

# Report of the annual meeting of the childhood TB Subgroup

**Wednesday 26 October 2016**

**Doubletree Hilton Hotel & Spa (Cannon Suite)  
6 Sir Thomas Street  
Liverpool L1 6BR, UK**



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## 1. Opening session

Mario Raviglione, Director WHO Global TB Programme, opened the annual meeting of the Childhood TB subgroup with a warm welcome on behalf of WHO GTB housing the Secretariat of the Childhood TB working group. He recognized that the subgroup is ever growing and very active (over 250 members, not including WHO staff). He thanked Dr Steve Graham for his leadership. Steve Graham has been Chair since February 2011 (two 3-year terms). During the summer, a call for nominations for the next Chair and voting by the core team took place. Later during the day, the next Chair of the subgroup was announced.

Mario Raviglione then referred to the Global TB Report 2016 which had been launched on 13 October 2016 showing that at least 1 million children become ill with tuberculosis each year. Children represent about 10-11% of all TB cases. In 2015, 210,000 children died of TB, including 40,000 TB deaths among children who were HIV-positive. To further improve our estimates and give insight to the level of under-reporting outside the NTP network, inventory studies are ongoing in China, Thailand, Indonesia, Philippines, Pakistan and Vietnam. Preliminary results from Pakistan show that there are at least twice as many children with TB in the private sector.

Since the launch of the child TB Fixed Dose Combinations (FDCs) on 2 December 2015, WHO and its technical partners have provided technical assistance to countries to switch to the new paediatric formulations in a step-wise manner. As announced by the Global Drug Facility on 5 October, already 27 countries are procuring the child TB FDCs. WHO GTB has submitted an application for inclusion of the child TB FDCs in the WHO Essential Medicines List for children. The application will be reviewed by a committee advising WHO in April 2017.

In terms of global tools and guidelines, during the Spring of 2016, WHO has issued updated guidelines for the treatment of drug-resistant tuberculosis. These guidelines include a recommendation on the shorter MDR-TB regimen for use in adults and children. In addition, WHO published an updated guideline on Delamanid, recommending use of this new drug in children above 6 years of age and in adolescents. Additional data are expected in the upcoming months on use of Delamanid in children 3-6 years of age. Unfortunately, no data are available on the use of Bedaquiline in children (patients younger than 18 years). Such data are needed for WHO to be able to make a recommendation. The Roadmap for childhood tuberculosis: towards zero deaths is now available on the WHO website in English, French and Spanish. The WHO Guidance for national TB programmes on the management of Tuberculosis in Children: second edition 2014 has also been translated into French and Spanish.

Continued efforts are being undertaken to ensure that paediatricians/childhood TB experts are participating in national TB programme reviews and to ensure that countries are including paediatric TB in TB National Strategic Plans and GF concept notes.

Mario Raviglione concluded that the 2016 annual meeting will again highlight country experiences in scaling up the response to childhood TB and on what needs to be done to move the agenda forward. He wished the subgroup members a very productive meeting.

## 2. Report from the Chair on 2016 activities of the childhood TB subgroup – Steve Graham

Steve Graham gave an update on the activities of the working group since the last annual meeting in December 2015 in Cape Town, South Africa. The purpose of the 2016 annual meeting is to share national and regional experiences in scaling up the response to childhood TB and discuss how to operationalize the End TB Strategy with a focus on childhood TB and presented next steps to move the agenda forward.

He highlighted the importance of “Knowing your epidemic”. The Global TB Report 2016 shows that in 2015, 1 million children 0-14 fell ill with TB (about 10% of the total caseload). The Male:Female ratio is 1.1-0.9. About 40% of the childhood TB cases can be found in South East Asia and about 31% in Africa. There were 210,000 deaths among children including 40,000 in children living with HIV. Childhood TB notifications have increased to 6.3% of the notified cases globally. For the first time, the Global TB Report has made an attempt to include country specific data. However, there are still gaps in the data that need to be addressed. Not all countries are reporting disaggregated by age. It is estimated that 25,000 children developed MDR-TB in 2014 although the vast majority (>95%) were not detected and treated. The burden of child MDR-TB will be the highest in countries with the largest MDR-TB burden. There are new opportunities to treat more children with MDR-TB. Under certain conditions, the short course regimen can be used in children; there is a move towards replacement of injectables in the longer MDR-TB regimen; and the new drugs (DLM/BDQ) are not necessarily contraindicated even if there are very few/no safety data. We continue however to see poor treatment outcomes for adolescents with TB.

With respect to prevention of TB in children, early identification and effective treatment of infectious TB and MDR-TB cases will reduce the burden of child TB and child MDR TB. The main benefit of neonatal BCG is protection against severe disseminated forms of TB in children but there are challenges around the availability of BCG (UNICEF has been quite agile in addressing it to some extent).

Contact screening and Latent TB Infection (LTBI) management provide an opportunity to detect other cases with TB already in the household (e.g recent experiences in Uganda). The focus of Latent TB Infection (LTBI) management is on individuals infected with TB that have greatest likelihood of developing active TB disease following infection – this includes young children and HIV-infected children of any age. The WHO Guidelines on the management of latent TB infection include strong recommendations for at risk populations in high TB burden settings where the TB incidence rate is  $\geq 100$  per 100,000 population. However, despite these recommendations, the uptake by families and implementation by national TB programmes remains poor.

The Global Plan to End TB 2016-2020 includes the following targets for 2025:

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

And the “top ten” indicators for monitoring the implementation of the End TB Strategy include the following indicator relevant to preventive therapy in children under 5 years of age:

- 90% or more of children aged <5 years who are household contacts of TB cases started on treatment for LTBI.

Data on eligible child contacts that started preventive therapy included in the Global TB Report 2016 show that, in 2015, 87,000 children started on “preventive treatment” or 7% of the estimated 1.2 million young children who are household contacts of bacteriologically confirmed TB cases in 2015. Only 9 of 30 high burden countries reported data. Afghanistan and Bangladesh reported the largest number, around 10,000. The WHO African region reported 28% of the total.

There are global and national indicators to evaluate LTBI management:

- Proportion of children who are household contacts who have completed evaluation for TB.
- Proportion of those eligible for prevention that have started treatment.
- Proportion that have completed treatment.

It is estimated (Yean et al. Public Health Action 6(2), 83-96, 2016) that in 2014, 2.4 million young children (<5 years) and 5.1 million older children (5-14 years) were living in households of patients with TB. Of these, around 240,000 (10%) of the young children and 420,000 (8%) of the older children will develop TB. Of the remaining 2.16 million young child contacts and 4.68 million older children contacts without TB, it was estimated that 848,453 (or 39%) and 2,660,885 (or 57%) were infected. Therefore, the global target of 90% or more of exposed children translates to:

- At least 6.2 million child contacts of all ages treated with preventive therapy if screening did not include testing for LTBI
- Around 2 million if preventive therapy was limited to young children contacts.

For detection of LTBI, we currently face major shortages of tuberculin solution. A novel skin test, the C-Tb test, has been developed at Statens Serum Institute, Copenhagen. It uses specific *M.tuberculosis* antigens (ESAT-6 and CFP-10) with a cut-point of 5 mm induration established. C-Tb is more specific than TST as it is not affected by prior BCG vaccination. When evaluated in patients with active TB, the sensitivity is lower than for TST and reduced in PLHIV with marked immunosuppression as measured by CD4 count (as for TST). However, compared to IGRA, C-Tb does not require a laboratory and is likely to be low cost.

As indicated in the WHO Guidelines on the management of latent tuberculosis infection, the treatment options for LTBI include: 6H, or 9H, or 3 HP weekly rifampine plus isoniazid, or 3RH (strong recommendation based on moderate to high quality of evidence). The 3RH is now available as a fixed-dose combination (the FDC for children with TB for the continuation phase!).

We need to ensure that we close the policy-practice gap in the management of child contacts of tuberculosis cases. Children are often at great risk for infection in health facility settings including TB wards; TB clinics and HIV clinics. We also should not forget the benefits of proper implementation of infection control.

The WHO symptom based approach is good for a decentralised approach and is feasible at the community level.

In terms of M&E tools needed for contact management, we need to collect data on numbers screened; numbers (%) diagnosed with TB; numbers (%) eligible for preventive therapy; numbers (%) received preventive therapy; and numbers (%) completed preventive therapy. We need contact screening registers and IPT registers to this extent.

In 2016, countries have started to procure the child TB FDCs. The FDCs are comprised of the most commonly used drugs to treat childhood TB. These are treatments that are in the correct doses, are easy to administer, and taste good to children.

Rifampicin 75mg + Isoniazid 50 mg + Pyrazinamide 150 mg (two-month intensive phase of treatment)  
Rifampicin 75mg + Isoniazid 50mg (four-months continuation phase of treatment)

The child TB FDCs are also very affordable. It costs \$15.54 for a six-month course of treatment (for an average weight band.) That's approximately 30% less for those currently dosing correctly by cutting or chopping pills and approximately 20% price increase for those under dosing by using the other products on the market in lower doses. These treatments offer an opportunity to simplify and improve treatment for children everywhere. The introduction and roll out of the new FDCs in Kenya shows that this is a far easier way of managing TB.

Clinical challenges are the diagnostic challenges: young age; acute severe pneumonia; diagnosis of TB in HIV-infected children and in malnourished children; diagnosis of MDR-TB in children. Xpert is not as sensitive as for adults, but the diagnostic yield in India was twice as high as smear using Xpert under programmatic conditions, being higher among inpatients than outpatients. A negative Xpert MTB/RIF test-result does not rule out TB in children and further research is needed to inform optimal usage in children under programmatic conditions. However, a major indication is to utilise Xpert in children with presumptive MDR TB.

In terms of job aides, the Union has just launched the third edition of the Union desk guide for diagnosis and management of TB in children (English and french). The Sentinel project has produced an updated version of the field guide on the management of multidrug-resistant tuberculosis in children (2015, 2<sup>nd</sup> edition). In May, WHO launched the 2016 update of the WHO treatment guidelines for drug-resistant tuberculosis and in October, updated guidance on the use of Delamanid in children >6 years and adolescents. The Union has developed an online course on the management of MDR-TB in children.

The membership of the subgroup has increased by 30%. New members of core group include Mandy Slutsker from WHO Civil Society Group, and Dr Sally Gatchalian from the Philippines who replaced Dr Telly How. Core team conference calls were conducted in February and July and a face-to-face meeting is taking place in October 2016. A new Chair will be announced later today.

Technical assistance and training were provided in Sri Lanka, Nepal, Vietnam, The Philippines, Kenya, Indonesia, Myanmar and PNG.

Subgroup members participated in the following TB meetings and conferences (among others): the annual WHO STAG-TB meeting in Geneva; NTP managers meeting on the implementation of the End TB Strategy in Geneva; the Pan African Thoracic Society meeting in Nairobi; the annual PhilCAT Convention in Manila; the European Union meeting in Bratislava; the PNG Paediatric Society meeting in Port Moresby; the Western Pacific Regional NTP manager's meeting in Manila; the IMCI review meeting in Geneva; the UNICEF integration meeting in collaboration with WHO and TB Alliance, New York; a 3-day interactive seminar on 'Where is TB in Maternal and Child Health' held on the MSH LeaderNet platform; the annual meeting of the American Society of Tropical Medicine and Hygiene annual meeting in Atlanta; and the 47<sup>th</sup> Union World conference on Lung Health in Liverpool.

