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REVIEW

The management of infection with *Mycobacterium tuberculosis* in young children post-2015: an opportunity to close the policy-practice gap.

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Keywords: tuberculosis; preventive therapy; child; contact screening; LTBI

Abstract

Introduction: The treatment of infection with *Mycobacterium tuberculosis* in young children is supported by universal policy based on strong rationale and evidence of effectiveness, but has rarely been implemented in tuberculosis endemic countries.

Areas covered: This review highlights a number of important recent developments that provide an unprecedented opportunity to close the policy-practice gap, as well as ongoing needs to facilitate implementation under programmatic conditions and scale-up.

Expert commentary: The WHO's End TB Strategy and Stop TB Partnership's Plan to End TB provide ambitious targets for prevention at a time when National Tuberculosis Programs in tuberculosis endemic countries are increasing attention to the challenges of management and prevention of tuberculosis disease in children. This opportunity is greatly enhanced by recent evidence of the effectiveness of shorter, simpler and safer regimens to treat tuberculosis infection. The scale of the challenge for implementation will require a decentralized, integrated, community-based approach. An accurate and low-cost point-of-care test for tuberculous infection would be a major advance to support such implementation. Specific guidance for the treatment of infection in young child contacts of multidrug-resistant tuberculosis cases is a major current need while awaiting further evidence.

1. Introduction

The most recent estimates by the World Health Organization (WHO) are that in 2014 there were one million children (<15 years) with tuberculosis disease, representing 10.7% of the global caseload, and that there were 136,000 deaths in children due to tuberculosis [1]. The uncertainty of the estimates are widely acknowledged and mainly due to a combination of diagnostic challenges, especially in young children, and under-reporting of child tuberculosis cases to National Tuberculosis control Programs (NTPs) and therefore to the WHO [1-3]. Nonetheless, as child mortality due to other common childhood infections has fallen in recent decades, tuberculosis is increasingly important in relative terms as a treatable and preventable cause of morbidity and mortality in infants and young children (<5 years of age) [4]. The potential of therapy to prevent active tuberculosis in at-risk children that have been infected with *Mycobacterium tuberculosis* is well recognized and supported by policy recommendations that are almost universally accepted [5,6]. However, implementation has usually been limited to low tuberculosis-endemic and resource-rich settings [7,8]. This review aims to highlight a number of recent developments that provide an unprecedented opportunity to address the current wide policy-practice gap in implementation in tuberculosis-endemic settings.

2. The terminology for this review

The WHO's definition for latent tuberculosis infection (LTBI) is a state of persistent immune response to stimulation by *Mycobacterium tuberculosis* antigens without evidence of clinically manifested active tuberculosis. In recognition that the spectrum of "latency" is difficult to define, especially in recently infected young children, the term "tuberculosis infection" will also be used to refer to children presumed to have been infected with *M.tuberculosis* and that do not have evidence of active tuberculosis. The term "tuberculosis" usually refers to the disease state caused by *M.tuberculosis*, but will also be referred to as "active tuberculosis" or "tuberculosis disease" in this review for the sake of clear distinction from "tuberculosis infection". The "treatment of tuberculosis infection" is the terminology currently preferred by many commentators and has the same meaning as "preventative therapy" or "LTBI management".

3. The rationale for the management of tuberculosis infection in young children

Among children exposed to and infected with *M. tuberculosis*, young age (<5 years) is a powerful determinant of risk for developing active tuberculosis [8,9]. Young age is also associated with a higher risk of developing severe forms of disseminated disease, such as tuberculous meningitis, and a higher risk of tuberculosis-related mortality than in older children (5-14 years) [9-11]. In addition to these risks, infants and young children (0-4 years) present greater challenges to accurate case detection of tuberculosis disease than other age groups. Difficulties of bacteriological confirmation mean that most young children with tuberculosis require a clinical diagnosis with frequent overlap of clinical presentation with other common causes of severe disease in young children such as pneumonia, meningitis and malnutrition [4]. Recent evidence from tuberculosis-endemic settings highlight the risks for tuberculosis disease and mortality in young children that are living in households with tuberculosis [12-14]. Many of the young children that present to health facilities with tuberculosis, including severe forms, represent missed opportunities for treatment of infection before the development of disease [15].

