Towards early inclusion of children in tuberculosis drugs trials: a consensus statement

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Children younger than 18 years account for a substantial proportion of patients with tuberculosis worldwide. Available treatments for paediatric drug-susceptible and drug-resistant tuberculosis, albeit generally effective, are hampered by high pill burden, long duration of treatment, coexistent toxic effects, and an overall scarcity of suitable child-friendly formulations. Several new drugs and regimens with promising activity against both drug-susceptible and drug-resistant strains have entered clinical development and are either in various phases of clinical investigation or have received marketing authorisation for adults; however, none have data on their use in children. This consensus statement, generated from an international panel of opinion leaders on childhood tuberculosis and incorporating reviews of published literature from January, 2004, to May, 2014, addressed four key questions: what drugs or regimens should be prioritised for clinical trials in children? Which populations of children are high priorities for study? When can phase 1 or 2 studies be initiated in children? What are the relevant elements of clinical trial design? The consensus panel found that children can be included in studies at the early phases of drug development and should be an integral part of the clinical development plan, rather than studied after regulatory approval in adults is obtained.

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Introduction

Tuberculosis is a major, but often unrecognised, cause of morbidity and mortality in children in the middle-income and low-income countries. The proportions of people infected probably underestimate the global disease burden, with childhood cases accounting for an estimated 6% of all reported cases,[1] and at least double this percentage in tuberculosis endemic areas.[2] Underdiagnosis (and thus underreporting) is of particular concern in young children who are at greatest risk of disease progression after exposure and infection, and in whom microbiological, or other diagnostic confirmation of both tuberculosis infection and disease is not straightforward.[3] HIV infection increases the risk of tuberculosis disease and death, especially in the absence of antiretroviral treatment.[4–10] Another concern is that the number of children with drug-resistant tuberculosis is increasing worldwide.[11–16] Treatment, including that for drug-resistant tuberculosis, can be effective for children,[17] but is limited by poor service delivery and scarcity of child-friendly drug formulations and of data for safety, dosing, and drug–drug interactions.[17–22] A crucial gap persists for the treatment of drug-resistant tuberculosis. Additionally, new drugs and regimens are needed for children, and more data are needed to strengthen the evidence base to guide the use of existing second-line drugs,[18,23] decrease fragmentation of the paediatric medicines market, and improve access to these drugs.[24] This consensus statement builds on previous similar efforts[25,26] and presents findings from an expert panel to promote strategies for the timely gathering of evidence for safety and dosing of drugs in children, to guide clinical management and optimise the care of children with tuberculosis. The Consensus questions consisted of four key questions that needed to be addressed by expert panellists during the workshop: What drugs or regimens should be prioritised for clinical trials in children? Which populations of children are high priorities for study? When can phase 1 or 2 studies be done in children? What are the relevant elements of clinical trial design?

Consensus statements preparation

A literature review was done and the papers were used to help prepare consensus statements for discussion by the panel. Expert clinicians, researchers, and opinion leaders for paediatric tuberculosis were invited to a workshop, "Towards earlier involvement of children and pregnant women in trials of new TB drugs", organised by the National Institutes of Health in Bethesda, MD, USA, 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 panellists.

Draft statements were circulated to panellists for review and comment, discussed on teleconference calls, revised accordingly, and drafts distributed to participants before the workshop. The timed discussions used a group consensus approach that allowed modification of the statements in real time on the basis of panellists' suggestions. Edited statements underwent a panel vote. Voting rules consisted of two options: agree or disagree, shown by a show of hands. Consensus was declared for a statement if 75% or more of panellists 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 panellists to finalise consensus.

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State of research into new tuberculosis drugs

Trials in progress and planned trials

The literature review highlighted that new drugs and combinations—many with novel mechanisms of action and strategies to treat tuberculosis—are under investigation. Clinical trials for drug-resistant tuberculosis in adults are underway for new nitroimidazoles (delamanid and pretomanid), oxazolidinones (sutezolid, linezolid, and AZD5847), 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 the Global Alliance for tuberculosis Drug Development's NC006 (NCT02342886; pretomanid, moxifloxacin, and pyrazinamide), NC005 (NCT02193776; clofazimine, bedaquiline, pretomanid, and pyrazinamide) trials, and STREAM trial (NCT02409290).[34,35] Unfortunately, the number of studies in children lags substantially behind adult studies; safety and pharmacokinetic studies of drugs for use in children are in progress or planned for very few of these novel treatments (ie, delamanid and bedaquiline). This lag is shown in research and development investments for paediatric tuberculosis, which accounts for just 2% of the total funding invested in drug research overall[36] but 25% of the estimated need.[37] Figure 1 shows the main phases in drug development and table 1 summarises relevant treatment studies in children.

