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Conducting efficacy trials in children with multidrug-resistant tuberculosis: what is the rationale and how should they be done?

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Abstract

Traditionally paediatric tuberculosis (TB) treatment trials have been limited to phase I/II studies evaluating the pharmacokinetics and safety of drugs in children, with assumptions about efficacy made by extrapolating data from adults. However, it is increasingly recognised that in some circumstances, efficacy trials are warranted and required in children. The current treatment for children with multidrug-resistant (MDR)-TB is long and toxic; shorter, safer regimens, using novel agents require urgent evaluation. Given the changing pattern of drug metabolism, disease spectrum and rates of TB disease confirmation with age, decisions around inclusion criteria require careful consideration. The most straightforward MDR-TB efficacy trial would include only children with confirmed MDR-TB and with no additional drug resistance. Given that it may be unclear at the time treatment is initiated whether the diagnosis will ultimately be confirmed and what the final drug resistance profile will be, this presents a unique challenge in children. Recruiting only these children would however limit the generalizability of such a trial since, in reality, the majority of children with TB do not have bacteriologically confirmed disease. Given the good existing treatment outcomes with current routine regimens for children with MDR-TB, conducting a superiority trial may not be the optimal design. Demonstrating non-inferiority of efficacy but superiority with regard to safety, would be an alternative strategy. Using standardized control and experimental MDR-TB treatment regimens is challenging given the wide spectrum of paediatric disease. However, using variable regimens would make interpretation challenging. A paediatric

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CONFLICTS OF INTEREST

ACH and ATGP participate in the Otsuka Phase I/II Paediatric trials of Delamanid (Otsuka 232 and 233).

MDR-TB efficacy trial is urgently needed, and with global collaboration and capacity building, is highly feasible.

Keywords

Tuberculosis; Children; Multidrug-resistant; Trial

INTRODUCTION

After decades of neglect, the last few years have seen significant interest in clinical research for improved treatment of tuberculosis (TB) in children, with increases in funding and advocacy. TB disease caused by *M. tuberculosis* that is resistant to isoniazid and rifampicin is called multidrug-resistant (MDR)-TB.¹ In contrast to the poor outcomes seen in adults with MDR-TB, where only 50–60% achieve a favourable outcome with current routine regimens,^{2,3} outcomes for children with MDR-TB are typically good, with cure or probable cure achieved in nearly 90%.^{4,5} However, MDR-TB treatment in children remains long and disruptive for children and families, and is associated with significant toxicity.⁶ Children, like adults, are frequently treated with a daily injectable medication for the first 4–6 months of their MDR-TB regimen and at least a quarter of these children develop hearing loss.⁷ One reason that so few children are appropriately treated for MDR-TB is the reluctance of healthcare workers to treat children with the currently available long and toxic regimens, which also frequently require hospital admission.⁸

A CHANGING PARADIGM FOR PAEDIATRIC MDR-TB

The trial landscape in adults with MDR-TB is rapidly evolving, with a focus mainly on the use of novel agents in regimens. Based on phase IIb data, bedaquiline received accelerated approval from the U.S. Food and Drug Administration in 2012, and delamanid received conditional approval from the European Medicines Agency in 2014. Table 1 shows a summary of key phase II/III trials of MDR-TB treatment in adults that are recently completed, ongoing or planned.

For novel TB drugs and regimens which could be used in children, it has traditionally been felt sufficient to extrapolate efficacy from adult studies. Given the more limited forms of TB disease seen in most children and typically low organism load (paucibacillary TB), it has been argued that if a drug or regimen is efficacious in adults, then it will be at least as efficacious in children. Efficacy trials had therefore been deemed unnecessary in children. Formulation development, pharmacokinetic and safety studies were considered the main priority. Ongoing and planned paediatric pharmacokinetic studies of novel and existing anti-TB medications aim to establish the appropriate dose of each medication across the age spectrum and with consideration of HIV infection. Although children often tolerate medications better than adults, some adverse effects may have a disproportionately large impact on young, developing children (such as hearing loss). Establishing the safety of these medications in children is therefore critical. Table 2 shows completed, ongoing or planned paediatric studies of anti-TB drugs used for the treatment of children with MDR-TB.

