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EDITORIAL

Community perspective on child-friendly medications for drug-resistant TB: importance, priorities and advocacy

Each year, it is estimated that more than 25,000–32,000 children develop TB caused by *Mycobacterium tuberculosis* strains resistant to rifampicin (RR-TB).[1] Globally, the burden of RR-TB varies dramatically, but it remains a disease of poverty. Eight countries, including South Africa, the Philippines and India, account for two thirds of global TB cases,[2] and these are also among the 10 countries with the highest burden of drug-resistant TB (DR-TB).[3] Children with TB continue to be underdiagnosed and even among children diagnosed with TB, rifampicin resistance is routinely overlooked. Children left untreated, or treated with less effective drugs, suffer serious consequences, including death.

Treatment for RR-TB in children lags behind adult treatment regimens/formulations and are often not child-friendly. Although researchers have noted that there is value in, and a need for high-quality paediatric TB research,[4] there has been limited investment in new TB medications for children, or in paediatric TB research in general. For instance, in 2021, investment in paediatric research accounted for just 8% of the total research budget for TB, even though children accounted for 12% of all cases.[5] This results in delays in accessing new and better treatment strategies, as medications must first be evaluated for safety, dosing and tolerability in children. This is often done much too late.[6] Even when safe, effective treatments are available and dosing is well-understood, the medications often have poor palatability. This makes adherence more difficult and can also complicate accurate administration and dosing, especially in young children.[7,8]

We believe that the people most affected by RR-TB have the most to contribute towards finding solutions to the challenges in treating TB. However, people with RR-TB and survivors are often not included in strategies to address these challenges. Children are most likely to be excluded from important research that could benefit their treatment. It is encouraging that RR-TB survivors are increasingly being involved in the process of creating international guidelines – a move that we believe should be encouraged and expanded. Children with RR-TB and their families should be involved in clinical, operational and socio-behavioural research that goes beyond gathering data on dosing and safety, but also addresses important aspects such as acceptability, palatability, preferences, models of care, stigma and education. In response to the challenges faced by children, in our capacity as representatives of and advocates for communities where children are affected by RR-TB, we strongly urge that the following actions should be prioritised in the fight against paediatric RR-TB:

1. Medications for the treatment and prevention of RR-TB should be developed for children as a priority, not as an afterthought. Although there are paediatric formulations for almost all second-line TB drugs through the Stop TB Global Drug Facility (GDF), new formulations are developed for adults, with children only considered at much later stages. Often, as was the case with bedaquiline (the first drug developed to treat TB in more than 50 years), treatment was made available for adults, but it took a further 11 years before it became available to children of all ages. The WHO only recommended its use in young children in 2022.[1,9] This pattern is being repeated with pretomanid. More than 3 years have passed since pretomanid was first approved by the US Food and Drug Administration, and we are still waiting for paediatric investigations to begin.[10] We need to have these medications available for children as an urgent matter of human rights and to change this pattern with the next generation of TB drugs. We urge that formulations for children should be developed alongside adult regimens – this will only be possible if children are included in research earlier and much more efficiently.
2. Even when TB formulations are safe for children, they may not be designed to take into consideration the needs, preferences or lives of children. This includes treatment specifications such as taste, texture, mode of delivery or treatment duration. The assessment of formulations and preferences in this context should prioritise the input of children and their caregivers, instead of relying solely on data derived from evaluations conducted with adults. The recent implementation of a taste evaluation study for linezolid and moxifloxacin is an example of how the preferences of children can be included in future treatment development.[11] We also know that preferences vary according to setting, patient age and other factors such as if multiple children and their caregiver are on treatment together. Developing diverse treatment formats, including dispersible functionally scored tablets and medications that are palatable for children should be a

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priority for paediatric-friendly formulations. Where options are available, children's and caregivers' preferences should inform treatment/preventive therapy regimen.[4]

3. Administering treatment to children impacts not just the child, but also the family, household and the wider community over a prolonged period.[12] TB in children is often a reflection of epidemiology and service availability in the wider community. Integrated family care should be prioritised when considering treatment plans for children. In addition, the treatment requirements of other household members should be included in planning treatment schedules and dispensing, such as treatment for caregivers living with HIV or other comorbidities. Plans for care should be streamlined to minimise the burden on households and appropriate adherence support provided in collaboration with local healthcare services. Additionally, children's educational and developmental needs should be considered, and clinical care provided in a way that minimises school absenteeism.
4. As new RR-TB regimens become available, and as guidelines rapidly change, we need to prioritise meaningful community engagement, including children and their caregivers. Information dissemination should be on appropriate platforms accessible to affected communities and families. Relevant and easily understandable health information regarding RR-TB should be available at community level. Moreover, communities, including community advisory boards, should be involved as advisors and implementers to ensure stronger advocacy for more sustainable health for children. The voices of communities affected by RR-TB, including survivors, need to drive the research and care agenda for children. For example, Ciara Goslett (17 years old), a TB advocate from South Africa, was diagnosed with RR-TB when she was 11 years old. Her treatment journey lasted 8 months and included multiple tablets and daily painful and toxic injections at the time. She emphasises that concrete actions are needed in the fight against RR-TB:

   > So many children get sick with drug-resistant TB every year – I don't want them to go through the painful experience I went through.[13]

5. Even when TB treatment is developed for children and recommendations are made for better, more acceptable paediatric formulations, barriers in accessing treatment persist. There are delays in harmonising the adoption of WHO guidelines to country-specific policies, which affects TB programme preparedness and ultimately, disadvantages those most in need of improved regimens. There is also a disconnect between the development of drugs in trial contexts, the adaptation of WHO recommendations and the implementation of these recommendations at local level. For instance, in 2022, it was reported that in some parts of India, injectable kanamycin was still being administered to people with DR-TB, despite 2018 WHO recommendations against the use of ototoxic injectables for RR-TB.[14,15]
6. At the local level, multiple barriers have been documented for both diagnosis and linkage to care.[16] Without improved access, the development of improved second-line paediatric formulations are futile. More needs to be done to ensure that children are diagnosed and can access the best possible treatment.

We call for children affected by RR-TB and their caregivers' perceptions, preferences and values to be prioritised along the entire care cascade and in research. There is an undeniable need to direct funding towards the development of RR-TB treatment for children and provide access to these once developed. Although some projects have been paving the way for better treatment for children affected by RR-TB, there is still much to do.[4,11,17–22] Researchers, care providers and policymakers should put children and their families front and centre. We need to listen to the voices of children – they deserve better.

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