

## Paediatric formulations of second-line anti-tuberculosis medications: challenges and considerations

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### SUMMARY

There is a growing number of children worldwide accessing second-line anti-tuberculosis drugs for multi-drug-resistant tuberculosis (TB); however, there are very few child-friendly formulations. For paediatric use, dispersible tablets offer distinct advantages over liquid formulations and other approaches. This is particularly relevant for TB, where stability, long shelf-life and reduced manufacturing, transport and storage costs are all critical to ensuring that drugs are accessible and affordable. In addition, fixed-dose combinations that reduce the pill burden and provide adequate taste masking may promote long-term adherence to anti-

tuberculosis treatment and prevention regimens likely to last many months in children. Partial adherence may result in treatment failure and the further selection and spread of resistant mycobacteria. Unfortunately, no second-line TB paediatric drugs exist in dispersible formulations. We discuss here the main obstacles to developing such tablets and present strategies for overcoming them. We also advocate for timely anticipation of paediatric use when new TB drugs are being developed, and for the development of child-friendly anti-tuberculosis formulations in general.

**KEY WORDS:** CMC; TB; FDC; rifampicin; linezolid

TUBERCULOSIS (TB) is a serious health problem among children worldwide, causing an estimated 136 000 deaths and at least 1 million new cases each year.<sup>1</sup> Moreover, there appears to be an increase in the number of children with multi- (MDR) and extensively drug-resistant TB (XDR-TB).<sup>2</sup> Unfortunately, the development of paediatric TB medications trails behind those made available to adults. As the orally formulated, immediate-release, adult-strength tablets available were generally not designed for flexible/alternate dosing, they are difficult to adapt to redosing based on age and/or weight, which is customary in children.

One common makeshift solution is to crush tablets normally intended for adults and administer a portion of the powder to the child, a procedure that comes with a number of problems: inaccurate dosing (due to lack of information of what is appropriate), disruption of the coating (potentially affecting exposure and worsening palatability), improper/imprecise dose administration and a potential waste of the active pharmaceutical ingredient (API). These problems may worsen adherence, as these drugs are generally to be taken over a period of many months, often at home.

As an alternative, some of the second-line TB drugs

are provided as liquid solutions or in suspension. However, these come with their own problems: the containers that contain these are bulky; liquids are generally less stable even when refrigerated; taste-masking is difficult; storage, packaging and safe transportation are expensive; and care givers prefer tablet formulations over suspensions for chronic conditions such as HIV.<sup>3</sup>

A third, and now preferred option, as outlined in the World Health Organization (WHO)/United Nations Children's Fund (UNICEF) new 2008 children's medicine guide is dispersible tablets,<sup>4</sup> which are dispersed in water before intake. Their main advantages are ease of administration, transport, storage and opportunities for taste masking. One successful example of taste masking in a drug for another condition is Coartem<sup>®</sup> Dispersible (Novartis, Basel, Switzerland), an anti-malarial developed especially for children as a sweet-tasting, cherry-flavoured tablet ([www.mmv.org](http://www.mmv.org)). Another example of taste-masking for paediatric use is the development of a quinine formulation with decreased solubility that ensures that the bulk of this bitter API is not released in the mouth but further down in the gastrointestinal tract.<sup>5</sup>

Another advantage of dispersible tablets is that

**Table 1** Paediatric formulations of second-line anti-tuberculosis medications: overview of challenges, ongoing work and recommendations