There is now increasing appreciation that in some instances efficacy trials are required for children. Because children usually have more limited TB disease, which is typically paucibacillary, it may be possible to treat children with regimens of fewer drugs or shorter durations than adults. Efficacy trials would be needed to demonstrate this definitively. The recently initiated Shorter Treatment for Minimal Tuberculosis in Children (SHINE) trial (ISRCTN63579542), compares the efficacy of four months of WHO-recommended first-line therapy to the standard six months in children with non-severe drug-susceptible TB.⁹

Here, we discuss key considerations for designing and conducting efficacy trials for the treatment of children with MDR-TB, including study design, which children should be included, the composition of control and intervention arms, and other important trial implementation elements.

TRIAL DESIGN

Deciding on a superiority trial, a non-inferiority trial or some other type of innovative trial design requires careful consideration. Given the high proportion with favourable outcome among children treated for MDR-TB currently, demonstrating improved efficacy may not be required for a regimen to be useful in children. A regimen that is shorter, less toxic, more tolerable and more acceptable may have a favourable risk-benefit profile even with small improvements in, or slightly worse, efficacy. A non-inferiority design would evaluate whether a regimen is not unacceptably worse than the control with the margin of non-inferiority based on clinical and public health considerations. The multi-arm multi-stage (MAMS) design^{10,11} currently used in several adult TB trials, is useful when several regimens are ready for testing concurrently, particularly in seamless phase II/III studies,¹² where, at intermediate stages, test arms are compared to the control using intermediate objective outcomes (e.g. sputum smear and/or culture conversion), and only promising arms advance to the final stage to be evaluated on definitive outcomes. Sensitive and specific intermediate outcomes are needed to correctly screen out clearly inferior regimens and move only promising regimens to the final stage. Given the current lack of appropriate intermediate outcomes in children treated for TB, particularly if including children with probable (unconfirmed) disease who would not have microbiological endpoints, MAMS designs are not appropriate for paediatric trials at the moment.

WHICH CHILDREN SHOULD BE INCLUDED IN MDR-TB EFFICACY TRIALS?

The spectrum of TB disease in children is influenced by age and by immune status.¹³ Young children (<5 years) tend to develop primary TB which is mainly paucibacillary, but are also at elevated risk of developing disseminated, severe forms of disease including miliary TB and tuberculous meningitis, especially children younger than 3 years of age (Table 3). Although the majority of children 5 to <15 years also develop primary pulmonary TB, from age 8 years they also become more prone to developing large pleural effusions (usually paucibacillary) and adult-type cavitary disease (usually with higher bacillary loads). Older adolescents (15 to <18 years) are more likely to develop adult-type TB, and to respond to anti-TB treatment and have pharmacokinetic parameters more similar to adults. As the rationale for a paediatric efficacy trial is that children tend to have less severe TB disease

and would be expected to respond better than adults, older adolescents would therefore not be suitable candidates to include in such a trial. Older adolescents should be included in late-phase adult TB trials to ensure that they are not excluded from research. Children also tend to have more extrapulmonary TB than adults (up to 30%); the most common form of extrapulmonary TB is peripheral TB lymphadenitis, which is usually a non-severe form of TB and which is currently treated with standard regimens with good outcome.¹⁴ Only children with osteoarticular TB and tuberculous meningitis are usually given longer duration of treatment and/or different drugs, to ensure osteoarticular and meningeal penetration. These two types of TB should therefore probably be excluded from general MDR-TB efficacy trials in children and should be studied in dedicated trials with a focus on the pharmacokinetics of drug penetration into these sites of disease. The severity of TB disease, as classified by Wiseman and colleagues,¹⁵ could influence the outcome of treatment trials, so randomising children to treatment not only within age groups but also according to disease severity could be considered. At a minimum, severity of TB disease should be well documented for subgroup analysis in efficacy trials and chest radiographs should be systematically and rigorously evaluated.

Microbiological confirmation of MDR-TB requires phenotypic identification of *M. tuberculosis* with subsequent drug susceptibility testing (DST) or genotypic identification of both *M. tuberculosis* and genes associated with drug resistance. Confirmation is more likely in children with severe compared to non-severe disease,¹⁶ but the majority of children (60–70%) will not be microbiologically confirmed. Instead, most have probable MDR-TB, defined as evidence of clinical and/or radiologic findings consistent with TB disease together with recent exposure to a known infectious MDR-TB source case.¹⁷ Although limiting study enrollment to confirmed MDR-TB cases would increase confidence that the included children definitely had MDR-TB and allow the use of microbiological endpoints in all trial participants, it would exclude the majority of children with MDR-TB and limit the generalizability of results.

