Child
& Adolescent
TB Working Group

Annual meeting of the Child and Adolescent TB working group
Wednesday 30 October 2019

Hitex Exhibition Centre, Hyderabad, India

Objectives and expected outcomes of the meeting - Secretariat of the Child and Adolescent TB Working Group

In October 2003, the DOTS Expansion Working Group agreed to create a Childhood TB subgroup.
We have had annual meetings from October 2004 onwards:
As subgroup: 2004 Paris; 2005 Paris; 2006 Paris; 2007 Cape Town; 2008 Paris; 2009 Cancun; 2010 Berlin; 2011 Lille; 2012 Kuala Lumpur; 2013 Paris; 2014 Barcelona; 2015 Cape Town; 2016 Liverpool & from January 2017 as Working group also including a focus on adolescents: 2017 Kigali; 2018 The Hague; 2019 Hyderabad.
Membership has grown from: 23 members in 2004 to 59 in 2007 to 380 members (not including WHO staff) at present. The main purpose of the annual meetings is to provide a forum for exchange of global developments and country experiences.

Morning programme (8:45- 12:45):
Introduction: Report from the Chair & Update on the new Global Fund cycle and opportunities for childhood TB by Anna Scardigli, the Global Fund.
Session 1: Screening, contact investigation and prevention – Chaired by Connie Erkens (KNCV Tuberculosis Foundation) with presentations on: Improving childhood TB detection through facility-based integrated approaches in Kinshasa, DRC by Aime Loando (EGPAF); Paediatric TB transmission outside the household by Leo Martinez (Stanford University) with Ben Marais as discussant; TB screening in migrant children by Nicole Ritz (University of Basel); Maternal TB and implications for neonates by Jyoti Mathad (Weill Cornell) as well as a panel discussion with representatives from countries, the private sector and communities on contact investigation and prevention.
Afternoon programme (14:00- 17:00):
Session 2: Developments in diagnosis of TB in children and adolescents – Steve Graham (University of Melbourne & The Union) will facilitate a panel discussion on the use of new diagnostic tools (Ultra, Fuji LAM, digital CXR), alternative specimens (NPA and stool), and improving TB diagnosis in children with HIV, pneumonia and malnutrition followed by Q&A
Session 3: Developments in treatment of DS and DR-TB in children and adolescents – chaired by Tony Garcia Prats (DTTC). This session starts with a call for data for the new Unitaid granted BENEFIT Kids project followed by presentations on the SHINE trial by Di Gibb and Vidya Mave; the Use of new drugs for children with DR-TB by Alena Skrahina; and, experiences with the prevention of DR-TB including an update on the TB CHAMP trial by Simon Schaaf (DTTC).
Afternoon programme (14:00- 17:00):
Session 4: Peer-reviewed publications <u>not</u> to be missed – chaired by Ben Marais during which James Seddon will present summaries of selected peer-reviewed articles

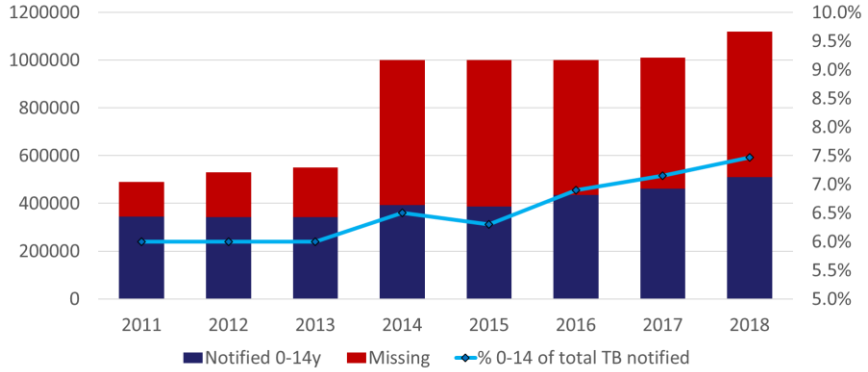
Report from the Chair of the Child and Adolescent TB working group - Ben Marais, Vice Chair, Child and Adolescent TB Working Group

Epidemiology update:

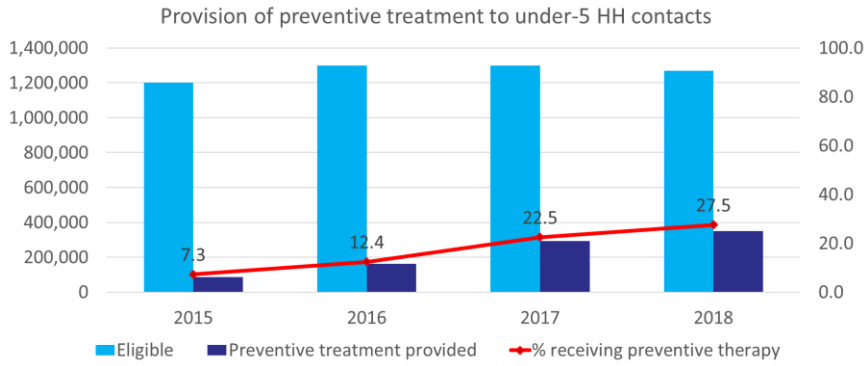
- An estimated **1.12 million children (<15y)** became ill with TB in 2018, **~50% <5 years**
- Children represent ~10% of all TB cases; higher (~ 15%) in high burden countries
- An estimated **205,000** children died of TB, including **32,000** TB deaths (15.6%) among children living with HIV [1]

- Data on TB among adolescents (10-19y) cannot be easily analysed as countries report on age groups 0-4, 5-14 years (children) and 15-24 - reporting mechanisms need further refinement
- In addition, researchers estimate that **~70 million** children are infected with TB (have LTBI), while at least **25,000** develop multi-drug resistant TB every year[2]

Trends in childhood TB notifications, 2011-2018:



Progress in provision of TB preventive treatment to eligible under 5 household contacts:



The case detection gap for all children under the age of 15 stands at 54% based on the estimates and notifications for 2018. The gap is largest for young children under the age of 5 years: it is 63% for that age group. This gap has decreased a little from 69% in 2017, but a lot of young children with TB still need to be found and reported. For the age group between 5 and 14 years, the gap now stands at almost 46%, an increase from 40% in 2017. This can be due to a reduction in over-diagnosis of older children in some countries. The overall gap for children under 15 years is over 54%, compared to almost one third for all TB cases over 15 years of age.

The prevention gap remains huge, with almost 73% of eligible children under the age of 5 years, who are in close contact with a patient with infectious TB, not receiving TB preventive treatment and thus at risk of developing active TB in the near future. It is hoped that this gap will be reduced as countries scale up contact investigation activities and start implementing shorter and more child-friendly TB preventive treatment regimens such as 3 months of daily rifampicin and isoniazid (3RH).

Activities in 2018/2019:

Farhana Amanullah was elected to represent the Implementation Working Groups in the Stop TB Partnership Board (2019-21) and participated in the Strategic and Technical Advisory meeting on TB (STAG-TB) from 11-13 June 2019.

Core team members provided input to the revision/updating of the Global Fund Modular Tool, which now includes children as a vulnerable population for TB. Several partners (USAID, EGPAF, UNICEF, CDC, TAG, STP and WHO) set up the "Paediatric Operational and Sustainable Expertise Exchange (POSEE)" group to support countries with NSP development and GF applications. The group is preparing costing tools to assist countries in applying for child and adolescent TB funding.

Progress since UNGA HLM on TB:
Roadmap translations: French – completed in May 2019 (available at: https://www.who.int/tb/publications/2018/tb-childhoodroadmap); Russian and Spanish in progress
WG members provided input into "Management of MDR-TB in children, a Field Guide" – published by the Sentinel Project in February 2019 (Jen Furin, Simon Schaaf, James Seddon, Mercy Becerra and others). WHO conducted regional meetings (AFR March 2019; WPR April 2019; SEAR May 2019) to consider ways to reach the UNGA HLM targets for LTBI and DR-TB management. These meetings included sessions on children and adolescents.
National TB Programme reviews with paediatric TB experts: Mozambique, Nov 2018; Pakistan, February 2019; Papua New Guinea, May 2019; Nepal and Cambodia, June 2019; Liberia, July 2019; Myanmar, Aug 2019; Bangladesh and Cameroun, Sept 2019; Timor Leste (MTR), Sept 2019; eSwatini, Oct 2019. A comprehensive tool for assessing child and adolescent TB programmes was developed.
Alena Skrahina presented in The Union Asia-Pacific conference and provided a briefing to the NTP Philippines and WHO country office on the implementation new drugs and injectable free regimens in April 2019. Lisa Obimbo provided an update on childhood TB and launched a call for action to end Child and Adolescent TB during the Kenya Paediatric Association Conference in April 2019 and during the Kenya Lung Conference in June 2019. GF/TDR/WHO WCA TB organized a workshop to take forward best practices and lessons learned in TB case finding and treatment, with a special focus on community approaches and childhood TB, 1-3 July 2019. Shakil Ahmed and Rina Triasih participated in the PPM working group meeting and a youth advocacy event in Jakarta 15-18 July 2019.

Meetings and coordination:
- Annual meeting of the CATWG – The Hague, 24 October 2018
- Core team meeting – The Hague, 25 October 2018; Core team calls April and September 2019
- First Paediatric Anti-TB Drug Optimization meeting (PADO-TB1) meeting, 14-15 February 2019: Consensus on priorities for single drug development for DS-TB, DR-TB and LTBI. The priorities were presented by WHO during the GAPf webinar on 27 February 2019.

Planned activities for next year:
- Planned regional meetings (focus on implementation of key actions from the Roadmap): 26-28 November, Hanoi, Vietnam: inter-regional consultation for EMR/SEAR/WPR
- Q3/4, 2020: Consultation on scalability of Unitaid paediatric TB projects, possibly as part of the AFR End TB summit (tbc)
- Development of a Child and Adolescent TB Handbook
- Update to the 2018 LTBI guidelines
- Updating of the 2014 Childhood TB guidelines
- Programme reviews (joint monitoring missions) with paediatric experts: India, SA, Indonesia

- Continuing to highlight challenges and opportunities in all relevant fora; Promoting research and development; Continuing to organize annual meetings of the Child and Adolescent TB working group with regional engagement of all relevant stakeholders; Assisting countries to move from single projects to programmatic approaches.

The new Global Fund cycle and opportunities for childhood TB - Anna Scardigli, the Global Fund

Impact and results of Global Fund investments for 2018 included (in countries where GF invests): 5.3 million people with TB treated; 114,000 people with DR-TB on treatment; 332,000 HIV-positive patients on ART during TB treatment; 142,740 children in contact with TB patients received preventive therapy and 6,771 people with XDR-TB treated.

