

**Annual meeting of the Childhood TB Subgroup
Monday 27 October 2014**

Tryp Barcelona Condal Mar hotel, c/Cristobal de Moura, 138, 08019 Barcelona, Spain

Meeting Report

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Executive summary

The annual meeting of the Childhood TB subgroup took place in Barcelona, Spain on Monday 27 October 2014. The meeting was attended by over 90 participants representing paediatricians, NTP managers, technical and financial partners, community TB representatives and WHO staff from regions and countries. This year, the meeting focused on scaling up childhood TB activities at country level with interesting experiences from Bangladesh, the Democratic Republic of the Congo, UR Tanzania, Kenya and Vietnam. Participants were also briefed on the regional activities, in particular the workshops with multiple stakeholders to prepare national action plans for scaling up childhood TB. The Chair gave an update on the work of the subgroup since October 2013 and on the plans for 2015. An update was given on progress made with the implementation of the Childhood TB Roadmap, one year after its launch. New training materials on childhood TB were announced including the WHO/Union training modules and an e-learning tool for health workers at the lower levels of the health care system that will become available soon. The TB Alliance presented progress made towards the development of childhood-friendly TB formulations that may become available during the second half of 2015. WHO gave an update on the childhood TB estimates including the work on estimating the burden of TB in adolescents. USAID presented the childhood TB landscape analysis which is currently under development in close collaboration with partners and countries. TAG shared the key messages of the 2014 TB R&D tracking report showing funding trends for R&D on paediatric TB and highlighting areas for advocacy. The meeting concluded with an update on current research focusing on new TB treatment strategies in children; an update from the Sentinel project; and, an update on significant recent research papers that have been published since the meeting in 2013. The meeting concluded with the following action points: Bring childhood TB to STAG-TB 2015 and invite colleagues working on maternal and child health as well as HIV/AIDS to facilitate integration; Document and publish scaling up activities; Assist countries to include Childhood TB in all steps of the Global Fund New Funding Model (e.g. NTP review, National TB strategic plan, gap analysis, concept note); Encourage countries to identify national and regional champions on paediatric TB; Build and expand regional capacity to address growing requests for technical assistance in particular in light of the development, finalization and implementation of national action plans for scaling up childhood TB.

Summary of the meeting

1. Opening and welcome – Mario Raviglione

The annual childhood TB subgroup meeting was opened by Steve Graham (Chair) and Mario Raviglione (Director, WHO Global TB Programme). In his opening address, Mario Raviglione welcomed the participants on behalf of the WHO Global TB Programme and recognized that the subgroup is very active and ever growing. He also congratulated Steve Graham for his leadership. In his openings remarks, Mario Raviglione referred to the launch of the Childhood TB Roadmap, now one year ago. The Roadmap, outlining steps to end childhood TB related deaths, has generated increased awareness on TB in children and provided an opportunity to build linkages beyond the TB community-especially with partners working in the maternal and child health field. Mario Raviglione then briefed the subgroup on WHO's work since the last annual meeting on 29 October 2013 in Paris. WHO has published the second edition of the Guidance for national tuberculosis programmes on the management of tuberculosis in children (April 2014). The document is available during the annual meeting, at the WHO booth at the Convention Centre, as well as on the WHO GTB website. WHO and the Union have jointly updated the Childhood TB training modules (a facilitator's manual and PPT modules). WHO and the Union are also finalizing an e-learning online training package for primary and secondary health workers in remote areas (with funding through USAID TB CARE I). New estimates on childhood TB are included in the Global TB Report 2014 which was launched on 22 October in Geneva and WHO has initiated work on the burden of TB in adolescents (until now a rather neglected age group). WHO is closely collaborating with the TB Alliance, principle recipient of the UNITAID -funded STEP-TB project for the development of child-friendly formulations. Important

progress has been made this year: child-friendly fixed-dose combinations are likely to become available on the market during the second half of 2015.



Credit: Malgosia Grzemska

Several of the members of the childhood TB subgroup have been involved in National TB Programme reviews to evaluate childhood TB activities, identify gaps and ensure that childhood TB is included in TB National Strategic Plans and Concept Notes to the Global Fund New Funding Model. In order to further address the gap between policy and practice, several regional meetings on childhood TB have taken place since our last meeting (29 October 2013 in Paris). These regional consultations bring together a variety of stakeholders: representatives of the NTP and MCH; representatives of national paediatric associations; major technical and financial partners; and, community representatives. The aim is to jointly develop action plans for scaling up childhood TB activities in their respective countries. Next step is to develop full short and intermediate term action plans, seek national endorsement and support, engage all relevant stakeholders and develop a 5-year action plan 2016-2010. Many countries will request TA for this in 2015, for which funding will need to be identified. Subgroup members will be invited to provide such assistance if funding can be identified. Today's meeting will be focused on sharing the regional and country experiences in scaling up childhood TB activities. We still need much more of that and we need to document these experiences. In addition, there will be an update on research and tools including an update on the USAID childhood TB landscape analysis; the work of TAG on funding trends for R&D on Paediatric TB; and, an update on ongoing research and significant research papers. Mario Raviglione concluded by wishing the subgroup members a productive meeting.

2. Report from the Chair on the 2014 activities of the Childhood TB subgroup – Steve Graham

Steve Graham gave an update of the work of the subgroup since the annual meeting of the subgroup on 29 October 2013 in Paris. Membership of the subgroup is still rising with over 175 members. The core team has also three new members: Anne Detjen (The Union), Lindsay McKenna (TAG), and

Connie Erkens (KNCV Tuberculosis Foundation). Still wider representation is being sought. New terms of reference, in line with the Childhood TB Roadmap, were adopted. The Partnership secretariat provided new SOPs and the position of Chair is likely to become available next year. In May 2014, WHO's member states adopted a global strategy and targets for tuberculosis prevent, care and control after 2015. The strategy includes innovative approaches (community-based, wider health sector involvement, preventive therapy, and operational research).

The launch of the Childhood TB roadmap on 1 October 2013 has led to an increased recognition that TB is increasingly important cause of morbidity and mortality in infants and young children globally. It becomes relatively increasing important as a cause of pneumonia, meningitis, etc.

As we reach out to the maternal and child health sector, and child survival, we therefore need to continue to emphasise the potential importance of tuberculosis within the context of child survival. Knowing the epidemic is critical to everything we do. We need data disaggregated by age.

The Global TB Report 2014 includes a section on TB in women and TB in children. Estimates are incredibly important. Today, we will have a presentation on TB in adolescents. Since our last meeting in Paris, the Guidance on the management of tuberculosis in children was updated. It includes many strong recommendations with low quality of evidence as children are not often included in research. It is important operational research is conducted on the use of Xpert MTB/RIF in children. The guidance includes the revised treatment dosages. While we are awaiting the new TB FDC for children, annex 5 shows how to use the existing FDCs to reach the right doses in various weight bands.

WHO and the Union also updated the Childhood TB training modules. They are now available on the WHO GTB website as follows: <http://www.who.int/tb/publications/2014/en/>

At the same time, with support from TB CARE I, Anne Detjen and James Seddon have been developing an online training tool for district level health care workers.

There has been an increased demand for participation of paediatricians in national TB programme reviews. Subgroup members have participated in national TB programme reviews in PNG, UR Tanzania, Kenya, Bangladesh, Swaziland, Malawi, DPR Korea and Sri Lanka. During the upcoming year, we will continue to focus on national TB programme reviews. We will also try to come up with practical guidance for the implementation of community-based contact screening. This has already been done by Jennifer Furin around DR-TB. Similar work is needed for DS-TB, and subgroup members will coordinate with Jennifer and Mercedes on this.