	LVX	MFX	Ethionamide
Existing formulations	250 mg scored tablets 500 mg scored tablets Suspension/solution of 25 mg/ml (not available via GDF) Note: some film-coated 250 mg tablets are not scored	400 mg non-scored, film-coated tablet	250 mg film coated, non-scored tablet; non-film coated tablet
PK work in children (summary of data/ongoing work)	10–20 mg dose needed, with higher doses needed for MIC of >0.25 µg/ml <sup>6</sup> Levofloxacin dose 15–20 mg/kg in children of all ages <sup>7</sup> Ongoing work in Cape Town evaluating dosing of 15–20 mg/kg	Dose of 7.5–10 mg/kg in children of all ages <sup>7</sup> No published PK data in children aged <7 years Ongoing work in Cape Town	15–20 mg/kg is appropriate dose <sup>8</sup> Ongoing work in Cape Town unlikely to result in dose change
Dosing recommended for children <sup>14</sup>	WHO: 7.5–10 mg/kg once daily Expert opinion: 15–20 mg/kg once daily.	WHO: 7.5–10 mg/kg once daily	WHO: 15–20 mg total daily dose given twice daily; Expert opinion: 15–20 mg/kg total daily dose, given once daily twice daily if not tolerated
Challenges with existing formulations	Difficult to crush and mix; may reduce exposure when mixed with certain food and drinks	Not scored, difficult to crush, may reduce exposure when mixed with certain foods and drinks	Not scored, difficult to crush, may reduce exposure when mixed with certain foods and drinks
Increasing demand, clinical	Given to almost all children treated for DR-TB Use can be promoted by global networks providing training of treatment and prevention of DR-TB	Given to children treated for DR-TB; needed for XDR-TB regimens Use can be promoted by global networks	Given to almost all children treated for DR-TB. Use can be promoted by global networks.
Potential for inclusion in future research studies	MFX or LVX essential part of most backbone regimens Essential in preventive therapy trials	MFX or LVX essential part of backbone regimen Could be part of preventive therapy trials	Needs to be part of most backbone regimens

LVX = levofloxacin; MFX = moxifloxacin; PAS = para-aminosalicylic acid; GDF = Global Drug Facility; MIC = minimum inhibitory concentration; MDR-TB = multidrug-resistant TB; PK = pharmacokinetic; TB = tuberculosis; WHO = World Health Organization; DR-TB = drug-resistant TB; XDR-TB = extensively drug-resistant TB.

different pill strengths can be produced in order to finetune dosing by age and/or weight. These tablets can be scored (shaped with break-marks to allow easy division into two or four equal-sized parts) to provide further dosing flexibility. Unfortunately, no second-line dispersible anti-tuberculosis tablets exist today (Table 1). We review here the main obstacles that prevent the development of such formulations and how these problems could be successfully tackled.

## DEFINING THE NEEDS

### *Policy and dosing guidelines*

One of the key difficulties in developing dispersible tablet formulations of second-line TB medications is the absence of paediatric dosing guidance. Simple allometric scaling and extrapolating adult exposure to children usually will not suffice due to adult/child differences in gastric emptying and pH, gastrointestinal tract permeability in absorption surface area, expression of some drug transporters, biliary func-

tion, drug metabolism and renal clearance.<sup>16</sup> The required absolute drug dose in children may thus vary 100-fold,<sup>17</sup> and it is dangerous to assume that exposure will be comparable (can simply be scaled) even between older and younger children. Because of well-established differences between older and younger children and infants, the International Conference of Harmonization has recommended that childhood be divided into five stages with respect to clinical drug use.<sup>18</sup> Establishing paediatric exposure will therefore require dedicated clinical studies.

A summary of the pharmacokinetic data that are available to date is presented in Table 1, and a detailed discussion on paediatric dose-finding is provided in another article in this Supplement.<sup>19</sup> Once age-dependent dosing requirements have been established, dispersible tablets can be scored or manufactured in a small set of easily distinguishable shapes and strengths to accommodate dosing requirements. Established dosing guidelines are essential before the regulatory authorities can approve the

Table 1 (continued)