The simplest paediatric MDR-TB trial would include children with *M. tuberculosis* strains resistant to only rifampicin and isoniazid, as standardised control and intervention arms could then be used. However, modelling studies suggest that of children with MDR-TB, 35% have additional resistance to the fluoroquinolones, the injectables or both.¹⁸ Not only would it be more challenging to conduct a trial in only children with MDR-TB without second-line drug resistance, due to fewer eligible children, but it would result in less generalizable and programmatically relevant data.

Because anti-TB treatment should be rapidly initiated in children to prevent disease progression, morbidity and mortality, and because microbiological confirmation and DST can take a number of weeks following appropriate sampling, confirmation status and DST profile may not always be available at the time of study entry and randomisation. One strategic approach would therefore be to include children with both confirmed and probable MDR-TB disease, but to ensure that confirmed cases are well-represented using enrichment. Although children with the full range of DST profiles could be recruited, only those without second-line drug resistance could be randomised to intervention and control arms. Children with additional second-line resistance would be recruited, but not in sufficient numbers to

have power to evaluate efficacy. However, including these children in the trial in a separate treatment arm would provide much needed information on the treatment of this poorly described population.

COMPOSITION OF THE CONTROL ARM

A single, well-defined regimen for the control arm would allow for unambiguous interpretation of trial findings. If the control arm regimen is based on local practice (usually based on WHO guidelines which allow for flexible regimens which evolve with scientific knowledge), the interpretation of the results may be difficult because the experimental treatment is benchmarked to a poorly defined and potentially changing target. However, the use of one control regimen for children with a wide range of disease severities and drug resistance profiles may be either inadequate or excessive.

Currently, a wide variety of regimens are used to treat children with MDR-TB, with regimens varying in drug composition and duration. These are influenced by drug availability, staff expertise, severity of TB disease, degree of second-line drug resistance and local uptake of WHO policy recommendations. Even though a more standardized 9–12 month shortened regimen has recently been approved by WHO for the treatment of MDR-TB in children without second-line drug resistance,¹⁹ experience with this regimen is limited in both children and adults, and it would not be an appropriate choice for children with more extensive resistance. It should be noted that the majority of adult MDR-TB treatment trials currently underway use local standard of care as the control arm, leading to regimens that differ by patient and by site. To date this variability has not led to concerns about the validity of these studies. Two options, therefore exist. The first (in our opinion less ideal) would be to use a variable control arm that includes any WHO-endorsed treatment regimen. The second (our preferred) option would be to use a fixed control arm but limit it to those with either more restricted disease severity or resistance profile.

COMPOSITION OF AN EXPERIMENTAL ARM REGIMEN

Thinking regarding the ideal composition of regimens for the experimental arm of a paediatric MDR-TB trial is evolving, due to the increasing pace of clinical trials and a dynamic and evolving regulatory and international guideline environment. Given the high prevalence of irreversible toxicities in children with MDR-TB treated with the injectable agents,⁷ and the increasing availability of more effective and less toxic drugs, it is more and more difficult to justify the inclusion of injectables in paediatric MDR-TB regimens. Clofazimine, linezolid and delamanid are all among the agents currently recommended by WHO for use in children with MDR-TB.^{19,20} No paediatric data on bedaquiline are yet available. Overall, the choice of regimens in an MDR-TB trial should take into account the drugs' differing mechanisms of action, toxicities, mechanisms of resistance, absorption/bioavailability and ease of use. In addition emerging data for both novel drugs, like delamanid and bedaquiline, and novel MDR-TB regimens in adults should be considered, as well as the suitability of combining these drugs into combination regimens, including in HIV-infected children. An additional essential consideration is the current or future availability of child-friendly, palatable, taste-optimized drug formulations. Dispersible

formulations have the advantage of stability and storability without requiring a cold chain, and easy measurability even at the lowest doses.²¹ Table 4 describes several candidate anti-TB agents for inclusion in potential paediatric MDR-TB trials, along with their attributes. In designing an experimental regimen, the potential for drug-drug-interactions, including antiretroviral drugs, and additive toxicity between the various elements in a novel regimen deserves attention in children. Overlapping or additive toxicities, such as QT prolongation (bedaquiline, fluoroquinolones, clofazimine, delamanid) or mitochondrial toxicities (linezolid and NRTIs) need to be carefully considered in regimen design. The current lack of pharmacokinetic and safety data in children, or child-friendly formulations is a major limitation to potential experimental arm regimens in a paediatric trial. Bedaquiline, a component of many novel regimens under evaluation in adults, is only now being studied in pediatric phase I/II trials, with data on optimal dosing across children of all ages and including HIV-infected children, likely years away still. Paediatric phase I/II trials of pretomanid, also a promising novel drug in phase III adult studies, are only in the early planning stages. A paediatric efficacy trial must therefore either wait years for these data, or build its experimental arm regimen with other available and novel agents. The current lack of data on some drugs, like bedaquiline, highlights the negative impact that delays have in evaluating novel or repurposed TB drugs in children.

