

A bitter pill to swallow: the need for better medications for drug-resistant tuberculosis in children

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SUMMARY

The large and growing access gap between the number of children who become sick with drug-resistant tuberculosis (DR-TB) and those who are treated for the disease each year represents a significant health systems failure. While there are multiple reasons why children with DR-TB are not diagnosed and treated, a serious challenge is the medications used to treat the disease. This paper presents three child DR-TB cases who were treated incorrectly; the cases are used to illustrate some of the problems with existing second-line medications. Challenges, including the perception that the drugs are more dangerous than the disease, lack of

proper dosing recommendations and formulations, and the high cost of current treatment, all contribute to a perverse situation in which the most vulnerable pediatric patients are provided with a lower standard of care. This situation can be reversed with novel partnerships and training models, pharmacokinetic studies of the relevant drugs, increased collaboration, and dedicated funding, grounded in a rights-based approach to DR-TB in children.

KEY WORDS: children; medication; drug-resistant TB; access

ALTHOUGH THERE IS DEBATE about the number of children who become sick with drug-resistant tuberculosis (DR-TB) each year,^{1,2} there is little doubt that only a small proportion of these are offered appropriate treatment.³ The gap in access to treatment for children with DR-TB is at a crisis level.⁴ Coordinated efforts are underway to address the diagnostic barriers that limit access to care among children with DR-TB.⁵ However, there has been little attention given to improving the medications used to treat and prevent DR-TB,⁶ including some of the newly approved medications. This has serious consequences for tens of thousands of children each year.⁷

This paper presents three cases that illustrate some of the problems with the existing medications for treating DR-TB and explore how these drug-related problems contribute to the growing pediatric DR-TB treatment gap. Addressing these issues will result in more children being offered effective, safe and more tolerable interventions for DR-TB.

CASE 1

TG is a 2-year-old child (weight 9 kg) diagnosed with DR-TB 2 weeks after his father started treatment for DR-TB. His chest radiograph (CXR) revealed infiltrative disease. An induced sputum sample was obtained and was positive for *Mycobacterium tuberculosis* with rifampin (RMP) resistance. In addition to kanamycin 150 mg/day (15–20 mg/kg) intramuscular injections, TG was prescribed the regimen given in Table 1.⁸ As the pharmacy only had adult formulations, the tablets had to be split, crushed and mixed with powdered milk by the nurses every day. The nursing staff were worried about administering the medications, especially cycloserine, which comes in capsule form and had to be opened and half the contents added to milk. At a weight of 9 kg, tablets administered whole or divided in half would not give the recommended mg/kg dose (Table 1).

TG did well and gained 3 kg in 6 weeks. He was continued on the same dosage despite the weight increase, as it was easier to prepare due to the size of

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Article submitted 2 May 2015. Final version accepted 13 August 2015.

Table 1 Bodyweight doses (mg/kg) of oral second-line medications in a child treated for drug-resistant tuberculosis

	Available strength and formulation	Recommended dosing range (mg/kg) ⁸	Child's weight: 9 kg		Child's weight: 12 kg	
			mg/kg dose with ½ tablet/capsule	mg/kg dose of 1 tablet/capsule	mg/kg dose with ½ tablet/capsule	mg/kg dose of 1 tablet/capsule
Levofloxacin	250 mg tablet	15–20	13.9	27.7*	10.4*	20.8*
Ethionamide	250 mg tablet	15–20	13.9	27.7*	10.4*	20.8*
Cycloserine	250 mg capsule	15–20	13.9	27.7*	10.4*	20.8*
Ethambutol	400 mg tablet	15–25	22.2	44.4*	16.7	33.3*
Pyrazinamide	500 mg tablet	30–40	27.8	55.5*	20.8*	41.7*

* Outside the recommended range.

the adult formulations. The nurses began training TG's mother and the health center staff on administering the medication. The staff at the health center were reluctant to take on the additional work required to treat TG in the community, and a decision was taken to keep him in the hospital for treatment. After 3 months, his family had to move to live with relatives in another city, as they became homeless when TG's father was hospitalized. TG's prescriptions and instructions for administering the drugs were sent to the hospital in the new location, but a nurse there reports that 'the family never brought TG over for treatment'.