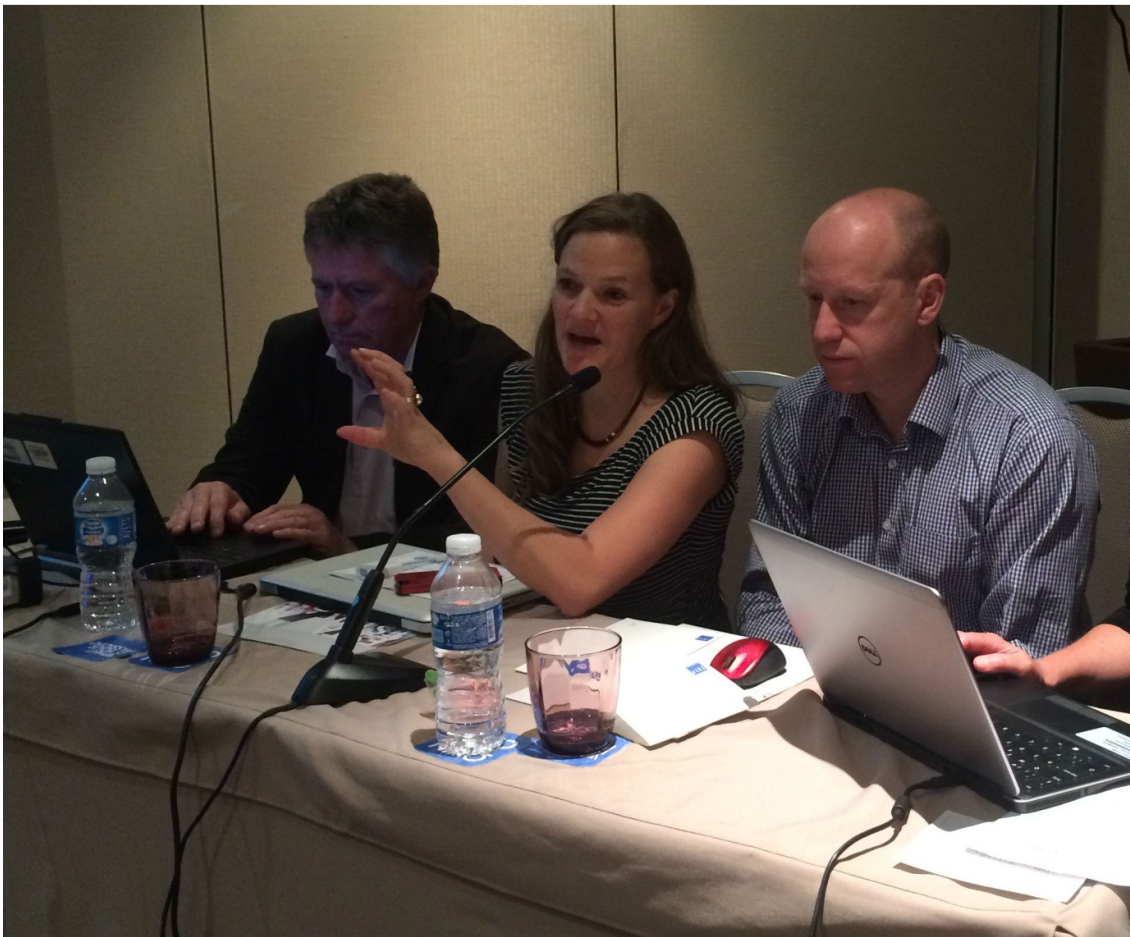
The subgroup has made suggestions to the Global Fund because a lot can be done with what we already have. Countries should take the lead and plan ahead; data recording and reporting can be improved; the child health sector should be engaged; training can be supported – emphasizing integration of childhood TB into ongoing training related to TB, TB/HIV, etc.

During regional and national workshops, we have been trying to bring together NTP and MCH with paediatric associations. This is done mostly at regional level and now also need to increasingly be done at national level. Children do not reach NTPs. It is a link that works and it has been done in the past. But we need to overcome the negativism about paediatric TB like Edith Lincoln already expressed in 1961! It is challenging but not impossible. We need to convince paediatricians. It is a political challenge. NTPs can start by setting up a child TB working group. In addition to regional meetings, subgroup members participate in many other meetings (see slide 26). In the meantime, advances in the area of diagnosis of TB in children remains absolutely central. Inclusion of children in research remains crucial. In 2011, Luis Cuevaz compared the number of research publications on TB diagnostics between adults and children. The number of publications on research involving children was very low. The recently launched TAG report shows that despite an increase in research funding trends in 2013 compared to 2012, it is still around 25% of what is needed. However, there are new opportunities. In this respect, the Chair acknowledged UNITAID for the STEP-TB project on the development of child-friendly drug formulations. Further research is needed on new diagnostics, preventive therapy (DS and DR) and shorter regimens. Research results need to be published.

How much are we achieving by measuring what we already do and look at some of the challenges more carefully. The Union has strengthening OR capacity in countries including some studies in children.

3. TBCARE I childhood TB online training & plans for roll-out and assessing of impact – Anne Detjen & James Seddon

Anne Detjen and James Seddon presented the upcoming “e-TB-kids: learning in childhood TB” currently under development by the Union and WHO with funding through USAID TB CARE I. The e-TB-kids is an online platform for childhood TB training that hosts courses and gives people opportunity to link as a community. It will also have a possibility to provide additional resources. The first course under development is on childhood TB for health care workers at primary and secondary level (not specialists). The course is based on the WHO 2014 guidance for national TB programmes on the management of tuberculosis in children.



Credit: Malgosia Grzemska

The course contains six modules including an epidemiology module plus one comprehensive module to review knowledge obtained. It is an interactive course and therefore complementary to WHO/Union training modules. The idea is that at the end of the course the participant will receive a certificate hopefully endorsed by both WHO and the Union.

Anne Detjen showed the childhood TB learning portal through the Internet. Four modules are up so far. They include pictures for which informed consent has been obtained.

The materials include, among others, 8 cases where you have to make a diagnosis. For treatment, you need to calculate the appropriate doses. The course also contains learning materials on how to

deal with side effects of treatment. And there is a prevention module including a little bit on BCG but then focusing on contact screening. The participant will learn who should go for IPT or who should go for diagnosis. In this module there is also follow-up on the decision made. The idea is to launch the course in December 2014 through dissemination among NTPs, and at medical and nursing schools. Anne Detjen finished by inviting subgroup members to test the online learning platform, to share suggestions for dissemination, and to come up with a good name for the learning platform. During the discussion that followed, subgroup members expressed their interest in this learning tool and mentioned that the materials would need to be translated into local languages. They would also need to be downloadable in areas that have Internet connection challenges. Anne Detjen responded that the course materials will be available on USB keys (easy to translate) and that the materials can indeed be down- and uploaded to work off-line. A simpler version of the course may become available as a smart phone app. If you would like to test the materials, kindly contact Anne Detjen at: adetjen@theunion.org

4. Progress Towards Appropriate Medicines for Childhood TB: Update on the UNITAID-funded STEP-TB project on the development of child-friendly formulations – Cherise Scott

Cherise Scott started her presentation by stating the problem. Children with TB are the neglected of the neglected. Currently not enough children are being treated or not being treated appropriately. The market for paediatric medicines is “broken” and needs repair and requires: better estimates of how many children get TB and where they are located; clarity on drug registration pathways; consistency of treatment policies and practices; and, prioritization by governments, donors, in-country stakeholders (i.e. NGOs, private sector) and drug companies.

Through the UNITAID funded Speeding treatments to End Paediatric TB (STEP-TB) grant, the TB Alliance and WHO (as implementing partner) are trying to increase access to correctly dosed, properly formulated, affordable, high quality paediatric TB medicines. TB Alliance is also received funding from USAID for this project. The three key outcomes of the project are:

(i) Market catalyzed: Market research – How many patients? Where? How are they currently being treated?; Manufacturers commitments; Momentum and visibility.

(ii) Drugs available: correct dosage & dispersible form for HRZ, HR, and E; Shorted gap between approval of adult products versus paediatric products;

(iii) Uptake influenced: Global treatment guidelines adopted; national guidelines developed and health workers trained; child TB included in NSPs and Global Fund concept notes; and, Funding committed for product and implementation.

The project was launched in 2013. In 2014, three manufacturing partners were secured and it is likely that the new TB FDC will become available on the market in the second half of 2015 through GDF and/or importation waivers. Work has started on dosing guidelines for children <5kgs. Early 2015, manufacturers will submit for WHO prequalification and local registration.

Key product information:

Rifampicin 75 mg + Isoniazid 50 mg + Pyrazinamide 150mg

Rifampicin 75mg + Isoniazid 50 mg

Availability : mid to late 2015 from at least one manufacturer

Formulation : dispersible ; flavors –mango, stawberry, raspberry

Price : close to currently available paediatric products, dependent on anticipated volumes.

Ethambutol 100mg

Isoniazid 100 mg

Availability/registration: later timeline – 6-12 months behind FDCs ; one manufacturer committed

Formulation : dispersible

Price : close to currently available products, dependent on anticipated volumes.

