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Towards earlier inclusion of Children in Tuberculosis (TB) drugs trials: Consensus statements from an Expert Panel

Sharon Nachman, **Amina Ahmed**, **Farhana Amanullah**, **Mercedes C Becerra**, **Radu Botgros**, **Grania Brigden**, **Renee Browning**, **Elizabeth Gardiner**, **Richard Hafner**, **Anneke Hesseling**, **Cleotilde How**, **Patrick Jean-Philippe**, **Erica Lessem**, **Mamodikoe Makhene**, **Nontombi Mbelle**, **Ben Marais**, **Helen McIlleron**, **David F Mc Neeley**, **Carl Mendel**, **Stephen Murray**, **Eileen Navarro**, **Gloria E Oramasionwu**, **Ariel R Porcalla***, **Clydette Powell**, **Mair Powell**, **Mona Rigaud**, **Vanessa Rouzier**, **Pearl Samson**, **H. Simon Schaaf**, **Seema Shah**, **Jeff Starke**, **Soumya Swaminathan**, **Eric Wobudeya**, and **Carol Worrell**

SUNY at Stony Brook, Stony Brook, NY (SN), Levine Children's Hospital at Carolinas Medical Center, Charlotte, NC (AA), Indus Hospital, Pakistan (FA), Harvard Harvard Medical School, Boston, MA (MCB), European Medicines Agency, London, United Kingdom (RB1), Médecins Sans Frontières, Access Campaign, Geneva, Switzerland (GB), NIH/NIAID/DAIDS, Bethesda, MD (RB_2, RH), TB Alliance, New York, NY (EG, CM, SM), Desmond Tutu TB Centre, Department of Pediatrics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa (AH, HSS), Department of Pharmacology and Toxicology, University of the Philippines, Manila (CH), HJF-DAIDS, a Division of The Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc., Contractor to NIAID, NIH, DHHS (PJP), Treatment Action Group, New York, NY (EL), NIH/NIAID/DMID, Bethesda, MD (MM), Department of Medical Microbiology, University of Pretoria, Pretoria, South Africa (NB), Marie Bashir Institute for Infectious Diseases and Biosecurity (MBI) and the Sydney Emerging Infectious Diseases and Biosecurity Institute (SEIB) and The Children's Hospital at Westmead, Sydney Medical School, University of Sydney, Sydney, Australia (BM), Division of Clinical Pharmacology, Department of Medicine, University of Cape Town (HM), Novartis Pharmaceuticals (DFM), Division of Anti-

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Corresponding Author, Sharon Nachman, MD, Department of Pediatrics, Childrens hospital of Long Island, State University of New York at Stony Brook, HSC SUNY Stony Brook, Stony Brook, NY 11794-8111, sharon.nachman@stonybrook.edu.

*Current affiliation: Medical Director, Product Safety Team Lead, Infectious Disease Therapeutic Area, Global Pharmacovigilance, Abbvie, North Chicago, IL

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Infective Products; Office of Antimicrobial Products, Office of New Drugs, CDER, FDA (EAN, ARP*), US Centers for Disease Control and Prevention, Division of Tuberculosis Elimination, International Research and Programs Branch (GEO), US Agency for International Development, Washington, DC (CP), New York University School of Medicine, NY, NY (MR), GHESKIO, Portau-Prince, Haiti (VR), SDAC-CBAR/Frontier Science, Harvard School of Public Health, Boston, MA (PS), Department of Bioethics, NIH Clinical Center, Bethesda, MD (SS_1), Baylor College of Medicine, Houston, TX (JS), Director, National Institute for Research in Tuberculosis, Chennai, India (SS_2), Makerere University Johns Hopkins Research Collaboration, and Mulago National Referral Hospital, Kampala, Uganda, (EW), Eunice Kennedy Schriver, National Institute of Child Health, NIH (CW)

Abstract

Children represent a significant proportion of the global tuberculosis (TB) burden, and may be disproportionately more affected by its most severe clinical manifestations. Currently available treatments for pediatric drug-susceptible (DS) and drug-resistant (DR) TB, albeit generally effective, are hampered by high pill burden, long duration of treatment, coexistent toxicities, and an overall lack of suitable, child-friendly formulations. The complex and burdensome nature of administering the existing regimens to treat DS TB also contributes to the rise of DR TB strains. Despite the availability and use of these therapies for decades, a dearth of dosing evidence in children underscores the importance of sustained efforts for TB drug development to better meet the treatment needs of children with TB. Several new TB drugs and regimens with promising activity against both DS and DR TB strains have recently entered clinical development and are in various phases of clinical evaluation in adults or have received marketing authorization for adults. However, initiation of clinical trials to evaluate these drugs in children is often deferred, pending the availability of complete safety and efficacy data in adults or after drug approval. This document summarizes consensus statements from an international panel of childhood TB opinion leaders which support the initiation of evaluation of new TB drugs and regimens in children at earlier phases of the TB Drug development cycle.

