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SUPPLEMENT ARTICLE

Partnerships to Design Novel Regimens to Treat Childhood Tuberculosis, *Sui Generis*: The Road Ahead

Tawanda Gumbo,[1,2] Mamodikoe K. Makhene,[3] and James A. Seddon[4]

[1]Center for Infectious Diseases Research and Experimental Therapeutics, Baylor Research Institute, Baylor University Medical Center, Dallas, Texas; [2]Department of Medicine, University of Cape Town, Observatory, South Africa; [3]Division of Microbiology and Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland; and [4]Centre for International Child Health, Department of Paediatrics, Imperial College London, United Kingdom

There has been a recent expansion of preclinical models to predict the efficacy of regimens to treat adults with tuberculosis. Despite increasing global interest in childhood tuberculosis, these same tools have not been employed to develop pediatric regimens. Children differ from adults in bacillary burden, spectrum of disease, the metabolism and distribution of antituberculosis drugs, and the toxicity experienced. The studies documented in this series describe a proof-of-concept approach to pediatric regimen development. We propose a program of investigation that would take this forward into a systematic and comprehensive method to find optimal drug combinations to use in children, ideal exposures, and required dosing. Although the number of possible drug combinations is extensive, a series of principles could be employed to select likely effective regimens. Regimens should avoid drugs with overlapping toxicity or linked mechanisms of resistance and should aim to include drugs with different mechanisms of action and ones that are able to target different subpopulations of mycobacteria. Finally drugs should penetrate into body sites necessary for treating pediatric disease. At an early stage, this body of work would need to engage with regulatory agencies and bodies that formulate guidelines, so that once regimens and dosages are identified, translation into clinical studies and clinical practice can be rapid. The development of child-friendly drug formulations would need to be carried out in parallel so that pharmacokinetic studies can be undertaken as formulations are created. Significant research and development would be required and a wide range of stakeholders would need to be engaged. The time is right to consider a more thoughtful and systematic approach toward identifying, testing, and comparing combinations of drugs for children with tuberculosis.

Keywords. tuberculosis; children; future; investment; PK/PD; hollow fiber.

We are privileged to live in a time when new drugs to treat tuberculosis are becoming available [1]. In addition, many drug classes developed for the treatment of other bacterial infections are being increasingly shown to be effective against *Mycobacterium tuberculosis* (*Mtb*). This excitement has, understandably, led to hope that therapy duration could be shortened from the current short-course chemotherapy of 6 months, to 4 months, or even 8 weeks, not just for drug-susceptible disease but also for multidrug-resistant (MDR) tuberculosis (defined as *Mtb* resistant to isoniazid and rifampin). Several research programs exist to achieve this in adults, which include preclinical models followed by clinical trials. We propose that there is an opportunity and an even greater possibility of achieving this in children with tuberculosis, hitherto ignored [2].

The last 15 years have witnessed an explosion of tools for use in predicting outcomes of regimens [3, 4]. The models were, by and large, developed specifically for pulmonary cavitary tuberculosis in adults by virtue of both the *Mtb* physiology and pharmacokinetics employed [4–9]. They include refined mouse models that are capable of cavitary disease (the so-called Kramnik mouse), the resurrection of the guinea pig model, and the use of nonhuman primate models [3, 10]. The hollow fiber model of tuberculosis was specifically designed for identifying optimal doses and regimens, and has been successfully used and qualified by the European Medicines Agency (EMA) and endorsed by the US Food and Drug Administration (FDA) as a drug development tool [5, 11–15]. However, the disease in children can be more varied, from adult-type disease in teenagers to disseminated tuberculosis in many infants and toddlers, rendering the "typical" adult manifestations of tuberculosis less applicable in many pediatric age groups [16, 17]. Moreover, owing to both age-dependent maturation and body size effects, the pharmacokinetic parameters of many drugs in children will vary due to rapid metabolism and relatively different volumes of distribution that alter drug concentrations, which rapidly change as a function of growth and development in children [18–21]. This affects both concentration-driven efficacy and toxicity. Thus, dosing children by simply using dose denominated to weight (eg, milligrams per kilogram [mg/kg]) fails to address this

Correspondence: J. A. Seddon, Centre for International Child Health, Department of Paediatrics, Imperial College London, Norfolk Place, London W2 1PG, UK (james.seddon@imperial.ac.uk).

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identified dynamic and fractal geometry–based pharmacokinetic variability. Moreover, although the bacillary burden of tuberculosis in children is likely lower than that in adults, treatment duration has been mirrored tightly to that for adults [16, 17]. Thus, many treatment aspects that have been derived from adults, and then applied to children, could be suboptimal for the treatment of pediatric tuberculosis.

A NEW DAWN FOR PEDIATRIC TUBERCULOSIS?

