive the most benefit from preventive therapy. While IGRAs were initially recommended for school-aged children due to high rates of indeterminate results in younger children, more recent data support the use of IGRAs in younger children, as IGRAs correlate more with TB contact than TSTs,[3,8] and indeterminate results were found in <1% of children.[3]

Treatment: short-course regimens and direct observation strategies

Preventive therapy for tuberculous infection is recommended for all children with infection in the United States, unless there are specific contraindications for therapy. The rationale is that although few children with tuberculous infection will progress to disease, therapy is well tolerated, and until recently, identifying which children with a positive test of infection would progress to disease was impossible. More widespread use of IGRAs should reduce the number of children receiving preventive therapy without benefit. Adherence to the primary US-recommended preventive therapy regimen (9 months

Table 2 Management of children with TB exposure and infection*

Regimen	Dose (maximum dose)	Duration	Indications for use
Exposure†			
INH, daily	10–15 mg/kg (300 mg)	Until second TST or IGRA is placed: if negative, child can stop medication; if positive, the child should continue medication to complete a full course of therapy for tuberculous infection‡	Daily dosing often used in young infants to minimize volume and prevent emesis
INH, biweekly	20–30 mg/kg (900 mg)		Intermittent therapy should only be administered under directly observed therapy
RMP, daily	10–20 mg/kg (600 mg)		INH monoresistance in source case; INH intolerance
Infection§			
INH, daily	10–15 mg/kg (300 mg)	6–9 months¶	Standard first-line therapy for infection; effectiveness is limited by the low (∼50%) rate of adherence to the regimen
INH, biweekly	20–30 mg/kg (900 mg)	6–9 months¶	Intermittent therapy should only be administered under directly observed therapy; consider use in high-risk contacts (e.g., children identified via contact investigations) to optimize adherence
RMP, daily	10–20 mg/kg (600 mg)	4 months	INH monoresistance in source case; INH intolerance; desire for shorter-course regimen
INH+RMP, daily	INH: 10–15 mg/kg (300 mg) RMP: 10–15 mg/kg (600 mg)	3–4 months	Desire for shorter-course regimen that can be administered by families
INH+RPT, weekly#	INH: 15 mg/kg (900 mg) RPT: 10–14 kg: 300 mg 14.1–25 kg: 450 mg 25.1–32 kg: 600 mg 32.1–50 kg: 750 mg >50 kg: 900 mg (900 mg)	12 weekly doses	Availability of directly observed preventive therapy; desire for shorter-course therapy

* Does not include children exposed to or infected with MDR-TB, where management is controversial. In the United States, children exposed to MDR-TB are usually followed with serial physical examination, infection tests, and chest radiographs without initiation of preventive therapy. Children with MDR-TB infection are treated after source case susceptibilities are available. Optimal treatment is unclear. Some experts use fluoroquinolone monotherapy, as combination therapy for MDR-TB infection is poorly tolerated and default due to adverse effects is common in several series. Inadequate data currently exist to recommend one regimen over another for this cohort of children.

† Children with human immunodeficiency virus infection, malnutrition, or other causes of immunocompromise should also be treated for TB exposure. The optimal strategy for these children is unclear. One strategy that is used in resource-rich settings prior to a patient receiving immunosuppressive therapy is to obtain both a TST and an IGRA and to treat for infection if either test were to be positive. Another approach for an immunosuppressed child with close contact to a source case would be to offer that child a full course of preventive therapy for tuberculous infection.

‡ Optimal timing of the second TST in young infants is unclear; many experts recommend continuation of INH until the infant is at least 6 months of age and repeating the TST at that time.

§ Preventive therapy does not offer protection against future reinfection. While this is less of a concern in low-burden settings such as the United States, it may occur in persons with prolonged stays in TB-endemic regions.

¶ The World Health Organization recommends 6 months of INH, whereas the US Centers for Disease Control and Prevention recommends 9 months of INH.