Keywords

childhood TB; drug resistant TB; pharmacokinetics; ethics; clinical trial; new anti-TB drugs

INTRODUCTION

TB is a major, but often unrecognized, cause of morbidity and mortality among children in the developing world. Current figures probably underestimate the global disease burden, with childhood TB cases accounting for an estimated 6% of reported cases, [1] and at least double this percentage in highly TB-endemic areas. [2] Underdiagnosis (and thus underreporting) is of special concern in younger children who are at greatest risk of disease progression following TB exposure and infection, and in whom microbiologic or other diagnostic confirmation of both tuberculous infection and disease is most problematic. [3] HIV infection increases the risk of TB disease and death, particularly in the absence of antiretroviral treatment. [4–10] Of further concern is that the number of children with DR-TB is increasing globally. [11–16] TB treatment, including treatment for DR-TB, can be effective

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for children, [17] but is limited by poor service delivery, a lack of child-friendly drug formulations, and a scarcity of data on safety, dosing, and drug-drug interactions. [17–22] A critical gap persists for the treatment of DR-TB: new drugs and regimens are needed for children, and more data are needed to strengthen the evidence base and guide the use of existing second-line drugs [18, 23] decrease pediatric TB medicines' market fragmentation and improve access to these drugs. [24] This document, which builds on previous similar efforts [25, 26], presents consensus statements from an expert panel to promote strategies for the timely collection of evidence on safety and dosing of TB drugs in children to guide clinical management and optimize the care of children with TB.

CONSENSUS STATEMENTS PREPARATION

Search strategy and selection criteria

Before the workshop, relevant literature was surveyed (SN, RB_2, PJP) to review evidence and prepare statements for discussion. The databases we searched included PubMed, Medline, Embase with an emphasis on English language papers published during the past 10 years in peer-reviewed journals. Some older papers were also included if they were judged to be important by the authors. Search terms included "TB", "childhood TB", "Anti TB treatment", "MDR-TB treatment", "MDR-TB outcomes", "Drug Exposure", "Pharmacovigilance", "clinical trials", "Drug Development", "HIV-infected", "Pharmacokinetics", "Ethics".

Consensus generation

Expert pediatric TB clinicians, researchers, and opinion leaders were invited to a workshop, "Towards Earlier Involvement of Children and Pregnant Women in Trials of New TB Drugs", organized by the National Institutes of Health (NIH) in Bethesda, MD, in May 2013. The expert Panel's consensus on pregnant or lactating women is reported separately. Members from regulatory agencies were invited to attend as non-voting panelists.

Draft statements were circulated to panelists for review and comment, discussed on teleconference calls, revised accordingly and drafts distributed to participants before the workshop. During timed discussions, a group consensus approach was used, that included modifying the statements in real time based on panelists' suggested modifications. Edited statements underwent panel vote. Voting rules included 2 options: agree or disagree, as indicated by a show of hands. Consensus was declared for a statement if ≥75% of panelists agreed to the final draft statement. All statements were further reviewed in a final plenary workshop session. After the workshop, additional conference calls were held with panelists to finalize consensus.

STATE OF RESEARCH ON NEW TB DRUGS IN CHILDREN

Ongoing and planned trials

This is a particularly exciting time in TB drug research. New drugs, many with novel mechanisms of action, novel drug combinations and strategies to treat TB are being investigated. Clinical trials for DR-TB in adults are currently underway for new nitroimidazoles (delamanid, PA-824), oxazolidinones (sutezolid, linezolid, AZD5847),

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bedaquiline, and clofazimine. [27–30] Some of these drugs have received accelerated approvals for marketing. [31–33] Novel combinations that include both new chemical entities and older or repurposed drugs are being tested in adults in studies such as 'REMox'(Rapid Evaluation of Moxifloxacin in the treatment of sputum smear positive tuberculosis), the Global Alliance for TB Drug Development's 'NC002' (PA-824, moxifloxacin, and pyrazinamide) and 'NC003' (clofazimine, bedaquiline, PA-824 and pyrazinamide) trials, and the 'STREAM' (The Evaluation of a Standardised Treatment Regimen of Anti-Tuberculosis Drugs for Patients with multidrug-resistant [MDR]-TB) trial. [34–36] Unfortunately, studies in children lag significantly behind adult studies, and safety and pharmacokinetic studies to support a pediatric indication are currently on-going or planned in children for very few of these novel treatments (delamanid and bedaquiline). This lag in developing studies in children is reflected in research and development investments for pediatric TB accounting for just two percent of the total funding invested in TB research overall [37] but a quarter of the estimated need. [38] Figure 1 illustrates main phases in TB drug development and Table 1 summarizes relevant TB treatment studies in children, known to the authors.

Ethical considerations

Children are a vulnerable group with limited or developing autonomy and are legally disallowed from providing informed consent. Children, therefore, require special measures to protect them from exploitation and harm. Many international guidance documents and regulations specify acceptable risk/benefit ratios and require that research involving children offers a prospect of benefit, or poses minimal risk. [39] An acceptable risk/benefit balance for the involvement of children in clinical trials depends not only on the risk/benefit ratio of a study for the individual child, but also on the available alternatives and the social value of the research [40], which for children depends on the burden of the disease being studied and the need for the intervention in that population.

