

Pediatric tuberculosis drug market: an insider perspective on challenges and solutions

I. Usherenko,* U. Basu Roy,[†] S. Mazlish,[†] S. Liu,[†] L. Benkoski,[†] D. Coutts,[†] S. Epstein,[†] M. Qian,[†] S. Rafiq,[†] C. Scott[†]

*The Global Alliance for TB Drug Development, New York, New York, [†]The Solutions Lab, New York University, New York, New York, USA

SUMMARY

Representative stakeholders were consulted on how they felt access to pediatric tuberculosis (TB) drugs could be improved. A key recommendation is the development of new child-friendly, adequately dosed formulations with a good shelf life in all climate zones. There is also an urgent need to improve the diagnosis and reporting of children with TB. Manufacturers of pediatric TB medications are to be incentivized through improved

coordination among all stakeholders, with streamlined regulatory approvals and increased consumer education on drug and regimen guidelines. Finally, pooled procurement is advised to ensure sustained market supply against affordable prices.

KEY WORDS: access to medicines; supply chain; procurement; market sustainability

TUBERCULOSIS (TB) exerts a heavy toll on children worldwide, a problem that is aggravated by poor access to suitable medication. Improving the supply of pediatric TB treatments through enhanced coordination and an increased focus on critically failing links in this chain could significantly reduce TB prevalence and mortality among children. To begin this process requires an understanding of what the various partners in the supply process see, from their perspective, as the largest obstacles and how these could be overcome (Figure 1).

METHODOLOGY

In-depth, open-ended interviews pertaining to specific aspects of the pediatric TB drug market were conducted to understand the different stakeholders' perspectives. The interview instrument is available on request. The consulted key opinion leaders (KOLs) included four manufacturers (MF), three non-profit organizations (NPOs), and representatives from two non-governmental organizations (NGOs). These specific KOLs were interviewed due to their direct experience of the TB treatment market. The comments made by interviewees and cited in the paper were based on their experience and represents the opinion of the respondent. The anonymized responses were contextualized with rigorous secondary research.

Pediatric TB: under-diagnosed, under-reported, poorly serviced and inappropriately treated

TB affects both adults and children, but symptoms are less specific in the latter, making diagnosis difficult and contributing to an underestimation of pediatric TB incidence. Moreover, not all cases are reported to the World Health Organization (WHO).¹

The WHO guidelines for treating children (age <15 years) were revised in 2010² and recently updated.³ The recommendations are based on the four first-line drugs that are used in adults, with dosing adapted according to the child's weight and treatment phase. Because of a lack of data, there is a gap in the guidelines for young babies weighing <5 kg. Yet the 'number of children in this weight bracket could be considerable' (NPO2).

Pediatric dosing guidelines are usually based on observations in adults; generally speaking, drug exposure in children cannot be (safely) extrapolated from adult data.^{4,5} Pharmacokinetics often differs qualitatively between adults and children and even between children from different age categories, and dosing needs to be established in clinical trials. Moreover, many drugs present specific safety problems in children, including treatment for TB.⁶ Clinically established safe, effective dosings for pediatric TB medications are often unknown.

This combination of inadequate pediatric diagnosis and treatments is a frustrating 'chicken-and-egg problem' (NPO1) that hinders the discovery of

