

Accelerating clinical drug development for children with tuberculosis

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SUMMARY

Despite urgent need, the development, approval and availability of child-friendly anti-tuberculosis drugs lag significantly behind that of adults, with children having been ignored in anti-tuberculosis drug development research. This paper outlines possible strategies for accelerating and better integrating the development of drugs and regimens for pediatric tuberculosis (TB) into existing drug development pathways for adults: initiation of pediatric studies of new treatments as soon as promising efficacy data have been generated in adults

following successful phase II studies, shifting from the current age de-escalated approach to concomitant enrollment of children from the various age groups in studies, and leveraging the concepts of both the Unified Pathway and regimen development that have helped speed the study and development of novel regimens in adults.

KEY WORDS: trial design; formulation; ethical guidelines; medicines; infectious disease; pediatric; tuberculosis

ALTHOUGH IT IS CONSIDERED a productive time in terms of ongoing research in the field of tuberculosis (TB), with new products and regimens being evaluated in adults, pediatric research initiatives are generally following at a slower pace.¹ It is widely accepted that the treatment of pediatric drug-susceptible (DS-TB) and drug-resistant TB (DR-TB) is hampered by factors such as high pill burden, long treatment duration, coexistent toxicities and a lack of child-friendly drug formulations. As such, against a background of historical neglect, the medical need for improved and appropriate pediatric TB treatment remains unmet.

The collection of data in children is often delayed compared to adults, and this scarcity of pediatric data has underlined the need to address the numerous knowledge gaps in this population, including pharmacokinetic (PK) and adverse effects profiles of old second-line and new anti-tuberculosis drugs and regimens; optimal duration of treatment and follow-up; adequate drug combinations and relevant doses for disease manifestations more common in children (e.g., osteoarthritis, meningitis); the optimal duration of anti-tuberculosis treatment in human immunodeficiency virus (HIV) positive children and characterization of drug-drug interactions as well as the optimal duration of treatment for multidrug-resistant TB (MDR-TB) in children with minimal disease (uncomplicated hilar adenopathy).^{2,3}

These development needs are further emphasized by the increasing number of children with TB globally;^{4–6} however, it will be many years before the novel drugs and regimens now being approved and deployed for adults will reach children. Whereas pediatric research needs are increasingly recognized by key documents such as the Stop TB Partnership's Global Plan to Stop TB,⁷ existing funding and incentives available to support these activities remain inadequate. Although children represent about a quarter of the global TB burden,⁸ pediatric TB research and development (R&D) accounts for just 2% of total R&D funding.⁹

Another critical aspect further contributing to the delayed development of anti-tuberculosis medicines in children is the frequent lack of age-appropriate pharmaceutical formulations. Following the World Health Organization's (WHO's) 2010 revisions to first-line drug FLD dose ranges,¹⁰ new, child-friendly formulations that take into account these updated dose ranges for FLDs have only recently become available. Age-appropriate formulations do not exist for most second-line agents, and some of those that do exist are deemed inadequate.¹¹ The current use of second-line agents in children with TB is guided by sparse or incomplete data;^{11,12} hence the current practice of makeshift and potentially dangerous dosing options in children with TB, such as crushing or partitioning tablets intended for adults.

REGULATORY LANDSCAPE

Among opinion leaders and policy makers alike, consensus has grown that harmonization and streamlining of requirements and processes may help optimize pediatric drug development.¹³ In the European Union (EU), this entails early agreement on a pediatric investigation plan (PIP) that states key binding, time-bound measures that incorporate details on the development of age-appropriate formulations. As per the EU Paediatric Regulation (Regulation EC No. 1901/2006),¹⁴ developers are requested to prepare their envisaged pediatric development program no later than upon completion of PK studies in adults and subsequently to discuss and agree upon it with the EU regulator.

TB trials should enroll only children with confirmed or probable TB disease, as defined according to the published case definitions for DS- and DR-TB.¹⁵ In particular, children aged <5 years suffering from TB disease and those with HIV/acquired immune-deficiency syndrome constitute the most susceptible groups for research prioritization. In the previously mentioned age group, TB disease presents more often with extrathoracic locations, warranting further examination and evaluation of treatment outcomes, while PK in young children may differ substantially from that of older children.

