CHILDHOOD TUBERCULOSIS

A journalist's exploration

A collection of articles by Dr R Prasad
Science Editor, The Hindu &
Recipient, REACH Lilly MDR-TB Partnership
National Media Fellowship

CHILDHOOD TUBERCULOSIS

A journalist's exploration

Published in March 2014

TABLE OF CONTENTS

Foreword

Every day, more than 200 children under the age of 15 die from tuberculosis (TB) globally – a disease that is preventable and curable. The World Health Organization (WHO) estimates that six to 10 per cent of all TB cases are among this age group, but that the number could be even higher because many children are simply undiagnosed. TB is a disease that presents a grave health challenge to India's most vulnerable, especially, its children. Young children are at the greatest risk of severe disease, especially when they are in close contact with an adult with TB. Approximately 85,000 children are treated for various forms of TB every year, under the Revised National TB Control Program (RNTCP).[1] It is likely that an equally large number are treated in the private sector. Due to the fact that diagnosis is often difficult to confirm, the actual numbers of children suffering from or dying due to TB is unknown. Further, many child deaths due to underlying TB are probably misclassified as deaths due to pneumonia, HIV or malnutrition – all conditions that often co-exist with TB and that are difficult to differentiate.

*The Roadmap for Childhood TB: Toward Zero Death*s was released last year on October 1, 2013. The Roadmap is the first ever comprehensive plan to address a hidden epidemic of pediatric TB. The Roadmap was developed in close collaboration between WHO, STOP TB, UNICEF, IUATLD and other leading agencies in the fight against TB, including the National Institute for Research in Tuberculosis (ICMR), Chennai. *The Roadmap for Childhood TB: Towards Zero Deaths* includes ten actions that, if implemented, could help save thousands of children's lives, including children infected with both TB and HIV. The actions include training and fostering leadership among health workers, integrating TB into child health programs, actively seeking out children at risk and providing preventive therapy, and closing the funding gap for childhood TB.

India is committed to MDG Goal 4 and addressing TB in children will be an essential part of reaching the goal of a two-thirds reduction in under-five child deaths. As a first step towards this, we should improve diagnosis for TB among children by adopting new technologies, investigate hidden cases and register and treat them at the earliest. Contact tracing, screening for TB and provision of

1 Kumar, Ashok et al., "Updated National Guidelines for Pediatric Tuberculosis in India, 2012", Central TB Division, Journal of Indian Medical Institution, Available at: http://link.springer.com/article/10.1007/s13312-013-0085-1#page-2

preventive treatment for all children younger than six years in households with active TB is important. Increasing access to newer molecular diagnostics will help detect more cases. Guidelines for treatment have been recently revised in India and these must be implemented. WHO recently stated that children are as likely to have drug resistant TB as adults – doctors need to be aware of this and undertake appropriate investigations, in order to prescribe the right course of treatment. Above all, we should strengthen awareness and provide training to all types of health care providers to ensure prevention, control and treatment to bring down the rate of new infections.

The series of articles written by Dr R Prasad of *The Hindu* in 2013 cover all aspects of childhood TB and highlight important gaps and challenges in the management of this condition. The articles investigate various aspects of diagnosis, prevention and treatment and discuss recent advances in this field. He has managed to succinctly summarize the recent scientific literature on the subject in an easy-to-read format. He has also interviewed leading researchers and child TB specialists from different parts of the world and posted the interviews online, in addition to the written pieces. This kind of extensive and comprehensive coverage of childhood TB in mainstream media is quite unprecedented and served to raise awareness among the general public about this important, but neglected condition. I would like to express my gratitude and great appreciation for this remarkable collection of articles.

Every child is precious. I believe that we need to commit ourselves to eliminating deaths due to TB and reducing the number of new TB infections in children in India. On World TB day 2014, I appeal to all workers involved in child health to commit themselves to this goal.

SOUMYA SWAMINATHAN, MD
Director, National Institute for Research in Tuberculosis, Chennai

About The National Fellowship

The National Media Fellowship for Reporting on TB was awarded for the first time in 2013, and is intended for journalists to undertake research on tuberculosis-related issues at the national level. One senior journalist will receive the Fellowship every year. It is hoped that the work published by the Fellow will have policy-level implications for tuberculosis care and control in India.

A call for applications was issued in April 2013 and a total of 11 applications were received. For the first time, applicants also sent in a five-minute video statement, introducing themselves and explaining the TB-related issue they wished to explore if chosen as the National Fellow. From this, the REACH team shortlisted three applications for evaluation by an independent expert. The final round was a blind evaluation and all information pertaining to the identity of the applicants was removed from the document sent to the external evaluator.

All applicants were judged on their responses to three key questions:

a. What do you think is the most important TB-related issue in India? Why?
b. What do you like to research and investigate? Why do you think that it's a good story and must be told?
c. What is the best health-related story you have ever done, that you are most proud of? Why?

After a rigorous and competitive evaluation, Dr R Prasad, Science Editor of The Hindu was chosen as the first National Fellow.

It was also decided that the National Fellow would benefit from being mentored by a senior scientist through the Fellowship period. REACH therefore requested Dr V Kumaraswami, a senior scientist formerly associated with the National Institute for Research in Tuberculosis and currently an independent consultant, to mentor Dr Prasad. The Mentor was asked to offer the Fellow research guidance in:

a. Carrying out background research that will inform his stories;
b. Identifying specific story ideas based on the chosen theme;
c. Identifying the right experts to speak to;
d. Directing the Fellow towards any relevant resources.

The Fellowship period was from June-December 2013.

Mentor's Note

Dr. Prasad's collection of essays written as a National Fellow of the REACH Lilly MDR-TB Partnership Media Fellowship programme focus on multiple aspects of childhood tuberculosis (TB) – a neglected area of TB diagnosis, management and for that matter tuberculosis control programmes too.

His set of essays while pointing out the current inadequacies in diagnosis, management and lack of attention to the problem of childhood TB globally highlights the seriousness of the problem that confronts the India programme. He identifies important challenges in determining the burden of the illness that are not merely due to the granularity of the diagnostic tools but the absence of unambiguous guidelines. Similarly, his profile of childhood multi drug resistant tuberculosis (MDR-TB) draws attention to the magnitude of a largely unrecognized and hidden threat and the need to urgently address this important issue in both clinical and programme settings. Drawing extensively from epidemiological, microbiological and clinical studies he forcefully argues for action to prevent the problem of MDR-TB spiralling out of control.

Dr. Prasad laces his stories with crisp summaries of the latest developments, even-handedly presenting both sides of arguments besides providing readers exciting sneak previews of what is in the offing in clinics, laboratories and field units. Though his reach is international, Dr. Prasad painstakingly highlights facets that are unique to our national situation providing important recent Indian references and discussions with leading national researchers in childhood tuberculosis. His ability to extract key messages from the mass of publications and package them into tight spaces dictated by editorial mandates provides readers a rich reading experience.

Another unique feature of this set of stories (and a trademark of Dr. Prasad's writings) is the extensive use of interviews with opinion makers and global leaders in the field of tuberculosis to provide readers the absolute latest and authentic information. Lastly, his well-established skills in translating complex technical terminologies into simple, readable and comprehensible language ensure authoritative synopses of critical themes in childhood tuberculosis. While each story is a "stand-alone" piece this compendium of essays, I am sure, will for a long time serve as a useful reference collection for researchers in the management and control of childhood tuberculosis.

This note cannot be complete without mentioning the joy of mentoring Dr. Prasad as he crafted these stories for his Fellowship. His insatiable appetite for "references" and exhaustive discussions to identify core issues kept us fully engaged during the Fellowship. Throughout this period, I admired his ability to ferret out references, identify sources scattered all over the world and his twin obsessions of checking every fact and ensuring proper acknowledgements were in place even as he met his deadlines professionally. Finally, I am sure you will enjoy this collection of stories as much as I did reading them and more importantly watching them taking shape in Dr. Prasad's skilful hands.

Dr. V. KUMARASWAMI,
Scientist G (Retd)
National Institute for Research in Tuberculosis
(Indian Council of Medical Research)

SERIES ON CHILDHOOD TB BY DR. R. PRASAD

Programme to prevent TB in children neglected

3 October 2013

Health workers are unaware of contact screening and preventive therapy in children below five years in households with newly diagnosed active TB patients

The Revised National TB Control Programme (RNTCP) that came into being in 1997 has to its credit some enviable accomplishments. For instance, it achieved country-wide coverage in March 2006 and achieved 86 per cent treatment success rate in recent years. More than 15,000 suspects are examined for the disease every day and about 3,500 patients are started on treatment. And to its credit, for the very first time in 2007, RNTCP achieved the global target of 70 per cent case detection (53 cases per 100,000 population per year).

Despite these impressive achievements, India has the highest TB burden in the world — 3.5 million active TB cases. The number of new active TB cases detected every year is over two million; it was 2.2 million in 2011. And the disease kills two people every three minutes. Incidentally, the incidence and prevalence figures are not a true indicator of the ground reality — the number of patients treated by the private sector is not known.

But why is India continuing to record the most number of TB patients in the world every year? A closer inspection reveals that the programme is far from perfect and may require a thorough re-examination of both design and implementation. The massive country-wide drug stock-out crisis that played out recently is, but, just one of the malaises that the programme faces.

To start with, is the programme identifying and treating all the patients? The national TB control programme (RNTCP) uses a passive system for diagnosing TB patients. The design of the system is such that it waits for patients to walk into the centres to get tested. It is well known that patients walk into these centres quite late in the day. And in the process, they end up infecting many people. That a single active TB patient who is not on treatment is capable of infecting 10 or more people in a year shows how badly our RNTCP programme is in need of a reorientation. It has to necessarily shift gears and seriously consider changing its strategy from the current passive case-detection system to an active mode of detecting cases.

How far we are from even contemplating a radical change in our case-detection approach can be assessed by looking at how the WHO-recommended, RNTCP-approved contact screening of children below five years in households where an adult has been recently diagnosed with active pulmonary TB (sputum smear positive) is carried out. Children below five years from such households are most vulnerable to getting infected and probably developing active TB.

As a preamble, one has to only examine the differences between the WHO guidelines and the RNTCP guidelines to understand the extent of disconnect. While the WHO recommends contact screening in children below five years, RNTCP has it as below six years!

Screening children would help in diagnosing those who have already developed the disease (active TB) as well as those who have been infected but yet to develop the disease. While treatment for those who have developed the disease would be through the routine multi-drug regimen, children who have been infected but have not yet developed the disease are ideal candidates for a preventive therapy.

Children who are infected but have not yet developed the disease may not have symptoms like history of cough and/or fever and/or weight loss and/or weight gain. The use of a single drug — isoniazid — daily at 10 mg/kg for six months would "greatly reduce the likelihood of developing TB during childhood," the WHO guidelines note.