In the 2017-2019 funding cycle, the allocation for TB was 1.85bn out of a total of US$ 12bn. Additional investments include TB catalytic investments (US$ 190 million), post program split (≈ US$ 50 million), TB portfolio optimization (≈ US$ 151 m) and increased domestic financing leveraged for TB in this funding cycle. The catalytic fund for TB (2017-2019) to find missing people with TB targets 13 countries that account for 75% of missing people with TB and 55% DR-TB globally. The expected outcome is to find 1.5 million additional people with TB by the end of 2019 (including children). WHO and Stop TB Partnership implement the strategic initiative (US $ 10 million) to support the 13 countries in catalyzing their efforts to find missing people with TB, TB/HIV and DR-TB, including through PPM. The rise in TB case notification globally over the last 10 years (2008 – 2017) has been very slow with only about 700,000 additional cases notified at the end of that period: i.e. 70,000 additional cases yearly compared to an increase of about 600,000 between 2017 and 2018 (WHO Global TB Report 2019). The 1.5 million additional TB cases target between 2015 – 2019 agreed upon in the 13 TB SI countries is definitely ambitious and reflects the drive by Global Fund, WHO, Stop TB and other partners to identify more people with TB who are missed by the systems in these countries and put them on treatment. Almost 1.2 million additional TB cases are projected to be notified by the end of 2019 (80% of target). An additional $151 million is awarded through TB portfolio optimization (PO) to countries since July 2018. This includes $ 40 m loan buy-down in India and $ 45 million for transition to the newer MDR-TB treatment regimens. Through PO, GF was able to exhibit its flexibility and responsiveness in adapting to changes in global guidelines. Prioritized areas for TB portfolio optimization include MDR/RR-TB treatment regimens transition; TB case finding and treatment (including key populations, community, PPM etc.) and; TB prevention (including uptake of new WHO guidelines/regimens). Other initiatives include the West and Central Africa TB regional support 2018. Provision of support to 19 countries in the West and Central Africa region through a collaborative initiative (with several partners) aimed at identifying barriers to TB case finding and good treatment outcomes, sharing of lessons learned and best practices within the region and providing possible solutions to challenges identified. A major outcome of the workshop was the resolution made by participating countries called the Cotonou TB declaration. In strong collaboration with partners, the 15 WCA countries are supported to explore challenges and share tools and opportunities to improve TB response in children and adolescents, including at community level; discuss how to foster better collaboration between traditional and non-traditional actors, addressing also the need for community, rights and gender approach in the planning and implementation of TB programs and; plan the implementation of best practices and innovative approaches related to community engagement and responses and to childhood and adolescents TB prevention and care.

Investments in innovation scale up in TB include:

- The science of scale-up: Strategic initiative to find missing people with TB – including children; Scale up of evidence-based approaches – e.g. PPM; Support data & evidence generation by countries - TB prevalence surveys, DRS, OR and other surveys; Scale up Community-based TB interventions; Technical support for PMDT through the rGLC
- Diagnostics: Scale-up of GeneXpert and other molecular tests (e.g. LPA); Capacity building on DST; Sputum transportation – different approaches; Scale up of connectivity etc.; Digital X-rays; Supranational laboratory networks
- Drugs/treatment: Support the adoption of new and repurposed drugs; Support the adoption of paediatric formulations; Switching from Longer to Shorter MDR-TB regimens; Support transitioning to the new regimens for DR-TB (including OR) – preparatory work in several countries; Promote patient-centred approaches; Promote the use of preventive therapy – including 3HP and 3HR

Upcoming opportunities through the new funding cycle: The sixth Replenishment Conference pledged US$14.02 billion for the next three years. This is the largest amount ever raised for a multilateral health organization, and the largest amount by the Global Fund. The funds will help save 16 million lives and end the epidemics of AIDS, tuberculosis and malaria by 2030. The TB Strategic Initiative for 2020-2022 will continue with the 13 current and 7 additional countries - these 20 countries account for 82% of the missing people with TB globally (US $ 150 million: Matching Fund for 20 countries to find missing people with all forms TB and US $ 14 million for the Strategic Initiative).

Packaging of TB services:

- Case finding: Active and Intensified Case Finding, innovative private-provider and community engagement; New screening and diagnostic tools and Artificial Intelligence (x-ray readings), connectivity solutions.
- Treatment: Patient-centered, decentralized, patient support; All-oral regimen for DR-TB
- Prevention: Contact investigation shorter combination drugs for TPT, infection control

Elaborating the strategic focus within the package: PPM, community, programme quality improvement and efficiency and service integration.

Global Fund mechanisms & opportunities for financing TPT scale-up: GF Funding Requests based on grant allocations – TB and HIV technical partners should support countries to include TPT scale-up plans in their FRs; Joint Strategic Initiative on TB Preventive Therapy – proposed for the next funding cycle (TB & HIV) and inclusion of TPT in the next TB Strategic Initiative on finding missing people with TB; Financing of Technical Assistance to support countries in the planning and implementation of interventions aligned with the current WHO LTBI guidelines including operational research; Additional resources through TB portfolio optimization and in-country optimization – e.g. US$ 1.55 million approved as ‘Award Now’ for Vietnam and Cambodia in the last 7 months. Additional US$ 3 million as ‘award later’; Increased role in the market-shaping and facilitation of affordable/sustainable pricing for new & repurposed drugs for TPT such as 3HP and 1HP; Increased advocacy (with TB and HIV stakeholders) for increased domestic and donor funding for TPT.

Application resources for the new funding cycle are available on the GF website, including Frequently Asked Questions for the 2020-2022 Funding Cycle; Modular Framework Handbook; The Applicant Handbook; Funding Cycle Brochure; Information Notes and Technical Briefs.

Update on the new TB modular framework and the key elements related to pediatric TB in the Modular Framework Handbook: The Modular framework handbook includes the modular frameworks for the 3 diseases & RSSH, developed to manage programmatic and financial data across the grants. It comprises of a list of standard modules, interventions and indicators. The Modular framework is not a template to fill but serves as reference data for drop-down lists in Performance Frameworks, budgets and progress updates. Link: https://www.theglobalfund.org/en/monitoring-evaluation/framework/

Key changes to the Modular Framework: The purpose of the revision was to ensure that it was up to date and aligned with the latest technical guidance and partners recommendations. The focus is on cross-cutting systems approach including provision of integrated and people-centered services at community and PHC levels. A new module was added: "Removing human rights and gender related barriers to TB services". There are new Interventions under TB/HIV for Screening & Diagnosis, Treatment and Prevention as well as under the three core modules (TB Care and Prevention, TB/HIV, MDR-TB) for key populations – Children, Miners & mining communities and Mobile populations (refugees, migrants and internally displaced people). Indicators related to TB preventive therapy were revised and new indicators were included for human rights and gender related barriers to TB services, aligned with latest technical guidance. An additional indicator disaggregation was included (by age, gender and HIV status).

Childhood TB ("key populations - children") is a new intervention under TB care & prevention, TB/HIV and MDR-TB modules. This includes the three modules (TB; DR-TB case finding: diagnosis, treatment and prevention interventions specifically targeted at children and; TB/HIV collaborative activities: HIV testing, TB screening and case finding, treatment and prevention interventions specifically targeted at children with HIV). Examples were provided: Active case finding through collection and testing of pediatric specimens and use of chest radiography; Contact investigation among children for drug-susceptible TB including through community-based approach; Provision of treatment with child-friendly TB medication formulations; Provision of TB preventive therapy including the new combination drugs (3HP and 3RH) to eligible children in contact with TB patients and; Training and capacity building focused on response to childhood TB including mentorship and supportive supervision of child TB services including clinical diagnosis of childhood TB and specimen collection, contact tracing, prevention.

Conclusions:

- Finding missing people with TB - case finding for TB treatment and for TB prevention: an opportunity to increase TB detection among children and to offer TPT to children in need
- Coordination at country level is needed to enable integration and leveraging funding opportunities for childhood TB (discussions on national health sector plans and disease strategies, advocacy for the integration of maternal and child health and disease specific policies, Country Coordinating Mechanisms to participate in the country dialogue process and preparation of Global Fund requests etc.)
- Funding requests to include and prioritize evidence-based interventions for childhood TB, maternal and child health and services integration – RSSH Integrated approach to community

service delivery e.g. innovative & integrated approaches to TB screening with HIV, Nutritional services, immunization campaigns, SMC campaigns
- Global Fund is and will be working with countries and partners to support rapid adoption of new guidelines- e.g. MDR-TB and LTBI.
- Opportunities exist within the grants and beyond grant allocations (SI, PO and other initiatives)

Discussion:
Allocation to TB for next funding cycle is not yet known. Tracking of paediatric TB expenditure: at this moment, this is difficult to track. POSEE group working on budgeting tools for various childhood TB activities. Countries are encouraged to make use of these tools once they are available.

Session 1: Screening, contact investigation and prevention

Improving childhood Tuberculosis detection through facility-based integrated approaches in Kinshasa, DRC - Aimé Loando, EGPAF DRC

CaP-TB is a 4-year project (until September 2021) in ten countries (West, Eastern and Southern Africa, India) with the goal to contribute to reduction in morbidity and mortality due to paediatric TB. The expected outcome is that critical access barriers will be removed to facilitate scale-up of paediatric TB. The project has a pilot phase (year 1 and 2) with a small number of sites and proof of concept. During the expanded implementation phase (year 3 and 4), implementation will expand to a larger number of sites with the aim to be catalytic for national uptake. Key collaborators include GDF, IRD, TAG, University of Sheffield and SAATHII.

DRC: Population: Approx. 90 million; TB incidence: 322 per 10,000 persons; Number of notified TB cases in 2018: 18,453; Percentage Paediatric TB: 11%; TB treatment coverage: 57%; Among the top 30 countries with the highest TB burden. Paediatric notifications are slowly increasing, but the proportion of childhood TB cases has remined at 11% of all TB cases.
Characteristics of CaP-TB in the DRC: Pilot phase: January 2018 – December 2019, 21 pilot sites in Kinshasa; Scale-up phase: January 2020 – September 2021, 50 sites in Kinshasa and Tshopo provinces; Hub and spokes model (hub activities: TB screening and investigation, Contact investigation, Collection procedures for respiratory e non respiratory samples, GeneXpert, CXR, Initiation and follow-up of latent TB infection treatment, Initiation and follow-up of active TB treatment, Hospitalization, One-site training; spoke activities: TB screening and investigation; Contact investigation; Sample collection and transportation to Xpert service; Initiation and follow-up of latent TB infection treatment; Initiation and follow-up of active TB treatment); Strong collaboration with NTP.

The CaP-TB baseline assessment showed the following barriers to child TB detection: TB services are not integrated with other entry points including maternal and child health (MCH) and nutrition settings; Health care workers are not trained in paediatric TB; Lack of materials for sample collection procedures , i.e. sputum induction, gastric aspiration (GA), nasopharyngeal aspiration (NPA), fine needle aspiration (FNA); Systematic contact tracing at community and facility level are not implemented; Lack of sample collection and transportation system; Xpert limited to presumptive DR-TB and coinfected TB-HIV patients; Limited access to CXR investigations for paediatric TB diagnosis.
Key activities at site level include: Integration of TB screening and identification of children with presumptive TB in all child health entry points: MCH, nutrition, out-patient department (OPD), in-patient

department (IPD), and HIV; Introduction of CaP-TB form to record presumptive TB case information and to allow prospective follow up till treatment initiation (clinical symptoms, diagnosis and treatment); Paediatric TB training provided to health care providers from all key entry points (TB screening with intensified case finding tool (ICF), clinical management of paediatric TB, sample collection procedures); Intense programme for on-site support and supervision (Week 0-2-4 –schedule, Check list); Training of Community Health care workers to support sample and patient referral; Provision of consumables and implementation of sample collection procedures (GA for the time being); Using Xpert as first TB test for paediatric presumptive TB patients.

