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Recent Innovations in Diagnosis and Treatment of Pediatric Tuberculosis

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Abstract

Purpose of Review Tuberculosis is leading cause of global morbidity and mortality and a significant proportion of the burden of disease occurs in children. In the past 5 years, a number of innovations have improved the diagnosis and treatment for children with both latent tuberculosis infection and active disease.

Recent Findings This review discusses three key areas of innovation. First, we assess utilization and performance of interferon-gamma release assays (IGRAs) in different clinical and epidemiologic scenarios. Recent literature has demonstrated good performance of IGRAs for diagnosis of latent tuberculosis infection, particularly in low-incidence settings such as TB control programs in North America. For high-incidence populations, or when testing is done for possible active TB disease, IGRA performance has some important limitations, but IGRA sensitivity when measured against culture proven disease may be better than earlier studies suggested. The second area of innovation is in increased uptake of nucleic acid amplification (NAA) tests and broader application in non-sputum samples for both pediatric pulmonary and extrapulmonary tuberculosis. Finally, recent studies have provided solid evidence in support of shorter treatment courses for pediatric latent tuberculosis infection, such as 12 weeks of weekly isoniazid and rifapentine or 4 months daily rifampin, that improve compliance and may reduce resources required for TB control.

Summary Many recent innovations in pediatric tuberculosis relate to an improved understanding of how to optimally use existing tests and treatments. Until diagnostic tests and interventions such as vaccination are developed that can dramatically alter the paradigm of pediatric TB management and control, it is important for stakeholders to have a nuanced understanding of tools currently available.

Keywords Tuberculosis · Latent tuberculosis infection · Pediatrics · Interferon-gamma release assay · Nucleic acid amplification test

Introduction

Approximately one quarter of the world's population is infected with *Mycobacterium tuberculosis* (Mtb) and it is the leading global cause of death [1, 2]. Among children, tuberculosis (TB) is responsible for more than 200,000 deaths per year globally [2]. The burden of disease begins early in childhood, and infants and toddlers are at high risk of progressing from infection to severe disease [3]. Even among children who do not develop active disease immediately after infection, there is a significant lifetime chance of reactivation, (often stated to be 10%, but potentially higher and dependent on age and timing of initial infection) the majority of which will occur in the first 5 years after infection [4, 5]. Furthermore, cases of untreated latent tuberculosis infection (LTBI) in children represents the reservoir from which future generations of active and contagious cases will emerge, and thus pose a significant long-term obstacle to global aspirations of TB elimination.

There are many challenges in diagnosis and treatment of tuberculosis that are unique to children. Clinically, active tuberculosis disease in children occurs more frequently in disseminated or extrapulmonary forms than in adults, and initial presentation may have only subtle manifestations such as fever or failure to thrive [6]. Challenges in clinical identification

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of TB are compounded by a diagnostic armamentarium with significant limitations. For instance, abnormalities on chest radiographs are often subtle or present only in intrathoracic lymph nodes obscured by thymus or other hilar structures [7]. Tests for immunologic evidence of tuberculosis infection (tuberculin skin test (TST), interferon-gamma release assays (IGRAs)) have limitations in both sensitivity and specificity for active disease and LTBI. Accurate interpretation of these tests is further compounded in early infancy by uncertainties of immune maturation or immune dysfunction in the setting of malnutrition [8]. Sputum testing also has significantly less utility in children: pulmonary disease is typically paucibacillary and young children lack adequate coordination or cooperation to produce sputum samples, which are commonly AFB smear-negative and frequently also culture-negative [9].

Special challenges in pediatrics extend to many aspects of treatment for both LTBI and active tuberculosis. Antituberculous medications require pharmacologic characterization at multiple ages, and in many cases, pediatric pharmacokinetic/pharmacodynamic studies for both common and less common drugs have lagged significantly behind adult studies [10]. Young children often require compounding to make liquid formulations, which may alter efficacy or stability [11]. Assuring compliance with long courses of TB or LTBI treatment also presents challenges unique to children such as adamant refusal to accept dosing in a toddler, or social pressure or rebelliousness in a teenager.