Subgroup members contributed to the development of the following TB guidelines: NTP guidelines; WHO consolidated guidelines on LTBI management; WHO MDR-TB guidelines; WHO guidance on the use of new drugs in children; WHO guidance on the use of chest radiography in TB detection; and the NIH SOPs for diagnostics.

In terms of research, we need research on new (and old) diagnostics including biomarkers; new (and old) preventive therapy for drug susceptible and drug resistant TB; shorter treatment regimens; shorter LTBI management regimens; secondline and new drugs –PK and safety; and implementation research. Steve highlighted the TAG 2016 pipeline report (<http://www.pipelinereport.org>) which is tracking the pipeline for paediatric TB treatment studies and formulation development. It now also includes a special section tracking paediatric TB diagnostic research. It includes recommendations for researchers, regulators, policy makers, and donors to help fill critical knowledge gaps, expedite development and facilitate access.

Since 2010, TAG is also tracking the resources available for TB R&D (<http://www.treatmentactiongroup.org/tbrd2016>). In the period 2011-2015, paediatric TB R&D investments make up about 3% of the total TB R&D spending and most is on drug development (60%). That is far behind the targets included in the Global Plan to End TB 2011-2015 and the Childhood TB Roadmap.

Steve Graham concluded by acknowledging the support from the secretariat housed at the WHO Global TB Programme, the core team members the NTP managers and regional WHO TB programmes, the TB Alliance and USAID.

During the discussion Mario Raviglione referred to the importance of patient pathway analyses and the cascade of care. It is important to consider where children seek care first and how to reduce delays. They go to MCH programmes or a paediatrician rather than to TB clinics and it is therefore important to establish links. A second issue is that of digital surveillance. There should be a push to use digital tools to get more granular data.

### **3. Updated WHO MDR-TB treatment guidelines and the use of new drugs in children – Malgosia Grzemska**

#### Latest epidemiological data

In 2015, among the total estimated number of cases (10.4 million), there were 1 million children (10%). Among the estimated 1.8 million people who died of TB in 2015, 210,000 children died of TB (170,000 children who were HIV-negative and 40,000 who were HIV-positive). Proportionally more children die than adults due to late diagnosis or under-diagnosis. The fact provide the main arguments for implementation of contact screening and earlier diagnosis. WHO has no official estimate of MDR-TB among children. Dodd et al in Lancet (21 June 2016), estimate that over 67 million children are infected with TB and therefore at risk of developing disease in the future (among whom 5 million with INH resistance; 2 million with MDR-TB and 100,000 with XDR-TB). They also estimate that every year about 25,000 children develop MDR-TB and 1,200 develop XDR-TB.

MDR-TB in children is mainly the result of transmission of a strain of *M.tuberculosis* that is MDR from an adult source case, and therefore often not suspected unless a history of contact with an adult pulmonary MDR-TB case is known. Referral to a specialist is advised for treatment.

### Existing guidelines on the management of MDR-TB in children

The WHO Guidance on the management of TB in children: second edition, 2014 provides the following general management principles:

- Do not add a drug to a failing regimen;
- Treat the child according to the drug susceptibility pattern (and using the treatment history) of the source case's *M. tuberculosis* strain if an isolate from the child is not available;
- Use at least four drugs certain to be effective;
- Use daily treatment only; and,
- Directly observed therapy is essential.

In addition, they recommend that the child's caregiver should be counseled at every visit and support and advice should be provided about adverse events and the importance of compliance and completion of treatment. It is essential to provide follow up: clinical, radiological and bacteriological (mycobacterial culture for any child who had bacteriologically confirmed disease at diagnosis).

With correct dosing, few long-term adverse events are seen with any of the more toxic second line drugs in children.

### 2016 update of the DR-TB treatment guidelines

In 2016, WHO launched updated guidelines on the management of drug resistant TB in children as well as updated interim policy guidance on the use of Delamanid in the treatment of multidrug-resistant tuberculosis in children and adolescents.



Key changes include:

- A shorter MDR-TB treatment regimen is recommended for RR-/MDR-TB patients (under several conditions)
- The design of conventional MDR-TB regimens uses a different regrouping of second-line medicines
- Recommended treatment of children with RR-/MDR-TB based on a first-ever meta-analysis of individual-level paediatric patient data for treatment outcomes
- Recommendation on partial lung resection surgery

In patients (adults and children) with: rifampicin-resistant TB or MDR-TB; who have not been previously treated with second-line drugs; and, in whom resistance to fluoroquinolones and second-line injectable agents has been excluded or is considered highly unlikely, a shorter MDR-TB regimen of 9–12 months



may be used instead of a conventional regimen (*Conditional recommendation – very low quality of evidence*).

Main remarks:

- Standardized regimen; only limited modifications are possible;
- 4-6 Km-Mfx-Pto-Cfz-Z-H <sup>high-dose</sup> -E / 5 Mfx-Cfz-Z-E
- Recommendation applies to adults, children, and PLHIV;
- Ideally, patients are tested for resistance to fluoroquinolones and second-line injectable drugs; not recommended in case of second line drug resistance, extrapulmonary disease and pregnancy;
- Lowered costs (<US\$1,000 in drug costs/patient);
- Monitoring for effectiveness, relapse, and harms (active TB drug safety monitoring and management (aDSM)) applies; and,
- Trials expected to provide high-certainty evidence.

The 2016 update regroups the second line drugs as follows:

<b>GROUP A</b> <b>Fluoroquinolones</b>	Levofloxacin Moxifloxacin Gatifloxacin	
<b>GROUP B</b> <b>Second-line injectable agents</b>	Amikacin Capreomycin Kanamycin (Streptomycin)	
<b>GROUP C</b> <b>Other Core Second-line Agents</b>	Ethionamide / Prothionamide Cycloserine / Terizidone <b>Linezolid</b> <b>Clofazimine</b>	
<b>GROUP D</b> <b>Add-on agents</b> <i>(not core MDR-TB regimen components)</i>	<b>D1</b>	Pyrazinamide Ethambutol High-dose isoniazid
	<b>D2</b>	Bedaquiline Delamanid
	<b>D3</b>	<b>p-aminosalicylic acid</b> Imipenem-Cilastatin Meropenem Amoxicillin-Clavulanate (Thioacetazone)

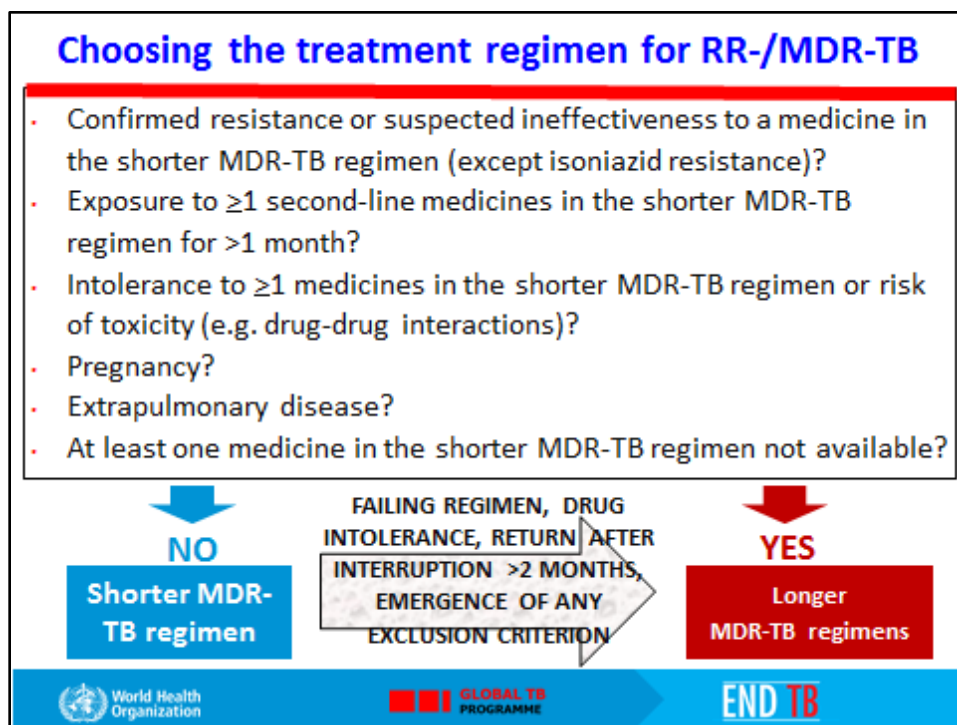
It should be noted that Linezolid and Clofazimine are now in group C and PAS is now in group D3.

The recommendations on the longer MDR-TB regimen are still in place. In patients with rifampicin-resistant TB or MDR-TB, a regimen with at least five effective TB medicines during the intensive phase is

recommended, including pyrazinamide and four core second-line TB medicines – one chosen from group A, one from group B and at least two from group C. If the minimum number of five effective TB medicines cannot be composed as recommended above, an agent from Group D2 and other agents from Group D3 may be added to bring the total to five. The regimen may be further strengthened with high-dose isoniazid and/or ethambutol.

Choosing the regimen will depend on resistance patterns, exposure to second line medicines for more than a month, intolerance, pregnant women, extrapulmonary TB. If any drugs which are missing for building the shorter regimen then the longer regimen should be used.

Choosing the treatment regimen for RR-/MDR-TB:



Following an expert meeting in June 2016, WHO updated the interim guidance on the use of Delamanid. WHO now recommends that Delamanid can be used in children aged 6 and above as follows:

- Children (6 – 11 years) - 50 mg – 2x /day for 6 months ;and
- Adolescents (12-17 years) – 100mg 2x /day for 6 months in adolescents aged 12 to 17
- Delamanid may be added to a WHO recommended longer MDR-TB treatment regimen (*conditional recommendation, very low confidence in estimates of effects*)

Delamanid may be given to:

- Patients with additional resistance or intolerance to fluoroquinolones or second line injectable drugs;
- Patients with extended lesions, advanced disease and others deemed at higher baseline risk for poor outcomes; and,
- Patients with XDR-TB

Studies excludes paediatric cases with reported QTc prolongation (greater than 500msec); Paediatric patients with HIV co-infection; and the drug has not been tested in patients with extra-pulmonary MDR-TB. Currently there are no data on the effect of Delamanid in children younger than 6 years of age and weighting under 20kg but studies are underway.

There are no data available on the use of Bedaquiline in children (patients younger than 18 years). So far, the Janssen BDQ compassionate use programme has excluded paediatric patients.

#### Research gaps:

More research (randomised control trials) especially on new drugs and regimens are needed for both adults and children. Reporting of outcomes in children should be separate from adults. Studies are needed to identify factors which determine the optimal duration of treatment for children. PK studies to determine optimal drug dosing and safety are also needed as well as studies to improve diagnostics and DST methods for children. Studies on preventive chemotherapy for children in contact with MDR-TB patients are also urgently needed.

#### Conclusions:

MDR-TB in children is recognized and guidelines are available. There are finally evidence based recommendations for treatment of RR-TB and MDR-TB in children. However, more data are needed, especially on the use of new drugs and new regimens. And, evidence is needed to promote preventive chemotherapy for children in contact with a confirmed MDR-TB case in the household.

#### **4. Prevention and management of MDR-TB in children – H. Simon Schaaf**

Prevention of tuberculosis, including multidrug (MDR) and extensively drug-resistant tuberculosis (XDR-TB) is a top priority for global TB control. Rapid detection and timely initiation of effective treatment is critical to rendering MDR/XDR-TB cases non-infectious. Optimised infection control measures in hospitals and clinics are critical to protect other patients. Among infected contacts, preventive therapy promises to reduce the risk of disease progression. This is supported by observational cohort studies (Fox GJ, Schaaf HS, et al. Preventing the spread of multidrug-resistant tuberculosis and protecting contacts of infectious cases. *Clin Microbiol Infect*, 2016).