Ethical concerns

Children are a susceptible vulnerable group with little or developing autonomy, and are legally not allowed to provide informed consent. Therefore, they need additional measures to protect them from exploitation and harm. Many international guidance documents and regulations specify acceptable risk–benefit ratios, and require that research with children offers a prospect of benefit, or poses minimum 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 is contingent on the burden of the disease and the need for the intervention in that population.

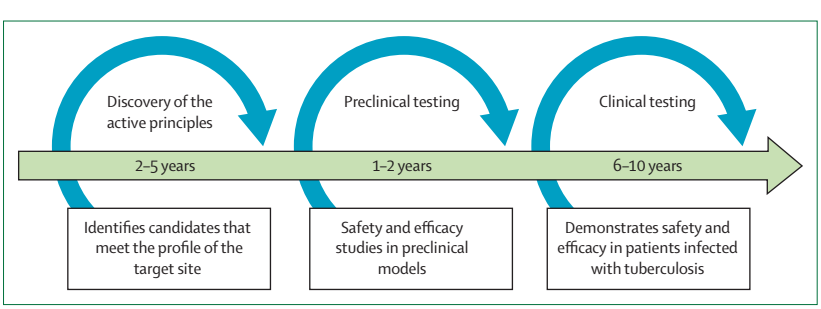

Figure 1: **Tuberculosis drug development phases**
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One concern is that inclusion of children in research at earlier stages of drug development could expose them unnecessarily to investigational drugs with uncertain future and undocumented safety risks. Some ethics guidance documents require that children be enrolled in research only if the research cannot be done in adults.[41] Other guidelines propose initiating paediatric studies (phase 1 or 2), especially in children with serious and life-threatening diseases who could benefit from the study intervention, after preclinical safety data and evidence of effectiveness from adult studies have been obtained.[42,43] Both tuberculosis in young children,[10] and drug-resistant tuberculosis in all children,[20,44] are serious and life-threatening disorders with few treatment options in which affected children are potentially further harmed by the dearth of data to guide use of existing drugs. Thus, tuberculosis drug research can and does, in such instances, offer potential direct benefit to children that outweighs the risks of paediatric trials with incomplete (ie, before phase 3) adult data. For these reasons, early involvement of children in specific trials might be ethically justified.

Regulatory environment

Although drug regulatory legislation in both the USA[45] and Europe[46] similarly provides incentives for the inclusion of children as part of any product's development plan, the requirements for studies in children with orphan drugs differ. In the USA, drugs intended to treat tuberculosis generally qualify for orphan designation under the orphan drug regulations,[47] and inclusion of children in prelicensure trials is not required.[45] Similarly, drugs intended to treat tuberculosis can have orphan medicinal product status in Europe; however, no exemption is given for inclusion of children in trials investigating new treatments, and a paediatric investigation plan has to be agreed on with the European Union regulators.[48] In South Africa, the Medicines Control Council pays special attention to the conduct of research in minors to ensure that clinical trials in tuberculosis 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 should be specifically authorised and deemed to contribute substantially to generalisable knowledge.

Summary of expert panel consensus

What drugs or regimens should be prioritised for clinical trials in children?

When a new tuberculosis drug or regimen is assessed for study in children, characteristics (preclinical and adult clinical data) that suggest outcomes at least as favourable as established alternatives in the study setting should guide the drug and regimen selection, and prioritisation. These characteristics include: similar or improved effectiveness compared with an available alternative; improved safety, toxicity, and tolerance profiles as compared with a standard regimen; potential for a shortened

treatment or simplification of the administration schedule; prospect for administration of a fully oral regimen; fewer drug–drug interactions, especially with antiretroviral drugs; and availability in an appropriate formulation for the targeted age group, or group.