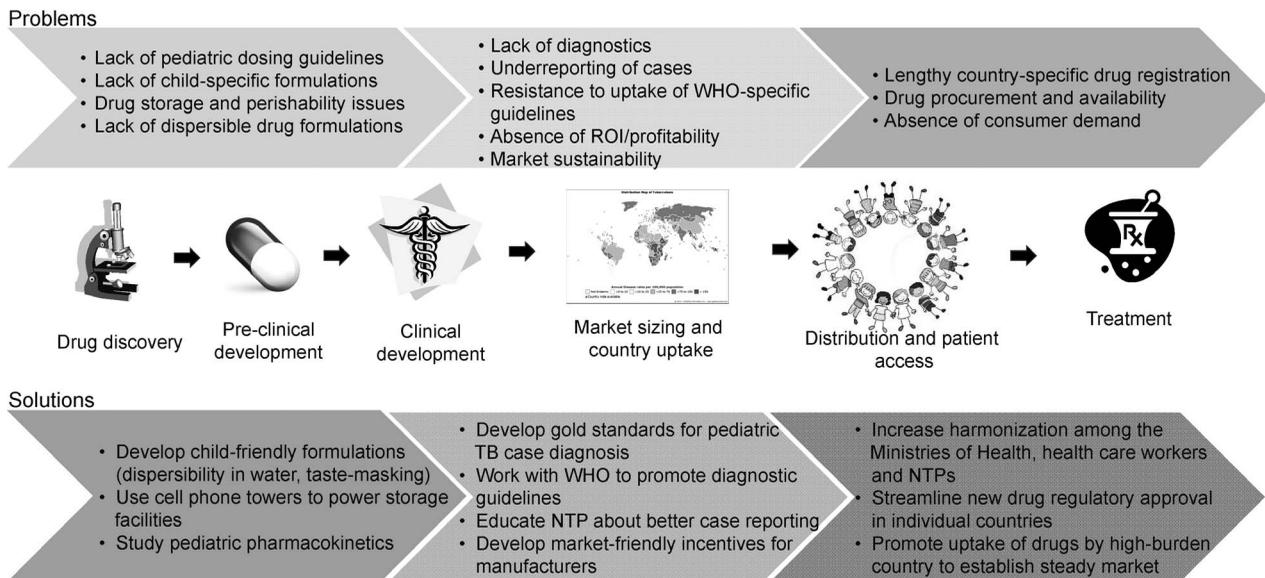


Figure 1 Problems in the pediatric tuberculosis drug pipeline and possible solutions identified by key opinion leaders. WHO = World Health Organization; ROI = return on investment; NTP = national TB control program. This image can be viewed online in color at <http://www.ingentaconnect.com/content/iatld/ijtld/2015/0000019/000012s1/art00005>

urgently needed drugs.⁷ Clinical trials in children are difficult to perform due to practical, safety and ethical considerations.^{8,9} ‘Children could potentially be included’ (MF2) in the many TB trials that are ongoing for adults, but testing medications in children is often ‘forbidden, and there are no drugs to compare with’ (MF1).

Another problem is that tablet strengths and formulations are designed for adults. No appropriately dosed, child-friendly formulations have been developed since the revised 2010 WHO guidelines. As a stopgap solution, ‘adult’ tablets are crushed and portioned, potentially resulting in dosing errors. Taste-masking formulations are urgently needed to prevent treatment failures due to interruptions of the 6-month curative regimen; children are particularly responsive to the bitter taste of most TB drugs. ‘They will spit it out’ (MF4), and the problem of the taste is worsened when the tablets are crushed. There has been significantly more progress in developing taste-masking formulations for malaria and human immunodeficiency virus (HIV) infection than for TB; ‘pediatric TB drugs are more difficult to make’ (NGO2). Other aspects of acceptability, such as dosing frequencies and tablet texture, size and volume, also impact children’s preferences.¹⁰ To increase adherence and to prevent the spread of drug resistance associated with monotherapies, the WHO and the International Union Against Tuberculosis and Lung Disease (The Union) recommend that the three to four anti-tuberculosis drugs that make up the first-line regimen be formulated in fixed-dose combinations (FDCs).¹

One approach to making anti-tuberculosis drugs more child-friendly that was emphasized by many

KOLs is to make tablets dispersible. Adult-sized tablets and capsules are often difficult for children to swallow, but uncoated formulations that homogeneously disperse within 3 min in water or in a small quantity of breast milk offer numerous advantages. Although this is ‘technically challenging’ (MF1), such tablets can be ‘dissolved in food materials to mask taste’ (MF4) and ‘improve dosing accuracy and adherence’ (NGO2).

Another ‘important aspect of formulation is storage’ (MF3), particularly when tablets include rifampin (RMP), which is ‘highly susceptible to degradation’ (MF3). It is recommended to store all four first-line anti-tuberculosis drugs (ethambutol, isoniazid [INH], pyrazinamide [PZA] and RMP) at ‘room temperature’. The general International Conference on Harmonization (ICH) guidelines are primarily intended for climatic zones I/II (cool, temperate),¹¹ but pediatric TB occurs in less-than-ideal ‘hot and humid conditions’ (NGO2), where suspensions and syrup formulations are even more perishable. Quality loss due to inappropriate storage has been reported in India¹² and Thailand.¹³ The main problems in formulation and availability identified by KOLs are summarized in Figure 2.

MARKET SIZING AND DYNAMICS

Problems with reporting pediatric TB cases

According to the WHO, at least 550 000 children became infected with TB in 2013.¹⁴ However, this number is most likely an underestimate due to a lack of surveillance, mis-diagnosis and under-reporting.¹⁰ Suppliers of TB treatments rely on data from health management and logistics information systems from

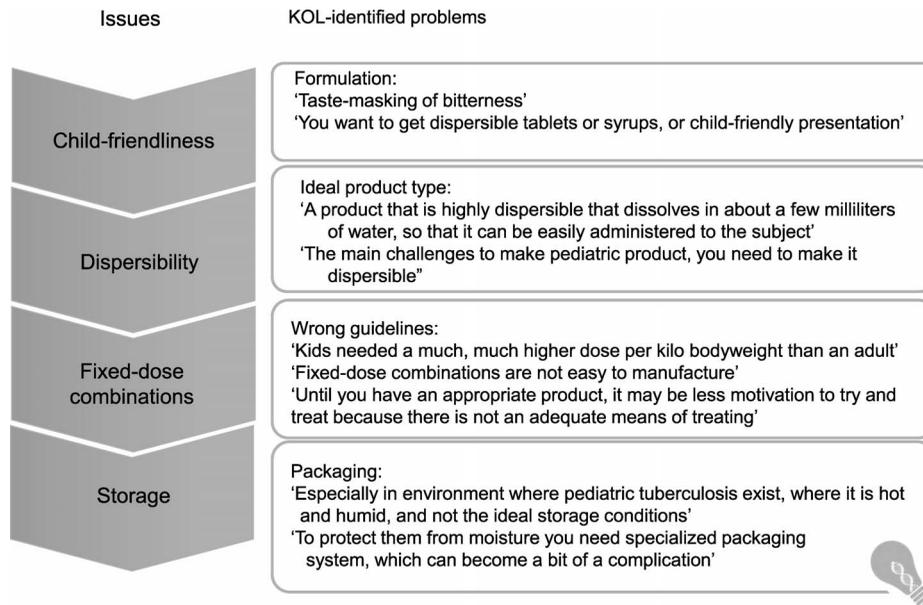


Figure 2 Issues in pediatric tuberculosis drug formulation and availability, as identified by KOLs. KOL = key opinion leader.

