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Diagnosing and preventing TB in children

By Theo Smart

Key points

- Most children get TB from a family member, and families or households where HIV is present pose a particularly high risk of TB for children.
- Household contact tracing of adult TB cases should include children. Several interventions are described in this edition of HATIP which improved case detection in children using a community-wide approach.
- An HIV diagnosis in an infant or child should also raise the level of suspicion for tuberculosis, and children with HIV should be screened regularly, especially those who are not yet receiving antiretroviral treatment.
- TB is more difficult to diagnose in children. This edition of HATIP includes a scoring tool which may assist in diagnosis, and a compilation of recent expert opinion and research on the best range of symptoms for use in screening children for TB. More research is needed in this area.
- There is very limited provision of isoniazid preventive therapy to children of TB cases and to children with HIV, and there are still questions about how well IPT protects against primary TB infection in neonates.
- The most important intervention to protect infants and young children against TB is to diagnose and treat TB in their mothers and other household members, and to ensure that anyone with TB and HIV is receiving antiretroviral therapy.
- TB prevention in children will also be improved by ensuring that all pregnant women are offered HIV counselling and testing, and by ensuring that those eligible receive antiretroviral therapy. Some countries such as Malawi now provide antiretroviral therapy for all pregnant women with HIV: in practice this is likely to be the simplest means of preventing HIV transmission and reducing the prevalence and incidence of TB both among mothers and children.

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Focusing on the elimination of TB in children

Last week, HATIP published the first in our two-part series addressing the unmet needs for TB prevention, diagnosis and treatment in women and children, especially those with HIV in high TB burden settings — linked to World TB Day's special focus on childhood TB.

The first part looked at TB in mothers and pregnant women, and how TB and HIV case finding activities could be integrated into maternal, neonatal and child health services.

This edition looks first at some efforts to improve TB case detection in children, which highlight problems in defining how TB should be diagnosed in children, before moving on to examine several consensus definitions. It then looks at prevention of TB in children, and the concluding part features expert comment on the key challenges in integrating TB and HIV into maternal, neonatal and child health services.

Introducing a collaborative approach to TB and HIV in maternal and child health services

On the eve of World TB Day, the Directors of the World Health Organization's HIV and Stop TB Departments released a joint message urging that the life-saving TB/HIV collaborative activities be implemented in women and children. The following is an excerpt from their statement:

"Just a month ago, we launched the updated WHO policy on collaborative TB/HIV activities. We estimate that nearly 1 million lives have been saved between 2005-2010 thanks to implementation of TB/HIV collaborative policies in countries. Thus, the importance of implementing the new policy, and in particular, in addressing the needs of most-at-risk and key populations, such as women and children must be emphasized. Delivery of the Three I's for HIV/TB (including isoniazid preventive treatment, infection control for TB, and intensified case finding for TB) and earlier antiretroviral treatment for eligible people, including women and children, can dramatically reduce the number of new cases, saving millions of lives in the coming years.

On this World TB Day 2012, the detrimental effects of HIV and TB on women and children need to be reiterated:

- Pregnant women living with HIV are ten times more likely to develop active TB than those without HIV.
- TB is a leading infectious cause of death during pregnancy and delivery, particularly among women living with HIV.
- TB during pregnancy increases the risk that babies will be born prematurely or with a low birth weight.
- TB in a pregnant woman living with HIV more than doubles the risk of vertical transmission of HIV to the unborn child.
- Most children get TB from a family member.
- In 2010, there were some 10 million children globally who were orphans because of TB among their parents.
- TB is both preventable and curable in women and children, regardless of HIV status. The Three I's for HIV/TB and earlier ART significantly reduce the risk of TB."

The statement also cites a scientific review that was published in the *Journal of Infectious Diseases* "on the magnitude and challenges of maternal and childhood TB in high TB and HIV burden settings together with related recommendations for policy, programming and research. It provides further in-depth evidence on the scope of the problem, as well as opportunities we have at hand to overcome the challenges."¹

The review called for essential TB activities to be made available at the entry points of care for most women and children in maternal, neonatal and child health services, including services to prevent the vertical transmission of HIV.

We would like to stimulate further discussion with experts in the world of TB, HIV and MNCH about the feasibility of these recommendations in [our discussion blog](#). Some initial feedback we received is presented in the latter half of this edition.

What follows is not a comprehensive overview of childhood TB, which HATIP has attempted to do in the past (in issues [124](#), [126](#) and [127](#)), but is primarily based upon presentations describing some of operational experiences in improving diagnosis, treatment and prevention of childhood TB, at the STOP TB Symposium on Maternal and Childhood TB at the Union World Conference on Lung Health in Lille, France, in October 2011, plus some other news from the last year that relates to the subject.

From these presentations, it is painfully clear that more research is needed to improve our understanding, and develop better tools to diagnose, prevent and treat TB in children — but in the meantime, scaling up and implementing what we do know should save lives.

Improving TB case detection in children at community level

“A comprehensive intervention involving existing front line TB workers can increase childhood TB detection at microscopy centres and at the upazila (sub-district) level and should be scaled up in Bangladesh,” said Dr. Khurshid Talukder, Research Coordinator at the Centre for Woman and Child Health in Savar, Bangladesh, who described the development of the intervention, which was then validated in a cluster randomised trial.

In Bangladesh, case detection and treatment success rates have been steadily improving among adults over the last several years. Among children however, there was far too little case detection among children, particularly when they were compared to case detection rates in neighbouring Madhupur, India, which were five times higher.

To understand why so few children with TB were being diagnosed, field visits were conducted to microscopy centres, their adjacent upazila health complexes and their catchment areas to assess how childhood TB was referred and diagnosed. They found a number of barriers to increasing childhood TB detection in Bangladesh. For instance, there were no guidelines available to field staff or doctors on diagnosis of childhood TB, and no training for field staff or doctors. There were very low levels of household contact tracing and preventive therapy provision for children (contact tracing was only being performed by about 23% of DOTS centres in the country). In addition, smear microscopy was picking up very few cases, even though hundreds of symptomatic children were being screened.