Despite decades of neglect, the last 5 years have seen increasing interest and funding for childhood tuberculosis. In March 2011, a meeting was organized in Stockholm; 110 participants came together to discuss the challenges and possible solutions to managing pediatric tuberculosis. The meeting resulted in a call to action for childhood tuberculosis. This was subsequently endorsed by >800 individuals and organizations from nearly 100 countries [22]. The "No More Tears, No More Death" initiative was launched by the Stop TB Partnership in March 2012, and later that year UNITAID made a $17 million commitment to develop pediatric antituberculosis drug formulations. This has been implemented by the Global Alliance for Tuberculosis Drug Development (TB Alliance) and the World Health Organization (WHO); new, child-friendly, fixed-dose combinations of the first-line antituberculosis drugs were launched at the end of 2015. Another seminal publication, the International Roadmap for Childhood Tuberculosis, was published in 2013 and documents the steps required to reach zero tuberculosis deaths among children [23]. All this is exciting and much welcomed. However, none of this to date has specifically addressed MDR tuberculosis in children.

RATIONAL SYSTEMATIC APPROACH

Proper drug dosages for children with MDR tuberculosis are unclear and out of desperation; pediatricians frequently use toxic regimens advised for adults, where treatment is given for at least 18 months, and more than one-quarter of children develop hearing loss [24, 25]. As one newspaper headline succinctly summarized: "14 600 pills over two years—there has to be a better way to treat TB" [26]. The treatment of extensively drug-resistant (XDR) tuberculosis (ie, MDR tuberculosis with additional resistance to an injectable and a fluoroquinolone) in children is in an even worse state, with more toxic drugs and even longer durations of therapy advised. The pediatric community waits expectantly for discoveries from the adult world, with the hope that perhaps then pediatric formulations will follow.

The laboratory approach that starts with the hollow fiber model of disseminated tuberculosis, followed by computer-aided clinical trial simulations, promises to bypass such expectant approaches, and to develop regimens specific to young children, as outlined in this supplement [27]. This strategy proposes a deliberate program to design many new regimens to treat children, starting in the laboratory. Hollow fiber laboratory models for adult tuberculosis have been found to be 94% accurate in predicting the required exposures and dosages found subsequently in clinical studies [12]; if the pediatric models were similar, this would allow the rapid development of regimens for children. Mouse models of disseminated tuberculosis could also be used as an extra validation point, provided that the pharmacokinetics in children could be matched and the models "humanized." This would give a "2-model" approach allowing an immediate move to phase 3 clinical trials in children with drug-susceptible, MDR, or XDR tuberculosis.

Work could start with examining several of the regimens currently being used to treat children, developed out of necessity by pediatricians. Streptomycin, isoniazid, pyrazinamide, rifampin, and ethambutol were identified in that order, and drug combinations were developed as drugs became available, using 3–4 of these drugs together, and given at the dosages developed for monotherapy [9, 28]. It was not an optimal way to construct a regimen. In the clinical studies and experiments outlined in this supplement, we learn that combination therapy should not depend on the arbitrariness of add-ons [29]. There are implications, not only on synergy and antagonism in efficacy but also on toxicity [30, 31]. There is need for a deliberate scientific process that examines the best drugs to combine, as well as their optimal dosages in that combination. This should leverage additivity and synergy, and minimize antagonism and toxicity. One rational approach is to use antimicrobial pharmacokinetics/pharmacodynamics (PK/PD) science [32–34].

SCIENTIFIC AND MATHEMATICAL RATIONALE FOR DRUGS TO BE USED IN COMBINATION

Many agents are available for use in combination therapy in adults and children. Given the large number of drugs (n) to be combined into combinations of r drugs in the regimen, one would need to study the following possible combinations (C) as first proposed by Pascal and Fermat in 1654:

$$C = \frac{n!}{r!(n-r)!} \quad (1)$$

where C is the number of possible drug combinations based on selection from the set of "n" drugs currently available, for a regimen composed of r drugs. There are currently about 20 antituberculosis compounds (ie, n = 20) in several drug classes that are available to treat drug-susceptible and drug-resistant tuberculosis, as recently listed and summarized in the updated WHO drug-resistant tuberculosis treatment guidelines [35]. Assuming a 3-drug regimen (ie, $r = 3$), this would lead to 1140 possible drug combinations based on equation 1. If we were to test up to 7 combinations of each drug in 7×7 matrices of concentrations, in triplicate, we would need to test 167 580 replicates! That is not going to be possible given the cost of PK/PD studies and time available. Therefore, we propose using several simple

and rational rules to choose the antibiotics that would undergo combination PK/PD studies, and would constrain the combinations from 1140 to about a dozen or so.

