Child
& Adolescent
TB Working Group

Annual meeting of the Child and Adolescent TB working group
Wednesday 24 October 2018

Crowne Plaza, The Hague, The Netherlands

Photo credit: Shakil Ahmed

Opening address by Dr Tereza Kazaeva, Director Global TB Programme

Dr Kasaeva opened the meeting, welcoming all participants on behalf of WHO. She summarized epidemiological data based on the Global TB Report 2018: In 2017, 1 million children (0-14 years) developed TB (10% of the total TB burden), 52% below 5 years of age. 233,000 children died of TB, including 39,000 children living with HIV, which means that nearly 650 children die of TB every day. Since the launch of the first roadmap in 2013, a lot of progress has been made: child and adolescent TB has been firmly placed on the global agenda; we now have better data on the burden; there is increased advocacy and awareness; global and regional working groups and new coalitions have been established; guidance, training and assessment tools are available; child-friendly fixed dose combination formulations have been developed and over 85 countries are procuring them (see the *WHO document on Best practices in child and adolescent TB care, available at: http://apps.who.int/iris/bitstream/handle/10665/274373/9789241514651-eng.pdf?ua=1).*

Major detection and prevention gaps remain: E.g. In 2017, 69% of children under 5 and 40 % of children aged 5-14 years were missed (pointing to under-diagnosis and under-reporting). Out of the 1.3 million eligible household contacts under 5 years of age, over 75% did not access preventive treatment. These gaps relate to persistent challenges and missed opportunities: (a) insufficient advocacy, political leadership and stakeholder engagement; (b) persistent policy-practice gaps in developing, implementing and scaling up evidence-based programmatic approaches (including prevention and finding the missing children with TB); and, (c) lack of implementation of integrated, family and community-centered strategies. In addition, current recording and reporting systems urgently need improvement and research on child and adolescent TB needs to receive more priority (*see the document developed by the Child and Adolescent Working Group and TAG on paediatric TB research priorities, available at: http://www.treatmentactiongroup.org/sites/default/files/Paediatric_TB_ResearchPriorities_10_8_18_Web.pdf).*

Ending the epidemic of tuberculosis by 2030 requires Universal Health Coverage, leaving no one behind, but also action beyond the health sector to address the risk factors and determinants of disease. The political declaration of the UN HLM on TB provides a major opportunity to galvanize such multi-sectoral action. The declaration includes two major global targets for the next five years: (i) 40 million people with TB to be reached with care during the period 2018 and 2023, including 3.5 million children and 1.5 million people with drug-resistant TB; and, (ii) at least 30 million people to be reach with TB prevention services during the period 2018-2023 including 4 million children under 5 years of age, 20 million other household contacts and 6 million people living with HIV (including children).

To catalyse global efforts to support the achievement of these targets, WHO, the Stop TB Partnership and the Global Fund to Fight AIDS, Tuberculosis and Malaria have launched a joint initiative entitled "Find. Treat. All. #End.TB". The 2018 Roadmap towards ending TB in children and adolescents launched on 24 September 2018, just prior to the UN HLM on TB (today exactly one month ago) at an event co-organized by WHO, UNICEF and the Stop TB Partnership, is calling for high political will, strong leadership and accountability to address TB in children and adolescents. It includes key actions that are aligned with the global targets (*the second edition with post-HLM updates is available at: http://apps.who.int/iris/bitstream/handle/10665/275422/9789241514798-eng.pdf*).

WHO is looking forward to close collaboration in order to reach the global targets set and to assist countries implement age-responsive strategies for prevention and care which require the engagement

of all relevant stakeholders at global, regional and national levels, from public and private sectors, from those already engaged in TB to those engaged in the HIV, nutrition and maternal and child health agendas.

Objectives and expected outcomes – Annemieke Brands

The main purpose of the annual meeting of the Child and Adolescent Working Group (WG) was an exchange of global developments and country experiences. The expected outcomes included: ideas on how to further scale up prevention efforts, moving from successful pilot projects to sustainable programmatic responses to prevent TB in children, adolescents and families.
The objectives of the annual meeting were:

- To provide an update on the activities of the WG since the last annual meeting on Monday 9 October 2017 in Kigali, Rwanda ;
- To present the 2018 Roadmap towards ending TB in children and adolescents and accompanying documents;
- To provide WHO policy updates on BCG, programmatic management of LTBI and the key changes to treatment of multidrug- and rifampicin-resistant tuberculosis (MDR/RR-TB) as per the rapid communication;
- To learn from country experiences in scaling up childhood TB activities with a focus on contact investigation and preventive therapy;
- To provide an update on trials of TB prevention in children and pregnant women; and,
- To share recent papers on child and adolescent TB with a focus on contact investigation and preventive therapy.

Report from the chair – Farhana Amanullah

Farhana Amanullah emphasised that no child should die of TB and that TB in children can be treated and prevented. The mortality rate in children (23%) is higher than the overall rate (16%), and affects mainly young children. Although there is some progress in case notifications and prevention, it is still too slow.

Activities in 2017/18:

The Annual meeting of the Child and Adolescent TB WG was not coupled with the 48th Union Conference last year as many RMNCAH colleagues from Africa were convening in Kigali and the main theme of last year's meeting was "Integration across child health services", so it made perfect sense to hold the WG meeting along with the WHO/AFRO RMNCAH managers meeting with a key talk from on childhood TB in their session. The 48th Union Conference was important as last year Jeffery Starke, an icon clinician researcher and child TB advocate was the keynote speaker at the Conference inauguration. The first Global Ministerial Conference held in Moscow was another first for TB and was very well attended including representation from the WG.
The Sentinel Group meeting on child friendly formulations for second line TB drugs was held and was attended by the WG Chair and Lindsay McKenna. Jennifer Furin from Sentinel helped several country representatives align their needs and project orders for child friendly formulations of levofloxacin, ethambutol, and other drugs. The WHO position paper on BCG was launched in February, attended by

the WG secretariat. WHO launched the consolidated LTBI guidelines in February as well, with important updates on preventive therapy and Infection management beyond the under-5 year age group. World TB day was marked by a commentary by the WG (Anne, Lindsay, Farhana, Ben, and Steve) in The Lancet Global Health (*see https://www.thelancet.com/action/showPdf?pii=S2214-109X%2818%2930108-6*). The 2nd International meeting on Childhood Tuberculosis, pTBNet was held in Vilnius, Lithuania, in March. WHO launched WHO Quality of care standards for children and young adolescents in health facilities with a quality statement on children at risk for TB and/or HIV infection in May. A small writing team meeting to review first draft of the updated roadmap was hosted at KNCV in The Hague, in May as well. The Union organized a side event to the World Health Assembly (WHA) "United to end TB - priorities for the UNHLM on TB" with launch of a Union publication on “Silent epidemic: a call to action against child tuberculosis”. GDF included child-friendly formulations of second-line drugs in the catalogue from May. The UN HLM Civil Society Hearings took place on 5 June 2018, in NYC, USA and was attended by Farhana, Anne, Lindsay and Catherine Connor (EGPAF). The 18th Strategic and Technical Advisory Group (STAG) meeting was held on 6-7 June in NYC, USA. Other activities at global level included the Initiative on Stigma in Children by the Global Coalition of TB Activists (Blessi Kumar), the design of a logo for the WG, the WHO Rapid Communication for MDR and RR TB in August (relevant for paediatric MDR-TB regimens) and the 12th International Child TB training course organized by the Desmond Tutu TB Centre, in September in South Africa. Two days before the UNGA HLM on TB, UNICEF, WHO and STP organized a side event “Committing to end TB in Children, Adolescents and Families to launch 2018 Roadmap and accompanying documents, at Scandinavia House, NYC, USA. A social media kit for child and adolescent TB was developed for this event. The UNGA HLM on the fight against TB on 26th September was attended by Malgosia, Monica Dias and Anne Detjen. A meeting with project countries of Unitaid paediatric TB grants, was held on 22 October in The Hague, The Netherlands.

UNICEF Executive Director Henrietta Fore and WHO Director-General Tedros Adhanom Ghebreyesus with the Roadmap at the UN (photo credit: Anne Detjen)

Regional activities included the RMNCH & Nutrition Program Managers' meeting for Eastern and Southern African countries in October 2017 in Kigali, Rwanda and the Global Fund/TDR workshop on finding missing TB cases in countries of West and Central Africa in March 2018 in Cotounou, Benin.

Global and regional action by WHO and all partners should include: highlighting challenges and opportunities in all relevant fora; Addressing childhood TB as a child health issue within WHO across departments as well as with partners through better collaboration and harmonization; Continuing to organize annual meetings of the Child and Adolescent TB working group with regional working groups and variety of stakeholders; Assisting countries to find ways and mobilize resources to move from projects to a programmatic approach; Promoting research and development: point of care diagnostic

tests for TB disease and infection; shorter treatments; more effective vaccines; country specific pathway analysis with an equity focus; cost savings of integrated versus NTP alone ("vertical") approaches; analysis of the cost of action versus cost of inaction.

WHO policy updates – Malgosia Grzemska

Malgosia Grzemska presented case notification data for the 30 TB high burden countries (HBCs), highlighting that more children are being missed in the younger age group. In some countries, the proportion of older children that are notified is much higher than for younger children, showing that it is easier to make the diagnosis in older children. But in a few countries, the proportion is over 100%, suggesting possible over-diagnosis. Most HBCs now also report on preventive treatment for eligible children under-5, showing wide gaps in many countries.

Despite progress made since launch of first roadmap in 2013, major detection and prevention gaps remain relating to persistent challenges and missed opportunities, including: Insufficient advocacy, political leadership and stakeholder engagement; Persistent policy-practice gaps in developing, implementing and scaling up evidence-based programmatic approaches (including prevention and finding the missing children with TB); Lack of implementation of integrated, family and community-centred strategies; Inadequate recording and reporting systems and; Insufficient research on child and adolescent TB.

The ten key actions highlighted in the 2018 Roadmap are: 1) Strengthen advocacy at all levels; 2) Foster national leadership and accountability; 3) Foster functional partnerships for change; 4) Increase funding for child and adolescent TB programmes; 5) Bridge the policy-practice gap; 6) Implement and expand interventions for prevention; 6) Scale up child and adolescent TB case-finding and treatment; 7) Implement integrated family- and community-centred strategies; 8) Improve data collection, reporting and use; and 10) Encourage child and adolescent TB research.

The WHO position paper on BCG (February 2018) recommends the following: In high TB and/or leprosy burden countries as well as where Buruli ulcer occurs, a single dose should be given to all healthy neonates at birth or at earliest opportunity thereafter. Countries with low incidence of TB or leprosy may choose to selectively vaccinate high risk neonates. BCG can be safely co-administered with other routine vaccines including the hepatitis B birth dose. Revaccination is not recommended even if even if TST or IGRA is negative. BCG is recommended for unvaccinated, TST or IGRA negative school children coming from/moving to high incidence/burden settings as well as older groups at risk through occupational exposure. Children who are HIV infected should not receive BCG vaccination. However, HIV infected individuals, including children, who are receiving ART, are clinically well and immunologically stable should be vaccinated. Neonates born to women of unknown HIV status should receive BCG. However, neonates with unknown HIV status born to HIV-infected women should be vaccinated if they have no clinical evidence suggestive of HIV infection, regardless of the mother's ART status. Additionally, neonates with HIV infection should delay BCG vaccination until ART has been started and are immunologically stable. Neonates born to mothers with pulmonary TB: Asymptomatic neonates born to mothers with bacteriologically confirmed PTB should receive preventive treatment (after exclusion of TB disease). If the infant remains asymptomatic on follow-up, without immunological evidence of TB, and is

HIV-negative, BCG vaccination should be provided using a normal infant dose (after completion of preventive treatment).
WHO LTBI guidelines (February 2018): the number of groups prioritized for LTBI testing and treatment has expended: apart from all persons living with HIV and under 5 years, additional high risk groups are: HIV-negative children $\geqslant$ 5 years, adolescents and adults who are contacts of TB patients and contacts of patients with MDR-TB. Testing options have also been expanded in all countries: TST or IGRA. Active TB should always be ruled out before prescribing preventive treatment. Options for preventive treatment are expanding as well: two new shorter regimens are now recommended as an alternative to 6H: 3HP for adults, adolescents and children; 3RH for children and adolescents < 15 years – this should facilitate adherence. New recommendations for MDR-TB contacts: In selected high-risk household contacts of patients with MDR-TB, preventive treatment may be considered based on individualised risk assessment and a sound clinical justification (Conditional recommendation, very low-quality evidence). Important issues include: Careful assessment of exposure, resistance pattern of source case; Recommendations are for household contacts at high risk (e.g. children, PLHIV); Drug selection is based on drug susceptibility profile of source case; Confirmation of infection with LTBI test is required; Strict observation and close monitoring of all contacts for 2 years should be done; Results of ongoing placebo-controlled trials will be used for updating recommendation; Drug choice: later generation fluoroquinolones (e.g. levofloxacin [Lfx] or moxifloxacin [Mfx]) unless the source case is resistant (There is concern regarding retardation of cartilage development in children – but this has not been demonstrated in humans).