The desired decline in global TB incidence rates to reach the 2035 targets as included in the End TB Strategy requires new diagnostics and health care for all and the introduction of new tools including vaccine, treatment of TB infection and disease.

The general priority indicators and targets to try to achieve the END TB Strategy targets are: Treatment coverage should be >90% (i.e. >90% of all who have TB should be on treatment); TB treatment success rate should be >90% and preventive treatment coverage for those at high risk of TB (including children) should be >90%

Priority actions to address the global MDR-TB crisis, as included in the WHO Multidrug-resistant Tuberculosis: 2014 update, include:

1. Prevent the development of drug resistance through high quality treatment of drug-susceptible TB
2. Expand rapid testing and detection of drug-resistant TB cases
3. Provide immediate access to effective treatment and proper care
4. Prevent transmission through infection control
5. Increase political commitment with financing.

To this, we should add a sixth priority action: 6. contact tracing and preventive therapy.

Prevention is critical. No randomized control trials have been done to evaluate preventive therapy for MDR-TB contacts. But prospective observational studies have shown the potential of preventive therapy for MDR-TB contacts.

Child contacts of MDR-TB:

- In children, the term “TB infection” instead of LTBI is preferred, as they are usually recently infected and could still be in the phase of progression to disease
- The majority (90%) of infected children who will develop disease will progress to disease within 12 months – almost all in 2 years
- Biomarkers to determine which individuals have the highest risk of progression to TB disease are lacking
- The risk of TB disease among contacts exposed to MDR-TB is considerable. In a meta-analysis of 25 studies, 7.8% of household contacts of MDR-TB patients developed TB, most within three years. Source: Shah NS et al. Yield of contact investigations in households of patients with drug-resistant tuberculosis: systematic review and meta-analysis. CID 2014;58:381-91
- Strain concordance of household members with DR-TB is high in child contacts <5 years with 75-88% concordance
- No RCTs have been done to evaluate preventive therapy for MDR-TB contacts
- However, a number of prospective observational studies (some unpublished) have shown the potential of preventive treatment in preventing MDR-TB
- Despite this, the debate on the management of MDR-TB contacts is ongoing
- If then prevention is so important, why are we not “putting our money where our mouths are”?

Simon Schaaf mentioned that a policy brief on “Post-exposure management of multi-drug resistant tuberculosis contacts: evidence-based recommendations” has been developed for the Center for Global Health Delivery in Dubai, Harvard Medical School with input from Seddon, Fred, Amanullah, Schaaf, Starke, Keshavjee, Burznshi, Furin, Swaminathan and Becerra (2015). This policy brief followed from a meeting of >50 TB practitioners from 19 countries on MDR-TB prevention. The current evidence base includes at least ten observational studies (published and unpublished), including more than 600 contacts treated for presumed MDR-TB infection with a high rate of success. The group felt strongly that the time for MDR-TB preventive treatment has come. A fluoroquinolone-based preventive regimen with 2-3 drugs is preferred, however, randomized controlled trials need to confirm efficacy. Three RCTs for MDR preventive therapy are planned to evaluate the effectiveness of preventive therapy for infected MDR-TB contacts: V-QUIN, TB-Champ and Phoenix.

Study	Regimen	MDR-TB contacts/ sites
V-QUIN	Levofloxacin vs Placebo	Adults & children – Viet Nam
TB-CHAMP	Levofloxacin vs Placebo	Children <5 years – South Africa
PHOENIx	Delamanid vs isoniazid	Adults and children – International (multi)

In conclusion, MDR preventive treatment could be effective in preventing MDR-TB in children. There is an urgent need to address this issue in (a) randomized controlled trial(s). Single drug preventive treatment with a fluoroquinolone (e.g. levofloxacin) is considered (RCTs planned). However, the prevention of XDR-TB remains a problem. Can the new drugs be used to this extent? Careful follow-up and possibly high-dose INH (no evidence) – treat as XCR-TB if TB develops. In both MDR and XDR-TB regular clinical follow-up is indicated, but the pendulum is swinging towards preventive therapy.

#### Managing MDR TB in children

We are in a time of rapid change with many new developments. For clinicians treating children with MDR-TB it is both an exciting and a confusing time. There are many “new” developments and changes that they need to take into consideration while they also have to stick to basic principles of good TB treatment.

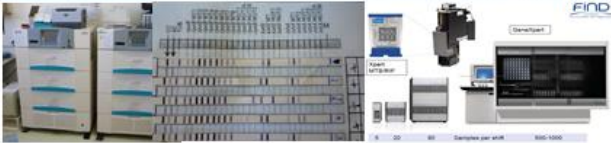
What is “new” in MDR-TB management? New rapid diagnostics; new data on doses (PK data) of “old” anti-TB drugs; new drugs – repurposed and true novel drugs; new (WHO) drug group classification; new regimens; new adverse effects to consider; new ideas of treatment shortening regimens and preventive therapy regimens; new patients identified and new health care workers managing these MDR-TB patients.

With respect to new “rapid” diagnostics, Simon Schaaf highlighted that:

- Xpert MTB/RIF has taken many developing countries with a high TB burden by storm, however, it has its limitations and problems;
- Xpert Ultra promises to be more sensitive;
- In cultured isolates, the line probe assays (LPA) mainly has been used for drug susceptibility testing (DST) for first-line drugs INH and RIF;
- With the new shorter MDR-TB regimen, there is a need for rapid second-line DST and second-line LPA has now been approved by WHO (Genotype MTBDRsl), however, phenotypic (culture-based) DST is still required.

Simon Schaaf then showed a slide in which he compared Culture (and LPA) versus Xpert MTB/RIF.

Characteristic	Culture and DST	Xpert MTB/RIF
Speed	Slow (2-6 weeks) LPA DST – 1-2 days	Rapid (2 hours – capacity limit)
Positive yield	30-70%	60-70% of culture-POS cases
Detection threshold	10-100 cfu/ml	130-150 cfu/ml (Xpert-ULTRA 10-100?)
DST	Any drug DST/LPA	Only RIF DST
Specimens	Any type	Resp specimens, increasing number of other specimens



Line Probe Assays (LPA) are needed for first and second line drugs and for the shorter regimen.

There are also developments in whole genome sequencing and drug resistance gene discovery. A recent publication by Zhang et al. entitled “mechanisms of drug resistance in Mycobacterium tuberculosis: update 2015” which was published in the *Int J Tuberc Lung Dis* 2015;19:1276-1289 observed that there are over 100 genetic loci that seem to be associated with drug resistance. This may suggest that drug resistance may be more complex than previously realized. However, whole genome sequencing seems to be the future and the cost will be coming down. It will inform and refine dosing recommendations.

Promising work (still unpublished) is also on its way to significantly reduce pain related to Amikacin injections.

Despite the developments, clinicians need to stick to the basic principles of MDR-TB treatment which remain the same:

- Give 4 or more drugs to which the patient’s isolate is susceptible and/or naïve. Number of effective drugs depends on extent of disease and availability of drugs;
- Drugs in previously failed regimen likely not effective;
- Be aware of the different drug groups and cross-resistance (and co-resistance) amongst these drugs;
- Second-line drugs are generally more toxic than first-line drugs;
- Follow-up: clinical, radiographic and by culture – decide on duration of treatment; and,
- NEVER add one drug to a failing regimen.

To build a regimen for MDR/XDR-TB clinicians need to select:

- Group A: A Fluoroquinolone – levofloxacin or moxifloxacin
- Group B: A 2<sup>nd</sup>-line injectable drug – kanamycin, amikacin or capreomycin (high rates of cross-resistance)

- Group C: Other core drugs in combination:
  - Ethionamide/Prothionamide (*inhA* mutation?)
  - Cycloserine/Terizidone
  - Clofazimine
  - Linezolid
- Group D1: Add-on drugs (not counted as effective drugs?)
  - high-dose INH (low-level INH resistance / *inhA* mutation)
  - pyrazinamide; ethambutol
- Group D2: New drugs: Delamanid; Bedaquiline
- Group D3: PAS; Amoxiclav plus Carbapenem

The WHO new shorter regimen for RMR/MDR-TB is:

- ONLY for Rifampicin Resistance-TB or strictly MDR-TB (INH+RIF resistance, no FQN/SLID resistance)
- 9-12 month regimen (response to treatment)
- 4-6 Km Mfx Cfz H-hd E Pto Z / 5-6 Mfx Cfz E Z
- What about children?
  - Levofloxacin vs Moxifloxacin? – Mfx does not exist in a child-friendly formulation
  - Clofazimine dose? – 50 or 100 mg gelcaps only – dosing?
  - Prothionamide/Ethionamide AND high-dose INH? Both or according to INH mutation?
  - Still injectable agent?
  - Are 2 effective drugs in continuation phase sufficient? (high rates Ethambutol & pyrazinamide resistance).
  - There are only a few long-term follow-up observational studies of regimens.

Simon Schaaf then presented a long list of adverse effects, some of which are “new”, which underline the importance of pharmacovigilance (source: expert opinion drug safety 2016 – Schaaf et al):

- **Arthralgia/arthritis:** FQNs/PZA/RFB
- **Blood dyscrasias:** INH/RIF/PZA/LZD/FQNs/PAS and more
- **Central nervous system toxicity:** headache, drowsiness, seizures, weakness, insomnia, hallucinations: FQNs
- **Depression/Psychosis:** INH/ETO/TZD
- **Endocrine effects – hypothyroidism:** PAS/ETO, gynaecomastia: ETO/INH
- **Flu-like syndrome:** RIF/RFB/PAS
- **GI disturbances – nausea, vomiting, abdominal pain, diarrhoea:** Many! ETO/PAS/FQNs/CFZ/LZD/BDQ **Hearing impair/ototoxicity:** AM/KM/CM
- **Hair loss (alopecia):** INH/ETO
- **Idiopathic intracranial pressure:** FQNs
- **Jaundice/hepatotoxicity:** PZA/INH/RIF/ETO/PAS/MFX
- **K<sup>+</sup> decrease:** Electrolyte disturbance : CM/PAS
- **Lactic acidosis:** LZD
- **Myelo-suppression:** LZD
- **Nephrotoxicity:** AM/KM/CM/SM
- **Optic neuritis/vision disturbance/colour blindness:** EMB/LZD/INH/ETO/PAS
- **Peripheral neuropathy:** INH/ETO/LZD/TZD
- **Pancreatitis:** LZD
- **QTc interval prolongation:** FQN/CFZ/CLA/BDQ/DLM

- Rashes: PZA/FQNs/TZD/PAS and many other
- Skin discolouration – red skin: CFZ
- Tendinitis/tendonopathy: FQNs
- Uveitis: RFB
- Vestibular toxicity: AM/KM/CM/SM

Simon Schaaf finished by summarizing the new ideas with respect to the management of drug-resistance in children:

- Injectable-free MDR-TB treatment regimen (already possible in non-severe disease – low organism load)
- Child-friendly formulations: get them AVAILABLE as soon as possible
- Short-course MDR-TB regimen (6 months) for MDR- and XDR-TB cases
  - we have a number of “new” bactericidal drugs (Lzd, Cfz, Dlm, Bdq, FQNs)
  - in adults already a 6-month trial in XDR-TB cases and it is time for an efficacy trial in younger children
- Single-drug preventive therapy for MDR-TB contacts is urgently needed.