The potential effectiveness of therapy to reduce the risk of developing tuberculosis in children infected with *M. tuberculosis,* also known as preventive therapy, was first demonstrated in a randomized placebo-controlled trial of isoniazid (commonly referred to as isoniazid preventive therapy or IPT) conducted more than 50 years ago [16]. Further evidence from large randomized trials that included children as well as observational studies with long duration of follow-up support the effectiveness of IPT [17-19]. Protective efficacy of IPT has been estimated to be at least 90% for individuals with evidence of infection (i.e. tuberculin skin test or TST positive) and with full adherence to IPT including young HIV-infected children [17,20]. The prevalence of isoniazid resistance is higher than when the original studies were conducted [21]. It is not known whether IPT at the current recommended dosage of 10 mg/kg (range 7-15 mg/kg) is less protective if infected with isoniazid resistant tuberculosis. High-dose (15mg/kg) IPT may be effective where the index case has low level resistance, conferred by *inhA* mutation, but unlikely to be effective for tuberculosis infection with high level isoniazid resistance (*katG* mutation). In the context of tuberculosis endemic settings, this information is rarely available to the care provider. However, a number of recent studies from tuberculosis-endemic settings have observed

that less than 1% of young child contacts developed tuberculosis disease after receiving IPT following contact at current recommended dosages, suggesting ongoing effectiveness [12,22,23].

The established benefit of treatment of tuberculosis infection for this high-risk group of young children informs the current WHO recommendation for low- and middle-income settings which is that "children of less than 5 years of age who are household or close contacts of people with tuberculosis and who, after an appropriate clinical evaluation, are found not to have active tuberculosis should be given 6 months of IPT - strong recommendation, high quality of evidence" [4]. While characteristics of the index case are not specified within the WHO recommendation, NTP guidelines for low-resource countries often prioritise screening and treatment of infection for contacts of sputum smear-positive cases. With increasing utilisation of the Xpert MTB/RIF assay, consideration should be given to include Xpert positive cases, including those that are smear-negative. It has been reported that 30-40% of child contacts of index cases with sputum smear-negative pulmonary tuberculosis become infected [9]. Further, the recommendation for IPT is limited to contacts of known or presumed cases with drug-sensitive tuberculosis.

Infants and young children that are HIV-exposed (both HIV-infected and uninfected) are also commonly exposed to *M.tuberculosis* as close contacts of parents and other family members living with HIV[24,25]. Although HIV infected individuals with tuberculosis may not transmit as well as HIV uninfected index cases, they are at higher risk of developing tuberculosis which they may transmit to child contacts. Further, the risk in HIV-infected infants and children of developing tuberculosis following infection and of tuberculosis-related mortality is higher compared to those that are not HIV-infected [26]. Therefore, HIV-infected children of any age that are in close contact with tuberculosis and that do not have tuberculosis should receive IPT [4]. Whether this risk of disease following infection with *M.tuberculosis* is also higher in HIV-exposed uninfected infants compared to HIV-unexposed infants is not known. Nonetheless, all HIV-exposed uninfected infants in close contact with tuberculosis and that do not have tuberculosis should receive IPT as is the case for HIV-unexposed infants [4,5]. It is also recommended that "children living with HIV with no known contact with a tuberculosis case who are more than 12 months of age and who do not have active tuberculosis on symptom-based

screening should receive six months of IPT as part of a comprehensive package of HIV prevention and care" – strong recommendation, moderate quality of evidence [27].

Despite the strong rationale, the high to moderate quality of the supporting evidence base, and the WHO recommendations that are almost universally adopted by NTPs in resource-constrained and high incidence settings, the abovementioned recommendations on treatment of tuberculosis infection for young children are rarely implemented in tuberculosis-endemic settings [8].