As per June 2018: 85 countries have ordered child-friendly TB fixed dose combinations (FDCs) from the Global Drug Facility (GDF). Kenya was the first country to roll out child-friendly TB FDCs through direct procurement from MacLeods.

Diagnosis of TB in children: There is not much new. The recommended approach for diagnosis of TB in children is a "package" consisting of: careful history (including history of TB contact and symptoms consistent with TB); Clinical examination (including growth assessment); Tuberculin Skin Testing; Chest X-Ray (if available); Bacteriological confirmation whenever possible (respiratory or non-respiratory samples); Investigations relevant for suspected pulmonary TB and suspected extrapulmonary TB; and, HIV testing. Xpert MTB/RIF should be used as the initial diagnostic test in children suspected of having MDR-TB or HIV associated TB. Xpert may be used as the initial test in all children suspected of TB. Children have paucibacillary disease and therefore, negative test results do not exclude TB in children. In 2017, WHO reviewed the next generation Xpert MTB/RIF Ultra cartridge. After review of the latest evidence, WHO recommendations now also apply to the Ultra assay.

An estimated 25,000 children <15 years fell ill with MDR-TB in 2014 but less than 10 % of them were diagnosed and had access to treatment (Dodd *et al* 2016 & Jenkins *et al* 2014). The rapid communication published by WHO in August 2018 (*available at: http://www.who.int/tb/publications/2018/WHO_RapidCommunicationMDRTB.pdf?ua=1*) will remain valid until publication of updated WHO PMDT guidance (expected end 2018). The rapid communication used new evidence from meta-analysis of individual data from clinical trials, cohort/observational studies and programmatic implementation of longer and shorter MDR-TB regimens. Treatment outcome

data was used for policy formulation. Treatment options are becoming more individualized: effective and fully oral treatment regimens are feasible for most patients (including children), as long as additional drug resistance is excluded before starting patients on treatment. The patient safety and treatment response needs to be closely monitored.
Key medicine changes include: Regrouping of medicines recommended for use in longer MDR-TB regimens into three categories, ranked based on the latest evidence about the balance of effectiveness to safety.
Group A (to be prioritized): Levofloxacin (Lfx) or Moxifloxacin (Mfx), Bedaquiline (Bdq), Linezolid (Lzd);
Group B (to be added next): Clofazimine (Cfz), Cycloserine (Cs) or Terizidone (Trd);
Group C (Add to complete the regimen and when medicines from Groups A and B cannot be used): Ethambutol (E), Delamanid (Dlm), Pyrazinamide (Z), Imipenem-cilastatin (Ipm-Cln) or Meropenem (Mpm), Amikacin (Am) (or Streptomycin S), Etionamide (Eto) or Prothionamide (Pto), p-aminosalicylic acid (PAS).
Guidance on paediatric dosing will be provided at the time of release of the final WHO guidelines. News is that GDF, in addition to the child-friendly TB FDCs since December 2015 (Rifampicin/Isoniazid 75mg/50mg and Rifampicin/Isoniazid/Pyrazinamide 75mg/50mg/150mg), offers additional child-friendly formulations for both drug-resistant (DR) and drug-sensitive (DS) TB since May 2018. WHO GTB, with input from GDF, is currently preparing application to the 7th Essential Medicines List for children.

WHO plans for 2019-2012 include: Dissemination and adaptation of Roadmap towards ending TB in children and adolescents – regional meetings in Africa and Asia; Comprehensive Child and Adolescent TB Handbook with new policies and implementation guidance (2019); and Updated WHO Guidance for National TB Programmes on the Management of TB in Children and Adolescents (2020-2021).

Update on trials of TB prevention in children and pregnant women – Anneke Hesseling

Anneke Hesseling provided an update on paediatric TB trials. She presented a trial decision tree: if it is reasonable to assume that children have a similar disease progression and response to interventions as adults, and a similar end response, then the following studies should be conducted: 1) PK studies aimed at achieving drug levels similar to those in adults; and, 2) safety trials at the appropriate dose.

Overview of priority studies for children:

Research Area	Gaps for children	Priority studies
DS-TB	• Dose optimization (rifampicin) • Treatment of Severe TB • Treatment shortening: non-severe TB	• PK studies first-line drugs at higher doses: OptiRif Kids • PK/efficacy study in children: SURE, TBM-Kids • SHINE

DR-TB	• PK/dosing second-line drugs (FQ, aminoglycosides, linezolid, clofazimine, hd INH) • New drugs: PK and safety (bedaquiline, delamanid, PA-824, sutezolid) • Injectable sparing shorter regimen	• Modeling existing data, testing doses predicted to achieve PK targets • PK/safety studies bedaquiline, PA-824, DLM, BDQ and combinations: MDR PK1, MDR PK2 • P1108, C211, Otsuka 232/233, P2005 • IMPAACT 2020 (SMART-Kids)
Co-treatment TB/HIV	• Super boosting LPV/r in young children taking HRZE • EFV-based regimen in children < 3 years • INSTI-based ART with standard TB drugs (HRZE)	• DnDI: Super-boosted PI with HRZE • EFV+HRZE in slow CYP2B6 genotype • RAL or DTG-based ART with TB drugs: Odussey
LTBI	• 3 HP: Safety/tolerability/PK once-weekly • 1 HP: Safety/tolerability/PK once-weekly • MDR-TB prevention • MDR TB prevention	• TBTC Study 35 • CAP 543 • Efficacy and safety: TB CHAMP, V-QUIN, PHOENIX: phase III

Specific trials:

- SHINE: shorter treatment for minimal TB in children: a randomized trial of therapy shortening for minimal TB with new WHO-recommended doses/FDCs in African and Indian HIV-infected and non-infected children. Status: n=1204 patients enrolled: f/u ongoing: results expected early 2020
- OptiRif kids: Data show that the AUC (area under the curve, representing total drug exposure across time) of rifampicin is 1.7 times higher in adults compared to children. Dosing cohorts: n=20 per cohort: 60 (20 per cohort) to 100 evaluable child participants (i.e. 5 dosing cohorts) enrolled; At least 3 dosing cohorts required, to demonstrate exposures in children similar to those achieved in adults; No age de-escalation. Children enrolled in 3 age groups, with children in all 3 age groups included in each dosing cohort: Age group 1: Age $\geqslant$ 6 to < 12 years (completed), Age group 2: Age $\geqslant$ 2 to < 6 years (completed); Age group 3: Age $\geqslant$ 0 to < 2 years: open (October 2018).
- MDR-TB trials: Treatment response is generally much better in children than in adults. PK gaps are used in order to design phase 3 treatment regimens.

Key second-line TB drugs, key knowledge gaps in children and ongoing or planned paediatric studies

Drug	Current	Key gaps	Ongoing/planned studies
Levofloxacin	PK data in TB across ages; low exposures	Optimal dose and safety; formulation	MDRPK1, MDRPK2
Moxifloxacin	PK data in TB, >8y only; low exposures	PK data in <8y; optimal dose and safety; formulation	MDRPK1, MDRPK2 (interim analysis ongoing)
Bedaquiline	No PK data	PK data, optimal dose, safety; HIV	P1108; Jannsen-trial; IMPAACT capsule (BDQ-DLM)
Delamanid	PK data >6y	PK data in children <6y, safety; HIV	Otsuka 232/233; IMPAACT 2005; IMPAACT capsule (BDQ-DLM)
Linezolid	PK data in non-TB across ages	PK data in TB, optimal dose, safety; formulation	MDRPK2 (interim analysis ongoing)
Clofazimine	Limited published PK data	PK data, safety optimal dose; formulation	?? – IMPAACT Capsule

Phase I/II paediatric bedaquiline trials:

	C211: Bedaquiline PK and safety in HIV-uninfected children (n=60)	**IMPAACT P1108: PK, safety and tolerability of bedaquiline with OBR in HIV-infected and uninfected children with MDR-TB (n=54-72)**
Sponsor	Janssen Pharmaceuticals	NIH (DAIDS, IMPAACT)
Design	Age de-escalation	Modified age de-escalation
Inclusion	0-<18y, HIV-uninfected only	0-<18y; both HIV-infected and uninfected
Accrual	Open 2106 - South Africa, Philippines, Russia, India	Open 2018 – South Africa, India, Haiti Younger cohorts open in parallel (0-2 and 3-5 years)
Other	Adult, pediatric formulations	Adult formulation, whole, crushed ? pediatric formulation
Progress	Data from cohort 1 (12-17y) shared with WHO	Data from cohort 1 (6-17y) shared with WHO

Bedaquiline crush study:

Design	Randomized open-label two-period crossover study
Objectives	Primary: To evaluate BA of whole vs crushed BDQ Secondary: To characterize 1) rate of absorption, 2) short term safety, 3) acceptability of whole vs crushed BDQ
Setting	TASK (Cape Town, SA); Sponsor – DAIDS/IMPAACT
Patients	Healthy adult volunteers
Dosing	Sequence 1: 4 x 100 mg BDQ whole, then 4 x 100 mg BDQ dissolved, both with food Sequence 2: 4 x 100 mg BDQ dissolved, then 4 x 100 mg BDQ whole, both with food
Assays	UCT – HPLC-MS/MS for BDQ and M2
Analysis	NLME (primary endpoint = bioavailability parameter)

Results: Difference in bioavailability dissolved vs whole tablets not statistically significant (p=0.92, CI95% 94-108%) - Bioequivalence criteria fulfilled

- ***Novel TB drugs in children:***
  - Delamanid: Children 6-17y – same indications as in adults; Children <6y – case-by-case basis; Access?; DLM CRUSH?
  - Bedaquiline: Children >12y – same indications as in adults; Children <6y – case-by-case basis; Access in younger kids?; Watch "this" space
- ***IMPAACT 2020 (SMaRT Kids)***
  - Design: Phase 2 multi-centre trial
  - Eligibility: Children 0 to <15 years of age; Probable or confirmed pulmonary or extrapulmonary MDR/RMR-TB/Rif-R, and MDR-TB with additional SLI-res or FQN-res; HIV-infected and uninfected; Exclusion - Probable or confirmed Stage 2 or 3 TB meningitis or osteo-articular TB
  - Assignment to 1 of 2 arms based on FQN-susceptibility: Arm 1 – FQN-Susc – 26 weeks BDQ-DLM-Lfx, 8 weeks Lzd; Arm 2 – FQN-Res – 26 weeks BDQ-DLM-CFZ, 8 weeks Lzd
  - Objectives – 1st - Safety; 2nd - outcomes, PK, others; N=148

Prevention (DS-TB)

- 3HR: Rigorous implementation science is needed to guide optimal and cost effective implementation of 3HR - including health systems strengthening (FDCs to support preventive therapy already WHO prequalified)
- 3HP: PK and safety data on rifapentine (RPT) and INH (12 doses over 12 weeks in total) : TBTC Study 35 in 0-12 years (HIV+/-) will open in Q1 2019 under FDA IND, for licensure, with Sanofi: will include HIV+ (EFV, dalutegravir)
- 1 HP: Paediatric PK and safety data needed (HIV-/+): IMPAACT 543
- 1 HP vs. 3 HP?: Safety, completion: PROTEA
- 4 R: any need for paediatric data?