## 5. Treatment of MDR-TB in children and adolescents with the shorter regimen in 9 African countries – Valérie Schwoebel

Until 2016, WHO-recommended regimens for the treatment of multi-drug resistant tuberculosis (MDR-TB) were long (>20 months) and had low cure rates (<55%). In 2010, Van Deun et al. reported 88% [83%-92%] cured without relapse in 206 patients treated by a 9-month regimen 4KMGfxPtoHCfzEZ/5GfxCfzEZ in Bangladesh.

An observational study was launched in 2013 in francophone Africa to determine the effectiveness and tolerance of a modified “Bangladesh” regimen for MDR-TB: **4KmMfxPtoHCfzEZ/6MfxCfzEZ**. Although the observational study only included adults, the Bangladesh regimen was used for children and adolescents aged <18 years in the participating 9 countries. The objectives of the work presented were: to determine the effectiveness of this shorter regimen in children and adolescents; and, to document its adverse drug events.

The following 9 countries in francophone Africa participated: Benin, Burkina Faso, Burundi, Cameroon, Central African Republic, Côte d’Ivoire, DR Congo, Niger and Rwanda. Between 1 January 2013 and 31 March 2015 (27 months), 1006 adult patients were included in the study. Data were collected over the same period on all children and adolescents <18 years treated with the Bangladesh regimen who had met the following criteria: bacteriologically confirmed TB (microscopy, Xpert or culture); confirmed rifampicin resistance (RR) by molecular or phenotypic drug susceptibility test; and, no history of treatment with secondline drugs.

The patients were managed by the NTP (hospital-based, ambulatory or mixed). Strict daily Directly Observed Treatment (DOT) was conducted throughout treatment. Monthly clinical, biological and bacteriological (smear and culture) examinations were undertaken during treatment and 6 months after treatment termination. DST was performed on initial strains and if strains were isolated at 6 months of treatment or later.



A total of 72 patients under 18 were diagnosed with Rifampicin Resistant Tuberculosis (RR-TB). 58 of these patients were started on the “Bangladesh” regimen of which 47 were recruited early enough for cohort analysis. The study population had the following characteristics:

Characteristics		N (%)
Age group	0-9 years	5 (11%)
	10-14 years	10 (21%)
	15-17 years	32 (68%)
Sex	Female	23 (49%)
New case	Yes	17 (36%)
HIV infected	Yes	9 (19%)

Drug dosages (mg/kg) that were used were similar among adults and children.

Drug	Min	p25	Median	p75	Max
Kanamycine	12.5	14.2	<b>16.7</b>	18.1	26.3
Prothionamide	8.6	12.3	<b>13.2</b>	16.3	31.2
Isoniazid	5.0	8.0	<b>10.0</b>	11.1	15.0
Moxifloxacin	5.2	7.1	<b>9.5</b>	10.5	16.7
Clofazimine	1.3	1.8	<b>2.4</b>	2.6	3.8
Ethambutol	10.5	17.5	<b>19.0</b>	20.0	30.0
Pyrazinamide	21.1	24.1	<b>27.8</b>	30.0	50.0

Applying the WHO 2013 definitions of treatment success (cured plus treatment completed), the study showed a success rate of 39/47 or 83%. The treatment failed in 3 patients, 4 patients died and 1 patient

was lost to follow up. The success rate was similar in children under 10 years of age (80%) and in older children/adolescents (83%). Among patients who survived (excluding deaths), treatment success did not differ significantly by HIV status: 100% in HIV-positive and 89% in HIV-negative patients. All adverse drug events were mild/moderate (grade <3). Kanamycin was given intermittently or stopped < month 4 for 4/15 patients with reported hearing problem. The biggest adverse drug effects were gastro-intestinal and hearing loss, which was not severe for most patients.

Discussion: All patients <18 years (except 1) were treated with the short regimen in the participating countries which minimized the selection bias. Information was abstracted from patient cards and was sometimes incomplete. The sample size was small and very few patients were less than 10 years old. Therefore, care should be taken before generalizing results. In conclusion, the outcomes for children treated with shorter regimens were excellent, for both HIV and non HIV- infected. All adverse effects were generally mild, none resulted in discontinuation of treatment.

During the discussion, programmatic implementation of the shorter regimen was discussed. Simon Schaaf referred to South Africa where there is a high Isoniazid and Ethambutol resistance and where only 2 drugs-susceptible TB drugs in the continuation phase may be of concern. Anthony Enimil from Ghana raised the issue of informed consent, the understanding of adverse effects and the need for monthly testing of (irreversible) hearing loss.

## **6. Outcomes of the UNICEF integration meeting and update on the TB/HIV adapted iCCM pilots and country case studies – Anne Detjen**

Anne Detjen presented the objectives and the outcomes of the UNICEF integration meeting which took place on 1-2 June 2016 in New York, USA.

The meeting showed that integration has different meanings for different actors. For patients, it means comprehensive care. For care providers, it means collaboration with other providers and services to ensure routine and systematic management of co-morbidities. For health managers, it means commitment and coordination between health programmes and shared accountability. For policy makers, it means negotiation, prioritization and strengthening of the overall health system. For donors, it means coordination of investments, flexibility and a systems focus.

During the meeting in New York, participants from the NTP and Mother and Child Health (MCH) sectors looked at activities that would improve a child's pathway through care. It turned out that most of the interventions to improve the pathway could take place at primary care level and could be implemented by front line health care workers (except diagnosis and treatment initiation).

Integration to improve prevention, diagnosis and care for children affected by TB, should also strengthen primary health care systems in general. We need to understand the priorities of the Mother, Newborn and Child Health (MNCH) community. It is essential that we show the impact of TB on key maternal and child health outcomes so TB becomes part of their agenda as well.

In order to strengthen the TB capacity at the lower levels of the health systems, countries need to identify best ways to integrate TB services in existing community platforms.

Case studies on childhood TB integration were conducted in Uganda and Malawi taking into consideration the broader context (TB burden, stigma, pathways, actors, etc.) as well as the different

levels and functions of the health system. The studies mapped positive and negative factors that influence integration. The case studies successfully initiated a dialogue between key health actors in both countries. Collaboration and joint planning between the NTP and MCH/IMCI at national level set the scene for broader integration. Case studies helped to get an initial understanding of the possible pathways of integration and main health systems requirements. Both countries developed targeted action plans for key health actors.

Moving forward requires champions, building of coalitions between TB and MCH and data for decision making including costing. The current funding environment contributes to fragmentation and verticalization. But there are opportunities including funding by the Global fund through National TB Strategic Plans and scale up of Integrated community case management (iCCM). We can also tap into non-traditional funding sources such as the Global Financing Facility, a multi-stakeholder partnership that supports country-led efforts to improve the health of women, children and adolescents.

At the country level, this requires a lot of collaboration with all actors. It requires defining of roles and responsibilities and shared accountability. It requires data for decision making and establishment of priorities, milestones and benchmarks.

Stakeholders can assist countries by: continuing to engage new actors; conducting research to further strengthen data and evidence; conducting Integrated Management of Childhood Illness (IMCI) reviews; scaling up iCCM; and, securing catalytic funding.

## **7. Panel discussion on the outcomes of recent national childhood TB stakeholders meetings in UR Tanzania, Philippines and Pakistan**– Moderated by Farhana Amanullah

**Tanzania** (Nemes Joseph Iriya, WHO Tanzania): During the national childhood TB stakeholders meeting in July 2016, discussions took place on the new child TB FDCs and a plan for the introduction of the child TB FDCs was developed. The meeting was very well attended with numerous participants from academia. During the meeting a childhood TB working group was set up. This working group will meet on a quarterly basis. Tanzania has recently updated the childhood TB guidelines reflecting the new global recommendations and a training is planned to be conducted soon. In terms of integration with MNCH, a childhood TB module has been included in the updated IMCI. An algorithm has also been developed and is currently being validated.

**Pakistan** (Farhana Amanullah): The national stakeholders consultation on childhood TB was conducted in September 2016. Even though there is already a strong focus on childhood TB (with updated childhood TB guidelines available and 10% of TB case load among children), likely half of the childhood TB cases are currently being missed. There are lots of health system issues including issues related to integration. During the meeting, presentations were given on the global childhood TB burden and response as well as on the childhood TB burden in Pakistan. The TB Alliance gave a presentation on the childhood TB FDCs. Various initiatives to scale up the response to childhood TB were shared which brought out current issues at the field level. The meeting brought together the core local level expertise that exists right now in Pakistan, with people who are able to address local context issues. The preliminary results of an inventory study focussing on child TB showed that a lot of cases are being missed. It sheds light systems and referral issues in both the public and private sector in Pakistan.

**Philippines** (Telly How): The Annual Convention of the Philippine Coalition against TB took place in August 2016 and was focused on childhood TB. Highlights: clinical practice guidelines have been updated and shared; the child TB fixed dose combinations were discussed and the FDCs have been

accepted in principle by the pharmacists; the new TB law will probably lead to more resources including for child TB. During the meeting, Steve Graham has given a presentation on prevention and diagnosis of TB among children. Patient tracking also receive attention. The Philippines aim to find the missing cases by engaging with private practitioners. Data need to be further disaggregated by age and sex. There is a need for more IPT.

**Kenya** (Immaculate Kathure, Child TB Focal point in the NTP): Kenya is the first country to have rolled out the child TB FDCs. The NTP was struggling with the previous formulations, as the regimens were complex. It was not sure that children were receiving the right dosages, because of the large number of tablets, maternal literacy issues and in situations with more than one child on treatment. The commodity supply chain suffered as well. The new FDCs are expected to improve the situation and a lot of sensitisation on childhood TB has been done in the country to make the roll out of the new child TB FDCs a success.

## 8. Summary of impact publications in the last 12 months – James Seddon

James Seddon identified 883 studies on PubMed, of which 71 looked very interesting and, after review of abstracts, 35 were selected for his presentation covering, among others, studies on: biomarkers; BCG; cost effectiveness; sensitivity of TST and IGRAs; gastric and nasal pharyngeal aspirates for Xpert.

Below is a list of the studies highlighted:

Zak DE et al. A blood **RNA signature for tuberculosis disease risk: a prospective cohort study**. Lancet, June 2016. In this prospective cohort study, over 6000 healthy, South African adolescents aged 12-18 years from the adolescent cohort study (ACS) who were infected with M tuberculosis were followed for 2 years. Blood samples were collected from study participants every 6 months and monitored the adolescents for progression to tuberculosis disease. The whole blood tuberculosis risk signature prospectively identified people at risk of developing active tuberculosis, opening the possibility for targeted intervention to prevent the disease.

Fletcher et al. **T-cell activation is an immune correlate of risk in BCG vaccinated infants**. Nature communications, April 2016. The researchers performed a case-control analysis to identify immune correlates of TB disease risk in Bacille Calmette-Guerin (BCG) immunized infants from the MVA85A efficacy trial. They concluded that the causes and impact of T-cell activation on disease risk should be considered when designing and testing TB vaccine candidates for these populations.

Harris et al. **The potential impact of BCG vaccine supply shortages on global paediatric tuberculosis mortality**. BMC Medicine, 2016. The modelling shows the impact of BCG shortages over 15 years and shows that >100,000 deaths could have been averted.

Hesseling et al. Vaccine, April 2016. **Delayed BCG immunization does not alter antibody responses to EPI vaccines in HIV-exposed and HIV-unexposed South African Infants**. The study results show that delayed HIV exposure, but not the timing of BCG vaccination, was associated with antibody concentrations to Hib, pertussis, HBV and tetanus primary immunization.

