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ORIGINAL ARTICLE

## Improving access to tuberculosis preventive therapy and treatment for children

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latent tuberculosis, child, health services accessibility, 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<sup>1</sup>, 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 mono-resistant TB<sup>2</sup>. The huge disease burden suffered by children in TB-endemic countries was rarely appreciated in the past<sup>3</sup>, but this has changed with high-level advocacy and better data to improve visibility<sup>4-6</sup>.

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<sup>4</sup>." The WHO estimates that 1 million children developed TB in 2015, resulting in 210,000 deaths<sup>2,7</sup>. 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)<sup>7,8</sup>.

In the absence of routine drug-susceptibility testing (DST), MDR-TB estimates are highly variable and the number of affected children often underappreciated<sup>7,8</sup>. 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<sup>9-11</sup>. Children dying from TB, including drug-resistant disease, are often incorrectly classified as pneumonia, meningitis, HIV/AIDS or malnutrition deaths<sup>12</sup>.

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<sup>13</sup>. In these settings, TB is likely to be a substantial cause and comorbidity of childhood pneumonia<sup>14</sup>. Autopsy studies suggest that TB is a major contributor to under-5 mortality in sub-Saharan Africa, irrespective of the child's HIV status<sup>15,16</sup>, 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<sup>17</sup>.

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<sup>18</sup>. 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<sup>19</sup>. Table 1 summarizes key barriers that continue to limit children's access to TB preventive therapy and treatment<sup>20</sup>.

## 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<sup>21</sup>. 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<sup>22</sup>. 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<sup>23</sup>.

Although this is rarely implemented in TB endemic settings and massive policy-practice gaps remain<sup>24</sup>, the creation of a latent TB infection (LTBI) taskforce and publication of evidence based LTBI guidelines in 2015<sup>25</sup> 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- $\gamma$  release assay (IGRA) and chest radiograph are required for adequate screening. However, symptom-based screening offers a safe and feasible alternative<sup>26-28</sup> and is recommended by the WHO for contact screening in resource-limited settings<sup>23</sup>. qChest radiography has little value in completely asymptomatic children<sup>27,29</sup> 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<sup>23,27</sup>.

### 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<sup>20,24</sup>. 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
<p><b>General</b></p> <ul style="list-style-type: none"> <li>• Lack of awareness at the local programmatic level</li> <li>• Inadequate training</li> </ul>	<ul style="list-style-type: none"> <li>• Persistent high-level advocacy, amplified at the national and local levels</li> <li>• Inclusion of childhood TB in medical and nursing training curricula, including MCH training programs</li> </ul>
<p><b>Preventive therapy for exposure and infection</b></p> <ul style="list-style-type: none"> <li>• Perceived inability to screen</li> <li>• Fear of creating drug resistance</li> <li>• Poor implementation of guidelines</li> <li>• Poor adherence with prolonged isoniazid preventive therapy (IPT)</li> </ul>	<ul style="list-style-type: none"> <li>• Symptom-based screening adequate</li> <li>• Education regarding minimal risk in children</li> <li>• Adequate monitoring and evaluation</li> <li>• Development of child-friendly short-course formulations (e.g., isoniazid-rifampentine combination tablet)</li> </ul>
<p><b>Treatment for disease</b></p> <ul style="list-style-type: none"> <li>• Diagnostic difficulties and poor laboratory infrastructure</li> <li>• Non-availability of high-quality chest radiographs</li> <li>• Young children presenting to unprepared MCH programs</li> <li>• Non-availability of quality-assured child-friendly formulations</li> </ul>	<ul style="list-style-type: none"> <li>• Systematic diagnostic approach in both active and passive case finding; expansion of access to Xpert MTB/RIF® and/or culture</li> <li>• Increase availability and improve interpretation of high-quality digital chest radiographs</li> <li>• In MCH programs, inclusion of training on childhood TB and incorporation of TB service delivery in endemic settings</li> <li>• Wide availability of new GDF-approved child-friendly formulations</li> </ul>
<p><b>Treatment for drug-resistant disease</b></p> <ul style="list-style-type: none"> <li>• No guidance on preventive therapy</li> <li>• Poor access to diagnosis and treatment</li> <li>• No child-friendly formulations</li> </ul>	<ul style="list-style-type: none"> <li>• Interim guidance on preventive therapy for drug-resistant TB exposure; research support</li> <li>• Expansion of access to Xpert MTB/RIF® and/or culture; treatment according to DST of most likely source case</li> <li>• 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</li> </ul>

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<sup>30,31</sup>.