Prevention (DR-TB)

	TB-CHAMP	**V-QUIN**	**PHOENIx**
Intervention	LVF vs. placebo daily for 6 months	LVF vs. placebo daily for 6 months	DLM vs. standard dose INH daily for 26 weeks
Target Population	<5 years regardless of IGRA or HIV status **Only study powered for efficacy in children**	• All ages • TST + • Children not yet treated	• HIV + • Children <5 years • TST/IGRA + >5 years
Sample size	778 Households 1556 contacts < 5 y	1326 Households 2785 contacts	1726 Households 3452 contacts
Sites	South Africa DTTC, Shandukani, PHRU Matlosana	Viet Nam NTP	ACTG & IMPAACT sites
Timelines	Open; n=230 enrolled	Open ; 70% enrolled	Q1 2019
Funder, PI	BMRC/Wellcome Trust/DFID, SA MRC SHIP; Hesseling MRC CTU at UCL	Australian MRC Fox, Nguyen SA NTP	DAIDS, ACTH/IMPAACT Churchyard, Gupta, Hesseling, Swindells

TB-CHAMP: Cluster randomised phase III superiority trial of Levofloxacin vs. placebo for the prevention of TB in child contacts of DR-TB index cases; Levofloxacin 15-20 mg/kg vs. placebo, 6 months: n=1556; Novel formulation: 100 mg scored dispersible

Publication: Towards early inclusion of children in tuberculosis drugs trials: a consensus statement (*available at: https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(15)00007-9/fulltext)* - "A deterioration in the control of TB thus immediately hurts the youngest generation".

Discussions

- HBCs: emphasis on missing children will assist with improving overall case detection
- MDR-TB regimen: 3 cardio-toxic drugs included
    - Prefer lfx over mfx when using bdq
    - Trials ongoing, dosing data not yet available (bdq-cfz-lfx combination); Adult study on bdq-dlm co-administration safety

    - Monitor safety carefully (aDSM), including ECG – generate rigorous data; Major gain: no need to monitor ototoxicty anymore
    - MSF: no additional cardiotox in kids on dlm-bdq-cfz with FQ – probably over-worried but monitoring critical; Other trials also not showing additional cardio-toxicity
    - Possible other reason: limited number of drug metabolites (responsible for toxicity)
- Delamanid: contradicting recommendations for children
    - Interim guidance depends on treatment access, age
    - Trial using paediatric formulation, which is not yet available in the field – Dlm crush study needed
    - Clinicians willing to take risks in kids with severe forms of XDR and high risk of mortality
- Lfx dosage: practical guide regarding dosages?
    - 15-20 mg/kg appropriate, but formulations important as well (in trials routine formulations used); Caution with higher doses, 30-40mg/kg not recommended
    - Dispersible tablet: better bioavailability
    - Neurotoxicty described (from mild to severe, but rare) – generally safe, well tolerated
- Gap between trials and getting formulations available in the field – what can be done in terms of lobbying for registration etc.
    - Working with PADO group – planning to include TB drugs as well – efficient mechanism, looking at bigger picture: Established pathway for ARVs; Follow-up meeting in December 2018
    - Application to include new formulation for second line drugs to be included in EML (December 2018)
- Access to individualized treatment regimens challenging in many countries – short Bangladesh regimen can still be used in children, limited ADRs – push for injectable-free regimens for children, replacing injectable by bdq
    - Aiming for injectable free regimens for everyone, but sometimes you don't have a choice
    - Reminder: detailed guideline is not yet out, only drug groups – implications for procurement
    - Sentinel group issuing advice on possible paediatric regimens, to be included in interim handbook in close collaboration with WHO (while evidence not yet available) – mid November
    - Global consultation on transition to new regimens: November 2018 – to include presentation by Jennifer Cohn on paediatric implications
    - Transition: GF working with country teams and partners to help with planning
- Manufacturing/availability problem FDC: only one manufacturer at present (shortage of molecule required for production)
    - Submission to pre-qualification programme
    - Problem not only supply, also of demand – programmes need to include child FDCs in budgets, GF applications
    - FDCs should not be left on the shelves to expire – facilities need to distribute and make them available. Efficient links in HBCs.
- LTBI guidance: Why is 3HR only recommended up to 15 years and not in older adolescents

- Formulation available for children <25kg, adult formulations can be used for older children (although it is not clear in guidance that this is possible)

- UN HLM: transmit declaration at national level to keep the momentum going

Developments in child and adolescent TB with a focus on contact investigation and prevention (1)

TB prevention: an under-prioritized yet critical intervention to reduce child TB morbidity and mortality – Moorine Sekadde

Moorine Sekadde presented in the context of the earlier discussed case detection and prevention gaps, and the data on provision of preventive treatment in the TB high burden countries, reminding the audience that there is more than enough evidence to support TB preventive treatment (TPT) (including the recent mathematical modelling study by Pete Dodd *et al* on the potential effect of household contact management on childhood TB (*available at:* *https://www.thelancet.com/action/showPdf?pii=S2214-109X%2818%2930401-7*).

Examples of implementation of TB preventive treatment (TPT) under routine national programmes:

A. Evaluations of current programmatic practice				
Study	**Setting**	**Study population**	**Methods**	**Findings**
Osman, 2013	14 primary health care facilities in Cape Town	< 5 year old household contacts	Retrospective review of electronic data records	• 33.3% of 1179 records of infectious adult TB cases had no documentation of contacts • Of the 525 contacts aged <5 years who were documented, less than half were screened for TB • 141 (27%) contacts initiated IPT • Only 18 (13%) completed IPT
Van Wyk, 2011	Primary community clinics in Cape Town	< 5 year old household contacts	Record review of routinely collected program data	• 46% (310) of the TB case clinical charts did not have contacts documented • 4 of the 149 under five contacts were screened • Only 1% (2) were initiated on IPT • 2 of the 56 under five contacts of non-infectious cases were screened and 1 was started on IPT contrary to recommendations
Claessens, 2002	44 districts hospitals in Malawi	< 5 year old household contacts	Cross sectional study by the Malawi NTP	• Only 21% of 659 smear positive patients had been informed about the need to screen their children for TB • Only 9% of the 365 children were screened for TB • 22 (6%) of children received IPT
Adjobimey, (2016)	Benin NTP Clinics	< 5 year old household contacts of smear positive TB	Integrating the contact management program under the NTP	• 496 under 5 year old household contacts were initiated on 6 months IPT with an initiation rate of= 99.6%; • The IPT completion rate was 86.1% with adherence based on clinic attendance
Van Soelen, 2013	Urban clinic setting in Cape Town	< 5 year old household contacts	Introduction of an IPT register in the clinic	• More child contacts per adult case were identified (0.7 (54 children) vs. 0.3 (24 children)) as compared to pre-register • An increase in the number of children started on IPT (54 vs. 4) was observed

				• 37% of those who started, completed therapy compared to no information during pre-register period

Gaps in TB contact management policy and implementation:

- Care giver related factors: Lack of awareness; Attitude – giving medicines to a well child; Concern for undesired effects; Transport costs; Patient transfers; Relocation; Lack of convenient appointment times; Duration of therapy.
- Health provider related factors: Limited health worker confidence; Unclear eligibility criteria; Fear of long-term isoniazid resistance; Concern over availability of the supplies; Sub optimal implantation of active contact investigation.
- Health system related factors: Lack of standardized of policy guidelines; Lack of a sensitive TB screening tool; Varying eligibility for non-HIV infected individuals (different WHO eligibility criteria for low and high TB endemic settings); Lack of standardized management tools (including reporting) for TPT; Sub optimal implementation of contact tracing; Need for accreditation of health facilities in some countries; Cost; Lack of program indicators on IPT; Interrupted supplies; Fragmentation of monitoring and evaluation systems among multiple service providers; Large, unregulated private health sector.

Opportunities for improving contact management (based on the WHO health system building blocks):

- Service delivery: TB Contact investigation; Child survival programs (IMCI, ICCM); Monitoring and evaluation tools. Important: Education of patients with PTB about contact management, screening, preventive treatment
- Health work force: Effective training and mentorship strategies
- Information: Guidelines; Monitoring and evaluation tools; Community engagement (ENGAGE-TB); E-HMIS; Documentation/registration – long hanging fruit
- Medical products, vaccines, and technologies: Shorter TB preventive regimen; Child friendly formulations; Rapid TB diagnostics – Xpert MTB/RIF; E-Health Information System
- Financing: Country specific budgets; Bilateral and Multilateral agencies; Global Fund (Medicines, Diagnostics, Catastrophic costs)
- Leadership and Governance: Country specific multisector plans; Child and Adolescent TB Road map 2018; END Strategy; Commitment from the UN HLM

Until no child dies of TB!

Contact investigation and prevention in Rwanda – Eugene Niringiyimana

Eugene Niringiyimana started with an outline of the epidemiological situation in Rwanda. TB notifications in Rwanda are approaching the estimated incidence, but there are still large gaps in case detection for the 0-4 and 5-14 years age groups.

TB contact screening among adult and children was initiated in 2008. In the same year, under the leadership of MoH, NTP in collaboration with the paediatric association developed a TB diagnostic algorithm specific to children. In 2009 a chapter on TB in children was introduced in the national TB

guideline. In 2014, NSP recommended to conduct investigation before treatment and end of treatment. Separate TB childhood guidelines were developed in 2014 and updated in December 2017. In 2015, TB investigation among children under 5 years was integrated in the IMCI register.
Strategies to improve childhood TB detection and management included ensuring early detection of childhood TB; Capacity building aimed at building knowledge, skills and confidence of health workers to screen and diagnose TB in children; Implementation of a paediatric mentorship programme to district hospitals with support of the Rwanda pediatric association (RPA); Improving collaboration with the maternal child and community health division in order to strengthen TB diagnostic services.
At the community level, the tasks of community health workers (CHWs) include: IEC in the community; Identification of people with cough and signs suggestive of TB and recommend them to attend the healthcare facility; Counselling to family members of a TB patient about the importance of contact examination and preventive treatment for children < 5 years; Administration of DOT in the community; Tracing of irregular patients and defaulters; and participation in monthly meetings at the healthcare facility.
Implementation steps for contact investigation were the following: 1) Development of a policy and strategies for contact tracing; 2) Revision of the patient treatment card to include contact tracing; 3) Training of trainers for each district on the policy and strategies; 4) Regular training of healthcare providers (HCP) on the policy and strategies; 5) Conducting contact tracing at the begin and end of TB treatment index case; 6) Recording all contact cascade in the register of contact tracing; and, 7) Validation of data during quarterly evaluation meetings.
Contact tracing is done by establishing a list of names of all contacts living with the index case by the HCP before treatment initiation of the index case; Conducting home visits for TB symptom screening. If a contact absent during the home visit, the CHW nearest to the index case will explain the importance of screening to the family member; Symptomatic children are referred or examined to the TB clinic for full physical examination and diagnostic testing according to the national algorithm to confirm or exclude TB. All children under 5 years without TB symptom or those with symptom but active TB excluded by investigation are enrolled on IPT initiation. At initiation of IPT a supply of isoniazid (INH) for two weeks is provided to the mother after which follow up is done monthly. Counselling is provided about TB infection measures and early screening in case of any symptom related to TB for all contact above 5 years screened negative for to TB.
Data elements that are collected include: Number of child contacts of TB cases index and their age; Contact screened of TB cases index and their age; TB cases diagnosed among Contact screened of TB cases index and their age; Number children under five who initiated on IPT; Number of children initiated on IPT who complete a full course of therapy.
Results: IPT coverage has increased over the past 4 years, and was over 95% in 2017. The IPT completion rate has increased from 73 to 98% between 2013 and 2017. The number of child TB cases increased slowly over the past years, but there is still a significant gap. The proportion of TB cases that are below 15 years of age increased from 5.8% to 6.6%, although it is not yet reaching the target of 8%.
In conclusion, Rwanda made good progress on contact tracing and investigation. CHW play an important role in sensitization and reference of contact in health facilities.