Despite these challenges, a focus on pediatric TB presents significant opportunities for TB controllers. Encounters with health care in childhood are regular and universal in most of the world's populations through primary care or immunization programs, thus presenting an opportunity for TB screening. A child with TB infection is often an indicator of an infectious adult case in the household and thus screening in pediatric care can lead to "reverse" contact investigation. Prevention and treatment of pediatric TB infection will reduce the future global TB burden. And finally, development of a pediatric TB vaccine capable of long-term protection will likely be a key step in global TB elimination.

In recent years, there have been significant developments in diagnosis and management of pediatric TB. This review will focus on three key areas of improvement: improved understanding and implementation of IGRA-based diagnosis (especially in young children); broader implementation of nucleic amplification assay diagnostics; and shorter, better tolerated, and effective treatment courses for latent tuberculosis.

Utility of IGRAs in Young Children

Microbiologic confirmation of tuberculosis is particularly challenging in pediatrics. In cases of active disease, a significant number will be extrapulmonary, and pulmonary cases are paucibacillary. Due to difficulty obtaining sputum and induced sputum samples in young children (though it can be done, even in infants [12]), diagnostic testing is often performed on gastric aspirate samples, which have low sensitivity for AFB smear and mycobacterial culture, and are difficult and burdensome to obtain [13, 14]. Moreover, in LTBI, there is no microbiologic test. Thus, TB diagnosis often relies in part (for active TB) or all (for LTBI) on assessments of immunologic evidence of infection, using either the TST or IGRA.

The TST measures a delayed-type hypersensitivity reaction to a diverse set of mycobacterial antigens following intradermal injection. Despite long experience (Mantoux first described intradermal injection of tuberculin in 1908 [15]), ubiquitous use and relative affordability of TST, there are a number of significant disadvantages of the test. These include technical skill required for placement, measurement of induration, and interpretation (which varies according to the clinical context). However, foremost among disadvantages of TST are the simultaneous lack of both sensitivity and specificity. In pediatrics, false negative results are associated with disseminated disease (when reliable testing is most important), malnutrition, immune compromise including HIV infection and incorrect test placement, among others. False positive results occur primarily as a result of cross-reactivity with antigens in BCG, and to a lesser extent, other non-tuberculous mycobacteria [16].

These disadvantages have led to increasing utilization of IGRAs for diagnosis of TB and LTBI in both adults and children. The two currently available IGRAs (Quantiferon (QFT; multiple generations: QFT-TB, QFT-Gold, QFT-Gold In-Tube, QFT-Plus; Qiagen, Hilden, Germany) and T-SPOT.TB, Oxford Immunotec, Oxford, UK) measure in vitro release of gamma-interferon from sensitized lymphocytes in response to selected antigens that are more specific for *M. tuberculosis* than antigens in TSTs. There is a growing body of literature on the performance of IGRAs in diagnosis of pediatric TB and LTBI. However, when considering this literature, the utility of IGRAs must be evaluated in specific clinical contexts—particularly whether IGRAs are used for diagnosis of active TB or latent tuberculosis, and whether testing is occurring in BCG-vaccinated or BCG-unvaccinated children. It is also important for stakeholders to understand the fundamental differences between test performance as measured by sensitivity or specificity and performance measured by positive or negative predictive values. The latter are influenced by the underlying rates of TB or LTBI in the testing population.

