

Annual meeting of the Childhood TB Subgroup Thursday 3 December 2015

***Table Bay Hotel
6, Victoria & Alfred Waterfront, Breakwater Boulevard,
Cape Town, 8001, South Africa***



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1. Opening

The annual meeting of the Childhood TB subgroup was organized on Thursday 3 December 2015 in Cape Town, South Africa. The meeting was open to all members of the childhood TB subgroup representing a wide variety of stakeholders including paediatricians, NTP managers, MCH representatives, technical and financial partners, community TB representatives and WHO staff from Headquarters, regional and country offices.

The meeting was opened by the Chair of the subgroup, Steve Graham and Malgosia Grzemska, coordinator, Global TB Programme, WHO Geneva (and the Secretary, Childhood TB subgroup).

In her opening address Malgosia Grzemska welcomed the participants on behalf of the Global TB Programme and noted with pleasure that the subgroup is growing and now has more than 210 members. In her opening remarks Malgosia Grzemska noted that childhood TB epidemic now is in the global spotlight with the 2015 Global TB report estimating that at least 1 million children become ill with tuberculosis each year. While producing estimates of TB incidence among children is challenging progress is being made, based on collaborations established in 2013 between WHO and academic groups working on the estimation of TB disease burden among children. She reflected on the new End TB Strategy with the ambitious goal of ending the TB epidemic and that its focus on patient centred care is an important step forward for families and children. Progress has also been made in including paediatric TB as a specific item in Joint Monitoring missions (JMMs) and meeting participants were asked to provide information to the subgroup secretariat on upcoming JMMs in 2016 to ensure that consultants will be available.

Malgosia Grzemska informed the participants that the website is being redone and that copies of documents published in last few year are availed in the room including information on the KNCV collaboration and the benchmark tool that will be presented later in the day. She also was pleased to note strengthening links and collaboration between child health and TB and that the focal point in UNICEF is participating in the meeting.

The main purpose of the annual meeting was to share country experiences in scaling up the response to childhood TB and to discuss next steps to move the agenda forward.

More specifically, the objectives were to:

- To share the latest estimates of the childhood TB burden;
- To discuss how to operationalize the End TB Strategy with a focus on childhood TB;
- To share progress made in collaboration with MCH and other health services;
- To share country experiences in scaling up childhood TB activities;
- To learn about community-based projects; and,
- To discuss the uptake of the new paediatric TB Fixed Dose Combination (Childhood TB FDC).

The agenda of the meeting is found in Annex 1 and the list of participants in Annex 2.

2. Report from Chair on the 2015 activities of the Childhood TB subgroup

The Chair of the subgroup Steve Graham presented an overview the activities of the group in 2015 and highlighted the issues as the group moves forward. The membership of the group is growing and there are new several new members of the core group on 2015, namely:

- Betina Mendez Alcântara Gabardo, Chair, Child TB Advisory Committee of the Americas
- Anna Scardigli, The Global Fund
- Valérie Schwoebel, The Union
- Keri Lijinsky, USAID, Bureau for Africa
- Ya Diul Mukadi, Senior TB Advisor, USAID Global Health Bureau
- Eleanor (Ellie) Click, CDC USA
- Pervaiz Tufail, Civil Society
- Anne Detjen, UNICEF

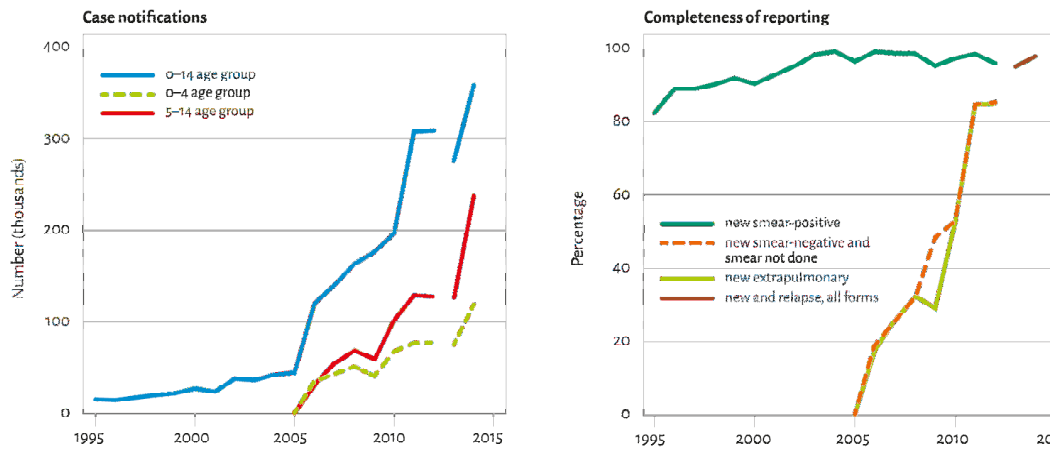
It was also pointed out that the subgroup needs to consider the election of a new chairperson by the next annual meeting. The core group had three conference calls in 2015: March 10, July 14, and October 6.

There is growing recognition that TB is an increasingly important cause of morbidity and mortality in infants and young children globally. Most countries (all but 5) are now reporting new TB cases disaggregated by age and the majority of countries are also reporting previously treated TB cases disaggregated by age. However, more needs to be done to better link with all services attending to children and get the paediatricians on board; diagnosed children are still not always being reported.

In 2014 countries reported a total of 358,521 cases of TB in children (0-14 yrs.). This is 30% higher than for 2013. However the best estimates show that there are 1,000,000 cases (UI: 900,000-1,100,000) or 10.4% of total caseload with 140,000 deaths (cf.80,000 estimated for HIV uninfected in 2013). There is a need to further improve the estimates as an important tool for advocacy and to get attention to the problem. There is also a need to get better data on adolescents as they are being reported within two age groups, children and young adults.

Figure 1: Global reporting of TB among children

Global progress in reporting of TB cases among children, 1995–2014.^a Left panel: Number of notifications of cases among children reported to WHO. Right panel: Percentage of case notifications reported to WHO that are age-disaggregated.



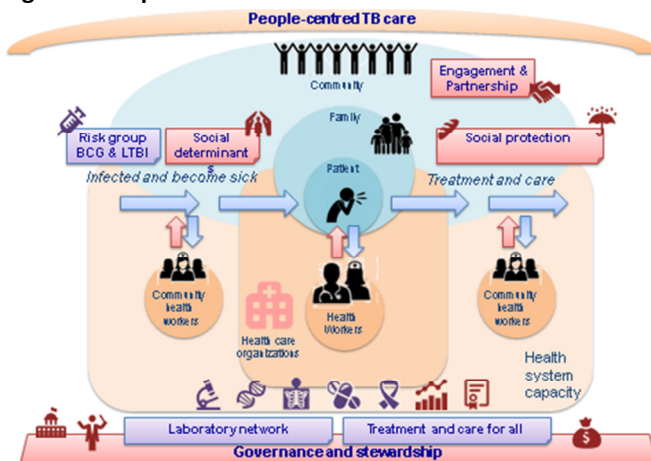
^a Before 2013 childhood case notifications included smear-positive, smear-negative, smear not done and extrapulmonary TB for all new patients. After 2013 (shown as a gap in the graph) childhood case notification include all new and relapse cases irrespective of case type.

Both the End TB strategy and the UN Sustainable Development Goals provide a lot of opportunities for children on prevention, hopefully also in research and development, and the patient centred TB care ,which is equally important for children (Figure 2)

Of the top 10 indicators to monitor the implementation of the End TB strategy, which are also included in the Stop TB partnership Global Plan, two are potential game changers:

- LTBI treatment coverage
90% or more of children who have been exposed to TB receive preventive therapy
- Contact investigation coverage
90% or more of people in close contact with all people diagnosed with TB should be evaluated for TB

Figure 2: People centred TB care



The Treatment Action Group started tracking *paediatric* TB research and development (R&D) spending in 2010. The actual paediatric TB R&D spending is tracked against the \$200 million target for 2011–2015 published in the Roadmap for Childhood Tuberculosis. The Global Plan to End TB includes some paediatric Preventive therapy – DS and DR

- Shorter treatment regimens
- Second line and new drugs – PK and safety

Table 1 presents the highlights of activities to address childhood TB in 2015.

Table 1: Highlights of activities to address childhood TB

| Area | Activity |
|---|--|
| Technical assistance | During 2015 technical assistance on TB in children has been provided to a number of countries: Sri Lanka, Pakistan NTP review, Bangladesh, Nepal, India – JMM, China – ToT, Viet Nam and the Philippines |
| Childhood TB as an integral part of regional TB meetings | <ul style="list-style-type: none"> • Childhood TB consultation for the African region, April 20-21, Johannesburg • Eastern Mediterranean NTP Manager's meeting, Sept 6-8, Cairo • Regional Meeting on child TB in the Americas, October 21-22, Brasilia • South-East Asian Regional NTP meeting, October 26-30, Colombo • Regional consultation on child TB in European Region, November 11-15, Copenhagen • Western Pacific Regional NTP manager's meeting – postponed to Q1, 2016. |
| STEP TB project | <ul style="list-style-type: none"> • The launch of new dispersible FDCs for treatment of children with drug-susceptible TB on 1st December 2015. • A manufacturer has been identified – 15 USD per course • WHO collaborating with TB Alliance and UNICEF. |
| Development of tools (guidelines, training material etc.) | <ul style="list-style-type: none"> • Framework for addressing childhood tuberculosis in the African Region for National TB Programmes (WHO AFRO) • Desk guide for the management of tuberculosis in children (The Union) • Management of MDR-TB in children: a field guide (The Sentinel Project) • The Union Childhood TB learning portal. The portal supports the development of knowledge, skills and networks for those involved in the prevention, diagnosis and management of children with TB <ul style="list-style-type: none"> • Childhood TB for health care workers – an online course • To come in 2016/17: Facilitator guide for online training • Childhood MDR-TB for Healthcare Workers: An Online Course • Policy brief: Post exposure management of multidrug-resistant tuberculosis contacts: Evidence based recommendations (Harvard Medical School). |
| Other activities of importance to childhood TB: | <ul style="list-style-type: none"> • WHO consultation on research for TB – Stockholm, Nov 2014 • World TB Day 2015 – launch of e-learning course • Ethics meeting, May 2015, Switzerland • STAG TB, June 2015, Geneva – session on child TB • Global Health Practitioner Conference, Washington, October • KNCV – child benchmarking tool developed • NIH new diagnostics - SOPs • TAG's annual pipeline report • Advisory Panel for Global TB Alliance, NY |

3. Global developments in childhood TB: update on treatment trials and on progress in linking with RMNCAH services

Update on planned and ongoing paediatric trials - Anneke C. Hesselning

There is a huge need for research in paediatric TB. However, a lot is happening as compared to a few years ago. We know that if children are diagnosed they will in general do well and respond well to treatment with the exception of TB meningitis. One aspect that is unique is the spectrum of disease in children which leads to many unique trial design issues.

Table 2 below outlines research areas, gaps and priority studies for childhood TB

Table 2: Overview of research areas, gaps and priority studies for childhood TB

| Research Area | Gaps for children | Priority studies |
|---------------------|---|---|
| DS-TB | <ul style="list-style-type: none"> • PK/safety first-line drugs at higher doses, esp. infants, HIV+ • Optimal treatment for TB meningitis • Treatment shortening DS-TB • Rifampicin dose optimization | <ul style="list-style-type: none"> • PK studies first-line drugs at higher doses • PK/efficacy study in children • SHINE, nested PK |
| DR-TB | <ul style="list-style-type: none"> • PK/dosing second-line drugs (FQ, aminoglycosides, linezolid) • Injectable sparing shorter regimen • New drug PK and safety (bedaquiline, delamanid, PA-824, sutezolid) | <ul style="list-style-type: none"> • Modelling existing data, testing doses predicted to achieve PK targets • Non-inferiority trial • PK/safety studies bedaquiline, PA-824, DLM, BDQ and combinations |
| Co-treatment TB/HIV | <ul style="list-style-type: none"> • Super boosting LPV/r in young children taking HRZE • EFV-based regimen in children < 3 years • INSTI-based ART with standard TB drugs (HRZE) | <ul style="list-style-type: none"> • Super-boosted PI with HRZE • EFV+HRZE in slow CYP2B6 genotype • RAL or DTG-based ART with TB drugs |
| LTBI | <ul style="list-style-type: none"> • Safety/tolerability/PK once-weekly INH/RPT regimen for youngest children • DDI with ART • MDR LTBI | <ul style="list-style-type: none"> • RPT dose for children under 2 for weekly INH/RPT; tolerability/bioequivalence child-friendly formulation • Efficacy and safety of long-term use of fluoroquinolones |

A major area for trials being planned is MDR-TB. The burden is enormous, however children do well but current treatment are not patient friendly and are toxic. It is essential that we can improve treatment for the future. Main methodological challenges are how to make decision on including children in the treatment. A report is planned for next year on what the new regimens could look like.