Results of the Titi-study in Benin, Burkina Faso, Cameroon, and the Central African Republic (West and Central Africa) - Valérie Schwoebel

Valérie Schwoebel presented the first results of the Titi study (Transmission Investiguée de la Tuberculose Infantile). Following a workshop organized by The Union in 2014 with national TB programmes (NTPs) and paediatricians from 10 countries in francophone Africa, implementation of contact investigation and preventive therapy was selected as a priority action. A study was launched in 2015 in 4 countries with financial support of the French 5% Initiative. The aim was to demonstrate the feasibility and document the effectiveness of contact investigation and preventive therapy for children < 5 years of age within the framework of NTP, with five specific objectives: 1) Estimate the number of children < 5 contacts of bacteriologically confirmed PTB cases (PTB+); 2) Determine the prevalence and risk factors for active TB and for TB infection at inclusion; 3) Determine the incidence of active TB during and after preventive therapy; 4) Assess children adherence to preventive therapy and adverse drug events; and, 5) Develop simple standardised recording & reporting tools.

Methods: Study period: April 2016 to September 2017 (18 months); Study sites: Benin, Burkina-Faso, Cameroon and Central African Republic in 13 basic management units in 4 large cities: Cotonou (1), Ouagadougou (4), Douala (4) and Bangui (4). Study population: all adults with recently diagnosed PTB+ were eligible if residence within ~ 5 km of the BMU; Permanent residence for > 3 months; Children < 5 years living at home; Patients were enrolled after informed consent for a home visit by nurse and social worker. Family questionnaire: house, family structure, type of contacts; Child questionnaire: symptoms, first physical examination, Tuberculin skin test (TST), appointment for BMU visit and chest X-Ray. Preventive therapy regimens used were: 6 months of isoniazid (6H) in Benin, or 3 months of rifampicin+isoniazid (3 RH75/50) in Burkina Faso, Cameroon and CAR. Monthly visits during treatment : adherence, symptoms, side effects and 3-monthly visits up to 12 months after treatment termination.

Results: 1,100 index cases included in the study (92% of eligible) and 1,973 child contacts (ratio: 1 to 1.8 contacts per index case). Risk factors for more than 10mm TST result that were significant included: playing with index case (every day) (aOR 1,53 [1,18 - 1,97]) and sleeping in the same bed with index case (everyday) (aOR 1,84 [1,44 - 2,35]). At initial screening, 61% of child contacts had any of the 4 symptoms in the screening questionnaire, 14% had a chest X-ray (CXR) suspicious for TB and 29% were referred to a clinician for further evaluation. CXR Inter-reader agreement with reviewers was graded as “slight”. 105 children had a “decision to treat” for TB. The diagnosis was based on the initial evaluation, although 17 cases were diagnosed after the child had started preventive therapy. 102 children received TB treatment: treatment outcomes were 88% successful treatment, 12% non-evaluated. No incident cases were reported during preventive treatment. A total of 1,770 contacts started TB preventive treatment (TPT). 2% developed symptoms (jaundice or vomiting). The TPT completion rate was 92.2%, 0.3% died, only 0.1% (1 child) developed an adverse drug event (ADR).

Discussion: There was uncertainty around the ~ 5% estimated prevalence of TB (Low bacteriological confirmation and wide inter-country differences). Despite common protocol / training / tools, there were differences in the implementation of diagnostic procedures by NTPs due to differences in the assessment of symptoms by nurses, NTP guidelines (e.g. in Benin symptomatic children have to be

referred to a medical doctor), medical practice and experience (experience in TB rare among paediatricians, experience in infants rare among pneumologists/radiologists), interpretation of CXRs (particularly in infants), referral procedures, and bacteriological examinations. Interpretation of systematic chest X-ray was a real challenge, which is consistent with findings of other authors (Triasih 2015, Berteloot 2018). The uptake of preventive therapy was good (>90%) with 92% completing treatment. Reported adherence was excellent in those who completed treatment, without difference according to the regimen used (6H vs 3RH). Very few adverse drug events were reported, with only one leading to treatment termination (3RH).

In conclusion: Contact investigation is feasible in the NTP context. The ratio contact children / notified bacteriologically confirmed TB could be proposed to monitor contact investigation activities. Implementation of procedures for TB diagnosis needs: Training of nurses and doctors; Simple and clear referral procedures; and standardized tools. It may be better to restrict the use of CXR to symptomatic children. The 3RH regimen is well tolerated and appears as effective as 6H in preventing TB in children, although results are still preliminary as post-treatment follow-up has not been completed.

Contact investigation and prevention in Indonesia - Rina Triasih

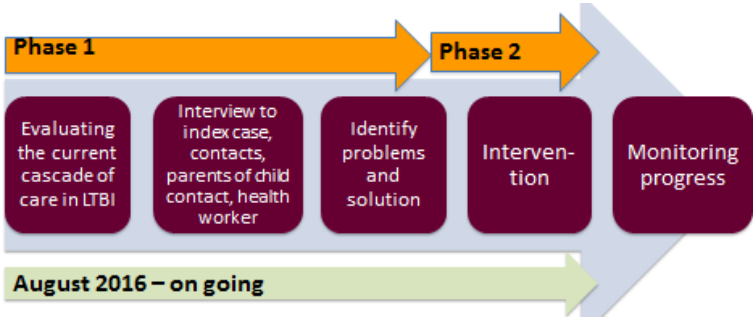
Rinah Triasih started her presentation highlighting the TB epidemiology in Indonesia. In 2017 the estimated burden was 842,000 (319 per 100,000) with an estimated number of children (<15) of 49,000 (5.8%). A child TB working group (established in 2005), consists of the NTP, the Indonesian Paediatric Society, the National Child Health Program and partners. A national guideline of child TB has been available since 2006 (separated from the adult guideline) and was revised in 2013 and 2016. Training of trainers on the management of child TB for health workers at national level is conducted and technical assistance is provided by international experts. The proportion of children (<15) notified was very low until 2007, after which it jumped up to over 11% (reasons for this included a new scoring system and strengthening R&R), but has been declining since, to around 6% in 2014.
The childhood TB benchmarking tool was used in December 2016, and data from the assessment showed that 6-8% of child TB cases were smear positive, and 12-13% EPTB. Only 2-3 MDR-TB cases are reported every year. No data were available on contact investigation and provision of preventive treatment.

Activities implemented to enhance contact investigation and IPT provision: Development of a national guideline on contact investigation and IPT; Development of forms for recording and reporting of contact investigation & IPT; Pilot implementation in 7 provinces; Studies and innovations; and preparations for HP as TPT. IPT uptake was 27% for the country in 2017 (ranges for provinces from 0-107%).

Studies:

ACT4 - Enhancing LTBI management, a cluster randomized trial: PI: Dick Menzies (McGill, University, Montreal Canada), funded by: CIHR, Canada; 6 countries: Benin, Brazil, Canada, Ghana, Indonesia, Vietnam. This is a pragmatic cluster randomized trial, testing a two phase programmatic public health package: 1) A standardized public health evaluation and analysis and 2) implementation of appropriate solutions and strengthening of the LTBI program. Objectives: To estimate the increase number of

household contacts initiating IPT per newly diagnosed index patient and; to evaluate the cost effectiveness of this two phase intervention.
In Bandung: Team: Centre of TB/HIV study, Fac of Medicine, Padjajaran University; Principal investigator: Prof. Dr. Rovina Ruslami; Investigators: Dr. Bachti Alisjahbana, dr. Panji Hadisoemarto



Evaluation of the care cascade of contact investigation: Loss of 94% between identification of contacts and starting TPT. Structured interviews to explore reasons for the high % of loss:

- Index cases and contacts/parents: Did not consider medical evaluation/treatment of asymptomatic contacts necessary
- Healthcare workers: Lack of time as a perceived barrier (more time spent on non-TB related activities (incl. administrative work)
- Both: Lack of knowledge & information

After this evaluation, in-service training was conducted every week for the first 2 months, every 2 weeks for 2 months and then monthly for the last 2 months. Electronic reminders were used for patients, educational material using flip chart was developed and used and a "gift" was provided for child contacts. These interventions led to a reduction of the loss between identification of contacts and starting TPT from 94% to 60%.

<u>Strengthening health systems to improve contact investigation and treatment for tuberculosis contacts in Timika, Indonesia</u>

Study sites: 3 PHCs, 2 hospitals. Interventions: Child TB Management Training; Regular CQI meetings; Educational brochure for patients; TB forms; Regular feedback and evaluation.
The proportion of index cases with contacts investigated increased from 1% (baseline) to 48% (PHC facilities)/18% (all facilities) in August 2018, with IPT uptake around 60%. Main reasons for not taking up IPT included: TB symptoms (30%), the child not coming to the clinic (22%), the parent refusing IPT (18%), age >5 years (11%).

In conclusion there has been improvement in contact investigation and IPT provision in Indonesia, but more efforts and innovations are required to enhance the coverage of contact investigation and IPT

Discussions

- Titi study:
    - Deaths reported: no details known (reported by parents)
    - CXR interpretation: did this show over- or under-diagnosis? – only quality of interpretation assessed (inter-reader agreement etc.)
    - Study limited the distance to the facility for inclusion of index patients – conclusion that PT is feasible, but limitation of distance may be a confounding factor.
- How difficult is it to identify/locate contacts and screen/evaluate them?
    - In Rwanda not a big challenge, in villages making use of VHWs who know their communities well
    - Indonesia: CI not done routinely (HCWs not aware) – trainings done, community workers engaged (works well in PHC settings, but not in hospitals as catchment areas are wide)
- What can be done to move more easily between child and adult services? - Silos between different programmes – missed opportunities
    - Pushing for integration at all care points – strengthen capacity, awareness on CI
    - Platform for CHWs critical – known members of community
- Indonesia: Jump between % of child TB between 2007 and 2008 – what is contribution of CI?
    - CI not yet implemented, so no influence; new scoring system implemented, with increased awareness in HCWs, strengthening in R&R
- Transitioning lessons from research setting to programmatic implementation
    - Rwanda: no additional resources were allocated (except training and registers) – integrated in existing packages
    - Titi study: need for additional resources to scale up (Titi used motorbikes, cost for home visits etc.)
    - Indonesia: After training of HCWs concern regarding additional workload – motivation of HCWs regarding importance of CI and prevention for future of children; support needed after completing trainings, e.g. WhatApp groups, in-service trainings, mentoring, recording and reporting for sustainability
    - Uganda: NTP prioritized CI (after prevalence survey, included in NSP) – SOPs developed, approved by senior management, and GF application (DETECT TB scale up), support from PEPFAR and other partners. Tapped in to community platform and included in tools for CHWs, integration in IMCI etc. Volunteers: no remuneration, also used by other disease programmes, integration needed, included in community registers (adults on TB treatment, symptom screening). Major challenge: explain that well child needs treatment; ensuring that symptomatic children are evaluated – challenge role of CXR
    - Global fund: can CI be made a requirement – encouragement (not forcing) is possible – e.g. through implementation notes (include CI and child TB interventions)

- CDC: PEPFAR prioritizing TPT (focus on PLHIV, 10% children), will assist with addressing systems issues for general implementation
- Reminder about resources section on Union child learning portal (site) – many useful resources on contact investigation and TPT

Roadmap game

Shakil Ahmed led a game based on the second edition of the Roadmap.

Photo credit: Husne Osmany

Developments in child and adolescent TB with a focus on contact investigation and prevention (2)

Contact investigation and prevention in Brazil -Betina Mendez Alcântara Gabardo

Betina Mendez Alcântara Gabardo started by explaining that although a contact investigation policy was in place in Brazil since 2014, this has not resulted in an improvement in the proportion of contacts of new PTB patients that are evaluated (static around 60%).