Some important principles could help guide the choice of drugs to include in new regimens. Each of the standard first-line drugs (isoniazid, pyrazinamide, and rifampin) causes hepatotoxicity; rifampin might even accentuate or drive the metabolism of these companion drugs to increase the chances of hepatotoxicity [36]. Thus, a first lesson that we can learn from the current first-line regimen is to avoid drugs with overlapping toxicity, a prospect made more likely by the current diversity of antituberculosis drug classes. Second, it would be important to choose drugs with different mechanisms of antimicrobial effect, and avoid those with overlapping targets. As an example, concentration-dependent antagonism of isoniazid and rifampin-pyrazinamide, as well as that of gatifloxacin and rifampin, have been demonstrated in murine tuberculosis, in the hollow fiber model, in adult sterilizing effect, and in childhood tuberculosis [29, 37–42]. The mechanisms are unclear, but may be related to the drugs acting in the same biochemical pathway. Similarly, one would not combine pretomanid with the other nitroimidazole, delamanid, or moxifloxacin with another fluoroquinolone. Third, it would be important to combine drugs without overlapping mechanisms of resistance. Some target site mutations inactivate antibiotic targets to different drugs, as, for example, isoniazid and ethionamide. Similarly, ethambutol and isoniazid could share the same efflux pumps, as do bedaquiline and clofazimine [43–45]. Fourth, there would need to be enough drugs in the regimen with activity against the different metabolic subpopulations of *Mtb*-nonreplicating persisters and logarithmic phase growth organisms, so that an adequate number of drugs in the regimen would have bactericidal and sterilizing effects. Finally, for extrapulmonary tuberculosis, drugs that can penetrate into meninges and peritoneum would be candidates for combination, as would drugs that accumulate intracellularly. These simple rules would reduce the number of possible combinations dramatically.

PK/PD SCIENCE AS A RATIONALE FOR THE DESIGN OF PEDIATRIC ANTITUBERCULOSIS REGIMENS

Preclinical PK/PD science has been used to develop many anti-infective agents, including antiretroviral combination regimens that are now the standard of care [32–34, 46–49]. The science has begun to change dosing and regimen development in adult tuberculosis, and standards for PK/PD science for antituberculosis drugs were recently published [3]. This scientific approach can be heavily leveraged to achieve these same successes in the development of antituberculosis regimens for children.

PK/PD science involves identifying the optimal exposure (an index of concentration denominated with minimum inhibitory concentration [MIC]) for microbial kill and suppression of acquired drug resistance, in our case for intracellular *Mtb*. Another crucial aspect identified is the optimal dosing schedules; this means intermittent schedules should not arise merely out of convenience but be driven by optimal kill. In pediatric tuberculosis, laboratory models that also examine the relationship between concentration and toxicity have been incorporated into the same experiments examining microbial effect [30, 50]. The exact shape of the concentration-time curve, and its periodicity, have been found to be important in the determination of microbial effect against *Mtb*; it is therefore crucial that pediatric pharmacokinetics be used. In general (but not always), infants and toddlers achieve shorter drug half-lives, lower peak concentrations, and lower area under the concentration-time curves (AUCs) than when the same dose in mg/kg is given to nonobese adults. On the other hand, for several antibiotics, the opposite is encountered, and there is reduced clearance due to impaired liver and kidney function caused by immature phase II xenobiotic metabolism enzyme systems, especially in neonates and preterm babies. Thus, PK/PD studies for children should recapitulate these exact concentration-time profiles if microbial responses in children are to be identified. In developing the optimal combination regimen, combination exposures that lead to antagonism, synergy, or additivity are identified for both microbial effect and toxicity. It is the quantity of the peak/MIC, or AUC/MIC, or percentage of time the concentration persists above MIC ($\%T_{MIC}$) associated with optimal microbial kill, suppression of resistance, and minimum toxicity, that is translated from the preclinical model to clinical studies in children.

This iterative process is performed for different combination regimens, for *all* known anti-tuberculosis compounds, including both new and repurposed agents. Then, the kill slopes of the different regimens are compared to each other, and to the standard therapy regimen of isoniazid, rifampin, and pyrazinamide. Because we know the performance of the standard regimen in children with drug-susceptible tuberculosis, the slopes of novel regimens could be indexed to that of the standard regimen. This could provide some information about how fast the experimental regimen might sterilize *Mtb* from the child, as compared to the standard regimen. This may allow an understanding of the required duration of therapy, and whether it may be possible to use a shorter treatment regimen than the standard 6-month regimen used to treat drug-susceptible disease.