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<sup>32</sup>. 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<sup>33</sup>. 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<sup>24</sup>. Although health-care services are overburdened, TB contact screening can be implemented with minimal additional 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<sup>18,28</sup>.

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<sup>34</sup>, but recent field trials have demonstrated that good adherence is possible under programmatic conditions<sup>35,36</sup>. 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 rifampentine<sup>37</sup>.

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<sup>38</sup>, 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

rifampentine 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<sup>38</sup>. 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<sup>39,40</sup>. 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<sup>41</sup>.

### 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<sup>42</sup>. Unlike adults, treatment outcomes for children with drug-resistant TB are excellent, but few are able to access proper diagnosis and care<sup>43</sup>.

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<sup>®</sup> 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<sup>44</sup>.

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<sup>45</sup>. Children tolerate most second-line drugs well, but close monitoring is important to limit drug-related adverse effects<sup>44</sup>. 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<sup>46</sup>.

## 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<sup>47</sup>:

(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.

## REFERENCES

1. World Health Organization (WHO). The End TB Strategy. [accessed 2016 Oct 1]. Available from: <http://www.who.int/tb/strategy/end-tb/en/>
2. World Health Organization (WHO). Global Tuberculosis Report 2016. Geneva: World Health Organization; 2016.
3. Marais BJ, Schaaf HS. Childhood tuberculosis: an emerging and previously neglected problem. *Infect Dis Clin North Am.* 2010;24(3):727-49. DOI: <http://dx.doi.org/10.1016/j.idc.2010.04.004>
4. Goosby E. Out of the shadows: shining a light on children with tuberculosis. *Int J Tuberc Lung Dis.* 2015;19 Suppl 1:1-2. DOI: <http://dx.doi.org/10.5588/ijtld.15.0411>
5. Dodd PJ, Gardiner E, Coghlan R, Seddon JA. Burden of childhood tuberculosis in 22 high-burden countries: a mathematical modelling study. *Lancet Glob Health.* 2014;2(8):e453-9. DOI: [http://dx.doi.org/10.1016/S2214-109X\(14\)70245-1](http://dx.doi.org/10.1016/S2214-109X(14)70245-1)
6. Seddon JA, Jenkins HE, Liu L, Cohen T, Black RE, Vos T, et al. Counting children with tuberculosis: why numbers matter. *Int J Tuberc Lung Dis.* 2015;19 Suppl 1:9-16. DOI: <http://dx.doi.org/10.5588/ijtld.15.0471>
7. Jenkins HE, Tolman AW, Yuen CM, Parr JB, Keshavjee S, Pérez-Vélez CM, et al. Incidence of multidrug-resistant tuberculosis disease in children: systematic review and global estimates. *Lancet.* 2014;383(9928):1572-9. PMID: 24671080 DOI: [http://dx.doi.org/10.1016/S0140-6736\(14\)60195-1](http://dx.doi.org/10.1016/S0140-6736(14)60195-1)
8. Dodd PJ, Sismanidis C, Seddon JA. Global burden of drug-resistant tuberculosis in children: a mathematical modelling study. *Lancet Infect Dis.* 2016;16(10):1193-201. DOI: [http://dx.doi.org/10.1016/S1473-3099\(16\)30132-3](http://dx.doi.org/10.1016/S1473-3099(16)30132-3)
9. Kendall EA, Fofana MO, Dowdy DW. Burden of transmitted multidrug resistance in epidemics of tuberculosis: a transmission modelling analysis. *Lancet Respir Med.* 2015;3(12):963-72. DOI: [http://dx.doi.org/10.1016/S2213-2600\(15\)00458-0](http://dx.doi.org/10.1016/S2213-2600(15)00458-0)
10. Marais BJ. The global tuberculosis situation and the inexorable rise of drug-resistant disease. *Adv Drug Deliv Rev.* 2016;102:3-9. PMID: 26855302 DOI: <http://dx.doi.org/10.1016/j.addr.2016.01.021>
11. Ragonnet R, Trauer JM, Denholm JT, Marais BJ, McBryde ES. High rates of multidrug-resistant and rifampicin-resistant tuberculosis among re-treatment cases: where do they come from? *BMC Infect Dis.* 2017;17(1):36. DOI: <http://dx.doi.org/10.1186/s12879-016-2171-1>