CASE 2

PM was a 20-month-old child admitted to emergency care due to loss of consciousness and seizures. His aunt, now his primary care giver since the death of his mother 2 months before, reported he was well until 6 weeks before, when he had stopped eating and 'seemed irritable all the time'. He had been taken to his local health center 2 days before for persistent vomiting, where he was treated with oral rehydration solution and sent home. However, PM became progressively lethargic, refusing to take anything orally, and had been sleeping for the past 24 hours. That evening the aunt found him fitting. His CXR showed diffuse, nodular infiltrates, consistent with primary, progressive TB. Human immunodeficiency virus (HIV) test results were negative and a lumbar puncture was unsuccessful. On further questioning, his aunt produced PM's mother's TB treatment card, which revealed that she was being treated for DR-TB. A diagnosis of miliary TB and tuberculous meningitis was made, and PM was admitted to the hospital and started on treatment for drug-susceptible TB. In the light of his close contact with a DR-TB patient, his clinical team contacted the National TB Program (NTP) for second-line drugs (SLDs). They were referred to the country's national TB guidelines and told that 'because of the risks associated with their use and the high costs of these medications, SLDs can only be given in cases of confirmed multidrug-resistant TB (MDR-TB)'. The treating team attempt-

ed another unsuccessful lumbar puncture and obtained a gastric lavage. PM died awaiting culture results, which came back negative.

CASE 3

RT is a 3-year-old, previously healthy child from a high DR-TB burden setting. She was admitted to the in-patient ward of a large urban teaching hospital with cervical lymphadenopathy, a 1-month history of poor food intake and reduced playfulness. She had no household contacts with known or presumed TB patients. A cervical lymph node biopsy was sent for Xpert[®] MTB/RIF (Cepheid, Sunnyvale, CA, USA) testing, culture, and pathology. Three days later, the Xpert test performed on the lymph node specimen confirmed the presence of *M. tuberculosis* with RMP resistance.

Further review identified no TB exposure and no identifiable risk factors for DR-TB. RT was diagnosed with TB lymphadenitis. In the absence of a known DR-TB contact, her treating team assumed that the RMP resistance result was false-positive. Her medical notes document that 'given the multiple risks and adverse events associated with the SLDs used to treat MDR-TB and the lack of a known contact, the risks of treating for MDR-TB in this patient outweigh the likely benefits'. By consensus, she was placed on drug-susceptible anti-tuberculosis treatment and her condition monitored. She showed little improvement, and the cultured sample from her lymph node became contaminated, yielding no additional results. RT's health continued to deteriorate and she was transferred to a private facility for additional care.

These cases demonstrate unnecessary morbidity and mortality due to DR-TB in children, where suboptimal treatment decisions were made despite strong evidence and policy recommendations.^{9–14} Why did these children suffer needlessly? Certainly there is the need for better diagnostics and dissemination and application of global guidelines,¹⁵ but these cases—and many others like them—suggest that the treatment regimen itself is a barrier to the appropriate treatment of children with DR-TB.

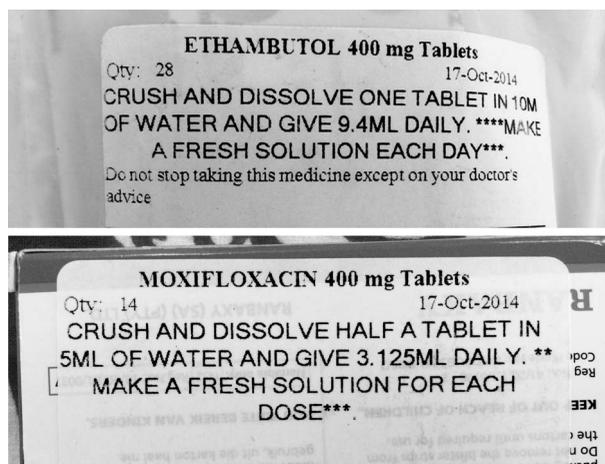


Figure Sample prescriptions for a child being treated for drug-resistant tuberculosis. This image can be viewed online in color at <http://www.ingentaconnect.com/content/iatld/ijtld/2015/00000019/000012s1/art00012>