A concern is that involvement of children in research at earlier stages of drug development may expose them unnecessarily to investigational drugs with uncertain future and undocumented safety risks. Some ethics guidance documents require that children be enrolled in research only if the research cannot be conducted in adults. [41] Others propose initiating pediatric studies (Phase I or II), particularly in children with serious and life-threatening diseases who could benefit from the study intervention, after obtaining preclinical safety data and evidence of efficacy from adult studies. [42, 43] Both TB in young children, [10] and DR-TB in all children, [20, 44] are serious and life-threatening conditions with limited treatment options, with affected children potentially further harmed by the dearth of data to guide use of existing drugs. Thus, TB drug research can and does, in such instances, offer a prospect of direct benefit to children that outweighs the risks of proceeding to pediatric trials with relatively incomplete (i.e. before Phase III) adult data. For these reasons, the earlier involvement of children in specific TB trials may be ethically justified.

Regulatory environment

Although drug regulatory legislation in both the United States (US) [45] and Europe [46] similarly provides incentives for the inclusion of children as part of any product's development plan, the requirement for studies in children in an orphan indication differ. In

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the US, drugs intended to treat TB generally qualify for orphan designation under the orphan drug regulations, [47] and inclusion of children in pre-licensure trials is not required. [45] Similarly, drugs intended to treat TB can enjoy orphan medicinal product status in Europe, however no exemption is given for inclusion of children in trials investigating new TB therapies, and a pediatric investigation plan has to be agreed with the European Union regulators. [48] In South Africa, the Medicines Control Council (MCC) pays special attention to the conduct of research in minors, ensuring that clinical trials in TB are consistent with the National Health Act. [49] To ensure that prospects of direct benefit accrue to the participant, the Act requires that all research be therapeutic; non-therapeutic trials must be specifically authorized and deemed to contribute significantly to generalizable knowledge.

SUMMARY OF EXPERT PANEL CONSENSUS

The following sections summarize consensus statements around four main questions and topics.

1. What types of drugs or regimens should be prioritized for clinical trials in children?

When considering a new TB drug or regimen for study in children, characteristics (preclinical and adult clinical data) that suggest outcomes at least as favorable as established alternatives in the study setting should guide the TB drug/regimen selection and prioritization. These characteristics include the following: (a) similar or improved efficacy/effectiveness compared to an available alternative; (b) improved safety/toxicity and tolerance profile as compared to a standard regimen; (c) prospect for TB treatment shortening or simplification of the administration schedule; (d) prospect for administration of a fully oral regimen; (e) fewer drug-drug interactions, especially with antiretroviral drugs; and (f) availability in an appropriate formulation for dosing the targeted age group(s).

Development of child-friendly formulations for accurate pediatric dosing is important, and planning should be initiated once minimally acceptable adult safety data have been constituted, sufficient pharmacokinetic and pharmacodynamics information is available, and when at least an efficacious dose range in adults has been established (Phase IIA results are available). Care must be taken to investigate tolerability, palatability and formulations (e.g., fixed dose combination, dispersible pills, granules, or sprinkles) for children across the pediatric age spectrum. However, the development of an appropriate formulation to allow accurate pediatric dosing, while preferred, should not delay the initiation of clinical trials in children but can be developed in parallel.

When designing trials for new regimens, in addition to the criteria for drug prioritization, the practicality and clinical effectiveness of any new drug or regimen needs to be considered. Key principles that ensure correct treatment and ease of programmatic use in high-burden settings in particular should be followed, and the feasibility for use in resource-limited settings (e.g. the need for refrigeration and the shelf-life of a drug) considered. [50] Table 2 presents the World Health Organization (WHO) classification of existing TB drugs and Table 3 briefly summarizes existing information on selected priority TB drugs in children including criteria for their prioritization and lists current knowledge gaps.

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2. Which populations of children are among the highest priority for study?

Once sufficient adult safety and efficacy data are available (discussed in the following section), it is recommended to initiate pediatric Phase I and II clinical trials. To this end, certain pediatric populations should be prioritized based on their medical needs. The greatest need for more effective, child-friendly, and less toxic drugs/regimens is in the management of children with DR-TB, [20] children in younger age groups [10, 51, 52] and, for preventative treatment, in those children exposed to or infected by an index case with DRTB. [53–56] Studies are particularly essential in children under 2 years of age (with specific inclusion of infants) in whom pharmacokinetics may be substantially different compared to older children and adults. [57] Children with conditions such as HIV infection or malnutrition that: (a) increase their vulnerability to TB, (b) influence the pharmacokinetic profiles of TB drugs, or (c) increase the likelihood of drug interactions, are also important populations to prioritize for studies. [4, 58–60]

Although evaluation of efficacy is not the main objective of studies of new drugs/regimens in children, optimizing benefit for and limiting unnecessary risks in children continue to be major driving aims of pediatric studies. Therefore, only children with a diagnosis of confirmed or probable TB as per published case definitions for DS or DR-TB should be enrolled in TB treatment trials. [61–63] Similarly, only children with documented significant exposure to DR-TB and evidence of infection as per accepted definitions (e.g., positive result from a tuberculin skin test or interferon gamma release assay) should be enrolled in TB prevention trials of new drugs/regimens.