A protocol for Surveillance of LTBI in Brazil with Information System for notification of people being treated for LTBI was implemented in 2018. The main goals were to identify people at greatest risk of develop active TB, especially contacts; to identify, to notify and to treat people with LTBI; to monitor and evaluate the treatment and; to guide the attributions of the Health Units and municipal, state and national TB control programmes. No data are available yet.

An evaluation of the Notification System of the Treatment of LTBI was conducted for the years 2009 to 2015 for patients <18 years in Paraná State. Results showed that 27% of contacts were under the age of 5 years, and 86% of contacts happened in residential settings. 70% of patients self-administered TPT, with over 96% on isoniazid. 2.2% of patients had an adverse reaction to INH (mainly gastric, and some cutaneous reactions). Over 83% completed the course of IPT.

Contact investigation and prevention in the USA - George McSherry

George McSherry (Penn State Children's Hospital and Rutgers Global Tuberculosis Institute) explained that TB control in the USA is based on two separate areas: 1) case finding and treatment (2016: 9,272 cases: incidence 2.9 cases/100,000, 4.2% in children) and Contact investigations (CI) (including source case investigations); and, 2) Targeted testing of persons with risk.

Diagnosis and treatment of LTBI is critical to control and elimination of TB in the USA. The objectives of CI are: Identification of all high and low risk contacts; Medical evaluation of all appropriate contacts; Identification of contacts diagnosed with LTBI and provision of appropriate treatment to completion of therapy thus preventing future disease; Identification of contacts diagnosed with TB disease and provision of appropriate treatment; Identification of contacts at high risk of developing TB disease (e.g., children, immunocompromised) and provide appropriate treatment until infection and disease is ruled out.

The most reliable TB control program is based upon aggressive and expedient contact investigations, rather than routine screening of large populations. The concentric circle principle in TB control is used (see figure). CI can be complex and may require lots of detective work.

Case study:

A 39 year-old female was admitted to a New Jersey hospital with fever, decreased appetite, 11 kg weight loss, cough for 1-3 months, night sweats. Chest radiographs were done and showed cavitation in the left upper lobe and a consolidation in the right lung. Sputa were 4+ AFB, later identified as sensitive *M. tuberculosis*. A presumptive case of TB was reported to the local health department. Place of employment: Daycare Center (DCC). The Health department nurse contacted the TB controller for the county. In the DCC an on-site assessment conducted by TB controller showed 35 high priority contacts: 30 children attend: All <4 years of age and 5 staff members: Adults and adolescents. The DCC is in a church basement. The Index patient was secretary with "little" contact with the children
Household and social contacts: 9 high priority contacts: 9; field staff felt that the index patient did not reveal all contacts. 4 of them are children: 2 are <1 year of age with recent history of pneumonia. After initial testing, 7 of the 35 contacts at the DCC were diagnosed with TB (all <5 years), 14 were TST positive. Out of the 9 household/social contacts, 2 had TB (both children <1 year old) and 5 were TST positive.

Targeted Testing for Tuberculosis in Children and Adolescents:

Children for whom immediate TST or IGRA is indicated: Contacts of people with confirmed or suspected contagious TB (contact investigation); Children with radiographic or clinical findings suggesting TB disease; Children immigrating from areas with high rates of infection (Asia, Middle East, Africa, Latin America, counties of the former Soviet Union); Children with history of significant travel to countries with endemic infection who have substantial contact with the resident population.
Children who should have annual TST or IGRA: Children with HIV infection.
Children at increased risk of progression of TBI to TB disease; HIV infection, Hodgkin disease, lymphoma, diabetes mellitus, chronic renal failure, malnutrition, prolonged or high-dose corticosteroid therapy, chemotherapy, tumour necrosis factor (TNF-alpha) antagonists.

In the US IGRAs are recommended in immunocompetent children >2 years of age [previously >5 years of age] in all situations where a TST would be used. TST is acceptable for all age groups and remains the

preferred test for those <2 years of age. In evaluating children for TB disease neither IGRAs nor the TST are perfect; always need for clinical judgement.

Treatment of LTBI in the US:

Regimens used for TPT: Isoniazid + rifapentine (3HP), Rifampin (4R) and Isoniazid (9H).

3HP for children: As effective as 9H, shorter course, higher completion rates, safe, directly observed treatment (DOT) or self-administered treatment (SAT), greater pill burden; Children >12 years of age: Recommended as equal alternative to 9 months of INH; Children 2-11 years of age: Recommended as equal alternative to 9 months of INH; Children <2 years of age: INH-RPT: Not recommended: Lack of safety and pharmacokinetic data in this age group.

Rifampin for 15-20 mg/kg/day (max. 600 mg) orally daily for 4 months (prior recommended dose 10-15 mg/kg): Acceptable regimen for LTBI treatment; As effective as 9H, shorter course, better adherence, higher dose safe; recommended if INH not tolerated; index patient isolate INH-resistant.

INH 10-15 mg/kg (max., 300 mg) orally daily for 270 doses; Efficacy approaches 100%; prevents TB meningitis; Poor completion rates due to treatment length; Alternative: Twice weekly directly observed (DOT) INH 20-40 mg/kg (max., 900 mg) orally for 72 doses; Monitor index case isolate sensitivities Hepatotoxicity from INH is rare in children: Monthly assessment for clinical evidence of hepatotoxicity should be made: malaise, loss of appetite or weight, nausea, vomiting, abdominal pain, jaundice. Routine monitoring of LFTs is not indicated, except if: Concurrent liver disease; Pregnancy or first 12 weeks postpartum; Concurrently on other hepatotoxic medications; Clinical evidence of hepatotoxic effects.

In summary: Contact investigations use the concentric circle model and target high priority/high risk contacts first; Programmes need to improve the number of contacts evaluated, started on and completing LTBI treatment; Diagnosis and treatment of LTBI is critical to control and elimination of TB in the U.S.; Short course treatment regimens (3HP and 4R) for LTBI are safe and effective in children and should lead to increased treatment completion rates which lead to a decrease in active disease among children following recent infection and a reduction of the reservoir of LTBI from which reactivation disease may develop in the future.

Discussions

- Management of non-household child contacts – guidelines (e.g. in Kenya) not explicit on day care contacts, while these may be close contacts and at risk of active disease as well
    - Structured system to identify people needing evaluation needed
    - School exposure to be regarded as high risk and contacts to be managed as per guidance on close contacts
    - Casual contact also important, but much more challenging to establish
- Importance of obtaining a specimen in symptomatic contacts (even infants)
- Reasons for not using 3HR in USA – included in guidance as alternative to 6H and 3HP
- Resistance to RIF – consequences for 4R regimen

- Stigma related to TB leading to incorrect information provided by source cases – learn from HIV and other programmes on how to deal with this
- RPT difficult to crush – approach Sanofi to demand child-friendly formulations (no manufacturer interested in generic formulation for HP)

Overview of recent research papers with a focus on contact investigation and preventive therapy - James Seddon

James Seddon found the first published paper on childhood TB by Dr. Green in 1840! He identified 924 studies on PubMed from the past 12 months (search terms child* and tuberc*), of which he thought 97 looked interesting. Review of abstracts brought the number down to 36. He has tried to focus on high impact articles and articles that have looked at contact investigations and preventive therapy.

Studies highlighted:

Nemes E *et al*. **Prevention of *M. tuberculosis* Infection with H4:IC31 Vaccine or BCG Revaccination**. N Engl J Med 2018; 379:138-149. DOI: 10.1056/NEJMoa1714021. 990 adolescents H4:IC31, BCG revaccination, or placebo. IGRA every 6 months for a year. H4:IC31 slight improvement in preventing sustained IGRA +. In this trial, the rate of sustained IGRA conversion, which may reflect sustained *M. tuberculosis* infection, was reduced by vaccination in a high-transmission setting. This finding may inform clinical development of new vaccine candidates.

Nemes E *et al*. **Safety and Immunogenicity of Newborn MVA85A Vaccination and Selective, Delayed Bacille Calmette-Guerin for Infants of Human Immunodeficiency Virus-Infected Mothers: A Phase 2 Randomized, Controlled Trial**. Clin Infect Dis. 2018 Feb 15; 66(4): 554–563. This double-blind, randomized, controlled trial compared newborn MVA85A prime vaccination (1 × 108 PFU) vs Candin® control, followed by selective, deferred BCG vaccination at age 8 weeks for HIV-uninfected infants and 12 months follow-up for safety and immunogenicity. MVA85A prime vaccination of HIV-exposed newborns was safe and induced an early modest antigen-specific immune response that did not interfere with, or enhance, immunogenicity of subsequent BCG vaccination. New protein-subunit and viral-vectored tuberculosis vaccine candidates should be tested in HIV-exposed newborns.

LaCourse SM *et al*. **Urine Tuberculosis Lipoarabinomannan Predicts Mortality in Hospitalized Human Immunodeficiency Virus-Infected Children**. Clin Infect Dis. 2018 May 17;66(11):1798-1801. doi: 10.1093/cid/ciy011. The study included 137 hospitalized HIV-infected children, mortality was 4.9-fold higher among those with positive LAM.

Kay AW *et al***. Interferon-γ Release Assay Performance for Tuberculosis in Childhood**. Pediatrics. 2018 Jun;141(6). pii: e20173918. doi: 10.1542/peds.2017-3918. California TB registry data for patients ⩽18 years. 778 cases of TB were reported; 360 were laboratory confirmed. ⩾5 years IGRA has greater sensitivity than TST.

Walters E *et al*. **Molecular detection of Mycobacterium tuberculosis from stool in young children using a novel centrifugation-free processing method**. Journal of Clinical Microbiology Jul 2018, JCM.00781-18; DOI: 10.1128/JCM.00781-18. Novel, simple, centrifugation-free processing method for stool specimens for use on the Xpert - two different stool masses: 0.6 g and a swab sample. 280 children. 15% vs. 25% for respiratory sampling.

Sabi I *et al*. **Xpert MTB/RIF Ultra assay for the diagnosis of pulmonary tuberculosis in children: a multicentre comparative accuracy study**. J Infect. 2018 Oct;77(4):321-327. doi: 10.1016/j.jinf.2018.07.002. 215 Children Tanzania: 64% vs. 54% sensitivity; 98% vs 100% specificity.

Togun TO *et al*. **Biomarkers for diagnosis of childhood tuberculosis: A systematic review**. PLoS One. 2018 Sep 13;13(9):e0204029. doi: 10.1371/journal.pone.0204029. The review included 29 studies of which 22 met the WHO criteria for a diagnostic test. Serology, transcriptomics, cytokines. The authors found that majority of the biomarkers for diagnosis of TB in children are promising but will need further refining and optimization to improve their performances. As new data are emerging, stronger emphasis should be placed on improving the design, quality and general reporting of future studies investigating TB biomarkers in children.

Buonsenso D *et al*. **Utility of Point-of-care Ultrasound in Children With Pulmonary Tuberculosis**. Pediatr Infect Dis J. 2018 Nov;37(11):e280-e281. doi: 10.1097/INF.0000000000002086. 232 children. Children with confirmed or unconfirmed PTB had a higher prevalence of Point-of-Care Ultrasound findings than children with unlikely TB. Pleural effusion, abdominal lymphadenopathy, splenic microabscesses.

Aggerbeck H *et al*. **C-Tb skin test to diagnose Mycobacterium tuberculosis infection in children and HIV-infected adults: A phase 3 trial**. PLoS One. 2018 Sep 24;13(9):e0204554. doi: 10.1371/journal.pone.0204554. The trial included 1000 symptomatic children, some asymptomatic controls. TST, IGRA and C-Tb similar sensitivities and specificities.

Mgode GF *et al*. **Pediatric tuberculosis detection using trained African giant pouched rats**. Pediatr Res. 2018 Jul;84(1):99-103. doi: 10.1038/pr.2018.40. Samples were collected from 24 TB clinics in Tanzania. They were first tested by rats and then by smear microscopy. Trained rats increase paediatric TB detection significantly and could help address the paediatric TB diagnosis challenges. Further determination of accuracy of rats involving other sample types is still needed.