So the researchers approached the Damien Foundation (DF), a charity that provides technical assistance to health systems and develops local health systems capacity in leprosy and TB care, to discuss what sort of intervention might improve childhood TB detection.

They decided to develop a comprehensive campaign, involving the development of new guidelines, healthcare worker trainings and community outreach. To see whether it would be worth the effort to scale up the programme country-wide, they also conducted a cluster randomised trial involving 18 intervention and 18 control microscopy centres and their respective upazila health centres with the support of the DF.

The study population included all children aged <15 years attending study microscopy centres either referred as a TB suspect or brought in from contact tracing. The hypothesis was that 12 months of intervention would result in an increase from 4% to 8% in case detection among referred children.

After conducting surveys to determine the rates of childhood TB referral and detection at each microscopy centre, staff at the microscopy centre and health centre were trained, and community

orientation sessions held on the early referral and detection of childhood TB.

Microscopy centre field staff were trained on the use of the 1996 WHO child TB score chart for case detection (reproduced on page 5), administration of the Mantoux Test (TST), how to weigh children and detect malnourishment; and when to refer the child to a doctor. They were also trained to conduct health education sessions at the health centres and in the community with messages on childhood TB, using the Child TB Flip Chart, and on how to fill out the research questionnaires.

Doctors were trained and orientated on the epidemiology and diagnosis of child TB, case scenarios and on treatment as per NTP guidelines

The community activities were extensive with monthly meetings on childhood TB at the health centres: IEC materials and posters were distributed, and educational sessions on childhood TB were held at the TB club and village doctor meetings. Over the longer term, there were quarterly monitoring meetings, and messages were given at meetings in schools and madrassas, girl guide and boy scout meetings. All the doctors in the county (including private practitioners) were orientated on childhood TB.

Educational and training materials such as a child TB management flowchart were developed for the microscopy centre. Training sessions were given for medical officers and government employees.

Results

Oddly, in both the control and intervention arms there was actually a decrease in the number of child TB contacts and suspects referred. However both in comparison to baseline and to the control, there was a substantial increase in child TB diagnoses — the total number of cases diagnosed in the intervention clusters increased from 75 to 175 (it also increased in the control group, by nowhere near as much, from 104 to 130 cases) and in particular there was an increase in diagnoses of smear-negative TB and EPTB.

The intervention did significantly change the source of referrals however. In the control clusters, technical personnel were the main identifiers of suspects, responsible for 56% of referrals, but among the intervention clusters, non-technical personnel referred most of the patients.

Intervention children (n=395) were brought in and diagnosed at a significantly younger age, than non-intervention children (a mean of 62 months old rather than 82 months old), with a similar percentage of boys and girls.

In addition, the project received a lot of positive qualitative feedback from parents, community members, health professionals and doctors.

“The comprehensive programme increased diagnoses, referrals, however, have not increased from the community though they are more from lay people,” said Dr Talukder. “And there was a good response from the public to key messages on child TB”

Consequently, Bangladesh is now developing a national child TB strategy and action plan based on the model. Training of microscopy centre and UHC personnel on childhood TB is already being scaled up. All the microscopy centres are being supplied with TSTs and weighing scales, chest x-rays will be available at all government health centres, and there has been an increase of community-based orientation of village doctors, community agents and health workers. And a national incidence study for childhood TB is also to be launched.

This turn around appears remarkable, yet one always wonders when one hears about multifaceted interventions whether each of

the activities is really necessary. However, the enthusiasm with which the programme has been greeted on the national level, now, after years of under-diagnosing and treating childhood TB would seem to be reason enough to implement the whole package.

Improving case detection in children: TB REACH experience in Yemen

Not every intervention presented at the meeting was as successful. For instance, a promising contact tracing campaign in Yemen — which relied upon home visits to provide improved access to TB diagnosis and treatment — was made virtually impossible by civil unrest.

As in many other places, very few children with TB receive a diagnosis or if they do, are reported. The National TB Programme didn't have enough staff with expertise to deal with children in health facilities. To get a diagnosis, children with symptoms had to be sent to, and sometimes stay in hospital. This costs money of course, and many parents default before the child's diagnosis is complete (and getting them to provide gastric aspirates is difficult). Even when they do get a diagnosis, they often fail to register the case and get treatment, and default on treatment is common.

One of the most likely ways to find cases of childhood TB is through contact tracing of adult smear-positive TB cases, but as in many parts of the world, it was not being done in Yemen.

With the help of TB Reach, a Stop TB Partnership initiative supporting innovative initiatives to increase case detection in poor and vulnerable populations in many different countries, the National TB Programme launched a project in Yemen to increase access and shorten the time to TB diagnosis for children, women, and the elderly via contact tracing.

The project in Yemen included several activities. The contact tracing involved home visits from one male or two female health workers, who would take morning sputum specimens from anyone in the household with symptoms of TB. They would take symptomatic children to the hospital for diagnosis (as keeping the children fasted and taking specimens in the early hours of the morning could improve yield) with samples collected from multiple anatomical sites on the same day.

The programme also included improved counselling, SMS messages to parents to support adherence, and strengthening Yemen's TB laboratory capacity.

"We expected to increase case detection in children, test the hypothesis that home visits are acceptable and link children in the community with diagnostic services, but sometimes life is complicated," said Dr Najla Al-Sonboli of Sana'a University who described the initiative. The project was to run from January to December 2011, but civil unrest broke out, especially in the last 6 months of the year.

There was no fuel, there were food shortages and electricity was rationed to 1-2 hours per day and civil unrest and US military action made it extremely difficult for outreach teams to reach households, take children to hospitals, take samples back to the laboratories, conduct smear microscopy/culture — some areas were simply out of bounds.

During this difficult time, many families moved away, there was limited electricity for incubators (for culture), and mobile phone networks were often down.

