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UPDATE OF REPORT "OUT OF THE DARK: MEETING THE NEEDS OF CHILDREN WITH TUBERCULOSIS"

NOVEMBER 2012

This document serves as an update to "Out of the Dark", a report published by MSF in October 2011, highlighting the need to prioritise the long-neglected area of paediatric tuberculosis (TB). This update will outline the key improvements and setbacks—the 'highlights' and 'lowlights'—that have occurred over the last year.

In 2012, paediatric TB was a focus of World TB Day and was the subject of a number of published articles. Even so, the scope of the problem remains unclear with figures on the number of children infected with TB only included in the World Health Organization Global Tuberculosis Report for the first time in October 2012. The data shows there were an estimated 500,000 cases of TB and 64,000 deaths among children in 2011. However, WHO highlights the challenges in obtaining these figures, which are based on assumptions, and are therefore likely underestimated. Furthermore, a recent article highlighted the difference in the numbers of children actually being treated, and the numbers being reported to the WHO in some countries. Without an accurate picture of the disease burden, it remains extremely difficult to advocate for the improvements and investments necessary to combat paediatric TB.

DIAGNOSIS

Establishing a timely and accurate diagnosis of paediatric TB is critical, considering the speed with which the disease progresses and spreads in children. However, diagnosis remains inadequate, primarily because existing tools are not suited to detecting paediatric TB.

HIGHLIGHTS

- **Microbiological confirmation**: **the role of Xpert MTB/RIF** : Evidence is showing that the Xpert MTB/RIF test significantly increases the number of paediatric TB cases detected compared to sputum smear microscopy (SSM) in an equally rapid timeframe (0-1 day). However, it is not as sensitive as culture, and cannot confirm diagnosis in many children with clinical suspicion of TB.[5,6,7] (Any tests based on bacterial load and on respiratory samples are unlikely to provide a major diagnostic solution for paediatric TB, considering the paucibacillary nature of the disease, with children not having adequate amounts of bacteria in their samples for such tests to provide accurate diagnosis.)
- **Consensus on definitions and methods for paediatric diagnosis:** In a process led by the US National Institutes of Health (NIH), a consensus was reached on a clinical case definition and methodological approaches in the evaluation of new TB diagnostic tests in paediatric populations. The consensus statements were published in the Journal of Infectious Diseases in May 2012 and should now be widely endorsed and implemented.[8,9] This consensus provides guidance for the assessment of TB diagnostic test performance and should open the door for academic groups and test developers to finally develop TB tests that work in children.

LOWLIGHTS

- **TB diagnostic tools remain untested in children**: Apart from efforts to clarify what role Xpert MTB/RIF could play in diagnosing TB in children, little else has happened in diagnostics for paediatric use. For example, the urine-based LAM test could be a potentially useful tool for diagnosing TB in children with suspected disseminated TB (TB that affects more than one area of the body) and HIV co-infection, but no public data on this exists yet.[10]

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Diagnosis continued...

- **Access to paediatric TB diagnosis remains limited**: A recently-published study assessed the availability of TB diagnostic procedures at sites providing paediatric HIV services in nine sub-Saharan African countries.[11] It showed that while SSM was available at 87% of sites, only half had access to culture tests or chest X-rays. The ability to collect samples via gastric aspiration (the suction of fluid samples from the stomach), sputum induction and nasopharingeal aspiration (suction from the posterior throat) was limited to 5%, 6% and 2% of sites, respectively. This illustrates the urgent need to build healthcare staff's capacity in sample collection in order to scale-up diagnosis of TB in children in endemic settings.

TREATMENT

Despite more accurate dosing having been recommended by WHO for children with drug-sensitive TB, the available pharmacokinetic and safety data of second-line drugs (SLD), needed by children with drug-resistant TB (DR-TB), remains limited. Currently, the most frequent practice for DR-TB treatment in children is manipulating adult formulations of SLDs, which carries a significant risk of under- or over-dosing.