According to WHO, the risk of developing the disease is "much greater" in infants and those below five years who have been infected than those above the age of five. In infected children below five years, if the disease does develop, it usually does so "within two years of infection." But in the case of infants, the disease can set in within a matter of 6-8 weeks of infection.

"Children below six years have more chances of developing active TB after exposure and also more chances of developing severe disease (disseminated TB, meningitis)," Dr. Soumya Swaminathan, Director of the Chennai-based National Institute for Research in Tuberculosis (formerly TRC) noted in her email to this Correspondent.

A 15-year follow-up study of household members in a rural community in south India found that unlike adults, children in the age group 0-4 years had seven times higher risk of developing infection when an adult had smear positive TB.

Hence, contact screening of young children combined with chemoprophylaxis (preventive drug therapy) would go a long way in breaking the TB transmission cycle and reducing the case load by preventing the number of people who would become TB patients.

And the best part is that contact screening does not require much additional resources and can be implemented through the existing system if compliance is ensured through adequate monitoring and supervision.

However, a few studies undertaken in India provide ample evidence that routine contact screening of children below five years is sub-optimal in operation and is not carried out as per guidelines. A 2009 study carried out in four TB units (two in Chennai city and two in rural Vellore district) by V.V. Banu Rekha *et. al.,* of NIRT, Chennai, provides some insights into the state of contact screening of children below six years.

Only 14 per cent of children aged 0-14 years were screened for TB and only 19 per cent (16 of 84 children) of children below six years were initiated on preventive therapy. There was no difference between urban and rural areas in terms of preventive therapy initiation.

Even the awareness level among health care workers (HCW) was sub-optimal. "Poor awareness," is how Dr. Swaminathan describes the awareness level among HCWs. "Two studies — in Tamil Nadu and Andhra Pradesh — have shown very low uptake of screening and chemoprophylaxis. Other district TB officers also report similar status," Dr. Swaminathan noted.

Worse, health-care workers in rural areas were themselves less aware of contact screening and preventive therapy in young children. Awareness level among HCWs that immediate family members are more susceptible to infection was "significantly lower" in rural areas. Only one-third of parents in rural areas were aware of contact screening and the need for preventive therapy in children below five years. "It has not been prioritised by RNTCP. No reporting of this activity is required," she said explaining the sorry state of affairs.

Shockingly, the DOTS TB treatment card of the adult (index patient) has no provision for documenting the details of contact screening, preventive therapy, follow-up and treatment completion.

In a follow-up study conducted in the same areas between October 2009 and August 2011 by the team led by Dr. Swaminathan, all the health workers — medical officers to DOTS workers — were provided basic training on all aspects of contact screening and preventive therapy. And a separate preventive therapy register and card were also introduced in line with the WHO recommendations.

A 2013 study reveals that the results were quite dramatic. The health workers were able to identify 82 per cent of child contacts. Sixty-one per cent (53 children below six years) were screened for TB disease and put on preventive treatment. Of the 53 children, 74 per cent (39 children) completed the treatment. This is a huge improvement compared to just 19 per cent children who were even initiated on treatment in 2008.

"Parents need counselling and explanation; they do accept if told properly," is how Dr. Swaminathan explains how receptive parents are in starting preventive treatment in young children.

(The article is the first of a series to be written on "Contact screening of children below six years in households with newly diagnosed active TB patients.")

Online at http://www.thehindu.com/sci-tech/health/programme-to-prevent-tb-in-children-neglected/article5193288.ece

Don't ignore the children

Editorial, 10 October 2013

After years of neglect, childhood tuberculosis — which accounts for over six per cent of the global TB burden — is finally getting due attention. WHO recently published its first-ever targeted road map outlining the steps needed to move towards zero childhood TB deaths. The report comes close on the heels of the organisation including for the first time the estimates of the global TB burden in children below 15 years in its 2012 global tuberculosis report. Last year also saw childhood TB getting special focus in the World TB Day theme. Though over half-a-million new cases are reported every year from across the world in those who are HIV negative, the actual TB burden must be much higher. The reasons are pretty obvious. Most of what is reported are only the cases of sputum smear-positive pulmonary TB. However, sputum smear-negative disease is most frequent even in pulmonary TB. Most often, all cases of extra-pulmonary TB go unreported even though this category of TB accounts for "approximately 20-30 per cent." Unlike adolescents, children under five may not produce sputum for examination. In the absence of sputum samples, there is no highly reliable and easily usable diagnostic tool to confirm the disease, especially in developing countries where TB is endemic and malnourishment is high. Hence, developing reliable and affordable tests has become a great research priority.

As a result, high burden countries like India, where 10-20 per cent of all TB occurs in children, need to find alternative strategies to target vulnerable children who are more prone to becoming infected and diseased. Implementing the WHO's close contact screening of children under five from households where an adult has been newly diagnosed with sputum smear-positive pulmonary TB would go a long way in achieving the desired results. Adults would have spread the infection to children in the same household before seeking treatment. A clinical examination of children combined with laboratory confirmation in suspicious cases would go a long way in revealing their TB status. This approach has twin advantages. While the diseased would be put on treatment without delay, the asymptomatic children would end up getting a preventive therapy. A prophylactic treatment

using a single drug — isoniazid — once daily for six months would cut down the number of young ones who may become diseased. It would reduce the TB load and the mortality rate. Yet, in India's TB control programme, contact screening is way down in the priority list. There are challenges, but training health workers and adopting minor changes to the existing system alone can yield good results. What's the government waiting for?

Online at http://www.thehindu.com/opinion/editorial/dont-ignore-the-children/article5218376.ece

TB: how many young children are wrongly diagnosed as disease-free?

16 October 2013

The results of a study published in PLoS ONE journal are one more reminder of the real challenge in diagnosing TB in young children

India's Revised National TB Control Programme (RNTCP) estimates that children comprise about 12 per cent of the total TB caseload in the country. But in all probability, 12 per cent may be an underestimation of the actual contribution.

A July 2011 study undertaken in Krishna district of Andhra Pradesh on 116 children below six years from 172 households with an adult who was recently diagnosed with sputum smear-positive pulmonary TB did not find even one child with TB disease!

The results of the study published in *PLoS ONE* journal is one more reminder of the real challenge in diagnosing TB disease in young children.

"The real reason for not being able to diagnose diseased children could be the non-availability of diagnostic tools like tuberculin for tuberculin skin test (TST) and X-ray facilities in peripheral health facilities or simply that such tests were never ever conducted. Or, health-care workers did not possess sufficient skills/knowledge to diagnose TB in children," a TB expert commented.

Missing out timely detection can have grave consequences. Children under five years have a greater risk compared to older children. According to WHO, infants have a "much greater" risk of developing the disease. And if those under five can progress to the diseased state "within two years of infection," it is just 6-8 weeks in the case of infants. Unlike older children and adults, children in this age group have greater chances of developing severe forms of the disease — disseminated TB and meningitis.

While those with active TB can be treated with multi-drug regimen, the asymptomatic children who have been infected but have not yet developed the disease can be given prophylactic treatment with isoniazid drug once daily for six months. This will prevent them from progressing from the infected stage to the diseased state.

But it's a fact that diagnosing TB in children under five years is a challenging task. As WHO's "Roadmap for childhood Tuberculosis," has pointed out, there are no "effective diagnostic tests." Unexplained loss of more than five per cent of the highest weight recorded in the past three months, or fever and/or cough for more than two weeks make TB more likely, especially when the child has been in contact with an infectious pulmonary TB patient in the same household. Yet, diagnosis cannot be made on the basis of clinical symptoms alone.

The first layer of complexity comes in the form of young children not being able to produce sputum. This is largely because their cough reflex is not fully developed; they tend to swallow the sputum. Sputum is the most basic and important sample for diagnosing pulmonary TB disease.

The next layer of complexity is that even when a sputum sample does become available, it may contain only a few TB bacteria. "Children tend to have TB with a smaller bacterial load. So, it is hard to see a few bacteria under microscopy," Dr. Madhukar Pai, Associate Professor, McGill University, Montreal noted in an email to this Correspondent. "So, paediatric TB is called 'pauci-bacillary disease' (fewer bacilli)."

"TB diagnostics have the following lower limits of detection" 10-100 colony forming units (CFU)/ml for culture and much higher for smear microscopy, Dr. Anne Detjen, Coordinator, TREAT TB Diagnostic Tools Initiative at the International Union Against Tuberculosis and Lung Disease said in her email to this Correspondent.

The sensitivity of diagnosis – by smear microscopy and culture – depends on the amount of bacteria present in the sample. "The sensitivity the of culture, depending on the age, disease severity and bacterial burden is 20-60 per cent, depending on what data you look for. For smear microscopy, it is 15-20 per cent," Dr. Detjen noted.

But even in the absence of sputum sample for micro-bacterial confirmation, much information can be gained from tuberculin skin test (TST) and X-ray results.

But considering that nearly 40 per cent of Indians are infected with TB, and TST can only confirm infection, how useful is it for those under five years? "It is definitely helpful. A positive TST always means evidence of TB infection, regardless of age. The significance is more in young kids because they have no

reason for being infected and suggests that some adult in their family has active TB," Dr. Pai underlined.

A positive TST gains importance considering that the targeted group is children under five years from households where an adult has been recently diagnosed with sputum smear-positive pulmonary TB.

Though all infected individuals would test positive for tuberculin skin test (TST), the sensitivity may get compromised in malnourished children. Though infected, TST can be negative in infants because their immune system is not mature. This is where chest X-rays come in handy.

"Positive chest X-rays (e.g. enlarged lymph nodes inside the chest) are also indicative of TB. But X-rays can be abnormal due to many diseases (e.g. bacterial or viral pneumonia, asthma)," Dr. Pai explained.

"If X-rays are abnormal, that pushes the diagnosis towards active TB, not latent TB. But X-ray results need to be used along with other tests. A positive TST and suggestive X-ray, plus history of close contact with a TB case in the house, and symptoms (e.g. not gaining weight, fever) are most likely to point to TB diagnosis."

The recently updated national guidelines on paediatric tuberculosis lay great emphasis on bacteriological confirmation using sputum samples even when chest X-ray is suggestive and TST is positive, and the child has received a complete course of antibiotic treatment.

"In cases where sputum is not available for examination or sputum microscopy fails to demonstrate AFB, alternative specimens (gastric lavage, induced sputum, broncho-alveolar lavage) should be collected, depending upon the feasibility, under the supervision of a paediatrician," notes the updated national guidelines for paediatric tuberculosis in India, 2012, published in the *Indian Pediatrics* journal on March 16, 2013.

Facilities to collect sputum using the two different lavage methods from those under five years are available only in the tertiary centres in the urban areas. So what percentage of children from the rural areas would end up getting correctly diagnosed and treated? Incidentally, RNTCP aims to achieve "universal access" to quality assured TB diagnosis and treatment during 2012-2017.

That's a very tall order considering that even tuberculin is often not available in peripheral health facilities! "Non-availability of a standardised tuberculin in the country was identified as a cause of great concern," notes the National Consultation on diagnosis and treatment of paediatric tuberculosis conducted early last year.

