RESEARCH PRIORITIES FOR **PAEDIATRIC TUBERCULOSIS**

Introduction

Tuberculosis (TB), while preventable and curable, remains a significant cause of illness and death among children globally *(1)*. An estimated one million children develop TB disease each year, and a further 7.5 million are exposed and in need of evaluation and treatment to mitigate the risk of developing TB *(2,3)*. Yet, existing approaches to prevent, diagnose and treat TB either do not meet the needs of children or are not available where they are needed the most. In recent years, increased attention and research and development (R&D) efforts have resulted in incremental advances for children with TB, but much work remains to end the unnecessary sickness and death borne by families affected by TB.

The commitments made by Heads of State during the United Nations High-Level Meeting on TB, held in September 2018, challenge national governments, global donors, health professionals, researchers, and members of civil society and affected-communities to work together to rapidly scale up existing TB interventions. Where interventions or technologies are inadequate, the commitments made during the High-Level Meeting on TB challenge these same stakeholders to support and undertake R&D to improve the prevention, diagnosis, and management of children and families affected by TB.

This document presents an overview of paediatric TB research efforts already underway and their limitations; and highlights priorities for future research initiatives in epidemiology, basic science, prevention, diagnosis, treatment and operational research. Also discussed are financial and other barriers that must be overcome to rapidly advance the paediatric research agenda laid out in this document.

TAG Treatment Action Group

Child & Adolescent TB Working Group

Existing paediatric TB research initiatives

Paediatric TB R&D efforts have largely focused on generating evidence to inform the use of existing technologies and treatments, which are designed for and proven in adults, for children. Yet children affected by TB have specific needs that merit a paediatric-focused research agenda. For example, the immune response to TB varies among children of different age groups and results in a wide spectrum of disease manifestations, requiring different approaches for diagnosis, prevention and treatment.

Diagnosis

Most current tests for TB, and many of those in development, require sputum from the lungs. Sputum-based diagnostic tests are inadequate for children, who often have fewer TB bacteria in their bodies, high rates of extra-pulmonary TB (TB outside of the lungs), and difficulty in producing sputum. Ongoing efforts to evaluate and optimize the performance of currently available tests for children, especially related to sample types other than sputum, remain important. To radically improve the rate of diagnosis among children with TB, a rapid diagnostic test – that uses easy to obtain samples and markers of the host's response to TB (as opposed to trying to identify the TB bacteria itself), and can be used at the point of care – will likely be required *(4)*.

Treatment

Paediatric TB treatment research efforts to date have largely centred on generating dosing (pharmacokinetic) and safety data necessary to inform the optimal dose at which existing and new TB medicines can be safely administered to children, including those that are living with HIV. Delays in the initiation of such studies, and in the translation of data into policy, have delayed the market introduction of paediatric formulations and the optimization of TB treatment for children. Expediting these studies, the translation of study results into policy, and the availability of quality-assured paediatric formulations is essential. In addition to efforts to tailor treatment options designed for adults to meet the needs of children, several efficacy studies that are underway or planned will evaluate whether it is possible to shorten and optimize treatment for drug-sensitive and drug-resistant TB, and TB meningitis among children *(5)*.

Prevention

The current TB vaccine – Bacillus Calmette-Guérin (BCG) – is widely administered but offers limited protection against TB. TB vaccine trials aimed at preventing TB infection, disease progression, or relapse are currently focused on adolescents and adults *(6)*. TB prevention research initiatives involving drugs (rather than vaccines) have been more inclusive of children, albeit inconsistently. Delays in the generation of pharmacokinetic and safety data, development of paediatric formulations, and implementation of long-proven preventive regimens have excluded young children exposed to TB from benefitting from shorter, simplified preventive regimens *(7)*.

Paediatric TB research priorities

Advancing a research agenda explicitly focused on the needs of children affected by TB will be critical to honoring the commitments made by Heads of State during the United Nations High-Level Meeting on TB.

Preventing needless suffering and deaths among children – who are among the most vulnerable to TB – is possible. Investments in key R&D areas to improve prevention, diagnosis and management of children and adolescents affected by TB are presented below.