International Conference on Harmonisation (ICH) guidelines state that: '[vulnerable] group should stand to benefit from the knowledge, practices or interventions that result from the [medical] research.' Novel therapeutic agents or regimens should therefore be considered for further study and development if there is a prospect for improved efficacy/effectiveness over the comparator or a better safety/tolerability profile. Alternatively, new drugs or regimens may hold the prospect of treatment shortening or simplification or obviate the need for parenteral drug administration. Age-appropriate formulations assuring accurate dosing, adequate tolerability and palatability should be made available and should ideally be used for PK and safety investigations in children.

For HIV co-infected patients, fewer drug-drug interactions would be considered an advantage over existing TB regimens. Nevertheless, while it is recognized that children with HIV and TB are one of the groups that is among the top priorities in terms of unmet need, the lack of adult drug-drug interaction studies between TB drugs and highly active antiretroviral therapy is clearly an important limiting factor, and may further hamper the generation of pediatric data in this subpopulation with very limited treatment options.

Although not counted as a formal regulatory requirement, sequential age-de-escalation is one of the frequently used enrolment strategies for pediatric studies. This conservative approach may, however,

not confer protection to younger cohorts. Due to the many and significant physiological and metabolic differences between the various pediatric age groups, data generated in older children do not necessarily predict what will happen in younger cohorts, nor do they mitigate the risks.¹⁶ In relation to the safety aspects, differences in the adverse event profile and drug interactions between children and adults due to existing biological differences between these groups cannot be excluded. Depending on the drug under evaluation, intense safety monitoring might therefore be necessary in children. Simultaneous enrolment of certain pediatric age groups into TB trials may prove to be an alternative viable option, and could be further discussed with regulators. It has to be recognized nevertheless that, apart from the above, further aspects also need to be considered and may lead to a delay in conducting the agreed studies in younger age groups, principal among which is the usual lack of availability of an age-appropriate pharmaceutical form at the time of conducting the pediatric studies.

PROPOSED STRATEGIES FOR ACCELERATED TUBERCULOSIS DRUG/REGIMEN DEVELOPMENT

Among the options available to accelerate anti-tuberculosis drug development in children, the following could be envisaged (see Table).

Initiate pediatric studies after successful Phase II trials in adults

It is generally accepted that efficacy can be extrapolated from adult studies. However, single- and multiple-dose PK studies that include the collection of safety outcomes have to be conducted to ensure that the dosing regimen used in children is adequate. The determination of the optimum dose cannot be achieved using simple allometric scaling based on weight and surface area.¹⁷ Prior to initiating trials in children, an adequate preclinical safety package and juvenile toxicity studies have to be performed.

Concomitant enrolment

Single- and multiple-dose PK studies conducted in all age groups simultaneously will help in selecting the appropriate dose to be used in children. These studies could be conducted in addition to the patient's standard treatment.

Development of drug regimens for children

Novel strategies employed to accelerate drug development in adults can also be applied to the pediatric drug/regimen development. One such strategy of 'regimen development' is to examine new drugs individually in animal studies and then in human phase I and early phase II, but to subsequently

Table An overview of historical and current development strategies and the newly proposed paradigm for drug development in pediatric tuberculosis

	Historical	Current	Proposed/accelerated pediatric development
Development strategy	No specific pediatric development; children are given adult doses, or doses are adjusted according to weight	Pediatric development is generally initiated once a drug or regimen is approved for adults, starting with adolescents and gradually moving to younger children	Single-dose PK studies begin as soon as successful phase II adult studies are complete. Study multiple dose/comprehensive PK and safety in all children (no age de-escalation) in parallel with phase III (in adults)
Challenges	Drugs in regimens are administered using ad hoc methods (administering adult-sized pills, crushing, dispersion in liquids etc.). Pediatric safe/efficient dosing often unknown	Significant delays for access to new drug or regimens for children	Overcoming traditional clinical and ethical considerations of how children can be studied

PK = pharmacokinetic.

evaluate these collectively within new regimens in late phase II and phase III studies.¹⁸ This regimen development strategy can greatly shorten the time to develop and register novel regimens in adults, and could be applied to children's development programs as well. If a new safety issue arises during the evaluation of a regimen, it might be necessary to do additional animal or phase I work to determine the cause/source of the issue. This is one of the limitations/risks of a regimen-based approach.