National TB Control Programmes (NTPs), which are in turn informed by clinicians; unfortunately this channel of information is extraordinarily underdeveloped. Manufacturers therefore struggle with evaluating their potential return on investment (ROI), and 'lack clarity on the extent that the sunk development costs can be recovered' (MF3); they need to be sure they are 'making drugs for the right type and number of patients' (MF2).

Due to shortages in training personnel and equipment and lack of agreed criteria, 'TB in children is often misdiagnosed as pneumonia' (MF1). Good diagnostics are also 'essential to monitor the efficacy of treatments' (MF4). One source of the problem was illustrated in a recent study that found a wide variation (6.9–89.2%) in the frequencies of TB cases diagnosed with nine structured diagnostic systems.¹⁵ The adult sputum test does not work well, and there is no effective, standard diagnostic procedure for TB in children.¹⁶

Even when the appropriate TB diagnosis is made, 'there is no proper reporting to the WHO' (NPO2). The reasons are, first, that TB-infected children are not highly infectious and are therefore not a health priority. Second, the 22 high-burden countries (HBCs) that represent 80% of all TB cases are generally poor and inadequately educated about the disease, which occurs in communities with limited access to health services and reporting channels. Finally, health care workers often lack adequate training.

It was recently reported that NTPs in 15 HBCs notify only 35% of the actual estimated pediatric cases with active TB and latent tuberculous infection (LTBI).¹⁷ This extrapolates into more than 53 million TB-infected children in the 22 HBCs (both active TB and LTBI). The

same study also identified the high proportion of children who are exposed to TB but are not reported, which is evident from the significant correlation between adult and pediatric cases (Figure 3):

We forget that children living with adult patients are the first to get infected. When an adult comes to the doctor, the easiest thing to do is to ask him/her about their children. That way we can nip the problem in the bud (MF4).

Deciding on pediatric treatments that work and the adoption of guidelines

Along with its 2010 guidance for the treatment of pediatric TB, the WHO recommended the procurement of prequalified pediatric anti-tuberculosis drugs for this purpose.² However,

...most of the information about pediatric formulations has come from trial and error. When [manufacturers] started manufacturing, [they] did not know what would work and what wouldn't. [They] were working on the assumption that (since it worked for adults), it should work for children. That's why [we] find it difficult to sell a formulation in another country. [We] need to convince them that this will work (MF4).

Once a reliable market size estimate has been made and unified treatment guidelines have been published, it is important for HBCs to 'adopt the WHO guidelines, in such a way that it provides a meaningful market to the manufacturers' (NPO2).

Estimating the pediatric TB market

Based on current median pediatric TB case estimates and a WHO-prescribed four-drug regimen for 6

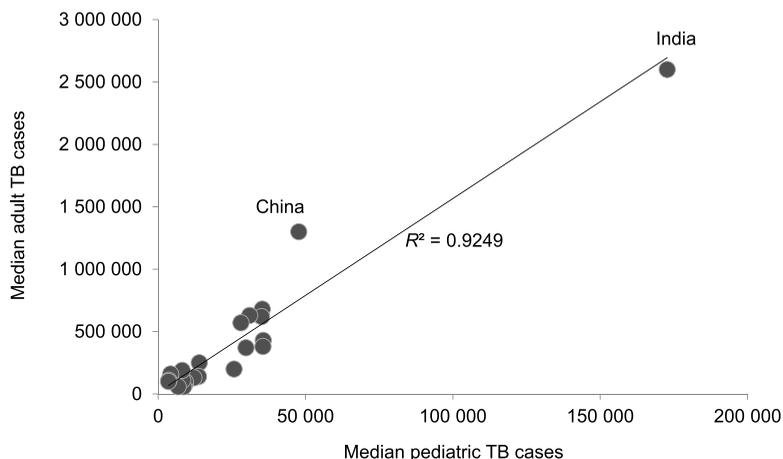
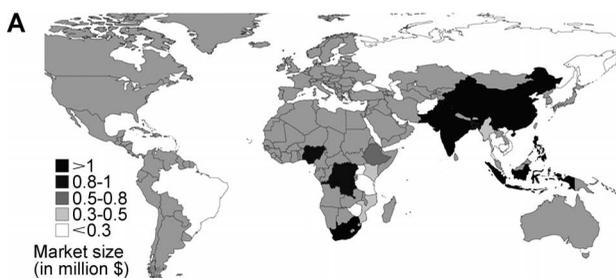