4. Opportunities to address the wide policy-practice gap

4.1 Political will

The WHO's post-2015 End TB Strategy [28] includes a far greater focus on prevention and more explicit reference to the needs of children than previous global tuberculosis control strategies that emphasized case detection and only included children within reference to "vulnerable populations". In 2015, WHO formed the Latent Tuberculosis Infection (LTBI) Taskforce with the target groups for treatment of tuberculosis infection in tuberculosis-endemic, resource-limited settings being young children (<5 years) that are close contacts of a tuberculosis case and people living with HIV (PLHIV) of any age, that do not have active tuberculosis [29]. The aim of the LTBI Taskforce is to raise the profile of programmatic management of LTBI with the purpose being to:

- Analyse bottlenecks, identify innovative approaches and unblock barriers for implementation of the guidelines at global and national level
- Develop a framework to monitor and evaluate the implementation of LTBI management, including standardised indicators
- Promote research on LTBI by identifying knowledge gaps, and define priorities in both fundamental and operational research
- Contribute to the process for the re-estimation of the global burden of LTBI

The first "Global Consultation on the Programmatic Management of LTBI" was held by WHO in April 2016, and recommendations from the consultation with NTPs in tuberculosis-endemic countries were to include the scale-up of LTBI management for child contacts and PLHIV in national strategic plans, with targets, indicators and effective systems for monitoring and evaluation [30]. The Stop TB Partnership's Global Plan to End TB includes the very ambitious

targets that 90% or more of children that have been exposed to tuberculosis receive treatment for tuberculous infection, and that 90% or more of people in close contact with a tuberculosis case be evaluated for active tuberculosis by 2020 [31].

The recent focus on prevention in eligible young child contacts has coincided with increased attention to children in the context of tuberculosis control activities. Estimates of the burden of tuberculosis in children were not included in the WHO's Global TB Report until as recently as 2012. In 2013, the international Child TB Roadmap was published that provided a framework for greater collaboration between the NTPs and the child health sector at regional and national levels [32]. The screening and management of young children that are close contacts of a tuberculosis case is an activity that requires synergy and cooperation between the NTP and child health sectors, and provides a focus to develop this critical link.

4.2 Decentralisation and community-based integration of contact screening and management

The screening of household or close contacts of tuberculosis cases has two main aims. The first is active case-finding of contacts of any age that have tuberculosis, and this includes young child contacts of whom around 10% will have tuberculosis at the time of screening [12,13,22,33]. The second is the provision of treatment for tuberculosis infection for eligible at-risk contacts that do not have active tuberculosis, and again this includes young children. Studies from a range of resource-limited tuberculosis-endemic settings have consistently reported a low uptake of child contact screening and management [34].

There are a number of consistent barriers to implementation of contact screening that have been observed [34]. Studies demonstrating poor uptake have usually been based in large urban hospitals that rely on passive screening, i.e. request tuberculosis cases to bring the household contacts to a hospital-based clinic for screening [34-36]. It is difficult for families (parents/guardians) to understand the rationale for the treatment of tuberculosis infection, especially for young child contacts who are well and asymptomatic. Previously, an additional major barrier was that contact screening and management guidelines required investigations (i.e. TST and chest radiography) that were often unavailable or difficult to access as required multiple visits and travel to a secondary or tertiary health facility, and that have inherent limitations of

diagnostic accuracy. In recognition of these challenges, WHO guidelines in 2006 included a symptom-based screening algorithm to child contact management when tuberculin was unavailable, with the same guideline included in the second edition published in 2014 [4]. Only symptomatic contacts need to attend health facilities for further evaluation.

The symptom-based screening approach was recently evaluated in a cohort study with one-year follow-up at the primary care level in Indonesia and was found to be effective and safe and lower cost compared to an approach that used TST and chest radiography for all contacts [22]. Further, the use of chest radiography in asymptomatic contacts did not identify additional children with active tuberculosis but rather was characterised by low yield and poor inter-observer agreement [37]. The findings are consistent with an earlier cross-sectional study of the symptom-based screening approach in South African children [33]. A decision analysis model was developed to estimate health and economic outcomes of different screening strategies in young household tuberculosis contacts and evaluated in the same high incidence setting of the Western Cape [38]. Screening for tuberculosis infection and provision of IPT in young children was found to be a highly cost-effective intervention, and for children less than 3 years, the most cost-effective screening strategy in resource-constrained settings was the "no-testing" strategy where IPT was given based on age and reported exposure.