So how many children are being wrongly diagnosed as disease-free as seen in the June 2011 *PLoS ONE*study?

Online at http://www.thehindu.com/sci-tech/health/tb-how-many-young-children-are-wrongly-diagnosed-as-diseasefree/article5240319.ece

Paediatric TB: should Xpert molecular test replace smear microscopy?

31 October 2013

Xpert MTB/RIF rapid molecular diagnostic test is certainly superior to smear microscopy

Unlike adults, children under five years of age are particularly vulnerable to getting infected with TB and may develop the disease very soon after infection. This is all the more true in the case of those from households where an adult has been recently diagnosed with sputum smear positive active pulmonary TB.

India's Revised National TB Control Programme (RNTCP) estimates that children account for about 12 per cent of the total TB caseload in the country. As WHO had pointed out, the estimated caseload in India, like in other countries, is a gross underestimation.

The main reason is that correct diagnosis of pulmonary TB infection and disease in children, especially in those under five years, is a big challenge. For instance, unlike adults, young children are unable to produce sputum — the most vital and basic sample to confirm infection/disease.

As a rule, only very few TB bacilli are present in the sputum sample of young children. This is particularly true in the case of children who are less ill. Other diagnostic methods — tuberculin skin test and chest X-ray — have their own limitations and challenges. And clinical symptoms can only serve as a useful indicator but cannot be used in isolation as children exhibit non-specific symptoms.

First diagnostic tool

Smear microscopy is the first diagnostic tool used to microbiologically confirm TB infection/disease. Unfortunately, smear microscopy performs poorly in children, especially in those under five years.

The sensitivity of microscopy — depending on the child's age, disease severity and mycobacterial burden — is about 15-20 per cent. Hence, even many active TB cases show up as sputum smear negative (meaning that the child is free of disease).

Culture is the gold standard in diagnosing TB. "[But] culture is not infallible – it has sensitivity limitations and takes time [several weeks] to yield a clinically useful result," a November 5, 2012 paper published online in *The Lancet* points out. "Where optimum culture facilities are available, confirmation is delayed and the combination of sputum smear and culture tests still misses many cases of childhood tuberculosis."

"The sensitivity of culture varies between 20 per cent and 60 per cent, depending on what you look at," Dr. Anne Detjen, Technical Consultant, The Union North America Office, childhood TB/child lung health, said in an email to this Correspondent.

For these reasons, researchers are looking for an alternative test that is more sensitive than smear microscopy and takes less time than culture to yield useful results. And the one that is currently available is Xpert MTB/RIF — a rapid molecular test. In 2010, WHO endorsed Xpert for rapid diagnosis of drug-sensitive and multi-drug resistant TB. Several studies have been done to test its usefulness in diagnosing TB in children and the results appear encouraging.

A WHO policy update released a few days ago on the use of Xpert in adults and children with pulmonary and extrapulmonary TB clearly states that the "overall pooled sensitivity of Xpert MTB/RIF against culture in children presumed to have TB was 66 per cent in 10 studies where expectorated sputum (ES) or induced sputum (IS) was used and 66 per cent in seven studies where gastric lavage aspirates (GLA) were used.

Pooled specificity of Xpert MTB/RIF against culture as the reference standard was over 98 per cent."

In the case of culture-negative specimens, the pooled sensitivity against clinical TB as the reference was very low at four per cent for ES or IS and 15 per cent for GLA.

"It is likely that the apparent poor performance of Xpert was the result of a clinical TB reference standard that lacked specificity," the policy update notes.

Xpert's sensitivity

Xpert's sensitivity in ES/IS among children with smear-negative results ranged

from 25 per cent to 86 per cent. But in the case of smear-positive results, the pooled sensitivity of Xpert in either ES or IS was 96 per cent. "The pooled sensitivity estimate in smear-positive children was 96 per cent and 55 per cent in smear-negative children. The findings were similar for Xpert in GLA, with an overall sensitivity of 95 per cent among smear-positive and 62 per cent among smear-negative children," the update states.

"Xpert MTB/RIF may be used rather than conventional microscopy and culture as the initial diagnostic test in all children presumed to have TB (conditional recommendation acknowledging resource implications, very low-quality evidence)," states the update.

Systematic review

"We have indeed performed a systematic review and meta-analysis of available data on Xpert MTB/RIF in children that contributed to the revised WHO policy guidance," Dr. Detjen said.

"The Xpert MTB/RIF Policy Guidance Update was reviewed by the WHO Guidelines Review Committee (GRC)," Dr. Christopher Gilpin, Scientist, Global TB programme, WHO, Geneva, said in an email to this Correspondent.

"The systematic reviews included studies with children below five years and stratified pooled sensitivity and specificity estimates for Xpert MTB/RIF (in expectorated and induced sputum) were determined for children aged 0-4 and 5-15 years. Xpert MTB/RIF in gastric lavage aspirates estimated accuracy for 0-4 year age group only," Dr. Gilpin stated.

"Xpert performs clearly superiorly to smear microscopy but is not good in children that are culture negative," Dr. Detjen noted.

She also pointed out other positive outcomes that would come once Xpert is made widely available. "It will increase the number of confirmed TB cases and can detect drug resistance. Health-care workers may actually start taking sputum specimens from children since the new tool is certainly more promising than microscopy. Currently, specimens are often not even taken in places where the only test that can be done is smear microscopy," she pointed out.

Fewer TB bacilli needed

The reason why Xpert performs much better than microscopy is because fewer TB bacilli are required to be present in the sputum sample. If Xpert's lower limit of detection is 131 colony forming units (CFU)/ml, and culture's is 10-100 CFU/ml, it is much higher in the case of smear microscopy.

But Xpert is very unlikely to become available in India for contact screening of children. There are currently 32 Xpert diagnostic machines and the government is in the process of procuring 300 more. But these are only for testing drug-resistant TB.

Online at http://www.thehindu.com/sci-tech/health/paediatric-tb-should-xpert-molecular-test-replace-smear-microscopy/article5290818.ece

Missing TB cases

Editorial, 7 November 2013

Although tuberculosis killed 1.3 million people across the globe in 2012 and nearly 8.6 million developed the disease, the world is on track to reach some important targets of the 2015 Millennium Development Goals. According to WHO's global tuberculosis report 2013 released recently, the incidence rate has been falling, and the mortality rate since 1990 has been reduced by 45 per cent. Yet, at 37 per cent, the reduction in prevalence during the same period is far below the half-way goal. In all likelihood, India may be responsible for the slow reduction in global TB prevalence. At 2.8 million (26 per cent), the country has the highest caseload. But the true incidence and prevalence would be higher if those approaching the private sector and remain unreported are also taken into account. The government's landmark decision last year to make TB a notifiable disease by the public and private sectors was meant to correct this anomaly. If implemented in earnest, every case detected would get reported and the actual extent of the disease will become known. Unfortunately, very little has been done to ensure that the private sector complies with the requirement. The government reluctantly made TB a notifiable disease, and has shown little interest in implementing the order.

WHO has taken special note of these missed out people. Globally, three million people who developed TB last year have been missed out by the national notification systems, it notes. If detecting and notifying all adult TB cases is found wanting in India, it is far worse in the case of children below 15 years. WHO has estimated that TB incidence among children is over half a million across the world. But its recently released road map for childhood tuberculosis clearly indicated that the actual burden would be higher. WHO's 2006 guidance on TB management in children indicated that about one million TB cases the world over occur in children. Though children can contract TB at any age, those under five are especially vulnerable, particularly those from households where an adult has been recently diagnosed with active pulmonary TB. Young children are more susceptible to getting infected and face an increased risk of progression to disease; they also acquire the more severe forms of the disease. It is for these reasons that WHO had recommended contact tracing. Though India's Revised National TB Control Programme (RNTCP) has also approved contact tracing of young children from such families, its implementation is at best sub-optimal. Thus,

while RNTCP estimates children with TB to be 10.2 per cent of the total TB caseload, only seven per cent of the cases were registered in 2011.

Online at http://www.thehindu.com/opinion/editorial/missing-tb-cases/article5322489.ece

TB: 'There is a clearly higher risk of mortality in children of 0-4 years'

8 November 2013

With 8.6 million people across the world developing tuberculosis in 2012 and nearly 1.3 million succumbing to the disease, and with the number of people with multi-drug resistant TB (MDR-TB) and extremely-drug resistant TB (XDR-TB) increasing every year, the focus has been on increasing case-detection and improving treatment rates.

In the process, no significant measures have been undertaken to prevent the disease. This is true in the case of developing countries, particularly in high-burden countries, including India.

This is despite the fact that we know one third of the global population (and nearly 40 per cent of the Indian population) is estimated to be latently infected with TB. Since 5-20 per cent of these latently infected people develop the disease at some point in their lifetime, the infected people serve as a huge reservoir.

One more glaring blind spot in our war against TB has been the near-neglect of children. This is despite ample evidence that many children who are infected when young become diseased as they age, even if they do not become diseased soon after infection.

But the focus is now shifting, and childhood TB is slowly getting its due attention. For the last two years, WHO in its annual report has been including the estimates of global TB burden in children below 15 years. And for the first time ever, WHO recently came up with a Roadmap for Childhood Tuberculosis. In 2010, WHO had come out with Rapid Advice for Treatment of Tuberculosis in Children. The global health body had earlier come out with guidelines for implementing contact tracing of children belonging to the most vulnerable group — under five years from families where an adult had been diagnosed with active pulmonary TB.

But countries, especially the developing ones, have shown little inclination in undertaking contact tracing despite knowing that many of the infected children become diseased in a matter of weeks and the mortality rate is also significantly high.

In a long-winding interview over email, **Dr Greg Fox**, *Post-doctoral Research Fellow at McGill University, Montreal explains to* **R. Prasad** *why and how important contact tracing of children aged under five is to win the war against TB.*

How high are the chances of children below five years becoming diseased in households where a person has been recently diagnosed with active pulmonary TB?

See our meta-analysis (2013 paper in the European Respiratory Journal by Gregory J. Fox et al.,) with data for children for the rates of disease and infection in children. Our study found: "In 95 studies from low- and middle-income settings, the prevalence of active TB in all contacts was 3.1 per cent, microbiologically proven TB was 1.2 per cent, and latent TB infection was 51.5 per cent."

What is the minimum time for a child below five years to get infected with TB when an adult in the household with active pulmonary TB is yet to start treatment?

If you define infection as the time from exposure to tuberculin skin test (TST) positivity, then there can be a delay of 8-12 weeks before TST becomes positive.

Compared with an adult, how vulnerable are children in this age group to TB infection when an adult in the household who is infected with active pulmonary TB is yet to start treatment?

In terms of disease, young children under five have a higher risk of disease than older children. A 2010 paper by Brooks-Pollock in PLoS ONE journal shows the age distribution of mortality in Ukraine. Young children are therefore very susceptible, and probably more susceptible than younger adults.