Development of child friendly formulations for accurate paediatric dosing is important, and should be planned when minimum acceptable adult safety data have been constituted, sufficient pharmacokinetic and pharmacodynamic information is available, and when an efficacious dose range in adults has been established (ie, phase 2a results are available). Care should be taken to investigate tolerability, palatability, and formulations (eg, fixed-dose combination, dispersible pills, granules, or sprinkles) for children across the paediatric age range. However, the development of an appropriate formulation to allow accurate paediatric dosing, although preferred, should not delay the initiation of clinical trials in children.

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	Status	Populations	Sponsors
Prevention			
P4v9			
4 months of self-administered daily rifampin for prevention of tuberculosis NCT00170209	Follow-up; results expected 2015–16	HIV-positive or HIV-negative children aged 0–17 years with LTBI	CIHR, McGill University
ACTG A5279			
4 weeks of daily rifapentine and isoniazid for prevention of TBNCT01404312	Enrolling; primary results expected 2018	HIV-positive adults and adolescents (aged 13 years and more) with LTBI	NIAID, ACTG, IMPAACT
IMPAACT/ACTG PHOENIX			
Levofloxacin-based regimen for prevention of MDR-tuberculosis	Planned	HIV-positive or HIV-negative infant, child, and adolescent household contacts with LTBI	IMPAACT, ACTG
TBTC 35			
Pharmacokinetic and safety of rifapentine and isoniazid FDC for prevention of tuberculosis	Planned	HIV-negative infants and children with LTBI (children aged <2 years old will get paediatric formulation)	TBTC, Sanofi
Treatment			
232			
Pharmacokinetic and safety of delamanid, OBR for treatment of MDR tuberculosis (NCT01856634)	Enrolling; primary results expected 2016	HIV-negative children aged 6–17 years with MDR tuberculosis	Otsuka
233			
6 months of delamanid, OBR for treatment of MDR tuberculosis (NCT01859923)	Enrolling; primary results expected 2017	HIV-negative children aged 6–17 years with MDR tuberculosis (<5 years old will get paediatric formulation)	Otsuka
IMPAACT 1108			
Pharmacokinetic and safety of bedaquiline, OBR for treatment of MDR tuberculosis	Planned; opening 2015	HIV-negative children 0–18 years, HIV-positive children aged 12–18 years with MDR tuberculosis (children <12 years will get paediatric formulation)	NIAID, IMPAACT
DATiC			
Pharmacokinetic of FLDs using 2010 WHO dosing guidelines for treatment of tuberculosis and interactions with lopinavir and ritonavir, and nevirapine (NCT01637558)	Enrolling; interim results expected 2015	HIV-positive or HIV-negative children aged 0–12 years with tuberculosis	NICHD, UNITAID/TB Alliance
Treat Infant TB			
Pharmacokinetic and safety of FLDs using 2010 WHO dosing guidelines for treatment of tuberculosis	Enrolling; interim results expected 2015	HIV-positive or HIV-negative infants younger than 12 months with tuberculosis	UNITAID/TB Alliance (Step-TB Project)
PK-PTBHIV01			
Pharmacokinetic of FLDs using 2010 WHO dosing guidelines for treatment of tuberculosis and interactions with nevirapine and efavirenz (NCT01687504, NCT01704144, NCT01699633)	Enrolling; primary results expected 2017	HIV-positive or HIV-negative children 3 months–14 years with tuberculosis	NICHD
SHINE			
4 versus 6 months with 2010 WHO dosing guideline–adjusted FLD FDCs for treatment of minimum tuberculosis	Planned; opening 2015	HIV-positive or HIV-negative infants, children, and adolescents with minimum tuberculosis	BMRC, DFID, Wellcome Trust, University College London
PATCH			
Safety and efficacy of levofloxacin and rifampin for treatment of tuberculosis meningitis	Planned	HIV-positive or HIV-negative infants and children with drug susceptible-tuberculosis meningitis	NICHD (pending)
IMPAACT 1106			
Pharmacokinetic of FLDs, SLDs, and antiretrovirals	Planned	HIV-positive or HIV-negative low-birth-weight or premature infants	NIAID, IMPAACT
MDR-PK			
Pharmacokinetic and safety of SLDs for treatment of MDR-tuberculosis	Enrolling; interim results presented 2013; final results expected 2016	HIV-positive or HIV-negative infants, children, and adolescents with MDR tuberculosis or LTBI	NICHD

(Table 1 continues on next page)