More child friendly formulation for prevention is also urgently needed. Three big trials are planned on prevention of MDR-TB. However, major issue for the trials are the drug formulations.

A detailed update on the research included in the presentation is found in Annex 3. The presenter thanked the partners in research, stressing the need for even better collaboration and more partnerships. It was stressed that part of the role of the international communities community is to partner in research to benefit children and their families.

Childhood TB activities in UNICEF (including overview of training opportunities) – Anne Detjen

How can UNICEF help to improve case detection for TB in children and provide access to the new FDCs as well as provide preventive services?

UNICEF's mandate is to promote the rights and well-being of children, guided by the UN Convention on the Rights of the Child. UNICEF is present in 190 countries and has 7 regional offices. The country offices operate within a 5-year country programme of cooperation with host governments. There are also specialized offices, like the supply division, that manage vaccines and other commodities. The programme division at HQ provides technical leadership and guidance, supports the country offices to support national programs to scale-up proven interventions, and manage and disseminate programme knowledge and experiences.

The UNICEF goals are to improve child health and survival through community case management and district health systems strengthening. Integrated community case management (iCCM) is an effective strategy for scaling up interventions at the community level. iCCM consist of a key set of interventions delivered by Community Health Workers (CHW), focusing on main killers of children: pneumonia, malaria and diarrhoea.

Childhood TB has not had a prominent place on the UNICEF agenda and it has become clear that the organization need to address childhood TB in a more comprehensive manner. TB has to enter in the 5 year programme collaboration with host governments. The iCCM is an ideal platform for TB interventions e.g. case finding and prevention. Integration of management of childhood TB needs to start where children at risk of TB access health care that is at the community level. At the same time it is essential to make sure that capacity to diagnose childhood TB is decentralized and not reserved to tertiary care. All aspects of the system need strengthening, including the referral system.

The UNICEF /WHO material for community health workers was further adapted in 2014. The material covers caring for the new-born at home, caring for the sick child in the community (iCCM), and caring for the child's healthy growth and development. Currently, childhood TB is not well integrated with other child health services. While there are already rather good data on some interventions for child TB at community level, there are also challenges to programmatic scale-up: TB is not the only disease that wants to use the community platform – it is 'yet another one'. The larger question is therefore:

what is the best package for a CHW in a given setting, what role does/should TB care play? Which intervention to prioritize? Who coordinates, pays, and supervises?

How can we best integrate TB and other conditions into the existing community platform? What is the operational feasibility? Can we maintain quality? What management and reporting tools are needed? How can we develop comprehensive training approaches? How can we harmonize M&E? What referral systems are needed? How to strengthen the preparedness of receiving facilities? And what are the costs, to the health system and to patients. Ultimately, as multi-disciplinary team – what is the best package of care at the community level?

Figure 3: The community platform – opportunities in a complex system

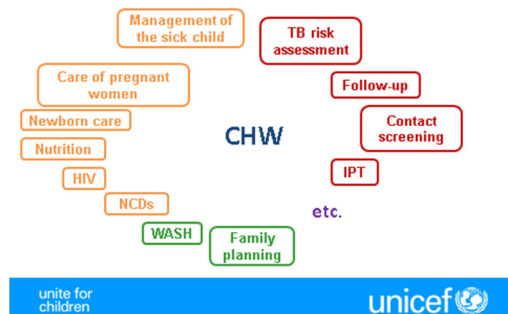
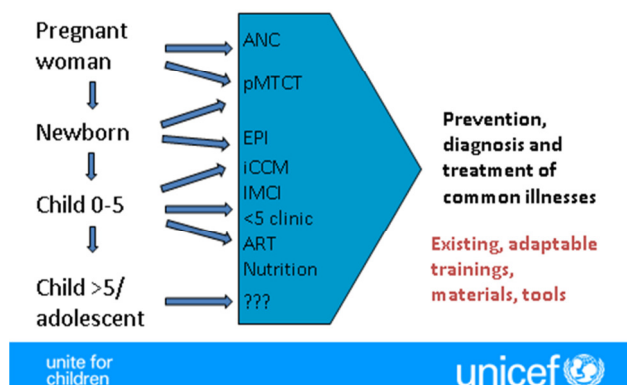


Figure 4: Many opportunities for linking TB to existing approaches along the MCNH continuum of care



There is clearly a need to build on existing initiatives and to learn from their approaches/successes/challenges. It is essential to start with the most basic and obvious interventions for TB as well as to ensure harmonization and coordination of efforts at all levels, by all stakeholders. There is increased agreement and commitment to integrate and utilize the community platform – at least among TB

stakeholders, but MNCH stakeholders are increasingly realizing the need to address childhood TB on a comprehensive and holistic way.

The TB community needs to engage UNICEF at country level. TB is new in UNICEF and there is a call for all country staff to start integration of TB into programme activities. We all need to do advocacy to move TB beyond the TB community. Advocacy is needed to increase the TB presence in the MNCH space, e.g. task forces, TWGs, conferences and publications, as well as to bring MCH people in to TB space to identify joint challenges and benefits and funding opportunities.

Integration has been encouraged by the Global Fund (GF) Board for some time. In 2010 the GF board meeting recommended that “Exploring options to maximize synergies with maternal and child health, the Board strongly encourages Country Coordinating Mechanisms (CCMs) to identify opportunities to scale up an integrated health response that includes maternal and child health in their applications for HIV/AIDS, TB, malaria and health systems strengthening.” The New Funding Model presents a key opportunity for such integration.

Lastly an update on childhood TB training initiatives was provided, see table 3 below.

Table 3: Update on childhood TB training initiatives

| Training initiative | Status |
|--|--|
| Childhood TB for Healthcare Workers: An Online Course | <ul style="list-style-type: none"> • 538 users have started the online course <ul style="list-style-type: none"> – 23% (123 users) have completed the course – 194 users have downloaded the offline course – 265 users registered but never downloaded the offline course or started the online course |
| Supporting online training (K. Du Preez, L. Du Plessis, A. Hesselings) | <ul style="list-style-type: none"> • The Desmond Tutu TB Centre, with funding from USAID TB CARE II, piloted the course in the Nelson Mandela Metro areas in the Eastern Cape Province of South Africa <ul style="list-style-type: none"> – The facilitation only included provision of computer centers, help with online course login, etc. • Almost 300 primary care nurses were trained using the course on a self-study basis |
| To come in 2016/17: Facilitator guide for online training | <ul style="list-style-type: none"> • Goal: to apply concepts learned in the online course to one’s work setting in order to improve the care of children with TB • Provides information necessary to lead a facilitated session • Can be adapted to different practice locations • Organized by module and follows format of the online course |

The discussion that followed highlighted the importance of linking research with implementation and how the information emerging from research is used including how it can be used in training.

The discussion then focused in ways to strengthen collaboration with services addressing malnutrition in children. The iCCM task force is reviewing opportunities to include TB screening in the nutrition space. Management of pneumonia is now part of the community packages and this could also be used as a vehicle for TB. The Sustainable Development Goals that were approved last September give a new platform from which we can work to make sure TB is included in implementation of child survival strategies. We also have to advocate for health system strengthening, which is a key UNICEF strategy. It was also suggested to establish a small internet group to discuss how we can better link with nutrition. More discussion is also needed at country level to strengthen collaboration between NTPs and UNICEF on childhood TB.

Finally the issue of shortages of BCG vaccine and tuberculin was discussed. A number of factors contribute to the shortage: the demand has increased, there is a lot of vaccine wastage, and there are very few manufacturers. The Childhood TB subgroup has discussed the problem and it has been felt we underestimate BCG as a first line of defence. A question was raised whether the group should make a joint statement, and it was agreed that such a statement would be drafted.

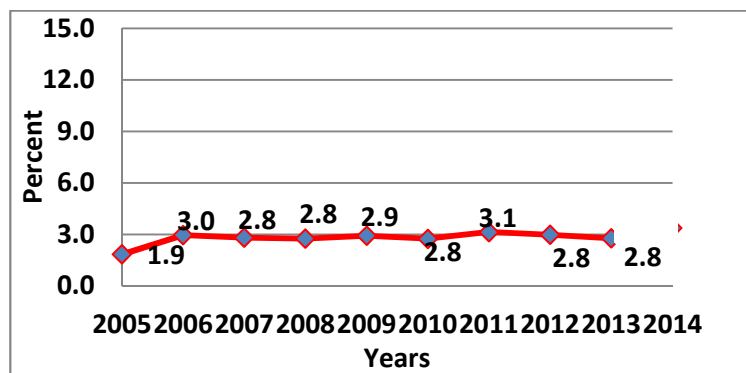
This also brought up questions related to the lack of a diagnostic tool for TB at community level. Until the issue of diagnosis of children in the community is solved (relevant tools developed), the community constantly will have to identify children with risk of TB and refer to higher levels in the health system. Thus, strengthening the collaboration between UNICEF, WHO, NTPs and the paediatric societies will facilitate the diagnosis and management of TB in children.

4. Country experiences in scaling up childhood TB activities

Increase in the child TB detection rate through capacity development: Bangladesh experience – Shakil Ahmed

Based on estimates in the Global TB report 2015 childhood TB accounts for over 10% of the total estimated cases of TB. Among the 22 High Burden Countries the figure varies between 1-10%. Figure 6 below shows the trend in case detection of child hood TB in Bangladesh between 2005 and 2013.

Figure 5: Pre-project trend in case detection of childhood TB



An assessment showed that the diagnosis of TB in children is considered difficult by medical practitioners and in general the clinical capacity to diagnose TB in children among doctors and other health care workers was low. In addition there was a lack of community awareness with regards to childhood TB.

A joint project between the Bangladesh Paediatric Association (BPA) and TB CARE II was developed to address the identified problems. Project implementation started in November 2013. The two strategic interventions of the project were the development of training materials and aids and the development and implementation of program on capacity development. Training material was developed (Table 4) and the subsequent trainings were completed in July 2014. The Dhaka Division was targeted for the first trainings and health workers in 17 districts and 123 UHCs were trained (Table 4).

Table 4: Development of training material

| Developments | Year |
|--|-----------|
| National Guidelines-1 st edition | 2012 |
| Second Edition- Finalized | Sept 2015 |
| Training modules for physicians | 2012-2013 |
| Facilitator's guide | 2012-2013 |
| Flip Chart for Health Care Workers | 2013 |
| Interactive training CD for GP | 2014 |
| Three teaching Video: <ul style="list-style-type: none"> • Mantoux Test • Gastric aspirate • Examination of a child with TB | 2014 |

Table 5: Persons trained

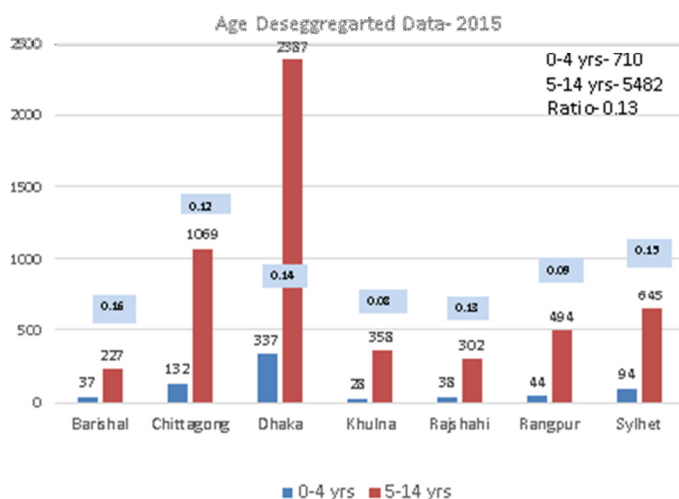
| Participants | Numbers Trained |
|--------------------------|-----------------|
| Doctors (4-day training) | 581 |
| GP (1-day orientation) | 544 |
| Facilitators (4-day) | 39 |
| HCW | 8358 |
| Others | 43 |

Data analysis for Dhaka division shows that the number of notified cases of childhood TB has increased markedly since the implementation of the project and that the increase is persisting (Table 6). However, the increase is mostly in the age group 5-14 indicating that there are still remaining problems in the diagnosis of TB in very young children (Figure 6).

