Childhood Tuberculosis Update World TB Day 2015

Dear Colleagues,

World TB Day 2015 brought many exciting updates for childhood TB – our joint advocacy efforts, as well as all of your contributions, are beginning to bear fruit.

The Union and WHO launched an e-learning course for childhood TB in order to support country-level implementation of childhood TB activities and improve diagnostic capacity so children can benefit from the much anticipated new fixed dose formulations once they become available. This course is already being used by researchers at the Desmond Tutu TB Centre in South Africa to train about 400 healthcare workers in the Eastern Cape. We also would like to give you an update on research into improved regimens for TB and MDR TB in children and attempts to streamline biomarker discovery. At the same time, TAG shows us how much our continued advocacy remains crucial to further improve development of child-friendly tools for TB.

Enjoy reading!
With the best wishes,

Steve Graham, Chair, Stop TB Partnership Childhood TB subgroup
Malgosia Grzemska, WHO, Secretariat Stop TB Partnership Childhood TB subgroup
Annemieke Brands, WHO, Secretariat Stop TB Partnership Childhood TB subgroup
Anne Detjen, Chair, Union Childhood TB working group
James Seddon, Co-Chair, Union Childhood TB working group

1. **The Union launches the Childhood TB Learning Portal and The Union/WHO Childhood TB for healthcare workers online course.** (The Union)
   The Union, in collaboration with World Health Organization, has launched an interactive online course, *Childhood TB for Healthcare Workers*. The six-module curriculum covers how to diagnose, treat and prevent childhood TB. The modules are interactive and ask participants to make decisions about patient care in various settings through case examples.

   The self-paced course, which takes six to eight hours to complete, is designed for healthcare workers at the secondary and primary level of the healthcare system. The content is based on WHO's 2014 *Guidance for national tuberculosis programmes on the management of tuberculosis in children*, as well as The Union's *Desk guide for diagnosis and management of TB in children*, and focuses on the clinical management of childhood TB. One full module is dedicated to TB prevention, focusing on household contact screening and provision of preventive therapy.

   Childhood TB for Healthcare Workers is the first major offering of The Union's new Childhood TB Learning Portal. The Learning Portal will offer a variety of resources aimed to support countries' efforts to address the 10-step plan outlined in *The Roadmap for Childhood TB*, published in 2013. The Roadmap stresses the urgent need for training and reference materials on childhood TB for health workers.

   The Global Health Bureau, Office of Health, Infectious Disease and Nutrition (HIDN), US Agency for International Development financially supported the development of the Childhood TB Learning Portal and the course through TB CARE I under the terms of Agreement No. AID-OAA-A-10-00020.

   Childhood TB for Healthcare Workers is offered at no charge, and learners receive a certificate of completion. Since its launch on March 24 over 300 people from over 65 countries registered for the course!
   To learn more or to register, please click here. For additional questions contact childhoodtb@theunion.org

2. **TB Alliance announces partnership with U.S. Fund for UNICEF to increase access to impending new child-friendly TB treatments** (TB Alliance)
   TB Alliance has announced a new partnership with the U.S. Fund for UNICEF that will dramatically increase the scope and impact of child and maternal health programs around the world to include the diagnosis and treatment of pediatric tuberculosis (TB), a significant cause of child mortality.

"Pediatric TB has stayed in the shadows for far too long," said Caryl Stern, President and CEO of the U.S. Fund for UNICEF. "We are thrilled to be working with TB Alliance to deliver new treatments that children around the world so desperately need and that will help us improve child survival."

The collaboration will help elevate childhood TB as a priority issue to improve child survival and integrate TB within UNICEF's child health services around the world. It will also facilitate the uptake of the first appropriate, child-friendly TB treatments that TB Alliance and its partners are developing, as part of a broader partnership with the World Health Organization (WHO), and which correspond to WHO's recommended treatment guidelines.

UNICEF, TB Alliance, and WHO will now work together to facilitate uptake of the new child-friendly TB treatments, which are expected to reach the market in 2016. The new treatments are expected to be included in the UNICEF supply chain, one of the world's largest purchaser and supplier of medicines and vaccines for children. The partnership will also connect the health providers in UNICEF's global network with better educational tools and information on pediatric TB with the goal of integrating TB into existing initiatives that address maternal and child health and pediatric HIV/AIDS.