Epidemiology

- Describe and monitor the burden of TB infection and disease (including drug-resistant TB), treatment issues and outcomes, and the socio-economic impact of TB among children and adolescents (including those living with HIV) at the national level.
- Describe the occurrence of residual morbidity after cure or completion of TB treatment (including among children and adolescents living with HIV), including long-term adverse effects and socio-economic impacts of TB treatment.
- Evaluate completeness of routine recording and reporting of childhood TB along the care cascade, including how to strengthen and standardize reporting of child contact management and the provision of preventive therapy.

Basic science (fundamental research)

- Characterize the immune response to TB infection and disease among children, considering variability by age, nutritional status, co-infections, disease phenotype, as well as mycobacterial and host genotype.
- Through multi-centre longitudinal paediatric cohort studies, support the discovery, evaluation and validation of novel biomarkers (including those that can: accurately distinguish children with TB disease from those presenting with similar symptoms; distinguish between infection and disease; predict risk of disease progression among children with TB infection; and be used to assess response to treatment and vaccination) among children with a broad spectrum of disease presentations.
- Other basic science priorities are included within the relevant sub-headings below.

Prevention

- Conduct pharmacokinetic and safety studies of new preventive drug regimens for children to inform optimal dosing, including for children living with HIV.
- Evaluate shorter and simplified drug treatment regimens for TB infection in children, including those that can be used to prevent TB among contacts of persons with drug-resistant TB.
- Develop a vaccine for neonates (with and without HIV-exposure), children or adolescents that improves on the safety and protective efficacy of BCG.

Diagnosis

- Identify, evaluate and validate host biomarkers derived from paediatric populations as potential novel tests for TB infection, disease, risk of disease progression and response to treatment among children.
- Identify novel assays that meet the criteria to be used as a highly sensitive "rule-out" screening test (requiring non-invasive samples and for use at the point of care).
- Identify, evaluate and validate novel host- and pathogen-associated biomarkers in paediatric populations as potential novel diagnostic tests for active TB (such as DNA, mRNA expression profiles, micro-RNA, next-generation lipoarabinomannan (LAM)-based assays).
- Optimize the current microbiological reference standard by: improving and harmonizing specimen collection; supporting laboratory research to improve specimen processing to optimize diagnostic yield using current assays; and improving phenotypic and genotypic drug-susceptibility testing on paediatric clinical specimens.
- Harmonize collection, processing and storage of well-characterized bio-repository specimens; support their maintenance; and improve collaborative efforts to allow testing of novel assays on larger, harmonized specimen banks.

Treatment

- Conduct timely pharmacokinetic and safety studies of new TB medications in children to inform optimal dosing, including for children living with HIV.
- Ensure adolescent inclusion in late-stage clinical trials of new TB drugs, regimens and treatment strategies.
- Evaluate treatment shortening and simplification strategies, including those that reduce treatment-related toxicities among children with TB, including drug-resistant TB.
- Evaluate regimens to improve treatment outcomes, including residual morbidities caused by TB and certain TB treatments, and reduce treatment duration among children with the most severe forms of TB, including TB meningitis.

Operational Research

- Determine the most appropriate and cost effective service delivery models for children of all ages (0–19 years) among the maternal and child health continuum of care.
- Evaluate programme integration strategies for paediatric TB, including with HIV, maternal, neonatal and child health, adolescent health, nutrition and other relevant programmes.
- Assess health system needs, including human resources and cost, for scaling up evidence-based interventions and programme integration for TB prevention and treatment at the national level.
- Identify pragmatic and scalable decentralized community-based strategies (such as family-centred models of care) for TB screening and provision of preventive therapy, and TB treatment to enhance early entry and retention in the cascade of care.
- Conduct qualitative research to better understand the pathways through which children and adolescents affected by TB access care, and facilitators of and barriers to provision of preventive therapy, diagnostic access, treatment adherence and effective management for families affected by TB.
- Conduct social research to better understand the impacts of stigma due to TB on education of school-aged children and adolescents.
- Determine efficient and reliable systems for specimen collection, transport and laboratory evaluation, especially important for following up children with smear-negative, paucibacillary specimens.