3. When can Phase I or II studies be conducted in children, and what data are needed to facilitate their inclusion?

Risks from initiating trials of new TB drugs at earlier phases of TB drug development can be mitigated when sufficient adult pre-clinical and/or clinical data are available to allow adequate evaluation of the risk/benefit ratio. Enrollment of children in TB drug research is acceptable when the following are available: (a) results are available from a full range of non-clinical studies including repeated dose toxicity studies of appropriate duration in adult animals, (b) a complete package of safety pharmacology and genotoxicity studies and appropriate juvenile animal toxicity studies are available, and when those results do not indicate serious cause for concern; (c) animal and adult human studies (early bactericidal activity [EBA] or other appropriate studies) have confirmed anti-*Mycobacterium tuberculosis (M.tb)* activity; (d) data on drug pharmacokinetics and pharmacodynamics in adult participants allow for the selection of appropriate pharmacokinetic targets in children or, alternatively, an efficacious and safe adult dose has been established (Phase IIB); and (e) for HIV-infected children, drug interaction information with antiretroviral drug(s) of interest is available from adult studies prior to opening similar studies for the pediatric population(s) of interest. Concurrent evaluations of more than one (unapproved) drug in a TB regimen may be appropriate when such studies have already been completed in adults and have acceptable safety, efficacy, and pharmacokinetic profiles with manageable drug-drug interactions. [64]

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When the above criteria are met, a smaller safety database or a higher threshold for acceptable risk may be acceptable for initiating studies in pediatric groups with the greatest medical needs. In most situations, safety data from Phase IIB trials in adults should be sufficient to allow for determination of an acceptable risk/ benefit profile for children. However, before undertaking pediatric studies, the following steps should ideally be in place: development of child-friendly formulations, and a feasible pediatric investigation plan. Therefore, TB drug developers should consider preparing for pediatric studies when a drug shows promising efficacy and safety in Phase IIA adult trials.

4. What are the relevant elements of clinical trial design?

Investigational approach

General considerations: Efficient and ethical study designs that produce the highest achievable quality of evidence should be adopted to determine the doses that are safe and achieve pharmacokinetic goals. This will help to limit the number of children exposed to experimental doses of a new drug or treatment regimen. Based on developmental pharmacokinetic principles, particularly rapid pharmacokinetic changes are expected in the first weeks of life, [65] while after 2 years of age, allometric scaling for size will, in the case of many drugs, allow prediction of pharmacokinetic targets based on those in adults. However, differences are expected between pediatric age groups. Therefore, the following age groups are proposed, as a guideline, for pediatric pharmacokinetic evaluations: 0 - < 3 months, 3 - < 24 months, 2 - < 5 years, 5 - 10 years, and > 10 years of age to adulthood. In most instances, novel TB agents should be evaluated in children concurrently receiving appropriate standard of care TB treatment. For children with mild disease, initial single agent therapy may be considered for pharmacokinetic studies, typically for up to 2 weeks.

Placebo-controlled studies are not generally necessary or helpful in children if the novel TB agent has proven efficacy in adult studies and sufficient adult data exists to suggest initial safe pediatric dosing. Use of a placebo should only be considered when (a) there is an extraordinary scientific need to evaluate complex toxicity and tolerance issues in children; (b) when placebo use does not pose a risk of serious harm or risk to trial feasibility; and (c) if the research addresses a question that is relevant to health priorities in the countries where it is undertaken. [43] Situations where placebo use may be appropriate include when there is need to evaluate safety signals for novel therapies or in situations where a high background of adverse events from the disease or from co-administered medications is anticipated.

Study outcomes and extrapolation of adult efficacy data: With the scarcity of data for drugs and regimens in children, evaluation of a new drug or regimen should preferably include the following outcomes: (a) equivalent serum concentrations to those achieved in adults at optimal dose including formulations bioequivalence studies, (b) safety and tolerability of child-friendly formulations, and when feasible or appropriate (c) time to culture conversion, mortality and morbidity data. Extrapolation of adult efficacy data to pediatric populations limits the number and size of pediatric trials while allowing efficient use of resources. As a result, children can have earlier access to safe, efficacious, and evidence-based therapies. Extrapolation is possible when the following three assumptions apply: a) the progression of disease is sufficiently similar in adults and the pediatric

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populations; b) response to intervention is similar in adults and the pediatric populations and, c) adult and pediatric populations have a similar exposure-response relationship. (See Figure 2) [66–68] Thus, efficacy studies in children for new drugs for intrathoracic TB, may not be necessary to allow for pediatric labeling. Similar response to treatment and exposure-response relationships in adults and children can be assumed for intrathoracic TB. However, efficacy studies may be needed for extrathoracic forms of TB and prevention studies in children.

Enrollment strategies: Although sometimes cited as an important safety protection, [69] enrollment strategies using sequential age de-escalation are not currently required by any regulatory body and delay drug evaluation in the youngest age groups. [70] If the TB drug to be evaluated in children does not exhibit any significant safety signals in pre-clinical and adult clinical studies, pediatric studies should be allowed to proceed directly to concurrent evaluation across all pediatric age groups, to the extent that appropriate formulations are available. Particular emphasis should be placed on inclusion of the youngest children. Enrollment by sequential age de-escalation should be used only rarely, such as when specific safety or pharmacokinetic concerns that warrant testing older children before proceeding to younger children are identified. Sequential enrollment of age cohorts may actually raise ethical concerns by delaying collection of critical pharmacokinetic and safety data in the age groups that are most likely to benefit from a new agent or regimen.

