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Towards Shorter, Child-Friendly Regimens for Treatment of Tuberculosis Disease and Infection in Children

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Tuberculosis (TB) is a major cause of morbidity and mortality in children and adolescents globally.[1] While children generally experience better treatment outcomes with less drug-related toxicity than adults when treated for TB disease or infection, the length of common treatment regimens poses a challenge to the implementation of child-friendly TB care. Undergoing TB disease treatment, which previously ranged from 6 months for drug-sensitive TB to up to 2 years for multidrug-resistant TB (MDR-TB), is socially isolating and often disrupts schooling for children and adolescents. The most common TB preventive treatment (TPT) regimen that has been used for decades is 6 months long, which contributes to low uptake and thus missed opportunities for prevention. Recent changes to recommended regimens have the potential to further improve TB disease treatment outcomes while reducing collateral social consequences, as well as greatly increase the uptake and completion of TPT.[2–4]

Incomplete adherence is a common barrier to treatment success for both disease and infection. "Loss to follow-up" is often the main category of unfavorable treatment outcomes in children reported by national TB programs.[1] Completing TPT for TB infection requires caregivers to administer medications to asymptomatic children. When treated for active disease, symptom resolution usually occurs well within the 2-month intensive phase, and specific education that emphasizes the importance of continued adherence is required to support treatment completion. Similarly, health workers need to take time to explain the rationale and requirement for a child who is well and asymptomatic to take medication daily as TPT. Thus, health system requirements for successful treatment outcomes include not just the availability of medications, but also treatment support, family education and counseling, and regular follow-up for monitoring of weight, symptom development, toxicities, and adherence. Given these considerations, shorter regimens can reduce demands on patients, families, and health services, as well as program costs.

While shorter regimens would benefit children with all forms of TB, shorter and more effective regimens are particularly needed for TB meningitis and MDR-TB, whose treatment has historically been hampered by long, toxic, and not particularly effective regimens.[2,3] TB meningitis is still associated with high mortality and often severe neurological disability among survivors despite 12 months of treatment, including in resource-rich settings.[2,4] The treatment of MDR/RR TB previously required a long treatment course with a combination of multiple drugs often associated with significant toxicity.[3] The inclusion of daily injectable aminoglycosides in regimens to treat MDR-TB often required prolonged hospitalization and commonly caused profound deafness, a major life-long disability, often in young children unable to report hearing loss.

This review highlights recent changes to policy recommendations by the World Health Organization (WHO) for treatment regimens for disease and infection[5,6] (Table 1), and the increasing use of child-friendly formulations of first- and second-line drugs.

TREATMENT OF DRUG-SUSCEPTIBLE TB

Traditionally, recommendations for treatment regimens in children have been extrapolated from evidence from clinical trials in adults. However, children with TB often

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TABLE 1. Recommended Regimens for Treatment of Disease or Infection With Drug-Susceptible TB

	Previous regimen	Recent shorter alternative	Considerations for use of shorter alternative regimen
Nonsevere pulmonary TB	2RHZ(E)[a] 4RH[b]	2RHZ(E) 2RH[c]	Follow definitions for classification of non-severe disease, which will require attention to implement
Peripheral lymph node TB	2RHZ(E) 4RH	2RHZ(E) 2RH	For young children, child-friendly dispersible and appropriately fixed-dose formulations available: R75/H50/Z150; R75/H50; E100
TB meningitis	2RHZE[d] 10RH[e]	6RHZEth[f]	The optimal rifampicin dosage is still being researched. Child-friendly formulations available: R75/H50/Z150; R75/H50; E100; Eto125
TB infection	6H or 9H[g]	3RH[h]	A child-friendly FDC (RH 75/50) is available for 3RH for children (<25 kgs) and has been associated with excellent uptake, feasibility and completion Dose by weight bands without need for breaking tablets or measuring volume of liquid
		4R[i]	4R using tablet formulation (300 mg) is suitable for older children and adolescents Syrup formulations required for young children but limited availability, storage challenges and greater risk of dosing error
		3HP[j]	3HP not yet recommended for contacts of less than two years of age Child-friendly formulations are not yet available but a dispersible formulation of rifapentine is under development Pharmacokinetic and safety data will inform future dosage guidelines for infants