An important challenge for uptake of treatment for tuberculosis infection in eligible young children is the time taken for health workers to educate and support families [34]. Not surprisingly, it is difficult for parents or guardians to understand why their healthy child needs to take medicine daily and for at least 6 months. Indeed, the health workers themselves at the primary and secondary facility level often do not understand the rationale for preventive therapy, and commonly have misconceptions of risk, such as high risk of toxicity to isoniazid and of driving drug resistant tuberculosis [34,36]. The introduction and implementation of household contact screening and treatment for infection in the community therefore requires training of primary and community healthcare workers along with tools for monitoring and evaluation. There are recent examples of successful community-based implementation under programmatic conditions with higher rates of uptake and adherence than are reported from facility-based studies [21,39-41]. An important advantage of the symptom-based management approach is that

screening and preventive therapy for eligible contacts can be provided by the same community and primary healthcare workers that are providing treatment support for the index case, utilising an established relationship of trust with the household, i.e. a model of an integrated family-based approach to patient-centred care and prevention which is consistent with Pillar 1 of the End TB Strategy [28].

A disadvantage of a symptom-screening approach that does not include a diagnostic test for evidence of infection is a lack of specificity so that young children who have not been infected will be commenced on treatment for tuberculosis infection. While the risk of serious toxicity in young children receiving isoniazid within the currently recommended dosage range of 7-15 mg/kg is extremely low, the risk increases with increasing duration of therapy and there are rare reports of hepatic failure [42,43]. The prevalence of tuberculosis infection as measured by TST in young child close contacts of a tuberculosis case at the time of screening is estimated to be around 35% [13]. Therefore, an unknown number of young child contacts will not be infected at time of screening and yet would receive treatment for infection when applying the symptom-based screening approach. On the other hand, there will be a sizeable proportion of child contacts that are infected, and so will benefit from treatment, that will not be detected by skin testing, such as those recently infected.

4.3 Shorter, simpler and safer regimens for treatment of infection

The major challenge for implementation in those families that do agree to the uptake of treatment of tuberculosis infection is to achieve complete adherence. Incomplete adherence to the full course is commonly reported from tuberculosis-endemic settings [34,36,44-46]. Effectiveness of IPT requires at least 6 months of therapy [20,47] and while it is biologically plausible that a shorter regimen of isoniazid alone might be effective in young children, this is not known. However, there are alternative regimens of shorter duration that are as effective as six or nine months of IPT (i.e. 6H or 9H) and that are endorsed by the WHO for use in low incidence tuberculosis settings [5]. These include 3 to 4 months of daily rifampicin and isoniazid (3RH or 4RH), 3 to 4 months of rifampicin alone (3R or 4R), and 3 months of weekly rifapentine and isoniazid (3HP) - as strong recommendation, moderate to high quality of evidence but without

full consensus of the panel [5]. The evidence for use of these regimens in children has been reviewed recently [20].

A potential game-changer for the implementation of the treatment of tuberculous infection is the evidence of similar effectiveness, less toxicity and improved adherence of 3HP compared to 9 months of daily isoniazid [48-50]. This short regimen is also as effective and safe in PLHIV [51]. The improved adherence is not surprising given that the 3HP regimen requires just 12 dosages given once per week compared to 180 daily dosages for six months of IPT, but it may also be due to medication being administered under direct observation [49,52]. A weekly schedule may increase the risk of failure if even a small number of dosages are missed and so directly observed may be preferable to self-administered therapy but this is not known under programmatic conditions in tuberculosis-endemic settings. Published clinical and pharmacokinetic studies have included children and adolescents [49,52,53], but not infants and young children of less than 2 years of age which is a high-risk age group that also has the greatest variability in dosage requirements for anti-tuberculosis treatments. A pharmacokinetic study of rifapentine that includes infants and young children is planned that could guide development of a fixed-dose combination (FDC) formulation. The 3HP regimen also has the potential to be highly cost-effective [54].