Even for the relatively less chaotic period from January to April, out of 385 index cases identified, most of whom had children, about half of them had sent their children away. Nevertheless, 395 children were screened, with a mean age of 84 (\pm 47) months [2 – 174], 155 of whom were classified as symptomatic (the symptom

screen was broad: including cough, fever, night sweats, loss of appetite, wheeze, chest pain, loss of weight, difficulty breathing, haemoptysis and others).

They collected specimens from about 118 of these children (including gastric aspirates in virtually all of them, sputum specimens in about 80% and nasopharyngeal aspirates in almost a third). Out of these, they identified six cases of smear or culture-positive TB — so roughly 3% of the index cases' homes had a child with TB.

Yields were higher among children who had been hospitalised: 29 children were hospitalised (two without samples, one absconded, one died). Their mean age was younger at 57 months, range 5-190 months. They were able to get sputum nasopharyngeal aspirates and gastric aspirates on most of these children, and these specimens were all smear-negative, but two (7%) of the sputum specimens were culture-positive, and three (11%) of the nasopharyngeal aspirates and gastric aspirates.

Nevertheless, as the situation unravelled in Yemen, it was clear that the project could not continue as originally planned. The team decided to try to invite relatives of index cases to come to the centre if they had any of a list of symptoms and they offered them subsidies for their transport. But large numbers of relatives, most of whom were asymptomatic, attended the centres and overwhelmed the staff.

"While the project did increase sensitisation of TB programme staff to the needs of children," and did identify some cases, she concluded it is *possible* to conduct contact tracing in a civil war situation, but she noted their ability to sustain culture facilities has become precarious.

One audience member pointed out: "What these two presentations highlight is that we aren't talking the same language when talking about the case definitions of childhood TB. The previous presentation used clinical definitions and you've used culture, and of course the clinical definition finds much higher rates of TB, and culture lower. We've got to find some way to standardise this. Culture is a sub-optimal gold standard, and further work needs to be done to try to identify childhood TB with greater sensitivity and specificity."

Luis Cuevas of Liverpool School of Tropical Medicine who was a co-author on the paper responded: "We have so many different ways of identifying TB it is very difficult to compare ... it was very difficult to make sense out of what people were reporting in different areas. Over the last several years, we have reached a consensus of clinical case definitions: because there is no good reference... we've come up with a rule based approach." He suggested that future studies ought to use that case definition so that uniform data can be collected, and that funding from large institutions ought to be conditional on use of the consensus definition.

The WHO score chart for diagnosis of TB is reproduced on the following page.

Score chart for the diagnosis of TB in children

SCORE IF FEATURE PRESENT

Feature	0	1	2	3	4	Score
General						
Duration of illness (weeks)	< 2	2-4		> 4		
Nutrition (% weight for age)	> 80	60-80		< 60		
Family history of TB	none	Reported by family		If proved sputum positive		
Tuberculin skin test				Positive		
Malnutrition				Not improving after 4 weeks		
Unexplained fever and night sweats			No response to malaria treatment			
Local						
				Lymph nodes		
				Joint or bone swelling		
				Abdominal mass or ascites		
				CNS sign sand usually abnormal CSF findings		
					Angle deformity of spine	
Total score						

Towards a better definition of TB diagnosis in children

As previously noted, smear microscopy and culture are insensitive for TB diagnosis in children, while others use symptom scoring systems that in clinical practice may lead to over-diagnosis and over-treatment of children. Consequently, clinical case definitions have varied from study to study – which is what has made their results often difficult to interpret, with data that are next to impossible to pool and analyse.

This section looks in more detail at the question of case definition.

WHO recommends a core approach,² but we've augmented it somewhat, adding some definitions and clarifications drawn from another article in the same supplement of *Journal of Infectious Diseases* by Graham et al on a proposed clinical case definition for classification of intrathoracic tuberculosis disease in children.³ This discussion also draws on a presentation Dr Anneke Hesselning gave at a WHO TB/HIV meeting in 2009.⁴

The approach to diagnosis of TB in children

- *A careful history including history of TB contact* (has the child been in household or close contact to a person with TB in the last 24 months? Note, that in neonates especially, it is not uncommon for the mother to have undiagnosed TB, especially extrapulmonary TB, so a high index of suspicion is warranted), *and symptoms consistent with TB* (see below)
- *Clinical examination including growth assessment* (see below)
- *Immunological evidence of TB infection*, as assessed by either *tuberculin skin testing* (the skin test is positivity (using 5TU PPD or 2TU RT23 (types of tuberculin) when there is an induration (reaction, bump) of ≥ 10 mm if HIV uninfected or ≥ 5 mm if HIV infected or severely malnourished, or a *positive interferon- γ release assay*
- *An HIV test* (note that whenever a child contact of a TB case, tests HIV-positive, their risk of disease is higher, so the HIV-positive result should probably be treated as a proxy for MTB infection)
- *Bacteriological confirmation whenever possible* (one positive acid-fast bacilli microscopy and mycobacterial culture of specimens is diagnostic, however smear microscopy and culture are both poorly sensitive for TB in children)

Investigations relevant for suspected pulmonary TB and suspected extrapulmonary TB (eg, Xpert MTB/RIF test, chest radiography, fine needle aspiration – specimens from other sites may have a better bacteriological yield.)

Naturally, there are a range of co-morbid conditions, especially in children with HIV, and care-givers need to approach diagnosis holistically, keeping in mind more likely differential diagnoses for symptoms based upon the local epidemiology. Nevertheless, many healthcare workers in maternal neonatal and child health systems need to have childhood TB on their radar.

Don't worry too much about the Z-scores, unless you are a doctor/researcher. But the Z-score is a way of classifying how well a child is growing/developing (weight-for-height, height-for-age or weight-for-age) relative to the reference population (in other words, what is normal for the population). Z-scores are calculated using this formula: $Z\text{-score} = \frac{(\text{the observed value} - \text{the median value of the reference population})}{\text{the standard deviation value of reference population}}$. However, Graham et al wrote that the

expert panel thought that "Z-scores might be too technical to apply as a field tool."