Impact: increase in paediatric case detection from around 225 to 325 per quarter in 21 sites. Number Needed to Screen to identify one child with TB (NNS) very low in nutrition clinic and contact investigation (both household and facility). Good NNS also in OPD and IPD. NNS very high in MCH.

Lessons learned:

- Finding missing people with TB - case finding for TB treatment and for TB prevention: an opportunity to increase TB detection among children and to offer TPT to children in need
- Coordination at country level is needed to enable integration and leveraging funding opportunities for childhood TB (discussions on national health sector plans and disease strategies, advocacy for the integration of maternal and child health and disease specific policies, Country Coordinating Mechanisms to participate in the country dialogue process and preparation of Global Fund requests etc.)
- Funding requests to include and prioritize evidence-based interventions for childhood TB, maternal and child health and services integration – RSSH Integrated approach to community service delivery e.g. innovative & integrated approaches to TB screening with HIV, Nutritional services, immunization campaigns, SMC campaigns
- Global Fund is and will be working with countries and partners to support rapid adoption of new guidelines- e.g. MDR-TB and LTBI.
- Opportunities exist within the grants and beyond grant allocations (SI, PO and other initiatives)

Discussion:
Samples tested for Xpert: sputum (70%), gastric aspirate, NPA (30% other specimens).
Total number of cases recorded – breakdown by bacteriological confirmation and clinical diagnosis: around 70% clinical diagnosis
Contact investigation had a high yield. TPT was provided for contacts under 5, using 6H for now, but planning to use 3RH in the near future.

Paediatric tuberculosis transmission outside the household: challenging historical paradigms to inform future public health strategies - Leo Martinez, Stanford University School of Medicine; Ben Marais (vice-chair) as discussant

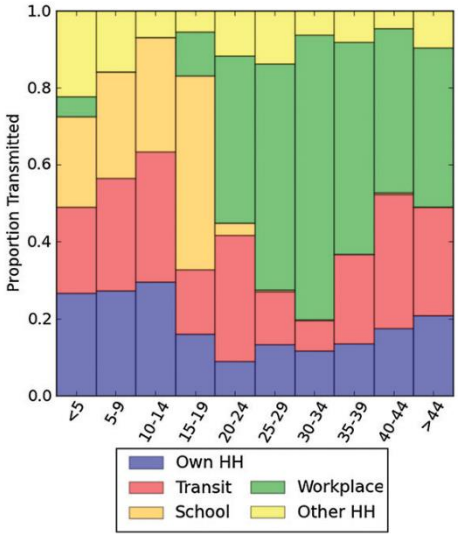
Recently there has been a lot of focus on paediatric TB, with attempts to estimates the true burden and mortality of TB in children. As a result, it is now recognized as a global problem. Because of gaps in understanding of paediatric tuberculosis, we are reliant on widely held beliefs with a weak evidence base. One of these beliefs is where transmission occurs. The prevailing belief in the field is that—on this topic—children are different than adults. Children spend most of their time in the home. Therefore, it

makes sense to assume that transmission to children occurs in the household setting. WHO guidelines concentrate on household contact tracing and don't really discuss community interventions. This is an unexplored area that has an important impact of how we target interventions to children with tuberculosis.

Therefore, we wanted to ask: “What Proportion of TB Transmission to Children is Attributable to Household TB Exposure?” Previously I conducted a systematic review of population-based tuberculin surveys and found that less than 20% of transmission to children occurred in households. To better evaluate the proportion of transmission that occurs inside and outside of households, we looked at the literature, to see if past studies could help us answer this question. Because assessing transmission links for tuberculosis is difficult, we looked at several study designs. First, we looked at tuberculin (TST) or Quantiferon (QFN) conversion studies and evaluated whether children who converted had household TB exposure. Among the three studies on this topic, the results were relatively consistent. They showed that 10-20% of children that converted their TST or QFN test occurred in households. Next, we looked at studies following a cohort of children for disease development. These studies are rare because you need a large population-based cohort of healthy children followed prospectively for a long period of time. Among two studies in South Africa most children that developed disease, again, did not have a household exposure at the time of developing TB or in the recent past. So, we found consistent results from these two cohort study designs which really surprised us and went against conventional thought. We wanted to further explore our findings and make sure they weren't limited to these study designs by looking at other ways of assessing transmission inside and outside households. We then looked at TB infection surveys. In these surveys, children are tested for TB infection at one point in time assuming infection has recently occurred considering their age. In these surveys, we assessed how many positive children had a household exposure either at the time of the survey or a history of household exposure. Several of these studies have been performed, many in the past five years. The results were, again, consistent – below 20% of infections in children occurred in households.

In adults, molecular epidemiological studies are used to answer the question about transmission location. However, in children, this design is difficult because most children are paucibacillary and not culture or smear positive. Therefore, when using this study design with children, your study population is restricted to only culture-positive children. Two studies have been performed, again showing a minority of culture-positive children with household links.

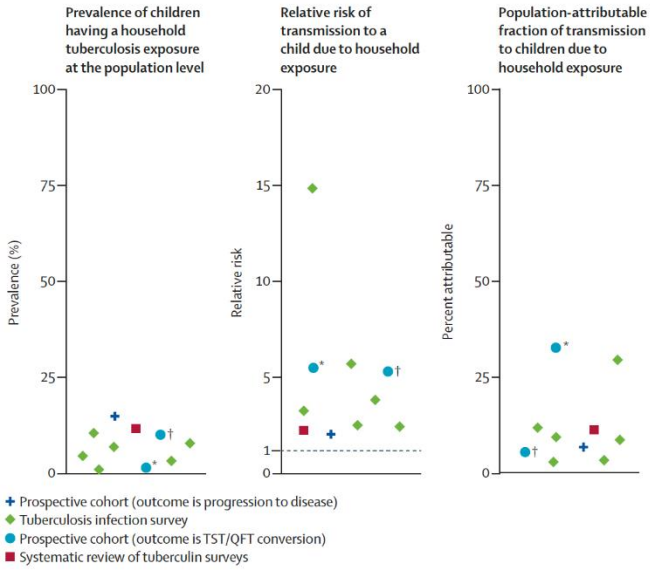
Lastly, there has been one mathematical modelling study which used social networking data and population-based tuberculin sensitivity data from South Africa to estimate where transmission occurs among all ages. The purple bar in this figure represents household transmission stratified by age groups. As you can see household transmission is relatively low among all age groups. Rates are slightly higher but relatively stable in children - between 20 and 25%.



Going back to our research question, we estimated next the population attributable fraction of TB transmission to children due to household exposure. In the formula (see below), the population attributable fraction uses both the prevalence of exposure in the general population and the relative risk of the factor at interest—which, in this case, is household TB exposure.

$$\text{Population-attributable fraction} = \frac{(\text{Prevalence of exposure} \times [\text{relative risk} - 1])}{(\text{Prevalence of exposure} \times [\text{relative risk} - 1]) + 1}$$

The prevalence of household exposure at the population level is very low – at times below 10%. This was true among all studies reviewed on this topic and all study designs. This may be surprising to many. The for this finding reason is “contact saturation”. In other words, children are repeatedly exposed to the same household members every day. However, they meet new people every day in the community and therefore—over time—are exposed to many more community members. The next component of the population attributable fraction is the relative risk. Being exposed in a household is an important individual risk factor for children. And children who are exposed are at increased risk. Then we put these two components together to calculate the population attributable fraction of TB transmission due to household exposure. Although exposure in the household is more intense and these children are at a higher individual risk, the number of exposures in the community drives the overall population attributable fraction.



It is not really known where in the community transmission occurs and in what proportion in certain locations. A before-and-after implementation study from Uganda evaluated the effect of strengthening diagnosis, treatment, and prevention of paediatric tuberculosis at peripheral health facilities (DETECT-TB). After implementation, a 140% increase in paediatric case notification was recorded, almost entirely driven by health-care facility interventions. This made us realize that the idea that most transmission to children occurs in the household is likely unsubstantiated. This suggests that household contact tracing 70% of cases will be missed when using this strategy. While we think this is a good individual level strategy and should be encouraged, it may not have the population level impact

that is needed. It needs to be complemented by large-scale community interventions, such as active case finding in high-risk, overpopulated areas.

Discussion by Ben Marais:
This study may be regarded as the elephant in the room. Transmission in community settings is difficult to quantify. Where do we need to focus our attention, where are the low hanging fruits? Older studies were based on industrialized settings, with a different epi environment. Current the global reality is different. If we want to move to TB elimination, we will need to do more. ACF will only find around 50% of cases, and further community-based strategies are needed. The household remains an important point of intervention: it is a clearly articulated risk group, with a high risk of progression, thus providing an opportunity to intervene. Maybe the impact may be low, but we have a moral obligation to care for these contacts: human rights versus public health. These interventions also have the lowest number needed to screen (NNS) to identify active cases. We need to constantly balance the realities and come up with creative, community-based strategies.

Response:
Contact investigation is highly effective, and we need to take advantage of this. But we also need to explore how to address transmission in the community, even though this poses a difficult setting.

TB screening in migrant children - Nicole Ritz, University of Basel

Data show that over 600 000 asylum seekers arrived in Europe in 2018. One third of these were under 18 years of age: over 191 000 children of which over 20 000 unaccompanied, mainly from Syria, Iraq, Afghanistan and Eritrea. 50% of refugee children spend over 6 months reaching Europe, with 21% reporting being held in locations against their will. Many report to have been forced to work and had lack of food.
Health status of migrants: the mortality ratio is highest due to infectious disease (TB, HIV)
Only a limited number of countries report on TB in migrants, with a large knowledge gap on TB in migrant children. TB has become a disease of foreign origin (especially in Western EU countries). Limited data are available, but recently a systematic review based on observational studies was conducted. This review showed a relatively low prevalence of active TB but a high prevalence of LTBI in refugee children globally, higher if from African countries compared to Middle East and Asia. There is also a high proportion of migrants among patients with MDR-TB (higher than all TB). MDR-TB is often acquired during the journey: especially in patients transiting through Libya.
There are different strategies for screening in different EU countries with confusing opinions in the literature. Challenges for screening include logistics, cost, follow-up and adherence.

It is very difficult to predict which way migration will go, e.g. depending on political decisions. What we can predict is that migration is here to stay with us.

Maternal TB and implications for neonates - Jyoti Mathad, Weill Cornell

A case study case study was presented, which highlighted delays in diagnosis of TB in neonates, related to the reluctance for invasive procedures, overlap of symptoms with neonatal sepsis. It also illustrated rapid progression of TB disease in neonates.