Cycloserine	PAS	Linezolid	Clofazimine
250 mg film coated hard caplet 250 mg capsule	Granules in sachets of 4 g or mixed; dosing spoon	600 mg non-scored tablets Suspension at 20 mg/ml (not available via GDF)	50 mg, 100 mg soft capsules
Limited work; 15–20 mg/kg is likely appropriate dose <sup>9</sup> Ongoing work in Stellenbosch University, on terizidone; unlikely to result in dose change	150 mg/kg total daily dose given once or twice daily in 10 children with MDR-TB <sup>10</sup> Ongoing work in Cape Town	Some work in children with cystic fibrosis shows need for higher dosing <10 years <sup>11</sup> Additional work needed, <sup>12</sup> as even adult dose not yet well established <sup>13</sup> No data on children with TB; ongoing work in Cape Town	No published PK in children
WHO: 10–20 mg/kg once daily	WHO: 150 mg/kg total daily dose given as split dose twice or thrice daily. Expert opinion: 150 mg/kg total daily dose given once or twice daily	WHO: None Expert opinion <sup>14</sup> : 10 mg/kg per dose given twice daily for children <10 years; 300 mg daily for children >10 years	WHO: none Expert opinion: 2–3 mg/kg or 3–5 mg/kg given once daily; if calculated mg/kg dose is lower than tablet/soft-gel formulation, could be given every other day <sup>15</sup>
Unable to be split, must open capsules and mix 'compound', may reduce exposure when mixed with certain foods and drinks Given to children treated for DR-TB. Use can be promoted by global networks.	Dosing spoon limited at lower weight bands	Not scored, difficult to crush; suspension not widely available  Given to children treated for DR-TB; needed for XDR-TB regimens. Use can be promoted by global networks.	Cannot be crushed or split  Important for a growing number of children with XDR-TB; may become very important if the 9 month regimen/STREAM trial shows non-inferiority. Use can be promoted by global networks
Could be part of backbone regimen		Component of some oral, injectable-sparing shorter regimens being tested in future regimens	Is being tested in STREAM part 2 trial; may become part of standard of care

submitted information package for the dispersible tablets for registration and approval. Dosing guidelines have recently been specified for first-line anti-tuberculosis drugs for drug-susceptible TB; however, to date there have been no such recommendations for MDR-TB.

#### *Stability and compatibility challenges with dispersible formulations*

A dispersible tablet has to meet the specifications of the disintegration test (dispersal under 3 min) and 'finesness of dispersion test' (dispersed powder should pass through a 710 µm pore aperture sieve).<sup>20</sup> A common approach to generating dispersible tablets is the inclusion of high amounts of disintegrants such as sodium starch glycolate, microcrystalline cellulose, crospovidone and/or croscarmellose, excipients that swell upon contact with moisture and help disintegrate the tablet. The problem with many of these excipients is that they are highly hygroscopic (moisture absorbing), resulting in spontaneous softening and swelling of the tablets over time. Moreover, storage conditions in most of the high TB burden

countries have high temperature and humidity. Dedicated manufacturing procedures and special packaging can reduce the risks of moisture ingress, using, for example, double-aluminium blisters. When flavourings and sweeteners are added, it is important to exclude the risk of interaction with the API(s); this means that long-term stability studies are necessary. Finally, all other excipient components in the mix should be thoroughly evaluated in combination for compatibility issues with the API. For example, the binding of quinolone antibiotics to divalent cations has been well-documented.<sup>21</sup>

#### *Taste masking*

The second-line anti-tuberculosis drugs available today comprise only a small set of chemical classes, and most have a highly bitter and obnoxious taste, for which children in particular have low tolerance. It is critical that these medicines, as used for children, are effectively taste masked and in addition contain child-adapted flavours. Poor palatability of medications has been shown to negatively impact treatment adherence in children,<sup>22</sup> which in the case of TB

could result in treatment failure, promote the emergence and spread of MDR-TB and waste resources. Today's anti-tuberculosis APIs are soluble and rapidly released, which tends to overwhelm taste masking and flavouring efforts. One strategy to mask the drug's taste involves adsorbing the drug onto a complex forming agent.<sup>23,24</sup> This can be achieved using ion-exchange resins that release their ligands at increased pH (upon entry in the duodenum). However these resins tend to display an unreliable ligand-release rate, complicating drug exposure. The API may also be complexed with cyclodextrins, but as these are required in large quantities, this leads to increased tablet size and manufacturing costs. Finally, barrier coating can be used to minimise the contact between the API and taste receptors with the help of insoluble polymers. Various manufacturing techniques are available to achieve such a formulation, for example spray drying, bottom spray, solvent evaporation, etc. These techniques require the use of specialised equipment to achieve a good barrier coat; moreover, the coatings may affect the API's release and exposure. Taste masking therefore needs to be balanced with effective drug release, and this process requires extensive experimentation; in most cases, changes in exposure that result from different formulations will need to be formally evaluated in pharmacokinetic studies in children.