Figure 3 Correlation between median adult¹⁴ and pediatric TB cases¹⁷ for 22 high-burden countries. TB = tuberculosis.

months at a price of US\$30.58,¹⁸ the current pediatric TB market is estimated to be US\$17.4 million in the 22 HBCs (Figure 4A), while a 6-month regimen of INH/RMP/PZA totals US\$11 million (Figure 4B). While both estimates may seem small compared to other pediatric drug markets such as HIV (US\$92 million for 2012),¹⁹ they are not an accurate reflection of true market size due to errors in diagnosis and reporting. A more realistic estimate would probably reach US\$30–40 million for the four-drug regimen in the 22 HBCs, based on a median margin of error of 50% in diagnosis. Because of the uncertainties in our understanding of present and future patient needs, today’s perception is that

‘..companies (like us) don’t see it rewarding enough profit-wise to make these products’ [M3].

Because of the small market, manufacturers ‘need to know data that can guarantee any ROI’ (MF2). Finally, because the pediatric TB drug market is spread out globally, with the highest burden of the disease in specific regions of the world, it may be preferable to have limited numbers of entrants populate the market so that it remains sustainable. It is not ideal to ‘encourage many companies to enter the marketplace because we want this to be a sustainable market’ (NPO2). However, manufacturers ‘...do not want only one manufacturer since [they] cannot keep up with the demand. Ideally, we



COUNTRY	Without ethambutol	With ethambutol
Afghanistan	0.2	0.3
Bangladesh	0.6	0.9
Brazil	0.1	0.1
Cambodia	0.2	0.3
China	0.9	1.4
Democratic Republic of Congo	0.6	0.9
Ethiopia	0.5	0.8
India	3.3	5.2
Indonesia	0.7	1.1
Kenya	0.2	0.4
Mozambique	0.3	0.4
Myanmar	0.3	0.4
Nigeria	0.5	0.8
Pakistan	0.7	1.1
Philippines	0.7	1.1
Russian Federation	0.1	0.1
South Africa	0.7	1.1
Tanzania	0.2	0.3
Thailand	0.1	0.1
Uganda	0.2	0.3
Viet Nam	0.2	0.2
Zimbabwe	0.1	0.2
TOTAL	11	17.4

Figure 4 **A)** Distribution of the pediatric anti-tuberculosis drug market in the 22 high-burden countries based on a WHO-prescribed isoniazid/rifampicin/pyrazinamide/EMB regimen for 6 months at a price of US\$30.577. **B)** Pediatric anti-tuberculosis drug market size (in millions of US\$) for the regimens without (US\$19.160) and with (US\$30.177) EMB, based on data from the Stop TB Partnership’s Global Drug Facility. WHO = World Health Organization; EMB = ethambutol. This image can be viewed online in color at <http://www.ingentaconnect.com/content/ijtd/2015/00000019/000012s1/art00005>

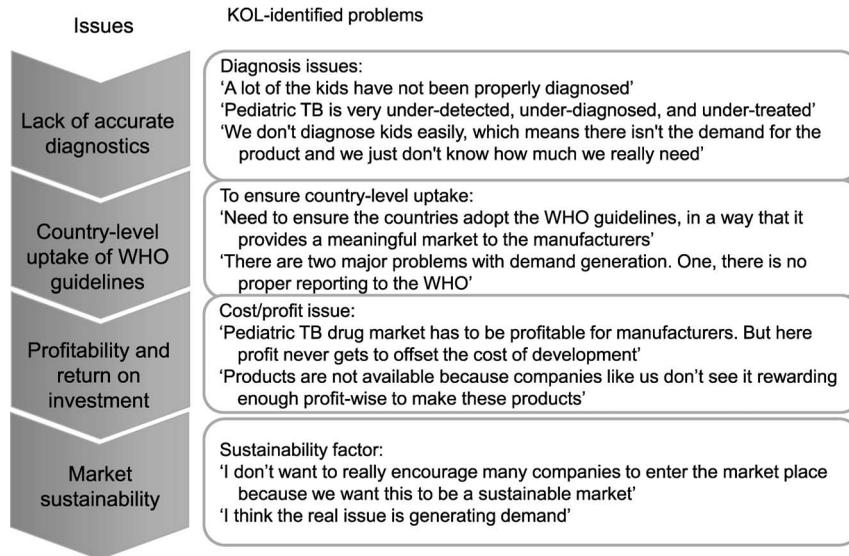


Figure 5 Issues in pediatric TB drug market sizing and dynamics. KOL = key opinion leader; TB = tuberculosis; WHO = World Health Organization.

would want to have a few manufacturers who ensure that a steady supply of good quality drugs are maintained and there is a cost-sharing mechanism' (MF4).

The main issues identified by KOLs for this area are summarized in Figure 5.