Clinical signs/symptoms suggestive of tuberculosis in a child
Persistent non-remitting cough lasting more than 2 weeks
Unexplained weight loss, of at least 5% when compared to the highest weight recorded for the child in last 3 months, and/or failure to thrive, defined as: <ol style="list-style-type: none"> 1. Clear deviation from a previous growth trajectory and/or 2. Documented crossing of percentile lines in the preceding 3 months and/or 3. Weight for age Z-score* of ≤ -2 in the absence of information on previous/recent growth trajectory and/or 4. Weight for height Z-score* of ≤ -2 in the absence of information on previous/recent growth trajectory and not responding to nutritional rehabilitation (or antiretroviral therapy if HIV infected)
Persistent unexplained fever for more than one week and unexplained fever ($>38_{\circ}\text{C}$) reported by a guardian or objectively recorded at least once.
Persistent, unexplained lethargy or reduced playfulness or activity reported by the parent/caregiver.
Additional signs and symptoms suggestive of tuberculosis in infants 0–60 days (or neonate)
<ol style="list-style-type: none"> a) Neonatal pneumonia or b) Unexplained hepatosplenomegaly or c) Sepsis-like illness

TB in children of caregivers with AIDS is common but screening them for TB isn't

TB contact tracing and access to diagnostic services need to be improved dramatically for children at risk of TB – especially among the children of people living with AIDS, according to a report which won the SA AIDS Conference Discovery Best Paper award when it was presented at the 5th South African AIDS Conference last June by Lucie Cluver, of Oxford University.⁵

"Kids are catching TB from their AIDS-sick carers and they are not accessing testing for TB," she told HATIP, noting that the findings are independent of parent-to-child transmission.

Cluver has been collaborating with South African academic and government partners, UNICEF, Save the Children and other NGOs, on an 'orphans and vulnerable children' research programme. The research programme includes the 'National Young Carers Study' a longitudinal study including 7000 children and 2600 caregivers in Kwa-Zulu Natal, Mpumalanga, and the Western Cape.

She presented findings based on the incidence of infectious disease and TB drawn from the Young Carers Study in KwaZulu-Natal – which involved a stratified sampling of children and caregivers from peri-urban and rural health districts with a greater than 30% HIV prevalence.

The cohort includes around 5238 participants (2600 matched child-caregiver pairs), with children aged 10-17 years old, who were interviewed using validated scales and clinical symptom checklists to comparing the health of children (AIDS-orphan, other-orphan and non-orphan) whose caregivers were symptomatic with AIDS, sick from other causes or healthy.

Results

There were no differences in non-infectious diseases based upon orphan status or the caregiver's health. However, children whose primary caregivers have AIDS (symptomatic) were more likely to

have a range of childhood illnesses (such as worms or diarrhoea) than children with healthy caregivers or other-sick caregivers.

"This cannot be due to vertical HIV infection as it holds equally true for children whose caregivers are their biological parents and those whose are not," Cluver told HATIP.

Children whose caregivers had symptomatic AIDS were also more likely to have two or more concurrent illnesses, and were more likely to have TB.

In fact, TB infection (with three or more TB symptoms) was five times more common among children of caregivers with AIDS (17.4%) than with healthy caregivers (4%, odds ratio: 5.0 after multiple logistic regression controlling for: child age, child gender, urban/rural location, safe drinking water, household toilet facilities). However, the risk of the child getting TB was significantly reduced if the caregiver was taking ART.

"The TB is explained by 80% of AIDS-sick caregivers having TB, and it seems that there is direct infection occurring within the households," Cluver told HATIP.

That is not so surprising. But what was disturbing was that only 14% of children with three or more pulmonary TB symptoms had ever been screened for TB, and only 4% of those whose caregivers have TB had ever had been screened for TB.

"The good news is that once they test, around 80% get treatment and a similar proportion adhere to their treatment for at least six months. Once they access TB diagnosis, treatment is good," Cluver said.

Nevertheless, it seems clear that among older children at least, the health services have been failing to identify and screen the very children who are most vulnerable to TB. The findings illustrate the clear need for the South African government's recently announced scale-up of intensified case finding/contact tracing (where outreach teams will visit the homes of notified TB cases to perform TB screening, HIV counselling and testing and other services). But while the new programme is rolled out, programmes must do more to strengthen adult/child referrals.

There may also be some denial on the part of family members of the risks of infections among their children. Families affected by AIDS clearly need more education and support to encourage caregivers living with AIDS and/or TB to bring their children for routine health services and TB screening — particularly when they have clear symptoms of TB.

Operational challenges in implementing isoniazid preventive therapy (IPT) in children

The next step from intensified case finding is to implement activities which provide isoniazid preventive therapy for prevention of tuberculosis.

Dr Mohammed Yassin of the Global Fund spoke at the 2011 STOP TB symposium about the operational challenges implementing contact investigation and IPT in children, and shared the experience in Hawassa, southern Ethiopia following a cohort of children who were contacts of smear-positive TB cases. He also described the TB REACH-Ethiopia-LSTM's innovative programme to implement community-based TB diagnosis, prevention and treatment, and described some of its early results, focusing on how the programme addressed contact tracing in children and IPT.

Children in contact with infectious TB cases are at a higher risk of infection and progression to disease. But it has been well established that IPT is effective in preventing TB progression.⁶ Consequently, WHO and most NTPs recommend contact screening

and provision of IPT for asymptomatic children under 5 years of age.⁷

But in practice, Dr Yassin said, "contact screening and IPT provision are often overlooked and many programmes don't do it."⁸ The gap between policy and practice related to contact screening and IPT is significant, especially in developing countries.⁹

Dr Yassin described the many challenges to implementing contact investigation and IPT, starting with contact screening.

"NTPs recommend contact screening — it's usually included in their guidelines or manuals — but most don't implement it, or those who do implement it, usually just ask index cases to bring their contacts to the facilities, adopting a "passive" approach," he said, adding that often staff don't even inform index cases about the need to bring in their contacts, possible due to lack of awareness of the policy. The majority of index cases who are told to bring their contact in, don't, because they haven't been made adequately aware, as parents or relatives, about the advantages of screening their children and the potential benefit of preventive therapy.