Among clinical scenarios, IGRA's may be most clearly advantageous in the context of LTBI evaluation of children in low-incidence settings, particularly when the patient population includes BCG-vaccinated individuals. This scenario is common in high-income countries where pediatric patients are

screened following immigration from higher-incidence countries, or following extended travel to those countries. In these settings, the specificity of IGRA over TST allows for fewer courses of LTBI treatment, and the increased IGRA cost and laboratory logistics are less relevant programmatic barriers. Grinsdale et al. reported screening more than 1000 children evaluated through the San Francisco Department of Public Health using QFT-TB Gold [17]. Among 179 foreign-born, BCG-vaccinated patients in this population who had both IGRA and TST testing, QFT negative/TST positive discordance occurred in 79% (142/179). When stratified by age, the rate of discordance < 5 years was 93% compared to 73% in older children. The authors were unable to present a precise calculation of sensitivity due to the lack of a gold standard test for LTBI diagnosis, but present indirect evidence of IGRA sensitivity based on an exposure gradient: children at higher risk of infection had higher rates of positive IGRA (contacts, 11%; foreign-born non-contacts, 7%; US-born non-contacts, 3%). More importantly, they report a negative predictive value of 100% for IGRA testing, based on the observation that no active TB cases occurred over a median observation time among QFT negative patients of 5.7 years (modified by treatment of two young, high-risk patients despite negative IGRA testing as discussed below).

We described IGRA testing performed on 3745 pediatric patients screened between 2011 and 2014 for LTBI at Denver Health, Denver, USA, an urban safety-net primary care network with a high proportion of children with travel or family origin in TB endemic countries, particularly in Latin America [18]. In this population, the rate of LTBI diagnosed using QFT-TB Gold was 2.1% compared to rates of 6–12% observed in two prior local surveys using TST [19, 20]. Treatment was offered to all IGRA-positive children, and no cases of incident TB among screened patients have been identified as of October, 2018 (unpublished data). Adequate sensitivity in our population was also demonstrated via exposure gradients, with increasing IGRA positivity with age, and in comparison with children screened in our affiliated refugee clinic (7.9% QFT+) and referral tuberculosis clinic (21% QFT+).

An important observation in these two studies and others is that IGRA tests appear to perform well among younger children in the context of LTBI screening. In San Francisco, 56 children < 2 and 236 age 2–5 underwent QFT testing, and in our series we report 1497 children in primary care, 364 in the Refugee Clinic, and 140 in the TB clinic between the ages of 2 and 5. Appraisal of test performance in this age range—particularly sensitivity—is challenging given the lack of gold standard for LTBI. But the more important question may be whether the use of IGRA's in young children works to meet stated programmatic goals: prevention of active TB cases while maximizing efficiency through elimination of unnecessary LTBI treatment courses. In this context, the lack of incident cases among QFT-negative young children suggests that the programmatic goals were met. Such an approach is now reflected in the most recent guidance on LTBI diagnosis from the American Academy of Pediatrics, in which IGRA is preferred for children > 2 who are BCG-vaccinated children or unlikely to return for TST reading, and equally acceptable for others [21]. Furthermore, there is preliminary data, including our own experience in Denver, that IGRAs perform adequately for LTBI screening in children under 2 in low-incidence settings, and future study to continue to define minimum age for testing will be important [22].

In low-income, high-incidence countries, limited resources for testing (TST or IGRA) factor more prominently in to approaches for diagnosis of LTBI, and in these settings the higher incidence of disease also diminishes IGRA and TST negative predictive values. Accordingly, 2018 World Health Organization guidelines for diagnosis of LTBI recommend that neither TST or IGRA is required to initiate preventative treatment for LTBI in high risk groups (HIV+ and household contacts under 5 years) [23]. When testing is part of LTBI evaluation, there is no preference in the guideline for TST or IGRA; test choice should be made on the basis of available resources and programmatic capacity, and after careful consideration of the differing logistical challenges presented by each type of test.