Similarly, the 'Unified Pathway' allows for parallel enrolment of both people with DS- and DR-TB into the same clinical trial. An example of such a trial is the recently completed NC-002 study of PaMZ (pretomanid + moxifloxacin + pyrazinamide).¹⁹ This greatly simplifies regimen development and removes the time and cost associated with developing new regimens for DS- and DR-TB independently. In this strategy, patients are included in clinical trials if they are infected with a strain of TB that is susceptible to the drugs in the regimen, irrespective of whether they could be qualified as drug-susceptible or drug-resistant, according to the existing definitions. This strategy is equally applicable to both children and adults.

To address potential challenges associated with this approach, appropriate pediatric TB specialists should be involved in drug safety monitoring boards. If required, the program could include long-term follow-up through the introduction of a drug registry and the collection of surveillance data to detect possible late effects on skeletal, behavioral, cognitive, sexual, and immune developmental maturation. It is nevertheless recognized that the above could prove challenging in resource-poor countries.

In addition, there is likely a practical need for additional capacity building for clinical trial sites and investigators. This capacity building can help improve the number of sites that are qualified to perform clinical trials in children, facilitate enrollment strategies, and overcome barriers posed by

institutional review boards and ethics committees (Table).

INCENTIVES TO INCREASE AND ACCELERATE PEDIATRIC TUBERCULOSIS DRUG RESEARCH

Regulatory standards on the collection of important pediatric data for novel TB drugs have been the main driving force behind the development of novel anti-tuberculosis drugs in children, but may still be insufficient for ensuring timely access to treatments for children. The European requirement for the agreement of a PIP prior to granting marketing authorization ensures that relevant pediatric PK and safety data will be collected and that a pediatric formulation will be developed.^{20,21} The United States Food and Drug Administration (FDA) allows drugs for orphan diseases, i.e., those that affect fewer than 200 000 individuals per year in the United States, such as TB, exemption from pediatric studies altogether.²²

Regulatory incentives, such as extended marketing exclusivity²³ and priority review vouchers²⁴ offered by the FDA, intended to encourage rather than mandate investigations in pediatric populations, have so far been ineffective for TB. As of March 2015, 210 products have been granted pediatric exclusivity, none of which are indicated for the treatment of TB in children.¹ Exclusivity and other market-driven incentives confer less benefit and attractiveness in the absence of a lucrative market and competition, as is the case for TB. Pediatric exclusivity has also left some age groups understudied, as once pediatric exclusivity is granted for studies conducted in older children, there is no additional incentive for conducting studies in younger age groups. Furthermore, pediatric exclusivity does little for products that have no remaining patent life, as is the case for most second- and third-line anti-tuberculosis drugs.

Alternative incentives, particularly those focused on creating an attractive market, may be more

effective for accelerating the development and availability of pediatric TB treatments. An advance market commitment (AMC) is a legally binding agreement for an amount of funds that is used to subsidize the purchase, at a given price, of an as of yet unavailable drug, diagnostic or vaccine.²⁵ AMCs attract developers by guaranteeing a certain volume of procurement and return on investment in the absence of a clearly defined market. AMCs by donor agencies such as the Global Fund for HIV, TB and Malaria (Global Fund, Geneva, Switzerland) and the US Agency for International Development (USAID, Washington DC, USA), or even by governments with well-established political will, such as that of South Africa, could help draw private-sector interest and investment in pediatric TB treatments.

While AMCs may be an effective strategy for drawing investment to what might otherwise be an unattractive market, revealing the true burden of TB among children is a longer-term, complementary strategy. Work to improve estimates of the global burden of TB in children, to develop more sensitive and non-sputum based diagnostic tools, and to integrate TB services with those for reproductive, maternal, neonatal and child health is critical to further elucidating the true potential market for pediatric TB medicines and hopefully creating market incentive.