In fact, if the health care staff have not convinced the TB patient of the utter necessity of bringing their children in for screening, it is really unreasonable to expect him or her to do so, if one stops to think about the ordeal it could be to gather together all the children in the household, particularly more than one, corral or carry them to the health facility, and probably endure half the day struggling with them in a crowded waiting room filled with sick and injured people.¹⁰

As for the challenges related to implementing IPT? Firstly, no one is going to provide IPT if there hasn't been a concerted effort to put an IPT programme in place, or if the resources and tools to support successful implementation are not available.

"IPT related recording and reporting systems often do not exist in most national programmes. There are no dedicated registers or patient contact cards," said Dr Yassin. In addition, without training, health care workers are often reluctant to initiate IPT in a young child because they are not confident in their ability to exclude active TB in a child, and fear that if they provide IPT and the child does have TB, it might lead to drug resistance. Moreover, the drug may not even be in stock — because no one has made it a priority to plan for it, established a supply system nor has the programme allocated resources for this purpose.

Consequently only a very few children initiate IPT and there is evidence that even active tracing may not improve IPT uptake significantly.¹¹ If someone does prescribe it for a child contact, that is probably all that is done — so adherence is probably very poor and whether it is prescribed or not, is not documented in the registers — assuming they exist.

In short, in most resource limited settings, there is very little if any access to services providing IPT to children exposed to TB, especially in rural communities.

The child contact tracing to IPT completion cascade

Dr Yassin presented a graph on child contact tracing and IPT that was very similar to the notorious 'PMTCT Cascade' — which showed that there were multiple step/events, a critical pathway, that had to be followed for an HIV-positive pregnant woman and her child to actually take the antiretrovirals to prevent vertical transmission of HIV, and for each step along that path, fewer and fewer women were retained in the programme, so that by the time of delivery, very few infants of pregnant women were actually receiving the benefits that the programme had been set up to deliver.

Something similar happens between contact tracing and completion of IPT.

“Only a fraction of children end up completing IPT, whereas you can start with a very large number of contacts, but not all contacts are informed or visited at home. But not all contacts are screened. But when we screen them, most of them will be asymptomatic. One might assume that all these children then start IPT, but not all children or their parents accept the offer of IPT, some refuse. And several studies in Africa have shown that only a proportion of children who start IPT actually complete the recommended six months prophylaxis,” said Dr Yassin.

There could be a number of other steps in this cascade. For instance, in the screening process, TST (which involves at least two steps) and chest x-ray can be helpful for screening wherever they are available, but their unavailability shouldn't preclude contact management, according to WHO's [Child TB guidelines](#), which state that “clinical assessment is sufficient to decide initiation of IPT for children with no symptoms.

Delivery of IPT might also increase, Dr Yassin believes, if healthcare workers were made aware that there are now a large body of data on IPT, including a review of thirteen IPT trials with over 35,000 participants, that showed low risk of resistance (RR 1.45, 95% CI 0.85-2.47).¹²

Cohort study in Hawassa, southern Ethiopia

Dr Yassin described a cohort study that they conducted between 2007-2010 among child contacts of TB cases to determine compliance to IPT and the risk of TB progression. This study also collected data on TSTs, IGRAs, and other potential biological markers for progression of TB.

Smear-positive cases were identified in three health facilities and their houses were visited and mapped by GPS. IPT started for children under five years old as recommended by the NTP. The study included 184 children (82 under five years old, 102 five years old and over) in contact with 83 index cases followed for a median period of 24 months. 46% of the children under five years of age, and 67% five years old and over had TST ≥ 10 mm, and 12% and 9% were HIV positive respectively. 82 children under five years of age initiated IPT and were followed monthly.

Twenty-seven took IPT for at least four months and only ten (12%) completed the 6-month course — illustrating the child contact tracing to IPT completion cascade.

“The main reason for interrupting IPT was that parents thought drugs were not necessary for their healthy children,” said Dr Yassin, who added that they remained difficult to convince even after a couple of interventions to change their minds.

None of those who initiated IPT developed active TB during follow-up. However, 11% (11) children under the age of five who didn't receive IPT developed active TB —none of these children were HIV-positive.

“But we learned that the risk of developing active TB among children in contact with smear-positive TB is very high even without HIV infection and IPT reduces this risk, though the numbers in our cohort were low,” Dr Yassin said.¹³

TB REACH Ethiopia-LSTM project

Dr Yassin also described the TB REACH Ethiopia-LSTM project, a community-based intervention project to improve TB control in Ethiopia. We previously reported another presentation Dr Yassin gave during the Union World Conference in HATIP 184. The project almost doubled TB case finding in the region of southern Ethiopia where it was implemented.

The programme trained community health extension workers who are part of Ethiopia's health services, already embedded and

providing comprehensive care within local communities, to provide household contact tracing in the community.

Concurrently, the project improved laboratory capacity and launched various advocacy, communication and social mobilisation activities, including awareness creation workshops on contact tracing and IPT targeting all levels of Ethiopian society, attended by over 1,200 political, community, religious leaders, stakeholders, health personnel and former TB patients.

In the course of their routine daily work, health extension workers visited homes to provide treatment and support, and screened for symptoms of TB. Health extension workers identified TB “suspects,” collected their sputum samples, and prepared the smears on slides for microscopy and phoned their supervisors to collect the smears. (They all have mobile phones to keep in contact with the supervisor). The supervisors would pick up the slides, take them to the lab technicians, who examined the smears, and reported results to supervisors (keeping slides for EDA). The supervisor would get the results, and make certain that treatment was initiated by smear-positive cases in their residences, screened household contacts and initiated IPT for children who were asymptomatic. Treatment support was provided by health extension workers who reported the outcomes and follows smear-negative cases within the communities.