Alternative shorter regimens of proven effectiveness and tolerability include 3RH which is routinely used in the United Kingdom [20,54]. While the treatment of tuberculous infection in young children is rarely implemented by NTPs in tuberculosis endemic settings, there is no incentive to procure or develop the appropriate formulations for young children. With the widespread use of FDCs as first-line treatment for tuberculosis, single drug isoniazid preparations that are required for implementation of IPT are now frequently unavailable [56]. Further, the 300 mg isoniazid tablet is difficult to use in young children to provide recommended dosages, although 100 mg and 50 mg tablet preparations are available. Child-friendly, dispersible FDCs are now available for the first-line treatment of tuberculosis in children and include a combination of rifampicin and isoniazid (RH–75 mg/50 mg) for use in continuation phase. This same preparation could be used for the shorter preventative therapy regimen of 3RH in young children as an alternative to 6H in tuberculosis endemic countries.

There are not specific recommendations for the treatment of infection in a child exposed to a case with isoniazid mono-resistance. The prevalence of isoniazid mono-resistance is likely to be higher than when the original studies of IPT were conducted [21], but whether IPT at the current recommended dosage of 10 mg/kg (range 7-15 mg/kg) is less protective in young child contacts of isoniazid mono-resistant tuberculosis is not known. However, a preventive therapy regimen containing rifampicin alone (4R) or in combination with isoniazid (3RH) should be considered.

There are concerns that the widespread use of shorter regimens containing a rifamycin alone or in combination will result in more cases of multidrug-resistant (MDR) tuberculosis [57]. There have been similar related concerns for IPT and isoniazid resistant tuberculosis despite evidence to the contrary [58]. A recent systematic review and meta-analysis of studies in adults concluded that the use of rifamycin-containing preventive therapy regimens did not significantly increase the risk of rifampicin-resistant tuberculosis [59]. However, there are still unresolved legitimate concerns including whether the risk may be higher when used under routine programmatic conditions [57]. Although there are no data from studies, the population risk of contributing to drug resistance is likely to be negligible when treating tuberculous infection in young children, including isoniazid or rifamycin-containing regimens, given the effectiveness of preventing disease and the low risk of transmission from those young children that do develop active tuberculosis while receiving treatment for tuberculosis infection.

5. The extent of the challenge

The target of achieving preventative treatment of 90% or more of children that have been exposed to tuberculosis by 2020 [31] is very ambitious and will be difficult to achieve. Nonetheless, it is important to set targets for contact screening and treatment of tuberculosis infection and to put in place the necessary tools for monitoring and evaluation. Estimates for all countries in 2014 of the number of child household contacts requiring evaluation, of the number with tuberculosis disease and of the number with tuberculous infection were recently published for two age groups, 0-4 years and 5-14 years of age [60]. It was estimated that in 2014 there were 2.4 million young children (<5 years) and 5.1 million older children (5-14 years) living in households of adult patients with known tuberculosis and that of these around 240,000 young

children and 420,000 older children will have active tuberculosis, or 10% and 8% respectively. Of the remaining 2.16 million young child contacts and 4.68 million older child contacts without tuberculosis disease, it was estimated that 848,453 (or 39%) and 2,660,885 (or 57%) were tuberculosis infected. Therefore, the global target of 90% or more of exposed children translates to at least 6.2 million child contacts of all ages treated for tuberculosis infection if screening did not include testing for LTBI, or around 2 million if treatment for tuberculosis infection was limited to young child contacts.