In addition to creating market incentives to attract investment, increasing donor and public funding for pediatric research and development is absolutely critical. A grant from UNITAID to the Global Alliance for TB Drug Development (TB Alliance, New York, NY, USA), a not-for-profit product development partnership with the mission of developing improved TB treatments, and its project partner, the WHO Global TB Program and Department of Essential Medicines and Health Products, is an example of a donor-initiated incentive that has successfully catalyzed the development and market introduction of pediatric TB treatments. The goal of the grant is to make available and improve access to correctly dosed, properly formulated, affordable, high-quality pediatric TB medicines meeting the current WHO guidelines for these drugs. Thanks to this investment, revised fixed-dose pediatric formulations of FLDs will finally be available, 5 years after the WHO issued the updated pediatric TB treatment guidelines. The US National Institutes of Health (NIH, Bethesda, MD, USA) is also contributing, funding a number of investigator-initiated and IMPAACT (International Maternal Pediatric Adolescent AIDS Clinical Trials Network) studies that will fill long-standing gaps for existing anti-tuberculosis drugs and advance investigations of novel TB drugs in children, including children who are HIV-positive.²⁶ Furthermore, the US Centers for Disease Control and Prevention-funded Tuberculosis Trials Consortium

(TBTC), where appropriate, includes children in their work, largely centered on the TB drug rifampin.^{27,28}

Funders could create further incentives for both public network and investigator-initiated research to include children. For example, study protocols or grant proposals that include children could be assigned a priority review status or extra points on scoring materials. Public funders could also mandate the inclusion of pediatric research components in all studies that follow successful phase 2 studies in adults. Such requirements could apply both to new drugs and regimens. Finally, the recently proposed 3P Project—‘Push, Pool, Pull’—combines incentives such as increased donor and public funding meant to ‘push’ promising drug candidates through earlier phases of development, with ‘pull’ incentives such as milestone prizes designed to financially reward the achievement of certain R&D objectives. While the 3P Project was conceived to address underlying issues hampering the development of new TB regimens, similarly, push/pull incentives could be applied to accelerate research and development in children, particularly if the mechanism could interest new funders that do not currently support TB and pediatric TB research.²⁹

Advocacy is another tool that can be used to raise awareness of the importance of timely investigation of TB treatment regimens in children, and hold drug sponsors, donors, and public funders accountable for ensuring its realization. Vocal reinforcement that inclusion of children in research is an expectation of the TB community will further encourage and accelerate the development of and access to anti-tuberculosis treatment for children.

CONCLUSIONS

The current approach to anti-tuberculosis drug development is not sufficient to rapidly address the urgent unmet medical needs of children with TB. Ample opportunities exist to improve today’s efforts. Overlapping pediatric development with ongoing adult development of anti-tuberculosis drugs and regimens (Figure), and applying the approaches of regimen development and the Unified Pathway to the development of pediatric formulations, will greatly accelerate the availability of new TB treatments for children. These strategies can be applied without compromising current safety or ethical standards. However, it would be highly desirable that more adequate incentives to conduct the necessary research for children are created and implemented. Augmenting existing incentives, such as the funding available for pediatric TB drug development, and new incentives, such as an AMC for pediatric drugs, are necessary to perform the clinical trials that address this unmet public health need.