In this presentation, Dr Yassin described in more detail the child contact investigation and IPT activities in the project. He said that that they only received INH supplies in May 2011, months after the project had started, so health extension workers received a refresher course of training in May-June.

Implementation of this aspect was purposely phased in. “This is a learning process as well, we didn't want to start IPT for everyone all at once,” said Dr Yassin. But the numbers put on treatment increased dramatically in the last few months of follow-up that Dr Yassin shared, so that 57% of the child contacts were receiving IPT.

Dr Yassin concluded by giving his view of what successful implementation and scale-up of IPT services depends on.

Planning and prioritising IPT	Proper planning and resource allocation within the NTP Ensuring availability of INH (preferably in blister packs) Separate registers, contact cards and reporting formats need to be provided Phased implementation and scaling-up of activities
Capacity building	Training of staff about diagnosis and the benefits of treatment for childhood TB, contact investigation and IPT Improving communities' awareness about the risk of TB after exposure and the role of IPT in mitigating this risk Counselling of parents about the importance of completing IPT

“Community-based contact screening and IPT provision and follow-up would probably improve access, uptake and compliance,” he concluded.

IPT in children in Brazil

Dr Clemex Couto Sant'Anna, of the Universidade Federal do Rio de Janeiro described how Brazil, a high burden TB country where BCG vaccination at birth is universal, has approached IPT in children.

Old Brazilian TB programme guidelines, which have now been changed, emphasised that, due to widespread BCG vaccination, for a TST to be considered suggestive of latent TB infection (LTBi), the reaction had to be larger than in the current guidelines (see below). The policy was to give six months of IPT to all child contacts (under 15 years of age) of TB cases, provided they were asymptomatic with a normal chest X-ray, with the highest priority given to children under five.

Brazil has experience and data from a number of retrospective studies on thousands of children put on IPT. Despite the federal policy, implementation varies between the states of Brazil (which have different economic and culture situations) — some states seem to have put different emphasis on the TST cut-off, for instance. Data from São Paulo in 2009 suggested the health system had been more successful giving IPT to adolescents over the age of 15 compared to children under 5. Data also from São Paulo in 2010, suggested that only 57.9% reported having completed their IPT. There were only a small number of deaths, active disease or adverse events in this cohort, and only 8% who were actually reported to be non-adherent, so the problem seemed to be one of recording and reporting. Dr Sant'Anna noted a recent prospective study in Rio, where 228 children with LTBi were put on IPT, and around 17% were reported to be non-compliant. Unfortunately, he didn't explain Brazil's secret for achieving such high adherence to IPT compared to the experience in other settings.

Subsequently an online electronic data system for IPT has been established to keep better track of the patient's data.

In 2010, Brazil's guidelines were updated so that now the cut-off for TST is ≥ 5 mm in > 2 years BCG-vaccinated children; or non BCG-vaccinated children or immunosuppressed patients, and ≥ 10 mm in < 2 years BCG-vaccinated children — which during the discussion, Dr Dráurio Barreira, who heads Brazil's NTP, emphasised is supported by the data the programme has gathered. The priorities for both contact tracing and IPT (now recommended for at least six months but ideally nine months) are 1) children under 5 years of age and 2) children living with HIV. Asymptomatic HIV-infected TB child contacts must start IPT independent of TST results, if their chest x-rays are normal.

As for HIV-infected patients in general (not specific to TB contacts), IPT is recommended for people without the symptoms of TB and a normal chest x-ray if their TST reaction is ≥ 5 mm — or if it ever has been ≥ 5 mm (unless they have subsequently been treated with a course of TB treatment or IPT, since a smaller TST reaction might merely be a sign of anergy developing). Again, TST results aren't needed if the patient is a household or institutional contact of a TB case, but in addition, any person living with HIV develops signs of TB sequelae on their chest x-ray should be put on IPT regardless of TST results (as long as active disease has been ruled out).

Challenges preventing TB in HIV-exposed neonates

Unfortunately, the management of TB in neonates didn't receive quite as much attention during the STOP TB Symposium, perhaps because one of the primary tools, IPT, doesn't have such a great track record in this population. One of the largest studies of IPT among HIV-exposed infants (three to four months of age at study entry) was published in the *New England Journal of Medicine* in July 2011.¹⁴

The study, which was performed in South Africa and Botswana, included 547 HIV-infected infants and 804 HIV-uninfected children, all of whom had been immunised with the BCG vaccine within the

first month of life, and randomly assigned to IPT or placebo. The results were hugely disappointing — IPT seemed to have no effect whatsoever improving TB disease-free survival among HIV infected children (98% of whom started ART during the study) or TB infection-free survival among the uninfected children.

HATIP has described this study before, and postulated that the exclusion of children who were discovered to have been exposed to TB (they were screened at each clinic visit and put on IPT if there had been exposure) could have reduced the chances for IPT to prevent TB. However, this only seems to have occurred in 11 of the HIV-infected children in each arm and 26 to 34 of the HIV-uninfected children. Focusing just on TB, there were still 69 protocol-defined TB cases in HIV-infected children 31 on the IPT arm and 38 in the placebo arm (a non-significant difference), and 79 cases among the HIV-uninfected children (again no significant difference between the arms).

The investigators believe that IPT's failure in these infants is not due to a sub-optimal isoniazid dose (the study used higher doses than WHO recommendations at the time), nor high levels of isoniazid resistance in the community, nor specificity of the study endpoints (in particular related to TB diagnosis).

Poor adherence does not appear to explain the finding. Adherence was measured by caregiver report, 62% to 92% reporting no missed doses between clinic visits — although there is always a possibility that caregiver reports are not very reliable. Dosing infants might also be complicated by their tendency to spit things out.

The authors theorised that IPT simply isn't very good at preventing 'primary TB infection' — which is what most infants develop, as opposed to the 'reactivation of latent TB' which the author's say is primarily what IPT has been shown to prevent in older children and adults, which is curious in light of evidence suggesting that in areas where there is a high rate of ongoing transmission, continuous IPT may be needed to prevent TB from recent or reinfections.