PERCEPTIONS OF 'RISKY TREATMENT': PROBLEMS WITH CURRENT SECOND-LINE DRUGS

Long duration and poor tolerability and safety of current treatment regimens

The treatment of DR-TB requires the administration of several second-line medications for prolonged periods (18–24 months).¹⁶ These medications have a substantial risk of adverse events, including hearing loss, peripheral neuropathy, seizures, psychosis, hypothyroidism, renal failure, and liver toxicity.¹⁷ Children have lower rates of adverse events than adults, although the potential impact of hypothyroidism and hearing loss on a developing child is likely to be more significant.¹⁸ Exposing children to these risks is intimidating, especially when compared with treatment for drug-susceptible TB, which is usually well tolerated.¹⁹ The potential risks of the medications often outweigh the consequences of delaying a diagnosis of DR-TB when making treatment decisions.²⁰ In addition to the risk of adverse events, current MDR-TB treatment requires the administration of a daily injection,²¹ which may cause both physical pain and have psychosocial consequences for children, their care givers and treatment providers.²² Another drawback of the current treatment regimen is the length of treatment: a 2-year treatment period may not be justified in children with minimal disease. Finally, better drugs are needed to simplify regimen composition, as the perceived complexities in regimen design and treatment delivery can be barriers to the initiation of appropriate treatment among children with, or at very high risk of having, DR-TB. Although many of these challenges are also faced when treating adults, and a large amount of work is ongoing to improve DR-TB treatment in adults, these problems are likely

to have a greater impact on treatment uptake in children. Bacteriological confirmation of TB disease in children remains a challenge, with only 30–40% of children with TB expected to obtain confirmed results. This means that 60–70% of children with DR-TB should be prescribed treatment based on the clinical risk of having DR-TB, especially in case of contact with infectious DR-TB patients or the failure to respond to conventional anti-tuberculosis treatment. These challenges make it difficult for health care providers to prescribe prolonged, poorly-tolerated regimens in children (Table 2). As in the cases described, many children may ultimately not receive treatment as a result, and will have poor outcomes.

Lack of pharmacokinetic and safety data in children

Data on both the pharmacokinetic and pharmacodynamic properties of SLDs in children are scarce, and current pediatric dosages for these medications are extrapolated from adult data. The lack of formal dosing recommendations from the World Health Organization (WHO) for the pediatric use of these drugs is another barrier to the development of child-friendly formulations. Such recommendations need to be based on pharmacokinetic findings. Without WHO dosing recommendations, companies will be reluctant to invest fully in developing pediatric SLD products.

Lack of child-friendly formulations

Not only are existing medications for the treatment of DR-TB associated with toxicity, they are also not available in child-friendly forms for preparation or administration.²³ The need for child-friendly formulations of first- and second-line anti-tuberculosis medications is examined in an article by Taneja et al. in this Supplement.²⁴ Preparing existing medications for pediatric use is intimidating for programs and providers, and may contribute to the DR-TB treatment gap.²⁵ Tablets need to be weighed, cut (even when unscored), crushed, and mixed with food or drinks in which they do not completely dissolve. This can interfere with drug bioavailability (Haraus L, et al. unpublished), and often leads to under- or over-dosing. Furthermore, as different foodstuffs are used to mix the medications, depending on the area of residence and socio-economic status of the child, this may also affect bioavailability. Furthermore, inappropriate formulations are unpalatable and can compromise adherence among patients on this already long and difficult treatment.²⁶ Lack of child-friendly formulations can result in inappropriate prescriptions of SLDs (Figure). While there has been global investment in child-friendly formulations of first-line drugs,²⁷ little has been done to move child-friendly SLD prototypes into the field.