Diagnostic criteria for congenital TB: Proven TB lesions in the first week of life, OR Primary hepatic complex or caseating granulomas in the liver, OR TB infection in placenta or maternal genital tract, OR Contact investigation excludes postnatal transmission. 80% have abnormal chest imaging (50% miliary or nodular), AFB/culture/PCR has a 75% yield if from early morning gastric aspirate. Mortality remains high: 53% before 1994, 34% post 1994.
Neonates get TB from their moms who often do not know they have TB or may be asymptomatic - 75% of mothers who transmit TB to their babies are not aware of it. Mortality of infants born to mothers with TB was 2.2x higher if mothers were asymptomatic. Immune changes in pregnancy mask symptoms – decrease in CD4, CD8, B cells, natural killer cells and cytotoxicity occur in the third trimester.
Outcomes of both pregnancy and of infants born to a mother with active TB are generally poor: Pre-eclampsia & eclampsia (2-fold), vaginal bleeding (2-fold), hospitalization (12-fold), miscarriage (10-fold), maternal mortality (25-fold for HIV-uninfected and 37-fold for HIV-infected moms). For the infant: Low birth weight (2-fold), lower Apgar scores, prematurity (2-fold), small for gestational age (2-fold), infant HIV (2-fold), congenital TB (rare), infant mortality (3.4-fold).
The IMPAACT study P1078 on risk of IPT in pregnancy found higher rates of stillbirth or spontaneous abortion, low birth weight and preterm delivery in HIV-infected pregnant women who were randomized to receive immediate versus deferred (to 12 weeks post-partum) TPT with INH.
Other studies currently ongoing: P2001: 3HP in pregnant/post-partum women; P2025: 1HP versus 3HP in pregnant versus post-partum women.
Needs for both neonatal and maternal TB include: For neonatal TB: Better screening guidelines, diagnostics (POC) and evidence-based treatment guidelines (DS and DR-TB). For maternal TB: Better screening guidelines, diagnostics- POC and improved sensitivity, evidence-based treatment guidelines (DR-TB, PZA). For both: PK studies from breastmilk.

Discussion:
Study on congenital TB in EU: examples of infants up to 7 months who got TB from their moms. These who the possibility of being infected and progressing quickly to active TB. Different transmission pathways exist in infants, but it is difficult to know for sure.

Panel 1:
Discussion with representatives from countries, private sector and communities on contact investigation and prevention and ways to integrate these activities into MCH and general health services

Monica Dias (representing the PPM Working Group):
Children with TB who miss out on access to quality care (over half a million) often access care in the private or unengaged public sector – there are clear areas of overlap between childhood TB and PPM. The big seven countries with missing children are India, Indonesia, Myanmar, Nigeria, Pakistan, Philippines and Bangladesh (around 400 000 children who are missed).
PPM to reach the missing people (including children and adolescents) with TB: PPM is a key component of WHO's End TB Strategy. WHO policies and global and national TB strategies have long acknowledged the need to engage all care providers, through PPM approaches. PPM encompasses diverse collaborative strategies. Public–public mix refers to engagement by the NTP of public sector providers of TB care that are not under the direct purview of the NTP (e.g. public hospitals, public medical colleges,

prisons or detention centres, military facilities, railways and public health insurance organizations). Public-private mix refers to engagement by the NTP of private sector providers of TB care (e.g. private individual and institutional providers, the corporate or business sector, mission hospitals, non-governmental organizations and faith-based organizations).
There are new opportunities for action through renewed high-level attention towards closing the gaps in care, could facilitate a major increase in private provider engagement for TB in the coming years: UNHLM, Find.Treat.All & Strategic Initiatives; Positive and promising examples can set an example for other countries inspiring them to be more ambitious. E.g. India, India, Pakistan, Bangladesh, etc. with rising PPM notifications; New digital technologies facilitate the engagement of all providers by transitioning from paper-based data to digital, case-based registration systems; Access to new and improved diagnostic and treatment tools, such as digital chest x-ray, Xpert and shorter MDR-TB regimens, has increased the value of collaboration to independent providers and; Social health insurance schemes in some countries are approaching full population coverage and will provide an opportunity to drive access to quality TB care amongst all providers.
The key actions in the PPM Roadmap link with the key actions in the Child and Adolescent TB Roadmap. We should use both Roadmaps to drive action to end TB.

Nyan Win Phyo (WHO Civil Society Task Force member from Thailand)
Stigma: Perception that TB and HIV are linked, leading to delays in diagnosis. Children are dying of TB: over 200,000 are dying of TB every year, especially young children. Most of these children do not have access to treatment.
In migrant populations, migrant children are often not regarded as risk group. Political and policy commitment are needed, with investment in childhood and adolescent TB. Affordable and sensitive diagnostic tools are needed. Controversies among clinicians regarding provision of TB treatment to children, especially in tertiary hospitals, have a negative impact on quality care for children with TB. Community engagement needs to be expanded, as in many areas community members are not involved in childhood TB, prevention and screening in communities and schools. More financial support is needed for these activities. Children are our future, they are precious!

Moorine Sekadde (Uganda)
There is ample evidence to suggest that contact investigation (CI) can identify and diagnose TB within and beyond the household. The question is how this can be strengthened to help reach the UN HLM targets. Integration of childhood TB into other programmes: the scope is wide: training materials, policies, resources, supplies etc. The DETECT child TB project (decentralization and implementation of contact investigation with provision of TPT) resulted in a 4-fold increase in the number of children initiated on TPT. Challenges experienced included travel related cost, and motivation of caregivers to give preventive. An example of integration at community level is integrated community case management (iCCM) with integration of TB and HIV: community assessment for malnutrition, pneumonia. An additional question on current TB exposure was introduced, with 0.6% of children identified as at risk for TB in the first period. The main barrier experienced is stigma (which is higher for TB than for HIV). Stigma needs to be addressed in rolling out CI. Lessons have been learned on recording and reporting and M&E approaches. Electronic data capturing, and data transmission is being evaluated. A comprehensive approach is important. CI provides the opportunity to reach the UN HLM targets. Evidence on shorter regimens will facilitate provision of TPT.

Tilaye Gudina (Ethiopia)

In Ethiopia, childhood TB is one of the key strategic initiatives at the National TB Strategic Plan 2014-2020. An accelerated Childhood TB Roadmap plan was developed for 2015-2018. The goal is to maximize childhood TB case notification and improve access to comprehensive child hood TB service, through promotion of program collaboration, service integration and contact investigation (CI), to assist in TB case finding and scale up of TB preventive treatment (TPT).

Advanced integration between TB and RMNCH is implemented at all levels of the health system, with revised integrated registers, patient records and job aids. GeneXpert is used as primary diagnostic test for children. The child-friendly FDCs were introduced and used since 2017. The Ethiopian experience with the implementation of the childhood TB Roadmap was included as one of the best practices in the document on Best Practices in Child and Adolescent TB Care.

The Childhood TB national Roadmap was updated in 2019, based on the updated global Roadmap. Focus areas of the updated Roadmap include addressing the policy-practice gap: Child survival strategy, adolescent TB, contact tracing and TPT; Strengthening programme collaboration and integration; Quality Childhood TB training including simulation on NGT aspiration technique; Operational research on child-friendly sample collection, and point of care diagnostics. The childhood TB training materials were updated, now covering 4 days, including NPA. Contact investigation and TPT registers were developed and distributed. The NTP is involved in validation of simple stool processing methods (with KNCV). The country changed the regimen for TPT from 6H to 3RH for children.

In 2018/19, of 114,233 notified TB cases, 10% were children aged below 15 years. 90% of DS-TB and 74% of DR-TB contacts were screened for TB symptoms at least once. 93% of under-five contacts were screened for TB, with 92% being asymptomatic, 65% of these were started on TPT.

Challenges include a limited number of partners supporting the TB programme; Data quality issues as a result of transitioning HMIS to DHIS 2 (some regions are facing challenges of using DHIS2 – training planned); Weak programme integration especially at subnational levels (TB-RMNCH platform); Lack of advocacy for adolescent TB prevention; Funding gap impacting on cascading training, availability of cartridges

The way forward includes: Strengthening the integration of childhood and adolescent TB at the facility (all child and adolescent service outlets) and community level (ICCM), especially PPM-facilities; introduction of adolescent-friendly services at high burden facilities; Scale up and strengthening the implementation of the 3RH for <15 years; Evidence generation to address the diagnostic difficulties (simplified stool and urine test operational research studies) and; Explore local funding for childhood TB

Discussions:

Addressing stigma through contact investigation could form an opportunity.

Why would stigma related to TB be higher than HIV – and how to address this? Limited social protection from TB, much more for HIV. Need to enhance information, education, and peer support.

TB-CHAMP update – Simon Schaaf

TPT for DR-TB contacts is a neglected topic but is very important in young children. In the provision of second-line drugs, we need to know what to give in FQ sensitive and resistant contacts.
TB-CHAMP is a randomised placebo-controlled trial in children under 5 who are contacts of MDR/XDR-TB: levofloxacin versus placebo (South Africa). The study opened 2015, enrolled 472 children to date. The initial sample size was 1500, which was later reduced to 1000. Funding was depleted, but Unitaid is now supporting completion of the trial under the BENEFIT Kids project. Low enrolment is mainly due to choices offered to parents (3 drug regimen or TB-CHAMP trial). A 4th site is to be added soon to speed up enrolment. An interim data analysis is awaited.
Other studies: VQUIN: levofloxacin versus placebo daily for 6 months in Vietnam: All ages, so far 30 children; PHOENIx: delamanid versus standard dose INH for 26 weeks in HIV infected children under 5 years in ACTG and IMPAACT sites, study was recently opened.

Session 2: Developments in diagnosis of TB in children and adolescents - Chair: Steve Graham

Panel 2:

Discussion on the use of new diagnostic tools (Ultra, Fuji LAM, digital CXR), alternative specimens (NPA and stool), and improving diagnosis in children with HIV, pneumonia and malnutrition

Edine Tiemersma (KNCV) – stool processing for Xpert Ultra

TB in children is hard to diagnose: Children often have paucibacillary disease so sensitive methods are needed (culture, Xpert (Ultra)). Sputum is hard to obtain and invasive methods are often used that are not available at lowest level health facilities. This leads to delays in the diagnosis. A simple test is needed with quick results and access at lower levels of healthcare where children report.
Stool is easy to obtain and has been shown to contain MTB in adults with pulmonary TB - MTB can be detected using Xpert MTB/Rif.
Xpert on stool can be used as a rule-in test for the diagnosis of TB in children: If it is positive, TB disease can be confidently diagnosed. A systematic review and meta-analysis included N=1681 children from 9 studies. The pooled sensitivity against the reference standard was 67% (95%CI: 52-79) and the pooled specificity 99% (98-99) (Journal of Clinical Microbiology, 2019).

The KNCV SOS - Simple One-step stool method is as simple as sputum testing with Xpert and feasible to perform in lower level health centres. It can be performed at every GeneXpert site without need for additional materials. Only a short training required for Xpert staff.