There could be another possibility: there is another population in which IPT has been shown to work less well: adults who are tuberculin skin test non-reactive (either due to the absence of a latent infection, or because the individual has become anergic and cannot mount an immune response to the tuberculin). Anergic people living with HIV are nonetheless at high risk of TB, IPT just doesn't stop it in them the way that it does when people's immune responses are more intact. And neonates of HIV-infected mothers have something in common with anaergic individuals — no functional immune response to TB. Perhaps isoniazid needs some support from the immune system to prevent TB, which is absent in neonates, particularly of HIV-infected mothers.

Furthermore, if IPT doesn't really prevent TB infections from taking hold, why are we recommending continuous IPT to prevent new TB infections and disease in adults? If the drug doesn't really work that way, it would be important to find out.

If IPT needs the help of the immune system to keep TB in check, however, it may be important to note that very few of the children in this study were ever breastfed — only around 13.3% of the HIV-infected children and 6% of the HIV-uninfected children. Breastmilk supplies maternal antibodies and immunoglobulins that infants cannot produce on their own — making formula-fed children more susceptible to a variety of infections. Indeed, it might be worth investigating whether IPT might work better in neonates in other parts of sub-Saharan Africa where breastfeeding is the norm. Without some immunological restraint, the force of the m.TB infection in formula-fed HIV-infected neonates may simply result in primary infection becoming full blown disease too rapidly, simply

overwhelming monotherapy. We may need more basic science research on TB to understand exactly what happened.

Mahdi et al concluded their paper by stating that their findings underscore the need to explore alternative options for the prevention and management of TB in HIV-exposed children. It isn't clear that an alternative drug would necessarily work better than improved detection of exposure to TB in children or pre-emptive treatment.

It should be stressed however that other studies have shown IPT to reduce TB in older HIV-infected children, including the cohort study conducted by Heather Zar and colleagues in South Africa in which access to ART was not as common (among other differences), and in uninfected children known to have had contact with someone with TB.¹⁵

For the time being, however, there appears to be no intervention that we can give neonates to prevent active TB. Thus our only practical option, it would seem, would be to reduce the risk of exposure — **by preventing or, when necessary, diagnosing and treating TB in their mothers (and households).**

New tools on the horizon

The final two presentations at the meeting focused on improving the tools for diagnosis and treatment in children... but if anything, despite some progress, they presentation really underscored how far we still have to go.

GeneXpert could speed up diagnosis but it still misses most cases in children

As South Africa and several other countries are going to considerable expense and effort to rapidly scale up the GeneXpert TB/Rif assay, there is immense interest in whether the test could improve access to TB diagnosis for children. Unfortunately, according to the results of a study presented by Dr Mark Nicol of UCT and National Health Laboratory Service, the answer is — not that much. It should pick up two times the cases that microscopy does, but that isn't saying much given that smear. Aside from the speed of the diagnosis, the GeneXpert is not a replacement for culture, which in itself is a rather poor gold standard for diagnosing TB in young children. (This study will be discussed in more detail in the upcoming HATIP on new TB diagnostics.)

When it comes to TB diagnosis in children, we are, as Dr Nicol said, “fumbling in the dark”. Based on clinical diagnosis, culture appears to be a poor reference standard (only picking up 20-50%) of the cases. Microscopy is infrequently helpful (detecting less than <10% of clinical diagnoses). However, clinical diagnosis is probably even worse: chest radiography interpretation is highly variable and clinical scoring systems seldom concur.

The lack of a gold standard for TB diagnosis is likely to create challenges for evaluating any new and potentially better diagnostic tool in children.

Formulating TB drugs for children: FDCs on the horizon?

“When you go looking for data on these drugs in children, you find precious little,” said Professor Gregory Kearns, University of Missouri, who described the barriers to getting TB medicines both old and new to children. He described some of the clinical pharmacological challenges knowing that a drug's dosage is achieving therapeutic concentrations in children of difference ages, sizes and in populations with difference in inherited differences in

metabolism. This is a subject HATIP covered extensively in a previous issue on TB in children (see [HATIP 127](#)).

He also reviewed changes in the recommended dosage of first-line TB drugs in children (see box), and described ongoing efforts to get the pharmaceutical industry to develop child-friendly fixed dose formulations for children that are affordable and practical in low resourced settings.

Given the risk of drug-induced hepatotoxicity, WHO recommends the following dosages of anti-tuberculosis medicines for the treatment of tuberculosis in children:

WHO recommended doses of TB drugs for children		
Isoniazid (H)	10 mg/kg (range 10–15 mg/kg)	Maximum dose 300 mg/day
Rifampicin (R)	15 mg/kg (range 10–20 mg/kg)	Maximum dose 600 mg/day
Pyrazinamide (Z)	35 mg/kg (30–40 mg/kg)	
Ethambutol (E)	20 mg/kg (15–25 mg/kg)	

The discussion on integrating TB activities into MNCH platforms begins

Collaborative TB/HIV activities have indeed become the standard of care for HIV programmes, though it took some time to happen, and in many resource-constrained settings we still have a long way towards implementing them consistently.

As WHO has pointed out, women, especially pregnant women and their children, represent populations whose TB needs are underserved, and particularly in countries with a high burden of HIV coinfection, this results in serious morbidity and mortality.

Delivering some of those services where women of child-bearing age and their children access care seems to make sense. But is it really that easy? There are clearly a number of differences in how HIV services and the MCH services are structured and delivered. So HATIP asked experts working in the fields of HIV and maternal, neonatal and child health what they think of the STOP TB Department's recommendations for TB integration.

Most of the discussion has been focused on two areas: feasibility, and whether IPT should really be the priority in pregnant women living with HIV.

“On my visits to the districts visiting primary health centres there, I have been sensitising doctors on the need for screening of TB among pregnant women and it is obvious this is not done in practice,” Dr Beena Thomas of the Tuberculosis Research Centre in Chennai told HATIP. She noted that the focus of the MCH programme in India right now is preventing maternal mortality and promoting institutional deliveries.