	Status	Populations	Sponsors
(Continued from previous page)			
IMPAACT 1101			
Pharmacokinetic and safety of raltegravir and interactions with rifampin-containing tuberculosis treatment (NCT01751568)	Open	Antiretroviral-naive HIV-positive children (3 years to <12 years) on rifampin-containing tuberculosis treatment	NIAID
Rifabutin-PK			
Pharmacokinetic and safety of rifabutin for treatment of tuberculosis	Planned	HIV-positive children and adults on PI-based second-line ART	ICMR, NACO
IMPAACT 5000			
Pharmacokinetic and safety of rifapentine for treatment and prevention of tuberculosis in pregnant women	Planned	HIV-positive or HIV-negative pregnant women	NIAID

LTBI=latent tuberculosis infection. CIHR=Canadian Institutes of Health Research. NIAID=National Institute of Allergy and Infectious Diseases. ACTG=AIDS Clinical Trials Group. IMPAACT=International Maternal Pediatric Adolescent AIDS Clinical Trials Network. TBTC=Tuberculosis Trials Consortium. FDC=fixed dose concentration. OBR=optimised background regimen. MDR=multi-drug resistant. FLD=first-line drug. NICHD=National Institute of Child Health and Human Development. UNITAD=Tous Unis pour Aider. BMRC=British Medical Research Council. DFID=Department for International Development. SLD=second-line drug. PI=protease inhibitor. ART=antiretroviral therapy. ICMR=Indican Council of Medical Research. NACO=National AIDS Control Organization.

***Table 1*: In progress and planned paediatric tuberculosis prevention and treatment studies**

	Drugs
Group 1: first-line oral agents	Pyrazinamide, ethambutol, rifabutin
Group 2: injectable agents	Kanamycin, amikacin, capreomycin, streptomycin
Group 3: fluoroquinolones	Levofloxacin, moxifloxacin, ofloxacin
Group 4: oral bacteriostatic second-line drugs	Para-aminosalicylic acid, cycloserine, terizidone, ethionamide, protionamide
Group 5: drugs with unclear role in treatment of drug resistant-tuberculosis	Clofazimine, linezolid, amoxicillin and clavulanate, thioacetazone, imipenem and cilastatin, high-dose isoniazid, clarithromycin

***Table 2*: WHO categorisation of drugs used for drug resistant-tuberculosis**

When trials for new regimens are designed, in addition to the criteria for drug prioritisation, 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, particularly in high-burden settings, should be followed up, and the feasibility for use in resource-poor settings (eg, the need for refrigeration and the shelf-life of a drug) assessed.[50] Table 2 presents the WHO classification of existing tuberculosis drugs and table 3 briefly summarises existing information on selected priority drugs in children including criteria for their prioritisation and lists the present knowledge gaps.

Which populations of children are high priorities for study?

Once sufficient adult safety and efficacy data are available, initiation of the paediatric phase 1 and 2 clinical trials is recommended. To this end, paediatric populations should be prioritised on the basis of their medical needs. The greatest need for more effective, child friendly drugs with low toxicity and simpler regimens is in the management of children with drug-resistant tuberculosis,[20] children in younger than 5 years age groups,[10,60,61] and, for preventive treatment, in those children exposed to or infected by an index case.[62–65] Studies are especially essential in children younger than 2 years (with specific inclusion of infants aged 0–6 weeks) in whom pharmacokinetics might be substantially different than in older children and adults.[66] Children with disorders such as HIV infection or malnutrition that can increase their susceptibility to tuberculosis, affect the pharmacokinetic profiles of tuberculosis drugs, or increase the likelihood of drug interactions, are also important populations to prioritise for studies.[4,67–69]

Although efficacy is not the main objective of trials of new drugs and regimens in children, optimisation of the benefits and reduction of unnecessary risks continue to be major aims of paediatric studies. Therefore, only children with a diagnosis of confirmed or probable tuberculosis as per published case definitions for drug-susceptible or drug-resistant tuberculosis should be enrolled in treatment trials.[70–72] Similarly, only children with documented substantial exposure to drug-resistant tuberculosis and evidence of infection (eg, positive result from a tuberculin skin test or interferon gamma release assay) should be enrolled in prevention trials of new drugs and regimens.

When can phase 1 or 2 studies be initiated in children?