Regardless of the approach used, sufficient evaluable subjects within each age cohort must be included to strengthen the quality of evidence generated. Furthermore, and to the extent possible, Phase IIB and later phase studies in adults should be designed to enroll children aged > 10 years, who are expected to have TB disease presentations similar to adults and are able to routinely provide sputum specimens due to adult type intrathoracic TB disease. Weight (and body surface area) differences within this group should be taken into account when establishing a- correct dose. Experts in studies of adolescents should be available to the investigators, and safeguards for protection of pediatric participants should be in place. Alternatively, if no expectation exists that the drug may interfere with progression through puberty or have a different safety profile in adolescents, the drug should be licensed for use in that age group without waiting for specific adolescent studies.

Dosing approach: Pharmacokinetic evaluation of single-dose administration of new drugs should be considered as a first step to inform multiple-dose pharmacokinetic studies; this approach has the potential to minimize risks of unwanted drug exposure. Alternatively, multiple dosing in a mini-cohort (i.e., using an initial sample size of no more than 3–6 children) can be used initially to provide preliminary safety and pharmacokinetic data while exposing fewer children. Subsequently, a final recommended dose may be established using a larger cohort. Modeling and simulation should be used to predict initial dosing in children for each age category. Selection of the initial dose in children can be informed by semi-mechanistic models adjusted for weight and other age-related changes such as volume of distribution, metabolizing enzyme maturation, and rate of drug excretion. As they become more accurate, physiologic-based pharmacokinetic models may increasingly contribute to initial dose selection. [71] Both safety and pharmacokinetic data from children should be

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incorporated into these models as soon as they become available, and should be used to improve subsequent dose prediction in successive cohorts of children. Real-time drug concentration analysis in individual study participants and multiple interim analyses of drug exposures in small cohorts within studies allow reduction of risk through rapid dose adjustment in individuals and cohorts.

Pharmacokinetic sampling strategies: Approaches that include methods to minimize pharmacokinetic sampling and sample volumes, rapid analysis of pharmacokinetic results to inform more accurate dosing in adaptively designed studies, and stratification by age, weight, and drug formulation schemas should be used when appropriate. Semi-mechanistic pharmacokinetic modeling using a population approach can enable opportunistic sampling and facilitate the use of variable sampling times and relatively sparse sampling schedules. The efficiency of this approach is enhanced further by the use of optimal sampling designs based on knowledge of the drug's pharmacokinetics, limiting the number of blood samples needed from each child. Special attention must be paid to the volume of blood sampled and the timing of samples in very young children.

Additional design considerations: In order to guide dose adjustments, important drug-drug interactions should be specifically studied in young children receiving TB treatment. The magnitude of drug-drug interactions in this age group may not be predicted by either adult studies or other pediatric age cohorts. As with adults, children should be recruited from diverse racial and ethnic backgrounds to explore relevant pharmacogenomic differences. [72] Safety and adverse event data should be disaggregated and analyzed by age group. Data pooling can be used to generate models from diverse sources. Mechanisms using similar study designs (as appropriate) and standardized data collection forms and procedures should be supported to facilitate both collaborative data sharing, combined analyses across studies and incorporation into models. Children aged 0–3 months usually benefit from specific pharmacokinetic and safety evaluations. Studies should plan to extend duration of drug treatment in children who tolerate the drug (and experience no safety issues), if it is expected to add benefit to the standard of care; however the duration should not exceed length of treatment from adult studies. These methods may increase the prospect of direct benefit from the intervention and allow for collection of extended safety data and limited treatment response data with more prolonged exposure.

Safety monitoring and long term follow up

Safety monitoring principles: Due to major biological differences between children and adults, adverse event (AE) profiles and drug interactions that occur in pediatric patients may not be exactly as predicted by adult studies. Depending on the drug(s) being investigated or anticipated AEs, initial dosing in an in-patient setting or other intensely monitored study setting may be warranted. Special monitoring (e.g. EKG monitoring or other specific laboratory measurements) may/may not be needed if data from adults do not suggest any specific associated toxicity. Passive reporting should be used only when safety parameters of the agent have been well defined in children. Caregivers should be carefully instructed and encouraged to promptly report observed signs and symptoms to investigators. Establishment of independent safety monitoring committees (SMC), which include experts in pediatric

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pharmacology, pediatric TB experts, researchers with special experience in pediatric trials, or other specialists as needed, can provide additional protection.

Participant long term follow-up: The need for long-term follow-up for specific populations and for particular study agents should be given special consideration and should be adapted to settings where the study is conducted and where the drug will be used after registration. In addition, while the safety profile from adult trials has relevance for children it may be less helpful when predicting late adverse effects on growth, development and maturation. Hearing loss for example, a known potential complication of aminoglycoside use was reported in 24% of children with DR-TB treated with an aminoglycoside, much higher than that seen in adults, with several patients continuing to have progression of hearing loss months after discontinuation of medication. [19]

Long-term follow up and/or drug registry and surveillance data, may be needed to determine possible late effects on skeletal, behavioral, cognitive, sexual, and immune developmental maturation. The duration of follow-up can be drug-specific, based on any signal or concern uncovered during pre-clinical studies or in earlier phase studies in adults. In studies for DR-TB in children, at least 24 months follow-up after treatment completion should be considered routine, since toxicity for some agents is duration-dependent, and the risk of disease relapse is greatest within the first year after treatment completion. Lastly, post marketing surveillance and patient registries may provide additional safety information that could not be detected from the limited pediatric exposures from clinical trials. In particular, post marketing pharmacovigilance activities, because of the greater cumulative drug exposures in the post marketing safety database, could detect rare, serious and/or patient-specific AEs.