In clinical scenarios where active TB is being considered a different set of priorities informs appraisal of IGRA performance in children, particularly in high-incidence settings. Sensitivity (i.e., not missing a case) takes higher priority over specificity (i.e., avoiding unnecessary treatments) because of the potential for significant morbidity from active TB. In this context, confidence in IGRA results has been hampered by heterogeneity in reported test sensitivity in children with active tuberculosis, with lower values often reported in LMICs and in younger children. For example, in a 2011 meta-analysis, Sun et al. report a pooled sensitivity of 70% for QFT and 62% for T-SPOT.TB for active TB cases [24]. Similar though slightly higher numbers were observed in two additional meta-analyses in 2011 and 2012 [25, 26]. However, studies included in these meta-analyses utilized varied methodologies, patient populations, and frequently combined culture-confirmed and suspected case definitions. IGRA sensitivity in these analyses was significantly better when assessed among children with culture-proven disease. One 2011 meta-analysis appears to have erroneously included a study that assessed IGRA sensitivity for active TB based on clinical case definitions in the sub-analysis of culture-proven disease, falsely lowering the calculated sensitivity [27]. A more recent meta-analysis by Laurenti et al., including only culture-proven disease in immunocompetent children, demonstrated more robust IGRA sensitivity for active disease (QFT 89.6%; T SPOT 88.5%) and no difference from TST (88.2%); 10 of 15 included studies took place in low TB-burden countries [28••].

These observations are further supported by a 2018 report of IGRA sensitivity of 93% among culture-confirmed active TB cases in California [29•]. TST sensitivity in this population was statistically equivalent, and both tests had slightly lower sensitivity among children < 2 years (80% QFT; 87% TST; $p > 0.99$; $n = 15$ in each group). In this population, a slight increase in sensitivity using combined TST and IGRA was achieved when compared to TST alone, but not to IGRA alone.

Thus, in the diagnosis of active TB—particularly in the very young where sensitivity is a priority—IGRAs can be broadly characterized as having sensitivity equal to or better than TST in most scenarios, in addition to better specificity. Nevertheless, clinicians need to remain aware that both tests are imperfect, and should not be relied upon exclusively to rule out TB disease, particularly when there is a strong clinical suspicion, highly suggestive epidemiologic/contact history, and/or when consequences (e.g., in infancy) of missing cases are high. However, the well-documented limitations of IGRAs should not be interpreted as suggesting that TST performs better; when TST is preferred, it is more appropriate to do so on the basis of cost and logistical factors that will depend on local circumstances. Additionally, cost analyses must incorporate a full accounting of resources that arise from test selection. Increased lab cost of IGRAs over TST may be offset by the need for fewer visits (both for TB programs and families/patients), cold chain requirements for TST, and unnecessary treatment courses for false-positive TST results.

Two additional potential barriers to broader IGRA uptake warrant mention, particularly in reference to young children: rates of indeterminate results using QFT and challenges with phlebotomy in young children. Initial reports suggested indeterminate rates as high as 35% in some pediatric populations, but more recent data suggests that with appropriate laboratory training and specimen handling, much lower rates can be achieved, even among young children [17, 30, 31]. For example, in our population in primary care at Denver Health, the overall rate of indeterminate QFT was 0.5%, and in children age 2–5 it was only marginally higher at 1.3% [18]. Similarly, low results (3%) were reported in the California Public Health study reported by Kay et al. described above [29•]. Similarly, phlebotomy is a technical skill that is not insurmountable (we performed over 1500 successful QFT's in children < 5 at Denver Health), but ongoing study will need to assess the significance of this as a barrier in lower resource settings, among infants and toddlers, and in the setting of evolving generations of IGRA that may increase the required amount of blood.

Advances in Molecular Diagnostics

Confirming the diagnosis of active TB in children is of paramount importance and yet traditional methods of confirmation—acid fast staining and mycobacterial culture—have very low yields, particularly among infants and young children in whom disease can be most aggressive. The need for confirmatory tests with higher sensitivity and more rapid results than culture have led to significant enthusiasm for nucleic acid amplification (NAA) tests. There is an increasingly robust body of literature demonstrating the utility of NAA-based diagnostics in both adults and children, particularly since the introduction of a rapid cartridge-based NAA Xpert MTB/RIF in 2010, which is designed to identify *M. tuberculosis* and rifampin resistance (a proxy for multidrug resistance) [32, 33]. A WHO Expert Group conducted a systematic review and policy update in 2013 of Xpert MTB/RIF in pulmonary, extrapulmonary and pediatric TB [34•]. The authors characterized the broadening spectrum of advantages from incorporation of Xpert MTB/RIF to diagnostic approaches including replacing or reducing number of smear microscopy tests; increasing sensitivity in smear-negative patients (including those with HIV); and rapid detection of rifampin resistance. On the basis of multiple pediatric studies, the report also formally endorsed utilization of Xpert MTB/RIF in for both pulmonary and extrapulmonary TB in children.