ADDITIONAL CONSIDERATIONS AROUND THE IMPLEMENTATION OF PAEDIATRIC MDR-TB TRIALS IN CHILDREN COMPARED TO ADULTS

Some additional aspects should be considered in the design and implementation of paediatric TB efficacy trials, which differ to adult studies (Table 5). The first is around the feasibility of recruiting enough children for a sufficiently powered trial. Although large numbers of children are estimated to develop MDR-TB each year, only a small proportion is currently diagnosed and treated, largely in specialist centres. Multiple sites globally would be required to recruit adequate numbers of children over a number of years, rendering such trials expensive. Given the under-diagnosis of MDR-TB in children in many settings, building capacity for an efficacy trial has the potential to increase the diagnosis of paediatric MDR-TB, improve care, and also enhance recording and reporting of paediatric MDR-TB. An efficacy trial would also be synergistic with improved active case finding of children with MDR-TB through new programmes and research, including several ongoing and planned phase III MDR-TB preventive therapy trials.

Another consideration is the ascertainment of adverse events. While older children and adults are able to articulate that they are experiencing symptoms such as pain, headache or nausea, younger children are less able to do so, and identifying such adverse events requires caregivers' perception and reporting. This issue is not unique to an MDR-TB trial. However one important consideration is hearing testing, given the expected inclusion of injectable drugs in a control arm regimen. Specialized audiologic equipment and expertise, particularly for those less than 5 years of age is limited in most settings with a high burden of MDR-TB. Capacity building around these aspects is therefore needed. Longer term follow-up may also be needed to capture neurodevelopmental effects.

Ethical issues surrounding research in children with MDR-TB must be carefully considered, with the well-being of the child central to decision-making. Historically, it could be argued that a narrowly applied approach to protectionism has resulted in perversely blocking children from access to rational evidence-based therapeutics from which they could benefit. Children cannot provide informed consent for participation in clinical research, and the youngest children (typically below 7 years of age) cannot provide informed assent. It is however imperative that children benefit from research on TB regimens to the same extent as adults and that caregivers and children are actively involved in decision-making regarding research participation. It is imperative that the burden of TB and its treatment be minimized for both children and their families by identifying safer, shorter, better tolerated, and effective regimens which ideally do not routinely require hospitalization. In order to understand how novel and repurposed pharmacological agents can best serve children with TB, these agents must be rigorously studied in children in appropriate regimens, with meticulous attention to efficacy, safety and pharmacokinetics. The alternative is widespread clinical use of drugs (or regimens) in the absence of any paediatric-specific evidence, in what otherwise would amount to an uncontrolled experiment and ongoing off-label use of drugs and regimens, as has been the case for most second-line anti-TB drugs in children to date. This historical approach has been associated with unacceptable toxicity and long treatments in many children with MDR-TB.

CONCLUSIONS

Traditional approaches to the identification of optimal paediatric TB treatment regimens for evaluation in clinical trials are being reconsidered and there is an increasing appreciation that efficacy trials are needed to treat children with MDR-TB optimally. Consideration should be given to including children with confirmed and probable MDR-TB disease and with the full spectrum of drug resistance. Conducting a rigorous MDR-TB efficacy trial in children would demonstrate that MDR-TB can be diagnosed and safely and effectively treated with shorter more child-and family-friendly strategies.

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Key phase II and III trials in adults of treatment for multidrug-resistant tuberculosis with their intervention arm components

Table 1.