The risks from trials of new tuberculosis drugs at earlier phases of drug development can be mitigated when sufficient adult preclinical or clinical data, or both are available to allow adequate assessment of the risk–benefit ratio. Enrolment of children in drug research is acceptable when the following are available: results from a full range of non-clinical studies, including repeated-dose toxicity studies of appropriate durations in adult animals; safety, pharmacology, and genotoxicity studies and appropriate juvenile animal studies for toxic effects are available and do not suggest serious cause for concern; studies of animal and adult human beings (early bactericidal activity or other appropriate investigations) have substantiated anti-*Mycobacterium tuberculosis* activity; data for 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 2b); and for HIV-infected children, information

	Present drug knowledge	Prioritisation needs and knowledge gaps
Delamanid (dinitroimidazole).[28,51,52] Inhibits mycolic acid synthesis	Phase 2b data; adult phase 3 studies underway, no interaction with CYP 450, attractive for ART co-administration. Concern: QTc prolongation	Optimal dosing in children younger than 5 years , safety profile in children, HIV-coinfected, drug interactions with ARTs
Bedaquiline (diarylquinoline). Inhibits bacterial ATP synthase	Promising efficacy, full studies underway, CYP 3A4 substrate, long half-life. Concerns: high death rate in treatment group, QTc prolongation	No pharmacokinetics or pharmacodynamics information, optimal dosing in children, drug interactions with ARTs
Rifapentine (rifamycin).[53] Inhibits DNA-dependent RNA polymerase	Low MIC, long half-life, potent activity against tuberculosis, effective in once-weekly treatment of LTBI. Concern: hypersensitivity	Optimum dosing in children younger than 2 years, drug shortening regimens
Levofloxacin and moxifloxacin (fluoroquinolones).[54] Inhibit topoisomerase II DNA gyrase	Approved in children for anthrax, plague; dosing from CAP studies;[2] solution formulation. Concerns: arthropathy, tendon rupture, nerve damage,[55] QTc prolongation	Optimum dosing in young children, role in drug susceptible tuberculosis and MDR-tuberculosis treatment
Linezolid (oxazolidinone).[56,57] Inhibits protein synthesis by binding to 23S RNA	Approved for multiple indications other than tuberculosis, no QTc prolongation. Concerns: visual loss, neuropathy, lactic acidosis, myelosuppression	Optimum dosing in tuberculosis and efficacy at reduced doses, toxicity at prolonged exposure
Clofazimine (riminophenazine). Unclear, possible production of reactive oxygen species of *Mycobacterium tuberculosis*	Prolonged half-life. Concerns: skin discoloration (reversible), QTc prolongation	Dosing in tuberculosis not established, no data from juvenile animal studies, no pharmacokinetics or pharmacodynamics data available
Pretomanid (PA-824; nitroimidazole).[58,59] Inhibits *Mycobacterium tuberculosis* F420-dependant synthesis of protein and cell wall lipids	Adult phase 2b studies underway, good safety profile, potential for shortening tuberculosis treatment, lacks interaction with CYP 450, attractive for antiretroviral co-administration	Optimum dosing in children, safety profile in children, adult efficacy studies not yet complete, possibility for treatment shortening, drug interactions with ARTs

ART=antiretroviral therapy. MIC=minimum inhibitor concentration. LTBI=latent tuberculosis infection. MDR=multidrug resistant.

***Table* 3: Present drugs of interest in tuberculosis treatment by drug class and mechanism of action**

about drug interactions with antiretroviral drug, or drugs, of interest is available from adult studies. Concurrent assessments of more than one unapproved drug in a tuberculosis regimen might be appropriate when such trials have been completed in adults and have acceptable safety, efficacy, and pharmacokinetic profiles with manageable drug–drug interactions.[73]

When these criteria are met, a small safety database or a high threshold for acceptable risk might be satisfactory for the initiation of studies in paediatric groups with the greatest medical needs. In most situations, safety data from phase 2b trials in adults should be sufficient to allow for identification of an acceptable risk–benefit profile for children. However, before paediatric studies are undertaken, a feasible paediatric investigation plan including development of child-friendly formulations and should be in place. Therefore, drug developers should consider paediatric studies when a drug shows promising efficacy and safety in phase 2a trials in adults.

What are the relevant elements of clinical trial design?