The TB Alliance is collaborating with RTI International (contact: Doris Rouse) on MANDATE (Maternal and Neonatal Directed Assessment of Technology) with funding from the BMGF. MANDATE was built because there was no quantitative process to evaluate and prioritize technology development options based on the potential to save maternal, fetal and newborn lives in low-resource settings. With the RTI International, the TB Alliance is also developing MAPIT, a model for assessment of paediatric interventions for tuberculosis. This is a tool for quantitative assessment of where innovation might have the greatest potential to reduce paediatric TB morbidity and mortality. The TB Alliance is further collaborating with Anneke Hesselings of the Desmond Tutu TB Institute at the Stellenbosch University in South Africa to collect the evidence on Second Line Drug formulations for children and to get manufacturers interested to produce such SLDs. Such evidence is needed in order for WHO to be able to publish treatment guidelines. Cherise Scott finished her presentation by showing a video entitled the anatomy of neglect. This video can be reviewed on YouTube as follows: <https://www.youtube.com/watch?v=o8zr5OMcuok>



Credit: Malgosia Grzemska

5. Update on estimates including the work on the burden of TB in adolescents – Babis Sismanidis & Kathryn Snow

Babis Sismanidis gave an overview of progress with TB disease burden estimation in children, work conducted by the WHO Global Task Force on TB Impact Measurement. The mandate of the task force (2006-2015) is to produce a robust, rigorous, widely endorsed assessment of whether the 2015 international TB targets are achieved (promoting direct measurement of TB disease burden); regularly report on progress towards impact targets in years leading up to 2015; and, strengthen national capacity in monitoring and evaluation of TB control. What does the task force offer to countries? Quantification of the level of TB burden & Monitoring of the effectiveness of TB control programmes by quantifying trends. The burden of paediatric TB disease is difficult to estimate because: (i) there is a lack of gold-standard, point-of-care, diagnostic tool (which leads to difficulties with case definitions); (ii) neglect of recording and reporting of the “non-infectious” childhood TB cases; and, (iii) Scarcity of robust, nationwide data on children. Since the call for action in 2011, much has happened. A first set of WHO estimates was published in the 2012 Global TB Report and updated estimates have been published in the 2013 Global TB Report. In January 2013, the STEP-TB project was launched and a global consultation on childhood TB estimates was convened in New York in September 2013. Independent attempts have been undertaken to estimate TB incidence among children: e.g. Pete Dodd & James Seddon did mathematical modelling to estimate the burden of childhood TB in the 22 TB high burden countries; Helen Jenkins et al. undertook a systematic review on the incidence of multi-drug resistant tuberculosis disease in children; and, Christopher Murray et al. did a systematic analysis for the Global Burden of Disease study 2013. The findings were heterogeneous and many data gaps continue to exist. WHO is therefore making estimates combining these independent estimates. In addition, WHO is advising countries to conduct TB inventory studies to measure under-reporting of TB cases to get a better idea of the real incidence.

In terms of mortality data, WHO encourages countries to implement vital registration. WHO estimates a total incidence of TB among children in 2013 of 550,000 (95% 470,000-640,000) or 6% of the total 9 million incident cases are children. In terms of childhood TB mortality in 2013, WHO estimates 80,000 cases (64,000-97,000) or 7% of the total 1,100,000 TB deaths (HIV negative) were children.

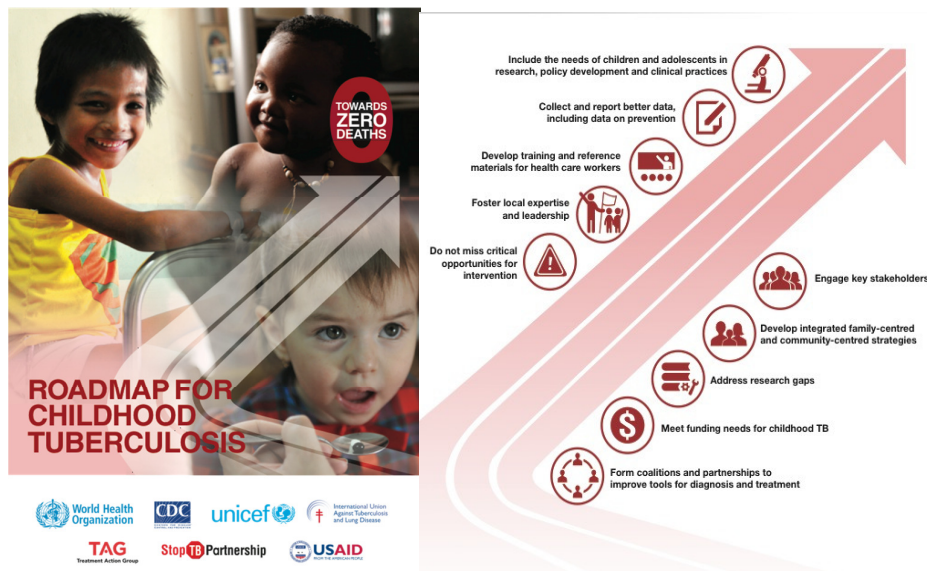
Work is ongoing to further refine the analytical work. In terms of TB incidence, WHO is trying to produce global and regional estimates disaggregated by HIV-status and MDR-TB status. In terms of TB mortality, WHO will try to produce global and regional estimates disaggregated by HIV-status. In terms of the data gaps, WHO will set priorities in empirical studies that could most improve precision of model-based estimates.

During the second part of this presentation, Kathryn Snow from the University of Melbourne, shared the outcomes of her work on the epidemiology of TB, TB/HIV and MDR-TB in adolescents.

“Child” and “Adolescent” have varied and often overlapping definitions which leads to overlapping data: Young child: <5; Older child: aged 5-9; Young adolescent: aged 10-14; Older adolescent: aged 15-19; Young adult: adult 20-24. Or, “child” under 15 and “adult” aged 15+.

Kathryn conducted a systematic review for setting-specific estimates of incidence and prevalence. She looked at cohort studies and national prevalence surveys. Out of about 3,496 hits, she selected 481 full texts out of which 5 included studies on TB and adolescents (Waako 2013 in rural Uganda (incidence), Mohamed, 2013 in Rural South Africa (incidence), Mohamed, 2013 in Rural South Africa (prevalence), Marais, 2015 in Cape Town (prevalence), and, Tupasi, 2009 in the Philippines (prevalence). With respect to incidence estimates, as for children under 5 years of age, many data are missing in the 15-24 years of age group. Based on analysis of these studies as well as disaggregation into 5 year age groups using data from countries with case based electronic surveillance systems, Kathryn Snow estimated that there were about 650,000 incident TB cases among adolescents in 2012. Kathryn Snow also found that smear negative and extrapulmonary disease appear to be more common than smear positive disease, even in older adolescents. Kathryn Snow concluded that there is a need for standardised reporting of age in published research, ideally for 5-year age groups <25 years. More work is needed on the global epidemiology of extrapulmonary disease. Programme data need to be collected on TB/HIV and MDR-TB among adolescents.

6. The Roadmap one year later - Malgosia Grzemska & Anne Detjen



Malgosia Grzemska and Anne Detjen went through the ten steps to zero deaths and summarized what did happen since the launch on 1 October 2013.

1. Include the needs of children in research, policy development, clinical practice:

Child TB should be included in Global Fund applications (concept notes under the NFM). Child TB is increasingly part of TB programme reviews (9 reviews in the period 2013/2014). The Post-2015 strategy aims to intensify case-finding, to better integrate TB care into other health care services and to better collaborate with community-based organisations and programmes. And STAG-TB will explicitly highlight childhood TB at its meeting in 2015. But despite these initiatives, the policy-practice gap still exists.

2. Foster local leadership

WHO/WPRO organized a regional meeting on childhood TB in Vietnam in March 2014. Country participants (NTP, MCH, representatives of Paediatric Associations, community TB representatives) worked on national action plans and set up an informal regional task force to provide assistance to finalization and implementation. Based on the WPRO experience, a global consultation for TB high burden countries from Asia (SEAR, EMR, WPR) took place in September 2014.

Next year, AFRO, EURO and SEARO are planning similar regional workshops and we need to pursue similar initiatives at national level.

We have also worked on collecting and reporting of better data. Jenkins et al and Dodd et al came up with revised global estimates (including MDR-TB). Estimates for adolescent TB have been made. Country assessments (supported by the TB Alliance) have been made in Nigeria, Pakistan and Indonesia. In 2013, the Global TB Report included for the first time a focus on women. Based on all these developments, new childhood TB estimates are included in the Global TB Report 2014.

3. Develop training and reference materials

In 2014, WHO published the second edition of the Guidance for national tuberculosis programmes on the management of tuberculosis in children. WHO and the Union updated the Childhood TB training package. And the Union and WHO are finalizing an e-learning course on childhood TB.

4. Engage key stakeholders

WHO/UNICEF adapted modules for Community Health Workers. The updated modules will be piloted in Zambia and Malawi. The Core group had a meeting in the Spring. CORE is an organization based in Washington DC that works in community health with a strong focus on MCH. The meeting included a session on child TB.

A childhood TB subgroup member (Dr Khurshid Talukder) presented the Childhood TB Roadmap at the Save the children strategic meeting in Nepal (Khurshid). As a result, Save the Children included child TB into their official agenda: increase referral and detection of child TB through existing platforms (OVCs, nutrition, HIV, PMTCT).

The Union has set up a working group on maternal and infant TB.

There have also been important publications among which: Lancet viewpoint: Child Survival and child TB (Graham 2014); and, the Core group/Union January framework for integrating child TB into community-based child health care.

5. Form coalitions and partnerships to improve tools and address research gaps

Anneke and James will give an update on research later today. The NIH organized a meeting on diagnostic biomarkers for paediatric TB in May 2014. However, still a lot more work needs to be done. We need implementation on the ground. Encouraging examples are appearing. E.g. Viet Nam has piloted and is planning a national scale up of contact screening and IPT.