The susceptibility to infection is a different question. It is difficult to say, since the lifetime cumulative incidence of TST positivity increases over the lifetime. By the time a person is in the 30s, in a high prevalence country, he/she will usually have a high prevalence of latent TB infection (LTBI). The incremental effect of additional life-time exposure in this group [under five years of age] is small.

Aren't children who have taken BCG vaccine on time naturally protected against TB, particularly in the first few years after vaccination?

BCG vaccine does not prevent primary TB infection. A 2010 paper in Clinical Infectious Diseases journal by Soumya Swaminathan and Banu Rekha states: "BCG vaccine has been shown to be protective against disseminated forms of TB in young children, with a summary protective estimate of 73 per cent (range,

67 per cent –79 per cent) against TB meningitis and 77 per cent (range, 58 per cent–87 per cent) against miliary disease."

In a TB-endemic setting like India, will children not be at risk of getting infected with TB from contacts outside the household?

Yes. Community transmission is probably the bulk of transmission in high prevalence settings. The evidence of the proportion of transmission that occurs in the household is limited to a few small studies using molecular epidemiology in the context of household contact investigation. For example, a January 17, 2004 paper by Suzanne Verver in The Lancet shows this. The evidence is limited in India, to my knowledge.

What is the rationale for having a cut-off age of five years? Will children older than five years not gain from preventive therapy?

The WHO guidelines recommend that children under five years (i.e. 0-4 years) should be a priority for contact investigation. As in studies such as those by Brooks-Pollard, there is a clearly higher risk of mortality in children of 0-4 years. Hence this is a priority for screening. Of course, there is still benefit for all other ages — however the ages 5-18 have a substantially lower rate of mortality.

How effective is isoniazid as a prophylactic? For how long does the protective effect last?

The sustained effect is primarily related to the reduction in transmission that occurs as a result of the latent TB infection (LTBI) treatment in the community, but depends upon factors including treatment completion rates, the uptake of LTBI therapy in the community etc.

Is the six-month treatment a standard treatment regimen across the world or are there different timeframes depending on how endemic TB is in a region?

Six months is inferior to 12 months. Many countries use nine months. It also depends upon the proportion of treatment that is actually taken (completion of >80 per cent of a 12-month course results in a 90 per cent reduction, compared to a 60 per cent overall observed effect in real life setting.

Does the isoniazid drug cause any side-effects in children, especially those who are one year and two years of age?

The risk of complications of isoniazid is lower in younger children, but nonetheless they do occur.

How accurately is the dosage of 10 mg per kg calculated in reality? Are there any problems when the dosage is more?

This depends on how accurately the child is weighed. The theoretical risk of drug induced liver injury increases with dose, which has been shown in animal models.

[WHO "Rapid advice for TB treatment in children" for current dosing guidelines states: "Infants (aged 0–3 months) with suspected or confirmed pulmonary tuberculosis should be promptly treated with the standard treatment regimens. The treatment may require adjustment of dosages to reconcile the effect of age and possible toxicity in young infants. The decision to adjust dosages should be taken by a clinician experienced in managing paediatric tuberculosis."]

How prudent is it to expose young children, especially one-year-old and two-year-old children, to X-rays when they don't even have the disease?

Child contacts with suspected TB (on the basis of symptoms) should have a chest X-ray. The risk of a single chest X-ray is minimal. The advantage of diagnosing potentially life-threatening TB is substantial. Given the high risk of TB disease in child contacts, the risk-benefit calculus strongly favours an X-ray. In child contacts, where available, chest X-ray is a useful screening test for active TB (note that TST is often not available in many settings). However, symptom screening alone has been shown to be effective if this is all that is available.

How aware are health-care workers and doctors of the need for undertaking contact screening of children aged under five in high-burden countries?

Contact investigation is not frequently undertaken. A 2011 paper in the International Journal of Tuberculosis and Lung Diseases by T.J. Hwang et al., states: "Contact investigation contributes to improving early case detection of

tuberculosis (TB). However, its implementation in low-income, high TB-burden countries remains limited."

As a norm, are children in the developing countries on prophylactic treatment regularly followed-up for any symptoms of TB disease? How frequent are such follow-ups?

Follow-up depends on the setting. Generally, most programmes have single screening interventions near the time of exposure. The WHO recommends only a single-screening intervention.

On average what is the default rate? Which developing country has the highest adherence rate to drug treatment (six months)?

A 2012 paper in Cochrane Database Systems Review has some good examples. In countries like Canada, the U.S. and Australia, treatment completion rates can be very good because there is close supervision and regular follow-up during the entire treatment.

When children with latent TB default after some time, do they become more vulnerable to developing resistance to isoniazid?

The risk of developing isoniazid resistance is very low and not clinically significant in the treatment of children with latent TB infection where active disease is excluded. If a child stops taking isoniazid, then there is no selective pressure to develop isoniazid resistance again. If they repeatedly stop and start isoniazid during active disease, then yes, this would predispose them to increased risk — but that is why active disease should be excluded (clinically and/or radiologically).

On average, what is the success rate of putting children on prophylactic treatment for the number of children contacted, both in the developing and developed countries?

There is little information on this as no data is routinely collected by different national TB programmes. A 2012 paper in BMC Research Notes by Merrin E. Rutherford et al., is a good illustration of how this can be done (in Indonesia, they found compliance was only about 25 per cent).

How much do poor nutrition, small dwellings and crowded settings facilitate children developing the disease when an adult in the household has been recently diagnosed with active pulmonary TB?

The risk of infection and disease will vary depending upon the local epidemiology. If the prevalence of active disease is higher, then the risk of TB would also be higher.

The risk factors you identify (poor nutrition, overcrowding) are certainly recognised to be associated with increased incidence of TB. Social determinants of disease are important. An April 2011 paper in the American Journal of Public Health is informative.

How cost effective is contact screening of children and putting them on treatment?

Cost-effectiveness of treating latent TB infection varies substantially depending upon local factors. One study in Canada (2008 paper in Value Health journal) is informative.

Is there a difference in children easily developing latent/active TB when an adult is infected either with drug-resistant TB or drug-sensitive TB?

The rate of infection in contacts of MDR-TB and drug susceptible tuberculosis appears to be similar (see September 24, 2013 paper in Clinical Infectious Diseases journal by Shah et al.,). However, there are arguments about the fitness cost of drug resistance (see 2009 paper by Borrell et al). However, as MDR-TB typically has a prolonged period of infectiousness, relating to delayed diagnosis, probably overall contacts have a higher risk of developing infection and disease.

Do you think mass awareness campaign like what was done in the case of HIV/AIDS would help in increasing the awareness level of contact screening in the community and increase/change the health-seeking attitude of people?

Mass awareness campaigns need to be carefully designed, or they can reinforce the stigma associated with TB. Generally speaking, childhood TB contact investigation should be seen as a part of the broader approach to TB control — with the message that there can be benefit to the children from being assessed. World TB

Day often provides a time for countries to focus upon TB in high-risk groups, such as child contacts, although I cannot quantify what proportion of countries make children a focus. Certainly the WHO Roadmap for Childhood TB is a part of an attempt to raise awareness of this issue. It is as much a challenge to educate policy makers and TB services about childhood TB as it is to educate patients, their contacts and the general public.

Online at http://www.thehindu.com/sci-tech/health/policy-and-issues/tb-there-is-a-clearly-higher-risk-of-mortality-in-children-of-04-years/article5329790.ece

'Age has a significant effect on the immune system in childhood TB'

14 November 2013

Prof Peter R. Donald, *Emeritus Professor in the Department of Paediatrics and Child Health of the Faculty of Health Sciences at Stellenbosch University, South Africa was awarded the highest honour, the Union Medal, of the International Union Against Tuberculosis and Lung Disease, at the 2010 General Assembly in Berlin.*

This medal is given to people who have made outstanding contributions to tuberculosis and non-tuberculosis lung disease. Prof. Donald was recognised for his contributions to child lung health and especially childhood tuberculosis.

Prof. Donald explained to **R. Prasad** *by email why childhood TB is a family disease in those aged less than five years and not every child in the same age band gets infected.*

Excerpts

You note that children in the 0-1 age group ran the highest risk of dying followed by children aged 1-3 years when TB medicines were not available. How can you be sure that death was caused by TB?

The clinicians working at that time had available chest radiography, tuberculin skin testing and cultures for Mycobacterium tuberculosis. This in addition to their clinical findings would have enabled them to make a fairly accurate diagnosis of TB.

Considering that children older than five years have greater contact with the community, can childhood TB still be considered as a family disease?

The older the child, the less likely it becomes that the family is the source of the tuberculosis. However, in young children, who have a very high incidence of disease after infection, it is very important to look for a history of contact in the family or household who will most often turn out to be the source of infection.

Your 2006 paper indicates that unlike the 0-1 age group, the 4-5 age group is less vulnerable. But the latter age group has greater contact outside the family and hence have greater chances of getting infected. Could you explain?

Tuberculosis infection in older children 4-10 years is much less likely to be followed by disease than in the younger children or adolescents.

Unlike smear-negative pulmonary TB, why is the risk of transmission considered to be higher when an adult has sputum smear-positive pulmonary TB?

This is most likely due to the numbers of bacilli in the sputum when it is smear-positive. Smear negative sputum may contain 10^3 bacilli while smear positive sputum may contain 10^5 bacilli.

Are there studies to show that young children are at greater risk when the mother rather than the father has active pulmonary TB?

There is little doubt about this and many studies confirm the risk of infection and subsequent disease in young close contacts

Why is a breastfeeding infant considered to be at higher risk of getting infected and progressing to a diseased state when the mother has smear-positive pulmonary TB?

I think this probably has to do with the closeness of contact with the mother as much as anything else

Not every child less than five years of age gets infected when exposed to an adult in the same household with sputum smear-positive pulmonary TB. What is the reason for this?

There is no sound answer to this; it may be chance or it may be genetics, but we do not know at present.

Is it true that in some cases primary childhood TB can "cure" itself or convert from active TB into a state of latent infection even without treatment? What's the reason for this?

Yes, it is true. Even in adult-type TB, many adults survived pulmonary tuberculosis before treatment was available. If an adult had smear positive tuberculosis before treatment was available approximately 50 per cent of individuals died, 25 per cent recovered completely and 25 per cent became chronic cases.

If that is the case, is it prudent to put every infected child aged under five years on prophylactic treatment?

This will depend on what you consider to be an acceptable risk of developing a possibly serious form of tuberculosis. It will also depend upon where you work.

A five per cent to 10 per cent risk of disease will probably make it worthwhile to give prophylaxis to a child. In a developed country even a positive tuberculin test might be considered an indication for prophylaxis at any age.

In a developing country as children get older it is more and more difficult to know who is recently infected so that we tend to draw a line regarding using chemoprophylaxis at five years of age and we emphasise that the younger the child the more urgent chemoprophylaxis is.