Svensson EM *et al*. **Relative bioavailability of bedaquiline tablets suspended in water: Implications for dosing in children**. Br J Clin Pharmacol. 2018 Jun 27. doi: 10.1111/bcp.13696. The study was conducted in 24 healthy adults. Whole or suspended bedaquiline: similar bioavailability.

Achar J *et al*. **Off-Label Use of Bedaquiline in Children and Adolescents with Multidrug-Resistant Tuberculosis**. Emerg Infect Dis. 2017 Oct;23(10). doi: 10.3201/eid2310.17030. The authors describe 27 children and adolescents <18 years of age who received bedaquiline during treatment for multidrug-

resistant tuberculosis. They report good treatment responses and no cessation attributable to adverse effects. Bedaquiline could be considered for use with this age group for multidrug-resistant tuberculosis when treatment options are limited.

Marcy O *et al*. **Mortality and its determinants in antiretroviral treatment-naive HIV-infected children with suspected tuberculosis: an observational cohort study**. Lancet HIV. 2018 Feb;5(2):e87-e95. doi: 10.1016/S2352-3018(17)30206-0. The study was conducted in Burkina Faso, Cambodia, Cameroon, and Vietnam and included 438 HIV+ children. Children started ART and TB treatment at the clinician's discretion and were retrospectively classified into one of three groups by TB documentation: confirmed by culture or Xpert MTB/RIF, unconfirmed, and unlikely. ART started during the first month of follow-up, confirmed TB, young age, CD4 less than 10%, miliary features, and elevated serum transaminases were all independently associated with mortality.

Garcia-Prats AJ *et al*. **Clinical and cardiac safety of long-term levofloxacin in children treated for multidrug-resistant tuberculosis**. Clin Infect Dis. 2018 May 16. doi: 10.1093/cid/ciy416. 70 children treated with levofloxacin MDR-TB disease. Children on treatment for MDR-TB received levofloxacin for a median of 12 months. The study showed that there were no QTc changes and that levofloxicin was safe and well tolerated.

Harausz EP *et al*. **Treatment and outcomes in children with multidrug-resistant tuberculosis: A systematic review and individual patient data meta-analysis**. PLoS Med. 2018 Jul 11;15(7):e1002591. doi: 10.1371/journal.pmed.1002591. The meta-analysis included 975 children with MDR-TB, 75% bacteriologically confirmed. There was a favourable outcome in 78% - more in clinically diagnosed and HIV negative children.

Kodama C *et al*. **Mycobacterium tuberculosis transmission from patients with drug-resistant compared to drug-susceptible TB: a systematic review and meta-analysis**. Eur Respir J. 2017 Oct 26;50(4). pii: 1701044. doi: 10.1183/13993003.01044-2017. The review included seven studies and showed an increased risk of TB infection in contacts of DR-TB vs DS-TB. No increased risk of disease (both prevalent and incident).

Oh CE *et al*. **High tuberculosis transmission rate in children with nursery exposure to undetected pulmonary tuberculosis**. Int J Tuberc Lung Dis. 2018 Sep 1;22(9):1031-1036. doi: 10.5588/ijtld.18.0053. The article describes a recent transmission in a nursery in the Republic of Korea. The first investigation enrolled 315 infants who had been in the nursery 3 months before the index patient was diagnosed with pulmonary TB. After a child who had stayed in the nursery 10 months before the diagnosis of the index patient was diagnosed with TB meningitis, a second contact investigation (among 1334 children) was conducted. The rates of LTBI were 42.5% and 18.7% for the first and second investigation, respectively.

Guthrie JL *et al*. **Genotyping and Whole-Genome Sequencing to Identify Tuberculosis Transmission to Pediatric Patients in British Columbia, Canada, 2005-2014.** J Infect Dis. 2018 Aug 24;218(7):1155-1163. doi: 10.1093/infdis/jiy278. The study included paediatric patients under 18 years of age with culture-

confirmed TB in British Columbia from 2005 to 2014 (n = 49). Genotyping was done. The study was able to determine source – home/overseas etc.

Arregui S *et al*. **Data-driven model for the assessment of Mycobacterium tuberculosis transmission in evolving demographic structures.** Proc Natl Acad Sci U S A. 2018 Apr 3;115(14):E3238-E3245. doi: 10.1073/pnas.1720606115. The TB transmission model incorporates country-specific demographic prospects and empirical contact data around a data-driven description of TB dynamics.

Snow KJ *et al*. **Incidence and prevalence of bacteriologically confirmed pulmonary tuberculosis among adolescents and young adults: a systematic review.** Epidemiol Infect. 2018 Jun;146(8):946-953. doi: 10.1017/S0950268818000821. The study included 10-25 year olds: 1.78 million cases per year. The majority of adolescents with TB were from the African and South-East Asia regions. A break down was provided by age groups 10-15, 15-20 and 20-25.

Gou X *et al*. **The association between vitamin D status and tuberculosis in children: A meta-analysis.** Medicine (Baltimore). 2018 Aug;97(35):e12179. doi: 10.1097/MD.0000000000012179. Ten studies were included in this meta-analysis. Vitamin D levels were significantly lower in TB patients than in controls, indicating that vitamin D deficiency was significantly associated with TB (Odds Ratio 1.78; 95% CI, 1.30-2.44) in children.

Black F *et al*. **An assessment of the isoniazid preventive therapy programme for children in a busy primary healthcare clinic in Nelson Mandela Bay Health District, Eastern Cape Province, South Africa.** S Afr Med J. 2018 Feb 27;108(3):217-223. doi: 10.7196/SAMJ.2018.v108i3.12639. In a primary health care clinic, out of 491 adults with TB, 261 child contacts <5 years were identified during a retrospective record review. Only 70% of contacts were screened for TB, 59% started IPT, and only 4 children (3.7%) completed IPT.

Malik AA *et al*. **Improving childhood tuberculosis detection and treatment through facility-based screening in rural Pakistan.** Int J Tuberc Lung Dis. 2018 Aug 1;22(8):851-857. doi: 10.5588/ijtld.17.0736. A total of 105 000 children were verbally screened in 4 hospitals in Pakistan. There were 5880 presumptive cases, of which 1417 children diagnosed with TB.

Sulis G *et al*. **Implementation of tuberculosis prevention for exposed children, Burkina Faso.** Bull World Health Organ. 2018 Jun 1;96(6):386-392. doi: 10.2471/BLT.17.201343. Epub 2018 Apr 20. An evaluation of a new TB infection register and training of staff for contact tracing was conducted. The evaluation showed an increase in numbers of children identified.

Kampmann B *et al.* **Evaluating UK National Guidance for Screening of Children for Tuberculosis. A Prospective Multicenter Study.** Am J Respir Crit Care Med. 2018 Apr 15;197(8):1058-1064. doi: 10.1164/rccm.201707-1487OC. 11 centres in UK. Child contacts of new TB patients were tested for TB infection with TST and IGRA. 431 children were screened. 12% of them had TB disease, 27% TB infection.

If children were TST positive and IGRA negative, no preventive treatment was given and none of them developed TB.

Diallo T *et al*. **Safety and Side Effects of Rifampin versus Isoniazid in Children.** N Engl J Med. 2018 Aug 2;379(5):454-463. doi: 10.1056/NEJMoa1714284. A total of 844 children TB infection received 4 months of rifampin or 9 months of isoniazid. 85% completed treatment among those receiving 4R vs 76% in 9H group. The study concludes similar safety and efficacy of rifampicin and INH.

Bagdasarian N *et al*. **A "Stone in the Pond" Approach to Contact Tracing: Responding to a Large-Scale, Nosocomial Tuberculosis Exposure in a Moderate TB-Burden Setting.** Infect Control Hosp Epidemiol. 2017 Dec;38(12):1509-1511. doi: 10.1017/ice.2017.228. The paper describes contact tracing practices in Singapore, based on a case study of a 29 year old nurse with TB who worked in a paediatric ward.

Armstrong-Hough M *et al*. **Drop-out from the tuberculosis contact investigation cascade in a routine public health setting in urban Uganda: A prospective, multi-center study.** PLoS One. 2017 Nov 6;12(11):e0187145. doi: 10.1371/journal.pone.0187145. This study evaluated the cascade from index case to home visit to screening contacts to investigating contacts. It demonstrated a low 5% probability of completing the cascade.

Assefa Y *et al*. **3-month daily rifampicin and isoniazid compared to 6- or 9-month isoniazid for treating latent tuberculosis infection in children and adolescents less than 15 years of age: an updated systematic review.** Eur Respir J. 2018 Jul 11;52(1). pii: 1800395. doi: 10.1183/13993003.00395-2018. This review compared 3HR versus 6H and 9H and included three studies. It showed better adherence to 3HR and no increase in adverse events or TB disease.

Cruz AT, Starke JR. **Completion Rate and Safety of Tuberculosis Infection Treatment With Shorter Regimens.** Pediatrics. 2018 Feb;141(2). pii: e20172838. doi: 10.1542/peds.2017-2838. The study was conducted in Houston, USA and included 667 children. 3HP was given to 40% of the children, 4R to 20%, and 9H to 40%. 9H showed more adverse events and poor completion: only 52% of children on 9H completed treatment.

Guix-Comellas EM *et al*. **Impact of nursing interventions on adherence to treatment with antituberculosis drugs in children and young people: A nonrandomized controlled trial.** J Adv Nurs. 2018 May 3. doi: 10.1111/jan.13692. The trial was conducted in Spain and included child contacts of smear positive TB. After the nursing interventions, adherence to treatment increased from 75% to 88%.

Gaensbauer J *et al*. **Better Completion of Pediatric Latent Tuberculosis Treatment Using 4 Months of Rifampin in a US-based Tuberculosis Clinic.** Pediatr Infect Dis J. 2018 Mar;37(3):224-228. doi: 10.1097/INF.0000000000001721. The study was implemented in a TB clinic in Denver, USA. There were a total of 395 children in the 4R cohort and 779 in the 9H cohort. Completion rates overall were significantly higher for 4R than 9H (83.5% vs. 68.8%).

Dodd PJ *et al*. **Potential effect of household contact management on childhood tuberculosis: a mathematical modelling study.** Lancet Glob Health. 2018 Sep 25. pii: S2214-109X(18)30401-7. doi: 10.1016/S2214-109X(18)30401-7. This study used modelling of household contact management activities using two scenarios. It showed that household contact management could prevent up to 160,000 TB cases and 110,000 deaths. Preventing one child death would require visiting 48 households, screening 77 children and giving 48 preventive therapy courses.

Hirsch-Moverman Y *et al*. **Tuberculosis preventive treatment preferences among care givers of children in Lesotho: a pilot study.** Int J Tuberc Lung Dis. 2018 Aug 1;22(8):858-862. doi: 10.5588/ijtld.17.0809. The pilot study was implemented in Lesotho in five health facilities in one district. 12 parents of children receiving PT were included. Pill burden, duration and dosing frequency were important issues.

Mueller-Hermelink M *et al*. **Universal screening for latent and active tuberculosis (TB) in asylum seeking children, Bochum and Hamburg, Germany, September 2015 to November 2016.** Euro Surveill. 2018 Mar;23(12). doi: 10.2807/1560-7917.ES.2018.23.12.17-00536. This paper describes screening for TB in children seeking asylum in Germany in Bochum and Hamburg. A total of 968 children were screened. In total, 58 had latent TB infection and 8 had active TB. None of these children had been knowingly exposed to TB.

Martinez L *et al*. **Effectiveness of WHO's pragmatic screening algorithm for child contacts of tuberculosis cases in resource-constrained settings: a prospective cohort study in Uganda.** Lancet Respir Med. 2018 Apr;6(4):276-286. doi: 10.1016/S2213-2600(17)30497-6. Lancet Resp Med. Mulago 1995-2008. Out of 1718 household child contacts, 126 (7%) had coprevalent TB and 24 (1%) developed incident TB. WHO's pragmatic, symptom-based algorithm was an effective case-finding tool, especially in children younger than 5 years.