Credit: Malgosia Grzemska

Next steps

What is needed? We need to develop integrated, family-centered and community-centered strategies.

Operational research is needed to produce data to convince maternal/child health community of the importance childhood TB.

We need models for successful scale-up and decentralization of childhood TB activities at country and regional level.

And we need to collect best practices for implementation of contact screening/IPT (who, how?)

If you have a story to share, please send it to the secretariat of the childhood TB subgroup and we will share it with the whole subgroup. We can also put them on the website.

We have several opportunities to push for childhood TB and to move our agenda forward: Global Fund applications and the new Challenge TB grant.

During the discussion that followed, Shakil Ahmed mentioned that many things are happening on the implementation of Childhood TB Roadmap in Bangladesh. But doctors and health care workers are really lacking the skills on childhood TB. The Bangladesh Paediatric Society, NTP, WHO BAN, with support from USAID developed a training module for medical doctors and trained already 800 doctors. Senait Kebede, Ethiopia said that in the African region we really need to advocate more for childhood TB. She just provided support to Uganda to finish the TB/HIV concept note to the Global Fund. All the components that we are discussing today have to be covered in concept notes in one way or another. In terms of OR, a public-private partnership has been established recently in Ethiopia. But we need more OR in Africa.

Vijay Edward from World Vision India and TB advisor to the civil society recipient of the Global Fund grant in India, said that they would welcome the development of a very simple childhood TB screening tool for use at the household level and among school children. WVI do advocacy with district TB officials. The next phase of the project will include providing support on INH (IPT). Anthony Enimil from Ghana works with the Ministry of Health and the Ministry of Education. He is currently collecting information on Rifampicin in children. There is currently probably a bit of under-dosing. While doing advocacy on Ebola in the schools, he also addresses airborne diseases like TB. John Baptist Nkarunga, a paediatrician and hospital director from Rwanda, mentioned that we need to build a system based on community health workers to easily detect children with TB. CHW can really make a difference screening for childhood TB. However, diagnosis remains a bit of a challenge. The MOH in Rwanda is trying to decentralize the Xpert MTB/Rif machine. Better access to GeneXpert testing will help.

7. Briefing on different regional activities: panel with Cornelia Hennig, Kefas Samson, Martin van den Boom, Khurshid Hyder and Malgosia Grzemska

Western Pacific region - Cornelia Hennig

WPRO conducted a regional workshop on Childhood TB from 26-28 March 2014 in Ho Chi Min City, Viet Nam. The meeting was attended by 21 country participants from 8 countries (Cambodia, China, Fiji, Lao PDR, Mongolia, Papua New Guinea, Philippines and Viet Nam). Each country team was composed of a focal point from national tuberculosis control programme (NTP), maternal and child health programme (MCH) and paediatric association. Also 17 observers and 2 temporary advisers from different technical agencies participated in the meeting. Priorities for strengthening childhood TB activities in the Region were identified; an informal Regional Childhood TB Task Force was established; and the countries drafted their country specific action plans. Cambodia, China, Fiji, Lao PDR, Philippines, Viet Nam have integrated childhood TB into their national strategic plans. Cambodia, Lao, multicountry-pacific region, Lao PDR, PNG, Solomon Islands and Vietnam are working on concept notes including childhood TB. The 7th TAG Pacific Islands has taken place from 20-22 October 2014 and included a session on childhood TB from global policy to local action. It also included clinical aspects, recommendations to strengthen R&R, diagnosis, prevention. With respect to 2015, the 5th Union Asia-Pacific conference will be held in Melbourne in 2015 and will provide an opportunity for follow up on the national childhood TB action plans. The post-2015 WPRO regional action plan will also include childhood TB. Mongolia will prepare a concept note to the Global Fund. There will be a programme review in Vietnam and one in Cambodia. WPRO will identify TA needs around introduction of the “new” FDC.

European region - Martin van den Boom

WHO/EURO has created an advisory committee on regional adaptation process of post-2015 TB strategy. Childhood TB will be part of that regional strategy. EURO continues to push countries to include childhood TB as part of NSP and CNs. Uzbekistan and Kyrgyzstan had a childhood TB component in programme reviews. The Task Force gives advice on national protocols for childhood TB e.g. screening of MDR-TB contacts. With respect to pillar 3 of the post-2015 strategy (research), Martin van den Boom mentioned that research protocols as part of the SORTED programme include a focus on childhood TB. EURO is currently developing a questionnaire on adolescents. It is challenging due to the overlap in age groups.



Credit: Malgosia Grzemska

African region - Kefas Samson (on behalf of Daniel Kibuga)

AFRO organized a regional childhood TB consultation from 1-3 July 2013 in Brazzaville, DR Congo. A regional roadmap for childhood TB has been developed. TAN, DRC and Mozambique have set up pilot projects. However, AFRO is facing significant challenges since the Ebola epidemic. AFRO regional framework for childhood TB has been developed in collaboration with USAID and other partners. It is under-going peer-review within the region. It will be printed as soon as possible. Since late 2013, the region has been actively supporting NTP to incorporate childhood TB in national TB programme reviews. Through engagement of experts some part of the childhood TB subgroup. AFRO is providing capacity building to NTPs on clinical management of TB in close collaboration with the Stellenbosch University in South Africa. In Q1 2014, we planned a regional workshop on childhood TB. The regional workshop was postponed because of the fact that Member States were busy with the development of concept notes to the Global Fund NFM and with the Ebola epidemic. Most likely, the regional workshop will take place in Q1 of 2015 along with the NTP managers meeting.

South East Asia - Khurshid Hyder

The scale up of childhood TB management was on the agenda of the SEA Technical Working Group on TB (an advisory body to WHO/SEARO) which took place on 28-29 April 2014. The Technical Working Group also recommended to WHO/SEARO to organize a regional meeting on childhood TB later in the year or in 2015. Many countries have developed a plan for scaling up childhood TB and are implementing. But the case notification is not yet sufficient. The JEMM Myanmar (December 2015) will include childhood TB component. Countries are including childhood TB components in NSPs and CNs. Recently, Indonesia hosted a Global Consultation on childhood TB for high burden countries in the Eastern Mediterranean, South East Asia and Western Pacific regions.

SEAR has an NTP managers meeting in New Delhi from 10-14 November during which Soumya Swaminathan will address childhood TB.

Global consultation on childhood TB - Malgosia Grzemska

The global consultation on childhood TB was organized on 29 September – 1 October 2014 in collaboration with EMP/HIS, WHO country office Indonesia and TB Alliance (all three co-sponsored the meeting). High TB burden countries of three regions: SEAR, EMR and WPR attended and were represented by a mix of stakeholders including NTPs, paediatric associations, WHO country and regional office staff (TB and MCH programmes) and community representatives. The aim of the consultation was to assist countries in scaling up their response to childhood TB. The consultation was facilitated by experts from the childhood TB subgroup along with the WHO staff.

The following countries were represented: SEAR: Bangladesh, India, Indonesia, Nepal and Thailand; WPR: China, Vietnam and PNG; and, EMR: Afghanistan and Pakistan.

Countries presented the status of the childhood TB activities in a poster session; some are very advanced. Bangladesh already has the national childhood TB guidelines and training material; Pakistan held a lot of training among NTP staff. But in all countries, NTP does not have close links with the private paediatricians and engagement of hospitals is a challenge. In the breakout sessions that followed, countries were asked to identify three immediate priority areas that would feature in their action plans. Most common among all countries were the following: (i) implementation of contact tracing and IPT; (ii) Engagement of communities and other health stakeholders (like MCH or child health services); and, (iii) Strengthening recording and reporting systems to get better data on the burden. Next steps for all is to develop short and intermediate term action plans (for next year), seek national endorsement and support, engage relevant stakeholders and develop a 5-year action plan 2016-20. Many countries will request TA for which funding will need to be identified. WHO and TB Alliance will discuss how to address the requests for technical assistance.

During the discussion, it was highlighted that we really need to assist countries to prepare themselves for the uptake of the new FDCs. If there is no demand from countries, the product will be made but the price may be too high.

Steve Graham mentioned that childhood TB will be a session in STAG-TB in 2015. Steve Graham is also a member of the WPR TAG. This meeting will take place at the beginning of December 2014. We are still trying to engage more with UNICEF. The TB Alliance is discussing to have a UNICEF paediatric TB focal point in NYC.

We have been discussing under-diagnosing and under-reporting, however, there is also the issue of over-diagnosing.

There is a need for further interaction between the TB and HIV communities. We are now jointly developing concept notes to the Global Fund but children are often forgotten.

The session concluded with a request to share best practices. They help to replicate activities in other countries.

8. Country experiences in scaling up childhood TB activities

Country experiences Bangladesh - Dr Khurshid Talukder

Bangladesh is the 5th TB HBC in the world. In 2013, there were 184,506 total new and relapse cases (Global TB Report 2014) of which 5051 among children aged under 15 years.