Not only is the risk of disease after infection higher the younger the child, but infection will also be more recent and we also know that the greatest risk of disease developing is soon after infection. In children with HIV-infection contact with TB at any age might be an indication for chemoprophylaxis.

Your 2004 paper "Childhood tuberculosis: the hidden epidemic" mentions that TB in children between 5-10 years of age could be considered as a "benign disease." Could you explain?

Like much else in tuberculosis, and other diseases, age has a significant effect on the immune system, the consequence of which is the variable response to infection seen very clearly in tuberculosis. Chicken pox, for example, in children is a very mild disease usually, but can be very severe in adults.

Why does the risk of infection shoot up at puberty? Considering that a large percentage of children <5 years progress from the infected to a diseased state within two years, what causes this peaking at puberty?

Again, all we know is that this does happen and that it is more likely in females than males. This must be linked to the endocrinological changes of adolescence, but what these are precisely remain unknown.

Online at http://www.thehindu.com/sci-tech/health/policy-and-issues/age-has-a-significant-effect-on-the-immune-system-in-childhood-tb/article5347615.ece

'Very few children in India are diagnosed and treated for MDR-TB'

20 November 2013

"A child with TB [is] as likely as an adult with TB to have MDR-TB [multi-drug resistant TB]," notes the WHO Global Tuberculosis Report 2013. that was released last month. "It is therefore essential that the identification of MDR-TB in children be strengthened."

WHO did not stop at that. "Efforts should be made to systematically conduct household contact investigation of all patients with MDR-TB, including children," it underlined.

The reason for the emphasis on MDR-TB detection is not difficult to fathom. Patients with MDR-TB do not respond to, or respond extremely poorly to standard first-line anti-TB drugs. A person is said to have MDR-TB when he is resistant to at least isoniazid and rifampicin, two of the first-line anti-TB drugs.

This makes it all the more important to trace the vulnerable groups well before they become diseased with drug-resistant TB. And children younger than five years from the same household as an adult (index case) who have been recently diagnosed with MDR-TB disease are one such vulnerable population. A 2002 study published in *Pediatrics* journal suggested two child contacts for every adult MDR-TB source patient in a high-burden setting.

"As many as a million children could be exposed to MDR tuberculosis globally each year, many of whom, in the absence of effective preventive therapy, will go on to develop MDR-TB disease," the 2002 paper notes.

"Preventive chemotherapy for children with second-line drugs is debated. Hence preventive chemotherapy for MDR-TB among contacts of MDR-TB patients is not a policy globally as enough scientific evidence is not available," Dr. K.S. Sachdeva, Additional Deputy Director General at Central TB Division, Ministry of Health & Family Welfare said in an email to this Correspondent.

But there is a gradual shift in policy outside India.

Incidentally, even the implementation of the WHO-recommended, RNTCP-approved contact screening and preventive therapy using the first-line drug

isoniazid for six months in children younger than five years who are asymptomatic or infected with drug-sensitive TB as a TB-diseased adult in the same household is "sub-optimal," as a few studies have revealed.

Even the diagnosis and treatment of children with MDR-TB disease is far below par. "Very few children are diagnosed and treated for MDR-TB," said Dr. Soumya Swaminathan, Director of the Chennai-based National Institute for Research in Tuberculosis (formerly TRC). "Awareness is itself low. Doctors think children can't get infected with MDR-TB."

This is despite the fact that India and China together carry nearly 50 per cent of the global MDR-TB burden. The prevalence of MDR-TB in India is estimated to be 64,000. The estimated percentage of new MDR-TB cases diagnosed by RNTCP is 2.2 per cent. It is 15 per cent in the case of retreatment TB cases. The number of MDR-TB cases diagnosed in 2012 was about 16,500; it was about 4,200 in 2011.

According to an October 25 article in the *Wall Street Journal*, 6.7 per cent of TB patients tested in 2012 at 18 sites using a rapid molecular diagnostic test — Xpert MTB/RIF — turned out to be drug-resistant TB cases, more than double the figure quoted by WHO.

"India has been offering all the four WHO recommended diagnostic tests for the diagnosis of MDR-TB. There are 51 laboratories which offer the Drug Sensitivity Test [DST]," said Dr. Sachdeva. "Some labs offer more than one DST facility." Of the 51 labs, 37 labs offer solid culture based DST, 12 labs offer liquid culture based DST also, and 41 labs offer Line Probe Assay [LPA]." In addition to the labs offering DST, "there are 38 Gene Xpert machines in 30 locations."

Gene Xpert can only reveal resistance to rifampicin drug. A vast majority of people who are resistant to rifampicin are also resistant to isoniazid.

"If Xpert shows rifampicin resistance in a patient with risk factors for MDR, one can begin second-line therapy while waiting for culture and full-drug susceptibility profile. So, one does not need to wait to act, but all Xpert Rif resistance results must be followed up with culture and DST," Dr. Madhukar Pai, Associate Professor, McGill University, Montreal clarified in an email to this Correspondent.

But all the four techniques — solid/liquid culture, LPA and Xpert — require sputum samples. And children aged under five years very often are unable to produce a sputum sample. Hence other techniques need to be used to get a sputum sample.

Besides the difficulty in getting sputum samples from young children, the number of TB bacilli present would be fewer even when sputum samples become available. "Diagnosing is difficult in children," Dr. Swaminathan said. "It is difficult to confirm the diagnosis bacteriologically even by culture."

The problem gets compounded in the case of extra-pulmonary TB. "Young children have nearly 30 per cent chances of having extra-pulmonary TB," she said. "The younger the child, the more the chances of seeing disseminated TB."

This explains why we see more instances of TB meningitis in young children. "But getting CSF [cerebrospinal fluid] and positive culture is so very rare. Maybe 10 to 15 per cent, not more than that," she said. "So in a vast majority of the cases won't get bacteriologically confirmed diagnosis for MDR-TB in extra-pulmonary cases."

The irony is that in such situations, there is no provision in the national TB control programme to treat the children. "The drug-resistant TB programme is looking for a confirmed bacteriological report from an RNTCP-accredited lab," she explained. "Unless they go with that report, they will not be started on MDR-TB regimen. [But] it is very rare for a young child to produce such a report."

Online at http://www.thehindu.com/sci-tech/health/policy-and-issues/very-few-children-in-india-are-diagnosed-and-treated-for-mdrtb/article5372234.ece

Sentinel Project gives a fillip to managing MDR-TB in children

27 November 2013

In cases where there is a serious disease like TB meningitis, the index of suspicion for MDR-TB should be very high

The Sentinel Project on Pediatric Drug-Resistant Tuberculosis is a collective power of a global partnership by experts and others who share the same vision of ensuring that no child dies of drug-resistant TB that is curable. "We are collaborating to raise the visibility of this vulnerable population of children, and to share evidence and resources that can increase children's access to prompt and effective treatment," Mercedes C. Becerra, Associate Professor in the Department of Global Health and Social Medicine at Harvard Medical School said in an email to this Correspondent.

It all started in April 2011 when Dr. Soumya Swaminathan, Director of the Chennai-based National Institute for Research in Tuberculosis and Prof. Becerra met in New Delhi at a workshop to examine the barriers to scaling up drug-resistant TB (DR-TB) treatment in India.

"[After our respective presentations] we realised that globally, despite much work being done on DR-TB, children with DR-TB were in essence invisible. This was itself a major barrier to advocacy for better science and improved treatment access for children," Prof. Becerra said. "Dr. Soumya and I thought that we should try somehow to raise the visibility of this vulnerable population, and that it should also be a way to link individuals who saw themselves as stakeholders."

The two of them came up with an idea of linking in a virtual network like-minded people who shared the vision that no child should die of DR-TB — a curable and preventable disease. The two individuals in their respective ways reached out to people in the same field across the world. "All of them supported the idea and expressed eagerness to join such a new virtual community," she noted. The project gained traction after an October 2011 international conference where the two made a public announcement of starting this virtual network and invited all interested colleagues to join.

Within a few weeks, over 200 scientists from over 20 countries responded to the call. Today, the Sentinel Project network includes over 300 people from over 50 countries.

"We have come up with a set of guidelines [a field guide] that will help in managing MDR-TB in children when there is no bacteriological report based on culture," Dr. Swaminathan explained. "The guidelines highlight the situations when you can actually suspect and call it [a case] as probable MDR-TB even when there is no [bacteriological] report [confirming the disease]."

According to Prof. Becerra, the field guide, along with a paper published in the *American Journal of Respiratory and Critical Care Medicine*, provides extensive and detailed practical recommendations to doctors about managing children with MDR-TB. The field guide, which is consistent with WHO and other guidelines, is one of the documents prepared by the Project.

Close contacts

One of the most important contributions of the Sentinel Project's field guide is its algorithm for managing a child who is in contact with an infectious adult with MDR-TB disease. Though WHO has not come out with guidelines on chemoprophylaxis for children, especially those younger than five years, who are close contacts of MDR-TB patients, several other agencies have come out with theirs. "The question about chemoprophylaxis is not addressed in the same way among several global guidelines," Prof. Becerra noted. "But the aim of the Sentinel Project has been to provide guidance on this and other challenges based on the collective expert opinion and observations of colleagues across the globe."

There are two instances when children aged younger than five years who are asymptomatic, growing well and have no clinical signs of TB but have been in contact with an adult (index case) would be eligible for preventive therapy. The first is when the index case is resistant to rifampicin drug alone. In such a case, the child needs to be treated with 15-20 mg/kg of isoniazid drug for six months. The second instance is when the index case has confirmed MDR-TB but is susceptible to ofloxacin. In such cases, the child may be treated as per the national TB programme, or by one of the five regimens listed in the Sentinel Project.

India focus

Dr. Swaminathan has conducted two training programmes — one in Chennai

(June this year) and another in Dhaka (July 2013) — for paediatricians. There were over 45 paediatricians for the Chennai training programme; RNTCP officials were also present. "I sent the recommendations to RNTCP and asked them to expand the guidelines to consider children for MDR-TB treatment under the following three conditions."

The three conditions are — if the child is a close contact of a person with known MDR-TB patient; or if children were close contacts of a person who is highly irregular on drug intake or has failed TB treatment or has died from TB; and finally in situations where a child is not improving or is actually deteriorating on [first-line TB] treatment.

"Especially in cases where there is a serious disease like TB meningitis, the index of suspicion for MDR-TB should be very high," Dr. Swaminathan explained. "We cannot wait endlessly till the child with meningitis goes on deteriorating, especially if the drug compliance is good… because it affects the brain permanently. These things need to be brought into the guidelines and people must be made aware of them."

Another important goal of the Sentinel Project is to come as close as possible in knowing the true burden of TB disease in children. Since bacteriological confirmation is difficult in children younger than five years, there is a need to have more data on the number of children suffering from drug-sensitive TB and drug-resistant TB. "Through the network, we hope to implement multi-site initiatives to improve our understanding of how many children at each location have TB disease in its different forms," Prof. Becerra said.