Table 5: Childhood TB case detection in Dhaka Division 2010 to 2015

| Year | Child TB case | % of Child TB |
|----------------|---------------|---------------|
| 2015 (30 sept) | 2787 | 5.09% |
| 2014 | 2879 | 4.31% |
| 2013 | 2299 | 3.55% |
| 2012 | 2187 | 3.59% |
| 2011 | 2119 | 3.74% |
| 2010 | 1849 | 3.26% |

Figure 6: Notification by age group by division



The capacity development program needs to be scaled up in other divisions of Bangladesh. This should include an increased emphasis on contact investigation with trained HCW to address case detection in the 0-4 age group. Scale up started in Sylhet division in October 2015 and should be completed in June 2016. For long term sustainability of the training activities BPA will work with the government to have the trainings incorporated into government plans.

Implementation of the KNCV benchmarking tool for Childhood TB policies and practice: experiences in Vietnam – Connie Erkens and Huong Thien Nguyen

The Benchmarking tool for childhood TB (developed by KNCV Tuberculosis Foundation) is a self-assessment tool with the purpose to identify policy gaps for planning purposes. The tool provides insight in the place of childhood TB in national TB policy; the appropriateness of the procedures to identify TB in children; the quality of case management of children with TB; the appropriateness of data collected on childhood TB; and the actions that need to be taken to improve approaches on childhood TB. The tool should be used preferably with all partners and stakeholders involved in the diagnosis and management of children with tuberculosis. When used it also contributes to consensus building on priorities, streamlining of activities and planning. If used periodically, it can be used for monitoring and evaluating and measuring progress. The tool is available in a word and in an excel version.

The Benchmark tool is divided into two sections: Part A has as summary of routine TB surveillance data for children; part B lists the 12 standards with their associated benchmarks. The standards are aligned with the latest WHO policies and are based on the second edition of the “WHO Guidance for national Tuberculosis programmes on the management of tuberculosis in children (2014)”.

The standards in the Tool are:

1. Political commitment
2. Childhood TB coordination and stakeholder engagement
3. Overall technical strategy
4. Engagement of all providers
5. Primary prevention
6. Contact investigation
7. Preventive treatment policy and practice
8. Childhood TB diagnosis
9. Treatment
10. Recording and Reporting
11. Human Resources for childhood TB
12. Enabling environment & patient centred care

Each standard will be assessed using three levels as illustrated in Table 6:

Table 6: Criteria for assessment

| Standard | Rule |
|-----------------|--|
| Met | All benchmarks are met |
| Not met | None of the benchmarks were met |
| Partially met | At least one but not all benchmarks were met |

An illustration of part B of the Benchmark tool is found in Table 7 below.

Table7: Example of part B of the Benchmark tool

Part B: Standards and benchmarks for childhood TB

For each standard, please assess whether the system is able to satisfy the associated benchmark(s). Indicate 'Met', 'Partially Met' or 'Not Met' in the Conclusions column. Indicate 'Met' for a standard if all associated benchmarks are satisfied. Indicate 'Partially Met' if not all is satisfied. Indicate 'Not Met' if none of the associated benchmarks is satisfied. Describe the current situation for each standard. If 'Partially Met' or 'Not Met', please describe actions or next steps agreed to improve the quality of this standard. It would be partner leading this action and the timelines for completion.

| STANDARD | BENCHMARK(S) | DESCRIPTION OF CURRENT SITUATION | CONCLUSION |
|---|--|----------------------------------|--|
| 1. Political commitment | | | |
| 1.1 There is evidence of political commitment for childhood TB | <ul style="list-style-type: none"> Childhood TB is included in the national strategic plan to prevent and control TB The national strategic plan includes sections on prevention, monitoring&evaluation, surveillance, operational research, diagnosis, treatment and technical assistance for childhood TB There is earmarked budget available for all components of childhood TB The budget for childhood TB is fully funded | | <input type="checkbox"/> Met <input type="checkbox"/> Partially met <input type="checkbox"/> Not met |

The process using the tool involves four steps:

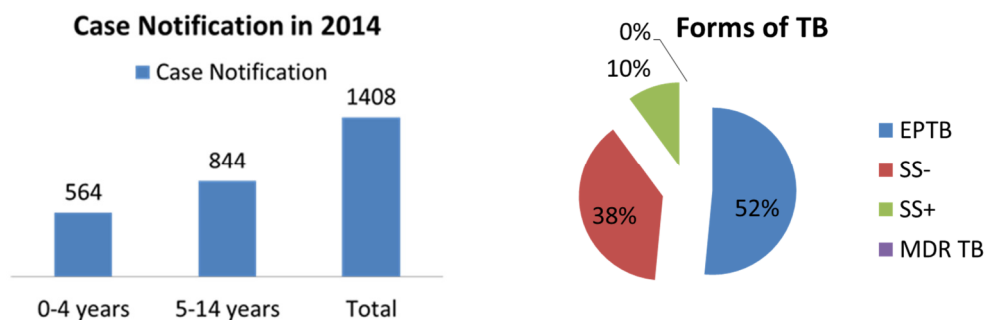
- Check state of affairs in the country against the benchmark
- Indicate if standard is met, partially met or not met
- Discuss what steps need to be undertaken to meet the benchmark
- Agree on who and when to take action

More information on the Benchmark tool is available at: www.kncvtbc.org (search for benchmark childhood TB policies, practice and planning).

The Benchmarking tool was used in Vietnam in March 2015 with the participation of NTP, KNCV, Head of Childhood TB group, NTP and stakeholders (HIV program, CCHD, Women Union, Farmer Union, WHO, FHI, KNCV, CHAI, and PATH).

An example of part of the result of data collection for part A of the tool is shown in figure 7 and examples of the findings and planned actions for standards are found in table 8.

Figure 7: Part A: Indicators for assessing activities to address childhood TB



Childhood TB as proportion of total TB: 1.4%

Treatment success rate : 92% (sample from 179 children in 3 provinces, not routinely reported)

Indicators that are not routinely reported:

- Treatment outcomes per age band;
- Percentage of children tested for HIV;
- Number and percentage of HIV positive children with TB;
- Number and percentage of children with TB known to be HIV positive who receive ARVs;
- Acceptance and completion rates of IPT.

Following the presentation a question was asked how case detection could be improved. The presenter commented that improving the diagnostic process in general will improve the child diagnosis. Efforts will be made to increase the contact screening. In Vietnam commune and district level staff is used. When a sputum smear positive TB case is confirmed at district level should ask about children and make contact with the commune health post. The commune health worker should invite the family for screening.

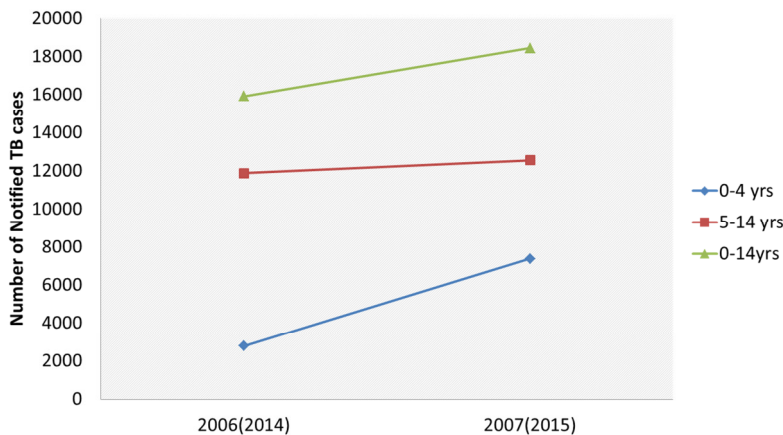
Table 8: Examples of the result of the application of the tool – selected indicators

| Indicator | Outcome of assessment | | Actions planned |
|-------------------------------------|--|--|--|
| | | | |
| 1. Political commitment | <ul style="list-style-type: none"> Childhood TB included in NSP NSP 2016 – 2020 childhood TB components are budgeted | <ul style="list-style-type: none"> Currently no earmarked funding For 2015 budget not fully approved: lack of funding for training and expansion of activities beyond early implementing provinces | <ul style="list-style-type: none"> Try to get approval for childhood TB plan 2016 – 2020 Try to get approval for all earmarked budget |
| 2. Stakeholder engagement | <ul style="list-style-type: none"> There is a formal childhood TB working group There is a NTP focal person for childhood TB | <ul style="list-style-type: none"> Not all relevant stakeholders are represented in the working group | <ul style="list-style-type: none"> For 2016 the paediatric association, representatives from mother and childcare and other relevant associations will be invited to the working group |
| 3. Overall technical strategy | <ul style="list-style-type: none"> Guidelines, SOP and strategy has been updated following latest WHO guidelines Technical assistance has been identified and planned | <ul style="list-style-type: none"> New strategy is not yet implemented in all provinces (currently in 10 provinces) | <ul style="list-style-type: none"> Continue implementation and training on childhood TB strategy: by the end of 2020 in all provinces Child contact screening and management has been scaled up countrywide : INH, registers and guidance distributed to all communes since Q1 2015 (current status of implementation unknown) |
| 4. Childhood TB diagnosis | <ul style="list-style-type: none"> Diagnostic algorithms are updated New clinical algorithm for diagnosis at district level | <ul style="list-style-type: none"> Indicators of HIV testing are currently unknown Diagnosis at district level is limited Limited capacity of CXR reading at district level | <ul style="list-style-type: none"> Routinely R&R about HIV testing in children More training to increase diagnosis at district level |
| 5. Treatment | <ul style="list-style-type: none"> Treatment guidelines are up to date Ambulatory care is provided as soon as possible DOTS is available | <ul style="list-style-type: none"> Paediatric formulations are not available No fixed dose combination of FL drugs available | <ul style="list-style-type: none"> If fixed dose combinations will be available for paediatric use they might be introduced |
| 6. Human resources for childhood TB | <ul style="list-style-type: none"> Training curricula have been developed In 10 provinces TB staff and paediatric staff at provincial and district level and HCWs at commune level have been trained | <ul style="list-style-type: none"> No training yet at commune level No training yet in other provinces | <ul style="list-style-type: none"> Budget for training has been planned in the 2016-2020 plan but has not been approved yet GF NFM Concept Note 2015-2017: Rejected training for HCWs at commune level |

Ethiopia Childhood TB Roadmap – Blen Ayele

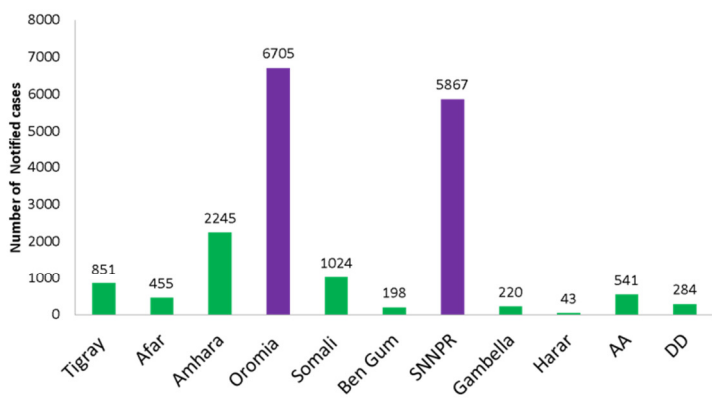
The number of cases of childhood TB reported in Ethiopia in 2014-2015 is shown in Figure 8 below. The number of TB cases notified between 0-4 age group still remains low compared with 5-14 age groups. The 13% increment shown in the green line in the figure below can be explained by the introduction of new molecular diagnostic technologies.

Figure 8: TB among Children in Ethiopia.2014-2015



Among the 4 big regions in Ethiopia, 2 of them report the highest numbers of TB cases among children. Case notification in the capital city still remains low.

Figure 9: Notified TB cases among Children by Regions in Ethiopia, 2015



The National Strategic Plan (NSP) was revised in 2013 covering the period from 2013-2020. Diagnostic algorithms were included in the national TBL and TB/HIV guidelines and training manuals, data on case finding was disaggregated by age and type of TB disease and trainings were organized for health care workers at PHU and referral centers.

Activities to address childhood TB at national level include:

- Incorporation of childhood TB initiative in NSP 2013-2020
- Development/adaptation of guidance on the management of childhood TB
- Recommendation on Xpert MTB/RIF assay as primary test for screening and diagnosis of MTB and DR TB
- Procurement of paediatric anti-TB drugs formulations
- Started to capture childhood TB data on national integrated disease reporting system /HMIS
- Organization of continuous medical education (CME) and capacity building activities for health care workers on childhood TB

Despite progress there are remaining gaps and challenges. The integration with other health programs is ineffective and the IMNCI/iCCM lacks focus on management of TB in children. There is inadequate participation of various key stakeholders and capacity building efforts often does not address HCWs at key entry points. The implementation of preventive interventions is suboptimal and there is no format for contact tracing activities in the community.

The “Childhood TB roadmap” (published in 2015) intends to address gaps and guide implementation of prioritized interventions both at health facility and community-levels. The aim is to optimize integration of childhood TB prevention and care activities into the standard child health models of care.