HIGHLIGHTS

- **New paediatric fixed-dose combination (FDC) compositions agreed upon by WHO**: In 2010, the WHO published Rapid Advice dosing guidelines for drug-sensitive TB treatment in children. With consensus now finally reached on the exact composition of the new FDCs that correspond to the new dosages, these have now been included on the WHO Expression of Interest (EOI) list. This finally sends a clear signal to drug manufacturers to develop the new FDCs (see box below).
- **Development of dosage spoons for second-line drug PAS**: The two manufacturers of para-aminosalicyc acid (PAS) formulations, Jacobus and Macleods, have developed dosage spoons for their products. These allow for the accurate measurement of the smaller doses required for children.
- **Pharmacokinetic (PK) studies in children are slowly closing the knowledge gap:** New PK data confirms the 2010 WHO dosage recommendations for drug-sensitive TB are suitable for children aged under two years.[12] Meanwhile, an ongoing study looking at PK data for SLDs in children should help establish the exact dosages required to adequately treat DR-TB in children.

LOWLIGHTS

- **Complicated 'interim' dosing guidelines for drug-sensitive TB in children:** Although the compositions of the new desired FDCs for paediatric TB are now on the WHO's EOI list, it is not clear when these will be available for children. The existing FDCs do not match the recommended new dosages, leaving health workers to grapple with complicated 'interim' dosing guidelines. Only 50% of surveyed countries have incorporated these new guidelines into their wider national guidelines,[13] which means many children are not receiving the new recommended doses.
- **Lack of data on paediatric dosing for drug-resistant TB (DR-TB):** The lack of data on dosages for DR-TB treatment in children and the unknown market size mean manufacturers are reluctant to develop paediatric formulations of SLDs. The only paediatric formulations currently available are PAS (via the above-mentioned dosing spoons), amikacin, levofloxacin and linezolid. The levofloxacin solution has been developed for short-term use in infections and its composition is not necessarily adapted for long-term use as required in TB. The rest of the drugs require manipulation, and the risk of inaccurate

WANTED: NEW FIXED-DOSE COMBINATIONS FOR CHILDREN WITH TB

The currently-available fixed-dose combinations (FDC) for children do not correspond to the dosages recommended in the current WHO treatment guidelines. Therefore, in order to benefit from the new recommendations, children have had to take a complicated combination of tablets (see *Out of the Dark* for more information). In 2012, WHO agreed on the composition of two new paediatric FDCs for drug-sensitive TB that correlate to the new dosages.

The following FDC compositions have been placed on the latest invitation for WHO Expression of Interest (EOI) list:
Solid dosage formulations for children, preferably dispersible or crushable tablets, in fixed-dose combination format:

- rifampicin 75 mg + isoniazid 50 mg + pyrazinamide 150 mg
- rifampicin 75 mg + isoniazid 50 mg

With this clear WHO guidance, the production of the appropriate FDCs can begin. But with the small market size, manufacturers lack an incentive. Mechanisms to encourage the development of these FDCs are needed. If the required steps are taken, new FDCs based on WHO guidelines could be available within three years.

THE SENTINEL PROJECT: UNITING RESEARCHERS, CAREGIVERS AND ADVOCATES ON PAEDIATRIC DR-TB

Paediatric DR-TB is both a preventable and treatable disease. Every child who dies from DR-TB is a sentinel for both ongoing transmission and inadequate treatment delivery systems.

In October 2011, the Department of Global Health and Social Medicine at Harvard Medical School (Boston, MA, USA) joined forces with the National Institute for Research in Tuberculosis (Chennai, India) to form a new collaboration called the Sentinel Project on Paediatric Drug-resistant Tuberculosis.[17] The global partnership is comprised of leading paediatric researchers, caregivers, and advocates from more than 30 different countries. It has been generating and disseminating knowledge and data for the optimal diagnosis, management, and prevention of DR-TB in children. It aims to develop and deploy evidence-based strategies to prevent child deaths from DR-TB and to ensure that these strategies are implemented worldwide. This project is committed to leading global action in the field of paediatric DR-TB.