In 2013, with support from UNITAID and USAID, TB Alliance and WHO launched an initiative to improve pediatric TB treatment and reduce child mortality. The initiative aims to deliver new, correctly formulated, child-friendly TB treatments, while enhancing the market understanding needed to accelerate the time in which new and better treatments will reach children in need. This new initiative with UNICEF allows the expansion of this work by leveraging UNICEF's global reach and presence in countries with high TB burdens.

3. **Progress on Research in Pediatric TB Diagnostic Biomarkers (**Mark Nicol, University of Cape Town, South Africa and Devasena Gnanashanmugam, NIH)
A child-friendly diagnostic test to distinguish TB disease from latent TB and other respiratory childhood illnesses, particularly in high TB endemic areas, is urgently needed. Important steps to achieving this goal are to better understand host and pathogen biomarkers that will facilitate TB diagnosis in children and to coordinate the efforts of researchers involved in biomarker discovery and validation. To this end, the NIH convened a workshop, "Pediatric Tuberculosis: Addressing Research Gaps in the Diagnostic TB Biomarkers" in May 2014, to prioritize research gaps in this field and map a path to address these gaps. At the workshop consensus recommendations were developed around priority needs for biomarker research, key study design issues, harmonization of clinical and laboratory standards and bio-repository requirements. Attendees from the workshop are currently working to implement these recommendations. A coordinating committee is actively working to identify critical specimens needed for innovative TB diagnostic biomarker discovery and evaluation, and collaborating with other repository experts, and will be compiling international standards for specimen collection, storage, and evaluation to enable harmonization across repositories and clinical studies. The goal of this "Pediatric TB Biomarker Working Group" is to have one specimen collection standard that is acceptable to nearly all pediatric TB researchers. Similarly, work will also begin on unifying clinical data collection and standards accompanying specimen collection to further strengthen collaboration among researchers. A key message from the workshop was that input from all stakeholders is critical to these efforts and that it is only with cooperation and coordination that the goal of an easy to use point of care diagnostic tool for pediatric TB can be reached.

A publication "A Blueprint to Address Research Gaps in the Development of Biomarkers for Pediatric TB" has been drafted with Mark Nicol as first author and has been submitted for peer review. At the same time, the NIH consensus panel standardized "Diagnostic definitions for intrathoracic tuberculosis in children" suggested for research reporting that was published in a supplement of J Infect Dis 2012 by Graham et al, has been updated following feedback and field experience since initial publication, and was submitted this month for peer review.

4. **Pediatric TB treatment studies** (Anneke Hesseling, Desmond Tutu TB Centre)
New drugs and treatments for TB in children are on the horizon! We are very excited to be able to share an overview of nine planned and ongoing research studies addressing preventive therapy and the treatment of both drug-sensitive and drug-resistant TB in children.

The Union International Union Against Tuberculosis and Lung Disease
Health solutions for the poor

Stop TB Partnership

Summary of ongoing and planned clinical research on evaluation of novel tuberculosis drugs and regimens in children

Protocol name/number Trial registration	Phase	Design	Indication	Objective	Special populations, design features	Funder, sponsor	Network, countries	Status (as of Q1 2015)
"SHINE" (Shorter treatment for mINimal TB in childrEn)	III	Randomised, non-inferiority, open label efficacy trial	Treatment DS-TB	Evaluate the efficacy of 4 vs. 6 months treatment for non-severe TB in children with new WHO-recommended first-line TB doses	Children, adolescents, infants HIV+/HIV- Nested PK studies Drug-drug interactions	BMRC/DFID/ Wellcome Trust	MRC CTU India, Uganda, Zambia, South Africa	Opening 2015
Treat infant TB	I	Intensive PK sampling, first line TB drugs, single drug formulation	Treatment DS-TB	Evaluate the PK and safety of first line antituberculosis drugs using 2010 WHO dosing in infants < 12 months	Infants HIV+/- Long term safety	Unitaid	TB Alliance South Africa	Enrollment completed
IMPAACT P1106	I	PK characteristics of cART and TB therapy in premature and LBW infants	Treatment DS-TB DR-TB	Evaluate the PK of ARV and first and secondline TB drugs in low birth weight infants	Infants HIV+/- Low birth weight, premature	NIAID	IMPAACT	Enrolling
"TB-CHAMP" (TuBerculosis CHild and Adolescent Multidrug-resistant Preventive therapy trial)	III	Randomized double blind placebo-controlled, superiority multicenter trial	Prevention DR-TB	Evaluate the efficacy of levofloxacin vs. placebo for the prevention of MDR-TB in child household contacts	Children < 5 years, infants HIV+/HIV- Household randomization	BMRC/DFID/ Wellcome Trust	BMRC CTU South Africa	Opening 2015
V-QUIN	III	Randomized double blind placebo-controlled, superiority multicenter trial	Prevention DR-TB	Evaluate the efficacy of levofloxacin vs. placebo for the prevention of MDR-TB in child and adult household contacts	Children < 5 years, infants, adolescents, adults HIV+/HIV- Household randomization	Australia NHMRC	Viet Nam	Opening 2015