Work on taste masking should be planned for and performed during the product development stage. Once a product is approved, significantly changing the composition requires extensive stability testing ( $\geq 2$  years). The early use of tools such as the 'artificial tongue'<sup>25</sup> and well-planned taste testing panels (involving children) would pay generous dividends.

#### *Bioequivalence studies*

Dispersible tablets represent an alternative solid dosage form to the existing immediate-release tablets. As previously mentioned, dispersible tablets contain different excipients and tend to release the API earlier. Bioequivalence studies are therefore required to characterise the rate and extent of API absorption and compare it with a comparator product representing the currently available dosage form. The paediatric dispersible tablet will contain a substantially lower amount of API than the currently available adult formulation. Multiple dispersible tablets will therefore need to be administered and compared with a single adult immediate-release tablet, or in some cases with multiple immediate-release tablets to achieve dose equivalence. The difference in release characteristics of the APIs and the formulations, combined with the different number of tablets, result in a complex bioequivalence evaluation scenario. Failure to properly evaluate all these parameters may trigger the need for further

clinical efficacy studies conditional to successful registration. Timely development and acceptance of dosing guidelines and a decision on the appropriate comparator products may facilitate the process. Funding these important studies is problematic. As bioequivalence studies are typically performed in adults, funding sources that focus on paediatric applications usually do not pay for them, and because the results are applied to children, sponsors who primarily address TB in adults do not pay for them either.

#### *Fixed-dose combinations*

All TB regimens today involve multiple drugs; combining these as fixed-dose combinations (FDCs) is highly desirable, mostly for reasons of patient adherence. However, the development of FDCs further complicates the previously described challenges, making this task even more formidable for most combinations. Another problem is that the combination ratio is indeed 'fixed'; if the planned combination consists of one drug that is given at a single dose to all populations and a second one that requires finely tuned age- or weight-based dosing adjustments, then the required FDC cannot be designed (or multiple FDCs may have to be designed wherein one drug is kept at a constant dose while the other is varied).

Ideally, FDC dispersible tablets are manufactured so that they can be dosed in multiples to meet the requirements of different age groups. Dosing guidelines become a critical factor in deciding the quantities of each API in dispersible tablets. Even in its simplest form, formulating a FDC tablet in which the APIs are uniformly distributed is challenging, and is further complicated by the need to use suitable taste-masking strategies. There is also the risk that the APIs themselves may interact. Physical interactions between the first-line anti-tuberculosis drugs have been well documented.<sup>23,24</sup> This can be overcome by designing bilayered tablets, i.e., FDC tablets in which the APIs are deposited in layers.<sup>26</sup> However, the manufacture of bilayered tablets with stable formulations is challenging and may require special equipment and multiple trials.

Finally, bioequivalence must be demonstrated for each API and compared to the individual pharmacokinetics observed in clinical efficacy studies; this may fail if the drugs have different release profiles. Given the rapidly evolving anti-tuberculosis treatment landscape, pursuing paediatric FDCs of second-line drugs may be challenging.

#### *Regulatory challenges*

One of the main problems in providing worldwide patient access to new, innovative formulations is that registration, a lengthy, bureaucratic process, needs to occur on a country-by-country basis for the most

part, with requirements that vary by country. Examples of these differences include batch size, number of batches, how and how many stability studies were performed, disagreement over dissolution profile interpretation, bioequivalence study design, and choice and formulation of the comparator in the studies.