Health workers at all levels will have specific roles and responsibilities for identification, diagnosis, referral and follow-up of children. The goal is to move towards zero TB death in children and the objectives are to (i) decentralize comprehensive childhood TB services to Primary health care level; (ii) strengthen hospital based childhood TB, TB/HIV and DR-TB services; and (iii) establish centre of excellence for paediatric services.

The national strategies to reach the objectives are to:

1. Strengthen the program management capacity and local expertise
2. Strengthen the information flow and use for decision making on the burden of TB in children
3. Engage key stakeholders and promote partnership
4. Community and facility level integration of childhood TB service
5. Focus on critical opportunities for interventions
6. Address children with special situation or risk factors for TB

National strategies towards TB free children in Ethiopia also include the establishment of a national TWG and capacitating coordination at regional health bureaus, providing trainings for HCWs. The HMIS system still lacks age-specific information on outcome of treatment and performance on preventive interventions, which will need to be addressed. It is essential to promote community ownership as the main strategy of NTP through empowering of the community to contribute in case finding, referral, and treatment support and follow-up. Even though one of the components of community TB care is identification of child TB contacts and screening, the current practice of active childhood TB case finding needs attention and improvement.

There are also recommended platforms for Integration of childhood TB services. Children with TB often do not present, and are not managed, within the context of specific TB care services but rather in the context of services that provide care to the sick child, including maternal and child health services and HIV care services. An important step towards improving the prevention and management of TB in children is the provision of integrated care at health facility level. TB should be considered in any sick child with other common illnesses especially in high TB burden countries. Recommended entry points for integration of one of more components of childhood TB services within the current health care delivery include integration of TB screening services in maternal services such as prevention of mother to child transmission (PMTCT), and ante natal care (ANC) & Health baby clinics like EPI. IMNCI/iCCM has also played key role in decentralization of childhood health care services down to the primary health care level (i.e. Health centers and health posts).

Critical steps to integrate TB screening questions in IMNCI/iCCM flow charts are:

- At initial evaluation of sick child
- At follow up evaluation of not improving child
- At evaluation of malnourished child

Children with HIV infection may carry increased risk for developing TB disease due to the immune-compromised state; therefore intensified case finding should be one of the mainstays for TB/HIV collaborative activities. TB should also be considered in a malnourished child who is not responding to standard nutritional therapy or in child who has failure to thrive or growth faltering.

Achievements to-date includes the establishment of the national childhood TB Technical Working Group (TWG). TWG composed of national TB and HIV programs, child health program, Ethiopian Paediatric Society (EPS), private sector program, developmental partners, and donors. Consultative workshop was conducted with all RHB coordinators and responsible stakeholders. Training material for HCWs has been prepared and training is planned to be conducted before end of December. Training mainly focuses on HCW serving in under 5 clinics and HCWs working PHU, CME is planned to be conducted for HCWs working in referral centers. The IMNCI is under revision and will include integrated required algorithms. The required budget has been mobilized and there are plans to conduct operational research to assess validity of developed tools, diagnostic algorithms, flow charts and to evaluate the impact of interventions and to identify best practices from local and international experiences.

In the discussion following the presentation Ethiopia was complimented for the substantial progress made. Ethiopia has a unique position as the community Health Extension Workers (HEW) provide a platform to link different interventions and to bring patients to health services. The new diagnostic algorithms including use of Xpert MTB/Rif platform, training at PHC units and referral are intended to address identified gaps and challenges. The community ownership is main push of the NTP as the main aim of the “roadmap” to decentralize TB child care to primary level, IMNCI/iCCM and to capacitate the HEW in clinical diagnostic capacity. Providing IPT in children is a challenge and will be piloted to determine how to best integrate. The MCH entry point shows different avenues for

screening sick children. It also highlights the need to ask for the health status of children when family members are sick.

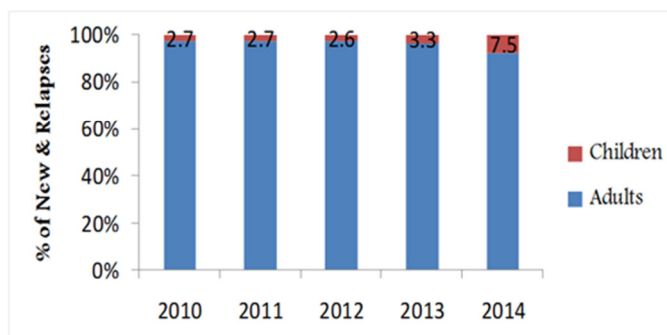
Updates on childhood TB in Uganda – Moorine Sekadde-Kasirye

Based on the 2014 census the total population of Uganda is about 35 million people; nearly half of the population are children under 15 years. According to the Global TB report 2015 TB incidence is 161 new and relapse TB cases /100,000 per year. The HIV prevalence is 7.3% (0.7% in children under five years) (Uganda AIDS Indicator survey 2011) and the TB/HIV co-infection 45%.

The trend in childhood TB cases and the disruption of cases is shown in figure 10. The increment in recent years is attributed to the revision of the recording tools. The majority of the cases are PTB, and clinically diagnosed. Most EPTB is adenopathy (the R&R forms do not capture this info). Estimates of childhood TB case detection rate indicate that only 38 – 50% of childhood cases are detected, compared to the adult case of 72% (Low and High estimates of 15 – 20% taken from Dodd et al (2014).

Figure 10: Trend in childhood TB and distribution of cases

Trend in childhood TB



Distribution of TB disease in children (New and Relapses in 2014)

| Child TB Disease Classification | Age group in Years | | |
|---------------------------------|--------------------|--------------|--------------|
| | 0 - 4 | 5 - 14 | Total (%) |
| Bacteriologically Confirmed PTB | 96 | 589 | 685 (21%) |
| Clinically Diagnosed PTB | 1084 | 801 | 1885 (57%) |
| EPTB | 326 | 420 | 746 (22%) |
| Total | 1,506 | 1,810 | 3,316 |

Childhood TB/HIV indicators (2014) and the treatment outcomes for children for the first half of the year 2014 are shown in table 9. It is highly possible that the children with TB/HIV are not diagnosed (given the complex presentation) or die before diagnosis. With regards to the treatment outcomes, the majority are treatment completed.

Table 9: Childhood TB/HIV indicators and the treatment outcomes for children

| Childhood TB/HIV indicators | | | | Treatment outcomes | | | |
|-----------------------------|--------------------------|----------------------|------------------------|--------------------|--------------------------------------|--------------------------------|-------------------------|
| TB/HIV Indicator | Childhood TB performance | National performance | National Target (2020) | Treatment Outcome | Performance in childhood TB (N=2603) | National performance (N=46176) | National Targets (2020) |
| TB cases tested for HIV | 73% | 95% | 100% | Treatment Success | 64% | 73% | 90% |
| TB/HIV co-infection | 34% | 45% | Not determined | Died | 6% | 8% | <5% |
| TB/HIV on CPT | 96% | 98% | 100% | Treatment Failure | 0% | 1% | Not determined |
| TB/HIV on ART | 79% | 81% | 100% | Lost to Follow Up | 10% | 11% | < 5% |
| | | | | Not Evaluated | 20% | 7% | 0 |

The national response towards childhood TB includes six strategic approaches. They are illustrated in table 10 together with the current status of implementation of key activities.

Table 10: The national response to childhood TB

| Strategic approach | Status of implementation |
|--|---|
| 1. Establishment of a childhood TB Technical Working Group | <ul style="list-style-type: none"> • NTLP led • Initiated in 2013 • Provides a consultative and consensus forum for the NTLP on the implementation of childhood TB activities |
| 2. Assessment of health facility capacity to manage childhood TB | <ul style="list-style-type: none"> • 112 public and private facilities assessed • Case notification reduced with decreasing level of health care • Lower cadre health workers are shouldering Paediatric TB diagnosis • Limited health worker knowledge, skills, and confidence • Limited access to standard recommendations |
| 3. Strengthening the M&E component for childhood TB | <ul style="list-style-type: none"> • Introduction of indicators for childhood TB • % of children among all forms of TB notified • # of close contacts of PTB cases provided IPT • Revision of the R&R tools • Inclusion of interventions targeting childhood TB in the NSP 2015-2020 |
| 4. Development of stand-alone guidelines | <ul style="list-style-type: none"> • Consultative approach • Guided by the childhood TB TWG |

| | |
|---|--|
| | <ul style="list-style-type: none"> • Draft of the first edition of the guidelines is in the final stages of approval at the MoH |
| 5. Development of a competency based curriculum | <ul style="list-style-type: none"> • Consultative approach • Process was guided by a local consultant with expertise in competence based training • Focuses on the knowledge required to perform a particular task and how to perform that task. |
| 5. Integration of TB into existing child health care services | <ul style="list-style-type: none"> • Intervention included in the NSP 2015-2020 • Implementation guidelines for TB/HIV integration are in the final stages • Discussions ongoing for TB/RMNCAH & TB/iCCM integration • DETECT Child TB project |

In collaboration with the Union, a new project has been launched to **decentralise TB services and engage communities to transform lives of children with TB – Detect child TB**. The project aims to strengthen health facility and community level health care delivery to improve childhood TB, case finding, treatment and prevention. The project areas are Wakiso (peri-urban) and Kabarole (rural).

A baseline survey conducted at the beginning of the project showed that TB in children accounted for only 7.4% and 10.8% of all TB cases diagnosed in Kabarole and Wakiso districts respectively. Lower level health facilities had minimal involvement in diagnosis and treatment of children with TB. Over 95% of TB cases in children from both districts were managed at hospitals. Only 60% of all children diagnosed with TB in the previous year had successfully completed their treatment. None of the public health facilities carried out contact tracing, which is important to find and treat child TB cases. And only 17% of health facilities provided Isoniazid preventive therapy to children.

Following the project implementation progress can already be noted. Below are listed the key achievements (January to September 2015):

- 299 health facility-level health care workers have been trained on childhood TB, bringing on board 78 lower level health facilities providing Childhood TB prevention, diagnosis and treatment.
- 173 community health workers (Village Health Team) have been trained to do household contact tracing, support adherence to treatment and conduct health education.
- A 40% increase in children diagnosed with TB was observed in the two districts in the reporting period July-September 2015, in comparison with the previous quarter. A higher increase was registered in Kabarole (60%) compared to Wakiso district (23%).

The early results clearly demonstrate that change is possible. However, while major progress has been made there are outstanding challenges:

- Human resources: Limited knowledge and skills. Health workers involved in TB are also being targeted by other “diseases” – and there is need for additional collaborative planning.
- Diagnosis: Limited access to sample collection; diagnostics; sample transportation.
- Medicines: Stock outs; Short expiries; lack of paediatric formulations.

- Funding: Underfunding for TB control.
- Health service delivery: Weak referral health system.
- Community level health care delivery: Limited community awareness on Childhood TB; involvement; support for the village health teams.

The progress in Uganda is fan - dam -tastic! Robert Gie

Update on activities of the Baylor Childhood TB Center of Excellence in Swaziland – Pilar Ustero & Anna Mandalakas

The Global Tuberculosis Program at Texas Children’s Hospital and Baylor College of Medicine is a global health clinical research program focusing on TB prevention, diagnostics, treatment, immunology, and education. The mission of The Global Tuberculosis Program uses the tools of research, education, and advocacy to prevent, diagnose, and treat tuberculosis in children. The long-term goal of the program is the establishment of a network of Childhood Tuberculosis Centers of Excellence built upon Texas Children’s existing clinical infrastructure in Sub-Saharan Africa. The Global Childhood TB Program team works in four inter-related areas including disease prevention, diagnostics, treatment, and immunology. These program domains are built upon a data collection core and complemented by rigorous epidemiological and operational research. The Baylor International Paediatric Aids Initiative (BIPAI) mission is to provide high-quality, high-impact, highly ethical paediatric and family-centred health care, health professional training and clinical research, focused on HIV/AIDS, tuberculosis, malaria, malnutrition and other conditions impacting the health and well-being of children and families worldwide.

The Baylor Childhood TB Center of Excellence, Swaziland

The Baylor Global TB team works in complementary clinical, educational, and research areas to improve the health and well-being of children affected by TB in countries where Baylor works. The program aims to more effectively prevent, diagnose, and treat TB infection and disease in children to support an ultimate goal of ending the TB epidemic as targeted by the WHO.

The Global Childhood TB Program has focused on the development of research infrastructure at our African partner sites and expanded efforts to support the 8 clinical research sites located in 8 countries.