[a]2RHZ(E): 2 months of daily rifampicin, isoniazid, and pyrazinamide with or without ethambutol.
[b]4RH: 4 months of daily rifampicin and isoniazid.
[c]2RH: 2 months of daily rifampicin and isoniazid.
[d]2RHZE: 2 months of daily rifampicin, isoniazid, pyrazinamide, and ethambutol.
[e]10RH: 10 months of daily rifampicin and isoniazid.
[f]6RHZEth: 6 months of daily rifampicin, isoniazid, pyrazinamide, and ethionamide.
[g]6H or 9H: 6 months or nine months of daily isoniazid.
[h]3RH: 3 months of daily rifampicin and isoniazid.
[i]4R: 4 months of daily rifampicin.
[j]3HP: 3 months of weekly isoniazid and rifapentine.

have paucibacillary disease which, though a barrier to bacteriological confirmation of diagnosis, is associated with a lower risk of treatment failure or relapse. The first randomized-controlled clinical trial of the treatment of presumptive drug-susceptible TB in children has shown that a 4-month regimen is non-inferior to a 6-month regimen to successfully treat non-severe forms of TB.[7] The SHINE trial included 1204 children (median age 3.5 years; range 2 months to 15 years) from multiple settings in Africa and India, of whom 11% were HIV-positive and 14% had bacteriologically confirmed disease. The trial reported very high retention and adherence, and similarly high rates of treatment success (97%) were reported for both arms of the study.

It is well recognized that some first-line drugs recommended for the treatment of TB meningitis have poor cerebrospinal fluid penetration, notably rifampicin and ethambutol.[2] Therefore, in South Africa, an alternative 6-month regimen that uses higher dosages of isoniazid and rifampicin and replaces ethambutol with ethionamide, has been the standard of care for over a decade.[8] As observational evidence from children treated for TB meningitis in South Africa reports much lower mortality than has been observed elsewhere using the 12-month regimen, WHO now recommends this shorter regimen as an alternative to the longer regimen using standard dosages (Table).[5] Rifampicin dosage requires consideration as recent evidence suggests improved neurodevelopmental outcomes among survivors of TB meningitis with higher dosages of rifampicin.[9,10]

TREATMENT OF MDR-TB

The recent WHO updates now recommend the use of bedaquiline and delamanid in children of all ages.[5] It is now possible to treat MDR-TB in children, including those with fluoroquinolone resistance, with the same all-oral regimens used in adults (e.g., all-oral bedaquiline-based shorter regimens and all-oral longer regimens). Since 2016, WHO has cautioned against the use of injectable aminoglycosides as second-line drugs in children, which often required prolonged hospitalization and commonly caused treatment-related toxicity associated with a permanent disability.[3] Bedaquiline is an effective Group A second-line drug, and experience of its use and safety profile in young children is now increasing. WHO has recently released a Rapid Communication on the use of even shorter (6–9 months) regimens with fewer medicines (≤ four medicines) for MDR-TB and more extensively resistant TB.[11] Efficacy and safety data for these short all-oral regimens are from studies in adults, and additional data will be needed to extrapolate the results to support use in children.

TREATMENT OF TB INFECTION

There are multiple short and effective TPT regimen options now recommended by the WHO and supported by evidence from trials that have included children and adolescents (Table).[6] Compared to at least 6 months of daily isoniazid, the newer rifamycin-based regimens have similar efficacy but are associated with less drug-related toxicity, improved adherence to completion, and lower costs. Specific issues for the rifamycin-based regimens are listed in the Table. For 3 months of daily rifampicin and isoniazid, a child-friendly dispersible, fixed-dose combination (FDC) is available in many TB endemic countries and has been associated with excellent uptake and completion.[12] This dispersible formulation may not be needed in children who weigh 25 kgs or more, and for such children and adolescents, either the adult rifampicin and isoniazid FDC or a 4-month regimen of daily rifampicin may be used.[5] A 3-month regimen of weekly rifapentine and isoniazid (3HP) is increasingly being used in TB-endemic countries. However, data to support the use of rifapentine in infants and toddlers (<2 years) is not yet available, and implementation of 3HP in children of two years and older requires caregivers to manipulate multiple tablets to administer (e.g., crushing the rifapentine). A dispersible formulation of rifapentine is under development and pharmacokinetic and safety data will inform future use for young children.