Work is ongoing and planned to generate evidence: ASTTIE (Continue data collection in parallel with routine testing on respiratory samples); CaP-TB (Pilot implementation in 3 selected sites); PODTEC (Gain insight into robustness of SOS method; Develop routine implementation and scale-up package; Test in routine in remote area) and head-to-head comparison (Compare KNCV SOS with TB-Speed sucrose flotation and FIND stool processing kit). Lessons learned from the SOS: It works – MTB and rifampicin resistance has been detected in pilot studies; Children can produce stool for testing; Laboratory staff can perform the test and; Low error rates (similar to sputum).

In conclusion: The KNCV SOS processing for Xpert will offer quick accurate diagnostic test that includes RIF resistance, simple processing (as simple as sputum) and access to diagnosis at decentralized level. KNCV aims for stool to be included as possible sample for TB diagnosis in new Xpert guidelines, Xpert stool test to be accepted as rule-in test and recommendations on stool testing in the new childhood TB guidelines based on evidence obtained.

Olivier Marcy (University of Bordeaux) – improving diagnosis of TB in children with severe pneumonia, HIV, severe acute malnutrition

The TB-Speed project aims to develop a feasible and cost-effective childhood TB diagnosis strategy through innovative diagnostic tools, decentralization and specific approaches for vulnerable children (severe pneumonia, HIV-infection, severe acute malnutrition (SAM)). Work-packages include operational/implementation research and clinical studies and technical work packages (sample optimization, cost-effectiveness). Diagnostic tools and approaches include systematic screening and strengthened clinical skills, specific tools/algorithms for children with HIV and SAM, microbiology: Xpert Ultra with G1 Edge on NPA and stools and digitalized X-ray with a simplified reading tool.
The TB-Speed pneumonia study aims to assess the impact of systematic molecular TB detection on 12-week mortality of children under 5 years with WHO-defined severe pneumonia. The intervention consists of Xpert Ultra on 1 NPA and 1 stool sample, added to the WHO-SOC (+ immediate anti-TB treatment initiation). This is a cluster randomized trial of 15 hospitals in Cambodia, Cameroun, Côte d'Ivoire, Mozambique, Uganda and Zambia. Since March 2019, 1209 (of 3780) children have been enrolled and 6 hospitals switched to the intervention phase. The last visit of last patient is expected in December 2020.

The ANRS 12229 PAANTHER study, conducted in Burkina Faso, Cambodia, Cameroon and Vietnam, aimed to develop a TB treatment decision algorithm in HIV+ children with presumptive TB. The TB treatment decision score was based on contact history, clinical features, Xpert on NPA and stools, CXR and abdominal ultrasound. TB treatment was started if the score was over 100. The algorithm had a sensitivity of 89% (95%CI 84–93) and a specificity of 61% (95%CI 53–69). The TB-Speed HIV study will conduct an external evaluation of the algorithm in 550 children with HIV with presumptive TB in Côte d'Ivoire, Mozambique, Uganda and Zambia, with results expected in Q2/3 2021. The TB-Speed SAM study is a diagnostic cohort study among 720 children under 5 years hospitalized with SAM. Diagnostic tests will include Xpert Ultra done on NPA, stool, sputum, contact history and clinical features, CXR and abdominal ultrasonography, CRP, Monocytes-Lymphocytes Ratio (+ Quantiferon in children with SAM) Plasma and urine will be bio-banked for future biomarker studies.

Other TB-Speed work includes: TB-Speed Decentralization study (feasibility, impact, cost effectiveness of decentralizing TB diagnosis at PHC versus district hospital); TB-Speed Stool Processing (testing a simplified stool processing method for use at PHC level (+ FIND stool processing kit and KNCV One-Step method)); NPA (Developing a low cost low-pressure aspiration device) and; TB-Speed TB-PK (evaluating pharmacokinetics (PK) and optimised dosages of TB drugs in children with SAM).

Prof. Kabra (AIIMS) – Xpert Ultra and Urine LAM

Xpert ultra in children:

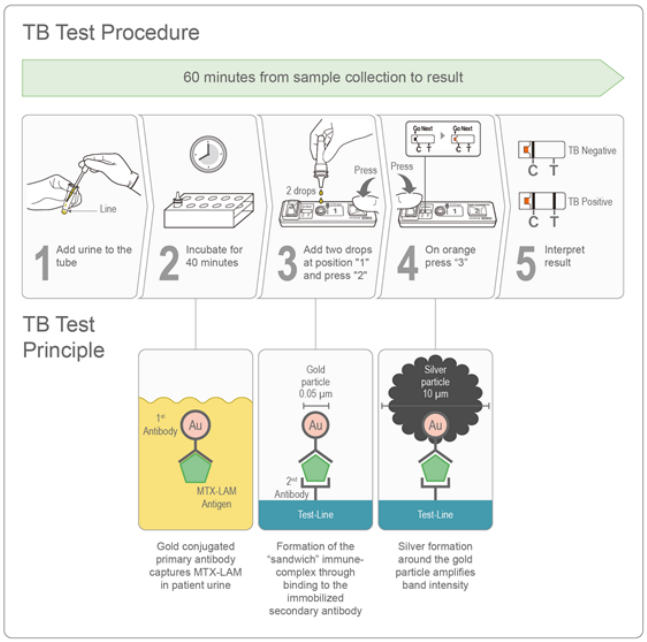
- Study by Nicole, 2018: 367 children <15 years, sensitivity Xpert 63%, Ultra 74% (incremental benefit 11%), specificity Ultra 97%
- Study by Zar et al, in press: Xpert Ultra in induced sputum/nasopharyngeal aspirates: 195 children [median age 23·3 months, 32(16·4%) HIV-infected]; One induced sputum and nasopharyngeal aspirate; Results: 130 had two nasopharyngeal aspirates; Culture confirmed: 40(20·5%); Ultra positive on nasopharyngeal aspirates: 26(13·3%) and Induced sputum in 31(15·9%); Sensitivity and specificity of Ultra on one nasopharyngeal-aspirate: 46% and 98% respectively; Similar by HIV status; Sensitivity and specificity of Ultra on one induced sputum were 74·3% and 96·9% respectively; Sensitivity of Ultra: two nasopharyngeal aspirates 54.2%; combining one nasopharyngeal aspirate and one induced sputum 80%; two induced sputum 87.5%
- Study by Sabi et al, 2018: 215 children in 2 sites in Tanzania, sensitivity Xpert 54%, Ultra 64% (incremental benefit 11%), specificity Ultra 100%
- Good potential but limited experience in children: Three studies on stored samples (samples used were stored - induced sputum in two and NP aspirate/Induced sputum in one); Sensitivity: 64-75%; Proportion of HIV infection 19-50%; Specificity: 96-100%
- Need for more studies on GA/IS/Stool/EPTB

Urinary LAM in PTB and LN TB:

- For detection of lipoarabinomannan antigen of mycobacteria in urine, lateral flow assay for Lipoarabinomannan, (Determine TB LAM Ag, from AlereTM) was used; Fresh urine samples used within 8 hours if kept at room temperature
- Children with presumed intra-thoracic TB: N: 280; mean age 8.6 years ± 3.90; ZN smear positive: eight (2.8%); MGIT positive: 50 (17.8%); GeneXpert positive: 56 (20%); LAM assay in confirmed TB sensitivity of 73.2%, specificity 73.2%, PPV 48.1% and NPV 88.9%.
- LAM in lymph node TB: N=101 mean age 10.27 years ± 3.36; ZN smear positive: 3 (2.9%); GeneXpert positive: 23 (22.7%); MGIT positive: 9 (8.9%); LAM: sensitivity was 76%, specificity 69.7%, PPV 45.2% and NPV 89.8%
- LAM in probable TB: Probable TB (microbiologically confirmed and unconfirmed TB): specificity improved to 93% and PPV to 90.7%; Probable LN TB: specificity 91.3% and PPV to 88%
- LAM in paediatric TB: N = 61 (suspected TB) (age 0-14 years); Probable TB 49 (21 confirmed and 28 unconfirmed); The urinary LAM level was higher in subjects with TB (1.80+1.02) mg/l compared to non-TB group (0.46+0.3) mg/l; p<0.001(independent t-test); If cut off 0.98 mg/L: Urine LAM had 83% sensitivity and 85% specificity; If cut off 1.69: 33% sensitivity and 60% specificity (Journal of Clinical and Diagnostic Research. 2017 Mar, Vol-11(3): EC32-EC35)

Pamela Nabeta (FIND) – Stool processing kit and Fujifilm LAM

Stool processing method: proof of concept and initial validation, with Sensitivity and specificity of Xpert stool assay as tested with paediatric clinical samples (Banada et al. PlosOne 2015) and performance of prototype assay combined with Xpert MTB/RIF on stool, compared with Xpert MTB/RIF on respiratory samples (Walters et al. JCM 2018). The final design of the stool processing kit is currently under clinical evaluation (as part of head to head comparison with KNCV SOS and TB-Speed flotation method).



FUJIFILM SILVAMP TB LAM (FujiLAM): Designed for the POC in LMIC's where patients seek care; Enhanced sensitivity to detect TB in PLHIV; High specificity for immediate treatment initiation; High patient impact. Test procedure: see image on the right. The first evaluation was conducted on 968 adults, HIV co-infected inpatients in a high-burden setting (frozen samples). The sensitivity of FujiLAM was significantly higher (22–35%) than AlereLAM, with 84·2% sensitivity in patients with CD4 ≤100 cells per µL. FujiLAM performance in children: further details in an e-poster session at the Union conference. There is ongoing assessment of the test on fresh urine samples (FIND & RaPaed).

Hannah Kirking (CDC) – ongoing studies on paediatric diagnosis and contact investigation

Update on three studies on paediatric diagnostics (which are ongoing).

- Comprehensive household contact tracing in Uganda: including NPA and stool – screening at household level, those who screen positive will be evaluated (implementation focused, based on national guidelines, with addition on stool and NPA). Started enrolment in May 2019. NPA seems less feasible at PHC facility level, while stool is highly feasible. To date 1600 contacts were screened, 74 children screened positive, 39 GA, 10 IS, 20 NPA, 54 stool. Increased ability to collect stool overcomes low sensitivity of Xpert.
- TB diagnosis in children in Mexico (part of a larger Xpert access study): children <10y admitted to hospital, adding NPA and stool samples. Value added of additional specimens may be different from Uganda. Enrolment is ongoing.
- Household based contact tracing in India: NPA and stool, as well as IGRA. Enrolment not yet started.

Moving forward: identification of implementation barriers, e.g. transportation, clinical diagnosis (remains necessary despite better tools).

James Seddon (DTTC) – digital chest X-ray

Advantages of digital chest X-ray: Remote reading, quality, manipulation, storage and research. CAD4TB is now also available for children over the age of 4 years, but more evidence is needed. The PAANTHER

study looked at diagnostics accuracy of CXR features as determined by final consensus (in a case-control sub-analysis). Overall the sensitivity of a CXR consistent with TB was 71.4% and the specificity 50%. Alveolar opacities and peri-hilar lymph nodes had the highest sensitivity. The post-test probability depends largely on the pre-test probability of TB (prevalence of TB). No matter how experienced a clinician, the amount of training received and the availability of artificial intelligence, the overlap between TB and not TB remains high. New data on use of chest ultrasound compared to CXR are available. We need to know the place of CXR in clinical decision making, e.g. regarding the sequence of tests, history, antibiotics trial.