In Swaziland for every 100,000 people, 1,382 have TB, 15-30 percent of which are children. The large percentage of the Swaziland population in treatment for HIV (31 percent of 18- to 49-year-olds) also contributes to the problem. In Swaziland, childhood TB is common, but finding children with disease and treating them remains difficult. Many children under five years of age are exposed to TB in their homes, but people often forget to evaluate these children for disease or give them life-saving medicine to prevent disease even after TB is found in their parents.

The Baylor Paediatric TB Center of Excellence expands on TB services provided at the Baylor College of Medicine. The Baylor clinic was started in 2006 and TB services were incorporated in 2008. Initially focus was on diagnosis and treatment of DSTB and IPT.

In 2012, a GeneXpert machine was added through a TB REACH grant. In 2013 funding from Texas Children's Hospital led to the development of a stand-alone TB clinic, and in 2014 the NTCP, through Global Fund, allocated a digital X-ray machine. In May 2015, the program completed construction of a clinical and laboratory facility to serve as a Swazi national referral center for paediatric TB and host a broad range of translational research projects.

Since opening in 2008, the Baylor Swaziland Center of Excellence has treated more than 1,300 children for TB and tested 65,997 children for TB. A large number of children with TB come from families affected by HIV. Many have one missing parent, leaving the other parent overwhelmed with the HIV burden and responsibility for many other children. This makes diagnosis more challenging because it often requires multiple visits to different facilities.

The new TB Center offers a TB-specific facility located on the same grounds as the existing HIV center. The TB Center is uniquely designed for children with child-friendly space and advanced laboratory and X-ray equipment that allows doctors to diagnose TB in one day rather than traditional approaches that can take up to six weeks. This comprehensive, one-stop-shop brings in new resources – both technology and personnel – and provides TB services including screening, specimen collection, testing and treatment as well as IPT services. With regards to costs for services, clients have to pay for chest X-ray; however, there are free vouchers for children who need an X-ray examination.

Additionally, the TB Center serves as a training center for doctors and nurses. The in house training includes sputum induction (TOT) and gastric aspiration. The center also conducts research. A study on contact tracing found that 82,2% of children with positive screening had neither GXP nor CXR completed, indicating a need for patient support. The results of school contact tracing are found in table 11.

Table 11: Outcome of school contact tracing

| | School contact tracing |
|--------------------|------------------------|
| Total screened | 1068 |
| Screening positive | 150 |
| Tested | 135 |
| Positive GXP | 0 |

Key partners include:

- National Tuberculosis Control Program: technical assistance for childhood TB
 - Development of guidelines, pilot new programs, trainings

- Stop TB partnership: TB REACH grant
- MSF, ICAP, Darmouth, PACT
- Rocking Horse Project
- Sentinel Project
- WHO child TB working group

There are also key partners missing to date e.g. UNICEF and UNAIDS.

Additional information is available at www.globaltbprogram.org. You can also visit the program on Twitter @GlobalTB.

National case finding strategies for childhood TB in Malawi - Isaiah Dambe, NTP deputy program manager Malawi

Based on its recent prevalence survey, Malawi's TB incidence estimates have increased from 26,000 to 38,000. The incidence rate is 227/100K, TB/HIV co-infection rate 54%, case detection rate 43% and the treatment success rate 82%.

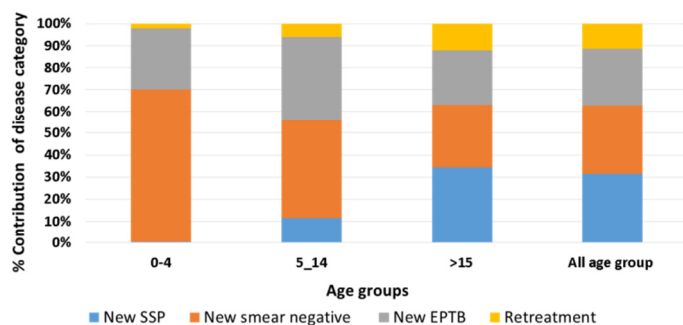
In 2014, children made up 11% of notifications in Malawi with 1,827 children 0-14 years notified. While the total TB notifications in Malawi have declined over the past 5 years, notifications of TB in children have slightly increased. The increase in paediatric TB notifications likely indicates improved case-finding and reporting, however, there are still considerable gaps in this area. The paediatric TB CDR is estimated at 40%¹, which is slightly lower than the adult CDR of 44%. This estimation has been made as follows: in 2014 it was estimated that there were 4,600 new paediatric cases of TB disease. 1,827 cases were notified among children leaving 2,773 "missing" TB cases among children.

The % of overall TB cases found in children varies widely by district, and is highest in the capital city and surrounds. Variations in age distribution and access to quality TB diagnostic services are likely to drive the differences across districts. Lilongwe and Zomba, both of which are highly urbanized districts, had the highest proportion of TB in children.

Smear-negative and extra-pulmonary TB are the most common forms of disease in children. In children 0-4 years, <1 % of the TB notifications are smear-positive, and diagnosis therefore relies heavily on clinical assessment and x-ray if available. Children 5-14 years old have a higher proportion of EP TB than any other age group, which is more difficult to diagnose (Figure 11). There is a need to elaborate on the most common forms of extra-pulmonary TB as well as on potential case finding challenges associated with EP TB.

1. ¹ Pediatric TB CDR = (# TB notifications in children)/(pediatric TB incidence); pediatric TB incidence = TB incidence * proportion of TB in children (where the proportion of TB in children was estimated to be 12% (WHO Afr region 2010 estimate)).

Figure 11: Distribution of disease type by age group, 2014



The NTP and Clinton Health Access Initiative (CHAI) conducted an assessment to understand drivers of the gap in case detection and the broader state of service delivery for paediatric TB. The objectives of the assessment were to:

- determine the extent to which current paediatric TB guidelines are being implemented in facilities;
- identify challenges that affect the quality of TB services being provided at facilities;
- understand the paediatric TB screening operations in place at facilities;
- Identify the barriers and potential solutions to increasing paediatric TB screening among clients.

Two methods were used for the assessment and Qualitative questionnaires: Head of Facility or Clinician in-charge, HTC Supervisor / Counsellor, TB, EID and ART focal person.

- Quantitative Data Collection: Register Review to measure number of children diagnosed with active TB, disaggregated by method of diagnosis.

38 facilities from the 6 districts with the highest paediatric ART treatment gap were selected for the assessment (28 health centres, 1 district hospital, and 9 rural /community hospitals). The six districts account for approximately 50% of the estimated paediatric ART treatment gap. District health management teams (DHMTs) identified facilities that had the greatest overall paediatric HIV and TB service delivery challenges. 7 of the 38 facilities selected were Christian Health Association of Malawi (CHAM) facilities. A CHAI-MoH team visited all the 38 facilities to collect the data.

Key assessment findings on paediatric TB service delivery shows that critical opportunities to identify presumptive case of TB are being missed in health facility setting.

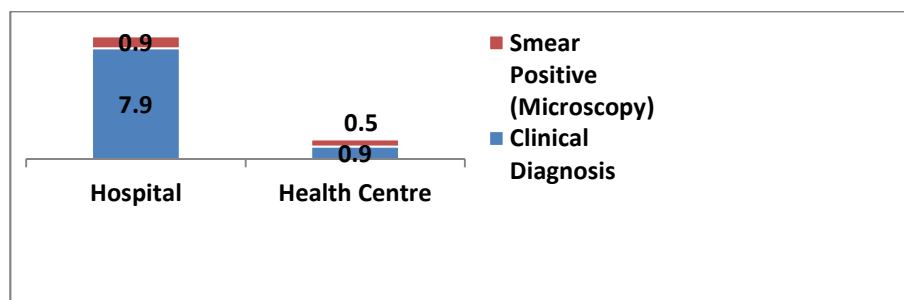
1. On the question “How do you choose children for TB screening?” 75% of respondents reported screening children who are family members of those diagnosed with TB, although there are some challenges with how this is implemented. Less than half of the respondents screen children who have been diagnosed with HIV.

2. The reliance on caretakers to bring contact children for screening undercuts the impact of this important intervention. On the question “Do you engage in paediatric TB contact tracing?” 97% of facilities responded yes. However, the majority rely on the TB index case (usually a parent or adult family member) bringing the child back for screening. Research from Malawi shows that <10% of caretakers will return (Nyirenda et al). Shifting towards more active paediatric contact tracing will lead to higher numbers of identified children.
3. Clinical diagnosis is the mainstay of case detection in children (89% of all pulmonary cases); laboratory systems struggle to support bacteriological confirmation. Most facilities (84%) where sputum collection is not available take longer than 24 hours to return sputum result to patient.

Respondents believe this is primarily due to shortage of staff at the laboratory, and to transport issues. GX is rarely used as the initial diagnostic for the majority of children. Chest x-ray confirmation is highly encouraged for clinical diagnosis.

Health centres need to refer for both Chest x-ray and GeneXpert. Given the high no-smear and smear-negative rates among children, it is a priority to increase access to x-ray and GeneXpert.

Figure 12: Avg. number of children diagnosed per facility per year by diagnosis type (18 HC, 9 hospital respondents)



4. Most clinicians (88%) interviewed believe they are not effective at providing paediatric TB services. Inadequate training is most frequently cited as the cause for ineffectiveness. There is a need to design and distribute materials that can support HCW to identify and manage TB in children, especially since diagnosis of children relies so heavily on the clinical judgement of the HCW. The need for general training materials on TB was also highlighted. Materials for paediatric TB screening were in high demand (TB screening algorithms and signs/symptoms).

Many health workers (89%) involved in TB service delivery do not have formal in-service training on TB. Among clinical officers, only 23% were trained; among medical assistants only 16% were trained; among Health Surveillance Assistants (HSAs) 11% were trained, and among Nurse

Midwife Technician (NMT) only 4% were trained. The need for training materials for HCW was also evident in other areas – for example, the lack of clarity on IPT guidelines.

A complete report of the assessment findings is available on request. Please contact louansafi@clintonhealthaccess.org.

The assessment had led to the development of additional strategies and activities to strengthen management of childhood TB. Currently the Care and Treatment Officer in NTP is responsible for childhood TB. Childhood TB is addressed extensively in national TB guidelines.

Improving performance on childhood TB is one focus of the national strategic plan (2015-2020), with emphasis on improving detection and diagnosis through integration with other child-focused departments (community through tertiary levels), prevention: improving coverage of IPT and improving capacity of health workers in management of childhood TB. The following strategies have been developed:

1. **Integrate TB into MCH settings:** the NTP will pursue integration of TB into MCH settings to increase reach. Immediate priorities include:
Introduce TB screening and referral of both mother and child:
 - a) At community level – in collaboration with iCCM, EPI outreach clinics, Community Based Maternal and New-born Care
 - b) At the primary health care level– in collaboration with IMCI, EPI Clinics, Antenatal Clinics, Postnatal clinics, U5/Child wellness Clinic, Community Management of Acute Malnutrition.
 - c) At the tertiary and secondary levels – in collaboration with Emergency Triage Assessment and Treatment (ETAT)/ Paediatric Hospital Improvement (PHI)
 - How: through iCCM, EPI outreach Clinics and Community Based Maternal and New-born Care
 - o Ensure all attendees are asked about contact with a TB patient
 - o Ensure all attendees are screened and referred where necessary
 - Who: Community Health Workers e.g. HSA, Community Health Nurses Community volunteers.
 - When: 2016 - 17
 - Funding: Challenge TB, UNICEF, Global Fund, Malawi Government
Baylor is also conducting systematic screening of TB in children's clinics.
2. **Strengthen Contact Tracing:** the NTP will also strengthen case finding through the introduction of a contact tracing SOP.
 - Guidelines encourage active contact tracing for all household contacts of pulmonary TB (sm+ and sm-) and MDR-TB cases
 - Contacts under 5 years of age and HIV-positive contacts (not on ART) are eligible for IPT
 - An estimated 1,970 paediatric TB cases could have been identified through household contact tracing in 2014 (~43% of incident cases)

- SOPs have been developed along with a new contact tracing register, training materials and forms (home visit, appointment).
- A pilot of these materials is running for 2 months through the end of January.
- Nation-wide rollout is expected to start in March 2016.

3. **Improve HCW Knowledge on Paediatric TB:** job aides and training materials will be rolled out to facilities to strengthen HCW capacity

- National guidelines will be revised and disseminated in 2016, including a paediatric section
- Paediatric TB trainings will be conducted nation-wide starting in the first half of 2016. Existing resources (Union, WHO) will be adapted for this training. Job aides will be disseminated.
- Integrated HIV/TB training packages will be developed in 2016.
- Childhood cluster documents and training materials will be revised and shared to other MoH departments/programs to integrate within their training programs in 2016.