Missed opportunities for diagnosis include: no implementation of contact tracing; No IYCF or growth monitoring; ARI brains; NTP focus on sputum; and MCH services not enough aware of TB.

If children with a positive CXR also have the following signs: positive TB contact; increased duration of cough; and, a TST positive, they are highly likely to have TB (Chishti, 2013).

How much child TB is there in Bangladesh? In 2008, the NTP diagnosed 4,375 children with TB. However, about 25,277 children with TB could have been diagnosed. Low pre-school TB notification is a marker of missed cases.

Bangladesh has a 21 member Childhood TB advisory Group with representatives from the NTP, academia, NGOs, the Bangladesh Paediatric Association etc. In 2012, national guidelines for the management of tuberculosis in children were developed as well as training modules for doctors: <http://tbcare2.org/content/national-guidelines-management-tuberculosis-children> As of now, one third of the Dhaka doctors are trained. A booklet for health workers has been developed in Bangla as well as “your child may have TB” posters and a poster on IPT. There are three immediate priorities: Contact tracing & IPT; Capacity building among doctors, health workers and community health workers; and, Engagement of new players with TB services (IMCI, MCH, national nutrition services, etc.).

In 2012, a study was published on increasing community TB detection in the International Journal of Tuberculosis and Lung Diseases. It showed that community involvement increased case detection about 3-fold.

How will the trained people work? Contact tracing will be implemented by DOTS workers, screening will be done by microscopy centre staff, and case detection will be done by doctors, usually attached to microscopy centres.

The Childhood TB advisory gap will look at the gaps in the system (e.g. documentation on implementation of IPT; stock outs of IPT; parents’ refusal; etc.) and will try to address the gaps accordingly. ? The Government did a pilot in 4 areas giving IPT to under 1-year of age. The data now need to be analysed. More Government and private sector doctors need to be trained.

Dr Talukder referred to an article by Philip et al in Plos Medicine on “Closing the Policy-Practice Gap in the Management of Child Contacts of Tuberculosis Cases in Developing Countries”. This article shows that there are a number of things we need to look in to before ask doctors to do contact tracing and IPT. Dr Talukder also referred to work by Dr Salim et al published in the WHO Bulletin on “Turning liabilities into resources: informal village doctors and tuberculosis control in Bangladesh”. It outlines Dr Salim’s experiences who trained 12,525 village doctors in 2002-2003. 11% of all TB cases with positive sputum smear were referred by village doctors. The rate of positive tests in patients referred by village doctors was 14.4%. 18,792 patients receive DOT from village doctors accounting for between 20 and 45% of patients on treatment during the 1998-2003 period. The treatment success rate was about 90% throughout the period.

A childhood TB roadmap has been developed for Bangladesh. It calls for: inclusion of children and adolescents in research, policy development and clinical practice; collection of better data including data on prevention; development of training and reference materials for health care workers; fostering of local expertise and leadership; do not miss critical opportunities for intervention; engage key stakeholders; develop family-centered and community-centered strategies; address research gaps; and, form coalitions and partnerships to improve tools for diagnosis and treatment. Many of these initiatives have started. Unfortunately, the Bangladesh concept note to the GF NFM may have a gap on childhood TB as drastic cuts had to be made.

Community based child TB control: experiences from UR Tanzania and DRC – Dr SS Lal, PATH

UR Tanzania is a TB high burden country. Due to challenges in diagnosis and reporting, the magnitude of childhood TB is difficult to ascertain. The NTP estimates that around 8% of all TB cases are childhood TB cases. PATH assisted UR Tanzania in the development and distribution of new guidelines, training materials and job aids. PATH is providing training of health care workers and ongoing mentoring. PATH is engaging community members and private health facilities. Community based interventions include: development of an appropriate ACSM strategy; a package of community-based TB interventions; support to the Council of Health Management Teams (CHMTs); training of community groups such as traditional healers, former TB patients, private drug dispensers, community owned resource persons and CBOs as well as supervision. Magnet theatre has been used

as well as “photo voice” (people take photos in the field and discuss issues). Through these interventions in six regions of UR Tanzania, the percentage of child TB cases among all cases doubled and childhood TB cases detected by the community doubled.

The Democratic Republic of the Congo (DRC) is a TB high burden country as well as a MDR-TB high burden country. Children comprise of 14.17% of all TB cases. PATH assisted the NTP in setting up collaborations, developing guidelines, an algorithm and a training curriculum. PATH worked in close collaboration with local NGOs to involve communities and community-based groups. Initiatives Inc. has built capacity of the local organizations for financial management and implementation of high-quality TB programmes. Capacity of local NGOs was built through training, coaching and mentorship in program design, implementation and M&E. Periodic assessment has showed improved capacity for NGOs to collect data and report results. NGOs supported the NTP to train community health workers in TB suspect identification, referral, follow-up, data collection and reporting. Lessons learned include: Involvement of community increases childhood TB significantly; Situational analysis is important to identify the issues; Collaborative approach among NTP, stakeholders and community creates ownership; Training community members without continued support and supervision leaves no impact; and, Long-term investments by Governments and child health community is essential for sustainability.

Scaling up child TB activities: the Kenyan Experience – Dr Lisa Maleche Obimbo

In Kenya, about 40% of population (39.4 million in 2006) is below 14 years of age. Before 2008, Child TB was under-recognized and under-represented at several fronts: (i) at policy level (minimal mention of child TB in policy documents and meetings); (ii) at health service delivery level (children were managed as small adults; health workers had inadequate knowledge and skills to diagnose and manage children; use of a scoring system was a barrier; much up-referral to paediatricians for diagnosis; and, use of adult drug formulations); (iii) at the monitoring and evaluation level (registers, treatment cards and outcome indicators were all tailored to adults); (iv) at the training materials and TB guidelines level (the childhood TB module was 2 hours in a 5-day training course; in the national TB guidelines 2006 there was no mention of children; only NTP personnel got trained rarely involvement of MCH or paediatric staff); and, (v) at the prevention level (child contact tracing was low; health workers were not confident at ruling out active TB in children; and, no INH prophylaxis was available). From around 2006, two paediatricians (including Lisa Obimbo) realized the lack of child issues in TB programme activities and began to invite themselves to MOH forums on TB to create awareness of child TB, the gaps and poor outcomes that they noticed in hospitals. And the advocacy did bear fruits. The NTP began to seek regularly technical guidance from the two paediatricians on child TB and lung diseases. The Kenya Paediatric Association organized a one-day symposium on child TB and invited the NTP. This was the beginning of the true scale up of the childhood TB activities. In 2009, AFRO organized a workshop on child TB involving all Sub-Saharan African countries. The Ministry of Health sent a provincial TB officer (NTP) and the two paediatricians who developed a matrix outlining strengths, weaknesses, opportunities and threats for scaling up childhood TB in Kenya. They also prepared actions and an implementation plan. The provincial TB officer was requested to handle the childhood TB agenda and coordinated activities and various technical partners to move the agenda forward. Stand-alone guidelines on the Management of Child TB were developed in 2010 based on the Union desk guide. In November 2011, the NLTP strengthened leadership in child TB: a Child TB technical working group was set up in the NLTP with multi-organisational representation; a NLTP officer in the national office was given a dedicated portfolio of child TB as a full-time responsibility; and, child TB was included in the NSP 2013- 2018 (with budget line). The child TB guidelines were officially launched on World TB Day 2012. In order to create awareness, the child TB guidelines were distributed at the Kenya Paediatric Association conference 2012. Child TB has also been included in the World AIDS Day ceremony programme. The Child TB technical working group organize a workshop for health workers to

manage child TB. The working group also developed job aids (screening for child TB; diagnostic algorithm; IPT dosage charts; and, drug dosage charts). The monitoring card has been adapted to include child-specific aspects. Training of health workers was rolled out in 2013 (county by county). NLTP staff are trained along with paediatricians, medical officers, MCH staff, hospital pharmacists, and lab staff. During the mid-term review of the national TB programme in February 2014, child TB was included as a separate area of focus. It was recommended to scale up CXR and Xpert MTB/RIF testing and make it free for children. It was recommended to scale up capacity building on diagnosis, management and prevention and to scale up child contact tracing to improve case finding and uptake of IPT. What has this meant for Kenya? The impact is not clear. Childhood TB cases have gone down among total TB cases during the last three years while an increase was expected. Efforts are being planned to further scale up the childhood TB response.