Trial name, identifier	Phase	Components of intervention arm/s
NC005: A phase 2 open label partially randomized trial to evaluate the efficacy, safety and tolerability of combinations of bedaquiline, moxifloxacin, pa-824 and pyrazinamide in adult subjects with drug-sensitive or MDR pulmonary tuberculosis; NCT02193776	II	PZA, BDQ, PTA, MFX
Opti-Q: Efficacy and safety of levofloxacin for the treatment of MDR-TB; NCT01918397	II	LFX+ standard of care
STREAM: Evaluation of a standard treatment regimen of anti-tuberculosis drugs for patients with MDR-TB; NCT02409290	III	Stage 1: hdMFX, PZA, EMB, KAN, hdINH, CFZ Stage 2: BDQ, CFZ, EMB, PZA, LFX, INH, PTO
NIX-TB: A Phase 3 Study Assessing the Safety and Efficacy of Bedaquiline Plus PA-824 Plus Linezolid in Subjects With Drug Resistant Pulmonary Tuberculosis; NCT02333799	III	LZD, BDQ, PTA
STAND: Shortening Treatment by Advancing Novel Drugs; NCT02342886	III	PZA, MFX, PTA
NEXT-TB: An Open-label RCT to Evaluate a New Treatment Regimen for Patients With Multi-drug Resistant Tuberculosis; NCT02454205	II/III	LZD, BDQ, PZA, LFX, ETO/hdINH/TZD
Trial 213: Safety and efficacy trial of delamanid for 6 months in patients with MDR-TB ; NCT01424670	III	DLM + standard of care
TB-PRACTICAL: Pragmatic clinical trial for a more effective concise and less toxic MDR-TB treatment regimens; NCT02589782	II/III	BDQ, PTA, MFX, LZD, CFZ
MDR-END: Treatment shortening of MDR-TB using existing and new drugs; NCT 02 619994	III	DLM, LFX, LZD, PZA
endTB: Evaluating Newly Approved Drugs for MDR-TB; NCT02754765	III	LFX, MFX, BDQ, DLM, LZD, CFZ
DAZZLE: Efficacy and tolerability of delamanid, linezolid, pyrazinamide and levofloxacin; NCT02975570	III	DLM, LZD, PZA, LFX

MDR = multidrug-resistant; TB = tuberculosis; PZA: pyrazinamide; BDQ: bedaquiline; PTA: pretomanid; MFX: moxifloxacin; LFX: levofloxacin; EMB: ethambutol; KAN: kanamycin; CFZ: clofazimine; INH: isoniazid; PTO: prothionamide; LZD: linezolid; TZD: terizidone; DLM: delamanid; hd: high-dose

Table 2. Summary of ongoing and planned clinical research on antituberculosis drugs in children with multidrug-resistant tuberculosis

Protocol Name/Number Trial Registration	Phase	Design	Primary objective	Special populations or considerations	Funder, sponsor, principal investigator	Network, countries	Status
Otsuka 232 and 233 NCT01856634/NCT01859923	I II	Open-label, single arm dose finding study of delamanid in HIV-negative children with MDR-TB	Evaluate the PK, safety, tolerability and anti-mycobacterial activity of Delamanid in combination with MDR-TB therapy for HIV-uninfected and HIV-infected children and adolescents	Children, infants, adolescents HIV-uninfected; Pop PK modeling; age de-escalation	Otsuka Hafkin J	N/A Philippines, South Africa	Enrolling; age group 1, 2,3 accrued; group 4 enrolling
IMPAACT 2005: Delamanid DDI	I/II	Open-label, single arm dose finding study	Evaluate the PK, safety, tolerability and anti-mycobacterial activity of Delamanid in combination with MDR-TB therapy for HIV-infected and uninfected children and adolescents	Children, infants, adolescents HIV-infected and -uninfected; Pop PK modeling	NIAID/NICHD Dooley K	IMPAACT network, South Africa, Botswana, Tanzania	Opening 2018
MDR-PK1 study NICHD-069169	N/A	Intensive PK sampling, routine 2ndline TB drugs	Evaluate the PK and safety of secondline antituberculosis drugs in HIV-infected and uninfected children	Children, infants, adolescents HIV-infected and -uninfected; drug-drug interactions with ARVs	NICHD-R01 HesseltingAC	N/A South Africa	Completed; in dissemination phase
IMPAACT P1108: Bedaquiline	I/II	Open-label, single arm dose finding and safety study	Evaluate the PK, safety, tolerability and anti-mycobacterial activity of Bedaquiline in combination with MDR-TB therapy for HIV-infected and uninfected	Children, infants, adolescents HIV +/- Pop PK modeling Age de-escalation	NIAID/NICHD HesseltingAC	IMPAACT South Africa, India, Haiti	Open to accrual (Q3 2017)