Some countries may refuse on principle to accept a new dispersible tablet on the basis of bioequivalence, requiring instead the demonstration of equivalent efficacy in clinical studies. Other countries do not use any FDCs. In some cases, it is mandatory that the reference product be sourced from within the country where approval is sought or the bioequivalence study be conducted in that country. Advances in this area include the WHO Prequalification Programme, which facilitates a joint review process and comprises an expanding set of countries and the introduction of the 'biowaiver procedure'.<sup>27</sup> The WHO Prequalification Programme is a 'quiet revolution' that addresses drug quality problems in countries with weak regulatory and legal monitoring.<sup>28</sup> The biowaiver implies that bioavailability and/or bioequivalence can in some cases be based on dissolution tests instead of new *in vivo* studies.

#### *Supply management*

The demand for second-line anti-tuberculosis drugs is very limited compared to first-line drugs. Manufacturers generally tend to maintain a low inventory to avoid expiration-related losses. Batch sizes are typically determined by production (equipment) capacity, shelf life and market demand. As a rule, batch manufacturing is to be initiated when 80% of the batch is covered by existing orders. In the subsequent steady-state marketing situation, batches are to be shipped with no less than 75–85% of shelf life remaining. In practice, however, the initial required order volume is often not reached, and an exhibit batch size is kept that is as small as possible, normally 125 000–200 000 tablets. A frequent problem is mass drug expiration. There is clearly room for suppliers, procurement agencies, customers and donors to overcome this waste by streamlining the production-to-patient flow. Stocking of these drugs through a central procurement mechanism such as the Global Drug Facility is another possible solution.<sup>25</sup> This option would ensure the ready availability of the product as needed.

### **LESSONS FROM DEVELOPMENT OF DISPERSIBLE AND FIXED-DOSE COMBINATIONS FOR FIRST-LINE PAEDIATRIC ANTI-TUBERCULOSIS DRUGS**

For first-line treatment of paediatric TB, dispersible tablets and FDCs have already been developed, overcoming the challenges listed above. Most of the

dispersible FDCs include rifampicin (RMP). One of the biggest hurdles in developing these was the stability problems associated with the combination of RMP and isoniazid (INH), and these APIs tend to generate a complex that results in a reduction in RMP bioavailability.<sup>23,24</sup> Problems associated with other APIs stem from hygroscopicity (a tendency to absorb water) of ethambutol, problematic divisibility of scored INH/RMP dispersible tablets and other difficulties. Other challenges included taste masking and bioequivalence when comparing with reference (comparator) capsules or film-coated tablets.

Progress in this area of development was made thanks to the productive collaboration between funders, regulators, manufacturers and the TB Alliance. Creative solutions such as adding RMP later in the blend of ingredients to minimise contact with INH and moisture and the judicious selection of packaging materials have helped create elegant drug products. These products are tested to very high standards under varying storage conditions. Many of the hard-earned lessons learned in the above undertakings will instruct future efforts in developing paediatric dispersible tablets for second-line anti-tuberculosis medications.

### **PROGRESS IN DEVELOPING DISPERSIBLE AND FIXED-DOSE COMBINATIONS FOR SECOND-LINE PAEDIATRIC ANTI-TUBERCULOSIS DRUGS**

Table 1 shows key APIs that are being considered for second-line paediatric TB treatment regimens, along with their key characteristics important for formulation-related decisions, and demonstrates the many knowledge gaps that must be addressed to move each of these forward as dispersible tablets. Many of the existing drugs and formulations have clearly been developed without considering their potential use in children; for example, some tablets are not scored. A more serious and recurring problem is that the pharmacokinetics/pharmacodynamics relation has not been established for children. Some prototypes of child-friendly formulations are early in development (Macleods Pharmaceuticals Ltd), including levofloxacin 100 mg dispersible tablets, moxifloxacin 100 mg dispersible tablets, ethionamide 125 mg dispersible tablets, cycloserine 125 mg capsules, and linezolid 150 mg dispersible tablets. However, substantial additional work would be needed on these formulations to bring them to market, including work on bioequivalence, quality assurance and regulatory approvals. These formulations are therefore unlikely to be available in the field in the short term; they are, nevertheless, an important step forward.