PRODUCT UPTAKE AND DEMAND CREATION

Delays in adopting the new guidelines

The interviewees felt that the low uptake of pediatric TB treatments was a major concern. One of the main reasons for the problem is the incomplete implementation of the new (2010 WHO) guidelines, chiefly because of a lack of awareness among health care workers who diagnose and treat potential pediatric TB cases. This is exacerbated by a lack of WHO-recommended FDCs for first-line pediatric anti-tuberculosis drugs, and a lack of dosage data for the development of appropriate pediatric formulations for multidrug-resistant TB (MDR-TB),²⁰ due to 'guidelines changing faster than new formulations were able to be developed' (NGO2). One example of the lack or delay of synchronization between guidelines being issued and care provided was a recent finding that only 55% of private health care workers (the main category of care providers) in one urban area in Western India, Pune, Maharashtra, were aware of the International Standards of TB Care through the Indian Revised National Tuberculosis Control Programme, although the revised programme's inception dates back to 2002.²¹

In this changing landscape of new guidelines and treatments, the sustained education of health care workers on correct drug and regimen guidelines is a key driver of product uptake and demand creation.

Country-specific drug registration and national manufacturing preferences

The national uptake of pediatric anti-tuberculosis drugs requires each drug to be registered with each country. Each country has its own set of requirements, resulting in serious administrative burdens and delays in gaining permission.

A significant improvement was the introduction by the WHO of the prequalification programme in 2001;²² approved drugs are safe and effective, with excellent quality, as the manufacturing facilities are subject to inspection. While the programme has been especially helpful for introducing new treatments in low-income HBCs, many of the manufacturers interviewed felt the prequalification review procedure was too long, taking 1–2 years, with another 2–3 years to complete registration.

Country-by-country registration is often frustrated by local, politically motivated measures. Indian and Chinese markets 'do not accept FDCs, and Russia wants to buy a tablet with studies that are conducted in that country itself' (NPO2). The second important problem raised by the KOLs is that countries raise increasingly protectionist manufacturing barriers. Thus, 'Thailand will not accept a product unless a Thai manufacturing partner is involved'. Another manufacturer felt there was a bias in South Africa toward local manufacturers or manufacturers with facilities in the country, although there is an open tender process in place, and that 'it would be a preference to have South African companies involved' (NPO2). Such mercantilist policies make no economic sense, as outlined two centuries ago in David Ricardo's classical work on 'comparative advantages' and Adam Smith's even older concept of economies of scale, but this short-sighted practice is probably even

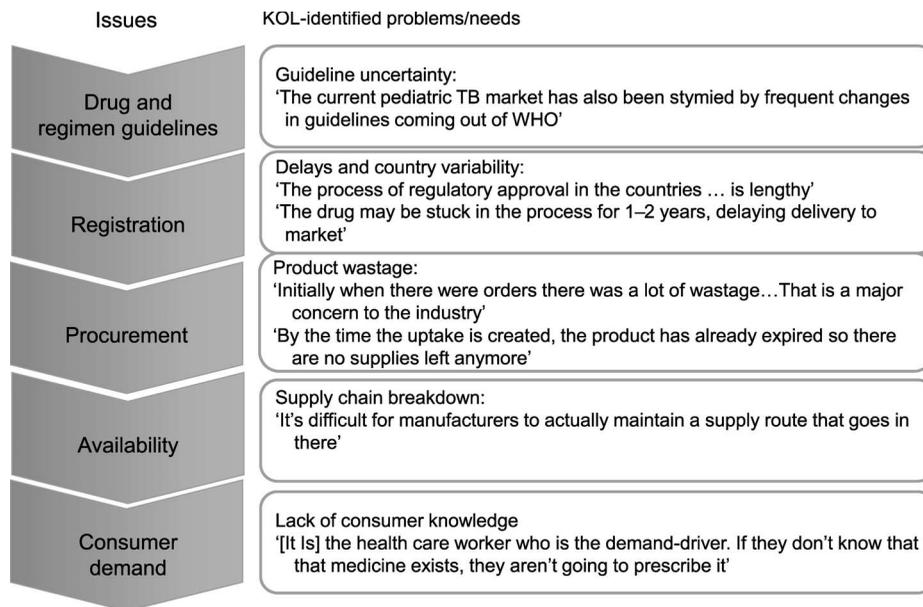


Figure 6 Issues in pediatric tuberculosis drug uptake and demand creation. KOL = key opinion leader; TB = tuberculosis; WHO = World Health Organization.

more damaging to TB care because it distorts the market, resulting in higher prices and supply and quality problems, all harming patient care. Moreover, facilities local to HBCs frequently fail inspection tests by the stringent regulatory authorities, ensuring their products remain limited to local markets.

Procurement and availability

Ensuring adequate supply and availability requires reliable forecasting with on-the-ground information on the number of patients enrolled in each NTP, how many patients will be taking what regimen, manufacturing lead and shipping times and what buffers are necessary.²³ It is abundantly clear that today's situation is suboptimal: a 2012 United Nations Report found that in some regions only half of the drugs needed to treat common conditions are available.²⁴ However, as overestimating demand results in manufacturers losing money, and 'for some orders there was a lot of wastage' (NGO2), procurement tends to 'err on the safe side', issuing smaller orders, resulting in stockouts and shortages. This problem is worse when local manufacturers, who tend to be small and poorly equipped to handle flexible production while maintaining quality, have to be engaged.