PHOENIX	III	Randomized open label, superiority multicenter trial	Prevention DR-TB	Evaluate the efficacy of levofloxacin and INH vs. INH for the prevention of MDR-TB in adult, child and adolescent household contacts	Children, adolescents, infants, adults HIV+/HIV- Household randomization	NIAID	ACTG/IMPAACT	Planned
TBTC Study 35	I/II	PK and safety of RFPT/INH co-formulation in children for prevention of TB	Prevention DS-TB	Determine the optimal dose and assess PK and safety of rifapentine, given in combination with INH, in children with LTBI	Children, infants HIV- Age de-escalation Pop PK modeling	TBTC, in collaboration with Sanofi	TBTC South Africa, USA, Kenya	Planned
Rifabutin trial	IV	PK and safety of rifabutin in adults and children	Treatment DS-TB	PK and safety of rifabutin in adults and children	Adults Children HIV-	ICMR, NACO	India	Planned
TBM-KIDS: Innovative PK/PD approaches to optimize TB meningitis treatment in children	II	Intensive PK, pop PK modeling	Treatment DS-TB	Evalute the efficacy and safety of levofloxacin and rifampicin for the treatment of TB meningitis in children	Children, infants HIV+/-	R01	N/A	Opening 2015

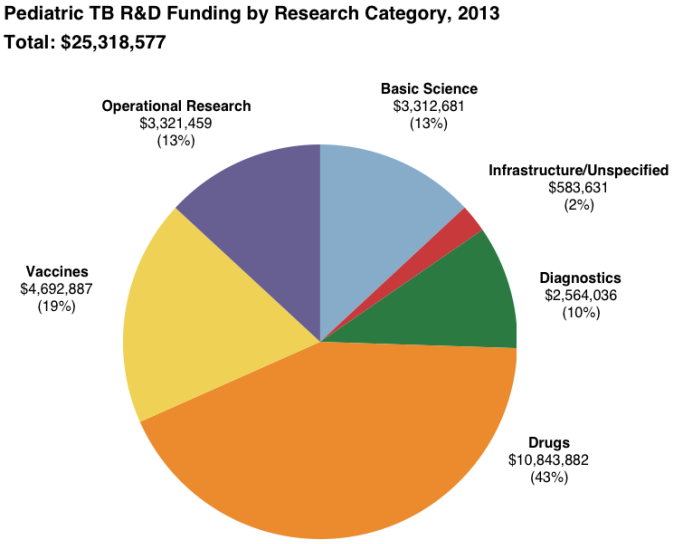
CIHR: Canadian Institutes of Health Research; DFID: Department for International Development (United Kingdom); FDC: fixed-dose combination; FLD: first-line drug; ICMR: Indian Council of Medical Research; IMPAACT: International Maternal, Pediatric, Adolescent AIDS Clinical Trials Group, U.S. National Institutes of Health; LTBI: latent tuberculosis infection; NACO: National AIDS Control Organization (India); NIAID: U.S. National Institute of Allergy and Infectious Diseases
NICHD: National Institute of Child Health and Human Development, U.S. National Institutes of Health; Australia NHMRC: National Health and Medical Research Council
NRF: National Research Foundation (South Africa)
OBR: optimized background regimen PI: protease inhibitor
PK: pharmacokinetics SLD: second-line drug
TB: tuberculosis TBTC: Tuberculosis Trials Consortium, U.S. Centers for Disease Control and Prevention
WHO: World Health Organization