Table 2 summarises challenges faced in developing dispersible formulations of existing second-line anti-tuberculosis drugs, and some potential solutions. Of note, the newly approved drug delamanid has an

**Table 2** Challenges with the development of child-friendly formulations of second-line anti-tuberculosis medications in children

	Challenges	Way forward
Policy and dosing guidelines	Currently a lack of existing dosing guidelines for existing second-line anti-tuberculosis medications Lack of guidelines inhibit regulatory agencies from approving paediatric formulations	Support PK studies of existing second-line anti-tuberculosis drugs in children of all ages International paediatric dosing recommendations based on PK data in children
Stability and compatibility challenges with dispersible tablets	Dispersible tablets use excipients which are highly moisture absorbing, and sensitive to high temperature and humidity conditions; long-term stability studies may be necessary Excipients in final formulation must be evaluated together for interactions with the API	Dedicated manufacturing procedures, such as use of double-aluminium blister packs, can limit the risk of moisture absorption
Taste masking	Existing second-line drugs are mostly bitter compounds, requiring substantial taste masking Taste-masking may impact drug exposure, increase tablet size, require specialised manufacturing techniques and increase manufacturing costs	Work on taste masking should be anticipated and performed early in product development Well planned tasting panels, including children where appropriate, and newer tools such as the 'artificial tongue' should be used
Bioequivalence studies	Bioequivalence studies are required for dispersible tablets Limited funding, as studies are for paediatric products but typically performed in adults	Ensure appropriate funding or incentives for these important studies
Fixed-dose combinations	Challenges with possible interactions between multiple APIs and excipients; may affect drug release, impacting bioequivalence May require specialised manufacturing techniques	Anticipate challenges and ensure appropriate funding and incentives Ensure PK of APIs are well described
Regulatory challenges	Need for country-by-country registration Regulatory processes may differ by country Limited market, so no financial incentive to register	Use and expand the WHO Prequalification Programme Use biowaivers to limit the need for bioequivalence studies, simplifying registration
Supply management	Limited demand results in challenges for production, storage and supply	Streamline production-to-patient flow of medication Use central procurement mechanisms, such as the Global Drug Facility

PK = pharmacokinetic; API = active pharmaceutical ingredient; WHO = World Health Organization.

advanced paediatric development programme, has completed pharmacokinetic testing in children as young as 6 years, is enrolling children aged <6 years in current PK studies, and has developed a scored, dispersible tablet of DLM (<https://clinicaltrials.gov/show/NCT01856634>). The other recently approved drug, bedaquiline, is just beginning to undergo pharmacokinetic testing in older children (Table 3).

An important final consideration is the price of the product. Efforts must be made to ensure that the cost of developing a paediatric formulation does not result in a product that is too expensive for TB programmes to procure and use in the field.

## CONCLUSIONS

While challenging, much can be learned from earlier reformulation successes for first-line TB treatments, and this can be used to guide development of subsequent formulations; their successful development also illustrates how the process can be driven by

productive partnerships. However, many gaps in knowledge in the use of most of second-line anti-tuberculosis drugs in children remain, especially regarding optimal dosing.<sup>29</sup> It is of the greatest importance that existing clinical trials and formulation efforts already take into account how new regimens can be administered to children, and that, at the very least, adequate data on adult drug exposure are available to guide subsequent paediatric formulation development. The need for paediatric formulations and, in particular, the development of dispersible tablets for the treatment of TB in children is a medical necessity.<sup>30</sup> Because most TB APIs have an unpleasant taste but must be taken over a long period of time, the importance of developing taste-masked dispersible tablets for children remains a high priority, forming an essential link in the chain that runs from patient detection and diagnosis and drug access to adherence and treatment success.