Efficient and ethical study designs that produce the highest achievable quality of evidence should be used to establish the dose that is safe and achieves pharmacokinetic goals. These designs will help to restrict the number of children exposed to experimental doses of a new drug or treatment regimen. On the basis of developmental pharmacokinetic principles, rapid pharmacokinetic changes are expected in the first weeks of life,[74] whereas after 2 years of age, allometric scaling for size will, for many drugs, allow prediction of pharmacokinetic targets on the basis of those in adults. However, differences are expected between childhood age groups. Therefore, as a guideline, we propose the following age groups, for paediatric pharmacokinetic assessments: 0 months to younger than 3 months, 3 months to younger than 24 months, 2 years to younger than 5 years, 5–10 years, and older than 10 years to adulthood. In most instances, novel tuberculosis agents should be investigated in children who concurrently receive appropriate standard-of-care treatment. For children with mild disease, initial single-agent therapy might 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 tuberculosis agent has proven efficacy in adult studies and if sufficient adult data exists to suggest initial safe paediatric dosing. Use of a placebo should be considered only when: an extraordinary scientific need to assess complex toxic effects and tolerance issues in children is apparent, when placebo use does not pose a risk of serious harm or risk to trial feasibility, and if the research addresses a question that is relevant to health priorities in the countries where it is undertaken.[43] Situations in which placebo use might be appropriate include when assessment is needed into safety signals for novel therapies, or in situations in which a high background of adverse events from the disease or from coadministered drugs is expected.

With the scarcity of data for drugs and regimens in children, assessment of a new drug or regimen should preferably include the following outcomes: equivalent serum concentrations to those achieved in adults at optimum dose, including bioequivalence studies of formulations; safety and tolerability of child friendly formulations; and when feasible or appropriate, time to culture conversion, mortality, and morbidity data.

Extrapolation of adult efficacy data to paediatric populations reduces the number and size of paediatric trials, allowing efficient use of resources. As a result, children can have early access to safe, efficacious, and evidence-based treatments. Extrapolation is possible when these assumptions apply to both adults and children: progression of disease, response to intervention, and exposure-response relations are much the same in the two populations. (figure 2)[75–77] Thus, efficacy studies in children for new drugs to treat intrathoracic tuberculosis might not be necessary to allow paediatric treatment, because a similar response to treatment and exposure-response relations in adults and children can be assumed for intrathoracic tuberculosis. However, efficacy studies might be needed for extrathoracic forms of the disease and prevention studies in children.

Although sometimes cited as an important safety protection,[78] enrolment strategies with sequential age de-escalation are not needed by any regulatory body and can delay drug assessment in the youngest age groups.[79] If the drug to be used in children does not show any substantial safety concerns in preclinical and adult clinical studies, paediatric studies should be allowed to proceed directly to concurrent assessment across all paediatric age groups, to the extent that appropriate formulations are available. Emphasis should be placed on inclusion of the youngest children. Enrolment by sequential age de-escalation should be used only rarely, such as when specific safety or pharmacokinetic concerns are identified that warrant tests on older children before tests in younger children are undertaken. Sequential enrolment of age cohorts might raise ethical concerns by delaying collection of essential pharmacokinetic and safety data in the age groups that are most likely to benefit from a new agent or regimen.