In addition to the challenges of improving and securing procurement and supply of therapy for tuberculous infection, it will be critical to decentralise contact screening with an integrated family- or community-based approach. Two separate calculations have used data from Malawi for 1998 and 2014 and both estimated that there were more than 7,000 young children eligible for preventive therapy each year [34,60]. Therefore, each district hospital would need to provide preventive therapy for an average of around 300 young child contacts per year compared to around 15 per year if this was managed at the primary health centre level.

6. The need for better diagnostics for tuberculosis infection

The limitations of the currently used tests for the detection of tuberculosis infection, i.e. TST or IGRA, are well recognised [61], and include limitations of accuracy, applicability, affordability and availability in tuberculosis-endemic and often resource-limited settings. Neither test can provide results at point-of-care. It is a focus of current research to develop an accurate point-of-care test for tuberculosis infection with candidates including blood-based biomarkers [62,63] but this is unlikely to be realised within the next decade. There is also promising research to identify markers that predict risk of progression to active disease [64]. A point-of-care test would need to be robust, affordable, accessible and accurate (highly sensitive and specific) including in infants, young children and PLHIV. Such a test has the potential to increase the uptake and effectiveness of the programmatic implementation of therapy for tuberculous infection and reduce the target population by limiting its use to only those with proven LTBI.

A novel skin test known as C-Tb (Statens Serum Institut, Copenhagen, Denmark) that uses the same specific *M.tuberculosis* antigens (ESAT-6 and CFP-10) that are the basis of the IGRA test

has been developed and recently field tested [65,66]. A cut-point of 5 mm induration has been established and C-Tb is more specific than TST as it is not affected by prior BCG immunisation. There is no gold standard in LTBI for evaluation of new diagnostics but when C-Tb was evaluated in patients with active tuberculosis, the positive predictive value was only modest with sensitivity lower than for TST and reduced in PLHIV with marked immunosuppression as measured by CD4 count (as for TST) [61,66]. Compared to IGRA, C-Tb does not require a laboratory and is likely to be low-cost, and if it was produced at scale may alleviate the increasingly frequent global shortages of tuberculin solution [61].

7. Treatment of tuberculous infection for young children that are MDR contacts

It is estimated that 25,000 children developed MDR tuberculosis in 2014 although the vast majority were not detected and treated [67,68]. The potential of treatment for tuberculosis infection in young children that are exposed to a case of MDR tuberculosis is of critical importance given that they are of similar high risk as young child contacts of drug-susceptible tuberculosis to develop active tuberculosis. As MDR tuberculosis has a poorer treatment outcome and requires a more prolonged, more toxic and more expensive treatment regimen that includes injectables with a substantial risk of permanent hearing loss, the potential for a favourable benefit to risk ratio and for cost-effectiveness is greater than for the treatment of drug-susceptible tuberculosis in young children. Indeed, these factors would support treatment to be considered for all contacts with tuberculosis infection of a MDR tuberculosis case including older children and adolescents. Furthermore, children and adolescents infected with drug-resistant tuberculosis are a reservoir from whom future cases will develop [67].

There is currently limited published evidence to guide the choice of a treatment regimen for an MDR tuberculosis contact with tuberculosis infection and without active tuberculosis. There is a lack of consensus on the inclusion of high dose isoniazid in a regimen, as it is likely that effectiveness will depend on the level of isoniazid resistance as conferred by genetic mutation as previously discussed. However, it is generally agreed that the regimen will contain a fluoroquinolone, preferably levofloxacin either alone or in combination with other drugs selected on the basis of the drug susceptibility profile of the index case if known. There are randomised placebo-controlled trials of levofloxacin commencing in 2016 that include children and adults

with tuberculosis infection that are MDR tuberculosis contacts. There is also likely to be additional evidence reported from observational studies over the next few years[69-71]. While awaiting higher quality evidence than what is currently available, the use of treatment for tuberculosis infection in MDR contacts, including young children, is a frequent, important question for appropriate individual and programmatic management. Current WHO recommendations are for "Strict clinical observation and close monitoring for the development of active tuberculosis among contacts of MDR tuberculosis cases preferably for at least two years over the provision of preventive treatment. Clinicians can consider individually tailored treatment regimens based on the drug susceptibility profile of the index case, particularly for child contacts below 5 years of age, when benefits can outweigh harms with reasonable confidence" [5].