Creation of consumer demand

In December 2007, the WHO launched the 'Make medicines child size' campaign as part of the Better Medicines for Children Initiative, alongside its first Essential Medicines List (EML) for Children.³ For pediatric TB, the EML includes the four first-line drugs with the reserve second-line drugs for the treatment of MDR-TB on the complementary list

(recently updated).²⁵ However, few of the 22 HBCs have thus far adopted the EML for Children.²⁶ With health care workers driving demand, the KOLs interviewed wondered who informs these doctors about the EML treatments available. Adding to the problem is the absence of child-friendly formulations on the EML. The main issues identified by KOLs for this area are summarized in Figure 6.

CONCLUSIONS AND RECOMMENDATIONS

Overcoming the obstacles that were identified throughout the interviews requires sustained efforts in a number of areas.

Develop child-friendly drug formulations and facilitate their testing

The basis to developing better formulations is a better understanding of safe and effective dosing requirements. More studies and research on pediatric pharmacokinetics and drug response are urgently required for all pediatric age cohorts.

A clear standardized protocol for recruiting and conducting clinical trials with pediatric TB patients should be in place. That is something the manufacturers, TB Alliance, the WHO and hospitals in HBCs can develop and help in sharing some of the costs associated with these trials (MF4).

Based on the knowledge about adequate dosing, child-friendly formulations are to be developed that address taste-masking and method of intake, such as developing a syrup form of the drug, a flavored formulation or water-dispersible tablets.

Improve shelf life

The design of optimal packages and formulations suitable for all climates in HBCs adds much-needed flexibility to the supply lines of anti-tuberculosis medications. This need not result in a cost increase with the use of Polyvinyl Chloride/Aclar® (Sepha Ltd, Belfast, Northern Ireland, UK) or double aluminium packaging. If refrigeration is essential and drugs are stored in rural areas, power from cell phone towers may provide an out-of-the-box solution (www.energizethechain.org).

Importantly, packaging should contain easy-to-understand information for use in pediatric regimens and how to store them. A good example from the malaria field is the innovative pictogrammed packaging for Coartem® Dispersible (Novartis, Basel, Switzerland).

Design better diagnostics and improve reporting

Better diagnostics for children who have TB are crucial, as is systematic, worldwide reporting. Accurate estimates of the pediatric TB population around the world would provide manufacturers with a clear picture of the size of the market.

Incentivize manufacturers

To ensure sustained ROIs for manufacturers and therefore continued production, a clear cash flow should be guaranteed. This could be established through in-country vouchers and subsidies. A cost-sharing mechanism was suggested, whereby

...the WHO, TB Alliance and individual manufacturers work together such that some of the initial research and manufacturing costs are defrayed by WHO and the TB Alliance (MF4).

One incentive can be funding of development so that you write off your development cost then it is mainly a supply price or price to sell the product (MF3).

To facilitate delivery of drugs through existing supply chains, a waiver of in-country registration fees should be considered. This could be achieved through cost-sharing mechanisms, whereby

WHO and NTCPs can pay (or waive fees) for the first 40% of the drugs distributed (MF4).

Removing uncertainties over patient numbers was also (again) seen as critical, particularly in view of the fragmented TB market.

A different approach to developing an attractive market is to utilize corporate employment-based health care programs in HBCs. Such programs, often a part of the corporate social responsibility policy in multinational companies, have been effectively exploited in the distribution of insecticide-treated bed nets for malaria prevention. Piggybacking pediatric

TB treatment programs on such initiatives would convince manufacturers of a sustained and reliable drug distribution channel that is not solely dependent on Ministries of Health, and indeed kick start such markets.

Increase consumer education on drug and regimen guidelines

Education on best practices for pediatric anti-tuberculosis treatment is needed to create reliable in-country markets. To increase harmonization, KOLs suggested having a

...strong international policy... [which includes] engaging with industry and actually promoting production of medicine. We really need to make sure how we are actually acting together as a global community to make sure we're demanding the right drug (NGO1).

Better education of health care workers was seen as crucial for increasing purchasing demand and product uptake, by 'getting to situations where we can train health care workers or where we can develop with training institutions' (NGO1).

Having a 'stronger connection between [health care workers] and the national TB programs' (NGO2) would encourage consistency in treatment regimens for children within and among each of the 22 HBCs.

Encourage collaboration across countries. So that we're demanding the same medicine (NGO1).

Due to the smaller size of the pediatric TB market, this harmonization is more essential and urgently needed in this niche market than in the larger market for adult therapy.

Streamline regulatory approvals in individual countries

The cumbersome new drug approval process is a major deterrent to TB drug manufacturers. It was felt that

...if there was a way to streamline the process of regulatory approval in the countries I think that would go a long way to speeding up the process that is lengthy (NPO1).

One suggestion was 'to create a fast-track', and that it would be 'helpful if Expert Review Panel status was applicable for pediatric TB drugs' (MF1) to accelerate the timing of the prequalification process for pediatric TB drugs without compromising on quality.

KOLs suggested that NGOs should advocate strongly for streamlining the regulatory drug approval process with NTPs, as they work hand-in-hand with Ministries of Health to administer TB control.

Somebody has to champion the cause. Someone has to talk to the authorities of the TB programs to

start using these drugs as soon as possible or to change over to the newer drugs (MF2).