Ritz et al, Vaccine, July 2016. **Comparable CD4 and CD8 T cell responses and cytokine release after at-birth and delayed BCG immunisation in infants born in Australia**. The study shows that Cellular immunity measured 10 weeks after BCG immunization was similar in infants given BCG at birth and in

those given BCG at 2 months of age. Although definitive correlates of protection against TB remain uncertain, these results suggest that delaying BCG immunization does not confer any immunological advantage in cellular immunity.

Usher et al. Archives of Public Health, July 2016. **Evaluating the neonatal BCG vaccination programme in Ireland.** This study compared the cost effectiveness between universal and selective BCG strategies. The results of the study support the protective effect of the BCG vaccine in infants and quantified the cost effectiveness of the current BCG vaccination strategy and the decremental difference in moving to a selective strategy. This analysis highlights that the additional protection offered by the universal vaccination strategy is small compared to that of the selective strategy. Consideration should therefore be given to the implementation of a selective vaccination strategy, and diverting resources to improve TB case management and control.

Stensballe LG et al. Archives Dis Child, July 2016. **BCG vaccination at birth and early childhood hospitalisation: a randomised clinical multicentre trial.** The BCG vaccine is administered to protect against tuberculosis, but studies suggest there may also be non-specific beneficial effects upon the infant immune system, reducing early non-targeted infections and atopic diseases. This was a randomised trial that tested the hypothesis that BCG vaccination at birth would reduce early childhood hospitalization in Denmark, a high income setting. The study showed that BCG vaccination at birth did not reduce the risk of hospitalization for somatic acquired disease until 15 months of age in this Danish study population.

Rieckmann et al. International Journal of Epidemiology, 2016. **Vaccinations against smallpox and tuberculosis are associated with better long-term survival: a Danish case-cohort study 1971-2010.** In this case-cohort study, 47 622 schoolchildren from Copenhagen, Denmark, born 1965 to 1976, were followed from their first health examination to 2010. This cohort experienced the phase-out of vaccinia and BCG vaccination programmes. The study concludes that vaccinia and BCG vaccinations were associated with better long-term survival, which was not explained by specific protection. Vaccines with beneficial non-specific effects may reduce overall mortality even after the target diseases are eradicated.

Dhooira S et al. Paediatric Pulmonology, April 2016. **A multicenter study on the utility and safety of EBUS-TBNA and EUS-B-FNA in children.** Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) and endoscopic ultrasound with an echobronchoscope-guide fine needle-aspiration (EUS-B-FNA) are useful modalities in the evaluation of mediastinal lymphadenopathy in adults. The aim of this multicenter study is to describe the efficacy and safety of EBUS-TBNA and EUS-B-FNA in children with mediastinal lymphadenopathy of undefined etiology. It concluded that both techniques are safe with a good diagnostic yield in the evaluation of children with mediastinal lymphadenopathy.

Debes AK et al. The Pediatric Infectious Disease Journal, October 2016. **Cost-effectiveness of diagnostic algorithms for tuberculosis in children less than 5 years of age.** The objective of this analysis was to assess the cost-effectiveness of TB diagnosis using Microscopic Observation Drug Susceptibility (MODS), Xpert MTB/RIF (Xpert), and empiric treatment for all patients, in addition to current clinical diagnostic practices in children less than 5 years of age in a national tuberculosis (TB) referral hospital in Uganda. The study concluded that the cost-effectiveness of diagnostic tools for TB in children depends on the population, natural history of untreated TB, and existing diagnostic practices. In settings where the risk of TB death is high, empiric treatment of all children for TB should be considered until a more sensitive, low-cost diagnostic test is available.

Laurenti P et al. BMC Infectious Diseases. **Performance of interferon- $\gamma$  release assays in the diagnosis of confirmed active tuberculosis in immunocompetent children: a new systematic review and meta-analysis.** The researchers concluded that QFT-IT and T-SPOT have higher specificity than TST for detecting active TB cases in immunocompetent children.

Marcy O. et al. **Performance of Xpert MTB/RIF in Alternative Specimen Collection Methods for the Diagnosis of Tuberculosis in HIV-Infected Children.** Clinical Infectious Diseases, February 2016. The study looked at 8 hospitals in Burkina Faso, Cambodia, Cameroon and Vietnam. The researchers conclude that the combination of nasopharyngeal aspirate and stool sample is a promising alternative to methods usually recommended by national programs. Xpert performed on respiratory and stools samples enables rapid confirmation of tuberculosis diagnosis in HIV-infected children.

Loveday M et al. Archives of Disease in Childhood, March 2016. **Dilemma of managing asymptomatic children referred with “culture-confirmed” drug-resistant tuberculosis.** The diagnosis of drug-resistant tuberculosis (DR-TB) in children is challenging and treatment is associated with many adverse effects. The study was conducted in KwaZulu-Natal in South Africa and aimed to assess if careful observation, without initiation of second-line treatment is safe in asymptomatic children referred with “culture-confirmed” DR-TB. The study concluded that bacteriological evaluation should not be performed in the absence of any clinical indication. If drug-resistant *Mycobacterium tuberculosis* is detected in an asymptomatic child with a normal chest radiograph, close observation may be an appropriate strategy, especially in settings where potential laboratory error and poor record keeping are constant challenges. The diagnosis of drug-resistant tuberculosis (DR-TB) in children is challenging and treatment is associated with many adverse effects.

Van der Zalm M et al. The Pediatric Infectious Disease Journal, June 2016. **The Effect of Deworming on Tests of Tuberculosis Infection in Children with Recent Tuberculosis Exposure: a Randomized Controlled Trial.** Helminth infestations are associated with T-helper cell type 2 (Th2) immune responses, leading to suppression of Th1 responses required to control *Mycobacterium tuberculosis* infection. The researchers hypothesized that deworming after documented *M.tuberculosis* exposure might improve Th1 immune responses. They concluded that deworming in children with recent *M.tuberculosis* exposure is associated with a trend toward a negative TST result. Timing of deworming may therefore influence interpretation of TST in settings with high burdens of tuberculosis and helminths.

Triasih R. et al. **An evaluation of chest X-ray in the context of community-based screening of child tuberculosis contacts.** Int J Tuberc Lung Dis, December 2015. The study aimed to describe the quality, findings and inter-observer agreement of CXRs in child TB contacts in Indonesia. The researchers performed antero-posterior (AP) and lateral CXR in children who had had close contact with a pulmonary TB case. The CXRs were interpreted independently by four reviewers. The study concluded that the CXRs of child TB contacts investigated in the community were characterized by low quality, low agreement and low yield. The findings support guidelines that CXR is not routinely indicated in asymptomatic child TB contacts in this setting.

Adjobimey M et al. Int J Tuberc and Lung Dis, August 2016. **Implementation of isoniazid preventive therapy in children aged under 5 years exposed to tuberculosis in Benin.** The objective of the study was to assess the feasibility and results of integrating a programme of isoniazid preventive therapy (IPT) in children aged <5 years exposed to TB as part of the existing routine activities of the NTP. The researchers concluded that in an African country with moderate TB incidence and a well-functioning NTP, the integration of IPT into the NTP for children aged <5 years exposed to TB in the family was

feasible based on simple tools associated with the follow-up of index cases. The rate of adherence to IPT was high (over 90% adherence).

Cruz AT et al. *Pediatr Infect Dis J*. July, 2016. **Safety and adherence for 12 weekly doses of isoniazid and rifapentine for pediatric tuberculosis infection.** Eighty children with TBI received a 12-dose once-weekly isoniazid/rifapentine regimen. 79 (99%) completed therapy, 94% reported no adverse events, 1 child had mildly elevated transaminases but 1 adolescent later developed pulmonary TB. Isoniazid/rifapentine is safe, is well tolerated and has much higher completion rates than traditional TBI regimens.

Bekker et al. *American Society for Microbiology*, April 2016. **Pharmacokinetics of Rifampicin, Isoniazid, Pyrazinamide, and Ethambutol in Infants Doses According to Revised WHO-Recommended Treatment Guidelines.** In summary, isoniazid and pyrazinamide concentrations in infants compared well with proposed adult target concentrations; ethambutol concentrations were lower but similar to previously reported pediatric studies. The low rifampicin exposures require further investigation.

Ramachandran G et al. *Pediatr Infect Dis J*, May 2016. **Low Serum Concentrations of Rifampicin and Pyrazinamide Associated with Poor Treatment Outcomes in Children with Tuberculosis Related to HIV Status.** To compare the pharmacokinetics of rifampicin (RMP), isoniazid (INH) and pyrazinamide (PZA) between HIV-infected and HIV-uninfected children with tuberculosis (TB) and correlate it with TB treatment outcome. HIV-infection was associated with lower C<sub>max</sub> of RMP and INH and AUC<sub>0-8</sub> of RMP. Over 90% of children in both groups had sub-therapeutic RMP C<sub>max</sub>. C<sub>max</sub> of RMP and PZA significantly influenced TB treatment outcome in children with TB. The findings have important clinical implications and suggest the need to increase anti-TB drug doses in children with HIV and TB.

Mave V. et al. *Int J Tuberc Lung Dis*, June 2016. **Isoniazid hair concentrations in children with tuberculosis: a proof of concept study.** Assessing treatment adherence and quantifying exposure to anti-tuberculosis drugs among children is challenging. The researchers undertook a 'proof of concept' study to assess the drug concentrations of isoniazid (INH) in hair as a therapeutic drug monitoring tool. Children aged <12 years initiated on a thrice-weekly treatment regimen including INH (10 mg/kg) for newly diagnosed tuberculosis were enrolled. INH concentrations in hair were measured using liquid chromatography-tandem mass spectrometry at 1, 2, 4 and 6 months after initiating anti-tuberculosis treatment. We found that INH hair concentrations in all children on thrice-weekly INH were detectable and displayed variability across a dynamic range.

Jullien S et al. **Six months therapy for tuberculosis meningitis.** Tuberculous meningitis (TBM) is the main form of tuberculosis that affects the central nervous system and is associated with high rates of death and disability. Most international guidelines recommend longer antituberculous treatment (ATT) regimens for TBM than for pulmonary tuberculosis disease to prevent relapse. However, longer regimens are associated with poor adherence, which could contribute to increased relapse, development of drug resistance, and increased costs to patients and healthcare systems. The objective of this Cochrane review was to compare the effects of short-course (six months) regimens versus prolonged-course regimens for people with tuberculous meningitis (TBM). Results: In all cohorts most deaths occurred in the first six months; and relapse was uncommon in all participants irrespective of the regimen. Further inferences are probably inappropriate given this is observational data and confounding is likely. These data are almost all from participants who are HIV-negative, and thus the inferences will not apply to the efficacy and safety of the six months regimens in HIV-positive people. Well-designed RCTs, or large prospective cohort studies, comparing six months with longer treatment regimens with

long follow-up periods established at initiation of ATT are needed to resolve the uncertainty regarding the safety and efficacy of six months regimens for TBM.