Management of TB in children in Vietnam: implementation and roll-out – Dr Nguyen Thien Huong, KNCV Tuberculosis Foundation/TB CAREI Vietnam

Children <5 years of age account for about 24% of the population (21 million children). The annual risk of infection is 1.67% or approximately 351,000 children infected with TB annually. WHO estimates that there are around 13,000 children with TB annually (2006 guidelines). The NTP reports 1200-1300 child TB cases each year. IPT is recommended since 2011 but not yet widely implemented. Vietnam has taken a new approach for the management of TB in children: (i) children that are close contacts (living in the same household) of a sputum smear positive TB case in the community need to be screened; (ii) IPT should be provided to child contacts aged <5years and all children with HIV once TB has been excluded at communal (primary care) health centre level; (iii) a diagnostic algorithm has to be applied for diagnosis of TB in children at the district (secondary care) level; and, (iv) The NTP is engaging the wider health care sector in strengthening links in particular with the child health sector. In the period 2010-2012, TORs for the childhood TB working group of the NTP were developed. The childhood TB working group developed national guidelines on the management of TB in children including child contact screening, diagnostic and treatment algorithms, and forms and registers. In the second half of 2012, training on childhood TB was provided to NTP staff, paediatricians, doctors at provincial, district level and health care workers at the community level. Isoniazid preventive therapy, forms and registers were made available for pilot implementation in 4 Provinces with 51 districts and 857 communities. The management of childhood TB was included in the 5-year national TB strategic plan 2016-2020 and childhood TB data were included in routine reporting and reviews. With Global Fund funds, the pilot project was rolled out to 6 more Provinces in 2013-2014 and will be rolled out to another 12 Provinces in 2015. Results of the pilot project in the four initial provinces (Hanoi, HCMC, Can Tho and Thai Binh) show that since Q4 2012, 6111 children (close contacts) were screened for TB. 2394 children were eligible for IPT and 1413 were put on IPT (59%). 459 children had active TB (44 SS+, 214 SS- and 203 EPTB). The IPT completion rate is 83.5%. The IPT default rate is 16.5% and the rate of side-effects is 0.2%. Vietnam has developed a national workplan for the roll-out of the management of TB in children for the period 2015-2020 with the goal to strengthen detection, treatment and preventive therapy for children towards decreasing childhood TB morbidity and mortality.

The four main objectives are:

1. Strengthening of advocacy, communication and social mobilization to ensure management of TB in children;
2. Strengthening of detection and early treatment for children, increasing the percentage of childhood TB in total new TB cases detected annually from 1.2% in 201 to 6% in 2020;
3. Strengthening the management, screening and IPT for children with close contact with a PTB case, to ensure 100% PTB cases are investigated for child contacts management, at least 80% child contacts eligible for IPT on IPT and 90% IPT completion rate; and,
4. Strengthening of monitoring, supervision and conducting research on management of TB in children.

Key indicators for 2020 have been included in the concept note to the Global Fund New Funding Model submitted in August 2014.



Credit: Malgosia Grzemska

9. Childhood TB landscape analysis: Progress to-date - Clydette Powell (through Webinar), Keri Lijinski, and Kelly Sawyer

The childhood TB landscape analysis is undertaken because of the lack of information on childhood TB and because the information that is available is not centralized.

The childhood TB landscape analysis will be a one-stop shop for information on childhood TB activities in 21 priority countries of Africa and 20 priority countries of Asia. It will show the status of childhood TB programming & provide mapping of recent/current studies, results and partners. It will be a tool for advocacy showing successes as well as gaps and challenges. It can help to define strategic opportunities to build child TB programming.

The childhood TB landscape analysis consists of three products: (i) a country tracker providing a quick overview of key parameters on childhood TB in selected countries; (ii) a database and report: overview of childhood TB activities at country level and analysis of results; and, (iii) country profiles: two-page reports on current epidemiology, national policies, partners working in the area of childhood TB, etc. The methodology used includes: document and literature review; interviews with key informants; analysis of WHO data; and, a survey to African NTP managers. Information is being collected on: political will; leadership & advocacy; data collection and reporting; availability of guidelines; paediatric FDCs; Prevention; screening and referral; and, operational research.

With respect to survey results, the NTP managers considered difficulties with diagnosing TB in children the biggest challenge followed by health system shortcomings, difficulties with identifying

and protecting children at highest risk of TB, lack of data to support funding and planning, and, lack of community awareness and CSO support. The landscape analysis can be used to respond to these challenges. Information collected will help to develop the childhood TB agenda and to identify funding for it (NSP, GF CNs, etc.). It will also provide guidance as to how to set the framework for service delivery (build capacity among health workers). USAID is seeking the support of the childhood TB subgroup members to: identify champions for childhood TB in the respective priority countries; clarify if childhood TB is reflected in the current TB NSP and in concept notes to the GF NFM in the priority countries; clarify if routine training on childhood TB is conducted in the priority countries; explain how the countries are operationalizing childhood TB contact tracing and monitoring of IPT completion; and, to map ongoing operational research on childhood TB.

10. Paediatric TB Research Funding Trends – Lindsay McKenna

The treatment action group is tracking tuberculosis research funding trends and just launched the 2014 report on tuberculosis research funding trends over the period 2005-2013. The report compares what has been spent on TB research to the targeted amounts set out in the Global Plan to Stop TB 2011-2015. The total TB R&D funding over the period 2005-2013 has been levelling off (to 876 million USD in 2013). The Global Plan to Stop TB 2011-2015 called for 9.8 billion USD while by 2013, donors have spent just 1.99 billion USD. It shows 9 years of funding gaps against the targets set out in the Global Plan to Stop TB despite the fact that one single philanthropic donor (BMGF) substantively increased its contributions and more funders are now reporting to TAG.

The analysis also shows that, between 2012-2013, the pharmaceutical industry have walked away from TB. Those that remain spent less than 100million in 2013 which is less than what they spent in 2009 during the peak of the financial crisis. 60% of the total TB R&D funding comes from public institutions; 60% of the public money spent on TB R&D comes from 1 country, the USA; 60% of industry funding for TB R&D come from 1 company, Otsuka; and 60% of TB basic science funding comes from INH. Private sector contributions have come down. In 2013, a total of 25 million USD was available for paediatric TB R&D. It was spent mostly on research on drugs. The childhood TB roadmap includes a need of 40 million USD per year or 200 million USD for the period 2011-2015. The world has however spent less than one quarter of the 200 million USD needed, a total of 47.2 million USD in the period 2011-2013. Where do we go from here? We must: call on countries, especially BRICS to invest in TB research; make the case that research and programmes are two sides of the same coin; engage in discussions on new funding targets for the 2016-2025 Global Plan to Stop TB; we need to call for inclusion of a paediatric-specific funding target; and, in order to avoid that the history will repeat itself, we need to engage the public more broadly by engaging TB affected communities in TB research.



Credit: Malgosia Grzemska

11. Update on significant recent research papers – James Seddon

James Seddon conducted a semi-systematic review of publications on PubMed on TB in children. It resulted in 29,000 hits. Since 1980, the number of publications on childhood TB has gone up substantially. However, if one looks at TB in general, suddenly there are 240,000 hits.

If we restrict the search on PubMed to publications on TB and children during the last 12 months (since Union conference in Paris in October 2013), it results in 746 hits out of which 28 articles looked pretty interesting based on James Seddon's own clinical and research interests. The outcome was therefore slightly biased towards clinical and epidemiological studies and towards drug resistance. The articles selected can be divided into five broad categories: epidemiology/natural history; diagnostics; treatment; prevention; and, vaccines.

With respect to the category "epidemiology/natural history", the following articles are noteworthy:

- Jenkins HE et al. Incidence of multidrug-resistant tuberculosis disease in children: systematic review and global estimates.
- Chun P-C et al. Risk for Tuberculosis in Child contacts: Development and Validation of a predictive Score.
- Dodd PJ et al. Burden of childhood tuberculosis in 22 high-burden countries: a mathematical modelling study.
- Naranbhai V et al. The association between the ratio of monocytes: lymphocytes at age 3 months and risk of tuberculosis (TB) in the first two years of life.
- Berti E et al. Tuberculosis in childhood: a systematic review of national and international guidelines.

In the category "diagnostics", the following studies were selected:

- Portevin D et al. Assessment of the novel T-cell activation marker-tuberculosis assay for diagnosis of active tuberculosis in children: a prospective proof-of-concept study.

- Planting NS. Safety and efficacy of induced sputum in young children hospitalised with suspected pulmonary tuberculosis.
- Reither K et al. Xpert MTB/RIF assay for diagnosis of pulmonary tuberculosis in children: a prospective, multi-centre evaluation.
- Anderson ST et al. Diagnosis of childhood Tuberculosis and Host RNA Expression in Africa.
- Nicol MP et al. Urine lipoarabinomannan testing for diagnosis of pulmonary tuberculosis in children: a prospective study.
- Raizada N et al. Enhancing TB Case Detection: Experience in Offering Upfront Xpert MTB/RIF Testing to Pediatric Presumptive TB and DR TB Cases for Early Rapid Diagnosis of Drug Sensitive and Drug Resistant TB.