"I think Sentinel project has had an impact at the global level," Dr. Swaminathan noted. "Many of the members of the Project are also involved in WHO policy making. A lot of advocacy has been done and the WHO is now taking seriously the problem of estimating TB burden in children."

The fact that the 2013 WHO Global Tuberculosis report has made mention of drug resistant TB indicates that the Project is beginning to have an impact.

Online at http://www.thehindu.com/sci-tech/health/sentinel-project-gives-a-fillip-to-managing-mdrtb-in-children/article5397973.ece

Malnourished children in India below three years are underdosed for first-line TB drugs

4 December 2013

"The ultimate goal of evidence-based drug treatment is to produce a desired pharmacological response in a predictable manner and also to minimise adverse effects," notes a June 2013 paper published in the *International Journal of Tuberculosis and Lung Disease*. The two goals can be achieved only when the correct therapeutic drug dosage of anti-TB drugs required by children, particularly those younger than five years, and the age-related differences in toxicity and pharmacokinetics are well studied and known.

"Pharmacokinetics is the metabolism of the drugs in humans," Dr. Peter R. Donald, Emeritus Professor in the Department of Paediatrics and Child Health of the Faculty of Health Sciences at Stellenbosch University, South Africa said in an email to this Correspondent. "The pharmacokinetics of first-line anti-TB drugs is not known for children younger than two years."

Since children have "relatively greater mass of liver in proportion to total body weight," they metabolise and eliminate drugs faster than adults. As a result, higher mg/kg body weight dosages are needed by them to achieve equivalent concentration of drug in the blood.

In 2010, the World Health Organisation (WHO) revised the first-line anti-TB drug dosage after several studies pointed out that children treated with the same dosage as given to adults achieved only sub-therapeutic effects. The 2010 revision by WHO was possible as the pharmacokinetics of the first-line TB drugs were generally known.

But despite following the WHO's revised dosages for three first-line anti-TB drugs — isoniazid, rifampicin, and pyrazinamide — children younger than three years in India were found to have "significantly lower rifampicin, isoniazid and pyrazinamide [serum] concentrations than older children. And 90 per cent of all children [across all age groups] had sub-therapeutic rifampicin peak concentration," notes a June 2013 study by Dr. Geetha Ramachandran and others.

Dr. Ramachandran is from the Chennai-based National Institute for Research in Tuberculosis (NIRT), and the results were published in the *International Journal of Tuberculosis and Lung Disease*.

The first of its kind study undertaken in India found that pharmacokinetics was affected in children who were younger than three years, stunted and weighed less for their age, and belonged to the rapid isoniazid acetylator group — who had more of the enzyme that converted the isoniazid drug into another compound (acetyl isoniazid) which is devoid of anti-TB properties.

"The concentration of the enzyme is genetically determined," said Dr. Ramachandran. "Indians are predominantly slow acetylators. About 60 per cent belonged to the slow acetylator group and 40 per cent to the rapid acetylator group." Slow acetylators tend to have higher isoniazid serum levels.

The study found that children who were malnourished had lower drug levels. "Absorption is likely to be impaired in a malnourished child leading to low drug levels in blood," she said. "Low drug levels could be due to various factors. So we cannot pinpoint one."

Besides the lower drug levels in this category of children, RNTCP has four fixed weight bands — 6-10 kg, 11-17 kg, 18-25 kg and 26-30 kg. Aside from the overall underdosing in stunted and underweight children who were rapid acetylators, the drug levels would get further affected in those falling in either extreme of a particular weight band.

"Sustained sub-optimal drug levels could predispose to development of drug resistance and poor treatment outcomes," the paper notes. But a 2011 paper in the *Antimicrobial Agents and Chemotherapy* journal states: "higher doses might not be required in paediatric populations with predominantly slow acetylators and would unnecessarily expose patients to a higher risk of side effects."

Indian population has nearly 60 per cent of slow acetylators. "Slow acetylators are restricted to only isoniazid and does not include other drugs," she pointed out.

An April 2009 paper in the *BMC Medicine* journal also found that while nutritional status of children who were HIV-negative improved significantly after four months of treatment, the rifampicin plasma "remained low, so that poor nutrition cannot fully explain this finding."

Online at http://www.thehindu.com/sci-tech/malnourished-children-in-india-below-three-years-are-underdosed-for-firstline-tb-drugs/article5422052.ece

Child-friendly, first-line TB combination drugs will be available in 2016: Dr. Mel Spigelman

15 December 2013

Dr. Mel Spigelman, President and Chief Executive Officer of the Global Alliance for TB Drug Development (TB Alliance) is regarded as one of the world's leading experts in tuberculosis and TB drug development. He was instrumental in forging key organisational partnerships and building the pipeline of TB drug candidates when he was the Director of Research & Development at TB Alliance. In an email to R. Prasad, Dr. Spigelman explained the various facets of paediatric TB drug development.

Is there a greater involvement by drug companies in producing paediatric TB formulations after UNITAID provided a grant of $16.7 million and USAID also contributed funds?

The goal of the grant is to develop first-line TB treatments designed for children, in the proper doses and formulations, but also to help catalyse paediatric TB drug development among pharmaceutical companies through a variety of incentives. More accurately defining the market, clarifying the regulatory pathways for new products, and addressing barriers to entry for manufacturers are all within the scope of our work, and will help bring new partners into the field.

We've already engaged and entered into collaborations with interested generic manufacturers, including Svizera, which will help improve access to treatments. It's also important to note that TB Alliance's work under this grant will aim to reduce the lag time between adult and paediatric formulations of new drugs, accelerating the availability of new TB drugs in paediatric form. For example, we are working with Janssen to speed up the availability of the paediatric formulation of bedaquiline, which was approved for the treatment of MDR-TB in adults last year.

Is this a big amount to attract pharmaceutical companies to get into paediatric drug development?

The funding provided in the grant is designated for a discreet set of projects; it is not a pot of money to be given to pharmaceutical companies to work on paediatric TB drug development in a broader sense.

The impact of the work from this grant, in addition to bringing new products to the market, is to create an environment conducive to sustained and productive efforts in the field of paediatric TB drug development. This will require the involvement of pharmaceutical companies, as well as numerous other sectors including regulators, clinical researchers, Ministries of Health and Finance, drug sellers and even patients and their families. By preparing the market for these products, we intend to lower the barriers for the necessary parties to work toward improved TB treatment for children over the long term, beyond the life of this grant.

Has any Indian pharmaceutical company shown interest in developing fixed-dose combination drugs for children?

The current paediatric TB fixed-dosed products sold through the WHO's Global Drug Facility are produced by Indian pharma companies (Lupin and Macleods). TB Alliance has already entered into an agreement with Svizera to produce new first-line treatments in the doses now recommended by WHO and we are in discussion with other Indian pharmaceutical companies.

Because of their experience, Indian manufacturers are among those for whom we see a likely role in producing new TB drug products for children.

How long would it take to come up with fixed-dose combination drugs for first-line TB drugs? How long would a clinical trial take and how many subjects are needed to test bioavailability?

One of the significant challenges to the development of new paediatric TB treatments is the need for additional clarity on what is needed for such a product to receive approval by the various regulatory authorities around the world. These studies can take 6 to 18 months to complete. The quantity and scope of these studies required for regulatory approval can vary by country. We are working to collect that information and disseminate it widely, so that those with the capacity to work in this space have a clear understanding of what needs to be done, how to do it, and what regulators need to see to make approval decisions.

That said, we expect that the first wave of new, simpler, fixed-dose combinations for children will be available in 2016, fulfilling a significant need.

Since we need several dosages to cater to different weight bands, will the cost of drug development become expensive?

Fixed-dose combinations of current first-line TB treatments are weight-banded for both adults and children. The improved first-line TB treatments for children that will be made available as a result of this grant will be weight-banded as well. Dose-ranging studies are underway for the small group of newborns for whom this information is not already available. Dispersible tablets allow the same tablet to be dissolved in water or other liquid; different amounts are then given for each of the different weight groups, which is a cost-effective means of delivery.

When do you think the first-line, fixed-dose combination drugs would become available?

Our goal is to have optimised formulations of existing first-line treatment for children available to be sold through a global procurement agency by 2016, with a phased market rollout to follow.

Are there any attempts to come up with child-friendly second-line drugs? Cancombination drugs be produced for second-line drugs, as the choice of drugs depends on the drug sensitivity test results?

There are a number of obstacles to developing fixed-dose combinations of the current second-line drugs for children, including the fact that not all the second-line TB drugs are administered the same way. Kanamycin and capreomycin are delivered via injection, for example. While many groups advocate for drug developers to develop child-friendly formulations of the current second-line drugs, in the long run, we need new drugs to treat MDR-TB. Only then can we shorten the long treatment time (up to two years) and avoid the many toxicities that are associated with today's MDR-TB treatments. Compared with adults, children respond better to second-line treatment — but no person should have to endure such a difficult regimen. With the development of new regimens for the treatment of drug-resistant TB with hopefully new drugs to which there is no pre-existent resistance, combination products will become readily available for treatment of what is now considered drug-resistant TB.

How long would it take and how many children are needed to undertake bioavailability of fixed-dose combinations drug trials?

The number of children to be enrolled and the timeline for either a bioavailability or bioequivalence study are agreed upon between the manufacturer and the regulatory authority reviewing the product for market authorisation/approval.

Will such trials have a control group that receives regular dispersible drugs/syrups?

Efficacy trials that require control groups are not needed to obtain regulatory approval for improved first-line paediatric drug formulations already in the market. Mostly bioequivalence and bioavailability studies on fixed-dose combinations are needed, which compare the combination tablet with the single drug and make sure they deliver the same dose.

Don't these dispersible drugs have their own problems — requiring refrigeration and having a shorter shelf life?

The manufacturer has to demonstrate the stability of the drugs they make. Today's FDCs do not require refrigeration, but must be kept at below 30 or 40 degrees C. They have a shelf life of 2 to 3 years.

But current treatments do have substantial problems. The most significant problem, as it relates to children specifically, is that current treatments are not manufactured in doses that match the WHO guidelines for paediatric TB treatment, which were issued in 2010. Therefore, in practice, providers and caregivers must crush or cut adults pills to reach the proper dose.

In addition, the length of treatment and side effects are a burden to [both] children and the adults caring for them. Parents must transport their child to receive treatment, ensure the child completes treatment, and often administer the treatment over six months or longer.

As part of the effort to develop new first-line TB drugs specifically designed for children, one of the options we are exploring is the more preferred formulations for such drugs — dispersibles, sprinkles, syrups, etc. Different formulations may have different profiles in terms of storage requirements and other characteristics with logistical implications for storage, manufacture, and distribution.

When the shelf life is shorter, can countries be able to procure drugs in large quantities and stock them for a long time? Will drug stock-out not become a regular feature?