FURTHER ISSUES TO BE ADDRESSED

Improving the understanding of TB treatment in children requires participation of all stakeholders involved in TB drug research design and implementation. Regulators should evaluate the existing options to harmonize requirements and streamline processes for pediatric drug development. For new TB drugs, regulators should require and agree upon a formal, time-bound pediatric development plan that includes the development of child-friendly formulations earlier in the drug development cycle. Investigators are encouraged to include children as soon as possible in studies, with appropriate safeguards, and should prioritize research questions most in need of answers, as described earlier. Drug companies/sponsors should initiate pediatric studies at the time points suggested previously, even if not a specific regulatory requirement. Sponsors should make all relevant information, not just safety and dosing information, available to facilitate further evaluation by research consortia and other non-commercial research bodies, particularly when multiple new compounds may be utilized in combination. Sponsors, in conjunction with investigators and community groups, should encourage the inclusion of children > 10 years in initial treatment trials in adults. Advocates should call for clear, harmonized guidance from regulators including requests for: early development of child-friendly drug formulations, the inclusion of children in drug safety, dosing, and efficacy trials, and better understanding of global and local pediatric TB disease burdens. They will also need to advocate for increased funding of

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pediatric TB research. [37, 73] New mechanisms of collaboration should be developed among all these stakeholders, such as the formation of a standing group to facilitate the earliest possible sharing of data and information on new TB drugs (to help determine when they should enter trials), make coordinated decisions and plans, enable harmonized approaches and address priorities on a consistent, ongoing basis, while minimizing resource duplication.

CONCLUSION

The scarcity of research of TB treatment in children represents a critical gap in global efforts to lessen the burden of TB infection and disease and to control the spread of drug resistance. Children, despite their increased vulnerability to TB, are subject to TB underreporting, and in some settings are at highest risk for exposure, infection and serious TB disease. Extrapolating from the adult treatment experience and adult clinical data may be inadequate for post licensure use of TB drugs in children, even if adult information suggests an acceptable risk/benefit ratio for children. Inclusion of children into studies should occur at the early phases of TB drug development and be an integral part of the clinical development plan, rather than as a post-approval activity. The consensus presented in this paper addresses ethical, regulatory, and methodological considerations that take into account the interests of and features unique to children, and promotes bold concepts that should accelerate the involvement of children in safe, ethical trials of new TB drugs and at earlier stages of the drug development cycle.

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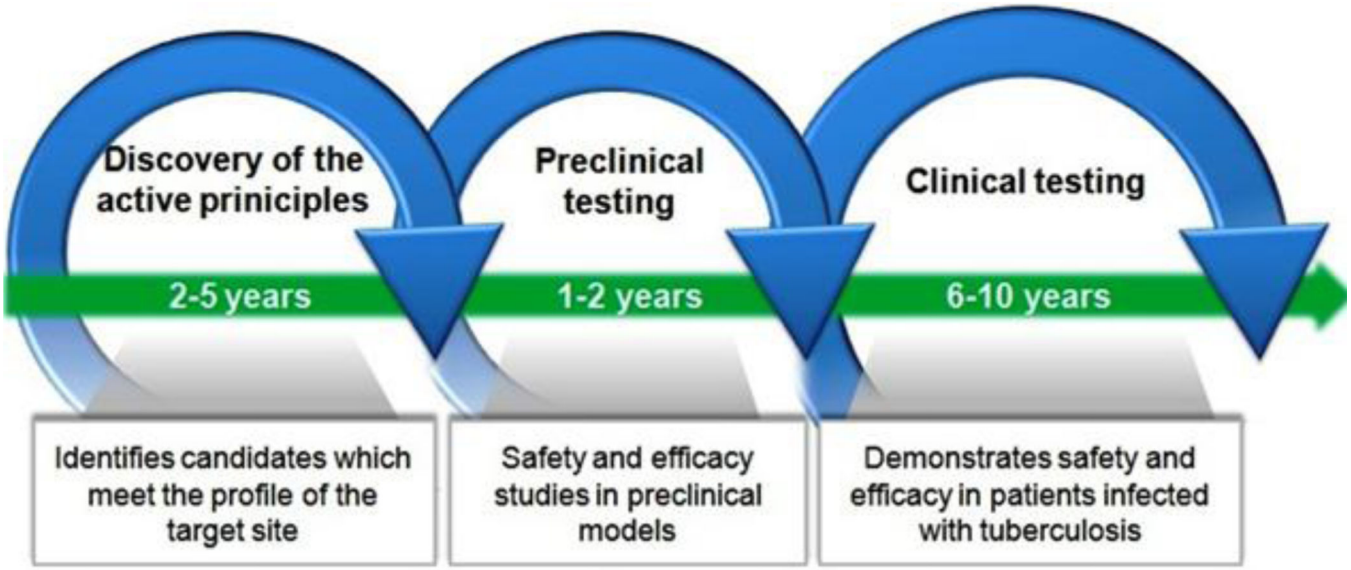