Protocol Name/Number Trial Registration	Phase	Design	Primary objective	Special populations or considerations	Funder, sponsor, principal investigator	Network, countries	Status
Janssen C211 Paediatric Bedaquiline NCT02354014	II	Open-label, single arm dose finding and safety study	Evaluate the PK, safety, tolerability and anti-mycobacterial activity of Bedaquiline in combination with MDR-TB therapy for HIV-uninfected children and adolescents	Children, infants, adolescents HIV-Age de-escalation	Janssen Danneman B	N/A Russia, South Africa, The Philippines	Opened to accrual (Q2 2016)
TASK-002: Bioequivalence of bedaquiline 400mg administered in crushed form compared to tablet form in healthy male and female adults underfed conditions (BDQ CRUSH Study)	I	Randomized, open label, two-period crossover, bioequivalence study	To evaluate the bioequivalence of bedaquiline 400mg (4x100mg) given to adult healthy male and female volunteers orally in crushed form, compared to the original tablet form under fed conditions.	Healthy adult male and female volunteers	NIAID du Bois J, Garcia-Prats AJ,	IMPAACT/ACTG South Africa	Completed, disseminated
MDR-PK2 IR01HD083047-01 Optimizing and operationalizing paediatric drug resistant TB treatment	N/A	Semi-intensive PK sampling, model-based analysis; focus on moxifloxacin, levofloxacin, linezolid	PK, safety, acceptability of modeled optimized doses of moxifloxacin, levofloxacin, and linezolid in children with MDR-TB	Infants, children, adolescents (0- <18 years), HIV-infected and HIV-uninfected	NICHD, R01 Garcia-Prats AJ, Savic R,	N/A South Africa	Enrolling

MDR = multidrug-resistant; TB = tuberculosis; PK= pharmacokinetics; Pop PK = population PK; NIAID = National Institute of Allergy and Infectious; NICHD = National Institute of Child Health and Development; IMPAACT = Infant Maternal Paediatric and Adolescent AIDS Clinical Trial network; ACTG = AIDS Clinical Trial Group

Expected differences in children with tuberculosis compared to adults with tuberculosis which could influence the treatment outcome of drug trials

Table 3.

Characteristic	Age <5 years	Age 5 to <15 years	Age 15 to <18 years
Drug metabolism	Most different from adults due to maturation and body composition	Still some pharmacokinetic differences observed compared to adults	Similar to adult metabolism, although body weight may vary
Type of TB	Mainly primary TB (paucibacillary), but progressive primary pulmonary TB and isseminated TB may occur especially in younger children	Mainly primary pulmonary TB (paucibacillary), but switch to adult-type cavitary TB occurs from puberty (8–12 years). Up to 30% extrapulmonary TB	Mainly adult-type cavitary pulmonary TB (high bacillary load). Large pleural effusions (paucibacillary) may occur
Disease severity	Varies depending on disease progression and dissemination especially in infants	More often non-severe but severe if adult-type pulmonary TB	Usually severe, as adult-type pulmonary TB
Microbiological confirmation	Most difficult obtaining appropriate specimens, but infants and those with progressive pulmonary TB often confirmed	Specimens more readily available if old enough to cough and expectorate. Yield low in primary TB, but high if adult-type pulmonary TB	Specimens easy to obtain. Both smear and culture yield high with pulmonary disease
Natural history of TB disease progression after infection	Highest risk of developing TB disease, but often not diagnosed because specimens not obtained or microbiologically negative results	Lowest risk of developing TB after infection 5–10 years of age, thereafter increasing risk of pulmonary TB as well as microbiologically positive (adult-type pulmonary TB)	Similar risk to adults to develop disease after infection, but may have community TB contact more often therefore confirming drug resistance more important

TB: tuberculosis

Table 4. A Summary of drugs to be considered for use in a paediatric multidrug-resistant tuberculosis regimen in the trial context