For pediatric pulmonary TB, the 2013 WHO review reported sensitivity of 55–90% for expectorated sputum, 40–100% for induced sputum, and 40–100% for gastric aspirate samples. For culture-proven disease, the Xpert MTB-RIF had a pooled sensitivity of 66% from both sputum and gastric samples in children, compared with a pooled sensitivity of 22–29% for smear microscopy. Furthermore, pooled sensitivity of Xpert MTB/RIF for identifying smear-positive children was 95–96% (depending on sample source) and 55–62% for smear-negative children. On the basis of these results, the expert group recommended that Xpert MTB/RIF be the preferred test for initial diagnosis of pediatric TB, including a strong recommendation for children with HIV or those suspected of having MDR TB, and that it should be considered as a replacement for smear microscopy. More recent studies in children have compared sensitivity of Xpert MTB/RIF directly with culture from non-sputum samples that have traditionally low culture-positive rates. From gastric aspirates, GeneXpert significantly outperformed traditional culture methodology (sensitivity 48% and 12%, respectively) and in a small study using bronchoalveolar lavage samples, Xpert MTB/RIF identified an extra 14% (2 additional cases) that were culture negative [35, 36]. However, contrary to those results, Bunyasi et al. report low sensitivity of Xpert MTB/RIF compared to culture from both induced sputa and gastric aspirates among young children < 4 years [37].

Nucleic acid amplification assays, and the Xpert MTB/RIF in particular, also offer potential advantages in the diagnosis of extrapulmonary TB, including lymph node biopsy and cerebral spinal fluid (CSF) [38]. Though the pooled sensitivity for

identifying culture proven TB meningitis in adults and children combined was relatively high in the WHO analysis (80%), culture itself has low sensitivity in children, and there is insufficient data to robustly assess NAA performance in children alone [34•]. For example, among 34 Indian children with clinically suspected TB meningitis, Xpert MTB/RIF outperformed traditional culture techniques in detecting *M. tuberculosis* in CSF [39]. The relatively low sensitivity (38% Xpert MTB/RIF; 14% culture) for both methods emphasizes a key point of NAA testing for extrapulmonary disease in children, or when non-sputum samples are utilized: negative testing should not be relied upon to rule out disease, particularly in children with suspicion of severe disease such as meningitis.

Future development of PCR-based diagnostics beyond Xpert MTB/RIF, such as multiplex PCR-assays, may hold the promise of additional sensitivity, particularly in tissues and body fluids with very low yield in both culture and Xpert MTB/RIF. As an example, a recent study comparing Xpert MTB/RIF to multiplex PCR in testing pleural fluid yielded sensitivities of 33% and 89% respectively [40]. There is also increasing interest in the use of NAAs, including Xpert MTB/RIF on stool samples [41]. Studies to date in pediatric populations are few and have low numbers of participants. The limited data that do exist suggest relatively low sensitivity, particularly when applied to smear- or culture-negative patients or those with milder disease. However, if future assays can improve sensitivity, stool may become an increasingly convenient initial sample to test, as a positive result may preclude further or more invasive sampling [42–45].