5. Funding shortfalls for pediatric TB research (Lindsay McKenna, Treatment Action Group)

The World Health Organization's *Roadmap for Childhood Tuberculosis* estimated that between 2011 and 2015 US$200 million was needed for research necessary to provide new tools to better prevent, diagnose, and treat TB in children. In 2013, research by Treatment Action Group (TAG) uncovered just US$25.3 million spent on pediatric TB R&D from 19 donors worldwide. This is more than double the US$10.3 million reported in 2012 from 14 donors, but not enough to reverse the significant shortfall in pediatric TB R&D funding. At the midpoint of the 2011–2015 period, the donors worldwide had spent just one-fourth of the targeted US$200 million. These findings mirror the larger trend of inadequate TB R&D funding described in TAG's *2014 Report on Tuberculosis Research Funding Trends, 2005–2013*.

In 2013, the Eunice Kennedy Shriver National Institute of Child Health and Development (NICHD) was the largest funder of pediatric TB R&D, spending US$4.7 million, or one-fifth of the total US$25.3 million reported. The NICHD is supporting pharmacokinetic research of optimal dosing of first- and second-line TB drugs in children with HIV and in pregnant women. UNITAID, which ranked third in pediatric TB R&D spending in 2013 with US$3.4 million, is supporting the TB Alliance to develop appropriately dosed, fixed-dose combinations of pediatric formulations of first-line drugs.

In order to achieve zero child TB deaths, new infections, stigma, and suffering, we urgently need increased investment in pediatric TB R&D to develop a vaccine that has lasting efficacy, a non-sputum-based point-of-care diagnostic test that is better able to detect TB in children, child-friendly formulations of second-line TB drugs, and research to better inform the treatment of children with new and existing TB drugs.



Monitoring investments in TB R&D is one approach to measure and evaluate the world's response to the global TB epidemic. Widely agreed-upon R&D funding targets are necessary to measure progress, hold funders accountable, and conduct advocacy to close existing adult-pediatric research gaps. As the *Global Plan to Stop TB, 2016–2020* takes shape, we encourage you to write to the Global Plan Development Task Force to reinforce the request to include pediatric-specific R&D funding targets to help end the neglect of children in TB research.

6. New and noteworthy publications

- A prospective evaluation of the symptom-based screening approach to the management of children who are contacts of tuberculosis cases. Triasih R. et al. Clin Infect Dis 2015;60:12-8
- Tuberculosis as a cause or comorbidity of childhood pneumonia in tuberculosis-endemic areas: a systematic review. Oliwa J et al. Lancet Respir Med
- Xpert for the diagnosis of pulmonary TB in children: a systematic review and meta-analysis. Detjen A et al. Lancet Respir Med plus an accompanying comment by Grant Theron.
- Regional initiatives to address the challenges of tuberculosis in children: perspectives from the Asia-Pacific region. Graham S et al. Int J Infect Dis 2015 166-169.
- The TB Alliance launched a video that details stories of children battling tuberculosis around the world – watch share widely! https://www.youtube.com/watch?v=uV_erwe29xc&feature=youtu.be

7. On the horizon

- 28 September – 2 October 2015: IXth International Childhood TB training course by Desmond Tutu TB Centre, Stellenbosch University. For registration and more information: Gwynneth Hendricks: gwynneth@sun.ac.za . Registration closes 31 July 2015
- 2-6 December in Cape Town: 46th Union World Conference on Lung Health. **The deadline for abstract submission is on 24 April 2015.** For more information: http://capetown.worldlunghealth.org/
- 3 December 2015, Cape Town: Annual meeting of the childhood TB subgroup in Cape Town.
- The next newsletter will be published prior to The Union conference and include an update on child health related events during the conference.

8. Feedback and suggestions

Was this information helpful to you? Would you like to suggest topics for the next newsletter? Please contact us with any feedback or suggestions on how to make this newsletter a useful resource for you!

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