Residência Pediátrica
Publicação Oficial da Sociedade Brasileira de Pediatria

Submitted on: 03/22/2017
Approved on: 04/30/2017

ORIGINAL ARTICLE

Improving access to tuberculosis preventive therapy and treatment for children

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Keywords:
latent tuberculosis,
child,
health services acessibility,
disease prevention,
drug resistance.

Abstract

In tuberculosis (TB) endemic countries, children suffer a huge burden of disease, which was largely invisible when TB control programs focussed exclusively on adults with sputum smear-positive disease. High-level advocacy and better data have improved visibility, but the establishment of functional pediatric TB programs remains challenging. The key issues that limit children's access to TB preventive therapy for TB exposure and TB infection, and to treatment for TB disease, in endemic areas are briefly discussed. Barriers to preventive therapy include: (a) the perceived inability to rule out active disease; (b) fear of creating drug resistance; (c) non-implementation of existing guidelines in the absence of adequate monitoring; and (d) poor adherence with long preventive therapy courses. Barriers to TB treatment include: (a) perceived diagnostic difficulties; (b) non-availability of chest radiography; (c) young children presenting to unprepared maternal and child health (MCH) services; and (d) the absence of child friendly formulations. Regarding drug-resistant disease, there is currently no guidance on the use of preventive therapy and treatment is usually restricted to cases with bacteriologically-confirmed disease, which excludes most young children from care, even if their likely source case has documented drug-resistant TB.

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INTRODUCTION

Although the World Health Organization (WHO) launched the ambitious End TB Strategy in 2015[1], tuberculosis (TB) remains the leading infectious cause of death worldwide. WHO estimates that 10.4 million people developed TB in 2015, of whom 580,000 had multidrug-resistant (MDR) or rifampicin monoresistant TB[2]. The huge disease burden suffered by children in TB-endemic countries was rarely appreciated in the past[3], but this has changed with high-level advocacy and better data to improve visibility[4-6].

Recently the United Nations Secretary-General's Special Envoy on TB Dr. Eric Goosby stated: "Far too long, children with tuberculosis (TB) have remained in the shadows. While there have been tremendous strides made in improving other areas of child health and survival, we have yet to see the parallel advances in pediatric TB. Instead, many children with TB die before they can be diagnosed and treated[4]." The WHO estimates that 1 million children developed TB in 2015, resulting in 210,000 deaths[2,7]. At least 5 000 children were likely to have died from multidrug-resistant TB and around 40,000 were co-infected with human immunodeficiency virus (HIV)[7,8].

In the absence of routine drug-susceptibility testing (DST), MDR-TB estimates are highly variable and the number of affected children often underappreciated[7,8]. This mainly results from the fact that the level of primary MDR-TB transmission within endemic communities is grossly underestimated when extrapolated from the MDR-TB rate observed among new TB cases only. In reality, the majority of MDR-TB diagnosed among retreatment cases also represents primary transmission[9-11]. Children dying from TB, including drug-resistant disease, are often incorrectly classified as pneumonia, meningitis, HIV/AIDS or malnutrition deaths[12].

Of the estimated 921,000 (95% CI 812,000 -1,117,00) pneumonia deaths that occurred in children under 5 years in 2015, most occurred among young children living in TB endemic areas[13]. In these settings, TB is likely to be a substantial cause and comorbidity of childhood pneumonia[14]. Autopsy studies suggest that TB is a major contributor to under-5 mortality in sub-Saharan Africa, irrespective of the child's HIV status[15,16]. and the same is likely to apply in other settings with uncontrolled TB transmission. TB is an important preventable cause of under-5 mortality, since children respond well to treatment if they are able to access care.

BARRIERS TO ACCESS TO PREVENTIVE THERAPY AND TREATMENT

High-level advocacy is essential, but it needs to be sustained and amplified at national and local levels to support effective implementation strategies. Few TB endemic countries have adequate strategies or resources allocated to implement TB prevention and care programs for children. The WHO Roadmap for Childhood TB also emphasizes the need for better linkage and integration with Maternal and Child Health (MCH) initiatives[17].

In some countries, significant progress has been made with child TB action plans jointly developed by national TB programs (NTPs), local paediatric societies and MCH programs[18]. In response to the Roadmap's call for better linkages, the United Nations Children's Fund (UNICEF) recently organized a consultation meeting on childhood TB integration in New York, exploring how best to strengthen community and primary health systems[19]. Table 1 summarizes key barriers that continue to limit childrens' access to TB preventive therapy and treatment[20].