“To that end incentives are being given, the village health nurses are being trained register and enter pregnant women's data into a computerised data system. But with the statistics of TB among pregnant women and children, it is reasonable or doable to screen all pregnant women for symptoms.”

However, they probably won't be using the WHO symptom screen to rule out TB in order to put women on IPT.

“There is no policy for INH among pregnant women. I am not sure if it will be accepted especially with the concerns of medication among pregnant women, when they have no symptoms and are afraid of any reactions affecting the foetus. We need to do a study on feasibility and acceptability of INH among pregnant women who

do not have symptoms – and if they have not been exposed to TB? I am not sure [it would be appropriate].”

She said the doctors she’s met don’t seem to consider asking whether the patient has TB symptoms, rather, they are more “concerned with ordering chest X-rays, and inducing sputum.”

In some settings, where women rarely go into the antenatal services, there are concerns that there may not even be much of an opportunity to do screening, let alone complete the diagnostic process.

“In our study there was a lot of difficulty in performing TB screening at delivery and postpartum, said Dr Jyoti Mathad, Fellow at Weill Cornell Medical College, who is doing studies on latent TB diagnostics and pregnant women in India with Dr Gupta.

“For delivery, women are discharged pretty quickly if they had vaginal deliveries and so it may be difficult to perform any kind of intervention besides a questionnaire and have them still be there for the outcome of the intervention (e.g. X-ray results, sputum microscopy, TST, etc). For the postpartum period in India, many women stay at home or go to their mother’s home with their child for essentially the whole first year. We thought intervention at the immunisation clinic would be an opportunity for screening, but even that proved to be difficult. We are not sure if children are just getting immunised elsewhere such as local community clinics,” Mathad said.

However, Dr Thomas thinks symptom screening could work in the context of the programme to prevent parent-to-child transmission – by relying on the community-based elements that facilitate that programme.

“We just need to sensitise health providers and also community workers (village health nurses, ASHA, etc) during their visits to look out for TB symptoms and then be engaged in [making effective] referrals.”

She thinks using these community-based mechanisms would facilitate integration into the antenatal clinic. “Home based monitoring, even collecting sputum and linking the patient to care should not be a problem, considering we have the village health nurses and the ASHAs who are on the job for the MCH programme. It could also be incorporated into the school health programme to screen all children for TB on a regular basis. That would be a good start as they do it for anaemia, eye problems, for example,” she said.

Professor Anthony Harries of the International Union Against Tuberculosis and Lung Disease gave his personal opinion about what interventions should be prioritised in HIV-infected pregnant women who have a high risk of TB.

“The best way to prevent this TB risk is to offer HIV testing and counselling to all pregnant women for HIV, and for those who are HIV-positive to offer Option B+ = this is triple ART for life for the pregnant women regardless of the CD4 count. This intervention will work first to reduce HIV transmission to the foetus and baby, and to the sexual partner, and to subsequent babies: a lower risk of HIV means a lower risk of TB. This intervention will work secondly to reduce maternal morbidity and mortality, maternal risk of TB and maternal hepatitis B infection,” said Dr Harries.

He noted all the challenges involved in getting a diagnosis of TB in pregnant women – which does not mean that it shouldn’t be done; it is just that the process is already labour intensive.

“If the pregnant woman is negative to the symptom screen, we know this does not completely exclude TB – some may have asymptomatic, culture-positive TB, but Steve Lawn and others in South Africa have shown that many of these persons develop symptoms in the subsequent few months. Thus, repeated screening

is necessary if only to identify those who will develop symptoms later on. In the continuous asymptomatic pregnant woman, IPT is probably safe and should reduce further risk of TB, although the benefit of IPT is only in those with a positive tuberculin skin test. This conundrum may prevent health workers going ahead and starting IPT despite WHO guidelines that it is feasible and pragmatic to give IPT to all.”

“It’s not easy. However, ART works regardless of tuberculin skin status and I think this should be the priority. So, I would focus my TB prevention efforts around HIV counselling and testing. I would aggressively promote ART for HIV-positive pregnant women and for HIV-negative pregnant women I would demand vigilance for those who are coughing for > 2-3 weeks and investigate them accordingly for TB,” he concluded.

Dr Chewe Luo of UNICEF wrote to tell HATIP that she agreed with Professor Harries’ analysis. “We should be pragmatic and need to move forward with what he suggests. Many countries are moving forward with option B+ as the preferred regimen for PMTCT but are not thinking about TB symptom screening at follow-up visits. If we want to see how the different PMTCT regimen options impact TB we should look at this more systematically.”

Professor Ben Marais of University of Sydney Medical School stressed that making sure that women were screened for HIV and put on treatment to prevent HIV transmission may indeed be the most important anti-TB intervention.

“It is amazing how HIV testing is not standard of care for pregnant women in South East Asia (though I can only speak for Vietnam, Indonesia and Bangladesh). It seems as if there are many cultural and stigma barriers and most doctors I’ve spoken to say they will offer it only to mothers who confess to be sex workers or IV drug users. Even then access to care is very limited, with strict CD4 criteria applied by the few HIV treatment centres that are in existence. The same applies to TB patients.

“But as a paediatrician, I can only echo that paediatric HIV is a preventable disease and every infected child in essence represents a failure of the “system, though I realise there are many practical hurdles.”

There is certainly no doubt that getting pregnant women living with HIV on ART is the higher priority – it prevents TB **and** vertical transmission of HIV. But whether IPT can be given safely on top of it, depends upon the ability to continue monthly symptom screening and keeping a close eye out for side-effects that are more common in women – and perhaps to perform TSTs in settings where fewer women are latently infected with TB.

However, as Dr Thomas suggested, community-health workers or expert patients may be able to manage some of these activities outside the clinical setting, perhaps in the home, though they would need to be trained and have those services integrated with their other responsibilities. But as Dr Yassin’s study showed in Ethiopia showed, health extension workers can do a great job increasing case detection by introducing screening strategies (contact tracing) into their routine activities, and could also scale-up IPT delivery.

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