Priorities include: SOP/consensus statement to guide conduct, storage and interpretation of digital CXR in children; Identify characteristics on CXR that are associated with TB; Identify best ways of using CXR for clinical care; Identify best ways of using CXR in research; Increase evidence for CAD4TB CXR in children and; Improve the experience in other imaging modalities.

Questions

- Acceptability of stool collection: KNCV Indonesia: good acceptability and feasibility for care givers. It takes about 1 day to get the sample (as it cannot be produced on demand). TB-Speed, FIND and CDC also reported high levels of feasibility.
- Age limit for stool samples: in principle stool can be used for all ages, especially for seriously ill patients, or those with special needs. We do need to bear in mind that stool is not the magic bullet, as sensitivity will remain low due to paucibacillary TB in children.
- How to deal with trace results for Xpert Ultra (lower specificity) – challenge to know if the result is truly bacteriologically positive. In children who are sick with trace result, expert advice would be to treat for TB. The question is if it is not more important to find all children with TB with the risk of over-diagnosing some.
- Decentralization of TB diagnostic services: digital CXR are often not available at lower levels. Use of CXR is often limited by the ability to take CXR and to transmit it to someone to read.
- LAM assays: performing better in PLHIV – what does the outer layer of Mtb got to do with the CD4 count? This is still not clear. For children, there was not much difference in performance between children with and without HIV.
- Scraping of tongue/oral swabs – possible future site for sample collection
- Repository of images for CAD4TB (FIND – WHO): how many images have been included and how will this impact on grey areas. The repository includes some images from children. The more data available, the stronger the reference standard will be, but currently more information is needed.
- Role of chest ultrasound: mainly to provide an indication of normal or abnormal, to help make a diagnosis, as another piece of the jigsaw.
- GDF is keen to include a stool processing kit in their diagnostics catalogue. Combined results are expected at the end of 2020 (comparing the different methods).
- Implementation and feasibility of diagnostics remains important, and capacity for clinical diagnosis will still be critical.

Session 3: Developments in treatment of DS and DR-TB in children and adolescents - Chair: Anthony Garcia-Prats

Systematic reviews for new Unitaid paediatric MDR-TB project – call for data - Anthony Garcia-Prats

The BENEFIT Kids Project, in collaboration with WHO, will be undertaking two systematic reviews and individual patient data meta-analyses:

1. Pharmacokinetics data on second-line TB medications in children
    - Studies reporting PK of all 2nd-line TB drugs
    - Published and unpublished data
    - Treatment of children with MDR-TB
    - Published or unpublished
2. Observational or trials
    - Retrospective and prospective
    - Update previous SR-IPDMA from 2015 (Harausz E et al, PLoS Med 2018)

The goal of these systematic reviews is to ensure guidelines are informed by the best evidence, so children receive the best possible care.

Therefore, this is a preliminary call for data for these 2 systematic reviews

- Data and collaborators
- Share interest, potential data
- Local approval, data sharing agreement
- If meets eligibility criteria, share de-identified data, respond to queries
- Assist core team with interpretation, dissemination

When: Formal call for data late 2019-early 2020

Who: Please contact – Tony Garcia-Prats (garciaprats@sun.ac.za), Anneke Hesseling (annekeh@sun.ac.za) or Tina Sachs (tinasachs@hotmail.com)

Update on SHINE trial - a phase III randomised trial of treatment shortening in children with minimal TB disease - Di Gibb and Vidya Mave

Shorter treatment for minimal TB in children (SHINE) is a phase III randomised open trial comparing 4 vs 6 months treatment in children (+/- HIV) with smear-negative non-severe TB in Africa and India, conducted by the MRC Clinical Trials Unit, University College London.

Children have been left out of TB trials because they are less infectious and are therefore 'less of a priority', because of difficulties in confirming the diagnosis and measuring endpoints. Generally, therapy for drug-susceptible TB is effective. However, we could be over-treating the majority of childhood TB and children have the right to benefit from child-focussed research as much as adults.

Looking at the natural history of TB in children, infants under 1 year of age have the highest chance of developing disseminated disease (miliary TB or TBM – 10-20%) as well as PTB (30-40%), while in children between 1 and 10 the proportion of both disseminated and pulmonary disease declines. The proportion of pulmonary disease increases again in adolescents over 10 years.

SHINE aims to answer the question: Can we safely reduce 6 months treatment to 4 months in children with smear-negative non-severe (minimal) TB?

After a 1989 trial in Hongkong on 3, 4 and 6 months TB regimens for smear-negative PTB, WHO guidelines recommended 4 months treatment for children with uncomplicated TB in 1993, although the decision was reversed in 1997, since when, 6-month regimens are recommended for all forms of

paediatric TB. These decisions were made with minimal paediatric evidence and no randomised trials. In 2018, a patient-level pooled analysis was published on 3405 participants from 3 adult trials of treatment shortening. This analysis showed that 4-month regimens were non-inferior to 6 months in individuals with less than 2+ positive sputum microscopy. The stratified medicine approach was to shorten the TB treatment regimen for mild disease (? 4 months), whereas patients with high smear grade and/or cavitation may need more than 6 months of treatment.
SHINE trial design: children aged under 16 are randomised to receive either an intensive phase of 8 weeks HRZ(E) and a continuation phase of 8 weeks HR or 8 weeks HRZ(E)/16 weeks HR. They are followed up for 18 months for the primary outcome assessment. All anti-TB drugs prescribed as per WHO 2010 dosing guidelines using the new FDCs and the new weight bands.
The population includes children <16 years with non-severe TB, smear negative, known HIV status and a decision to treat with standard 1st line regimen without known resistance. The primary end points are: Efficacy: Unfavourable outcome (TB treatment failure, relapse/re-infection or death) and safety (Grade 3/4 adverse events and SAEs). Secondary endpoints are: Mortality, adverse drug reactions up to 30 days of completing treatment, suppressed HIV viral load at 24 and 48 weeks in HIV-positive, bacterial infections requiring hospitalisation, adherence and acceptability and unfavourable outcome in those with confirmed TB. The Endpoint Review Committee (blinded to treatment arm) has three functions: To determine (in a consistency and independent way) the TB diagnosis at enrolment across sites (for the key secondary analysis of those with definitive TB); To adjudicate cause of death based on all available sources of data and; To determine the primary endpoint classification for all patients as favourable, unfavourable or assessable. The study is conducted in Cape Town (South Africa), Lusaka (Zambia), Kampala (Uganda) and Pune and Chennai (India). The first child was randomised on the 1st July 2016 and enrolment was completed on 20 July 2019 (fully in line with the targets for enrolment).

Baseline data:

- Median Age 3.5 years (1.5-7.0 yr)
  - *India **7.4*** years, IQR (4.4-10.5); *Africa **3.0*** years, IQR (1.3-6.3)
- 52% male
- HIV status: 131 (11%) HIV-infected (Zambia and Uganda)
- 1122 (93%) had abnormal CXR (local reports) TB Symptoms:
- 86% present with respiratory Symptoms:
  - 62% cough >2weeks
  - 51% fever
  - 52% poor feeding/appetite (5% severe malnutrition)
  - 51% had TB contact in last year, (93% with pulmonary TB)
- 77% had Mantoux test (despite world-wide shortage): 60% tested positive
  - IGRA tests done in South Africa only (n=34)
- Microbiological samples on all randomised children
  - 163 (14%) confirmed TB (GeneXpert and/or Culture)

Sub-studies conducted:

- PK sub-studies
  - PK 1: Describe PK of the first-line drugs in HIV- children <37 kg dosed according to currently recommended weight bands: New paediatric FDCs in recommended weight

band-based doses; Single intensive PK (1, 2, 4, 6, 8 and 12 hours after drug intake) (South Africa, Zambia, India)
  - PK 2: Evaluate PK interactions between anti-TB and ARVs in all ages of HIV/TB co-infected children in 2 intensive PK sessions of ARVs (EFV; LPV/r) with 1st PK during TB treatment; 2nd PK 4 weeks post TB treatment (South Africa, Zambia)
  - Lopinavir/ritonavir TDS PK: To evaluate whether modified LPV/r from BD to TDS dosing will achieve adequate blood levels of LPV/r in children co-treated with RIF; Evaluate acceptability and tolerability of TDS LPV/r dosing using 2 intensive PK sessions of ARVs - During and Post TB treatment (Zambia)
  - Hair PK: To assess the utility of hair assay for INH & PZA as a drug adherence and exposure tool and assess relationship between INH & PZA hair concentrations vs TB treatment outcomes (All sites)
- Palatability/acceptability sub-studies (SA): Explore patient, caregiver and healthcare worker experience of using FDCs; Explore child and caregiver experiences of the SHINE treatment and adherence
- Health Economics sub-study: Cost/cost effectiveness of shorter treatment
- Biomarker sub-study: To test host markers in serum and whole blood RNA to predict early and late treatment outcomes; Samples are collected at week 0, 2, 8, 16 and 24 and at relapse/recurrence/early exit. Assays include: cytokine and metabolite measurements in serum; multiplex qPCR on ex vivo RNA; microRNA in serum and whole blood; collaboration with Tony Hu (Tulane University) and other collaborators to evaluate different biomarkers
- Chest X-ray sub-study: Investigate CXR interpretation between clinicians and experts (experts are double or triple reading all CXRs at baseline for ERC adjudication of TB diagnosis); CXR features of children diagnosed with non-severe PTB on the SHINE trial (by age /HIV status /microbiological confirmation status /country); Methodology of CXR reading on clinical trials for paediatric TB; Using image library as reference
- Microbiology sub-study: TB testing harmonized across laboratories using key elements in TB laboratory procedures that: Have the greatest impact on microbiology endpoints of clinical trials; Allow for comparison of results among all trial sites (or from one study to another) and; Provide accurate test results to ensure safety of trial participants
- Pharmacogenetics sub-study: Evaluate genetic differences in drug metabolic pathways affecting individual responses to drugs in terms of therapeutic and adverse effects; To determine if there are differences between African and Indian ethnic groups

Use of new drugs for children with DR-TB - Alena Skrahina, NTP Belarus

Belarus has seen a gradually decreasing TB incidence in both adults (from 45 to 20 per 100,000) and children under 17 years (from 4.5 to 1.1 per 100,000). The same trend can be seen when looking at the absolute numbers: the absolute number of notified TB cases in the group 0-17 years decreased from 72 in 2009 to 21 in 2018. The proportion of child and adolescent TB proportion (1.2%) among all TB cases in the country is relatively low (0.7 % in children below 14 years). Belarus' national TB response is faced with the need to address an epidemic of multi- and extensively drug resistant TB. This trend is also seen in child and adolescent TB. 38% TB cases notified in 2018 had MDR-TB.