THE IN SILICO CHILD WITH TUBERCULOSIS

In 2009, Läer and colleagues advocated for the use of modeling and simulation to guide pediatric drug development, for the management of pediatric pharmacotherapy, and for its acceptance by regulatory bodies [51]. Several pediatric treatments and dosages have since been licensed based on modeling and simulation [52, 53]. In adult tuberculosis, modeling and simulation, especially via Monte Carlo experiments, have been used

since 2004 [11]. This approach takes the optimal exposures identified in PK/PD studies as described above, and the pharmacokinetic variability encountered in children discussed above, as well as the *Mtb* MIC variability, to identify combination therapy regimens that can be explored in clinical studies [54]. In the same simulations, concentration-dependent toxicity can be examined, and optimal dosages and dosing schedules chosen in such a way as to be lower than the concentrations associated with toxicity.

PRIORITY NEEDS IN PEDIATRIC PRECLINICAL STUDIES

Examination of multiple drug concentrations per drug, in combinations of 2 or 3 drugs, is expensive. This laboratory process uses in vitro raw materials, tissue platforms, and animal models that are themselves expensive. In addition, the studies take several months to complete, and about 1.5 years for the hollow fiber studies to identify and rank regimens. Modeling and simulation also require adequate computational power and time. Thus, if new regimens specific to childhood tuberculosis are to be quickly identified, preclinical studies and proof-of-concept clinical studies need to be prioritized both by researchers and global supporters of tuberculosis research and development (R&D).

Current R&D efforts in tuberculosis are geared mainly toward adult pulmonary disease, which, according to global R&D reports, is underfunded. Given the large numbers of patients involved and lives lost globally, research in pediatric tuberculosis should not divert from efforts in adult tuberculosis research. Rather, pediatric tuberculosis deserves its own consideration and prioritization. The Roadmap for Childhood Tuberculosis estimates that between 2011 and 2015 $200 million would be required to develop new tools to prevent, diagnose, and treat tuberculosis in children [55]. There is, however, a lack of attention to designing new regimens for children, *sui generis*. In addition to public funding through, for example, the US National Institutes of Health, the United States President's Emergency Plan for AIDS Relief, and the European Commission, R&D for the treatment of adult tuberculosis has been boosted by philanthropic foundations and private–public partnerships such as the Bill & Melinda Gates Foundation, the Wellcome Trust, the Critical Path for Tuberculosis Regimens, the TB Alliance, and the Innovative Medicines Initiative. This collective support has revolutionized the preclinical and clinical science for the treatment of adult tuberculosis. There is clearly a need for such focused attention to and sustained investment into childhood tuberculosis, including early studies evaluating new regimens, with lessons learned from adult tuberculosis.

THE ROLE FOR REGULATORY BODIES AND THE WHO

By the time a regimen is ready for clinical testing in children, a lot of investment has already taken place and regimen composition has usually been decided on. In adult tuberculosis, the paradigm has changed, with both the EMA and FDA involved in vetting preclinical study models such as the hollow fiber model [14, 15]. This paradigm should be considered for early engagement of pediatric tuberculosis preclinical laboratory models by the FDA and EMA, as well as buy-in by the WHO and ministries of health in high-tuberculosis-burden countries. This input and cross-talk will be crucial, not only in laying out clinical development priorities, but also in affecting the science early when it still matters. The requirements of regulatory agencies that license and then approve drugs, combinations, and regimens would be readily known. Moreover, it is the involvement of such regulatory and supranational authorities that often increases awareness for specific research needs. Sustained engagement of regulatory bodies and the WHO in the science and licensure of new regimens would permit timely approval and assimilation postdevelopment, so that regimens become quickly available to treat children with tuberculosis.

Once optimal doses and combinations are identified, they cannot be tested in children, unless appropriate formulations are available. Indeed, because the formulation affects both bioavailability and other pharmacokinetic factors, and pharmacokinetics is factored into models such as the hollow fiber system in the first place, there would need to be an iterative back-and-forth flow of data between those creating formulations and those involved in the PK/PD studies. Thus, it will be crucial for the WHO, international governmental bodies, drug manufacturers, and regulatory bodies to be involved in the design and execution of PK/PD studies in the hollow fiber model and in animal models.

CONCLUSIONS

We have focused on the steps required for the development of tuberculosis treatment regimens in children. The area of pediatric tuberculosis diagnostics, although closely related, still needs much clarification in its own right, and has therefore purposely not been discussed. We propose that the time is ripe for the formation of an international platform of stakeholders and scientists to have input into both the need for, and the design of, preclinical antituberculosis experiments and clinical studies to identify new regimens specific to children. The laboratory PK/PD processes will need to be conducted in parallel to both the design of new formulations for children and the pharmacokinetic studies of those formulations. This complex interaction requires the formation of a neutral supranational body and platform that is solely dedicated to the treatment of tuberculosis in children.

Notes

Disclaimer. The views expressed in this article are those of the authors and do not reflect the official policy or position of the National Institute of Allergy and Infectious Diseases (NIAID), the National Institutes of Health (NIH), the Department of Health and Human Services, or the U.S. Government.

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