Pouplin T. et al. BMC Infectious Diseases. **Naïve-pooled pharmacokinetic analysis of pyrazinamide, isoniazid and rifampicin in plasma and cerebrospinal fluid of Vietnamese children with tuberculous meningitis.** The researchers performed a prospective observational study of 100 consecutively treated children ( $\leq 15$  years of age) with tuberculous meningitis in Ho Chi Minh City, Vietnam. Children were treated according to the 2006 WHO recommended pediatric treatment regimen consisting of isoniazid (5 mg/kg), rifampicin (10 mg/kg) and ethambutol (15 mg/kg) for 8 months, with the addition of pyrazinamide (25 mg/kg) for the first 3 months and streptomycin (15 mg/kg) for the first 2 months. Pyrazinamide, isoniazid and rifampicin concentrations were measured in plasma at day 14 and in cerebrospinal fluid (CSF) at 1 month by HPLC-UV. A naïve-pooled non-compartmental data analysis was used to describe the pharmacokinetic properties of drugs in the two-age groups of children  $\leq 4$  years or  $> 4$  years of age. It was concluded that there is an age-dependent variation in the plasma and cerebrospinal fluid pharmacokinetics of rifampicin, isoniazid and pyrazinamide. The safety and efficacy of higher doses of rifampicin should be investigated for the treatment of childhood tuberculous meningitis.

Savic RM et al. Clin Pharmacol Ther, October 2015. **Pediatric Tuberculous Meningitis: Model-based Approach to Determining Optimal Doses of the Anti-Tuberculosis Drugs Rifampin and Levofloxacin for Children.** Pediatric tuberculous meningitis (TBM) is a highly morbid, often fatal disease. Standard treatment includes isoniazid, rifampin, pyrazinamide, and ethambutol. Current rifampin dosing achieves low cerebrospinal fluid (CSF) concentrations, and CSF penetration of ethambutol is poor. In adult trials, higher-dose rifampin and/or a fluoroquinolone reduced mortality and disability. To estimate optimal dosing of rifampin and levofloxacin for children, the researchers compiled plasma and CSF pharmacokinetic (PK) and outcomes data from adult TBM trials plus plasma PK data from children. A population PK/pharmacodynamic (PD) model using adult data defined rifampin target exposures (plasma area under the curve (AUC)<sub>0-24</sub> = 92 mg\*h/L). Levofloxacin targets and rifampin pediatric drug disposition information were literature-derived. To attain target rifampin exposures, children require daily doses of at least 30 mg/kg orally or 15 mg/kg intravenously. From our pediatric population PK model, oral levofloxacin doses needed to attain exposure targets were 19-33 mg/kg. The results provide data-driven guidance to maximize pediatric TBM treatment while we await definitive trial results.

Huimin Li MD et al. Pediatric Infect Dis J, June 2016. **Linezolid is associated with improved early outcomes of Childhood Tuberculous Meningitis.** Linezolid serves as an important component for the treatment of drug-resistant tuberculosis although there is little published data about linezolid use in children, especially in childhood tuberculous meningitis (TBM). The study data demonstrate that linezolid improves early outcomes of childhood TBM. The low frequency of linezolid-associated adverse effects highlights the promising prospects of its use for treatment of childhood TBM.

Enane LA et al. Int J Tuberc Lung Dis, October 2016. **Loss to follow-up among adolescents with tuberculosis in Gaborone, Botswana.** The objective of this retrospective cohort study of TB cases was to describe clinical characteristics and outcomes among adolescents with TB and compare loss to follow-up (LTFU) rates with that among youth and adult cases. The study concluded that Adolescents treated for TB had greater LTFU than youth and adults, particularly in the setting of TB-HIV co-infection. Further work should clarify the generalizability of these findings and investigate poor outcomes among adolescents with TB.



Schmidt BM et al. *Trials*, April 2016. **Engaging adolescents in tuberculosis and clinical trial research through drama.** Theatre, presented and motivated by adolescent peers, can raise awareness of TB, and assist clinical trial preparedness and further engagement between trial staff and their trial community.

Dodd PJ et al. *The Lancet Infect Dis*, June 2016. **Global burden of drug-resistant tuberculosis in children: a mathematical modelling study.** Far more drug-resistant tuberculosis occurs in children than is diagnosed, and there is a large pool of drug-resistant infection. This finding has implications for approaches to empirical treatment and preventive therapy in some regions of the world.

Pavlinac PB et al. *Int J Tuberc Lung Dis*, July 2016. **Mycobacterium tuberculosis bacteremia in adults and children: a systematic review and meta-analysis.** Among human immunodeficiency virus (HIV) infected adults living in tuberculosis (TB) endemic settings, *Mycobacterium tuberculosis* is a common cause of bloodstream infections. Although young children have an increased propensity for *M. tuberculosis* dissemination, *M. tuberculosis* bacteremia is infrequently described in children. While *M. tuberculosis* bacteremia appears relatively common in adults, particularly those with HIV infection, bloodstream *M. tuberculosis* appears to be rare in children.

Kunkel A et al. *BMC Infectious Diseases*, December 2015. **Smear positivity in paediatric and adult tuberculosis: systematic review and meta-analysis.** Tuberculosis (TB) diagnosis continues to rely on sputum smear microscopy in many settings. The researchers conducted a meta-analysis to estimate the percentage of children and adults with tuberculosis that are sputum smear positive. They concluded that children, especially those aged 0–4, are much less likely to be sputum smear positive than adults. National TB programs relying on sputum smear for diagnosis are at risk of under-diagnosing and underestimating the burden of TB in children.

Turkova A et al. **Prevalence, incidence, and associated risk factors of tuberculosis in children with HIV living in the UK and Ireland (CHIPS): a cohort study.** The researchers aimed to assess the incidence and prevalence of tuberculosis in children with HIV living in the UK and Ireland to understand rates, risk factors, and outcomes of the disease in this group. They concluded that the tuberculosis rates in HIV-infected children in the UK and Ireland were higher than those reported in the general paediatric population. Further study is warranted of tuberculosis screening and preventive treatment for children at high-risk of this disease to avoid morbidity and mortality in this population.

Crook AM et al. *BMC Medicine*, March 2016. **Tuberculosis incidence is high in HIV-infected African children but is reduced by co-trimoxazole and time on antiretroviral therapy.** TB incidence varies over time following ART initiation, and is particularly high during the first 3 months post-ART, reinforcing the importance of TB screening prior to starting ART and use of isoniazid preventive therapy once active TB is excluded. HIV-infected children continuing co-trimoxazole prophylaxis after 96 weeks of ART were diagnosed with TB less frequently, highlighting a potentially important role of co-trimoxazole in preventing TB.

Scott C et al. *Clin Infect Diseases*, June 2016. **Human Tuberculosis Caused by *Mycobacterium bovis* in the United States, 2006-2013.** Using genotyping techniques that have differentiated *Mycobacterium bovis* from *Mycobacterium tuberculosis* since 2005. The researchers reviewed the epidemiology of human tuberculosis caused by *M. bovis* in the United States and validated previous findings nationally. They concluded that children, foreign-born persons, Hispanics, and females are disproportionately affected by *M. bovis*, which was independently associated with extrapulmonary disease. Targeted prevention efforts aimed at Hispanic mothers and caregivers are warranted.

Lowenthal P et al. *Pediatr Infect Dis J*, March 2016. **High Discordance between Pre-US and Post-US Entry Tuberculosis Test Results Among Immigrant Children.** It is Time to Adopt Interferon Gamma Release Assay for Preentry Tuberculosis Screening? Since 2007, immigration applicants 2-14 years old with a tuberculin skin test (TST)  $\geq 10$  mm and an otherwise negative evaluation for tuberculosis (TB) are assigned a classification for TB infection and instructed to seek domestic evaluation upon arrival in the US in accordance with Centers for Disease Control and Prevention instructions. The researchers examined the characteristics and outcome of domestic evaluation of immigrant children who arrived in California with a positive TST on pre-immigration examination to inform the pre-immigration TB screening process. They concluded that the majority of immigrant children with a positive pre-immigration TST tested negative for TB infection on domestic evaluation using TST or IGRA. Inclusion of IGRA in pre-immigration TB screening is likely to reduce subsequent testing, treatment and cost of evaluations among immigrant children to the US.

Chiang SS et al. *Clinical Infectious Diseases*, July 2016. **Baseline Predictors of Treatment Outcomes in Children with Multidrug-Resistant Tuberculosis: A retrospective Cohort Study.** This retrospective cohort study included all children  $\leq 15$  years old with confirmed and probable MDR tuberculosis disease who began tailored regimens in Lima, Peru, between 2005 and 2009. Using logistic regression, the researchers examined associations between baseline patient and treatment characteristics and (1) death or treatment failure and (2) loss to follow-up. They concluded that high cure rates can be achieved in children with MDR tuberculosis using tailored regimens containing second-line drugs. However, children faced significantly higher risk of death or treatment failure if they had severe disease or were underweight. These findings highlight the need for early interventions that can improve treatment outcomes for children with MDR tuberculosis.

Tadolini M. et al. *ERJ*, 2016. **Compassionate use of new drugs in children and adolescents with multidrug-resistant and extensively drug-resistant tuberculosis: early experiences and challenges.** The aim of this report is to share initial experience and challenges of compassionate use of delamanid in children and adolescents at a global level. It also says that the lack of inclusion of children in bedaquiline trials to date is not acceptable and contributes to the current situation of very limited access to this drug among children. Case-by-case evaluation from independent bodies like the TB Consilium and endTB committee is a valuable support to clinicians and programmes in the use of the new drugs in children, particularly where the clinical cases are complex and in the absence of formal guidance for their paediatric use.

James Seddon concluded that a lot of paediatric work is being undertaken. Previously neglected areas such as BCG and adolescent health are finally getting some attention. However, gaps still remain.

### **ERS/WHO Consilium announcement – Marina Tadolini**

Treating MDR-TB and XDR-TB is difficult. The ERS/WHO Consilium is a free web-based platform that has been set up to provide expert opinion to clinicians managing difficult to treat patients. It is free of cost. Experts cover clinical aspects for both adults and children but also provide advice on laboratory, surgical, radiological, public health, psychological, and nursing aspects. The platform is managed by ERS, in collaboration with WHO Europe (through a formal agreement) and ECDC. Assistance is provided in English, Russian, Spanish, Portuguese and will soon be available in French.

The website address is: [www.tbconsilium.org](http://www.tbconsilium.org)

As of October 2016, the ERS/WHO TB Consilium has provided advice to over 200 cases in 31 countries, including 30 paediatric cases. Advice includes: guidance on treatment regimen and /or duration; advice for introduction of a new TB drug (Delamanid or Bedaquiline); Delamanid compassionate use; and, advice for the combined use of Delamanid and Bedaquiline and management of side effects. A new feature is that the platform helps to create links between treating clinicians across borders (when TB patients move from one country to another).

In the discussion that followed, subgroup members requested if it would be possible to give access to public health people and to consider to share the way cases have been managed (in an anonymous way) so that others can learn from them.

## **9. Implementation research on preventive therapy using 3HR in 4 African countries (Benin, Burkina Faso, Cameroon and Central African Republic) – Valérie Schwoebel**

### **The “Titi” study – Transmission investiguée de la Tuberculose Infantile**

In January 2014, the Union organized a workshop in Benin with the NTP (managers and childhood TB focal points) as well as paediatricians from 8 countries in Francophone Africa: Benin, Burkina faso, Cameroon, Central African Republic, Côte d’Ivoire, DRC, Madagascar, and Niger. The objective of the workshop was to identify key actions to improve the control of childhood TB. The workshop concluded that systematic investigation and preventive therapy for children <5years who are contacts of contagious TB cases, although internationally and nationally recommended, was only partially implemented and not fully documented.

The workshop recommended to conduct operational research:

- A study on how to implement and document systematic investigation and preventive therapy for contact children <5 years within the NTP framework; and,
- A study on how to implement a shorter RH regimen for preventive therapy in children < 5 years.

The Union and 4 country teams (Benin, Burkina Faso, Cameroon, and CAR) developed a protocol for implementation research combining the objectives of the above mentioned studies and submitted it to Expertise-France for funding. A research grant was obtained in 2015.