In conclusion, the key challenges for management of childhood TB are that:

- Paediatric TB is still mainly considered to be under the domain of specialists and not for front-line health workers;
- TB diagnosis in children remains a major challenge given the lack of training on alternative sample collection methods (gastric lavage, induced sputum, etc.) and the limited availability of x-ray machines; and,
- Training in paediatric TB is very limited, from the clinician to CHW level.

However, while there are challenges we have also seen that there are opportunities:

- The focus on increased TB screening through contact tracing and screening in MCH settings should lead to greater identification of presumptive TB cases in children;
- Baylor is planning district-level gastric lavage training, which should lead to increased bacteriological confirmation of TB cases in children; and,
- Resources such as the GeneXpert Ultra cartridges and new paediatric FDCs will also improve the management of TB in children.

In the following discussion it was pointed out how it is essential to do training and teaching in a context using interactive training methods and supervision. It is difficult to break out of the traditional training methods. As had been pointed out in most of the presentations, there is a need training more staff. This is a preferred strategy for capacity building rather than depending on peer learning. The need for resources for ongoing capacity building was stressed.

5. Panel on key issues and current uncertainties in childhood TB

Systematic review and IPD Meta-analysis of treatment & outcomes of children with MDR-TB-

Elizabeth Harausz

An estimated 32 000 children become ill with MDR-TB annually worldwide². There is a limited evidence base to inform MDR-TB treatment in children - no paediatric IPD meta-analysis³. Guidelines for treatment of MDR-TB in children are extrapolated from adults. Specific paediatric considerations include paucibacillary nature of disease, broad spectrum of disease, study definitions: confirmed vs clinical cases; definition of treatment outcomes in absence of much culture data. However, children respond well to anti tuberculosis treatment (81.7% treatment success in children² vs 54% in adults⁴).

The systematic review and individual patient data meta-analysis (IPD) of treatment and outcomes in children with MDR-TB was done with the aim to:

- Inform WHO MDR-TB treatment guidelines
- Address questions specifically relevant to the paediatric population with MDR-TB:
 - Treatment success of second-line drugs;
 - Data gathered and analysed regarding severity of disease;
 - Total treatment duration (analysis pending);
 - Duration of injectables (analysis pending);

A wealth of other demographic and clinical information was also collected.

The methods and eligibility criteria for the study are listed below:

- Minimum 3 children (aged <15 years)
- Clinically diagnosed or bacteriologically confirmed pulmonary or extra pulmonary MDR-TB
- Treatment outcomes reported
- Published and unpublished data included, without date restriction.
- Controlled and non-controlled retrospective and prospective studies and case series
- English, Spanish, French and Russian
- Eligibility criteria were applied at the individual level, so that studies reporting on both adults and children could be considered eligible if they otherwise met the specified criteria.
- All cohorts containing children included in a previous systematic review and individual patient data meta-analysis of MDR-TB⁵ were considered eligible
- Excluded: studies utilizing only combinations of rifampicin, isoniazid (INH), pyrazinamide (PZA), ethambutol (EMB) or streptomycin to treat MDR-TB

² Jenkins et al. Lancet. 2014 May 3;

³ Ettehad et al. Lancet Infect Dis 2012

⁴ Ahuja et al. PLoS Med. 2012

⁵ Ahuja et al. PLoS Med. 2012

The primary analyses estimated the odds of treatment success (versus fail/relapse/death), associated with the use of each drug among patients with bacteriologically confirmed MDR-TB but without confirmed XDR-TB. The analyses were repeated on patients with clinically diagnosed MDR-TB. A descriptive analysis on toxicity was done (sparse data). Data received from sites from 18 countries. Patients were included from 6 continents, majority from Africa. Four countries (Russia, Pakistan, India and South Africa) were among the 22 high burden TB countries (Figure 13).

Figure 13: Origin of patients included in the study

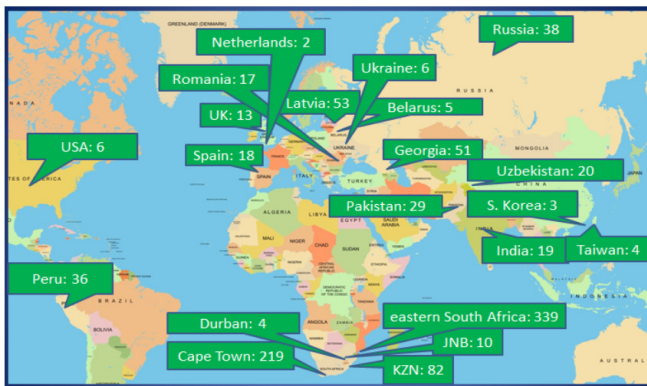


Figure 14: Overview of studies identified

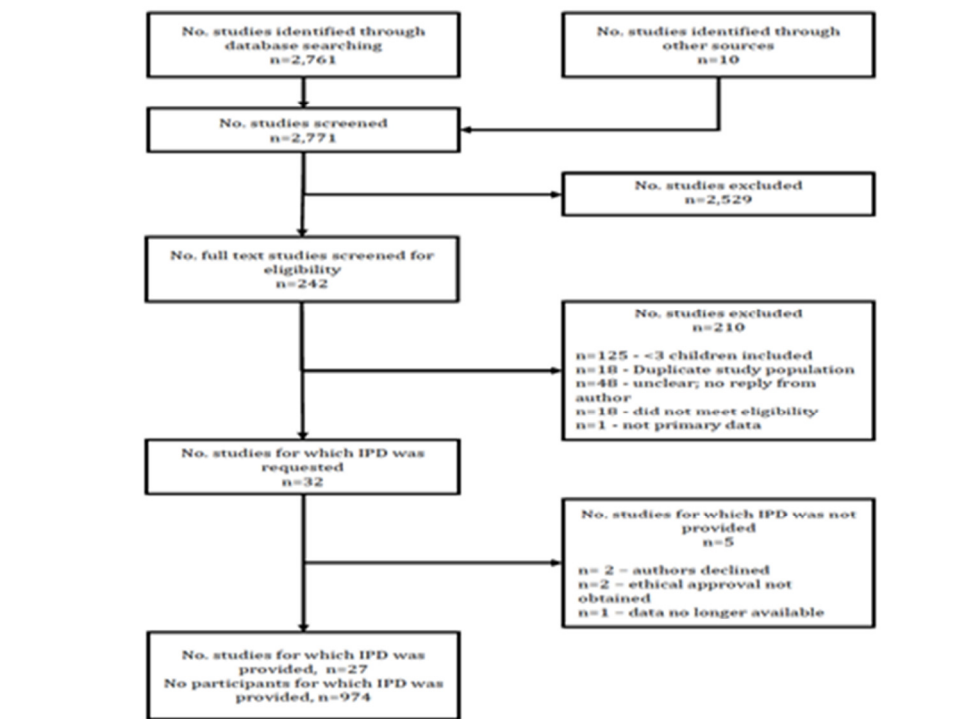


Table 12:

Key demographic and clinical characteristics among children with clinically diagnosed or bacteriologically confirmed multidrug-resistant tuberculosis

| | Clinically diagnosed MDR-TB n = 237 (%) | Bacteriologically confirmed MDR or Pre-XDR n = 701 (%) |
|---------------------------------------|---|---|
| Age | | |
| Under 5 years | 156 (66) | 231 (33) |
| 5 to <15 years | 81 (34) | 470 (67) |
| Malnourished | | |
| Yes | 47 (19.8) | 274 (39.1) |
| No | 67 (28.3) | 366 (52.2) |
| Unknown | 123(51.9) | 61 (8.7) |
| Severe Disease on CXR | | |
| Yes | 68 (28.7) | 519 (74.0) |
| No | 126 (53.2) | 163 (23.3) |
| Unknown | 43 (18.1) | 19 (2.7) |
| Severe Extra-pulmonary Disease | 24 (10.1) | 103 (14.7) |
| HIV status | | |
| HIV-infected | 36 (15.2) | 318 (45.4) |
| HIV-uninfected | 141 (59.5) | 300 (42.8) |
| HIV status unknown | 60 (25.3) | 83 (11.8) |

Based on GRADE tables for WHO Guidelines Meeting, all data was from observational cohort studies.

All data was graded as having:

Risk of bias: serious,

Inconsistency: serious;

Indirectness: not serious

Imprecision: not serious (except CFZ was serious due to low numbers)

Overall quality of evidence: very low

Effect estimates were adjusted for age, HIV status, gender, TB disease severity and study site (random effects model with clustering by site). The discussion on the results is presented in table 13 below:

Table 13: Discussion of the results of the systematic review

| | |
|---|--|
| Strong protective effect of high dose INH: | <ul style="list-style-type: none"> • High dose INH almost exclusively used in South African studies • Benefit persisted even following adjustment for site, but may still be residual effect. • Typically used in combination with ethionamide • Benefit may depend on epidemiology of INH mutation • A randomized controlled trial of high-dose isoniazid therapy for multidrug-resistant tuberculosis in adults found no increased risk of hepatotoxicity⁶ |
| Second Line Injectable (SLI) | <p>Significant protective effect of SLI</p> <ul style="list-style-type: none"> • Small total number not receiving SLI • Demonstration of treatment benefit may change if duration of treatment of |

⁶ Katiyar et al, *Int J Tuberc Lung Dis* 2014

| | |
|-------------------|---|
| | <p>injectable, combined with severity of disease, is also analyzed.</p> <ul style="list-style-type: none"> ○ For this analysis, any child who received a SLI was counted as being treated with a SLI, even if duration on SLI was relatively short. ▪ Impact of inclusion of PreXDRs in the analysis: SLI-resistance may be more likely to have not received SLI, and might be at risk for worse outcomes <ul style="list-style-type: none"> ○ Further analysis pending. • Ototoxicity is a well-known adverse effect; hearing loss is irreversible with dramatic impact on quality of life. <ul style="list-style-type: none"> ○ Study showed 24% of children treated with injectable had hearing loss. (Seddon et al. J Infect 2013) |
| FQ and PAS | <p>Lack of protection by late generation FQ and PAS</p> <ul style="list-style-type: none"> • FQ: very few children treated with moxifloxacin and levofloxacin • FQ and PAS: may have been residual effects from disease severity <ul style="list-style-type: none"> ○ When individual sites were examined, sites that had poorer outcomes with PAS and later generation FQ also had significantly higher rates of HIV, malnutrition, severe pulmonary disease and pre-XDR-TB. |

Summary of the findings:

- Overall high favourable treatment outcome regardless of high prevalence of HIV infection and severe disease
- In general, findings consistent across confirmed and clinically diagnosed MDR-TB
- Strong protective effect of high dose INH
- Lack of protection by late generation FQ and PAS: may have been due to residual effects from disease severity
- SLI show treatment benefits in bacteriologically confirmed cases, but may be able to limit use in non-severe cases.

Update on significant recent research papers – James Seddon

The graphics in figures 15 shows the increasing number of articles on childhood TB being listed on PubMed. However, as illustrated in figure 15, the numbers are small compared to the number of articles on TB in adults.

Figure 15: Tuberculosis publications listed on PubMed – childhood TB

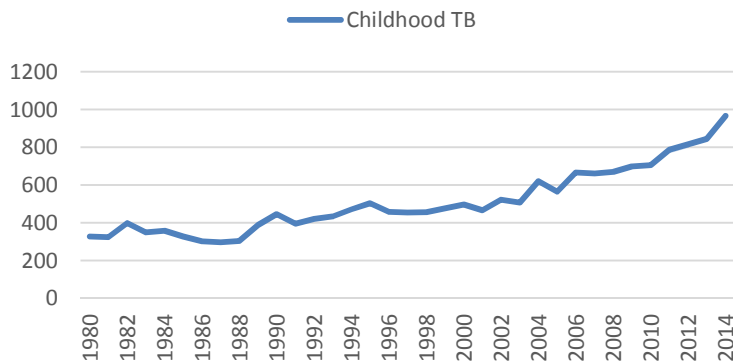
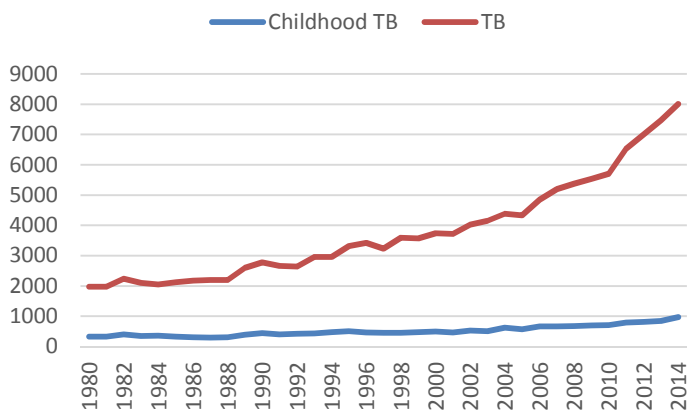


Figure 16: Tuberculosis publications listed on PubMed – childhood and adult TB



837 studies identified on PubMed in the period 1 December 2014 to 30 November 2015. On review of title 28 were selected based on presenter's own clinical and research interests, Slightly biased towards clinical/epi studies, slightly biased towards drug resistance. The papers were broadly divided into six categories:

- Policy statements
- Epidemiology
- Vaccines
- Diagnostics
- Treatment
- Prevention.