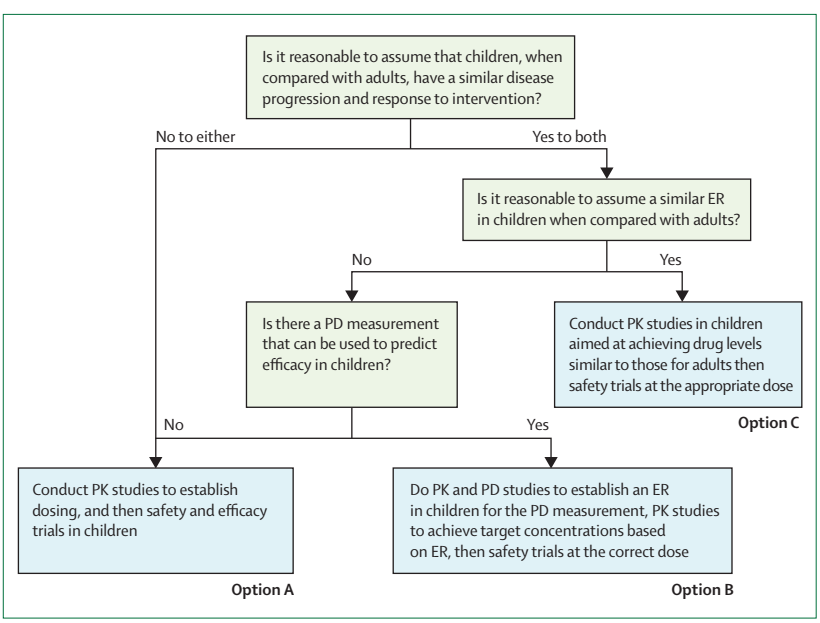

Figure 2: **Paediatric studies decision tree**
Reproduced from the US Food and Drug Administration.[66] ER=exposure-response. PD=pharmacodynamic. PK=pharmacokinetic.

Irrespective of the approach used, sufficient assessable participants within each age cohort should be included to strengthen the quality of evidence generated. Furthermore, if possible, phase 2b and later phase studies in adults should be designed to enrol children aged 10 years or older, who are expected to have tuberculosis presentations similar to adults and are able to provide sputa specimens because they have adult-type intrathoracic tuberculosis. Bodyweight (and body-surface area) differences within this group should be taken into account in decisions about correct dose. Experts in studies of adolescents should be available to the investigators, and safeguards for protection of paediatric participants should be in place. Alternatively, if the drug is not expected to 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 specific adolescent studies.

Pharmacokinetic assessment 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 minimise risks of unwanted drug exposure. Alternatively, many doses in a mini-cohort (ie, with an initial sample size of no more than three to six children) can be used initially to provide preliminary safety and pharmacokinetic data, while exposing few children. Subsequently, a final recommended dose could be identified in a large cohort. Modelling and simulation should be used to predict an initial dose for children in each age category. Selection of the initial dose in children can be informed by semimechanistic models adjusted for weight and other age-related changes such as volume of distribution, metabolising enzyme maturation, and rate of drug excretion. As these models become more accurate, physiological-based pharmacokinetic models might increasingly contribute to initial-dose selection.[80] Both safety and pharmacokinetic data from children should be 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 many interim analyses of drug exposures in small cohorts within studies allow reduction of risk through rapid dose adjustment in individuals and cohorts.

Approaches that include methods to minimise 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 schemes should be used when appropriate. Semimechanistic pharmacokinetic modelling using a population approach can enable opportunistic sampling and help with the use of variable sampling times and sparse sampling schedules. The efficiency of this approach is enhanced further by the use of optimum sampling

designs based on knowledge of the drug's pharmacokinetics, reducing the number of blood samples needed from each child. Special attention should be paid to the volume of blood sampled and the timing of sample taking in children younger than 2 years.

To guide dose adjustments, important drug–drug interactions should be studied in young children receiving treatment for tuberculosis. The size of drug–drug interactions in this age group might not be predicted by either adult studies or other paediatric age cohorts. As with adults, children should be recruited from diverse racial and ethnic backgrounds to assess relevant pharmacogenomic differences.[81] Safety and adverse event data should be disaggregated and analysed by age group. Data pooling can be used to generate models from diverse sources. Mechanisms with similar study designs, and standardised data collection forms and procedures, should help with collaborative data sharing, combined analyses across studies, and incorporation into models. Babies aged 0–3 months usually benefit from specific pharmacokinetic and safety assessments. Studies should plan to extend the duration of drug treatment in children who tolerate the drug (and have had 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 might increase the prospect of a direct benefit from the intervention and allow for the collection of extended safety data and restricted treatment-response data with long-term exposure.

Safety monitoring and long-term follow-up

As a result of major biological differences between children and adults, adverse event profiles and drug interactions that occur in paediatric patients might not be exactly as predicted by adult studies. Dependent on the drug or drugs investigated or the expected adverse events, initial dosing in an inpatient setting or other intensely monitored study setting might be warranted. Special monitoring (eg, electrocardiogram monitoring or other specific laboratory measurements) might not be needed if data from adults do not suggest any specific associated toxic effects. Passive reporting should be used only when safety indicators of the drug have been well defined in children. Caregivers should be instructed and encouraged to promptly report signs and symptoms to investigators. Establishment of independent safety monitoring committees, which include experts in paediatric pharmacology, paediatric tuberculosis experts, and researchers with experience in paediatric trials, or other specialists as needed, can provide additional protection.