BARRIERS TO PREVENTIVE THERAPY FOR TB EXPOSURE AND TB INFECTION

The most effective means to prevent TB infection (and subsequent disease) in children is to improve epidemic control[21]. However, in settings with ongoing TB transmission, efforts to prevent TB disease are necessary to reduce TB-related morbidity and mortality in the most vulnerable[22]. The WHO and the International Union Against TB and Lung Disease (The Union) advise preventive therapy for all immunocompromised children and those less than 5 years of age (due to their relative immunological immaturity) following proven TB infection or close contact with an infectious TB case[23].

Although this is rarely implemented in TB endemic settings and massive policy-practice gaps remain[24], the creation of a latent TB infection (LTBI) taskforce and publication of evidence based LTBI guidelines in 2015[25] demonstrates the commitment of the WHO to improve the delivery of preventive therapy to young and vulnerable children.

Perceived inability to rule out active disease

A major concern of health-care workers in resource-limited settings is their perceived inability to rule out TB disease with certainty, given the impression that a tuberculin skin test (TST) or interferon-γ release assay (IGRA) and chest radiograph are required for adequate screening. However, symptom-based screening offers a safe and feasible alternative[26-28] and is recommended by the WHO for contact screening in resource-limited settings[23]. qChest radiography has little value in completely asymptomatic children[27,29] and should not act as a barrier to the provision of preventive therapy in high-risk contacts (i.e., post-exposure prophylaxis). Detailed diagnostic work-up should be reserved for the minority of contacts with persistent symptoms suggestive of TB[23,27].

Fear of creating drug resistance

The exclusion of TB disease is important, since inadvertent treatment of active disease with one or two medications used in preventive therapy could select for drug resistance. Fear of selecting drug-resistant strains that will be transmitted within the community is the most frequently cited reason why health-care workers and countries are reluctant to implement preventive therapy strategies[20,24].The risk of acquiring drug resistance is greatest in diseased patients with

Tabela 1. Key barriers and proposed solutions to improve access to TB preventive therapy and treatment for children.

Key Barriers	Proposed Solutions
General • Lack of awareness at the local programmatic level • Inadequate training	• Persistent high-level advocacy, amplified at the national and local levels • Inclusion of childhood TB in medical and nursing training curricula, including MCH training programs
Preventive therapy for exposure and infection • Perceived inability to screen • Fear of creating drug resistance • Poor implementation of guidelines • Poor adherence with prolonged isoniazid preventive therapy (IPT)	• Symptom-based screening adequate • Education regarding minimal risk in children • Adequate monitoring and evaluation • Development of child-friendly short-course formulations (e.g., isoniazid-rifapentine combination tablet
Treatment for disease • Diagnostic difficulties and poor laboratory infrastructure • Non-availability of high-quality chest radiographs • Young children presenting to unprepared MCH programs • Non-availability of quality-assured child-friendly formulations	• Systematic diagnostic approach in both active and passive case finding; expansion of access to Xpert MTB/RIF® and/or culture • Increase availability and improve interpretation of high-quality digital chest radiographs • In MCH programs, inclusion of training on childhood TB and incorporation of TB service delivery in endemic settings • Wide availability of new GDF-approved child-friendly formulations
Treatment for drug-resistant disease • No guidance on preventive therapy • Poor access to diagnosis and treatment • No child-friendly formulations	• Interim guidance on preventive therapy for drug-resistant TB exposure; research support • Expansion of access to Xpert MTB/RIF® and/or culture; treatment according to DST of most likely source case • Creative administration methods - children do tolerate most second-line drugs and achieve excellent treatment outcomes; assurance that all new TB drugs have a pediatric development plan

TB - tuberculosis; MCH - maternal and child health; GDF - Global Drug Facility; DST - drug-susceptibility testing.

high bacterial loads and generally low if international screening guidelines are adhered to[30,31].

It is conceivable that the selective pressure imposed by population-wide preventive therapy will be substantial, even though no elevated risk of drug resistance has been observed among those receiving TB preventive therapy in small-scale studies of limited duration[32]. However, the use of preventive therapy in young children is associated with minimal risk, as they tend to develop paucibacillary disease and rarely transmit the infection[33]. Therefore, fear of creating drug resistance within the community is irrelevant and should not compromise the provision of preventive therapy to young children.