**Table 3** Delamanid and bedaquiline: two recently approved drugs

	Delamanid	Bedaquiline
Existing formulations	50 mg tablet	100 mg non-scored tablet
PK work in children (summary of data/ongoing work)	Ongoing work in children aged <6 years (the Philippines, South Africa) PK studies completed in children aged ≥6 years	Early PK work starting in older children
Dosing recommended for children <sup>14</sup>	For children aged ≥13 years, the dosing recommendation is the same as in adults (100 mg by mouth twice daily)	No recommendation
Challenges with existing formulations	Current tablet is film-coated, but company has developed a scored, dispersible tablet	Current tablet is not scored; development of paediatric formulation planned
Increasing demand, clinical	Access to this drug outside of clinical trials has been very limited; Has been given to children as young as 13 years on compassionate grounds; Important in children with resistance to FQs, injectables or both	Adult doses used in children as young as 16 years Important in children with resistance to FQs, injectables or both and where delamanid is not available
Potential for inclusion in future research studies	Awaiting results of PK and safety trials in children Could be important in injectable-free regimens for children Possible role in preventive therapy trials	Additional data on safety and dosing in children needed

PK = pharmacokinetic; FQ = fluoroquinolone.

### Acknowledgments

The authors thank R Hoof van Huijsduijnen for editorial assistance with the manuscript.

Conflicts of interest: none declared.

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## RESUME

Il y a dans le monde un nombre croissant d'enfants ayant accès aux médicaments antituberculeux de deuxième ligne pour traiter une tuberculose (TB) multirésistante, mais il y a peu de formulations vraiment pratiques pour les enfants. En médecine pédiatrique, les comprimés dispersibles ont des avantages nets sur les formes liquides et d'autres approches. Ceci est particulièrement pertinent en matière de TB, où une bonne stabilité, une longue durée de conservation et des coûts réduits de fabrication, de transport et de stockage sont tous cruciaux pour s'assurer que les médicaments sont accessibles and abordables. De plus, les combinaisons à dose fixe qui réduisent le nombre de comprimés et masquent suffisamment leur goût contribuent à une bonne adhésion à long terme aux protocoles de

traitement et de prévention de la TB pour les enfants, car ces protocoles peuvent durer de longs mois. Une adhésion partielle peut aboutir à un échec du traitement et à davantage de sélection et de propagation de mycobactéries résistantes. Malheureusement, aucun traitement de TB pédiatrique de deuxième ligne n'existe sous forme dispersible. Nous discutons ici des principaux obstacles à l'élaboration de tels comprimés et présentons des stratégies sur la manière dont on pourrait les surmonter. Nous plaidons également pour une anticipation précoce de l'utilisation pédiatrique lors de l'élaboration de nouveaux médicaments antituberculeux et pour l'élaboration de formulations anti-tuberculeuses en général acceptables par les enfants.

## RESUMEN

Cada vez un mayor número de niños en el mundo tiene acceso a los medicamentos de segunda línea contra la tuberculosis (TB) multidrogoresistente, pero existen muy pocas formulaciones de estos medicamentos que sean adaptadas al uso pediátrico. Los comprimidos dispersables, cuando se utilizan en pediatría, ofrecen ventajas claras con respecto a las presentaciones líquidas y otras preparaciones. Esta ventaja adquiere un interés especial en el caso de la TB, donde la estabilidad adecuada, un período de conservación prolongado y los bajos costos de producción, transporte y almacenamiento son características primordiales que favorecen la accesibilidad y la asequibilidad de los medicamentos. Además, las asociaciones en dosis fijas que disminuyen la cantidad de comprimidos y enmascaran el sabor facilitan el cumplimiento del

tratamiento antituberculoso y los regímenes preventivos, que suelen durar muchos meses. Un cumplimiento terapéutico parcial puede llevar a un fracaso y favorecer una mayor selección y la diseminación de las micobacterias resistentes. Desafortunadamente, no se cuenta aun con tratamientos antituberculosos de segunda línea en forma dispersable. En el presente artículo se analizan los principales obstáculos al desarrollo de este tipo de comprimidos y se proponen estrategias encaminadas a superarlos. Se preconiza también la anticipación oportuna del uso pediátrico de los medicamentos antituberculosos que están en vía de desarrollo y la obtención de formulaciones mejor adaptadas al uso pediátrico en general.