12. Graham SM, Sismanidis C, Menzies HJ, Marais BJ, Detjen AK, Black RE. Importance of tuberculosis control to address child survival. *Lancet*. 2014;383(9928):1605-7. PMID: 24671079 DOI: [http://dx.doi.org/10.1016/S0140-6736\(14\)60420-7](http://dx.doi.org/10.1016/S0140-6736(14)60420-7)
13. Liu L, Oza S, Hogan D, Hogan D, Chu Y, Perin J, Zhu J, et al. Global, regional, and national causes of under-5 mortality in 2000–15: an updated systematic analysis with implications for the Sustainable Development Goals. *Lancet*. 2016;388(10063):3027-35. DOI: [http://dx.doi.org/10.1016/S0140-6736\(16\)31593-8](http://dx.doi.org/10.1016/S0140-6736(16)31593-8)
14. Oliwa JN, Karumbi JM, Marais BJ, Madhi SA, Graham SM. Tuberculosis as a cause or comorbidity of childhood pneumonia in tuberculosis-endemic areas: a systematic review. *Lancet Respir Med*. 2015;3(3):235-43. PMID: 25648115 DOI: [http://dx.doi.org/10.1016/S2213-2600\(15\)00028-4](http://dx.doi.org/10.1016/S2213-2600(15)00028-4)
15. Bates M, Mudenda V, Mwaba P, Zumla A. Deaths due to respiratory tract infections in Africa: a review of autopsy studies. *Curr Opin Pulm Med*. 2013;19(3):229-37. DOI: <http://dx.doi.org/10.1097/MCP.0b013e32835f4fe4>
16. Bates M, Shibemba A, Mudenda V, Chimoga C, Tembo J, Kabwe M, et al. Burden of respiratory tract infections at post mortem in Zambian children. *BMC Med*. 2016;14:99. DOI: <http://dx.doi.org/10.1186/s12916-016-0645-z>
17. World Health Organization (WHO). Roadmap for Childhood TB: Toward zero deaths. [accessed 2016 Dec 1]. Available from: <http://www.who.int/tb/publications/tb-childhoodroadmap/en/>
18. Graham SM, Grzemska M, Brands A, Nguyen H, Amini J, Triasih R, et al. Regional initiatives to address the challenges of tuberculosis in children: perspectives from the Asia-Pacific region. *Int J Infect Dis*. 2015;32:166-9. DOI: <http://dx.doi.org/10.1016/j.ijid.2014.12.013>
19. United Nations Children's Fund. Strengthening community and primary health systems for TB: a consultation on childhood TB integration [accessed 2016 Dec 1]. Available from: [https://www.unicef.org/health/files/2016\\_UNICEF\\_Strengthening\\_PHC\\_systems\\_for\\_TB\\_FINAL\\_report\\_\(Web\).pdf](https://www.unicef.org/health/files/2016_UNICEF_Strengthening_PHC_systems_for_TB_FINAL_report_(Web).pdf)
20. Rutherford ME, Hill PC, Triasih R, Sinfield R, van Crevel R, Graham SM. Preventive therapy in children exposed to Mycobacterium tuberculosis: problems and solutions. *Trop Med Int Health*. 2012;17(10):1264-73. DOI: <http://dx.doi.org/10.1111/j.1365-3156.2012.03053.x>
21. Marais BJ, Obihara CC, Warren RM, Schaaf HS, Gie RP, Donald PR. The burden of childhood tuberculosis: a public health perspective. *Int J Tuberc Lung Dis*. 2005;9(12):1305-13.
22. Rangaka MX, Cavalcante SC, Marais BJ, Thim S, Martinson NA, Swaminathan S, et al. Controlling the seedbeds of tuberculosis: diagnosis and treatment of tuberculosis infection. *Lancet*. 2015;386(10010):2344-53. PMID: 26515679 DOI: [http://dx.doi.org/10.1016/S0140-6736\(15\)00323-2](http://dx.doi.org/10.1016/S0140-6736(15)00323-2)
23. World Health Organization (WHO). Guidance for National Tuberculosis Programmes on the Management of Tuberculosis in Children. 2nd ed. Geneva: World Health Organization; 2014.
24. Hill PC, Rutherford ME, Audas R, van Crevel R, Graham SM. Closing the policy-practice gap in the management of child contacts of tuberculosis cases in developing countries. *PLoS Med*. 2011;8(10):e1001105. DOI: <http://dx.doi.org/10.1371/journal.pmed.1001105>
25. World Health Organization (WHO). Guidelines on the management of latent tuberculosis infection. Geneva: World Health Organization; 2015. [accessed 2016 Dec 12]. Available from: [http://www.who.int/tb/publications/tb\\_document\\_page/en/](http://www.who.int/tb/publications/tb_document_page/en/)