A consultation was held in 2015 that included clinician researchers with experience and evidence of the use of treatment of tuberculosis infection for MDR contacts [69]. On the basis of available evidence, the majority felt that therapy would benefit household contacts of all ages of an MDR case with tuberculosis infection except if the source case had confirmed fluoroquinolone resistance. It was also felt that treatment for tuberculosis infection could be provided to young children (<5 years) and PLHIV on the basis of "significant" exposure alone due to risk and limitations in the sensitivity of tests for infection in these populations. If NTPs decided to prioritize high-risk groups, there was agreement with current practice to prioritize young children and any contact that was immunosuppressed, irrespective of age. A fluoroquinolone-based regimen of at least six months' duration with treatment support and supervision with clinical follow-up for at least 18 months from the time of screening [69].

8. Implementation, integration and health systems strengthening

The opportunity provided by the global End TB Strategy to increase attention to prevention in high-risk groups such as young children in resource-limited tuberculosis endemic settings has been highlighted above. This will require and hopefully result in increased attention and improvements in all other important aspects of child tuberculosis management. The Roadmap for Childhood Tuberculosis highlights the need for integration of activities in prevention, diagnosis and management along the full epidemiological spectrum from exposure to outcome, calling for

engagement of the maternal and child health services and strengthening of active collaboration with the NTPs [32,72]. There are particular challenges for diagnosis in young children in whom diagnosis is usually clinical and there is frequent overlap of symptoms with other common diseases in young children.

In many tuberculosis endemic settings, there is a lack of confidence and experience in child tuberculosis diagnosis outside of the tertiary care facility which can lead to unnecessary referral (a major barrier for access) or increases the risk of misdiagnosis, which includes over-diagnosis as well as missed diagnosis. Therefore, the implementation of contact screening and treatment for tuberculosis infection at the community or primary care level will commonly identify children with tuberculosis-related symptoms that require diagnostic evaluation and management [12,22,60]. Therefore, case detection and diagnosis at the primary and secondary care levels will need to be strengthened [7,72]. The decentralisation of the management and prevention of active tuberculosis in young children requires training of health workers as well as strengthening of monitoring and evaluation. A number of training aides have recently been developed including by the WHO and The Union [73,74], and an increasing number of NTPs are utilising and adapting these as they seek to strengthen services for tuberculosis in children.

9. Conclusion

The End TB Strategy provides an unprecedented opportunity to implement and scale up the treatment of tuberculous infection in young children living in tuberculosis endemic countries. The target population is large and there are considerable challenges to close the current wide policy-practice gap for child contact screening. Strengthening of health systems will be required for application and monitoring of community-based contact screening and management. Shortened regimens for treatment of tuberculous infection are likely to improve uptake and adherence. There is an ongoing need for an accurate point-of-care test of infection.

10. Expert commentary

Over the last decade, there has been increasing inclusion of the needs of children with tuberculosis in global and national tuberculosis control programs. The post-2015 End TB Strategy with its focus on patient-centered care and prevention provides an unprecedented

opportunity to close the wide policy-practice gap that currently exists in tuberculosis endemic countries in the management of children infected with *Mycobacterium tuberculosis* who are at high risk of developing tuberculosis disease within the first 12 months following infection. These high-risk groups are infants and young children (<5 years) and children of any age who are HIV-infected. The effectiveness and safety of the treatment of young children with tuberculosis infection, also known as "preventive therapy", is well established. However, there have been multiple challenges precluding implementation that include: lack of prioritization by National Tuberculosis Programs (NTPs) in resource-limited settings; efforts to implement have been characterized by poor access, uptake and adherence; and implementation requires strengthening of health systems to manage children with active tuberculosis, including diagnosis and treatment, at all levels of care.