Conclusions: Many studies evaluating contact tracing and preventive therapy. There has been some progress in last 177 years but a lot more work is needed inform and promote best practices.

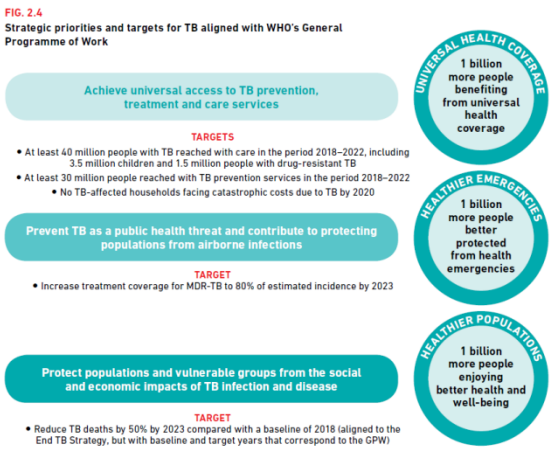
Discussions

- Issues of drug-drug interactions between dolutegravir (DTG) and rifampicin (RIF): Co-administration of DTG with RIF decreases DTG plasma concentrations. Current guidance is to adjust DTG dosing to twice daily instead of once daily, but further evidence is awaited.
- Role of CXR in screening for LTBI: the negative predictive value of screening without CXR is quite high (but adding CXR is of value for case detection)

Developments in child and adolescent TB with a focus on contact investigation and prevention (3)

Preventive therapy for children and adolescents in contact with confirmed MDR-TB – Simon Schaaf

As an introduction, Prof Schaaf highlighted the global epidemiology of DR-TB: 460,000 new cases of MDR-TB in 2017; 25-32,000 MDR-TB paediatric cases estimated (2010); 2 million children infected with MDR-TB. Current MDR-TB treatment is long, toxic, and expensive. MDR-TB prevention is important but no evidence from randomised controlled trials.



He argued that a key action on prevention should be added to the current five priority actions to address the global MDR-TB crisis highlighted in the WHO MDR-TB 2014: 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. The sixth priority action should be: 6) Contact tracing and preventive therapy.

The WHO Global TB Report 2018 refers to "universal access to TB prevention" but WHO guidelines on LTBI do not strongly support MDR-TB preventive therapy. Prof Schaaf highlighted the UNGA HLM on TB targets and commitments on prevention:

- 25. Commit to preventing tuberculosis for those most at risk of falling ill through the rapid scaling up of access to testing for tuberculosis infection, according to the domestic situation, and the provision of preventive treatment, with a focus on high-burden countries, so that at least 30 million people, **including 4 million children under 5 years of age**, 20 million other household contacts of people affected by tuberculosis, and 6 million people living with HIV, receive preventive treatment by 2022 …
- 26. Commit to overcoming the global public health crisis of multidrug-resistant tuberculosis through actions for prevention, diagnosis, treatment and care, including compliance with stewardship programmes to address the development of drug resistance …

Infection and prevention

MDR-TB in children is mainly through infection with MDR *M. tuberculosis* strains from infectious (adult) PTB cases. Although AFB sputum smear-positive cases are more infectious than smear-negative/culture-positive cases, the latter is also infectious. BCG does not provide good protection against infection and disease in children. Starting adult source cases on TB treatment or separating the child from the source case could prevent ongoing transmission but does not mean the child does not need preventive treatment (as the child may already be infected).

Child contacts of MDR-TB

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).*

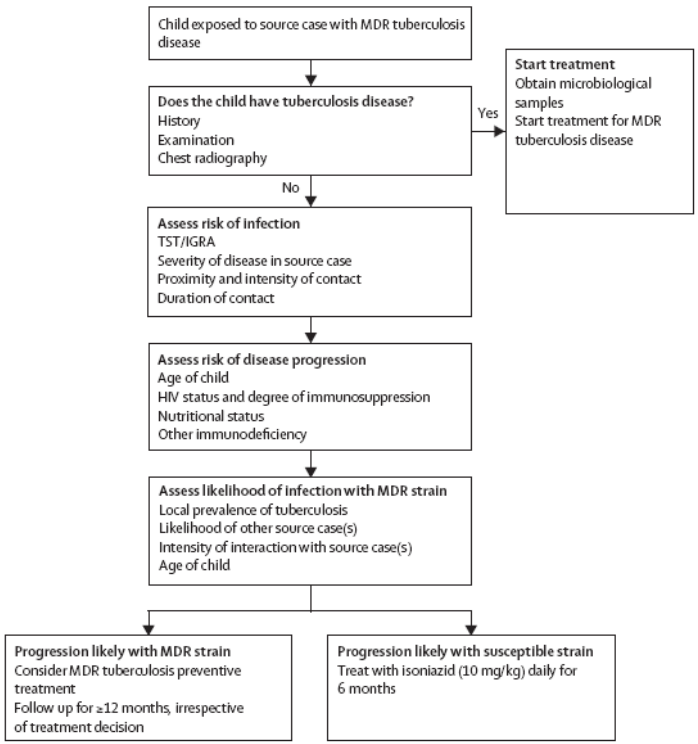
Golla V *et al*: The impact of drug resistance on the risk of tuberculosis infection and disease in child household contacts: a cross sectional study (BMC Infect Dis. 2017; 17: 593. Published online 2017 Aug 29. doi: [10.1186/s12879-017-2668-2]): Results: Of 538 children included, 312 had DS-TB and 226 had MDR-TB exposure. 107 children with DS-TB exposure had TB infection (34.3%) vs. 101 (44.7%) of children with MDR-TB exposure (adjusted Odds Ratio [aOR]: 2.05; 95% confidence interval [CI]: 1.34–3.12). A total of 15 (6.6%) MDR-TB vs. 27 (8.7%) DS-TB child contacts had TB disease at enrolment (aOR: 0.43; 95% CI: 0.19–0.97). Conclusions: The results suggest a *higher risk of TB infection in child contacts with household MDR-TB vs. DS-TB exposure, but a lower risk of TB disease*. Although potentially affected by residual confounding or selection bias, our results are consistent with the hypothesis of impaired virulence in MDR-TB strains in this setting. However, a significant risk for development of disease in child contacts of infectious MDR-TB cases remains.

Strain concordance of household members with DR-TB is high in child contacts <5 years with 75-88% concordance. No RCTs have been completed evaluating 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.

Rationale for preventive treatment

Prophylactic treatment is given after exposure to prevent TB infection, and treatment given after TB infection is intended to prevent progression to TB disease. Preventive treatment includes both these situations. To provide preventive treatment, contact with a source case and risk of infection needs to be established and TB disease should have been excluded. Individual risk assessment should take into consideration: TB contact's (child's) risk for progression to TB disease (age, immune status); infectiousness of the source case and the closeness and duration of contact with the source case; whether there is one or more source cases; the drug susceptibility (DST) pattern(s) of the source case(s); and, the risk for adverse events upon initiating preventive therapy.

Decision algorithm for assessing child contacts of MDR-TB:



Management of children exposed to multidrug-resistant Mycobacterium tuberculosis*. Seddon JA et al. Lancet Infect Dis 2012.*

How to investigate contacts?

- Clinical assessment should include: History (symptoms – not only chronic symptoms; closeness and duration of contact; DST of source case's isolate)
- Clinical examination (PTB/EPTB): Clinical assessment alone is sufficient to decide whether contact is well or symptomatic (developing countries)
- If available: TST (IGRA) – but even if TST/IGRA is negative and exposure has been confirmed, preventive treatment is indicated – reassess after 2-3 months?
- CXR (for diagnosis of disease) – or other imaging/tests
- If DR-TB is suspected and contact is symptomatic or has abnormal CXR: take specimens culture/DST before starting treatment.

NB: ART is essential in prevention of TB in HIV-infected children.

Observational studies that started to change opinions:

- CDC - Chuuk study, Micronesia: Contacts of 2 source cases: strain (A) resistant to HRZES; strain (B) resistant to HREto. Evaluation of MDR-TB contacts: 15 had MDR-TB disease, 5 had DS-TB, and 119 had LTBI with positive TST. LTBI contacts were offered preventive treatment. 15 of the 119 cases refused, preventive treatment was initiated in 104 contacts. A fluoroquinolone (FQN)-based regimen was used: FQN alone or in combination with Eto (strain A) or E (strain B) with DOT for 12 months. Of the 104 who started on MDR preventive Rx (93 completed) – none developed TB disease. 3 of 15 who refused preventive therapy developed MDR-TB disease (P = 0.002).
- Preventive Therapy for Child Contacts of Multidrug-Resistant Tuberculosis: A Prospective Cohort Study. Seddon/Schaaf *et al*. CID 2013: Risk factors: Young age, multiple source cases, HIV-positive status, poor adherence to prevention
- Many opinions published on preventive therapy in MDR-TB contacts (e.g. Policy brief: post-exposure management of MDR-TB contacts: evidence-based recommendations; How to manage children who have come into contact with patients affected by tuberculosis)

- Systematic review: Results: …. The estimated MDR-TB incidence reduction was 90% (9%–99%) using data from 5 comparison studies. We found … high treatment discontinuation rates due to adverse effects in persons taking pyrazinamide-containing regimens. Cost-effectiveness was greatest using a fluoroquinolone/ethambutol combination regimen. Conclusions—Few studies met inclusion criteria, therefore results should be cautiously interpreted *(Marks SM, Mase SR, Morris SB. Systematic Review, Meta-analysis, and Cost-effectiveness of Treatment of Latent Tuberculosis to Reduce Progression to Multidrug-Resistant Tuberculosis. Clin Infect Dis. 2017 Jun 15;64(12):1670-1677. doi: 10.1093/cid/cix208.)*
- WHO Consolidated Guidelines for Programmatic Management of LTBI: In high-risk household contacts of MDR TB patients, preventive treatment may be based on individualised risk assessment and sound clinical justification. (New, Conditional recommendation, low quality of evidence); Confirmation of infection with LTBI tests is required; Recommendation must not affect RCTs of PT for MDR-TB HHCs on ethical grounds since these trials are critical given current limited evidence.
    - Requirement of LTBI test prior to starting PT in DR-TB contacts - Not available in many low income countries, delays in tests becoming positive in young children
- Planned and ongoing trials: see presentation by Anneke Hesseling in this meeting (TB-CHAMP, V-QUIN and PHOENIx trials)

Guidelines that screening for excluding active disease is important (if disease, treat according to likely source case's DST pattern). Follow-up of exposed/infected individuals (especially people with high risk, such as children and immunocompromised patients) is essential (for 1-2 years). Although some older guidelines still do not recommend preventive therapy with second-line drugs, this opinion is definitely changing with more guideline agreeing on preventive therapy in at least high risk contact. Choice of regimens varies, but most guidelines agree that a fluoroquinolone should be included, with or without a second drug. RCTs are needed to prove effectiveness of preventive regimens – preferably a single drug.

In conclusion, MDR TB preventive therapy is likely effective in preventing MDR-TB in children. Randomised controlled trial(s) are ongoing – for choice of regimen, efficacy and safety. Currently, single drug preventive therapy regimens with a fluoroquinolone (e.g. levofloxacin) or a novel drug are considered. A child-friendly levofloxacin formulation for preventive therapy looks promising (acceptability, pharmacokinetics and safety). What about XDR-TB contacts? Careful follow-up and possibly a novel drug (delamanid) – treat as XDR-TB if TB develops. In both MDR and XDR-TB regular clinical follow-up is indicated, but there is a tendency to provide preventive treatment instead of 2-years observation as previously recommended.