Drug Name	Mechanism of Action	Mechanism of Resistance	Toxicity	Distribution/Penetration	Ease of Use	Paediatric Formulation Available or in Development? ^{21,22}
Bedaquiline ²³	ATP synthase inhibitor; bactericidal	Upregulation of efflux pumps	Mitochondrial toxicity; QTc prolongation	Not well understood	Bioequivalence of tablet and crushed form currently being evaluated in TASK-002 study	No (Bioavailability study of 20mg dispersible tablet completed by Janssen; not currently available)
Clofazimine ^{24,25}	Targets respiratory chain of MTB's outer membrane. Poor 14-day EBA; bacteriostatic	Upregulation of efflux pumps	QTc prolongation; hyperpigmentation; GI disturbance	Highly lipophilic and taken up extensively by body fat; poor CSF penetration	Gelcaps (soft capsules that cannot be split or cut)	No
Cycloserine/Terizidone (two molecules of cycloserine joined by terephthalaldehyde) ²⁶	Mycobacterial cell wall synthesis inhibitor; bacteriostatic	Resistance mediated by mutations in genes for D-alanyl-D-alanine synthetase	CNS toxicity (depression, anxiety, psychosis, dizziness, speech slurring; convulsions); Thyroid toxicity	Good CSF penetration: CSF concentrations equivalent to those in serum	Film-coated hard caplet or capsule; Capsules can be opened and dissolved in water in case of pill-swallowing issues.	Arguably (125mg minicapsule of cycloserine developed by MacLeods Pharmaceuticals, India)
Delamanid ²⁷	Mycobacterial cell wall synthesis inhibitor Bactericidal & sterilizing	Resistance mediated by mutations in mycobacterial F420 genes (necessary for activation of the prodrug)	QTc prolongation in adults; some GI intolerance	Poor oral bioavailability 25–47%	Twice daily dosing; ongoing trials and population PK models will establish the once daily dose	Yes (Scored, fully dispersible tablet in strawberry and cherry flavors (Otsuka))
Ethambutol	Mycobacterial cell wall synthesis inhibitor; Bacteriostatic	Resistance conferred by embCAB mutations	Optic neuritis; rare hepatotoxicity	Bioavailability reduced by 20% if given with antacids; poor CSF penetration	Can be dosed once daily (20mg/kg) or twice weekly (50mg/kg)	Yes (Dispersible tablet 100mg developed by MacLeods Pharmaceuticals, India)
Ethionamide ^{28,29}	Mycolic acid synthesis inhibitor. Bacteriostatic or bacteriocidal	Cross-resistance btw ethionamide/prothionamide and INH (via InhA mutations)	Gastrointestinal toxicity; hypothyroidism; CNS toxicity	Completely absorbed after PO administration; no first-pass metabolism; good CSF penetration	Can be dosed daily, twice daily, or thrice daily	Yes (Scored dispersible tablet developed by MacLeods)

Drug Name	Mechanism of Action	Mechanism of Resistance	Toxicity	Distribution/Penetration	Ease of Use	Paediatric Formulation Available or in Development? ^{21,22}
Isoniazid	Mycolic acid biosynthesis inhibitor. Highly bactericidal	Low-grade resistance (overcome with high-dose INH); InhA mutation. High-grade resistance: KatG mutation	Hepatotoxicity, rash, peripheral neuritis, psychosis	Genetically determined NAT2 acetylation status may impact the effective dose Good CSF penetration	Can be dosed once daily or twice weekly	Pharmaceuticals, India
Levofloxacin	Mycobacterial DNA gyrase inhibitor; Bactericidal	Resistance via mutations in the genes <i>gyrA</i> and <i>gyrB</i> , encoding mycobacterial DNA gyrase	Minimal QTc prolongation; GI intolerance; neurological complaints; arthralgia/arthritis	Excellent oral bioavailability Large volumes of distribution >2L/kg Good CSF penetration	Twice daily dosing for children under 5 years of age; once daily for children >5;	Yes (Dispersible tablet developed by MacLeods Pharmaceuticals, India)
Linezolid ³⁰	Mycobacterial protein synthesis inhibitor; Bacteriostatic (minimal EBA; no late bactericidal activity)	Resistance mediated by mutations in mycobacterial ribosomal protein L3 or 23S rRNA	Mitochondrial toxicity; Marrow suppression; neurotoxicity; optic & peripheral neuritis; pancreatitis; lactic acidosis	Excellent oral bioavailability of tablet (103%) Good CSF penetration	Non-scored tablets or suspension of 20mg/mL Thrice daily dosing	Yes (Dispersible tablet developed by MacLeods Pharmaceuticals, India)
Moxifloxacin	Mycobacterial DNA gyrase inhibitor; Bactericidal	Resistance via mutations in genes <i>gyrA</i> and <i>gyrB</i> , encoding mycobacterial DNA gyrase	QTc prolongation; GI intolerance; neurological complaints; arthralgia/arthritis	Excellent oral bioavailability Large volume of distribution >2L/kg Good CSF penetration	Once daily dosing Much larger tablet than levofloxacin	Yes (Dispersible tablet developed by MacLeods Pharmaceuticals, India)
Para-aminosalicylic acid (PAS) ³¹	Inhibits folate synthesis pathway of MTB, via a metabolite	Resistance via mutations in DHFS or chemical inhibition of DHPS	0.5% hypersensitivity reaction usually occurs in first 3 months (first sign is a rash)	Granules offer more sustained drug levels compared with the immediate-release formulation Poor CSF penetration	Coated granules in a sachet (PAS-Extended Release) ameliorate GI intolerance	Arguably (Granules manufactured by Jacobus; Dosing spoon—limited utility at the lowest weights)
Prothionamide	Mycolic acid synthesis inhibitor. Bacteriostatic or bacteriocidal	Resistance mediated by mutations in <i>InhA</i>	Gastrointestinal toxicity; hepatotoxicity; hypothyroidism; CNS toxicity	Completely absorbed after PO administration; no first-pass metabolism Good CSF penetration	Once-daily dosing (can be given twice daily if once daily is poorly tolerated)	No
Pyrazinamide	Mechanism unclear Sterilizing activity	Resistance mediated by mutations in <i>pncA</i> gene	Hepatotoxicity, hyperuricemia/arthritis	Excellent oral bioavailability and absorption Good CSF penetration	Once-daily or twice-weekly dosing	Yes (Dispersible tablet 150mg developed by MacLeods)