Long-term follow-up for specific populations and study agents should be given special consideration, and adapted to settings in which the study is done and where the drug will be used after registration. Additionally, although the safety profile from adult trials has relevance for children, it might be less useful for the prediction of 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 drug-resistant tuberculosis given an aminoglycoside, which is much higher than that seen in adults, including several patients with continued progression of hearing loss months after discontinuation of the drug.[19]

Long-term follow-up, drug registry data, and surveillance data might be needed to identify possible late effects on skeletal, behavioural, cognitive, sexual, and immune developmental maturation. The duration of follow-up can be drug-specific, based on any signal or concern uncovered during preclinical studies or in early phase studies in adults. In studies for drug-resistant tuberculosis in children, at least 24 months' follow-up after treatment completion should be considered routine, since toxic effects for some agents is duration dependent, and the risk of disease relapse is greatest within the first year after treatment completion. Post-marketing surveillance and patient registries might provide additional safety information that might not be detected from the few paediatric 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, or patient-specific adverse events.

Further issues to be addressed

Improvement in the knowledge of tuberculosis treatment in children needs participation of all stakeholders associated with drug-research design and implementation. Regulators should investigate the existing options to harmonise requirements and streamline processes for paediatric drug development. For new tuberculosis drugs, regulators should require and agree on a formal, time-bound paediatric development plan that includes the development of child friendly formulations early in the drug-development cycle. Investigators are encouraged to include children as soon as possible in studies, with appropriate safeguards, and should prioritise the research questions most in need of answers, as described previously. Drug companies and sponsors should initiate paediatric studies at the timepoints suggested previously, even if not a specific regulatory requirement. Sponsors should make all relevant information, not only safety and dosing information, available to help with further investigation by research consortia and other non-commercial research bodies, especially when many new compounds can be used in combination. Sponsors, in conjunction with investigators and community groups, should encourage the inclusion of children of 10 years or older in initial treatment trials in adults. Advocates should call for clear, harmonised guidance from regulators, including requests for early development of child friendly drug formulations; the inclusion of children in drug safety,

Search strategy and selection criteria

Before the workshop, relevant scientific literature was surveyed to review evidence and prepare statements for discussion. We searched PubMed and Embase for English language papers published between January, 2004, and May, 2014, before the meeting, and then updated our search after the meeting to December, 2014. Some older reports were also included if they were judged 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". Two authors (RBr and PJP) screened abstracts for relevance and reviewed full text articles deemed relevant to topics for consensus.

dosing, and efficacy trials; and improved understanding of general and local paediatric tuberculosis burdens. Advocates will also need to campaign for increased investment in research into paediatric tuberculosis.[36,82] New mechanisms of collaboration should be developed in all these stakeholders, such as a standing committee to help with the earliest possible dissemination of data and information on new tuberculosis drugs (to help to identify when children should enter trials), make coordinated decisions and plans, enable harmonised approaches, and address priorities on a consistent, continued basis and minimise resource duplication.

Conclusion

The scarcity of research of tuberculosis treatment in children is a crucial gap in worldwide efforts to lessen the burden of tuberculosis infection and disease, and to control the spread of drug resistance. Despite their increased susceptibility to tuberculosis, children are subject to under-reporting, and in some settings are at high risk for exposure, infection, and serious disease. Extrapolation from the adult treatment experience might be inadequate for post-licensure use of tuberculosis drugs in children, even if adult information suggests an acceptable risk–benefit ratio for children. Children should be included in studies at the early phases of drug development and be an integral part of the clinical development plan, rather than after approval. We have addressed the ethical, regulatory, and methodological issues that take into account the unique interests of children in new drug trials, and promote approaches that should accelerate the involvement of children in safe trials of new tuberculosis drugs at early stages of the drug-development cycle.

Contributors

All authors have participated in the preparation of the manuscript with contributions to draft statements in preparation for consensus, contributing to final consensus statements as panel members, drafting the manuscript, or providing revisions to content.

Declaration of interests

EL's employer, the Treatment Action Group, receives non-commercial support from the Bill & Melinda Gates Foundation, the TB Alliance, and receives funding from the US Department of Veteran Affairs to coordinate community engagement for the US Centers for Disease Control Tuberculosis Trials Consortium. DFM is employed by Novartis. JS is a member of the Data and Safety Monitoring Board for paediatric trials of delamanid. EG, CM and SM are employed by the TB Alliance. The other authors declare no competing interests.

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