

## **Report on meeting of childhood TB subgroup, Thursday 28 October 2004, Paris.**

### *Background*

Urgent and effective action is necessary to decrease the burden of childhood TB. The management of children with TB often falls outside the routine operations of National TB Programmes (NTPs). There is broad consensus on current international guidelines for case finding and treatment of children with TB, contact tracing of children at high risk of TB for preventive TB treatment, and including all childhood TB cases in routine NTP recording and reporting activities. However, many NTPs do not routinely include the management of children with TB as part of their routine operations. Improved care and prevention of childhood TB depend on: a) intensified efforts to ensure implementation of these guidelines; b) mobilisation of human resources; c) ongoing policy development; and d) research.

Upon the request of key partners, the DOTS Expansion Working Group (DEWG) approved the establishment of a subgroup on childhood TB in October 2003. The key partners that have promoted the development of the childhood TB subgroup of the DEWG include the International Union Against Tuberculosis and Lung Disease (IUATLD), International Paediatric Association (IPA), USA Centers for Disease Control and Prevention (CDC), USA National Institutes for Health (NIH) and WHO (Child and Adolescent Health Department and Stop TB Department). Beyond these key partners, other members of the subgroup include paediatricians in clinical practice in high TB incidence countries and representatives of academic and research institutions. As the subgroup develops, new members are likely to include representatives of a broad range of agencies and organizations sharing the goal and objectives of the subgroup.

In support of the subgroup's objectives to promote implementation of guidelines, mobilisation of human resources, ongoing policy development and research, the subgroup held its first meeting under the auspices of the DEWG on 28 October 2004 in Paris. The agenda appears in Annex 1 and the list of participants in Annex 2.

### *Main issues*

#### 1. Guidance for NTPs on prevention, diagnosis, treatment, follow-up and reporting of TB in children

The subgroup reviewed progress so far with the development of the guidelines coordinated by Lisa Nelson. The agreement that the title of the document should be "Guidance for National TB Programmes on the practical management of children with TB", reflected the main purpose to guide NTP managers in mainstreaming activities related to childhood TB as part of routine NTP operations. The subgroup also agreed on the importance of ensuring consistency as far as possible with current international policies, e.g. IUATLD policies on child lung health, WHO policies on the Integrated Management of Childhood Illness (IMCI), and WHO policies on TB control, in order to promote the uptake and usefulness of the final document.

The subgroup discussed the following outstanding technical issues:

a) BCG and HIV infection

The subgroup endorsed the WHO policy on BCG that all newborns in high TB prevalence countries should receive BCG as part of the Expanded Programme on Immunisation (EPI). Children who have missed BCG and who later present with symptoms of HIV disease or AIDS should not receive BCG.

b) Tuberculin skin testing in relation to BCG status

The subgroup noted the discrepancy in WHO policy in two publications: the proposed cut-off for a positive test in "TB/HIV: A Clinical Manual, 2<sup>nd</sup> edition" is 10mm irrespective of BCG status, whereas "Treatment of TB: guidelines for national programmes, 3<sup>rd</sup> edition" indicates a 10mm cut-off for children who have not had BCG and a 15mm cut-off for those who have. The subgroup recommended a 10mm cut-off irrespective of BCG status (with a cut-off of 5mm in HIV-infected children).

c) Doses of anti-TB drugs

The subgroup recognised that, as with many other drugs, anti-TB drugs have rarely been evaluated specifically to establish recommended doses in children. The subgroup recognised the lack of published pharmacokinetic and pharmacodynamic studies data on anti-TB drugs in children, including in those with HIV infection. The results of some pharmacokinetic studies are awaiting publication and several pharmacokinetic studies on isoniazid and rifampicin in children with and without HIV infection are under way.

The next steps in finalizing the document include the development of the next draft (led by Lisa Nelson) that reflects the subgroup's comments by end January 2005. The core group of the DEWG will review the document, with input from the NTP managers of the high TB burden countries, and by professional associations, e.g. IPA, by end March 2005. Different agencies can use their networks of partners and members to disseminate the final document, that the group will submit for publication as a consensus statement in the International Journal of TB and Lung Disease (which has a wide dissemination among the TB community).

## *2. Promoting child-friendly formulations of anti-TB drugs*

Peter Evans made a presentation on the potential use for children of the currently available individual TB treatment kits. The Stop TB Partnership recommends a 6 month treatment regimen for Category 1 patients using the four-drug fixed-dose combination (4FDC) of rifampicin, isoniazid, pyrazinamide and ethambutol in the intensive phase and the two-drug fixed-dose combination (2FDC) of rifampicin and isoniazid in the continuation phase for category one patients. Table 1 shows the formulations of the recommended 4FDC and 2FDCs and Table 2 shows the recommended drug doses (WHO "Treatment of tuberculosis: guidelines for national programmes. 3<sup>rd</sup> edition, 2003").