26. Marais BJ, Ayles H, Graham SM, Godfrey-Faussett P. Screening and preventive therapy for tuberculosis. *Clin Chest Med*. 2009;30(4):827-46. DOI: <http://dx.doi.org/10.1016/j.ccm.2009.08.012>
27. Kruk A, Gie RP, Schaaf HS, Marais BJ. Symptom-based screening of child tuberculosis contacts: improved feasibility in resource-limited settings. *Pediatrics*. 2008;121(6):e1646-52. PMID: 18519467 DOI: <http://dx.doi.org/10.1542/peds.2007-3138>
28. Triasih R, Robertson CF, Duke T, Graham SM. A prospective evaluation of the symptom-based screening approach to the management of children who are contacts of tuberculosis cases. *Clin Infect Dis*. 2015;60(1):12-8. PMID: 25270649 DOI: <http://dx.doi.org/10.1093/cid/ciu748>
29. Triasih R, Robertson C, de Campo J, Duke T, Choridah L, Graham SM. An evaluation of chest X-ray in the context of community-based screening of child tuberculosis contacts. *Int J Tuberc Lung Dis*. 2015;19(12):1428-34. DOI: <http://dx.doi.org/10.5588/ijtld.15.0201>
30. den Boon S, Matteelli A, Getahun H. Rifampicin resistance after treatment for latent tuberculosis infection: a systematic review and meta-analysis. *Int J Tuberc Lung Dis*. 2016;20(8):1065-71. DOI: <http://dx.doi.org/10.5588/ijtld.15.0908>
31. Fox GJ, Dobler CC, Marais BJ, Denholm JT. Preventive therapy for latent tuberculosis infection-the promise and the challenges. *Int J Infect Dis*. 2017;56:68-76. DOI: <http://dx.doi.org/10.1016/j.ijid.2016.11.006>
32. Mills HL, Cohen T, Colijn C. Community-wide isoniazid preventive therapy drives drug-resistant tuberculosis: a model-based analysis. *Sci Transl Med*. 2013;5(180):180ra49. DOI: <http://dx.doi.org/10.1126/scitranslmed.3007442>
33. Perez-Velez CM, Marais BJ. Tuberculosis in children. *N Engl J Med*. 2012;367(4):348-61. PMID: 22830465 DOI: <http://dx.doi.org/10.1056/NEJMra1008049>
34. Marais BJ, van Zyl S, Schaaf HS, van Aardt M, Gie RP, Beyers N. Adherence to isoniazid preventive chemotherapy: a prospective community based study. *Arch Dis Child*. 2006;91(9):762-5. PMID: 16737993 DOI: <http://dx.doi.org/10.1136/adc.2006.097220>
35. Adjobimey M, Masserey E, Adjonou C, Gbénagnon G, Schwoebel V, Anagonou S, et al. Implementation of isoniazid preventive therapy in children aged under 5 years exposed to tuberculosis in Benin. *Int J Tuberc Lung Dis*. 2016;20(8):1055-9. DOI: <http://dx.doi.org/10.5588/ijtld.15.0493>
36. Triasih R, Padmawati RS, Duke T, Robertson C, Sawyer SM, Graham SM. A mixed-methods evaluation of adherence to preventive treatment among child tuberculosis contacts in Indonesia. *Int J Tuberc Lung Dis*. 2016;20(8):1078-83. DOI: <http://dx.doi.org/10.5588/ijtld.15.0952>
37. Marais BJ. Twelve-dose drug regimen now also an option for preventing tuberculosis in children and adolescents. *JAMA Pediatr*. 2015;169(3):208-10. DOI: <http://dx.doi.org/10.1001/jamapediatrics.2014.3157>
38. TB Alliance. TB Alliance and Partners Announce World's First Availability of Appropriate, Child-friendly TB Medicines in Correct Doses [accessed 2016 Dec 1]. Available from: [www.tballiance.org/news/tb-alliance-announces-worlds-first-appropriate-child-friendly-tb-medicines](http://www.tballiance.org/news/tb-alliance-announces-worlds-first-appropriate-child-friendly-tb-medicines)
39. Roya-Pabon CL, Perez-Velez CM. Tuberculosis exposure, infection and disease in children: a systematic diagnostic approach. *Pneumonia (Nathan)*. 2016;8:23. DOI: <http://dx.doi.org/10.1186/s41479-016-0023-9>
40. TB Online - Desk guide for diagnosis and management of TB in children. [accessed 2016 Dec 1]. Available From: [www.tbonline.info/posts/2016/.../desk-guide-diagnosis-and-management-tb-children/](http://www.tbonline.info/posts/2016/.../desk-guide-diagnosis-and-management-tb-children/)
41. World Health Organization (WHO). Childhood TB Training Toolkit. [accessed 2016 Dec 1]. Available From: [www.who.int/tb/challenges/Child\\_TB\\_Training\\_toolkit\\_web.pdf](http://www.who.int/tb/challenges/Child_TB_Training_toolkit_web.pdf)