Table 2 Key challenges and action steps for ensuring equitable access to treatment for DR-TB in children

Key challenges	Action steps	Comments
Requirement for culture confirmation of DR-TB before initiating treatment in children	Allow high-risk children to start treatment while awaiting confirmation Ensure children who meet the definition of probable DR-TB can and do start treatment Develop clear operating procedures for when treatment can be started Use of more sensitive diagnostics methods in children (i.e., molecular tests vs. smear microscopy)	
Lack of PK data on SLDs in children	Continue funding studies to assess PK and PD profiles of SLDs in children Ensure all newly developed medications assess PK and PD parameters in children as early in the development phase as possible	
Lack of children-friendly SLD formulations	Encourage companies to develop child-friendly formulations Establish profiles of existing and novel formulations of SLDs when mixed with locally available foodstuffs	
AE profiles of existing SLDs	Reinforce training that children have fewer AEs than adults and generally tolerate treatment well Include children in assessments of better tolerated regimens	Hearing loss due to the injectable agent may have a more significant impact on a developing child than an adult
High costs of pediatric SLDs	Negotiate equivalent pricing for adult and pediatric formulations of SLDs Develop incentives or subsidies for national TB programs to procure pediatric formulations of SLDs	Successful models can be found in pediatric antiretroviral therapy
Need for better training in pediatric DR-TB for stakeholders at all levels	Expand global efforts for training in pediatric DR-TB using a variety of methods and tools Ensure pediatric DR-TB training included in all programmatic management of DR-TB funding proposals and plans	
Need for improved international collaboration and advocacy on pediatric DR-TB	Continue to strengthen global efforts to improve management of DR-TB in children; Consider the development of specific pediatric DR-TB task force within existing global collaborative efforts	Pediatric HIV/ART task forces and collaborative groups have had success in addressing similar challenges and could be used as models for pediatric DR-TB

DR-TB = drug-resistant tuberculosis; PK = pharmacokinetics; SLD = second-line drug; PD = pharmacodynamics; AE = adverse event; HIV = human immunodeficiency virus; ART = antiretroviral therapy.

High cost of existing medications

The high cost of existing DR-TB medications directly impacts children.²⁸ Although a considerable effort has been made to reduce the cost of SLDs,²⁹ real world budgetary constraints may lead to these drugs effectively being ‘rationed’ for those with confirmed disease.³⁰ Furthermore, the amount of medication needed for children of different weights may be difficult to build into existing forecasting and procurement methods and, once again, leaves children out of DR-TB treatment plans. Even where pediatric formulations can be made, or already exist, the cost and trouble involved in registering and supplying these medications to a relatively small number of children in many countries is a substantial barrier to making them accessible in the field.

The shortcomings of existing DR-TB drugs are perhaps most apparent in the area of treatment for latent DR-TB infection. Multiple studies have shown that children in households of DR-TB patients are at high risk of developing TB.^{31–33} It would be logical to assume that preventive therapy—which is highly effective in reducing morbidity and mortality due to drug-susceptible TB among children receiving isoniazid³⁴—would also be effective in treating latent DR-

TB infection. Several observational studies have reported on the benefits of administering SLD preventive therapy among children exposed to infectious DR-TB.^{35,36} Randomized controlled trials evaluating preventive therapy in children exposed to MDR-TB have been planned; however, the lack of child-friendly formulations, lack of clear dosing recommendations and cost of existing medications available for this purpose could complicate the uptake of preventive therapy should these trials show benefit.

Increasing benefit: collaboration to erase the treatment gap

Although the current medications used to treat DR-TB give rise to multiple problems that contribute directly to the treatment gap, there is also great potential for change. Any change will, however, require collaboration between researchers, clinicians, the industry, NTPs, ministries of health, and non-governmental organizations; some model coalitions are already seeing success.³⁷ For these collaborations to effectively impact the treatment regimens available for children with DR-TB, some key input is necessary.