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Drug Name	Mechanism of Action	Mechanism of Resistance	Toxicity	Distribution/Penetration	Ease of Use	Paediatric Formulation Available or in Development? 21,22
						Pharmaceuticals, India)

Table 5. Challenges and potential solutions in the conduct of treatment trials for children with multidrug-resistant tuberculosis

Challenges	Potential Solutions
Fewer than 50% children with clinical TB have confirmed disease	Include children with confirmed and probable TB but design the study to enrich the sample for those with confirmed disease. If possible power the study for a primary analysis to be done among those with confirmed disease. Every effort should be made to confirm the diagnosis through appropriate sampling.
A third of children with MDR-TB have second-line drug resistance	Include children with the spectrum of drug resistance profiles but design the study so that it is powered for the primary analysis focussed on those with MDR-TB and no additional resistance.
At the time the clinical diagnosis of MDR-TB is made the final bacteriological confirmation status and DST may be unknown	Include children with strong clinical evidence of MDR-TB and randomise at that point; complete careful bacteriological evaluation.
Only a small number of children globally are diagnosed with MDR-TB, making recruitment challenging	The trial itself will increase case detection as will training and education at trial sites. The increasing number of programmes and trials evaluating contacts of MDR-TB will identify increasing numbers of children with MDR-TB disease.
Deciding on a control arm is challenging given the wide range of presentations and drug resistance profiles seen	Providing one standard control arm for children with MDR-TB and no additional resistance would permit clean comparisons. By including children with more advanced resistance patterns, and providing a separate regimen for those children would provide valuable prospective observational data were none currently exist
Outcomes are already good for children who are diagnosed and appropriately treated for MDR-TB	Consider a non-inferiority trial to demonstrate similar efficacy but improved toxicity and acceptability.
Adverse events can be difficult to assess in children	Use rigorous validated case definitions; evaluation of adverse events should use objective measures and should be blinded to study arm, if possible.
Defining treatment outcomes is challenging in the absence of a microbiologically confirmed diagnosis at treatment initiation	Attempt to confirm the diagnosis microbiologically where possible using pre-treatment samples and collect samples at follow up to confirm microbiological cure. Where the diagnosis is not confirmed, use consensus definitions to classify outcomes. ¹⁷
Treatment duration of experimental and control regimens differ; the duration of follow up is unclear, too short a period of follow up does not permit assessment of relapse, too long may lead to children being re-infected and developing a second, separate TB episode	Use the same period of follow up for control and experimental arms to allow comparison of regimen efficacy selected to minimize the competing impact of these issues. Post-treatment follow-up resulting in differential total follow-up (treatment plus post-treatment) can be done per international guidelines and can serve as a secondary outcome.
A young child is unable to provide informed consent for inclusion in a trial	Engage with families in home languages and sensitise and mobilize communities. As soon as children are old enough to engage, request consent from the parents and assent from the child.

TB: tuberculosis; MDR: multidrug-resistant; DST: drug susceptibility testing