42. Fox GJ, Schaaf HS, Mandalakas A, Chiappini E, Zumla A, Marais BJ. Preventing the spread of multidrug-resistant tuberculosis and protecting contacts of infectious cases. *Clin Microbiol Infect.* 2017;23(3):147-53. DOI: <http://dx.doi.org/10.1016/j.cmi.2016.08.024>
43. Brigden G, Furin J, Van Gulik C, Marais B. Getting it right for children: improving tuberculosis treatment access and new treatment options. *Expert Rev Anti Infect Ther.* 2015;13(4):451-61.
44. Seddon JA, Schaaf HS. Drug-resistant tuberculosis and advances in the treatment of childhood tuberculosis. *Pneumonia (Nathan).* 2016;8:20. DOI: <http://dx.doi.org/10.1186/s41479-016-0019-5>
45. The Union. Childhood MDR TB for healthcare workers: an on-line course. [accessed 2016 Dec 1]. Available From: <https://childhoodtb.theunion.org/courses/CTB2/en/intro>
46. Nachman S, Ahmed A, Amanullah F, Becerra MC, Botgros R, Brigden G, et al. Towards early inclusion of children in tuberculosis drugs trials: a consensus statement. *Lancet Infect Dis.* 2015;15(6):711-20. DOI: [http://dx.doi.org/10.1016/S1473-3099\(15\)00007-9](http://dx.doi.org/10.1016/S1473-3099(15)00007-9)
47. TB Alliance Childhood. TB - Call to action. [accessed 2016 Dec 1]. Available from: <http://www.tballiance.org/downloads/children/Childhood-TB-Call-to-Action.pdf>