In the category “treatment”, the following articles are worth reading:

- CDC MMWR. Provisional CDC Guidelines for the Use and Safety Monitoring of Bedaquiline Fumarate (Sirturo) for the Treatment of Multidrug-Resistant Tuberculosis (25 October 2013).
- ERS/WHO Tuberculosis Consilium assistance with extensively drug-resistant tuberculosis management in a child: case study of compassionate Delamanid use.
- Link-Gelles R et al. Tuberculosis Immune Reconstitution Inflammatory Syndrome in Children Initiating Antiretroviral Therapy for HIV infection.
- Bose A et al. Intermittent versus daily therapy for treating tuberculosis in children (review).
- Seddon JA et al. High treatment success in children treated for multidrug-resistant tuberculosis: and observational cohort study.
- Chiang SS et al. Treatment outcomes of childhood tuberculous meningitis: a systematic review and meta-analysis.
- Garcia-Prats AJ et al. Linezolid for the treatment of drug-resistant tuberculosis in children: a review and recommendations.
- WHO. Guidance for national tuberculosis programmes on the management of tuberculosis in children: second edition.

In the category “prevention”, the following articles were listed:

- Jaganath D et al. Contact Investigation for Active Tuberculosis Among Child Contacts in Uganda.
- Cruz AT et al. Safety and completion of a 4-month course of rifampicin for latent tuberculous infection in children.
- Seddon JA et al. Preventive Therapy for Child Contacts of Multidrug-Resistant Tuberculosis: a Prospective Cohort Study.
- Sollai S et al. Systematic review and meta-analysis on the utility of Interferon-gamma release assays for the diagnosis of *Mycobacterium tuberculosis* infection in children: a 2013 update.
- Zelner JL et al. Bacillus Calmette-Guérin and Isoniazid Preventive Therapy Protect Contacts of Patients with Tuberculosis.
- Parr JB et al. Concordance of Resistance Profiles in Households of Patients With Multidrug-Resistant Tuberculosis.

In the category “Vaccines”, many studies on BCG were found:

- Mangtani P et al. Protection by BCG Vaccine Against Tuberculosis: A Systematic Review of Randomized Controlled Trials.
- Barreto ML et al. Causes of variation in BCG Vaccine efficacy: Examining evidence from the BCG REVAC cluster randomized trial to explore the masking and the blocking hypotheses.
- Idoko OT et al. Safety and immunogenicity of the M72/AS01 candidate tuberculosis vaccine when given as a booster to BCG in Gambian infants: An open-label randomized controlled trial.
- Kagina BMN et al. The novel tuberculosis vaccine, AERAS-402, is safe in healthy infants previously vaccinated with BCG, and induces dose-dependent CD4 and CD8T cell responses.

- Hollm-Delgado M-G et al. Acute Lower Respiratory Infection Among Bacille Calmette-Guérin (BCG)-Vaccinated Children.
- Roy A et al. Effect of BCG vaccination against *Mycobacterium tuberculosis* infection in children: systematic review and meta-analysis.

James Seddon concluded that these are exciting times for paediatric TB. There are lots of studies being published but there is lots more work to do as well ...

12. Update on current research focusing on new TB treatment strategies in children – Anneke C. Hesselning

Children have traditionally been excluded from TB treatment trials for a variety of reasons including paucibacillary disease; end point definitions; perceived ethical and practical challenges; and a small perceived market share.

This is no longer the case for novel drugs. We do not need efficacy data to move ahead. We need PK data and safety information for the development of appropriate formulations (phase I, II).

Research area	Gaps for children	Priority studies
DS-TB	PK/safety first-line drugs at higher doses, esp. infants, HIV+ Optimal treatment for TB meningitis Treatment shortening DS-TB	PK studies first-line drugs at higher doses PK/efficacy study in children <6 months
DR-TB	PK/dosing second-line drugs (FQ, aminoglycosides, linezolid) Requirement for injectables for limited disease	Modelling existing data, testing doses predicted to achieve PK targets Careful clinical cohort study PK/safety studies bedaquiline, PA-824 Safety/QT for BDQ + DLM in children
Co-treatment TB/HIV	Super boosting LPV/r in young children taking HRZE EFV-based regimen in children <3 years INSTI-bases ART with standard TB drugs (HRZE)	Super-boosted PI with HRZE EFV+HRZE in slow CYP2B6 genotype RAL or DTG-based ART with TB drugs
LTBI	Safety/tolerability/PK once-weekly INH/RPT regimen for youngest children DDI with ART MDR LTBI	RPT dose for children under 2 for weekly INH/RPT; tolerability/bioequivalence child-friendly formulation Efficacy and safety of long-term use of fluoroquinolones.

Novel TB drug candidates include:

Drug/class	Pharma	Target	Status
Rifapentine	Sanai	LTBI, disease	Adult phase IIB; paediatric PK in development (TBTC)
Bedaquiline	Janssen	MDR TB	Adult phase IIB; Paediatric trial in development
Delamanid PA-824	Otsuka TB Alliance	MDR TB LTBI, DS/DR TB	Adult phase IIB, paediatric trials ongoing Adult phase IIB
SQ 109	Sequella	LTBI, MDR TB	Adult phase IIB
Sutezolid Tedizolid	Sequella Cubist	MDR TB MDR TB?	Adult phase I Licensed for SSTI
Moxifloxacin Levofloxacin	Bayer Generics	DS/MDR TB	Adult phase II Paediatric trials underway

How can we work with TB programmes for existing drugs?

With respect to drug susceptible TB, the following trials are ongoing or are planned to start soon:

- The SHINE trial on shorter treatment for minimal TB in children. It is a randomised trial of therapy shortening for minimal tuberculosis with new WHO-recommended doses/fixed-dose-combination drugs in African and Indian HIV+ and HIV- children (children with smear-negative TB).
- The DATiC study at the University of Cape Town looking at PK and safety of first-line TB drugs in paediatric populations.
- An Infant PK study: Treat Infant-TB (infants <12 months with DS-TB). DTTC in partnership with the TB Alliance (UNITAID-funded STEP-TB project).
- DNDi: Superbooster for HIV/TB co-infection. A study to develop a stand-alone ritonavir (RTV) booster formulation to be added to the optimized LPV/r-based paediatric ARV regimen.
- Sure TB trial (not yet funded): short intensive anti-tuberculosis and anti-thrombosis phase II treatment for children <18 years (with or without HIV) with drug-susceptible TB meningitis comparing (i) the efficacy and toxicity of a short intensive anti-tuberculosis regimen with the standard WHO-recommended regimen (open label) and (ii) low dose aspirin (double-blind placebo-controlled).
- The TBM-Kids trial: optimizing treatment to improve TBM outcomes in children. A phase I/II randomized, open-label trial to evaluate the pharmacokinetics, safety, and treatment outcomes of high dose Rifampicin with or without levofloxacin versus standard treatment for paediatric tuberculosis meningitis. It is looking at penetration of drugs. The primary objective is to characterize the PK of rifampicin given. Secondary objectives are to assess outcome of children treated for TBM.

With respect to drug-resistant TB, studies are ongoing to characterize PK of second-line TB drugs and to optimize their use in current regimens; to establish shorter and safer treatment avoiding injectables; to evaluate novel drugs (phase I/II); to understand how to prevent MDR-TB; and to inform development of treatment guidelines and drug formulations.

- MDR-TB PK study NICD R01 to characterize the PK and toxicity of routinely used second-line anti-TB drugs in children. E.g. Amikacin by age and HIV status; levofloxacin for children.

- IMPAACT (International Maternal Pediatric AIDS Clinical Trials Network) P1108: in HIV-uninfected infants, children and adolescents with MDR-TB to evaluate the safety and tolerability of Bedaquiline over 24 weeks and to evaluate the PK of Bedaquiline over 24 weeks.
- A second IMPAACT trial on Delamanid (Otsuka) to establish its optimal use in HIV co-infected children. The aim is to have delamanid in paediatric formulations available by 2017.

With respect to XDR-TB, Anneke Hesselning referred to the following planned study in adults:

- Nix-TB: XDR-TB in adults. It will be a randomized, open-label trial assessing bedaquiline plus PA-824 plus linezolid plus pyrazinamide or bedaquiline plus PA-824 plus linezolid in subjects with pulmonary infection with extensively drug-resistant tuberculosis. It will include children >14 years but Anneke Hesselning and colleagues are trying to also include younger children who are exposed to transmission in household.

With respect to community-based contact tracing, Anneke Hesselning referred to the DR-TB CHAMP study, a community-based, multicentre, cluster randomised phase II superiority trial of LFX vs placebo for the prevention of MDR-TB in HIV-infected and uninfected child household contacts of confirmed adult MDR-TB source cases. The study tries to answer the following questions: (i) Is Levofloxacin (LFX), given daily for 6 months, effective to prevent MDR-TB in high-risk child and adolescent household contacts of MDR-TB cases?; (ii) Does LFX have acceptable toxicity and tolerability in children?; (iii) Is there a difference in mortality between study arms?; (iv) Is adherence similar between study arms?; (v) Are there differences in LFX resistance between study arms for children developing incident TB?; and, (vi) Is LFX cost-effective and acceptable to prevent MDR-TB in child and adolescent household contacts)

Lastly, Anneke Hesselning, Simon Schaaf, Tony Garcia-Prats, Jennifer Furin and James Seddon are planning to study paediatric MDR-TB by meta-analysis of individual patient data to gather evidence to inform the paediatric component of the revised WHO guidelines on the management of multidrug-resistant tuberculosis. Members of the childhood TB subgroup who have individual patient data regarding treatment outcomes for paediatric MDR-TB were invited to collaborate on this planned project (please contact Elizabeth Harausz at: epharausz@gmail.com).