Stock-outs of drugs can be caused by many factors, but a critical component is ensuring that the forecasted need for the drugs is close to the actual need. When planning, National TB Programmes include a buffer stock in any order to ensure

that if the forecast is a little off, there are sufficient products. However, if the projected need is miscalculated, then stock-outs can occur. A longer shelf life can help prevent a stock-out even when forecasts are inaccurate.

Ensuring access to the treatments we develop is a critical priority for TB Alliance. Among the attributes we consider when determining the viability of a product are its stability and shelf life. We do not develop products or formulations of products which we believe would impose new or significant challenges on storage and administration of treatment.

The child-friendly combination drugs are for those younger than five years. Do we know the disease burden in this age group?

For clarification, child-friendly TB products are limited to children under 30 kg which limits the use of the drugs by weight and not by age. Depending on the region of the world, median weights for different age groups can vary. Children five years and under are a critical group, since they are most susceptible to becoming sick and dying from TB; however, all children need improved TB treatment.

Determining the actual number of paediatric patients, including those who are younger than five years old is a challenge, given the overall challenges in diagnosing paediatric TB. However, as part of this grant and in conjunction with other groups such as WHO, we are working to develop a better estimate of this cohort than has previously been available.

How can formulations be developed when pharmacokinetics of the first-line TB drugs are not known for children under two years of age?

There are only a few studies in this younger population that provide evidence for the 2010 WHO recommendations, and WHO recommended additional studies in the smallest children to be sure of the correct dose. We do know that this group absorbs, metabolizes and excretes certain drugs differently. These differences may or may not require separate recommendations for first-line treatment. Rather than have caregivers guess the correct dose for these children, the project will obtain pharmacokinetic data of the first-line TB drugs for children less than 12 months old where there are no data, and publish recommendations for this group

to ensure that all children are treated optimally and are cured. There is a fairly good understanding of dose for children above 5 kg.

Since we don't know the true disease burden in those younger than five years, are we not underestimating the disease burden and hence the market size for paediatric drugs?

The current market size is based on the number of treated patients, whereas the potential market size involves disease burden, which includes both treated and untreated patients. One of the efforts of this grant is to determine a more accurate and complete estimate of the global paediatric TB market, current and potential. We are working with partners to develop a better model for estimating these numbers, and have many studies, both underway and planned, that will yield additional information that will enable the further refinement of that model.

We realise there is much that will improve our estimates, including identifying where children are treated and where they are lost in the diagnosis and treatment process. Importantly, systems to improve reporting of cases to the National TB Programmes need to be expanded and improved to ensure that all children with TB are counted. Some may be seeking treatment in the private sector and therefore not be counted. Also, it is thought that a significant amount of childhood TB is actually misdiagnosed, or mis-categorized and that a substantial amount of childhood TB "hides" in other morbidity categories, such as pneumonia.

What delayed the development of drugs for children — the unknown disease burden and hence unknown market size, unprofitable business, lack of interest as children do not spread disease, difficulty in doing trials, resources to conduct trials, unknown pharmacokinetics in young children (<5 years)…?

I think there are a number of factors that have contributed to the stagnation of activity in this field.

Lack of financial incentive: This dynamic is seen across all neglected disease areas, and is a major obstacle to engagement in TB in general.

Lack of understanding of regulatory approval requirements and mechanisms: A lack of clarity about how best to obtain regulatory approval in various regions for new TB drugs for children serves/served as a powerful disincentive to engagement.

Incorrect information regarding burden/market size: Most experts believe the global paediatric TB burden to be larger than official estimates state. This underestimation undersells both the urgency and level of return in addressing the problem.

Insufficient information regarding the treatment recommendations: Manufacturers were told of a new dose form shortly after they had developed the current form. As a result, they were not confident that the dose recommendations would not change again and they were unwilling to commit to development of a new product.

Traditional research strategy: When it comes to new drugs in development, new drugs are traditionally developed for adults first and then tested in children, of decreasing age, for ethical reasons. Having only been rekindled roughly a decade ago, it took several years for the pipeline of new TB drug candidates to reach the point where traditional drug development processes dictated that it was time to turn attention to paediatric patients.

Complacency: Greater advocacy around such issues, and TB in general, is needed to pressure all stakeholders to engage in this activity.

As a result of all this, a comprehensive approach, with a multitude of partners, is needed. TB Alliance appreciates UNITAID's grant in this area, which allows the organisation to kick-start this work. Clearly, more support is needed to see all of it through and end the neglect of children with TB.

What is the knowledge-sharing initiative that TB Alliance has undertaken? How will it improve the development of drugs?

TB Alliance intends to share all the lessons and insights learned throughout this endeavour widely available to those in high TB burden countries managing the TB epidemic, to the manufacturers, to new drug developers as well as to the general public. These efforts will take many forms, including a web portal that will be launched early next year where these groups can seek a range of information and gain answers to their questions. In reshaping the information landscape, we hope to lower the barriers for many to participate in advancing new treatments for children.

Will the regulatory requirements be the same for paediatric formulations as for adult formulations?

Some of the requirements are expected to be the same, whereas others will be different. Clarifying the regulatory pathway for new paediatric TB treatments is a key part of this initiative. We are in conversations with leading regulatory bodies and experts around the world and will communicate what we learn though both discussion and practice. It is envisioned that many of the lessons learned through the development of improved first-line TB treatments for children will translate to a clear and accelerated path for the development and approval for children of the new TB drug candidates just approved for adults or anticipated to reach market in the next few years.

The UNITAID grant includes defining the disease burden. But considering that 85-90 per cent of young children (<5 years) are smear-negative, how can you get to know the disease burden, even an approximation?

Children, smear-positive and smear-negative, are being clinically diagnosed; we just cannot confirm those diagnoses with sputum in smear-negative patients. Now, children are lost in the diagnostic/treatment process so there are significant complexities…and we intend to use various data and analyse that data in many different ways to reach better estimates. The model developed to estimate the global TB burden will be a living tool, and many studies of different types are scheduled and already underway to feed information into that model to continually refine and improve its accuracy. Examples of the types of data that can reveal insight into this question are: inventory studies of treatment programmes, investigation into practices of private treatment providers, sales figures of TB drugs, and many others.

What is the incentive for drug companies to keep producing child-friendly drugs for the 'poor' people who can't be charged a premium price?

When any organisation collaborates with TB Alliance on product development work, we insist they agree to make any products developed affordable to those who need them. However, we recognize that to maintain steady supply of a product, companies need to avoid losing money on the product; however, the price of these treatments will still be affordable. All around the world TB medicines are

made available free of charge to patients via the National TB Programmes. This arrangement is often possible with the commitment of donors and governments who recognise the need to invest in life-saving drugs for children with TB.

TB Alliance's involvement lowers the technical barriers, as we are working in partnership to help organisations tackle the challenges they face in this area. Additional incentives include the moral impetus of such work, potential innovative financing mechanisms, a likely larger than previously expected market for such products, and a simple procurement model — large quantities will be bought from certain core suppliers, such as the WHO's Global Drug Facility (GDF).

Online at http://www.thehindu.com/sci-tech/health/medicine-and-research/childfriendly-firstline-tb-combination-drugs-will-be-available-in-2016-dr-mel-spigelman/article5449118.ece

Clinical trials on child-friendly bedaquiline MDR-TB drug for children initiated

14 December 2013

"Before the BPCA [Best Pharmaceuticals for Children Act] and the PREA [Paediatric Research Equity Act] became law, more than 80 per cent of the drugs approved [by FDA] for adult use were being used for children, even though the safety and effectiveness had not been established in the latter. Today that number has been reduced to about 50 per cent," a FDA blog post notes.

The effects of BPCA and PREA are already beginning to show. Janssen Pharmaceuticals, whose new drug (bedaquiline) was approved by the FDA last year for use in adults with MDR-TB disease, has already initiated steps to produce a paediatric version.

"Janssen is conducting what's called a 'bioavailability study' where the pharmacokinetic and other parameters (such as taste) of two new paediatric formulations of bedaquiline (granules or water dispersible tablets) would be compared with the pharmacokinetic parameters of the current adult tablet formulation," Daniel De Schryver, Global Communications Leader, Infectious Diseases and Vaccines, Janssen Research & Development, Belgium stated in an email to this Correspondent.

"Such a trial is normally conducted in healthy adults," Schryver noted. "Once a suitable paediatric formulation is identified, a trial will then be conducted in paediatric MDR TB patients (up to age 18 years) to determine the safety and efficacy of bedaquiline in these patients taking either the identified paediatric formulation or the adult tablets, where appropriate."

Once it is tested in adults, children of different age groups would be studied, starting with the oldest group — 12-18 years. This age group would be given the adult formulation as very often they tend to develop adult-type TB disease. "Based on the results from this older cohort, the trial would then proceed to the next cohort, using an age-appropriate formulation, and so on until the youngest group (as young as 6 months of age) is reached," he explained. It is not clear when paediatric drug formulation of bedaquiline would become available for the youngest age group.

The three age groups of children (who tend to develop paediatric MDR-TB disease) to be studied are 6–12 years, 2–6 years, and 6 months–2 years respectively.

There is a compelling need to conduct clinical trials in children even when the safety, dosage and efficacy of the drug have been studied in adults. One needs to take a few steps backwards to understand this.

By default, the amount of TB drug does "not reach the same concentration in the blood of children compared with adults" for a given mg/kg body weight dosage. This results in under-dosing in children. The only way to overcome this is by increasing the dosage of TB drugs (mg/kg body weight) given to children. WHO revised upwards the dosing of TB drugs for children only in 2010!

"More science has been done and hence we are able to understand why we are not able to treat children correctly," Dr. Denis Broun, Executive Director of UNITAID said to this Correspondent over phone from Geneva while explaining why it took a long time for WHO to revise the dosing for children. "Not that it [science of dosing] was bad before, it has become better now."

And since the drug dosage for children has been increased, clinical trials to study pharmacokinetics and bioavailability have to necessarily be undertaken.

If the two FDA rules make it mandatory for Janssen to produce paediatric formulations of bedaquiline, UNITAID's grant of $16.7 million to TB Alliance in December last year to accelerate the development of paediatric TB regimens has provided an additional impetus.

"Developing paediatric [TB] drugs is a not a big market for pharmaceutical companies. Have faced this in the case of HIV too," Dr. Broun said. "The point is to put money upfront so companies would create new drugs."

"We are working with Janssen to speed up the availability of the paediatric formulation of bedaquiline, which was approved for the treatment of MDR-TB in adults last year," Dr. Mel Spigelman, President and Chief Executive Officer of the Global Alliance for TB Drug Development (TB Alliance) said in email to this Correspondent. "TB Alliance's work … will aim to reduce the lag time between adult and paediatric formulations of new drugs, accelerating the availability of new TB drugs in paediatric form."