Use in children would be increased if dissolvable INH+RPT combinations were to become available.

TB = tuberculosis; INH = isoniazid; TST = tuberculin skin test; IGRA = interferon gamma release assay; RMP = rifampicin; RPT = rifapentine; MDR-TB = multidrug-resistant TB.

of isoniazid [H, INH]) is approximately 50%.[8] Children who default often do so in the first 1–2 months of therapy, and default is rarely associated with adverse events. Rather, default often stems from parents' unwillingness to give long antibiotic courses to asymptomatic children, despite education on the risks of progression to disease. In one study, the only factor positively associated with completion of preventive therapy was provision of medication (enhanced self-administered therapy, where medications are supplied monthly with periodic reminder calls) or administration of medication by the health department (directly observed therapy, [DOT]), where completion rates were >90%.[9]

However, health department-administered therapy is costly and is not universally available. To that end, the use of shorter-course therapies (Table 2) or technology-assisted DOT may be more sustainable. The recent publication of a randomized trial of 3 months of isoniazid/rifapentine (3HP) compared to 9 months of INH (9H) in children aged 2–17 years showed that 3HP was as effective as and had higher completion rates than 9H (88% vs. 81%), with neither arm being hepatotoxic.[10] Severe INH-associated adverse events were seen in 0.2%.[10] Use of webcams or cellular phone videos to monitor the administration of medication remotely,[11] devices to register the opening of pill bottles, sensors to detect urinary concentrations of TB medication metabolites, or the use of ingestible sensors to confirm adherence[12] potentially expand the number of patients and locations for preventive DOT to be used.

Finally, the use of prophylaxis in children aged <5 years with normal physical test and radiograph results and initial negative tests for infection who have been exposed to a person with pulmonary TB

has been widely implemented. These children receive medication until 8–10 weeks after contact with the source case has been broken physically or microbiologically. This strategy, used among children at greatest risk of progression to disease during the period of potential TST conversion, is very well tolerated by children and acceptable to families.

CONCLUSION

For a low-incidence country, the most powerful way to see a continued decline in cases is to focus on prevention across the continuum—from screening prior to immigration to offering therapy to infected immigrants after arrival to identifying, testing, and treating at-risk children who have not left the United States. The last decade has seen innovations in testing and treatment that make this goal more realistic. The challenge is now how to sustain these gains against competing public health priorities.

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RESUME

Au cours du siècle dernier, les Etats-Unis ont opéré une transition d'une nation à taux élevé d'incidence de tuberculose (TB) vers une nation à taux bas. Un facteur majeur de ce déclin a été l'accent mis sur l'identification et le traitement des patients ayant une infection tuberculeuse. Si l'identification, les tests et le traitement préventif posent quelques défis, les développements récents en matière de TB de l'enfant offrent davantage d'options pour des stratégies efficaces qui sont acceptables à la fois par les enfants et par leurs familles. Ce sont le dépistage et les tests dans des lieux non traditionnels ; l'utilisation de tests plus spécifiques (test de libération de l'interféron gamma) ; et la mise en œuvre de protocoles de prévention plus courts.

RESUMEN

En el siglo pasado, los Estados Unidos pasaron de ser un país con alta incidencia de tuberculosis (TB) a un país con baja incidencia de la enfermedad. Un factor decisivo de esta evolución fue el hincapié en la detección y el tratamiento de los pacientes con infección tuberculosa latente. Aunque el reconocimiento de la infección, las pruebas diagnósticas y el tratamiento preventivo plantean dificultades, los progresos recientes en materia de TB de los niños ofrecen nuevas estrategias eficaces adecuadas para los niños y sus familias. Entre las estrategias se encuentran la detección sistemática y las pruebas practicadas en entornos no convencionales; el uso de ensayos más específicos (las pruebas de liberación de interferón gama); y la introducción de regímenes terapéuticos más cortos.