The national research teams consisted of one principle investigator and one co-investigator (NTP and Paediatrician or pulmonologist), one research assistant (a social worker or anthropologist), nurses and data managers.

The primary objective of the study was to demonstrate the feasibility of conducting contact investigation and preventive therapy within the framework of the NTP.

Specific objectives included:

Estimate the number of children < 5 years who are close contacts of sputum smear positive (SS+) cases;  
Determine the prevalence and analyse risk factors for active TB among contact children (at inclusion);  
Determine the incidence of active TB in children during and after preventive therapy using 6H or 3RH75/50;  
Assess children adherence to preventive therapy; and,  
Develop standardised simple recording and reporting tools.

Study sites included 13 Basic Management Units (BMUs) in the capital or a major city in each country: Cotonou; Ouagadougou; Douala; and, Bangui. A total of 2000 children were enrolled in the study (500 per country) through screening of all adult SS+ TB cases diagnosed in each BMU with children <5 years in the household. As a first step, a questionnaire was used to assess the eligibility for inclusion in the study and informed consent was sought from parents. The second step consisted of a home visit by a nurse and a social worker within 3 days after initial adult consultation. During this visit, for each child < 5 years, the contacts and symptoms were mapped and an appointment was scheduled at the BMU. During the clinical evaluation at the BMU, a TST was used. All children also had a Chest X-ray which were all read by a doctor using a standard form. Physical examination included (height, weight, temperature and RR). The child was referred to a paediatrician if signs/symptoms suggestive of TB (cough, fever, weight loss, reduced playfulness) and/or abnormal X-Ray results were found. If the child was not referred, or later found free of TB by the paediatrician, preventive chemotherapy was initiated. The Central African Republic, Burkina Faso and Cameroon used: RH75/50 during 3 months Benin used H10=mg during 6 months.

There was monthly follow-up during the preventive chemotherapy to check for TB symptoms (including physical examination), adherence to treatment and adverse reactions. After the preventive therapy, there was quarterly follow up up to 12 months after termination of therapy. If signs and symptoms suggestive of TB or suspicious adverse reactions were discovered, a nurse referred the child to the paediatrician.

A tool to review chest X-rays and a register for preventive therapy were developed.

The study has started successfully. Authorizations from the ethical committees (national and the Union) were obtained at the end of 2015 and study enrollment started on 1 April 2016 (and will last about 18 months). As of October 2016, already over 500 children have started preventive therapy. No major problems have been encountered in conducting home visits, BMU visits, doctor visits and monthly follow-up. Families are very participative and children are happy to take the RH74/50 FDC which has a good taste! The tools which were developed are useful.

Procurement of tuberculin has been challenging. The quality and interpretation of chest X-ray appear heterogeneous between countries. NTPs lack experience in doing chest X-ray in young children. The study also highlights the needs for training of NTP staff in clinical evaluation and in obtaining specimen (gastric aspiration) for TB diagnosis in children.

Final study results are expected for end-2018 but lessons can be learned from the preliminary results in the course of 2017.

During the discussion, there was a question about the use of chest X-ray which is not necessarily recommended. The use of Chest X-ray within this study is related to the study objective to look closer at prevalence. There was also a question about the comparison between 6H and 3RH regimens. Benin is using the 6H as they had just updated their national childhood TB guidance from 9 to 6 months of INH. It would have been confusing to use 3RH in this setting.

## **10. Panel discussion on issues related to demand, procurement and distribution of preventive therapy**

– Moderated by Eleanor Click (CDC)

Elie Click facilitated a panel discussion on preventive therapy. Rina Triasih from Indonesia, Maureen Sekadde from Uganda and Valérie Schwoebel, The Union participated in the panel.

Prevention of TB in children should receive priority. However, at practical level, there are many challenges. Children fall into treatment silos (e.g. HIV and TB programmes). Other challenges include issues related to: procurement; shelf life of the new formulations of which the continuation phase can be used as preventive therapy; coordination with other non-TB settings; distribution of drugs; monitoring and evaluation (knowing how many children need preventive therapy and monitoring progress towards that); screening – where to do it, how to make clinical decisions around treatment or prevention; lack of understanding in families and clinical side around the need for prevention (demand generation); and, finally adherence. Looking at different initiatives, it seems training is critical, and it is also important to have the right tools available. Save the Children integrated Intensified Case Finding (ICF) into a programme in Malawi to build ownership of local stakeholders and clinicians and generate demand for preventive therapy. UNICEF has plans to train a cadre of health workers in Nigeria in order to build understanding and implement a similar project. Kenya is engaging communities and grass root health workers.

It is interesting to hear how various countries are trying to address these practical challenges.

During the discussion, it seems that the biggest challenge for health workers is finding the time to spend with families to explain why a healthy child needs six months of preventive treatment.

Some countries, including Vietnam, give health workers a financial incentive when preventive therapy has been completed. However, such incentives also have a risk as it may lead to screening of additional people who do not need to be put on IPT. There are challenges for health workers to rule out active TB in children with HIV. If health workers cannot take a sample, they should rely on clinical diagnosis and manage the child according to the IMCI guidelines. In addition to clinical diagnosis, health workers should take the history into consideration, in particular the history of TB contacts.

There may be drug-drug interactions (hepatotoxicity) for children with HIV on NVP (nevirapine). Uganda has been looking at this but it turned out not to be a major issue. We also need to study simultaneous use of the child FDCs and cotrimoxazole.

## **11. Scale up of IPT in Uganda and Vietnam – Steve Graham**

### **Detect Child TB (The Union) Uganda Project 2015-2016**

The objectives of the Detect Child TB project are to improve the capacity of different levels of health facilities to detect child TB; to increase TB case detection among household contacts of all ages; to provide preventive therapy for eligible “at-risk” children according to the national guidelines; and, to improve treatment outcomes for children with TB. The project is implemented by the Union in close collaboration with the Uganda NTLP and in partnership with Baylor Uganda and MildMay Uganda. The project is pilot-tested in two provinces – Wakiso (periurban) and Kabarole (rural). Two out of 150 provinces. The budget available was USD 1.5 million. It was launched in January 2015. A baseline survey was conducted in April 2015 which indicated that no contact screening was implemented in public health facilities. It also showed that over 95% of all child TB cases were diagnosed in large provincial hospitals. And it highlighted stock outs of single dose isoniazid. Training of trainers (30 district health

care workers) was conducted in June 2015 in order to enable them to facilitate training of peripheral health care workers and to provide mentorship. In total, 200 village health teams (i.e. community health workers) have been trained and job aides have been provided. Achievements include: improved case detection and management of child TB; increased capacity of health workers to diagnose and manage TB in children at lower levels of the health facilities; successful training introduced and received; health system strengthening (the introduction of DETECT TB has coincided with an increased case detection of TB in adults); introduction of community-based contact screening of household contacts and preventive therapy; and, to strong support (including procurement of INH) from the NTLF. The Union also introduced the online training introduced which was well received.

Challenges include: scale-up and sustainability as funding unclear for 2017; high staff turnover; symptomatic contacts are not attending evaluation; the need to improve coverage of HIV testing; and, the need to understand barriers for families and health workers to improve access and care. An external evaluation of the project will be conducted in November 2016. Lessons learned so far: a focus on clinical diagnosis empowers health care workers at primary health care facilities (it gives them confidence to find and treat more children with TB) ; a focus on health systems strengthening improves TB case finding in both adults and children; and, provision of care at primary health facilities improves treatment outcomes.

### **Update on the scale up of IPT in Vietnam – USAID Challenge TB project led by the KNCV Tuberculosis Foundation**

In Vietnam, very few children are being diagnosed for TB (<1% of total caseload compared to WHO estimates of 10.7% globally). The NTP had no guidelines for preventive therapy and these were introduced in 2012, consistent with WHO guidelines.

Through the USAID funded Challenge TB project, the KNCV Tuberculosis Foundation piloted implementation of community-based child contact screening and preventive therapy. In 2011, training of trainers was conducted and tools were developed to monitor implementation. IEC materials were developed and distributed to the Community Health Centers. In 2012, the project was implemented in 4 pilot Provinces with 51 districts and 857 communities.

The pilot project has led to a work plan for childhood TB control in Vietnam 2015-2020 with the objectives to strengthen:

- 1) advocacy, communication and social mobilization in childhood TB control;
- 2) early detection and treatment for childhood TB;
- 3) child TB contact management; and,
- 4) monitoring and evaluation and research.

Targets include:

- Increase the proportion of child TB nationally to 6% in 2020 (from 1%) through active community awareness and demand generation;
- Treatment success rate >90% from 2016 onwards; and,
- At least 80% of eligible child contacts receive IPT.

Results from the four pilot provinces (Q4 2012-Q1 2015) show that, of children eligible, uptake of IPT is around 71%. IPT completion is about 87%. The project is now being scaled up including 16 Provinces to eventually cover the whole country. Registers, INH and guidance are available in all communities (10,732) in these Provinces. Preliminary results from the recently included 9 Provinces in 2014-2015 shows that

1,104 children were put on IPT and 1,045 completed IPT treatment (95%). The provision of financial incentives to communal health workers for completion of IPT might be one factor that explains the high treatment completion rates for IPT. While the numbers of children detected with active TB (smear positive around 13%) has increased in the provinces included, there is a much lower than expected yield of case detection from household screening. This might reflect the epidemiology of TB in Viet Nam which is particularly prevalent in old men, compared for example to Uganda where it is highly prevalent in young adults, often parents of young children.

Based on these outcomes of this project, contact management guidelines are being developed consistent with WHO and NTP guidelines. They include steps and an algorithm for community-based screening. All contacts of PTB cases are being screened. Preventive therapy for contacts of drug-sensitive TB is 6H if active TB is excluded and the child is younger than 5 years of living with HIV. It will include guidance on an individualised approach for young child contacts of MDR-TB patients. Such preventive therapy should include a fluoroquinolone.

## **12. Outcome of intensive case finding of TB in children (ICTB) project in Addis Ababa, Ethiopia – Senait Kebede**

Ethiopia is a TB High Burden Country. Ethiopia also has a high burden of MDR-TB. There is low case notification in general but particularly among children under 5 years of age. In 2015, 13.6% of all cases were among children. TB control is decentralised with integration of TB into HIV and MCH. Ethiopia has adopted the WHO guidelines.

Senait Kebede and her team implemented a cross-sectional study from April 2015- May 2016 to: assess the yield of intensive case finding of TB among children under 5 using a screening tool in MCH services; describe associated comorbidities and interventions namely nutritional status and HIV among children with TB; and, describe risk factors and outcomes of interventions for childhood TB.

The study was implemented in the St Paul Hospital Millennium Medical College, Addis Ababa and in the Felege Meles Health Center. The study team and health care providers received training on childhood TB. A structured questionnaire was used to screen eligible children followed by examination by an attending physician.

Enrollment criteria included:

- any child under 5 years of age that exhibited at least one of the following signs or symptoms: cough over 2 weeks, no remitting and unexplained; weight loss; persistent and unexplained fever; persistent and unexplained lethargy or decrease in playfulness reported by the parent/caregiver; and,
- all children under 5 with a household or closed contact with (suspected) TB or diagnosed with HIV.