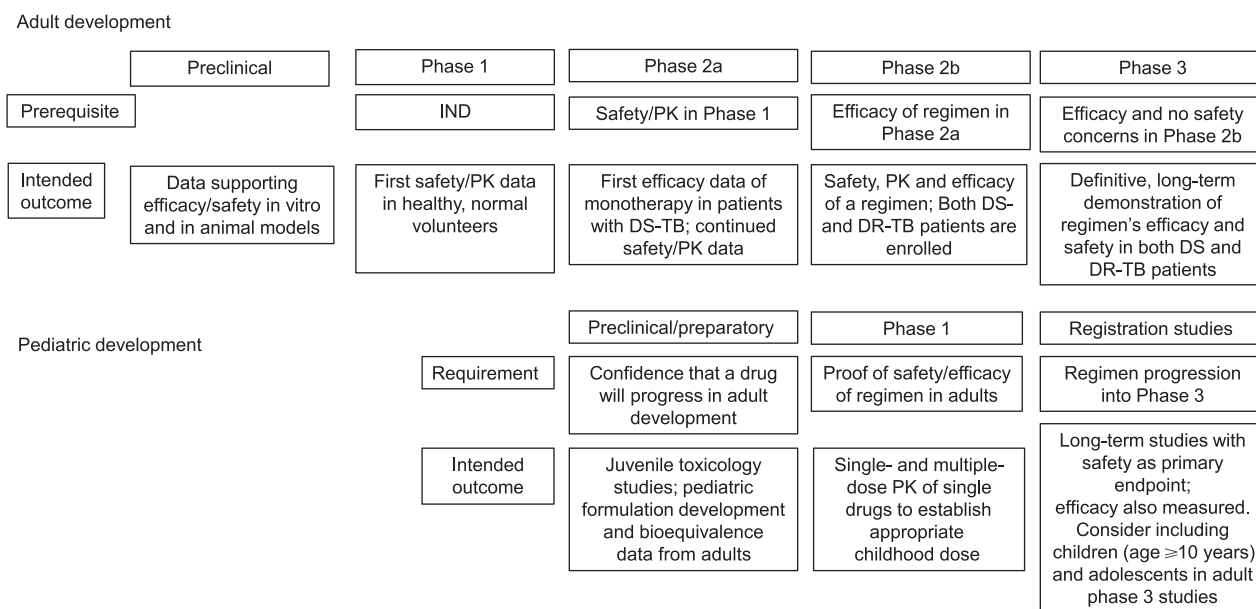


Figure Optimized anti-tuberculosis drug development: integrated adult and pediatric clinical trials. PK = pharmacokinetic; DS-TB = drug-susceptible TB; DR-TB = drug-resistant TB; TB = tuberculosis.

Acknowledgments

The authors thank R Hooft van Huijsduijnen and J Breitstein for editorial assistance with the manuscript.

The views expressed in this paper are the personal views of the authors and must not be understood or quoted as being made on behalf of or representing the position of the European Medicines Agency (London, UK) or one of its committees or working parties.

Conflicts of interest: none declared.

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RESUME

En dépit de besoins urgents, l'élaboration, l'approbation et la disponibilité de médicaments antituberculeux adaptés aux enfants restent à la traîne par rapport à ceux des adultes, les enfants ayant été largement ignorés dans la recherche et le développement des médicaments pour la tuberculose (TB). Cet article expose les stratégies possibles pour accélérer et mieux intégrer l'élaboration de médicaments et de protocoles pour la TB pédiatrique dans les voies de développement des médicaments TB pour adultes : initiation d'études pédiatriques des

nouveaux traitements dès qu'ils ont généré des données d'efficacité prometteuse chez les adultes (après des études réussies de phase II) ; passer de l'approche actuelle limitant les études chez les plus jeunes à l'enrôlement concomitant d'enfants de tous les groupes d'âge dans les études ; et amplifier les notions à la fois d'Unified Pathway et d'élaboration de protocoles qui ont contribué à accélérer l'étude et l'élaboration de nouveaux traitements chez les adultes.

RESUMEN

Pese a que existe una necesidad urgente, el desarrollo, la autorización y la puesta al alcance de los medicamentos antituberculosos adaptados a los niños no han avanzado al ritmo del progreso con las preparaciones destinadas a los adultos; en la investigación sobre los medicamentos antituberculosos se han ignorado en gran medida los niños. En el presente artículo se describen estrategias que podrían acelerar el desarrollo de medicamentos y mejorar la integración de los regímenes pediátricos en los mecanismos existentes de investigación farmacéutica dirigida a los adultos. Se proponen las siguientes medidas: la iniciación de estudios pediátricos con los

nuevos tratamientos, tan pronto como se hayan obtenido datos prometedores de eficacia en los adultos (luego de un resultado favorable de la fase II de los estudios clínicos); la transformación de la estrategia actual de escalonamiento regresivo en función de la edad, en una inclusión concomitante de niños de los diferentes grupos de edad en los estudios clínicos; la promoción de dos conceptos, a saber, la Vía Unificada (tuberculosis sensible y resistente en un mismo estudio) y el mecanismo de formulación de regímenes que ya ha contribuido a acelerar el estudio y la formulación de nuevas pautas terapéuticas dirigidas a los adultos.