This could include fee waivers, as noted by one KOL:

...in some countries, where registration for medicines costs 5000 dollars for a few years, [having an advocate] helps make sure that, for these low volume products, there are waivers [so manufacturers] do not have to pay fees for registration (NGO2).

The role of advocacy by manufacturers on entities that will procure and distribute drugs to the health sector such as Ministries of Health was seen as counterproductive, as manufacturers worry that

...if we, the manufacturers, go in and promote it, they will think it's just because we developed the product. It should be people with credentials known to the TB programs to promote the product, then it becomes easier for the countries to change over (MF2).

This would therefore be the role of NTPs. It was suggested that:

TB program managers could be involved in discussions and how these drugs are being developed and why they are being developed and what is the benefit over the currently procured pediatric TB drugs (MF2).

Promote uptake of drugs by high-burden countries through pooled procurement and manufacturing partnerships

Encouraging HBCs to accept appropriate drugs for pediatric TB from reliable manufacturers is essential to ensure an adequate and steady market. Learning from HIV and extending the lessons learned from pediatric antiretroviral drugs, one KOL cited the Clinton Health Access Initiative strategy of buying a drug from WHO pre-qualified manufacturers and supplying it to a number of sub-Saharan Africa countries (NPO1). Such a pooled procurement strategy provides manufacturers with a reliable buyer and the security that when their products are manufactured they will be purchased and used rather than expire on their, or a customer's, shelves.

For countries that insist on in-country drug production or supply, partnering international pharmaceuticals companies with national suppliers may be a pragmatic solution for supplying quality drugs. For example, Biocom (Stavropol, Russian Federation), a Russian manufacturer, partnered with Eli Lilly (Indianapolis, IN, USA) for MDR-TB treatments in Russia, with a technology transfer in 2007. Together they applied for the WHO prequalification programme to supply these drugs to Russia and many other former Soviet Union countries.²⁷

Access to proper medication for children with TB

requires that all elements in the supply chain are in place in a market that is sustainable from the perspective of all stakeholders. Our interviews with different experts who are active in this area have resulted in a set of concrete recommendations, which may now serve as a basis for further communication, coordination and cooperation to reduce the overall burden of TB in children of all ages.

Acknowledgements

The authors thank the following members of the TB drug development community for sharing their opinions: V Agarwal (Macleods Pharmaceuticals, Mumbai, India), B P van Amstel (Svizera, Imere, the Netherlands), L Hedman (World Health Organization), S Holland (Global Fund to Fight AIDS, Tuberculosis, and Malaria), M Jerath (Lupin, Mumbai, India), R Lorette (TB Alliance New York, NY, USA), T Sharma (Sandoz, Mumbai, India), N Sugandhi (Clinton Health Access Initiative, New York, NY, USA), R Taneja (TB Alliance). We also thank R Hooft van Huijsduijnen for editorial assistance with the manuscript.

Conflicts of interest: none declared.

References

- 1 World Health Organization. Childhood TB Factsheet. Geneva, Switzerland: WHO, 2013. http://www.who.int/tb/challenges/childtb_factsheetpdf?ua=1. Accessed September 2015.
- 2 World Health Organization. WHO rapid advice: treatment of tuberculosis in children. WHO/HTM/TB/2010.13. Geneva, Switzerland: WHO, 2010.
- 3 World Health Organization. Essential medicines for children. Geneva, Switzerland: WHO, 2014. www.who.int/childmedicines/tuberculosis/en. Accessed September 2015.
- 4 Ginsberg G, Hattis D, Sonawane B, et al. Evaluation of child/adult pharmacokinetic differences from a database derived from the therapeutic drug literature. *Toxicol Sci* 2002; 66: 185–200.
- 5 Merck. The Merck Manual. Kenilworth, NJ, USA: Merck, 2015. <http://www.merckmanuals.com/professional/>. Accessed September 2015.
- 6 Seddon J A, Thee S, Jacobs K, Ebrahim A, Hesseling A C, Schaaf H S. Hearing loss in children treated for multidrug-resistant tuberculosis. *J Infect* 2013; 66: 320–329.
- 7 Clayton P. TB drugs for children. Geneva, Switzerland: Treatment Action Group, 2013. <http://www.treatmentactiongroup.org/tagline/2013/spring/tb-drugs-children>. Accessed September 2015.
- 8 Laventhal N, Tarini B A, Lantos J. Ethical issues in neonatal and pediatric clinical trials. *Pediatr Clin N Am* 2012; 59: 1205–1220.
- 9 Bavdekar S B. Pediatric clinical trials. *Persp Clin Res* 2013; 4: 89–99.
- 10 World Health Organization. Guidance for national tuberculosis programmes on the management of tuberculosis in children. WHO/HTM/TB/2014.03. Geneva, Switzerland: WHO, 2014.
- 11 Molzon J A. The International Conference on Harmonization common technical document—global submission format? *Food Drug Law J* 2005; 60: 447–451.
- 12 John E A. Poor storage lowers quality of TB drugs. *New Delhi, India: Times of India*, 7 March 2014. <http://timesofindia.indiatimes.com/city/chennai/Poor-storage-lowers-quality-of-TB-drugs/articleshow/31572632.cms>. Accessed September 2015.
- 13 Rookkapan K, Chongsuvivatwong V, Kasiwong S, Pariyawatee S, Kasetcharoen Y, Pungrassami P. Deteriorated tuberculosis drugs and management system problems in lower southern Thailand. *Int J Tuberc Lung Dis* 2005; 9: 654–660.