For more information: http://sentinel-project.org/

dosing that entails. Safety and pharmacokinetic data is necessary to define appropriate dosing in children.

- **No paediatric formulation of new TB drugs:** Two new drugs that have been developed for TB—bedaquiline and delamanid—have been submitted for Stringent Regulatory Authority (SRA) approval, but their only registered use will be for adults. Though there is a paediatric development plan in both registration dossiers, their use in children is expected to be many years away.
- **Clinical trials on new regimens exclude children:** None of the clinical trials looking at shorter regimens for drug-sensitive TB and DR-TB include a paediatric component.[14,15,16] Children will therefore be excluded from any new developments in treatment regimens.

PREVENTION

Most TB prevention strategies are not specific to children and apply to all patients, except for the protective effects of the BCG vaccine. Better implementation of isoniazid prevention therapy (IPT) remains a key element to improving prevention in children[17] and the development of a better vaccine is crucial. Currently, there are 12 novel TB vaccine candidates in early trials in humans.

HIGHLIGHTS

- **New global strategy to develop new TB vaccine published:** TB Vaccines Initiative, Aeras and scientific advisors published 'TB Vaccines: A Strategic Blueprint for the Next Decade' in March 2012 which sets out an international plan to develop affordable and effective TB vaccines quickly.
- **Rifapentin and isoniazid for children over 12 years:** Children aged 12 years or over were shown to benefit from a once-a-week combination of rifapentin and isoniazid,[18] which improved adherence without increasing side effects and may be easier to implement than current IPT strategies at a programmatic level.

LOWLIGHTS

- **Still no prevention of DR-TB in children:** Current recommendations for children exposed to DR-TB are to observe them for two years.[19] No evidence yet exists on what preventative regimen may be suitable for this very vulnerable group.

THE WAY FORWARD – WHAT CAN BE DONE?

Although there have been a number of advances made in paediatric TB since 2011, much remains to be done to ensure that children receive the same quality of care as adults. As the speed of developments within the TB world increases, it is important to strengthen the focus on children with TB and ensure they are no longer left in the dark.

The majority of asks in 'The way forward' section of *Out of the Dark* remain, with an urgent need for them to be achieved. Additional action points include:

DIAGNOSIS

- Evaluate new diagnostics in children as soon as 'proof of principle' studies have been successfully carried out in adults, and optimise sample collection and processing procedures for given assays.
- Ensure wide endorsement and implementation of the consensus on clinical case definition and methodological approaches in paediatric TB diagnostics.
- Ensure there is a specific focus on childhood TB in the search for pathogen- and non-pathogen based TB diagnostic biomarkers, which could lead to the development of a point-of-care test for TB in children.
- Prioritise R&D efforts on diagnostics that use non-respiratory samples (i.e. urine or capillary blood).

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TREATMENT

- Ensure that the inclusion of the new desired paediatric TB FDCs on the WHO's Expression of Interest list results in the rapid development of these products. Manufacturers need to be engaged, supported and incentivised to develop these as soon as possible.
- There has been no comprehensive paediatric TB guideline since 2006. A new comprehensive guideline incorporating all elements of paediatric TB care should be released.
- Existing WHO guidance for childhood TB is aimed at national TB programme managers, so a practical guideline for clinicians or health care workers is required.

PREVENTION

- Push for better implementation of isoniazid prevention therapy (IPT) in children - especially where prevention of mother-to-child transmission of HIV (PMTCT) and early antiretroviral therapy for HIV have not been adequately rolled out. Also ensure IPT is part of national TB guidelines for children with and without HIV co-infection.
- Investigate the use of alternative prevention regimens in younger children to see if these improve adherence and uptake of IPT and are easier to implement at country level.

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