Table 1. Formulations of recommended 4FDC and 2FDC

4FDC

Rifampicin	150mg
Isoniazid	75mg
Pyrazinamide	400mg
Ethambutol	275mg

2FDC

Rifampicin	150mg
Isoniazid	75mg

Table 2. Recommended daily dose range for essential anti-TB drugs

Essential anti-TB drug (abbreviation)	Mode of action	Daily dose (range) mg/kg
Rifampicin (R)	Bactericidal	10 (8-12)
Isoniazid (H)	Bactericidal	5 (4-6)
Pyrazinamide (Z)	Bactericidal	25 (20-30)
Ethambutol (E)*	Bacteriostatic	15 (15-20)
Streptomycin (S)	Bactericidal	15 (12-18)

\* Note that the recommended dose range for ethambutol of 15-20 mg/kg refers to adults, and the recommended maximum daily dose for children is 15 mg/kg (WHO "Treatment of tuberculosis: guidelines for national programmes. 3<sup>rd</sup> edition, 2003").

In support of this standardization, the Global TB Drug Facility (GDF) has prepared patient kits that are being made widely available. These kits contain a complete treatment regimen for an average weight patient. These adjustable kits are designed to cover the adult weight range of 30kg to 60kg by adding or removing blister cards. However the weight range that the kit is suitable for could be extended much wider, including for children. The proportion of TB patients under 30kg in weight is relatively low. The use of new or separate products for this group of TB patients would make forecasting and avoiding stock-outs at health facilities very difficult. The existing kits could be used to treat TB patients less than 30kg in weight but would require administration of less than the current minimum of 2 tablets daily. By giving a partial but accurate dose, the weight range could be extended down to 5kg. The limiting factor is how easily and accurately tablets that should contain evenly distributed drug ingredients may be divided into discrete parts.

One of the major FDC manufacturers has indicated that double scoring of each tablet will allow them to be easily broken into discrete parts of 1/3, 1/2 or 2/3. This would allow the single-stocked patient kit to be adjusted for every patient between 5kg and 70kg in weight. For an infant less than 5kg in weight it would be necessary to follow current practice of crushing and dividing tablets. With the 2FDC and the 4FDC there would only be one tablet to crush and the division into half the crushed amount should reduce errors.

Table 3 shows the proposed daily doses of FDCs for children according to different weight bands, based on the recommended daily dose ranges for the four anti-TB drugs (shown in Table 2). The weight bands proposed are close, but do not correspond exactly, to the weight bands normally recommended for paediatric use (see Table 3).

Table 3. Recommended daily doses of FDCs for children in different weight bands

<b>Daily doses (tablets)</b>									
<b>Weight Band</b>	<b>0.33</b>	<b>0.5</b>	<b>0.67</b>	<b>1</b>	<b>1.5</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>
5-6 Kg	<b>X</b>								
7-9 Kg		<b>X</b>							
10-13 Kg			<b>X</b>						
14-19 Kg				<b>X</b>					
20-30 Kg					<b>X</b>				
31-39 Kg						<b>X</b>			
40-54 Kg							<b>X</b>		
55-70 Kg								<b>X</b>	
>70 Kg									<b>X</b>

The daily drug dose for children in a particular weight band should provide all children in that weight band with a dose of each drug that is in the recommended range (mg/kg).

Participants discussed the accuracy of breaking tablets resulting in even amounts of all of the active ingredients in the administered fragments. The breaking of scored tablets was not considered to be a big concern and many anecdotal solutions were given. A laboratory study had been commissioned and the results, not yet published, showed the dispersal of the ingredients met international pharmacopoeial standards even on the fragments. The eventuality of the unwanted fragment being kept was considered and found to be a concern. This would only be resolved through field trials. Such trials should be commissioned before the use of the kit for paediatric use was approved.

The subgroup therefore agreed on the following action points:

- a) The concept of modifying the GDF Patient Kits to treat children in Category 1 should be explored.
- b) Samples should be commissioned containing double scored tablets.
- c) Field trials should take place to observe the kits in use.
- d) A report of the trials should be made to the childhood TB subgroup of the DEWG.

*3. Update on plans to develop a proposal to support childhood TB activities*

WHO has received \$20,000 from CDC that could be used to contract a suitably qualified and experienced person to develop a proposal for funding of childhood TB activities. The subgroup secretariat requested participants to identify potential candidates and inform WHO.

Next meeting:

The subgroup agreed to meet as usual just before the annual IUATLD conference on lung health in Paris (scheduled in 2005 for 18-22 October).

## Annex 1: Agenda

	Topic	Presenter
09.00 - 09.15	Welcome and introduction	R Gie
09.15 - 10.00	Topic 1. Developing guidance for national TB programmes on prevention, diagnosis, treatment, follow-up and reporting of TB in children: a) progress so far b) clarifying the purpose, scope and target audience	L Nelson
10.00 - 10.30	Coffee break	
10.30 - 12.30	c) specific technical issues, including terminology, treatment (e.g. drug doses, intermittent treatment, use of steroids, management of TB meningitis and miliary TB, drug-resistant TB), recording and reporting, screening of contacts, TB/HIV	
12.30 - 14.00	Lunch	
14.00 - 15.00	c) specific technical issues (continued)	
15.00 - 15.15	d) widening the review process	
15.15 - 15.30	e) finalizing the guidelines - next steps	
15.30 - 16.00	Coffee break	
16.00 - 16.45	Topic 2. Promoting child-friendly formulations of anti-TB drugs: a) defining the role of the childhood TB subgroup b) a proposal for enabling the use of TB patient treatment boxes for children	P Evans
16.45 - 17.00	Topic 3. Update on plans to develop a proposal to support childhood TB activities - clarifying possible activities for a proposal and ways of developing the proposal	D Maher

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