Conclusion

The commitments made by Heads of State during the United Nations High-Level Meeting on TB present an opportunity for mobilizing the resources and political will necessary to advance the research agenda for children with TB.

Children represent 10% of the global burden of TB, yet funding for paediatric TB research represented only 3% of total TB research funding available in 2016 *(8)*. An investment of US$ 1.8 billion per year is required to implement the TB research agenda described in the Global Plan to End TB *(9)*. Commensurate with the global burden of TB among children, 10% of the US$ 1.8 billion annual TB research-funding target (i.e. US$ 180 million per year) could serve as an appropriate benchmark against which to measure progress towards increasing investments in paediatric TB research initiatives. One suggestion for meeting the annual US$ 1.8 billion funding target for TB R&D is for each country to dedicate to TB at least 0.1% of what it already spends on all forms of R&D (referred to as a country's gross domestic expenditure on research and development (GERD)). To ensure that paediatric-specific research objectives are met, countries could commit to dedicating 10% (0.01% of their overall spending on R&D) to paediatric TB.

Ensuring that research collaborations and funding commitments resulting from the United Nations High-Level Meeting on TB include paediatric-specific components will be critical to reaching this funding target and to advancing research to develop: a vaccine with better and lasting protective efficacy; less invasive and more sensitive diagnostic tests designed for children; and shorter, safer and more child-friendly regimens for TB prevention and treatment

Concerted efforts to take down barriers to paediatric research and obstacles that delay the benefits of scientific progress from reaching children will also be necessary. There is an urgent need to: ensure the earlier inclusion of children in research; harmonize regulatory requirements; build up clinical trial site capacity for paediatric studies; expedite the translation of research findings into policy; and rapidly close policy–practice gaps.

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References

1 Dodd PJ et al. The global burden of tuberculosis morality in children: a mathematical modelling study. Lancet Glob Health Dodd PJ, Yuen CM, Sismanidis C, Seddon JA, Jenkins HE. The global burden of tuberculosis morality in children: a mathematical modelling study. Lancet Glob Health 2017;5:e898-e906.

2 Global tuberculosis report 2017. Geneva: World Health Organization; 2017.

3 Yuen DM, Jenkins HE, Chang R, Mpunga J, Becerra MC. Two methods for setting child-focused tuberculosis care targets. Public Health Action 2016; 6(2):83–96.

4 McKenna L. The tuberculosis diagnosis pipeline for children. Pipeline report [website]. Treatment Action Group; 2018 (http://www.pipelinereport.org/2018/tb-peds-diagnosis-pipeline, accessed 29 August 2018).

5 McKenna L. The tuberculosis treatment pipeline for children. Pipeline report [website]. Treatment Action Group; 2018 (http://www.pipelinereport.org/2018/tb-peds-treatment-pipeline, accessed 29 August 2018).

6 Frick M. TB prevention pipeline report 2018. New York: Treatment Action Group; 2018 (http://pipelinereport.org/sites/default/files/pipeline_2018_tb_prevent_mf_web2.pdf, accessed 29 August 2018).

7 McKenna L. The tuberculosis prevention pipeline for children. Pipeline report [website]. Treatment Action Group; 2018 (http://www.pipelinereport.org/2018/tb-peds-prevention-pipeline, accessed 29 August 2018).

8 Frick M. The ascent begins: tuberculosis research funding trends, 2005–2016. New York: Treatment Action Group; 2017 (http://www.treatmentactiongroup.org/sites/default/files/TB_FUNDING_2017_final.pdf, accessed 29 August 2018).

9 Global plan to end TB: the paradigm shift 2016–2020. Geneva: Stop TB Partnership; 2015 (http://www.stoptb.org/assets/documents/global/plan/GlobalPlanToEndTB_TheParadigmShift_2016-2020_StopTBPartnership.pdf, accessed 29 August 2018).