'In 2003, RNTCP had eight lines in the guidelines that related to TB in children'

19 December 2014

After years of neglect by the World Health Organisation and almost all the national tuberculosis programmes [NTP] across the world, the global spotlight is now on childhood TB. Prof. Steve Graham from the University of Melbourne and Murdoch Children's Research Institute, Australia, and also The Union, France has seen the focus of WHO shifting to childhood TB from close quarters. He was the Chair of the Childhood TB subgroup of the Stop TB Partnership that led the Roadmap for Childhood Tuberculosis; the Roadmap was released recently.

In an email to R. Prasad, Prof. Graham detailed the several changes that have happened over the past few years before childhood TB finally got the attention that was long overdue.

After years of neglect, what was the sudden provocation in 2006 for WHO to realise that childhood TB needs special attention?

The momentum was building up for some time, not suddenly — going back to articles published around 2000 the recognition that at that time there were very few national tuberculosis programme (NTP) guidelines that addressed TB in children.

What role did researchers play in turning the spotlight on childhood TB? Did researchers from South Africa, by any chance, play a pivotal role in this?

Prominent researchers from South Africa (especially from Stellenbosch University in Cape Town) were involved including the founding Chair of the child TB subgroup when formed in 2003 (Prof. Robert Gie) as well as folks representing the resource-limited setting (such as myself in Malawi) where we had been doing original operational research and publishing nationwide data.

Till 2006, were there no guidelines provided by the WHO to NTPs on the management of childhood TB?

No — and most NTPs had their own guidelines where there might be at most one page on issues relating to children — including India. In 2003 (when I went

there to help RNTCP move forward) comprised eight lines in the guidelines that related to TB in children.

Did countries, especially South Africa, undertake or at least realise a need to conduct contact screening of children aged under five years from households where an adult has been recently diagnosed with sputum smear-positive pulmonary TB?

Household contact screening was about the only thing in most NTP guidelines (not just South Africa). Everyone acknowledged its importance and the policy was almost universally accepted. [Yet] it just did not happen [practised], except in low-burden well-resourced settings like U.K. or the U.S. etc.

Did countries — developed and developing — realise that children younger than five years are vulnerable to getting infected/diseased with TB from a TB diseased adult in the same household before WHO came out with the guidelines in 2006?

The knowledge of children being vulnerable and even the value of IPT [isoniazid preventive therapy] were available since the 1960s.

What were the main contributions of the childhood TB subgroup that was formed in 2003? How many members did it have when it started?

It developed a focus for folks interested in childhood TB in TB endemic countries — and the main first step was development of WHO 2006 childhood TB guidelines, plus representing children in other fora. Initial membership at the 2003 meeting in Paris was about 12. [There are currently 125 active members.]

Ever since 2006, WHO seems to have taken childhood TB quite seriously and has come out with several documents/guidance/desk guide etc. What was the reason for the tide to turn?

[It is a] Recognition of the importance of children as a vulnerable population — as WHO expanded its TB control strategy beyond the limited DOTS approach, which largely did not include children.

What led to childhood TB gaining a lot of traction in the last 2-3 years? Did the arrival of GeneXpert, a rapid molecular diagnostic technology, and its approval by WHO turn out to be the defining moment for turning the attention on childhood TB?

None of those — just the eventual development of momentum that gets to a critical mass that then becomes weighty enough. The first International meeting on Childhood TB was held in Stockholm in 2011 — joint ECDC and WHO Stop TB. At that meeting, I was elected to replace Prof. Robert Gie [of Desmond Tutu TB Centre, Stellenbosch University in Cape Town] as Chair. We took on a number of initiatives at the same time, including putting childhood TB into the World TB Day 2012, revision of guidelines, technical assistance drug issues, development of training materials and desk-guide.

What do you think was the most significant or game-changing moment in addressing childhood TB — the Stockholm childhood TB meeting?

I would say so, and coinciding with childhood TB subgroup meeting.

What was the significance of the Oct 2011 WHO Stop TB symposium at the 42 Union World Conference on Lung Health in Lille, France?

[This was the] First time a symposium [was] dedicated to the needs of mothers and children.

The World TB Day in 2012 had childhood TB as its theme. Quite strange, considering that there was a long neglect of childhood TB. Your comments.

Not strange given that WHO Stop TB was broadening its strategy to the less traditional focus of just smear positive cases all at same time. So, as for a wider group, children always bring wider publicity focus.

Considering that evidence of childhood TB was plentiful in scientific journals, what new evidence came up for the WHO to take childhood TB seriously?

Nothing particularly new except the impact of HIV on TB in children which was devastating — mainly the focus of WHO on children was new.

The resurgence of TB in the U.S. due to the peaking of childhood TB in the 1990s clearly demonstrated the vulnerability of children to TB disease. Why did WHO take no cognisance of this?

This issue is highlighted in retrospect and did not get a lot of attention (at least outside of the U.S.) at the time.

How did the Roadmap for Childhood Tuberculosis materialise? With the complete neglect of childhood TB clearly spelt out in the report, was it an admission of lack of action and a clarion call for action?

Many now recognised the need to move on from neglect and also recognised the need to spell out how to do that etc.

The WHO also revised the programmatic management of childhood TB guidelines. What was the provocation?

WHO revises guidelines every five years or so — trying to keep current — plus there were a few new things that needed consideration such as 2010 Rapid Advice drug dosages and Xpert and the need to have more on MDR-TB.

Coming out with the "No more crying, no more dying" report is telling. What is the background of this?

Not my favourite choice of title! It came out because the Roadmap had started to be developed — but along came World TB Day 2012 and the Roadmap was nowhere near ready to be launched, so we agreed to put together a short highlighting document.

From complete neglect to "zero TB deaths in children" the pendulum has swung to the other end in a matter of a few years. Your comments.

Ambitious goals are what the post-2015 global TB strategy is all about, so we need to fall in line — plus our advocates insisted on need for simple and ambitious goals.

Online at http://www.thehindu.com/sci-tech/health/medicine-and-research/in-2003-rntcp-had-eight-lines-in-the-guidelines-that-related-to-tb-in-children/article5459706.ece

Childhood TB: what we need to do now

The series of articles and in-depth interviews with various international experts as chronicled by Dr. Prasad brings to the forefront the urgent need to turn the spotlight on childhood TB. With the "Roadmap to Childhood TB: towards zero deaths" having been launched by the global TB leaders last year, this series of articles has examined the various facets of childhood TB at the most opportune time.

One of the key highlights of the series is that the true burden of childhood TB is not yet clearly understood. It is only for the last two years that the annual global TB control report has started reporting separately on childhood TB. There is a dire need for more information from the field in the form of surveys, improved notifications and recording and reporting of data on childhood TB. Understanding the true burden of childhood TB is vital, as experts believe that TB in children is an indicator of the TB control program in any country.

Another important concern the series by Dr Prasad identifies is that children are at a greater risk of developing TB depending on their age – the younger they are, the higher the risk. It is a common understanding that young children, especially those who are malnourished, are already vulnerable to infections. The fact that TB in younger children usually reflects infection in the household or from close contacts serves as an opportunity to screen and diagnose them earlier. In fact, several international guidelines in managing childhood TB have been developed and India has adopted the guidelines on contact tracing and chemoprophylaxis. Rigorous implementation of the guidelines through training of healthcare workers and periodic monitoring provides a window of opportunity to reach out to children earlier.

The series has also drawn attention to several challenges in the diagnosis of TB in children, the most important one being the lack of reliable diagnostic tools. Currently, sputum test is the most important diagnostic tool in detecting TB. However children are either not able to bring out sputum or have very few bacilli in the sputum, and this is a major obstacle in the detection of TB. There is an urgent need for developing child friendly diagnostic tools. If the sputum test is taken out of this equation, other tests such as tuberculin skin test, X-ray, clinical symptoms also have a role in diagnosis, each with differing strengths and limitations. Recently, several scientific studies have shown promising results with the use of new diagnostic tools such as Gene Xpert in the diagnosis of TB in children. This calls for a pressing demand to improve access to existing diagnostic services and for rapid deployment of new diagnostic tools.

In addition, Dr Prasad's work has highlighted the fact that when the children are diagnosed with TB and started on treatment, there is a risk of under-dosing them, especially among those aged less than 3 years and the malnourished ones. This could have a detrimental effect on the treatment outcome of these children. There is a need to generate more scientific evidence in this area. Children need to be approached holistically and their nutritional and growth status also needs to be assessed and taken into account. This also calls for better integration of the TB services with reproductive and child health programmes in the country. Developing child friendly fixed dose combination medicines also assumes greater importance.

The series has also underlined the challenge that when multi-drug resistant TB is added to this scenario, there could be catastrophic consequences for these children. The ray of hope is the Sentinel Project on Pediatric Drug-Resistant Tuberculosis which is a global partnership of researchers, caregivers and advocates whose vision is to ensure that no child dies of drug-resistant TB. Guidelines on identification and management of MDR-TB in children have to be urgently and widely disseminated to key stakeholders including paediatricians and the healthcare workers in the program.

Finally, dedicated performance-based indicators for childhood TB needs to developed and used to monitor the progress towards our collective goal. Civil societies and other key stakeholders need to be roped in to harness the support and resources required for preventing childhood TB. Scientific evidence ranging from drug studies to operational research in TB for this age group needs to be undertaken as a priority. The need of the hour is a holistic family centric approach and care to all TB patients, which would yield better chances of identifying the children with TB with very little "extra effort" and getting them on the road to recovery faster. The importance of patient and family counselling by all healthcare providers assumes paramount importance in this context.

Children deserve special attention and focus. It is our duty to set the wheel rolling on the road map to childhood TB: towards zero deaths.

In our fight against tuberculosis, let us pledge to not lose any more children to TB.

Dr RAMYA ANANTHAKRISHNAN
Executive Director, REACH

Acknowledgements

The publication of this compendium is supported by a United Way Worldwide grant made possible by the Lilly Foundation on behalf of the Lilly MDR-TB Partnership.

Dr. Prasad attended the 44th Union World Conference on Lung Health in Paris at the invitation of Global Health Strategies, New Delhi.

To read Dr. Prasad's complete series on childhood TB (22 articles and 4 podcasts in all), please visit http://www.media4tb.org

About REACH

REACH is a non- profit organization established in 1999 in Chennai (India) with a broad mandate that includes support, care for TB patients, advocacy and social mobilization for TB control at the rural grassroots level, research, capacity building, training of different stakeholders, engaging with national and local media to improve and increase reporting on TB, engaging with community volunteers , public education and communication.

Since 2010, REACH has been working with the media to improve the quality and frequency of reporting on TB through a fellowship programme for local language journalists, annual media awards and a dedicated portal with resources on TB for journalists.

Please visit www.media4tb.org and www.reachtbnetwork.org for more information.

Contact REACH

Email: reach4tb@gmail.com
Phone: 044-65211047 or 044-28132099
Facebook: https://www.facebook.com/SpeakTB
Twitter: @speakTB

COMPUPRINT • 2811 6768