The NTP has put in place several programmatic tools for rapid implementation of the new WHO recommendations. The MDR-TB consilium is one of the important elements. Each MDR-TB patient (including children) is discussed at the consilium. Designing a proper treatment regimen in line with the most recent WHO recommendations is the first priority. Other issues are also addressed including treatment adherence, management of co-morbidities, drug adverse events, social support, etc.
Scale up of rapid tests such as Xpert and LPA (to first and second line) is the second important element of new treatment regimens implementation. This has significantly improved diagnosis and reduces the time to start adequate treatment. In addition to this, DST to new and repurposed TB drugs such Bdq, Lzd, Cfz, Dlm has been implemented since the end of 2018.
Another important element is aDSM, meaning active and systematic clinical and laboratory assessment, management and reporting of suspected or confirmed drug toxicities. The paper and electronic-based forms have to be completed during each patient's visit, then summarized in review form. Data go to Electronic National TB register and to National and international Pharmacovigilance databases followed by analysis, report and recommendations.

40 children and adolescents with M/XDR-TB started on new drug-containing regimens. 16 patients on Bdq and 17 patients on Dlm were already successfully treated, no unfavourable treatment outcomes were recorded (treatment failure, lost to follow up, and death), the rest of patients are still on treatment. In Belarus full laboratory diagnosis for children is a challenge. In our cohort there are 33 patients with full laboratory confirmation (including all spectrum DST), 4 with partial laboratory confirmation such as Xpert positive and without other DST results, and in 3 patients treatment was based on contact case DST. A limited number of adverse events were recorded in the children. All were mild to moderate and did not cause any additional intervention or regimen adjustment. No severe adverse events were recorded.

Clinical case: 16-year-old boy with family contact was diagnosed with XDR-TB in July 2015. Sputum smear and culture positive. Resistant to R H E Km Pto Ofx, Lfx. On CT: right lung cavitary lesion. Conventional treatment started with Z Cm Mfx Pto Pas Cs. In the 3rd month, further clinical and radiological deterioration was observed (loss of appetite, weight loss, cavitation enlarged, consolidation appeared), remained smear and culture positive. Consilium decided to start new treatment: Bdq Cfz Lzd Tzd Imp Amx/clv. Central venous port system was implanted. On new treatment: smear and culture conversion were achieved in one month, further significant radiological improvement, closure of cavitary lesion were observed. No significant adverse events were recorded during treatment course. In October 2017, patient was considered cured.

In conclusion, the Belarus patient series will help increase the global knowledge base for paediatric M/XDR-TB patients treated with new drug-containing regimens under programmatic conditions. Interim results on new drug-containing regimens use in children and adolescents show good safety profile and excellent treatment outcomes. The experience gained can promote further expansion of this approach for children and adolescents with M/XDR-TB.

Session 4: Peer-reviewed publications not to be missed - Chair: Ben Marais

Selection of interesting peer-reviewed articles - James Seddon

- Berry, BMC PH, Gauteng (South Africa): TB treatment outcomes in age groups, <10, 10-15, 15-20, 20-25 and older, LTFU and ART coverage worst in 20-25 age group.
- Bunyasi, IJTLD, Cape Town (South Africa): *Mtb* infection in high school students 12-18 years. Two surveys 2005-2007 and 2014-2015, rates remained high at ~50% but highly impacted by SE group
- Cowger Lancet PH, USA, 2007-2017, Epidemiology of TB in children and adolescents, <15 and 15-17 years, 6000 cases over period and rate declined. Higher in those born or born to parents from high TB burden countries.
- Huerga, ADC, Armenia, 3 out of 150 MDR-TB household contacts had TB disease at baseline. There was a high prevalence of infection (60%). High incidence of TB infection but no additional cases of disease.
- Dodd, Lancet GH: Evaluation of impact and effort of two approaches to household contact management. If this is more comprehensive implemented, 160,000 cases and 110,000 deaths could be prevented.
- Jaganath, Uganda: Study on seasonality of childhood TB cases in Kampala from 2010-15, evaluating 713 cases. No relationship with season or temperature but with rainfall and number of notified influenza cases in hospital.
- Gafar, ERJ, Netherlands: Nationwide analysis of treatment outcomes of children and adolescents with TB: <18 years between 1993-2018, 3253 included, 95% cured or completed, 0.7% died, rest LTFU. Risks associated with death included TBM, age 2-4 years, HIV, miliary disease, drug-induced liver injury. Adolescents had higher rates of LTFU.
- Enane, PIDJ: Treatment outcomes in Botswana in adolescents/young adults aged 10-24 years, between 2008 – 2014. 68 adolescents and young adults were identified with an outcome of LTFU. Only 16 repeated treatment, 4 died, HIV was heavily implicated.
- Ganmaa CID: Part of a trial of vit D supplementation for incident TB infection in Mongolia among 10,000 6-13-year olds, of whom 10% had a positive IGRA. Risk factors for IGRA positivity included household exposure, vitamin D deficiency, and household tobacco exposure.
- Martinez, Lancet RM, as already discussed during the meeting: population-attributable fraction of TB transmission to children 10-30%.
- Reid, Lancet. Building a TB-free world (Lancet Commission on TB): Possibly the most important article on TB this year and although only a small part specifically focussed on children, children are included throughout the document. Outlines the vision and future of global TB services.
- Wang, BMC Med Imaging: CT-based predictive nomogram for differentiating primary progressive PTB from community-acquired pneumonia (CAP) in children in Beijing: children 0-13 years with 53 TB vs. 62 CAP. Divided 3:1 discovery and test. 970 features evaluated in discovery and 11 features found to be good at discriminating. These features were used together with duration of fever, then tested on test set. AUC 0.97, which is better than a radiologist.
- Sovershaeva AIDS: Study conducted in Zimbabwe (2017-2018) as part of breath trial with children aged 6-19 years (222 HIV-infected and 97 HIV-uninfected), no current TB or respiratory disease. HIV was associated with reduced nitrous oxide (NO) levels and previous TB was associated with reduced NO levels in HIV-infected children.

- Ped Pul, Cape Town. Study conducted in 2014-2016 which included 170 children, who were investigated for TB (confirmed, probable, unlikely).- The median age was 27 months. Effusion was found to be more likely in TB and lymph nodes bigger, and consolidation took longer to resolve in children with TB.
- Choudhary, JAIDS: Study conducted in Kenya, among HIV-infected children aged 12 years or under. Children had confirmed, unconfirmed, unlikely TB. Monocyte-to-lymphocyte (ML) ratio measured. 160 children with a median age of 26 months were included. ML in children with confirmed TB was much higher than in unconfirmed or unlikely TB. A level above 0.38 had a sensitivity of 77% and specificity of 78%, levels in confirmed returned to similar levels as in children with unlikely and unconfirmed TB when on TB treatment.
- Lancet HIV: South Africa (2013-2015): 96 HIV-infected children with TB (weight 3-15 kg, median age 18 months): all children were given Lopinavir:ritonavir in 3:1 ratio when not on rifampicin and 1:1 when on rifampicin. PK and safety were compared. In both groups a very similar proportion achieved lopinavir levels above the threshold.
- Dayal, ADC: India, 40 children aged 1-15 with TB were recruited into this PK study. Intensive PK was done at 15 days, with evaluation of INH and PZA at new WHO dosages for age and nutrition. INH was adequate, but PZA inadequate in children aged <3 years and malnourished.
- Garcia-Prats PIDJ: Cape Town, 12 children recruited aged 8-18. They were given amikacin with and then without lignocaine in a double-blind design. Pain was evaluated before, immediately after and at 30 and 60 minutes, and intensive PK was done. There was marked improvement in the immediate pain score and no change in PK AUC and Cmax.
- Radtke Lancet Child and Adol Health: Model undertaken based on population data from 20 countries with high TB burden. Number of children at different ages malnourished. They applied current WHO dosing weight bands, an algorithm based on weight and age and finally an ideal drug exposure algorithm. Then for each country, for each age band with and without malnutrition, determined the proportion achieving adequate drug exposures. Finally determined how this might translate into lives saved. 43% of children were under-dosed, and with better dosing 30% of treatment failures could be avoided.
- Garcia-Prats, PM: Cape Town study with 48 children on linezolid with intensive PK, comparing exposures to adults receiving 600mg od. Most children were achieving higher exposures with current dosing. Long term safety study in 17 children, of whom 10 had severe AEs. Authors proposed new weight bands proposed, ~10mg/kg od
- Indian J Ped: India (2007-2017): study in children with TB infection or disease, those treated before end 2011 received old dosages, those after had new WHO recommended dosages. 515 children, half before and half after. The rate of hepatotoxicity overall was 2-3%. None in IPT group (14%) developed drug-induced liver injury (DILI). There was no difference in DILI between old and new dosages.
- Chiang. JPIDS, Peru: 100 children with DS-TB and 94 with MDR-TB were included. Weights were measured and related to outcome. A poor weight-for-age z-score change at 3-5 months for DS-TB and at 7 months in MDR-TB predicted treatment failure.
- Hamada. Bull WHO Global. Modelling study on estimates of number of children in 2017 under 5 years eligible for PT. Number of reported cases in adults, and DHS data were used to estimate the number of children exposed. 1.27 million children eligible, but only 23% received TPT. African and SE Asia had the biggest burden of eligible children.

- MacLean, JCM. A systematic review/meta-analysis on diagnostic accuracy of stool Xpert, with 9 included. Ages between 1.3-10.6 years. Sensitivity was 67% and specificity 99%. Better in HIV and limited data in <5 years. Heterogenicity in findings.
- Malik, CID Pakistan: 2016-2017, implementation of TPT in DR-TB household contacts of TB patients at Indus hospital <5 years, and 5-18 years with +TST/IGRA or >18 with immunosuppression were given fluoroquinolone based TPT. 100 households with 800 contacts included. 215 were eligible contacts, 80% started TPT and 70% of those finished. No adverse events and no one got TB.
- Gupta CID: Feasibility study to start the Phoenix trial in 8 countries, conducted between 2015-2016, 1016 household contacts from 284 MDR-TB patients. 12% contacts had prevalent disease. TB infection was high at 72%, 20% of these were aged <5 years.
- Osman EID. Global. In this systematic review and meta-analysis, 37 children (<15 years) with confirmed XDR-TB were included (1999-2013) from 11 countries. 7 months intensive phase and 12.2 months continuation. 81% had a favourable outcome and 4 died.
- Rohlwink Nature Comms. RNA sequencing on blood and both ventricular and lumbar CSF. 21 TBM cases, 7 controls with CSF sampling and 24 healthy controls. Blood showed decreased T cell activation in TBM, ventricular CSF neuronal excitotoxicity and cerebral damage. Ventricular profile represents brain injury whereas the lumbar profile represents protein translation and cytokine signalling.
- Muenchhoff JID. 25 HIV infected children were included in this study. Before starting ART and 1 year after starting, HIV- TB and CMV- specific immune responses were measured. Pathogen-specific changes were seen after 1 year of ART in cytokine profiles of CD4 T-cell responses that were associated with shifts in memory phenotype and decreased programmed cell death 1 (PD-1) expression. The proliferative capacity of HIV- and PPD-specific responses increased after 1 year of ART. Of note, the recovery of CMV- and TB-specific responses was correlated with a decrease in PD-1 expression.
- Du Preez. Lancet GH. Cape Town. BCG vaccine supply has been problematic from 2015 in South Africa. Number of admissions for TBM at Tygerberg hospital increased in 2017 from annual average of 33 to 70, linked to BCG shortages.
- Usher. JAMA open. 1935-1938. About 3000 individuals were vaccinated 60 years ago as part of a clinical trial among native Americans in the US, 1500 were BCG vaccinated and 1500 received placebo. The mortality was 40-45% - not different between two groups and rates of cancer were similar but lung cancer was much lower in BCG vaccinated people with a HR of 0.38.