Figure 1. TB Drug Development phases
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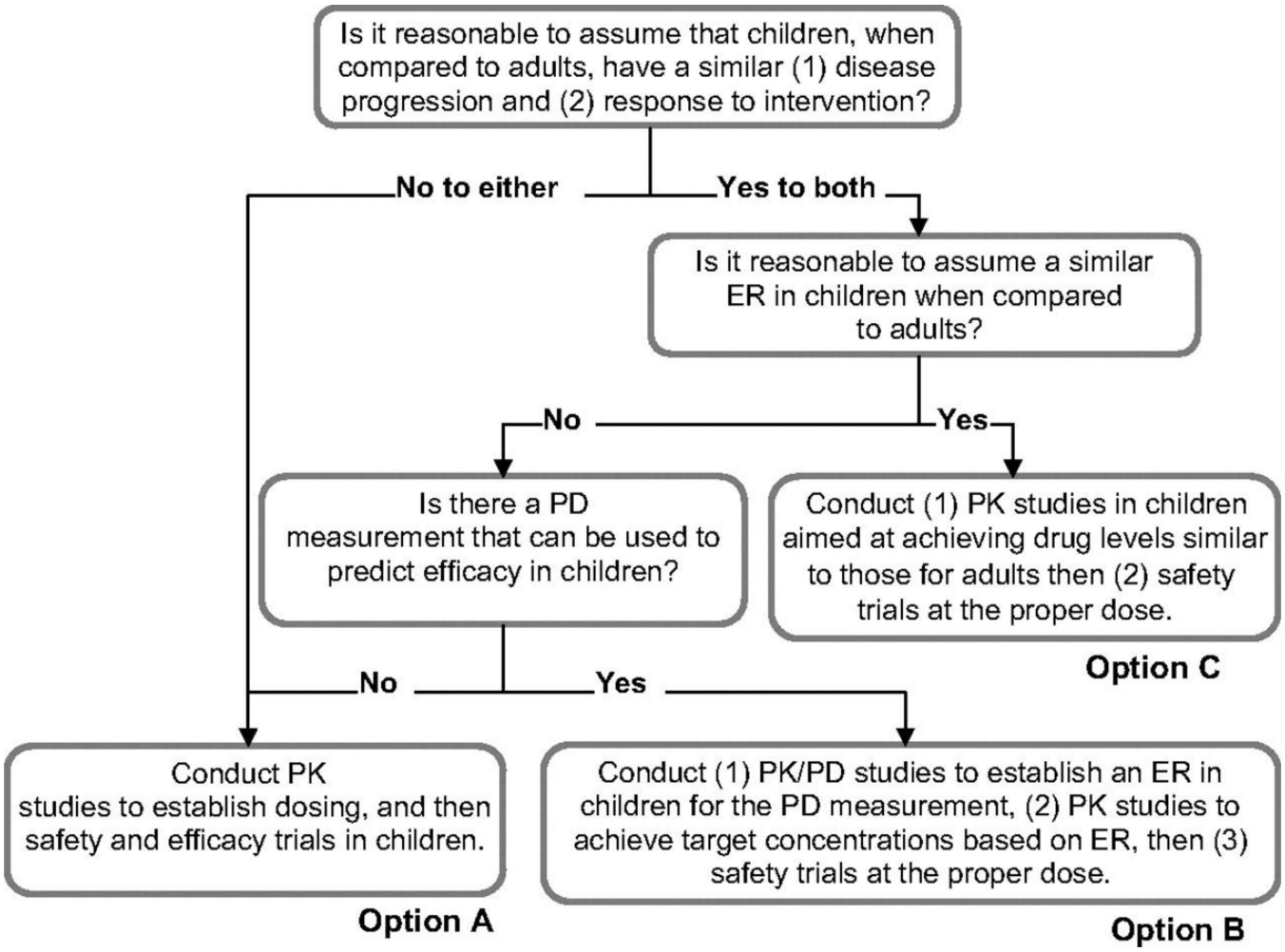

Figure 2. Pediatric studies decision tree

Reproduced from: http://www.fda.gov.ezproxy.nihlibrary.nih.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072109.pdf. Abbreviations: PK/PD: pharmacokinetics/pharmacodynamics; ER: exposure-response

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Table 1

On-going and planned studies in children (current as of December 2013)

Study	Sponsor	Status	Endpoint
Pharmacokinetics of first-and second-line agents in children with DS-TB and DR-TB	NIH	on-going	PK and safety
Pharmacokinetics of delamanid in children	Otsuka	on-going	PK, safety
Pharmacokinetics of bedaquiline in children	Janssen, IMPAACT[1]	Planned	PK, safety
SHINE –Treatment shortening in children with paucibacillary TB	British MRC[2]/ DFID[3]/ Wellcome Trust	Planned	Efficacy, safety, PK
Pharmacokinetics of first-line agents in infants	TB Alliance	Planned	PK
Rifapentine+isoniazid in children in LTBI[5]	TBTC[4]	Planned	PK, safety
Levofloxacin and isoniazid in children exposed to DR-TB	IMPAACT	Planned	Efficacy