13. Updates from the Sentinel project on paediatric drug-resistant tuberculosis – Soumya Swaminathan

The Sentinel project on paediatric drug-resistant tuberculosis is a network of researchers, caregivers, and advocates who share a vision of a world where no child dies of this preventable and curable disease. The network members collaborate to raise the visibility of this vulnerable population, and to share evidence and resources that can increase children's access to prompt and effective treatment. The Sentinel Project was established 3 years ago and has now over 300 members in more than 60 countries around the world.

The Sentinel Project is taking a practical approach for caring of children with DR-TB. Members of the network have developed a Field Guide on the Management of Multidrug-Resistant Tuberculosis in Children, an MDR-TB weight-based dosing chart for children, and, since 2013, have conducted workshops/trainings (France, Georgia, Tajikistan, India, China and Bangladesh) and a series of webinars of which videos are available on the website:

<http://sentinel-project.org/> A clinical review on Caring for Children with Drug-Resistant Tuberculosis: practice-based recommendations was published in November 2012 by Seddon JA et al in the American Journal of Respiratory and Critical Care Medicine.

At the moment, a case registry for childhood DR-TB is under development. A core data set has been defined. It is designed to capture information on how children with DR-TB are being diagnosed and treated (diagnostic criteria; baseline clinical and laboratory data; treatment regimens, including

regimen changes; adverse events; early treatment response; final treatment outcome). It will have and an electronic interface. Data will be freely available and can be used to generate local reports. An online survey was undertaken in the period July-September 2013 to identify the top research priorities for children with MDR-TB. The 104 respondents top-ranked the research question to identify the best combination of existing diagnostic tools for early diagnosis of drug-resistant TB in children. Treatment-related research questions include: reasons for poor treatment outcomes; adverse effects of anti-TB drugs; optimal treatment duration; and, interventions for improving treatment outcomes. In the epidemiology area, the prevalence of drug-resistant TB was the highest-ranked question. With respect to the development type questions, interventions for optimal diagnosis, treatment and modalities for treatment delivery ranked highest. The predominant discovery type questions focused on new drug evaluation and models for preventive therapy and for preventing new infections. The Sentinel Project on Paediatric drug-resistant tuberculosis operates pro-bono. The work is not funded.

Action points for October 2014 – September 2015:

- Bring childhood TB to STAG-TB 2015 and invite colleagues working on maternal and child health as well as HIV/AIDS to facilitate integration;
- Document and publish scaling up activities;
- Assist countries to include Childhood TB in all steps of the Global Fund New Funding Model (e.g. NTP review, National TB strategic plan, gap analysis, concept note);
- Encourage countries to identify national and regional champions on paediatric TB;
- Build and expand regional capacity to address growing requests for technical assistance in particular in light of the development, finalization and implementation of national action plans for scaling up childhood TB.

Annex 1: Agenda



**Annual meeting of the Childhood TB Subgroup
27 October 2014**

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AGENDA

Childhood TB subgroup meeting		08:30 – 18:00
Chair: Dr Steve Graham		
<i>08:30 - 09:00</i>	<i>Registration</i>	
09:00 - 09:15	Opening and welcoming words	Mario Raviglione, Director GTB & Steve Graham, Chair, Childhood TB subgroup
09:15 – 9:40	Report from Chair on the 2014 activities of the Childhood TB subgroup	Chair
09:40 - 10:00	TB CARE I Childhood TB online training & plans for roll-out and assessing of impact	Anne Detjen & James Seddon
10:00 - 10:20	Update on the UNITAID-funded STEP-TB project on the development of child-friendly formulations	Cherise Scott, TB Alliance
10:20-10:30	Discussion	All
<i>10:30 - 11:00</i>	<i>Coffee/Tea break</i>	
11:00 - 11:20	Update on estimates including the work on burden of TB in adolescents	Babis Sismanidis & Kathryn Snow
11:20 – 11:40	Discussion	All
Regional experiences in scaling up childhood TB activities Chair: Dr Khurshid Hyder		

11:40 – 12:00	Update on the implementation of the Childhood TB Roadmap	Anne Detjen & Malgosia Grzemska
12:00 – 12:30	Debriefing on regional activities e.g. AFRO (Harare meeting); AMRO (Panama); EURO (Task Force); WPRO (Meeting Vietnam and follow up); Global Consultation on Childhood TB in HBCs in EMR, SEA and WPR (Jakarta)	Kefas Samson for Daniel Kibuga, Cornelia Hennig, Martin van de Boom, Malgosia Grzemska
12:30 – 13:00	Discussion	All
13:00 – 14:00	Lunch break	
Country experiences in scaling up childhood TB activities Chair: Lisa Obimbo		
14:00 – 14:15	Bangladesh	Khurshid Talukder
14:15 – 14:30	Community based child TB (Tanzania and DRC)	Sadasivan S Lal, PATH
14:30 – 14:45	Kenya	Lisa Obimbo
14:45 - 15:00	Vietnam	Huong Nguyen, KNCV
15:00 – 15:30	Discussion	All
15:30 – 16:00	Tea/Coffee break	
Update on research and new tools Chair: Steve Graham		
16:00 – 16:15	Childhood TB landscape analysis	Clydette Powell, USAID (through webinar) & Keri Lijinski & Kelly Sawyer
16:15 - 16:30	Funding trends for R&D on pediatric TB: TAG's 2014 TB R&D resource tracking report findings	Lindsay McKenna
16:30 – 16:45	Update on significant recent research papers	James Seddon
16:45 - 17:00	Update on current research focusing on new TB treatment strategies in children	Anneke Hesselting & Soumya Swaminathan
17:00 – 17:30	Discussion on research needs and priorities	All
17:30 - 18:00	Wrap up, next steps and closure	Chair & Secretariat

Annex 2: List of participants (based on sign-up sheets)

Core team members:

Steve Graham (Chair)	Deron Burton
Anne Detjen	Connie Erkens
Anneke Hesseling	Cleotilde (Telly) Hidalgo How
Elizabeth (Lisa) Obimbo	Clydette Powell (through webinar)
James Seddon	Soumya Swaminathan

Subgroup members, presenters and other participants:

Lisa Adams	Rifat Mahfuza	WHO staff
Tope Adepooyibi	Mamodikoe Makhene	Ayodele Awe
Jalaluddin Ahmed	Anna Mandalakas	Maria Regina Christian
Shakil Ahmed	Kyi Minn	Erwin Cooreman
Valentina Aksenova	Godwin Mtetwa	Cornelia Hennig
Paula Akugizibwe	Ya Diul Mukadi	Khurshid Hyder
Jason Bacha	Sugata Mukhopadhyay	Daniel Kibuga
Adrie Bekker	Yamuna Mundade	Enang Enang Oyama
Oswald Bellinger	Karak Kanyan Narra (?)	Kefas Samson
Andrew Brent	Nicolay Nikolenko (?)	Sabera Sultana
Melissa Briggs	Katherine Ngo	Martin Van Den Boom
Miranda Brouwer	Huong Thien Nguyen	Fraser Wares
Liane Campbell	Brian Ngwatu	Michelle Williams
Chishala Chabala	John Baptist Nkuranga	
Sylvia Chiang	Betty Nsangi	Secretariat
Sushma Cornelius	Kosuke Okada	Annemieke Brands
Mark Cotton	Jacqui Oliwa	Malgosia Grzemska
Clemax Couto Sant Anna	Elana Robertson	Mario Ravigione
Andrea Cruz	Doris Rouse	Charalampos Sismanidis
Luis Cuevaz	Jill Sanders	
Anand Date	Kelly Sawyer	
Anne-Marie Demers	Anna Scardigli	
Gunta Dravniece	Simon Schaaf	
Karen Du Preez	Cherise Scott	
Vijaykumar Edward	Alena Skrahina	
Anthony Enimil	Kathryn Snow	
Deliana Garcia	Marina Tadolini	
Rachel Anne Golin	Khurshid Talukder	
Jeffrey Hafkin	Rina Triasih	
Shayla Islam	Dinihari Triya Novita	
Tina Monique James	Jeannette Ulate	
Francis Kanyike	Pilar Ustero	
Gagik Karapetyan	Irina Usherenko	
Senait Kebede	Shoji Yoshimatsu	
Kobto Ghislain Koura	Andre Zagorski	
Michelle Lafay		
Sadasivan S. Lal		
Daisy Lekharu		
Keri Lijinski		