Observational data show promise for the effectiveness of TPT for young child contacts of people with MDR-TB.[6] Levofloxacin has been most widely used in this context and the results from randomized controlled trials

of levofloxacin are pending with results available in 2023. However, all regimens under consideration currently are for 6 months and it is likely to be some time before there is evidence to support the use of shorter regimens.

CHILD-FRIENDLY FORMULATIONS

A major step forward in the treatment of TB in children has been the development and availability of dispersible, child-friendly formulations. FDCs of first-line drugs in appropriate ratios were introduced for young children in TB-endemic countries in 2016 and are now in use in over 100 countries. These formulations were used effectively and safely in the abovementioned treatment-shortening SHINE trial with feasibility and acceptability noted by families and health workers.[7] Additionally, ethambutol is available as a dispersible formulation as the fourth drug in the treatment regimen in settings with a high HIV prevalence and/or a high isoniazid resistance prevalence (Table). The dispersible FDCs can be used in the 6-month TB meningitis regimen along with a dispersible formulation of ethionamide.[2] In drug-resistant TB, all WHO-recommended oral medicines, with data to support their use in children, have a commercially developed child-friendly formulation available from the Global Drug Facility—available at https://www.stoptb.org/global-drug-facility-gdf/gdf-product-catalog. These include new medicines, like bedaquiline and delamanid, and repurposed medicines like linezolid, fluoroquinolones and clofazimine. Palatability for young children is critical[13] and there are ongoing efforts to improve the palatability of moxifloxacin. Child-friendly formulations to treat infection include the dispersible formulation of rifampicin (75 mg) and isoniazid (50 mg).[12] A dispersible formulation of rifapentine for use in young children is under development (Table 1).

CHALLENGES FOR IMPLEMENTATION

There are challenges for National TB Programs (NTPs) to adopt shorter alternative regimens (Table 1).[5] There are now two recommended regimens of different duration to treat drug-susceptible pulmonary TB in children with the choice of regimen dependent on the severity of the disease. A major challenge for the implementation of the 4-month regimen for "non-severe" pulmonary TB will be to enable the application of the criteria that define eligibility, which include the severity of radiologic abnormalities. There is limited availability of x-ray equipment and capacity for interpretation at the primary healthcare facility in TB endemic countries where children with nonsevere pulmonary TB is often initially present for care. Investment in diagnostic infrastructure and health care worker training is thus necessary for the adoption of the 4-month regimen. The Union has developed a freely accessible Diagnostic CXR Atlas to support treatment decision-making on basis of the severity of the disease.[14] Indeed, new WHO recommendations for shortened treatment regimens among all age groups provide multiple treatment options and without clear transition plans, NTPs may be challenged with inappropriate use, especially in lower-level facilities. Additionally, NTPs need to update the TB recording and reporting tools which would also inform accurate quantification of TB medicines.

Availability of medicines is also a common challenge, especially in settings where the requirement for use of those medicines can be limited. In TB endemic settings, ethionamide to treat TB meningitis may not be widely available at the primary or secondary facility level or outside MDR-TB treatment facilities. In low TB endemic settings, particularly high-income countries, child-friendly formulations may be challenging for NTPs to procure. However, there have been some successes by some national and state programs in Europe and Australia procuring through the Global Drug Facility.

CONCLUSIONS

Great strides have been made in recent years to develop the tools needed to improve the treatment of TB disease and infection in children. All-oral, shorter regimens and child-friendly formulations should help improve adherence and increase treatment completion. More work is still needed to find the children affected by TB and ensure they are diagnosed and treated appropriately. Child-friendly formulations should be available in all settings to facilitate adoption and implementation of new regimens by national TB programs.

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