- 14 World Health Organization. Global tuberculosis report, 2014. WHO/HTM/TB/2014.08. Geneva, Switzerland: WHO, 2014.
- 15 Hatherill M, Hanslo M, Hawkrigde T, et al. Structured approaches for the screening and diagnosis of childhood tuberculosis in a high prevalence region of South Africa. *Bull World Health Organ* 2010; 88: 312–320.
- 16 Peeling R W, Smith P G, Bossuyt P M. A guide for diagnostic evaluations. *Nat Rev Microbiol* 2010; 8 (Suppl): S2–S6.
- 17 Dodd P J, Gardiner E, Coghlan R, Seddon J A. Burden of childhood tuberculosis in 22 high-burden countries: a mathematical modelling study. *Lancet Global Health* 2014; 2: e453–459.
- 18 The Global Drug Facility. The Global Drug Facility Catalogue. Geneva, Switzerland: GDF, 2014.
- 19 Clinton Health Access Initiative. The state of the antiretroviral drug market in low- and middle-income countries. ARV Market Report. New York, NY, USA: CHAI, 2013.
- 20 McKenna L. Playing catch-up: pediatric tuberculosis treatment pipeline. Pipeline Report 2014. London, UK: HIV i-BASE, 2014: pp 217–231. <http://www.treatmentactiongroup.org/sites/g/files/g450272/t/201407/2014%20Pipeline%20Report%20Full.pdf>.
- 21 Bharaswadkar S, Kanchar A, Thakur N, et al. Tuberculosis management practices of private practitioners in Pune municipal corporation, India. *PLOS ONE* 2014; 9: e97993.
- 22 ‘t Hoen E F, Hogerzeil H V, Quick J D, Sillo H B. A quiet revolution in global public health: the World Health Organization’s Prequalification of Medicines Programme. *J Public Health Policy* 2014; 35: 137–161.
- 23 US Institute of Medicine, Forum on Drug Discovery Development and Translation. Developing and strengthening the global supply chain for second-line drugs for multidrug-resistant tuberculosis: workshop summary. Washington, DC, USA: National Academies Press, 2013.
- 24 Millennium Development Goals Gap Task Force. Report 2013: the global partnership for development: the challenge we face. New York, NY, USA: United Nations, 2013. <http://www.un.org/en/development/desa/publications/mdg-gap-task-force-report-2013.html> Accessed September 2015.
- 25 World Health Organization. The selection and use of essential medicines. Geneva, Switzerland: WHO, 2014.
- 26 Finney E. Children’s medicines: a situational analysis. Make Medicines Child Size. Geneva, Switzerland: WHO, 2011. http://www.who.int/childmedicines/progress/CM_analysis.pdf Accessed September 2015.
- 27 US Institute of Medicine Forum on Drug Discovery Development and Translation, Russian Academy of Medical Science. The new profile of drug-resistant tuberculosis in Russia: a global and local perspective: summary of a joint workshop. Washington, DC, USA: National Academies Press (US), 2011.

RESUME

Des partenaires représentatifs ont été consultés sur la manière dont ils percevaient que l'accès aux médicaments de la tuberculose (TB) pédiatrique pouvait être amélioré. Une recommandation clé consiste en l'élaboration de nouvelles formulations, acceptables par les enfants, suffisamment dosées, avec une bonne durée de conservation sous tous les climats. Il y a également un besoin urgent d'améliorer le diagnostic et la déclaration des enfants atteints de TB. Les

fabricants de médicaments pour la TB pédiatrique doivent être motivés grâce à une meilleure coordination de tous les partenaires avec des approbations réglementaires allégées et une meilleure éducation des consommateurs sur les directives relatives aux médicaments et aux protocoles. Enfin, des commandes groupées sont conseillées afin d'assurer un approvisionnement permanent à des prix abordables.

RESUMEN

En una consulta a los interesados directos pertinentes se evaluaron las posibles formas de mejorar el acceso a los medicamentos pediátricos contra la tuberculosis (TB). Una recomendación primordial consiste en el desarrollo de nuevas formulaciones farmacéuticas adaptadas a los niños, con dosis adecuadas y un tiempo de conservación conveniente en todas las zonas climáticas. Existe además una necesidad urgente de mejorar el diagnóstico y la notificación de la TB en los niños. Es preciso incentivar a

los fabricantes de medicamentos antituberculosos pediátricos mediante una mejor coordinación de todos los interesados directos, con mecanismos simplificados de autorización de la comercialización y una mejor educación del consumidor sobre los medicamentos y las pautas terapéuticas. Por último, se recomiendan las adquisiciones mancomunadas con el fin de lograr un suministro sostenido del mercado a precios asequibles.