Table 14 shows the classification of the 28 articles and a short highlight of the content.

Table 14: classification of the 28 selected articles

| |
|---|
| Policy statements |
| Nachmann LID Which children, which questions, when, how, timing Nichol CID biomarkers –diagnosis, disease, infection, treatment response, samples, timings, ethics Graham CID – Update – Include molecular diagnostics, 24-12, combine categories – confirmed, unconfirmed, unlikely |
| Epidemiology |
| Olivia – LRM – 1000 studies – autopsy and clinical cohorts, 14 studies identified, 7.5% TB, variable Moore – IJTLD 2005-2010, 774 children, 55% HIV, most confirmed, 20% died, only 400 known outcomes Patra – PM – 18 studies, 30,000 children, RR1.6 LTBI, RR 3.5 TB disease |
| Vaccines |
| Penn – Vaccine, SA RCT 60 recruited, 40 vaccine, 20 placebo, baseline and one month, safe and robust M72 T cell responses Tameris – Vaccine, 3 African sites 16-26 weeks, dose-finding phase and then safety phase, over 200 children in each, safe, low T- cell responses |
| Diagnostics |
| Solomons – CID, RSA, Evaluation of case definitions for confirmed, probable, possible TBM. High sen and spec Detjen – LRM, 60% sensitivity compared to culture, good spec, very poor sen compared to culture negative. Better than smear Giang – BMC ID, Vietnam, smear, xpert, culture – 10%, 20%, 30% Oberhelman – BMC ID, Peru, Well controls. High rates of false positive PCR in controls, higher in HIV+ 20% vs. 5%, culture + 1% HIV vs. 10% HIV – Raizada – P1 – India, 9000 specimens, 6% positive, better than smear x 2, 10% rif resistance, most not in children being lx for DR-TB Chiang – IJTLD – Peru, multiple barriers to diagnosis, stigma, education, access, contact tracing, training, shortages |
| Treatment |
| Levy PIDJ – France, 14 children less than 5 years, treated with EMB, VEP, 3 children developed visual impairment, all resolved Thee CID – RSA – 23 children aged 7-15 years, 10mg/kg, serum concentrations much lower than adults with 400mg Savic, Clin Pharm and Ther, Data from adult trials and paed PK, Rif PO 30mg/kg and IV 15mg/kg, lfx 19-33mg/kg Ablemism – JPIDS – 4 year girl, treated for TBM, problems with LFTs, reasonable response to FLDs, then deteriorated and MDR and then XDR Salazar – LID, 2 year old child developed XDR-TB after a visit to India, no risk factors Muckerjee IJTLD, India, 125 children, worsening clinical condition, relapse – 60% successful Achar EID, 9 month regimen, nausea, vomiting, tinnitus, abdo pain and headache Weaver BWHO, 15 studies in 11 countries - education, psychosocial support, care delivery, health system |

strengthening and social protection, x3 OR, framework developed

Prevention

Triasih – CID – Indonesia, 269 child contacts of 140 index cases, 8% disease, 40% infection, 100 children IPT, none got TB, some older got TB

Leeb Acta Paed Sweden – 277 children 40% elevated LFTs, most below 3x upper limit of normal, more common in younger children, 4 disc

Mandalakas AJRCCM 1300 children, 15 years. 8% disease, IGRA better correlated with exposure than TST. Consider for young and HIV children

Villarino JAMA Paed 1000 children randomised 9H or 3HP, 2 to 17 years. No TB in 3HP, 3 in 9H, safe 88% completion 3HP vs 80% 9H

In conclusion, these are exciting times for paediatric TB. A lot of studies are being published; however there is also lots more work to do.

6. Closure

Steve Graham and Malgosia Grzemska closed the meeting and thanked participants for their active involvement in the meeting. Childhood TB is now firmly on the global agenda and the End TB strategy as well as the UN Sustainable Development goals provide major opportunities for scaling up the response to childhood TB and we must embrace them.

The inventory studies that are planned for next year in six countries will further contribute to improving the childhood TB estimates which will enable further targeted planning to address the issues. The National Childhood TB stakeholder meetings for the uptake of the new childhood TB FDCs are another example on the increased efforts to address childhood TB and outcomes of the early meetings will provide valuable lessons for other countries.

The annual meeting of the Childhood TB Subgroup in 2016 will be in Liverpool, the venue of the 2016 Union World Conference.

Below are some of the pictures taken during the day. Other pictures will be shared via a special link.



Annex 1: Agenda of the meeting

| | | |
|--|---|---|
| Childhood TB subgroup meeting | | 08:30 – 17:00 |
| Chair: Dr Steve Graham | | |
| 08:30 - 09:00 | Registration | |
| 09:00 - 09:10 | Opening and welcoming words | Mario Raviglione, Director WHO/GTB & Steve Graham, Chair, Childhood TB subgroup |
| 09:10 – 09:30 | Report from Chair on the 2015 activities of the Childhood TB subgroup | Chair, Childhood TB subgroup |
| Global developments in childhood TB: update on treatment trials and on progress in linking with RMNCAH services | | |
| 09:30-09:50 | Update on treatment trials | Anneke Hesselting |
| 09:50-10:10 | Presentation by UNICEF on Childhood TB activities (including overview of training opportunities) | Anne Detjen, UNICEF |
| 10:10-10:30 | Discussion | All |
| 10:30 - 11:00 | Coffee/Tea break | |
| Country experiences in scaling up childhood TB activities | | |
| 11:00-11:15 | Increase in the child TB detection rate through capacity development: Bangladesh experience – Shakil Ahmed | Shakil Ahmed |
| 11:15-11:30 | Implementation of the KNCV benchmarking tool for Childhood TB policies and practice: experiences in Vietnam | Huong Thien Nguyen & Connie Erkens, KNCV Tuberculosis Foundation |
| 11:30–11:45 | Ethiopia Childhood TB Roadmap | Blen Ayele, NTP Ethiopia |
| 11:45-12:00 | Discussion | All |
| 12:00 – 14:00 TB Alliance Symposium on Improving Access to Appropriate Paediatric TB Medicines | | |
| 12:00-12:30 Arrival and Lunch | | |
| 12:30-12:40 Welcome and introduction | | |
| 12:40-12:45 Video | | |
| 12:45-13:15 Panel discussion on “Challenges and opportunities in preparing for the introduction of new | | |

| | | |
|--|---|--|
| paediatric TB drugs” 13:15-13:45 Panel discussion “Out of the shadows: Finding and treating children in need” | | |
| Country experiences in scaling up childhood TB activities (continued) | | |
| 14:00 – 14:15 | Updates on childhood TB in Uganda – Moorine Sekadde | Moorine Sekadde , NTP Uganda |
| 14:15 – 14:30 | Update on activities of the Baylor Childhood TB Center of Excellence in Swaziland | Pilar Ustero Alonso & Anna Mandalakas |
| 14:45 -15:00 | Key operational challenges with case finding for TB in children: successful case finding models in different settings among which Malawi | Isaiah Dambe, NTP deputy program manager Malawi and/or Ilhame Ouansafi, CHAI Malawi |
| 15:00 – 15:30 | Discussion | All |
| 15:30 – 16:00 | Tea/Coffee break | |
| Panel on key issues and current uncertainties in childhood TB | | |
| 16:00 – 17:00 | Evidence synthesis of paediatric MDR-TB outcomes – Liz Harausz Summary of impact publications in last 12 months – James Seddon Discussion | |
| 17:00 | Wrap up, next steps and closure | Chair & Secretariat |

Annex 2: List of participants

Steve Graham, Chair
Rob Aartnoutse
Lisa Adams
Shakil Ahmed
Gesit Metaferia Amaru
Blen Ayele
Jason Bacha
Mercedes Becerra
Adrie Bekker
Karin Bergstrom
Deron Burton
Chisala Chabala
Rebekah Chang
Silvia Chiang
Renia Coghlan
Clemax Couto Sant' Anna
Rachael Crockett (tbc)
Angela Crook
Andrea Cruz
Isaiah Dambe
Anne-Marie Demers
Anne Detjen
Lienki Du Plessis
Karen Du Preez
Anthony Enimil
Connie Erkens
Betina Mendez Alcântara Gabardo
Deliana Garcia
Tony Garcia Pratz
Diana Gibb
Robert Gie
Rachel Golin
Elisabeth (Liz) Haraus
Anneke Hesseling
S. Syed Hissar
Telly How
Akramul Islam
Shayla Islam
Fernanda Dockhorn Costa Johansen
Netty Kamp (tbc)
Senait Kebede
Salmaan Keshavjee
Aarte Kinikar
Suchritra Kulkarni
SS Lal
Keri Lijinski
Michael Lindeborg
Mark Lobato

Shelly Malhotra
Anna Mandalakas
Davide Manisero
Ben Marais
Olivier Marcy
Vidya Mave
Helen McIlleron
Lindsay McKenna
Huong Thien Nguyen
Giselle Obregon
Ilhame Ouansafi
Leena Patel
Elana Robertson
Carly Rodriguez
Andrea Maciel de Oliveira Rossoni
Stephanie Rotolo
Kelly Sawyer
Simon Schaaf
Cherise Scott
James Seddon
Moorine Sekadde
Valérie Schwoebel
Marina Tadolini
Khurshid Talukder
Jacqueline Teera
Rudi Thétard
Celestino Francisco Teixeira
Margaret Thomasen
Rina Triasih
Anna Turkova
Irina Usherenko
Pilar Ustero
Frieda Verheye-Dua
Henry Welch
Christine Whalen
Jessica Workman

WHO

Colleen Acosta
Shalala Ahmadova
Muhammad Akhtar
Geoffrey Bisoborwa
Annemieke Brands
Regina Christian
Malgosia Grzemska
Khurshid Hyder
Kassa Ketema
Nobuyuki Nishikiori

Abel Nkhola
Mario Raviglione
Kefas Samson

Babatunde Sanni
Anna Volz
Fraser Wares

Annex 3: Ongoing trials – update by Anneke Hesselning

SUMMARY OF ONGOING AND PLANNED CLINICAL RESEARCH ON TUBERCULOSIS DRUGS IN CHILDREN AND PREGNANT WOMEN

| Protocol name/number Trial Registration | Phase | Design | Primary objective | Indications | Special populations or considerations | Funder, sponsor, principal investigator | Network, CTUs, countries | Status |
|--|----------|---|---|---------------|---|--|--|---------------|
| <i>Paediatric Studies: PREVENTION, DS-and DR-TB</i> | | | | | | | | |
| P4v9 Trial NCT00170209 | III | Randomized open label positive-controlled multicenter trial | Safety and tolerability of 4 months rifampicin and 9 months Isoniazid for treatment of LTBI in children | DS - TB | Children, adolescents Children with LTBI at high risk of TB | Canadian Institutes of Health Research (CIHR) Menzies dick.menzies@mcgill.ca | N/A Canada, Australia, Benin, Guinee, Indonesia | Enrolling |
| ACTG 5279 NCT01404312 | III | Randomized, open-label multicenter trial | Evaluate the efficacy of an ultra short rifapentine-based regimen in adults and adolescents | DS - TB | Adolescents, adults HIV+ Drug drug interactions | NIAID Chaisson/Swindells rchaiss@jhmi.edu | ACTG; IMPAACT co-endorsed Thailand, Africa | Fully Accrued |
| TBTC Study 35 | I/I I | PK and safety study of RFPT/INH co-formulation in children for prevention of TB | Determine the optimal dose and assess PK and safety of rifapentine, given in combination with INH, in children with LTBI | DS - TB | Children, infants HIV- Age de-escalation Pop PK modeling | TBTC, in collaboration with Sanofi Hesseling/MacKenzie annekeh@sun.ac.za | TBTC USA, South Africa | Planned |
| “TB-CHAMP” (TuBerculosis CHild and Adolescent Multidrug-resistant Preventive therapy trial) | III | Randomized double blind placebo-controlled, superiority multicenter trial | Evaluate the efficacy of levofloxacin vs. placebo for the prevention of MDR-TB in child and adolescent household contacts | D R- TB | Children, adolescents, infants HIV+/HIV- Household randomization | BMRC/DFID/Wellcome Trust Hesseling/Seddon/Schaaf annekeh@sun.ac.za | BMRC CTU South Africa | Opening 2015 |