Non-implementation of existing guidelines

Despite the sound scientific basis underlying current recommendations national and supranational guidelines, contact screening is rarely implemented in TB-endemic settings[24]. Although health-care services are overburdened, TB contact screening can be implemented with minimal dditional resourcing and the use of simplified processes. This has been demonstrated by studies in Indonesia and with progressive country-wide roll-out of household contact tracing in Vietnam[18,28].

In reality, TB program implementation is largely driven by effective monitoring and evaluation. The fact that the WHO now requires National TB Programs (NTPs) to report on the provision of preventive therapy to child TB contacts will encourage NTPs to develop feasible strategies, set realistic goals, and monitor implementation progress.

Poor adherence with prolonged isoniazid preventive therapy

Poor adherence with prolonged isoniazid preventive therapy (IPT) is a concern[34], but recent field trials have demonstrated that good adherence is possible under programmatic conditions[35,36]. Feasibility and adherence would be greatly improved by short-course therapy options, such as 3 months of daily isoniazid and rifampicin or 12 weekly-doses of isoniazid and rifapentine[37].

The availability of a water-dissolvable fixed-dose combination tablet (containing 50 mg of isoniazid and 75 mg of rifampicin) offers excellent opportunities to revive preventive therapy programs and improve adherence[38], especially in settings with low rates of HIV co-infection where potential drug-drug interactions caused by rifampicin are not of concern. It is hoped that child-friendly isoniazid and

rifapentine combination tablets will also be developed, since this will greatly simplify preventive therapy administration and supervision.

Barriers to treatment for TB disease

An optimally formulated child-friendly dissolvable fixed-dose combination tablet, developed by the TB Alliance, has recently been made available via the Global Drug Facility[38]. Countries should ensure that this is purchased and made available to all children who require TB treatment. However, perceived diagnostic difficulties, the non-availability of chest radiography, and poor laboratory infrastructure, remain major barriers to accurate diagnosis and treatment in resource-limited settings.

Although better diagnostics and improved access to high-quality digital chest radiographs are urgently needed, most cases of childhood TB can be accurately diagnosed using a systematic approach - even in resource-limited settings[39,40]. Since most young children with symptoms suggestive of TB will present to MCH services and not to the NTP, it is essential that MCH programs in TB-endemic areas include training on childhood TB, incorporate TB into integrated management of childhood illness (IMCI) approaches and embrace TB service delivery. The WHO recently launched an on-line childhood TB training toolkit, which is freely available to all health care workers[41].

Barriers to treatment for drug-resistant TB disease

There is currently no formal guidance on the use of preventive therapy following drug-resistant TB exposure. Although more data are required, the available evidence suggests benefit to young children with documented infection following multidrug-resistant (MDR) TB exposure[42]. Unlike adults, treatment outcomes for children with drug-resistant TB are excellent, but few are able to access proper diagnosis and care[43].

Treatment for drug resistant TB is usually restricted to cases with bacteriologically-confirmed disease, which excludes most young children. Although it is important to expand access to Xpert MTB/RIF® and culture for bacteriological confirmation of drug-resistant TB, it is important for programs to endorse the treatment of young children according to the drug susceptibility testing (DST) profile of their most likely source case, in the absence of bacteriological confirmation from their own specimens[44].

The Union recently developed an on-line course on the management of childhood MDR-TB, which offers useful guidance to clinicians and health-care workers caring for children with TB[45]. Children tolerate most second-line drugs well, but close monitoring is important to limit drug-related adverse effects[44]. Given the limited information we have on the optimal administration of second-line drugs to children, it is essential to ensure that all new TB drugs have a pediatric development plan[46].

CONCLUSION

There is a need for better collaboration between paediatricians, NTPs and MCH initiatives in TB endemic countries to improve the detection and management of children with TB. Priority actions previously identified and emphasized by the "Child TB Roadmap" include[47]:

(A) Empower children, their families, and communities to advocate for improved access to TB prevention, diagnosis and care; (B) Step up programmatic efforts to identify children and adolescents at highest risk of TB and prevent, diagnose and treat them with the best diagnostic tools and medicines available; (C) Strengthen health-care systems at all levels and integrate - where possible - TB activities with programs focused on maternal and child health, HIV/AIDS, and nutrition; (D) Include children and adolescents in research activities at the earliest possible stage to accelerate the development of appropriate diagnostics and treatments; Scale up investment in the development of childhood TB diagnostics, treatment and vaccines, as well as the health-care systems that use them.

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