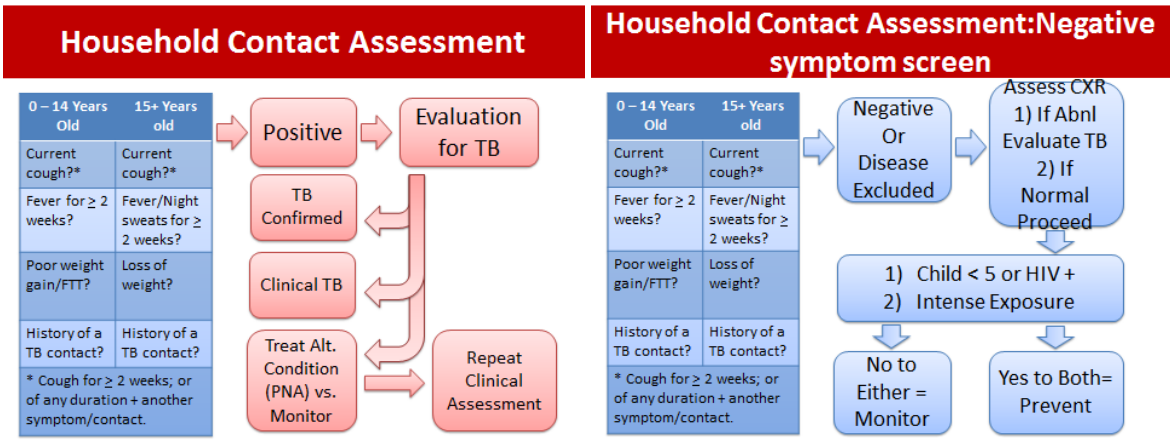
Eswatini NTCP and Baylor Clinical Pilot Program on DR-TB Contact Management – Debrah Vambe

Dr Debrah Vambe presented on a pilot programme for DR-TB contact management in Eswatini. She started by providing an overview of the epidemiological situation in the country: Estimated incidence and prevalence rates have dropped steadily since 2014, with notifications approaching the estimated incidence in 2017. The 2017 MDR Prevalence survey showed a prevalence of 3.7% (2.6; 5.2) in new patients and 10.9% (6.2; 17.3) in re-treatment patients. TB notifications have dropped from 9180 (860 per 100,000) in 2011 to 3226 (295 per 100,000) in 2017. 318 MDR-TB patients were notified in 2017. The

proportion of child TB cases (0-14 years) dropped from 12% in 2011 to 5% in 2017. The wide roll out of Xpert MTB/RIF has not increased the child TB proportion.

National efforts to increase child TB case finding include: Re-focusing attention on clinical diagnosis with Xpert and MTB Culture as complementary tools; Development and roll-out of contact tracing and IPT registers; Main emphasis has been DS-TB contact management; Began planning a DR-TB Contact Management Pilot.

Project development: Review of existing evidence; Consultation with international experts; Discussion among NTCP and Baylor; Presentation of existing data and plan at the tuberculosis technical working group (TWG); Ethical approval from NHRRB for the pilot. Four pilot sites: Good Shepherd = Urban referral hospital; Mankanyane = Rural referral hospital; Baylor Clinic = Urban outpatient clinic; Emkhuzweni Health Center = Rural Health Center.
DR-TB contact management strategy: Register confirmed index case with DR-TB; Home assessment performed to discuss; Infection control; Document all household contacts; Contact screening and collection of sputum for symptomatic individuals; Schedule clinic evaluation for children and adolescent contacts (0-18 years). Clinical Tools were developed for implementation, including a self-contained clinical folder for longitudinal follow-up, a card for families with scheduled visits and medication information and patient information was adapted into the local language.

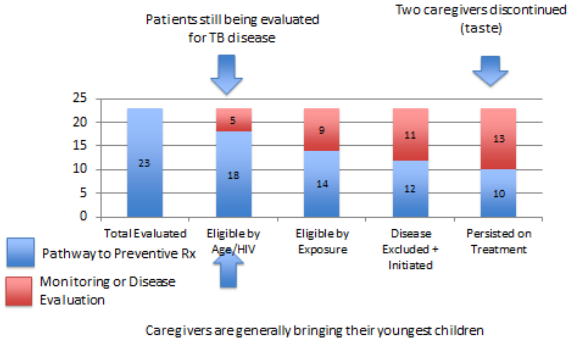


Assessment for Risk of Exposure

Exposure was quantified using the following list: TB infection could not be confirmed as TST and IGRA were not available in the public sector. LTBI treatment was limited to high risk individuals (Age < 5 and PLHIV). TST/IGRA sensitivity is reduced in these high-risk populations, and children in this group often also have co-morbidities such as helminth infection and malnutrition.

A standardized approach was used for programmatic implementation. Levofloxacin alone has been offered for children with INH-mono-resistance or poly-drug-resistance exposure and Levofloxacin with high dose INH has been recommended for children with MDR-TB exposure. Eswatini has high rates of ethambutol (EMB) resistance and good data on the rates of inhA versus katG mutations to inform regimen selection are not yet available. Specific and recent information will be available soon through a DR-TB Survey and implementation will be adjusted based on new data. The follow-up timeline is 18 months with more frequent visits for children placed on preventive therapy. Supportive supervision was done emphasizing active screening for TB symptoms at every visit as well as actively asking about a defined list of potential side effects.

Navigation through contact management algorithm



The cohort has been predominantly HIV negative. This reflects the successes of programs to reduce maternal to child transmission of HIV. Of particular note is that these children are heavily TB exposed with 52% having a prior household exposure to TB despite their relatively young age. The cases have not been evenly distributed. Emkhuzweni pilot site has enrolled the most cases due to an earlier start and the fact that this is a very rural area with high rates of poverty and very large homesteads including lots of children. Uptake in among these patients has been very good perhaps because they have been so heavily impacted by TB. Good Shepherd hospital also serves a similar demographic. Baylor serves a more urban population with smaller households in general. This project has only been underway for several months and so far 23 children have been enrolled. This cascade demonstrates their navigation through the contact management algorithm with blue representing the pathway towards preventive therapy and red reflecting those that have fallen into clinical monitoring or are being evaluated for TB disease. 12/23 (52%) have met criteria for preventive therapy overall. The majority of children evaluated have been under 5 and we are trying to get a better sense of how many children or adolescents. Only 2 children have discontinued treatment in both cases the infants did not tolerate the crushed levofloxacin and the parents were unwilling to continue. This speaks to the need again for child-friendly formulations.

TB disease evaluation: Positive TB Symptom Screen: 5/23 (26%); 4/5 negative by Xpert MTB/RIF, 1/5 symptom resolution (likely viral) and normal CXR; None of the 23 child contacts have been diagnosed with DR-TB; In several children, diagnosis is currently ongoing.

Potential adverse events: Active assessment of all potential medication side effects using a clinical booklet including guidance on how to report severe adverse events in aDSM. Only 2 children have reported mild, transient headache (one on Lfx and one on Lfx + INH).

Barriers: Transport; CXR quality and interpretation; Bitter taste of medication if crushed.

Facilitators: Strong clinicians and care teams at selected sites; Differentiated models provide clinical care (facilitated transport vs. home visits vs. financial support); Caregiver motivation; New guidance.

In conclusion: This is a new programme but scale up is planned, building on the experiences in these 4 sites to improve contact management nationally. More WHO guidance on prevention of RR-and MDR-TB is needed .

Discussions

- Children in Viet Nam study now allowed, until the end of the study (early 2019) – so limited numbers compared to adults
- Testing for LTBI (WHO guidelines 2018) does not apply to children <5 (only to older contacts)
- High dose INH can overcome low level INH resistance (many in the Western Cape have inhA mutation, conferring low level INH resistance)
- Added value of CXR to rule out active TB – this is done in conjunction with other investigations and symptom screening (majority of children in Eswatini are HIV negative)
- Modified short MDR-TB regimen for children (4-5 new groups A and B drugs only) – implications for use of Lfx/Eto/EMB for PT – if disease excluded, PT with fewer and less toxic drugs is the way to go
- Definition of "enough" exposure: to be sure that child was indeed in contact with DR-TB patient (treatment history, results of smears/cultures related to contact with the child) and eligible for PT. Most exposure prior to diagnosis. Pregnant mothers who are smear negative at time of birth: infants may not need PT.
- Awaiting results of efficacy of FQ alone for PT, currently preference to add other drugs

Annex 1:

AGENDA

Annual meeting Child and Adolescent TB working group **Chair: Farhana Amanullah**		**08:30 – 17:00**
08:00 - 08:30	Registration	
08:30 – 08:40	Welcome/Openings address	Farhana Amanullah, Chair & Tereza Kasaeva, Director WHO GTB
08:40 – 08:45	Objectives and expected outcomes of the meeting	Annemieke Brands, secretariat of the Child and Adolescent TB Working Group
08:45 – 09:15	Report from the Chair of the Child and Adolescent TB working group on recent activities including the 2018 Roadmap towards ending TB in children and adolescents and accompanying documents as well as the commitments from the UN HLM on TB	Farhana Amanullah, Chair, Child and Adolescent TB Working Group
09.15 – 09:45	WHO policy updates (including the updated 2018 WHO position on BCG and the updated and consolidated guidelines for programmatic management of Latent TB Infection 2018)	Malgosia Grzemska, WHO GTB
09:45 – 10:00	Update on trials of TB prevention in children and pregnant women	Anneke Hesseling, Desmond Tutu TB Centre, South Africa
10:00 -10:30	Discussion	All
10:30 – 11:00	Group photo Coffee/Tea break	
Developments in child and adolescent TB with a focus on contact investigation and prevention (1) **Chair: Ben Marais**		
11:00 – 11:20	TB prevention: an under-prioritized yet critical intervention to reduce child TB morbidity and mortality	Moorine Sekadde, Childhood TB focal point, NTP Uganda
11:20 - 11:40	Contact investigation and prevention in Rwanda	Eugene Niringiyimana, Director General of Murunda District Hospital on behalf of the MoH Rwanda
11:40 - 12:00	Results of the Titi-study in Benin, Burkina Faso, Cameroon, and the Central African Republic (West and Central Africa)	Valérie Schwoebel, The Union
12:00 – 12:20	Contact investigation and prevention in Indonesia	Rina Triasih, Indonesia
12:20 – 13:00	Discussion	
13:00 – 14:00 Lunch Break		

Developments in child and adolescent TB with a focus on contact investigation and prevention (2) **Chair: Steve Graham**		
14:00 – 14:20	Contact investigation and prevention in Brazil	Betina Mendez Alcântara Gabardo, Brazil
14:20 – 14:40	Contact investigation and prevention in the USA	George McSherry
14:40 – 15:00	Overview of recent research papers with a focus on contact investigation and preventive therapy	James Seddon, Desmond Tutu TB Center, South Africa & Imperial College London (UK)
15:00 - 15:30	Discussion	All
15:30 - 16:00	Coffee/Tea	
Developments in child and adolescent TB with a focus on contact investigation and prevention (3) **Chair: Farhana Amanullah**		
16:00 – 16:20	Preventive therapy for children and adolescents in contact with confirmed MDRTB	Simon Schaaf, University of Stellenbosch, South Africa
16:20 -16:40	Eswatini NTCP and Baylor Clinical Pilot Program on DR-TB Contact Management	Debrah Vambe, NTCP Eswatini & Alexander Kay, Baylor Eswatini
16:40 – 17:00	Discussion	All
17:00	Wrap up, next steps and closure	Chair and Secretariat

Annex 2: List of participants

1.	Farhana AMANULLAH, Chair
2.	Ben MARAIS, Vice Chair
3.	Abdekramane ABDECRAHIM
4.	Oumar ABDELHADI
5.	Akello Susan ADAKUN
6.	Lawanson ADEBOLA
7.	Menonli ADJOBIMEY
8.	Shakil AHMED
9.	Valentina AKSENOVA
10.	Pauline AMUGE
11.	Suzanna ANDERSON
12.	Mohamed ASSAD PEINOMOURTALA
13.	Nay Chi Htet Htet Lin AUNG
14.	Sanni BABAFUNDE
15.	Emmanuelle BAILLET
16.	Rupali Sisir BANU
17.	David BAPTISTE
18.	Tullia BATTAGLIOLI
19.	Kenza BENNANI
20.	Dane BLACK
21.	Ethias BOGUI
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