First, active partnerships between governments, NTPs, and front-line providers are needed. The cases presented in this paper illustrate that the policies, information and confidence needed to offer children appropriate DR-TB treatment are frequently lacking, even in well-established MDR-TB treatment programs. A clinic and community-based training and technical assistance model that supports families and providers in decision making about how best to treat children affected by this disease may be better able to address some of these issues. To do this, funding to support non-traditional capacity-building efforts—as well as clinical research efforts—specifically in children with DR-TB should be made available. All too often, children with DR-TB fall through the cracks, as DR-TB is not considered a serious child health problem, and children are not considered a priority population in DR-TB programs. This has been the case in efforts to find better drugs to treat child DR-TB. There also needs to be a financial commitment to ensure that the necessary products are developed and that these are priced at a level that ensures that they can be procured. There should be commitment to ensure that treatment for children with DR-TB is rights-based rather than driven by market forces or public health principles. Such approaches have led to the current untenable situation, and are not the best way to address the need for better medications in this vulnerable population.

Finally, there is an urgent need to include children in research on new drugs and treatment regimens; this topic is covered in detail in an article by Murray et al. in this supplement.³⁸ It is unlikely that the treatment gap in pediatric DR-TB will disappear without new, more effective and less toxic agents and regimens. The standard model is to first determine efficacy in adults, who have different patterns of disease than children, and this strategy might overlook a shorter or more effective regimen that could benefit children.

CONCLUSIONS

This paper shows that there are several limitations to the existing regimens used to treat DR-TB and that toxicity, formulations, and cost challenges of the existing SLDs may directly contribute to the widening pediatric DR-TB treatment gap. These challenges, ironically, end up setting the bar higher for the diagnosis and initiation of DR-TB treatment in children, where bacteriologic confirmation of disease is the exception rather than the rule. A recommitment to the ethical principles of treatment, access to fresh funding sources, and both setting and meeting measurable global targets is needed to obtain better medications for children who need them most. This is

not just about better and more convenient products—children's lives depend on it.

Conflicts of interest: none declared.

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RESUME

Le fossé vaste et croissant entre le nombre d'enfants qui contractent une tuberculose pharmacorésistante (TB-DR) et ceux qui sont traités pour cette maladie chaque année représente un échec significatif du système de santé. S'il y a de multiples raisons pour qu'un enfant atteint de TB-DR ne soit ni diagnostiqué ni soigné pour sa maladie, les médicaments utilisés pour son traitement posent un défi important. Cet article présente les cas de trois enfants atteints de TB-DR qui ont reçu un traitement inapproprié et utilise ces cas afin d'illustrer certains des problèmes liés aux médicaments de deuxième ligne existants. Les défis, notamment la

perception que les médicaments sont plus dangereux que la maladie, l'absence de recommandations relatives au bon dosage et aux formulations et le coût élevé du traitement actuel, contribuent tous à une situation perverse dans laquelle les patients pédiatriques les plus vulnérables reçoivent des soins de moins bonne qualité. Cette situation peut être renversée grâce à des nouveaux partenariats et à des modèles de formation, à des études pharmacocinétiques des médicaments concernés, à davantage de collaboration et à un financement dédié, tous fondés sur une approche de la TB-DR de l'enfant basée sur les droits.

RESUMEN

El desfase amplio y progresivo entre el número de niños que contraen la tuberculosis farmacorresistente (TB-DR) y el número de niños que reciben tratamiento por esta enfermedad cada año indica un fallo considerable de los sistemas de salud. Existen múltiples razones por las cuales no se diagnostica la TB-DR en los niños y no se les administra el tratamiento, pero un problema grave consiste en la elección de los medicamentos para tratar la enfermedad. En el presente artículo se presentan los casos de tres niños con diagnóstico de TB-DR que recibieron tratamiento inadecuado y, a partir de estos casos, se analizan algunas de las dificultades que plantean los medicamentos actuales de segunda línea. Los obstáculos como la percepción de que los

medicamentos son más peligrosos que la enfermedad, la falta de directrices de dosificación adaptadas y de formulaciones apropiadas y los altos costos del tratamiento actual favorecen la creación de una condición adversa en la cual los pacientes pediátricos más vulnerables reciben una atención de calidad inadecuada. Esta situación se puede invertir con la creación de nuevas alianzas y la propuesta de módulos de capacitación, la realización de estudios farmacocinéticos de los medicamentos de interés, una mayor colaboración y la obtención de financiamientos específicos; todas las iniciativas se deben fundamentar en enfoques basados en los derechos, dirigidas a la TB-DR de los niños.