The study enrolled 169 children. 94% of these children had received BCG vaccination. 48/169 had a history of TB contact. History of contact is therefore a major stratifying component. 19% of children enrolled had moderate/severe under-nutrition vs 21.9% of those with confirmed TB. Of the 112 for whom HIV test results were available, 19 were HIV-positive. Only 6 (3.6%) of the children under 5 with a history of contact were on IPT. After further evaluation during the study, 40 children were put on IPT. 75 (44%) of the children were further investigated for TB. 15 (8.9%) were reported as TB cases and started treatment. Only 4 cases were confirmed bacteriologically (2 via AFB and 2 via GeneXpert).

Challenges and limitations included: administrative and logistical barriers; challenges linking maternal records and services with child records; high turnover of staff; stock out of diagnostic supplies (e.g. sample containers for GeneXpert); breakdown in follow-up due to gaps in the referral system; poor connectivity and internet access limiting communication; and financial barriers.

This study has shown that there are multiple entry points for TB case finding. A high index of suspicion and use of a screening tool can enhance early case detection of TB in children. Challenges for early detection and intervention include: limited contact tracing & tracking and weak integration of services. Gaps in referral systems (e.g. lack of communication) and stock out of diagnostics further limit the potential for effective interventions. Implementation of IPT is low despite the opportunities for its use.

Strategic approaches are needed to address barriers for integration of TB in MCH services. A well-functioning tracking system for children and their families with TB needs to be established with community engagement. Innovative approaches are needed, using IT. In order to enhance bacteriological confirmation, it is critical to build capacity for efficient laboratory services and quality assurance. It is important to enhance training of care providers as well as research capacity.

In the discussion the issue of Non-Tuberculous Mycobacteria (NTM) was raised. NTM leads to smear positives, however, test results of GeneXpert will be negative.

### **13. Introduction of the new chair of the subgroup**

Steve Graham has been Chair of the childhood TB subgroup since February 2011. This is almost six years, the maximum time (two 3-year terms) accordingly to the Standard Operating Procedures of the Stop TB Partnership.

Over the summer of 2016, the Secretariat of the childhood TB subgroup therefore issued a call for nominations for a new chair specifying that the candidate should be a pediatrician, preferably from a high TB incidence/high TB burden country, with experience working on childhood TB with NTPs and MCH programmes outside his/her own country. All subgroup members were invited to send their nominations (including self-nominations) to the Secretariat by Friday 16 September 2016.

In September, the Secretariat reviewed the applications based on a set of screening criteria and the childhood TB core team members were subsequently invited to vote for the most suitable candidate.

During the annual meeting of the childhood TB subgroup, Steve Graham publicly announced that Dr Farhana Amanullah had been selected as the new Chair of the Childhood TB Subgroup and that she had accepted to take on that role.

Farhana Amanullah warmly thanked Steve for his leadership over the past 6 years and mentioned that it is a huge honour to take on this function. The subgroup members also acknowledged Steve Graham's excellent chairmanship. Steve was presented a special shield made in Kenya as a token of appreciation.

Steve acknowledged the support of the core team, the subgroup members as well as the Secretariat of the subgroup housed at WHO Headquarters.

### **14. Wrap up, next steps and closure**



Steve Graham and Malgosia Grzemska closed the meeting and thanked participants for their active involvement. 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.

In order to find more children with TB or at risk of TB, analyses of the patient pathway and the cascade of care will be useful. If we know where children seek care first, we can come up with strategies and approaches to increase awareness and further reduce diagnostic and treatment delays. As children usually go to MCH programmes or a paediatrician rather than to a TB clinic, it is important to establish links between NTPs and other programmes and take integration forward.

It is important to move to digital case-based recording and reporting.

In the coming year, we need to continue to assist countries to transition to the child TB Fixed-Dose Combinations (FDCs) and ensure that children who need them will have access to the formulations.

We now have evidence based recommendations for treatment of RR-TB and MDR-TB in children. Countries will seek our assistance to update their national policies accordingly. In the meantime, we need to collect more data, especially on the use of new drugs and new regimens. Studies are needed to identify optimal drug dosing, safety and treatment duration as well as to improve diagnostics and DST methods for children.

Prevention is a top priority for global TB control. In particular, studies on preventive chemotherapy for children in contact with MDR-TB patients are urgently needed.

The subgroup has nearly 300 members. It may be time to consider to request full working group status and be renamed to “Child and Adolescent Working Group”.

The annual meeting of the Childhood TB Subgroup in 2017 will be in Guadalajara, Mexico, the venue of the 2017 Union World Conference.

## Annex 1: Agenda



### **Annual meeting of the Childhood TB working group Wednesday 26 October 2016**

**Doubletree Hilton Hotel & Spa (Cannon Suite)  
6 Sir Thomas Street  
Liverpool L1 6BR, UK**

#### **Purpose of the meeting**

The annual meeting of the Childhood TB working group will be organized on Wednesday 26 October 2016 in Liverpool, UK. The meeting is open to all members of the working group 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 main purpose of the annual meeting is 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 are to:

- To discuss how to operationalize the End TB Strategy with a focus on childhood TB;
- To give an update on the activities of the working group since the last annual meeting on Thursday 3 December 2015 in Cape Town, South Africa
- To share the outcomes of the UNICEF integration meeting and discuss next steps
- To share country experiences in scaling up childhood TB activities; including collaboration with MCH and other health services at country level;
- To learn about community-based projects;
- To discuss the uptake of the new paediatric TB Fixed Dose Combination (childhood TB FDC);
- To highlight impact publications in the last 12 months; and,
- To give an update on ongoing and planned research.

## AGENDA

<b>Childhood TB working group meeting</b>		<b>08:30 – 16:30</b>
<b>Chair: Dr Steve Graham</b>		
08:00 - 08:30	Registration	
08:30 – 08:45	Opening and welcoming words	Mario Raviglione, WHO Global TB Programme & Lucica Ditiu, Stop TB Partnership/UNOPS & Steve Graham, Chair, Childhood TB working group
08:45 – 09:10	Report from Chair on the 2016 activities of the Childhood TB working group	Chair, Childhood TB working group & secretariat
<b>Global developments in childhood TB: update on treatment of MDR-TB and progress in linking with RMNCAH services</b>		
09:10 - 09:30	Updated WHO MDR-TB treatment guidelines and the use of new drugs in children	Malgosia Grzemska, WHO Global TB Programme
09:30 – 10:00	Prevention and management of MDRTB in children	Simon Schaaf, University of Stellenbosch, South Africa
10:00-10:10	Treatment of MDR-TB in children and adolescents with the shorter regimen in 9 African countries	Valérie Schwoebel, The Union
10:10 – 10:30	Discussion	
10:30 – 11:00	Coffee/Tea break	
11:00 – 11:20	Outcomes of the UNICEF integration meeting and update on the TB/HIV adapted iCCM pilots and country case studies	Anne Detjen, UNICEF
11:20 – 11:30	Discussion	All
<b>Country experiences in scaling up childhood TB activities</b>		
11:30 - 12:00	Panel discussion on the outcomes of national childhood TB stakeholders meetings in UR Tanzania, Philippines and Pakistan (5-minute summary by each of the NTP representatives followed by discussion)	Panel moderated by Dr Farhana Amanullah with NTP representatives from UR Tanzania, the Philippines, and Pakistan

12:00 – 12:20	Summary of impact publications in last 12 months	James Seddon, Imperial College London, UK
12:20 – 12:30	Discussion	
<b>12:30 – 14:30 Continuing Momentum in Improving Paediatric TB Treatment: a luncheon symposium organized by TB Alliance – Corinthian Grand Room, Doubletree Hilton Hotel &amp; Spa Liverpool, 6 Sir Thomas St, Liverpool L1 6BR, UK</b>		
<b>Country experiences in scaling up childhood TB activities (continued)</b>		
14:30 – 14:45	Implementation research on preventive therapy using 3HR in 4 African countries (Benin, Burkina Faso, Cameroon and Central African Republic)	Valérie Schwoebel, The Union
14:45 – 15:30	Panel discussion on issues related to demand, procurement and distribution of preventive therapy & discussion	Panel moderated by Eleanor Click, CDC with NTP representatives
15:30 – 15:45	Scale up of IPT in Uganda and Vietnam	Steve Graham
15:45 – 16:00	Outcome intensive case finding of TB in children (ICTB) project in Addis Ababa, Ethiopia	Senait Kebede
16:00-16:10	Introduction of the new chair of the working group	Steve Graham and new Chair
16:10-16:15	Wrap up, next steps and closure	Chairs and Secretariat
16:15	Tea	

*17:30 - Inaugural Ceremony of the 47<sup>th</sup> Union World Conference*

## Annex 2: List of participants

Steve Graham, Chair  
Kechi Achebe  
Lisa Adams  
Alufunlola Adedeji  
Oluwatosin Adeoye  
Adeola Afuntoye  
Valentina Aksenova  
Farhana Amanullah  
Emeka Anoje  
Jason Bacha  
Lada Baryshnikova  
Roksana Bialczak  
Miranda Brouwer  
Martina casenghi  
Chisala Chabala  
Rebekah Chang  
Silvia Chiang  
Eleanor Click  
Renia Coghlan  
Clemax Couto Sant'Anna  
Angela Crook  
Andrea Cruz  
Jerene Degu  
Anne-Marie Demers  
Anne Detjen  
Gunta Dravniece  
Karen Du Preez  
Leslie Enane  
Anthony Enimil  
Kayt Erdahl  
Betina Mendez Alcântara Gabardo  
Deliana Garcia  
Anthony Garcia Pratz  
Salvaceon Gatchalian  
Diana Gibb  
Rachel Golin  
Jeffrey Hafkin  
Elisabeth Harausz  
Heather Highsmith  
Yael Hirsch-Moverman  
Cleotilde Hildago How  
Hamidah Hussain  
Sharon Kasa Tom  
Immaculate Kathure  
Alexander Kay  
Senait Kebede  
Ilan Kitai  
Zhanna Kryvasheyeva  
Keri Lijinski  
Elisa Lopez-Varela  
Rifat Mahfuza  
Shelly Malhotra  
Olivier Marcy  
Carina Marquez  
Alberto Matteelli  
Lindsay McKenna  
Ya Diul Mukadi  
Sarah Mulera  
Maurine Muregna  
Rehab Mwahiki  
Katherine Ngo  
Huong Thien Nguyen  
John Baptist Nkuranga  
Betty Nsangi  
Elizabeth Maleche Obimbo  
Satria Arief Prabowo  
Patricia Paredes Jodrey  
Andrea Maciel de Oliveira Rossoni  
Natacha Rybak  
Kelly Sawyer  
Anna Scardigli  
Simon Schaaf  
Valérie Schwoebel  
Cherise Scott  
James Seddon  
Moorine Sekadde  
Alena Skrahina  
Kathryn Julia Snow  
Maura Soucy Brown  
Andrew Steenhoff  
Daria Szkwarko  
Marina Tadolini  
Khurshid Talukder  
Marc Terbruegge  
Lan Terhemba  
Margaret Thomason  
Rina Triasih  
Anna Turkova  
Irina Usherenko  
Sabine Verkuijl  
Fraser Wares  
Christine Whalen

Christine Whalen  
Genevieve Wills  
Eric Wobudeya  
Jessica Workman  
Kiley Workman Diop

**WHO**

Ayodele Awe  
Annemieke Brands  
Regina Christian  
Malgosia Grzemska  
Karina Halle  
Lisa Hedman  
Cornelia Hennig  
Khurshid Hyder

Nemes Joseph Iriya  
Tauhidul Islam  
Kassa Hailu Ketema  
Daniel Kibuga  
Nobuyuki Nishikiori  
Abel Nkolo  
Enang Enang Oyama  
Mario Raviglione  
Kefas Samson  
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