Highly ambitious targets have recently been set such as the Stop TB Partnership's Global Plan to End TB which aims to treat infection in 90% or more of children that have been exposed to tuberculosis by 2020. The extent of this challenge is highlighted by recent estimates that in 2014, there were 2.4 million young children (<5 years) living in households with an adult with tuberculosis that required screening, of whom an estimated 240,000 had active tuberculosis and an estimated 850,000 had tuberculosis infection. This will require the development or strengthening of systems that support community-based household screening and the treatment of tuberculosis infection and disease in high-risk groups such as young children that is integrated with treatment support for the index case. An important opportunity for progress is the emergence of new and "old" alternative preventative therapy regimens that are shorter, simpler to administer, safer, and as effective as the current recommended regimen of daily isoniazid for at least 6 months. A major priority is the development of a robust, low-cost point-of-care test of infection with *M.tuberculosis* that is more accurate and readily applicable than those currently available. Findings from clinical trials are required to strengthen the evidence base in order to develop specific guidelines for the management of infection in contacts of multidrug-resistant tuberculosis cases.

11. Five year view

Ambitious targets for screening and treatment of 90% or more of young children exposed to *Mycobacterium tuberculosis* have been set for 2020. Given that this is currently not being

implemented in most tuberculosis endemic settings, such targets will be very difficult to achieve over the next 5 years. Nonetheless, it is to be hoped there will be considerably more activity and programmatic experience than currently that will provide lessons learned, programmatic data reporting uptake and coverage of screening and treatment, as well as efforts to evaluate the impact of implementation on the overall burden of tuberculosis disease in children. The possibility of child-friendly, fixed dose combination regimens to treat tuberculosis infection that are shorter and as effective as the current recommendation of daily isoniazid for at least 6 months has already resulted in greater momentum towards programmatic implementation and evaluation in low and middle-income countries., Importantly, there will also be high-quality data available within the next five years to inform specific recommendations for the treatment of infection in contacts exposed to multidrug-resistant tuberculosis. There will certainly be improved knowledge and understanding of biomarkers that indicate tuberculosis infection in a range of populations but it is unlikely that an accurate, robust and low-cost point-of-care test would yet be avialable. Efficient and effective delivery models from a range of settings that initially focus on the high-risk populations for tuberculosis infection of young children and people living with HIV will inform screening and treatment strategies that target a wider population in efforts to accelerate improvements in the control of tuberculosis.

12. Key issues

1. Young children (<5 years of age) infected with *Mycobacterium tuberculosis* are at high risk of developing tuberculosis including severe forms of tuberculosis associated with a high mortality.
2. The treatment for tuberculosis infection is rarely provided to young children living in tuberculosis endemic countries despite known effectiveness and supportive policies.
3. The post-2015 WHO's End TB Strategy and the Stop TB Partnership's Global Plan to End TB combined with the increasing attention to childhood tuberculosis by National Tuberculosis Programs in high burden countries provide an unprecedented opportunity to close the current wide policy-practice gap.
4. Effective implementation will require a community-based and integrated approach to screening and treatment, as well as strengthening of the capacity of health workers at the

primary and secondary care levels to diagnose and manage young children with active tuberculosis.

5. The emergence of new and "old" combination regimens that effectively reduce the risk of active tuberculosis in young children infected with *M. tuberculosis* and that are shorter than the currently recommended regimen of daily isoniazid for at least 6 months is an important opportunity for improving implementation.
6. There is a need for the evaluation of effective models for treatment uptake and adherence for shorter regimens under programmatic conditions especially for a weekly regimen.
7. The recently developed fixed dose combination of rifampicin and isoniazid could be considered as an alternative treatment regimen for infection in high tuberculosis incidence settings, as it currently is in low incidence settings, following meta-analysis of the evidence and consideration of uptake, effectiveness, adherence and risk under programmatic conditions.
8. A stronger evidence-base will emerge within the next few years to inform the most appropriate treatment of infection for young children exposed to multidrug-resistant tuberculosis.
9. Current programmatic focus on the treatment of tuberculosis infection in young children provides an important opportunity to address the need to improve the case-finding and management of active tuberculosis in children.

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