High level dialogue to scale up services for children living with HIV and TB – Martina Penazzato

The Vatican platform for high-level dialogues

Rome 1 (April 2016): High-Level Meeting with representatives of Pharmaceutical and Diagnostic Industries Regarding Paediatric

Rome 2 (May 2016): Consultation organized by Pontifical Council for Justice and Peace, Caritas Internationalis, UNAIDS, PEPFAR on “Fast-Tracking Paediatric HIV Diagnosis and Treatment”

Rome 3 (November 2017): High-Level Dialogue on Scaling Up Early Diagnosis and Treatment of Children and Adolescents with a focus on accelerating development and introduction of medicines

Rome 4 (December 2018): High level dialogue to address remaining bottlenecks to quickly identify HIV-infected children and link them to testing and treatment with optimal regimens

Rome Action plan (Paediatric HIV): https://www.paediatrichivactionplan.org/

A few success stories:

- In 2017 US FDA made strong statement of support to **PSP submissions developed according principles of acceleration** as described by WHO-convened PAWG. EMA endorsed the same principles in 2018
- In 2018 USFDA-WHOPQ agreement led to the launch of **CRPlite** to accelerate in country registration of products approved by USFDA. Innovators and generics exploring CRP to accelerate in country registration
- **CRP for diagnostics** being initiated and donors are not funding repetitive country-by-country registrational studies for diagnostics
- **Innovators commitment to accelerate timelines and partner with key stakeholders to enable more rapid access**
    - i.e. ViiV and research networks committed to accelerate completion of clinical studies on DTG and rapidly share data to inform WHO guidelines and are now on track for submission at the end of the month. In addition, ViiV/CHAI/Unitaid partnership to accelerate generic development of a 10 mg scored DTG dispersible tablet
- **First all-in cost** (reagent rental) for a point-of-care nucleic acid test announced
- Better **alignment between implementing partners** on key steps (tools development, transition strategies, …)
- More **resources mobilized** to support key implementers (ie FBOs), impactful interventions (ie. POC EID)

Rome 5: purpose and specific objectives

- To assess **progress** on the commitments documented in the November 2017 and December 2018 Paediatric HIV Rome Action Plan;
- To highlight **remaining gaps and solutions** on paediatric HIV and diagnostics;
- To highlight **current gaps in TB prevention, diagnosis, treatment and care for children living with HIV**;
- To identify **solutions and commit to actions** that enable improved access to innovative, high quality, TB preventive therapy and affordable TB drugs and diagnostics for children exposed to or living with HIV

Identifying new commitments on HIV/TB:

- Work with **other stakeholders** (manufacturers, regulatory authorities, donors, etc.) to help identify and **take on further commitments**
- Work with partners to help **identify commitments they would like other stakeholders to make**
- Commitments should be **SMART**
    - Particularly important to be able to measure and document progress
    - Timebound commitments ideal

Share your thoughts: Annemieke Brands brandsa@who.int; Martina Penazzato penazzatom@who.int Lara Vojnov vojnovl@who.int; Jen Cohn jcohn@pedaids.org; Francesca Merico Francesca.Merico@wcc-coe.org

Annex 1: Agenda

AGENDA

Annual meeting Child and Adolescent TB working group **Chair: Ben Marais**		**08:00 – 17:00**
08:00 – 08:30	Registration	
08:30 – 08:40	Welcome/Opening address	Vice Chair WG & WHO GTB
08:40 – 08:45	Objectives and expected outcomes of the meeting	Secretariat of the Child and Adolescent TB Working Group
08:45 – 09:05	Report from the Chair of the Child and Adolescent TB working group	Ben Marais, Vice Chair, Child and Adolescent TB Working Group
09:05 – 09:25	The new Global Fund cycle and opportunities for childhood TB	Anna Scardigli, the Global Fund
Session 1: Screening, contact investigation and prevention **Chair: Connie Erkens**		
09:25 – 09:45	Improving childhood Tuberculosis detection through facility-based integrated approaches in Kinshasa, DRC	Aime Loando, EGPAF DRC
09:45 – 10:00	Discussion	All
10:00 – 10:30	Group photo Coffee/Tea break	
10:30 – 10:50	Paediatric tuberculosis transmission outside the household: challenging historical paradigms to inform future public health strategies	Leo Martinez, Stanford University School of Medicine Ben Marais (vice-chair) as discussant
10:50 – 11:10	TB screening in migrant children	Nicole Ritz, University of Basel
11:10 – 11:30	Maternal TB and implications for neonates	Jyoti Mathad, Johns Hopkins Center for Clinical Global Health Education
11:30 – 12:30	**Panel 1:** Discussion with representatives from countries, private sector and communities on contact investigation and prevention and ways to integrate these activities into MCH and general health services Questions and answers	NTP (India), Moorine Sekadde (Uganda), Tilaye Gudina (Ethiopia), Monica Dias (PPM Working Group), Blessi Kumar (GCTA)

12:30 – 12:45	Preventing TB: A game for all	Shakil Ahmed
12:45 – 13:30 Lunch Break		
Session 2: Developments in diagnosis of TB in children and adolescents **Chair: Steve Graham**		
13:30 – 15:00	**Panel 2:** Discussion on the use of new diagnostic tools (Ultra, Fuji LAM, digital CXR), alternative specimens (NPA and stool), and improving diagnosis in children with HIV, pneumonia and malnutrition Questions & answers	Prof. Kabra (AIIMS), Edine Tiemersma (KNCV), Olivier Marcy (University of Bordeaux), Pamela Nabeta (FIND), Hannah Kirking (CDC), James Seddon (DTTC)
15:00 - 15:25	Coffee/Tea	
Session 3: Developments in treatment of DS and DR-TB in children and adolescents **Chair: Anthony Garcia-Prats**		
15:25 – 15:30	Systematic reviews for new Unitaid paediatric MDR-TB project – call for data	Anthony Garcia-Prats
15:30 – 15:50	Update on SHINE trial - a phase III randomised trial of treatment shortening in children with minimal TB disease	Di Gibb and Vidya Mave
15:50 – 16:10	Use of new drugs for children with DR-TB	Alena Skrahina, NTP Belarus
16:10 – 16:30	Prevention of DR-TB including update TB CHAMP and experience with provision of preventive treatment to child contacts of DR-TB patients	Simon Schaaf, Department of Paediatrics & Child Health, University of Stellenbosch
16:30 – 16:40	Discussion	All
Session 4: Peer-reviewed publications not to be missed **Chair: Ben Marais**		
16:40 – 17:00	Selection of interesting peer-reviewed articles	James Seddon
17:00	Wrap up, next steps and closure	Chair and Secretariat

Annex 2: List of participants

1.	Ben MARAIS, Vice Chair
2.	Prof. Mohammed ABDUR RAHMAN
3.	Jay ACHAR
4.	Lisa ADAMS
5.	Galuh Budhi Leksono ADHI
6.	Shakil AHMED
7.	Valentina AKSENOVA
8.	Jane ANDERMAN
9.	Verlyn APIS
10.	Jason BACHA
11.	Dr. V.V. BANU REKHA
12.	Dr. BHANANI
13.	Lina BERSTRÖM-RANDALL
14.	Aleksey BOGDANOV
15.	Grace BOLIE
16.	Maryline BONNET
17.	Laurence BORAND
18.	Chris BUCK
19.	Maria CAMPOS
20.	Martina CASENGHI
21.	Chishala CHABALA
22.	Nancy CHANDA
23.	Silvia CHIANG
24.	Eleanor CLICK
25.	Jennifer COHN
26.	Sarah COOK-SCALISE
27.	Angela CROOK
28.	Fernanda DOCKHORN COSTA
29.	Mao Tan EANG
30.	Penny ENARSON
31.	Connie ERKENS
32.	Julie HUYNH
33.	Betina Mendez Alcântara GABARDO
34.	Fajri GAFAR
35.	Kateryna GAMAZINA
36.	Anthony GARCIA –PRATS
37.	Wayne van GEMERT
38.	Di GIBB
39.	Stephen GRAHAM
40.	Tilaye GUDINA
41.	Petra De HAAS
42.	Yael HIRSCH-MOVERMAN
43.	S. Syed HISSAR
44.	Jeremy HILL
45.	Devan JAGANATH
46.	Sarah May JOHNSON
47.	Madhusudan KAPHLE
48.	Alexander KAY
49.	Alexei KAZAKOV
50.	Aasti Avinash KINIKAR
51.	Hannah KIRKING
52.	Kobto Ghislain KOURA
53.	Lisa KÜBLER
54.	Blessina KUMAR
55.	Sathish Kumar
56.	Sylvia LACOURSE
57.	Aimé LOANDO MBOYO
58.	Gabriela Tanarez MAGNABOSCO
59.	Llang MAIME-MAAMA
60.	Anna MANDALAKAS
61.	Olivier MARCY
62.	Leo MARTINEZ
63.	Simba MASHIZHA
64.	Jyoti MATHAD
65.	Helen McILLERON
66.	Ayeshatu MUSTAPHA
67.	Criménia MUTEMBA
68.	Rahab MWANIKI
69.	Bakyt MYRZALIEV
70.	Pamela NABETA
71.	John Baptist NKURANGA
72.	Tichaona NYAMURDAYA
73.	Laura OLBRICH
74.	Joanna ORNE-GLIEMANN
75.	Megan PALMER
76.	Nyan Win PHYO
77.	Nicole RITZ
78.	Andrea MACIEL DE OLIVEIRA ROSSONI
79.	Nicole SALAZAR-AUSTIN
80.	J. SARASWATHY
81.	Anna SCARDIGLI
82.	Simon SCHAAF
83.	Valérie SCHWOEBEL
84.	Cherise P. SCOTT
85.	James SEDDON

86.	Moorine SEKADDE
87.	Tatiana SEVOSIANOVA
88.	Suvesh K. SHRESTHA
89.	Aliaksanr SKRAHIN
90.	Alena SKRAHINA
91.	Vela SOLOMON
92.	Ruben SWAMICKAN
93.	Khurshid TALUKDER
94.	Marc TEBRUEGGE
95.	Edine TIEMERSMA
96.	Rina TRIASIH
97.	Marieke VAN DER WERF
98.	Margaret THOMASON
99.	Henry WELCH
100.	Genevieve WILLS
101.	Eric WOBUDEYA
102.	Huochag YUDA
103.	Maria Regina CHRISTIAN
104.	Remi KUSIMO
105.	Chika OKORO
106.	Annemieke BRANDS
107.	Sabine VERKUIJL
108.	Jules MUGABO SEMAHORE
109.	Enang Enang OYAMA
110.	Martina PENAZZATO
111.	Haruna ADAMY
112.	Kyaw Ko Ko WIN
113.	Monica DIAS