[1] International Maternal Pediatric Adolescent AIDS Clinical Trials Group

[2] Medical Research Council

[3] Drugs For Neglected Infectious Diseases

[4] Tuberculosis Trials Consortium

[5] Latent TB Infection

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Table 2

WHO grouping of drugs used for DR-TB

Group	Drugs (abbreviations)
Group 1: First-line oral agents	pyrazinamide (Z) ethambutol (E) rifabutin (Rfb)
Group 2: Injectable agents	kanamycin (Km) amikacin (Am) capreomycin (Cm) streptomycin (S)
Group 3: Fluoroquinolones	levofloxacin (Lfx) moxifloxacin (Mfx) ofloxacin (Ofx)
Group 4: Oral bacteriostatic second-line Agents	para-aminosalicylic acid (PAS) cycloserine (Cs) terizidone (Trd) ethionamide (Eto) protionamide (Pto)
Group 5: Agents with unclear role in treatment of drug resistant-TB	clofazimine (Cfz) linezolid (Lzd) amoxicillin/clavulanate (Amx/Clv) thioacetazone (Thz) imipenem/cilastatin (Ipm/Cln)v high-dose isoniazid (high-dose H)b clarithromycin (Clr)

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Table 3

Information on selected priority TB drugs in children[1], prioritization criteria and knowledge gaps

Current Drugs of interest (Drug Class/ Mechanism of Action)	Current drug knowledge	Criteria for prioritization					Priority conditions /subgroups			Knowledge gaps
		Better efficacy	Better toxicity profile	Treatment shortening	Fully oral Regimen	Fewer DDI[2]	DR TB	<5 years	HIV[3]	
Delamanid[4]33 (Dinitroimidazole/ Inhibits mycolic acid synthesis)	-Phase IIB data; adult Phase III studies underway -Good safety profile -Lacks interaction with CYP 450 -attractive for ARV co-administration Concern: -QTc prolongation	x[75, 76]	x	?	x	x	x	x	x[77, 78]	-Optimal dosing in young children -Safety profile in children -Drug interactions with ARVs
Bedaquiline[5] (Diarylquinoline/ Inhibits bacterial ATP synthase)	-Promising efficacy, CYP 3A4 substrate, Long half-life, efficacious dose available -full efficacy studies underway Concern: -higher death rate in treatment group -QTc prolongation	x	-	?	x	-	x	x	x	-No PK/PD information -Optimal dosing in children -Drug interactions with ARVs
Rifapentine[5] (Rifamycin/ inhibits DNA-dependent RNA polymerase)	-Low MIC, long half-life, potent activity against TB -Effective in once-weekly treatment of LTBI Concern: -hypersensitivity	x	x79	x	x	-	-	x	x	-Optimal dosing in very young children
Levofloxacin & Moxifloxacin[5,6] (Fluoro Quinolones/ inhibit topoisomerase II DNA gyrase)	Levofloxacin: -Approved in children for anthrax, plague; -Dosing from CAP[2] studies; -solution formulation Moxifloxacin: -potential for shortening TB treatment but current data conflicting Concern: -arthropathy, tendon rupture, nerve damage [80], QTc prolongation	x	x	?	x	x	x	x	x	-Optimal dosing in young children -Role in TB treatment

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Current Drugs of interest (Drug Class/ Mechanism of Action)	Current drug knowledge	Criteria for prioritization					Priority conditions /subgroups			Knowledge gaps
		Better efficacy	Better toxicity profile	Treatment shortening	Fully oral Regimen	Fewer DDI[2]	DR TB	<5 years	HIV[3]	
Linezolid[6] (Oxazolidinone/ Inhibits protein synthesis by binding to 23S ribosomal RNA)	-Approved for multiple indications other than TB from birth -17 yrs. Used in DR-TB with some success No QTc prolongation Concerns: -Visual loss, neuropathy, lactic acidosis, -Myelosuppression	x[81–84]	-	?	x	?	x	x	x	-Optimal dosing in TB/efficacy at reduced doses -Toxicity at prolonged exposure
Clofazimine[5] (Riminophenazine/ Unclear, possible production of reactive oxygen species of *M.tb*)	Prolonged half-life Skin discoloration (reversible), Concern: -QTc prolongation	x	-	x	x	?	x	?	x	-Dosing in TB not established -No data from juvenile animal studies -no PK/PD data available
PA-824[85] (nitroimidazole/ Inhibits M.*tb* F420-dependant synthesis of protein and cell wall lipids)	-Adult Phase IIB studies underway -Good safety profile -Potential for shortening TB treatment (DS- and DR-TB) -Lacks interaction with CYP 450 -Attractive for ARV co-administration Concern: -None to date	x	x	x	x	x	x	x	x	-Optimal dosing in children -Safety profile in children -Adult efficacy studies not yet complete -Possibility for Rx shortening -Drug interactions with ARVs

"X": some evidence to support effect/ proposed use;

"-": some evidence against effect/proposed use;

"?": lack of evidence for/against effect/proposed use

[1] Drugs are not listed in order of priority and absence from this list does not necessarily indicate low priority

[2] DDI: drug-drug interactions; CAP: community acquired pneumonia

[3] Or other immune compromised states

[4] Delamanid has received conditional market authorization from the EMA

[5] Bedaquiline, Rifapentine and Quinolones (except Levofloxacin) are licensed in adults, but not children

[6] Levofloxacin, Linezolid and Clofazimine are licensed in both adults and children