Additional Treatment Options for Latent Tuberculosis Infection

Until recently, the preferred treatment in USA, European and WHO guidelines for LTBI in children was 6–9 months of daily isoniazid. The long duration is a barrier to successful preventative treatment for LTBI, and is a significant driver of extremely low rates of LTBI treatment initiation (estimated in 2016 to be as low as 7% globally) [46]. Multiple large clinical trials in adults have demonstrated at least equivalent efficacy and improved tolerance and compliance with a shorter 2-drug regime of once weekly isoniazid (INH) and rifapentine (RPT) (3HP), and recent data has extended these options to pediatric populations [47–49]. In 2015, Villarino et al. reported analysis of 1058 children age 2–17 years enrolled in the PREVENT TB trial conducted in 29 sites in North and South America, Asia and Europe [50••]. Subjects had high risk of TB disease based on exposure and TST testing and were treated with 3HP or 9 months of INH, administered under directly observed therapy. Treatment completion rates were higher in the 3HP group (88.1 vs. 80.9; $p = 0.003$). Adverse events leading to treatment discontinuation were more common in INH/RPT patients, but rare overall (1.7%). In the modified ITT analysis, 0/471 subjects in the 3HP group and 3/434 in the INH group developed clinical tuberculosis disease, which met the stated definition of non-inferiority. Given the putative correlation between completion rates and efficacy, reassuring safety profile in adults and children and efficacy comparable to longer courses, this shorter course is attractive to stakeholders—as evidenced by recent recommendations in CDC, AAP, and WHO guidelines for children > 2 [21, 23, 51]. There remain, however, important questions regarding use of 3HP in children, including assessment of tolerance and compliance in a less controlled non-clinical trial setting. Related to this question is whether DOT is required for this regimen to assure compliance and monitor for adverse reactions. In a multi-center, international trial in adults, compliance with self-administered therapy (SAT) was demonstrated to be non-inferior to DOT in the USA, but not overall or in sites in Spain, South Africa, or Hong Kong [52]. It is unclear if the findings in the USA can be extrapolated to children. In addition to these questions, there is a need to assess 3HP in children under 2, and develop water dispersible or dissolvable formulations that are tolerable and effective in small children [53].

An alternate short course for pediatric LTBI involves 4 months of daily rifampin, which has been the preferred regimen at the Denver Metro Tuberculosis Clinic since 2012 and is now included as an acceptable first-line treatment in current AAP guidelines [21]. Efficacy of this regimen is largely based on trials among high-risk adult populations and animal models, but appears comparable to 9 months of INH as described in a 2013 Cochrane review [54, 55]. Multiple studies in adults have demonstrated tolerance of this regimen and improved rates of completion compared to longer INH-based regimens, but until recently, little data on pediatric compliance and tolerance was available [56–58]. We recently reported observations from our pediatric population in Denver: compared to historical treatment with 9 months INH, 4R was well tolerated and significantly more likely to be completed (330/395; 83.5% vs. 536/779; 68.8%, $P < 0.001$) [59]. Though not a primary outcome of this study, no incident cases were noted in passive surveillance among 395 children with a median follow-up time of 4 years and 6 months. As 3HP is the shortest course and has only 12 doses, it will increasingly be the preferred regimen for pediatric LTBI, but 4R is likely to remain a common alternative in the setting of 3HP intolerance, INH resistance, very young children, and when rifapentine is unavailable—as is the case in many low-income countries at present.

Conclusions and Next Steps

Significant improvements and innovations in testing and treatment of childhood tuberculosis have been achieved over the past decade. However, as detailed in this review, the current armamentarium against pediatric TB is imperfect and many recent innovations involve only improved understanding and utilization of tools that are already available in clinical practice. In this context, it behooves practitioners to fully understand the nuances of the anti-TB toolkit, and to utilize those tools optimally, despite inherent limitations. With this approach, significant improvement in pediatric TB treatment and control can be achieved. However, achieving an ultimate goal of TB elimination will likely require the next generation of innovations to more dramatically shift the current paradigm, for example: identification of more accurate diagnostic tests for LTBI and active TB, or development of a tuberculosis vaccine. Thus, it is also essential that stakeholders remain committed to ongoing research directed at key aspects of pediatric tuberculosis.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

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