SUMMARY OF ONGOING AND PLANNED CLINICAL RESEARCH ON TUBERCULOSIS DRUGS IN CHILDREN AND PREGNANT WOMEN

| Protocol name/number Trial Registration | Phase | Design | Primary objective | Indications | Special populations or considerations | Funder, sponsor, principal investigator | Network, CTUS, countries | Status |
|---|----------|---|---|---------------|---|--|--|----------------|
| A5300a/2003a (PHOENIX) | III | Randomized open label, superiority multicenter trial | Evaluate the efficacy of delamanid vs. INH for the prevention of MDR-TB in adult, child and adolescent household contacts | D R- TB | Children, adolescents, infants, adults HIV+/HIV- Household randomization | NIAID Churchyard GChurchyard@auruminstitute.org Gupta agupta25@jhmi.edu | ACTG/IMPAACT | In development |
| Paediatric Studies: TREATMENT, DS-TB | | | | | | | | |
| DAtiC NICHD-069175 NCT01637558 | I | Intensive PK sampling, firstline TB drugs | Evaluate the PK of first line antituberculosis drugs using 2010 WHO guidelines across paediatric populations | DS - TB | Children, infants HIV+/HIV- Malnutrition Drug-drug interactions Pop PK modeling | NICHD R01 McIlleron University of Cape Town, South Africa helen.mcilleron@uct.ac.za | N/A South Africa, Malawi | Enrolling |
| DNDi: RTV Superbooster for HIV/TB co-infection | I/I I | Develop a stand-alone ritonavir (RTV) booster formulation to be added to the optimized LPV/r-based paediatric ARV regimen | PK ARV and TB drugs | DS - TB | Children, infants HIV+ | AFD, MSF, AECID Spain; SDC Lallemand Switzerland mlallemand@dndi.org | DNDi South Africa, Thailand; France | Enrolling |
| PK-PTB HIV01 NCT01687504 NCT01699633 NCT01704144 | IV | Open-label steady state PK of first-line TB drugs and ARV | Evaluate the pharmacokinetics and safety of the WHO recommended increased dosages of the first-line anti-TB medications in children with TB and HIV/TB co-infection | DS - TB | Children, infants HIV+/- Drug-drug interaction studies | NICHD R01 Awewura The Miriam Hospital, Rhode Island, USA AKwara@Lifespan.orgKwara | NA Ghana | Enrolling |

SUMMARY OF ONGOING AND PLANNED CLINICAL RESEARCH ON TUBERCULOSIS DRUGS IN CHILDREN AND PREGNANT WOMEN

| Protocol name/number Trial Registration | Phase | Design | Primary objective | Indications | Special populations or considerations | Funder, sponsor, principal investigator | Network, CTUs, countries | Status |
|--|-------|---|---|---------------|--|---|---|---------------------------------|
| “SHINE” (Shorter treatment for mINimal TB in childrEn) | III | Randomised, non-inferiority, open label efficacy trial | Evaluate the efficacy of 4 vs. 6 months treatment for minimal TB in children with new WHO-recommended first-line TB doses | DS - TB | Children, adolescents, infants HIV+/HIV- Nested PK studies Drug-drug interactions | BMRC/DFID/Wellcome Trust BMRC CTU at University College London (UCL) Gibb diana.gibb@ucl.ac.uk | MRC CTU Endorsed by IMPAACT India, Uganda, Zambia, South Africa | Opening 2015 |
| Treat infant TB | I | Intensive PK sampling, first line TB drugs, single drug formulation | Evaluate the PK and safety of first line antituberculosis drugs using 2010 WHO dosing in infants < 12 months | DS - TB | Infants HIV+/- | Unitaid, Step-TB Project Hesseling/Bekker Stellenbosch University, South Africa annekeh@sun.ac.za | TB Alliance South Africa | Enrolling |
| Rifabutin PK trial | IV | PK and safety of rifabutin in adults and children | PK and safety of rifabutin in adults and children | DS - TB | Adults Children HIV- | ICMR, NACO Swaminathan National Institute for Research in Tuberculosis (NIRT), Chennai, India doctorsoumya@yahoo.com | Pending India | Planned |
| Optimizing treatment to improve TBM outcomes in children: the TBM-KIDS trial | II | Intensive PK, pop PK modeling | Evalute the efficacy and safety of levofloxacin and rifampicin for the treatment of TB meningitis in children | DS - TB | Children, infants HIV+/- | NICHD (R01) Dooley/Gupta/Swaminathan Johns Hopkins University Kdooley1@jhmi.edu | IMPAACT co-endorsed India, Malawi | Undergoing regulatory approvals |

SUMMARY OF ONGOING AND PLANNED CLINICAL RESEARCH ON TUBERCULOSIS DRUGS IN CHILDREN AND PREGNANT WOMEN

| Protocol name/number Trial Registration | Phase | Design | Primary objective | Indications | Special populations or considerations | Funder, sponsor, principal investigator | Network, CTUS, countries | Status |
|---|----------|--|--|--------------------------------|---|--|--------------------------------------|-----------|
| IMPAACT P1101 Raltegravir PK NCT01751568 | I/I I | Dose-finding, safety, tolerability, drug-drug interaction and PK study of RAL-naïve children who have received ≥ 1 week and ≤ 20 weeks of rRIF-based TB therapy prior to initiation of ARV therapy | To determine the pk and appropriate dose of RAL when administered with a RIF-containing anti-TB therapy in HIV/TB co-infected children | | ARV naïve HIV/TB co-infected children ≥ 3 to < 12 years old | NICHD MIAID Meyers tammy@myers.net | IMPAACT South Africa | |
| IMPAACT P1106 | I | PK characteristics of cART and TB therapy in premature and LBW infants | Evaluate the PK of ARV and first and secondline TB drugs in low birth weight infants | DS - TB D R- TB | Infants HIV+/- Low birth weight, premature | NIAID Mirochnik/Cotton Mark.Mirochnik@bmc.org | IMPAACT | Enrolling |
| Paediatric Studies: TREATMENT, DR-TB | | | | | | | | |
| Otsuka 232 and 233 NCT01856634/ NCT01859923 | I II | Open-label, single arm dose finding study of delaminid in HIV-negative children with MDR-TB | Evaluate the PK, safety, tolerability and anti-mycobacterial activity of Delaminid in combination with MDR-TB therapy for HIV-uninfected and HIV-infected children and adolescents | D R- TB | Children, infants, adolescents HIV- Pop PK modeling Age de-escalation | Otsuka Jeffrey.Hafkin@otsuka-us.com | N/A Phillippines, South Africa | Enrolling |

SUMMARY OF ONGOING AND PLANNED CLINICAL RESEARCH ON TUBERCULOSIS DRUGS IN CHILDREN AND PREGNANT WOMEN

| Protocol name/number Trial Registration | Phase | Design | Primary objective | Indications | Special populations or considerations | Funder, sponsor, principal investigator | Network, CTUS, countries | Status |
|---|----------|--|---|---------------|--|---|---|----------------|
| IMPAACT 2005: Delamanid DDI | I/I I | Open-label, single arm dose finding study | Evaluate the PK, safety, tolerability and anti-mycobacterial activity of Delaminid in combination with MDR-TB therapy for HIV-infected and uninfected children and adolescents | D R- TB | Children, infants, adolescents HIV+ Pop PK modeling | NIAID kdooley1@jhmi.edu | IMPAACT | In development |
| MDR-PK 1 NICHD-069169 | I | Intensive PK sampling, routine 2ndline TB drugs | Evaluate the PK and safety of secondline antituberculosis drugs in HIV-infected and uninfected children | D R- TB | Children, infants, adolescents HIV+/HIV- Drug-drug interactions | NICHD R01 Hesseling Stellenbosch University, South Africa annekeh@sun.ac.za | N/A South Africa | Enrolling |
| MDRPK2 1R01HD083047-01 Optimising and operationalizing paediatric drug-resistant TB treatment | I/I I | Semi-intensive PK sampling, model-based analysis; focus on moxifloxacin, levofloxacin, linezolid | PK, safety, acceptability of modeled optimized doses of moxifloxacin, levofloxacin, and linezolid in children with MDR-TB | D R- TB | DR-TB | Infants, children, adolescents (0-<18 years), HIV+/- | NICHD, RO1 Garcia-Prats AJ, Stellenbosch University, garciaaprats@sun.ac.za ; Savic R, University of California San Francisco, rada.savic@ucsf.edu | Enrolling |
| IMPAACT P1108: Bedaquiline | I/I I | Open-label, single arm dose finding and safety study | Evaluate the PK, safety, tolerability and anti-mycobacterial activity of Bedaquiline in combination with MDR-TB therapy for HIV--infected and uninfected children and adolescents | D R- TB | Children, infants, adolescents HIV+/- Pop PK modeling Age de-escalation | NIAID Hesseling annekeh@sun.ac.za | IMPAACT South Africa | Opening 2016 |

SUMMARY OF ONGOING AND PLANNED CLINICAL RESEARCH ON TUBERCULOSIS DRUGS IN CHILDREN AND PREGNANT WOMEN

| Protocol name/number Trial Registration | Phase | Design | Primary objective | Indications | Special populations or considerations | Funder, sponsor, principal investigator | Network, CTUS, countries | Status |
|---|----------|--|--|---------------|--|--|--|----------------|
| MDRPK2 1R01HD083047-01 Optimising and operationalizing paediatric drug-resistant TB treatment | | Semi-intensive PK sampling, model-based analysis; focus on moxifloxacin, levofloxacin, linezolid | PK, safety, acceptability of modeled optimized doses of moxifloxacin, levofloxacin, and linezolid in children with MDR-TB | D R- TB | Infants, children, adolescents (0-<18 years), HIV+/- | NICHD, RO1 Garcia-Prats AJ, Stellenbosch University, garciaaprats@sun.ac.za ; Savic R, University of California San Francisco, rada.savic@ucsf.edu | N/A South Africa | Enrolling |
| <i>Pregnancy studies (including infants): PREVENTION</i> | | | | | | | | |
| IMPAACT P1078 “TB Apprise” NCT01494038 | IV | Randomized double blind placebo-controlled multicenter trial | Evaluate the safety of antepartum vs. postpartum INH in HIV-infected pregnant women | DS - TB | Pregnant women HIV+ | NIAID Gupta; agupta25@jhmi.edu JHU | IMPAACT India, South Africa, Uganda, Botswana, Malawi, Zimbabwe | Enrolling |
| IMPAACT 2001 Rifapentine in pregnant women | I/I I | PK and safety of rifapentine and INH in HIV-infected pregnant women | Evaluate the PK and safety of rifapentine and INH given as part of an LTBI regimen in HIV-infected and uninfected women and their infants. | DS - TB | Pregnant women Infants | NIAID Mathad jsm9009@med.cornell.edu | IMPAACT | In development |
| <i>Pregnancy studies (including infants): TREATMENT</i> | | | | | | | | |
| IMPAACT P1026s NCT00042289 | IV | Drug-drug interactions in management of TB/HIV in pregnancy | Peripartum and postpartum PK of first line TB drugs in women with and without ART | DS - TB | Pregnant women HIV+ | NIAID Mirochnik Mark.Mirochnick@bmc.org . | IMPAACT USA, Brazil, Botswana, Uganda, South Africa | Enrolling |

SUMMARY OF ONGOING AND PLANNED CLINICAL RESEARCH ON TUBERCULOSIS DRUGS IN CHILDREN AND PREGNANT WOMEN

| Protocol name/number Trial Registration | Phase | Design | Primary objective | Indications | Special populations or considerations | Funder, sponsor, principal investigator | Network, CTUS, countries | Status |
|---|----------|---|---|---------------|---|--|--------------------------|-----------|
| TSHEPISO Study: The effect of TB and its treatment on HIV-infected pregnant women and their infants. R01HD064354-04 | IV | Study the impact of TB/HIV co-infection in pregnancy on maternal and infant outcomes; characterize the impact of TB treatment using rifampin on the PK and PD of NNRTIs used for PMTCT. | Nested PK studies in pregnant women and infants | DS - TB | Pregnant women HIV+/- Nested PK studies Drug-drug interactions | NAID RO1 Johns Hopkins University Chaisson rchaiss@jhmi.edu | N/A South Africa | Completed |
| Evaluation of PK between Depo-medroxyprogesteron eacetate (DMPA), Rifampicin, and Efavirenz in HIV and TB co-infected women | I/I I | Estimate optimal dosing frequency of DMPA for TB/HIV+ women on RIF/EFV. Determine whether MPA levels will be adequate to suppress ovulation through 12 weeks in these women | Nested PK studies | DS - TB | Pregnant women HIV+ Nested PK studies | NIAID Mngqibisa University KwaZulu Natal mngqibisa@ukzn.ac.za | ACTG | Enrolling |