Report of the meeting on TB medicines for children
WHO Headquarters, Geneva, Switzerland
8-9 July 2008

Executive summary

In July 2008, a group of paediatric experts and WHO staff members met to review the evidence supporting current formulation and dosage guidelines for paediatric TB drugs. The meeting followed a literature review of the pharmacokinetics of three paediatric TB medicines on the Essential Medicines List. As a result of this consultation, the group recommended changes to the current drug doses of first line drugs, including fixed dose combination products, and identified future research areas required to define the ideal fixed dose combinations. This report details the new recommendations, summarizes the existing evidence and provides an overview of the meeting's outcomes.

Declaration of interests

Participants of the TB medicines for children meeting reported the following:

- Dr Peter Roderick Donald reported that his department received research support ($750,000) from Bristol-Myers Squibb in 2005. He also reported being a consultant to Tibotec in 2007 and to the Global Alliance for TB Drug Development.
- Dr Kalle Hoppu reported having been a consultant (€ 5000) for Lundbeck A/S in 2007. (€ 5000)
- Dr Gregory Kearns reported research support for pharmacokinetics studies from Wyeth Pharmaceuticals, Astellas Pharma USA, Cubist Pharmaceuticals, Amylin Pharmaceuticals, and GlaxoSmithKline. In addition, Dr Kearns has done consultancy work for Procter and Gamble, BioDelivery Sciences, Merck, Altana Pharma, Morton Grove Pharmaceuticals, Cubist Pharmaceuticals and Abbott Laboratories. He also serves as a member of the United States FDA Clinical Pharmacology Advisory Committee and receives research support from the National Institutes of Health.
- Dr Stephen Spielberg reported being a principal investigator for the Institute for Paediatric Innovation, a not-for-profit organization.
- Dr Jeffrey Starke reported providing expert opinions for the American Academy of Paediatrics, a not-for-profit organization, on tuberculosis policies.
- Dr Anita Zaidi reported that her department received research funding ($32,000) from Wyeth in 2007 for work on respiratory infections.
- Dr Lisa Adams, Dr Rohini Fernandopulle, Dr Robert Gie and Professor Cleotilde Hidalgo How reported no conflict of interest.

Introduction

As widely recognized, the doses of TB drugs prescribed for children require adaptation to yield the same exposure as in adults. The manner in which this adaptation is made has been the subject of considerable controversy, so a number of rules and conversion factors have been developed to arrive at appropriate doses. However, most of these factors were little understood at the time of the development of the current 'first-line' drugs. The aim of the July 2008 meeting was to bring together paediatric pharmacology and TB experts to review the existing evidence on the matter. The group considered the need for any revisions to the existing recommendations and identified future areas of research needed to achieve ideal doses of first line TB drugs for children.

Meeting background

Meeting objectives

1. Review the evidence on first line drugs for the treatment of tuberculosis in children with a view to making changes in the recommended doses.
2. Determine whether existing fixed dose combination products of first line drugs for children are appropriate in light of the dosing recommendations.
3. Define ideal fixed dose combinations or recommend on research required to define the ideal fixed dose combinations.

Preparatory work

A comprehensive review of the pharmacokinetic studies of pyrazinamide, isoniazid and rifampicin was carried out by Dr Donald prior to the meeting. This review served as the basis for the meeting participants to make recommendations. Dr Donald's literature review and all other background documents are available upon request.

Meeting process

Before the meeting began, potential declarations of interests were identified and assessed prior to developing recommendations, and no participants with significant interests were identified.

Discussions focused on the existing evidence on pyrazinamide, isoniazid and rifampicin for the treatment of tuberculosis in children. Dr Donald's comprehensive literature review was outlined during the meeting and served as the basis upon which participants were able to discuss appropriate recommendations. Their recommendations took account of quality of evidence, data gaps, and safety issues. Consensus on the wording of the recommendations was achieved during the course of the meeting. Meeting presentations are also available upon request.

Summary of meeting discussion

The WHO meeting on TB medicines for children, which met in Geneva from 8 to 9 July 2008, was opened on behalf of the Director-General by Dr Hans Hogerzeil (Director of the Department of Medicines Policy and Standards) and by Dr Mario Raviglione (Director of the Stop TB Partnership). Both highlighted the scarcity of medicines adapted to children and emphasized the possibility of driving innovation in this field by revising guidelines through an evidence-based review of the current first-line drugs.

Background information
(Available upon request)

Dr Grzemska presented the current recommendations on first-line TB medicines for children. She outlined the existing treatment regimens and described the operational problems of treatment delivery.

Dr Matiru provided an overview of the current paediatric TB market. He suggested that any revision of the current recommendations may have a substantial impact on drug suppliers.

Dr Qazi summarized the previous publications on the review of ethambutol[1] including the evidence on its related ocular complications. The recommendations following that review were to amend the daily dose of ethambutol for children of all ages to 20 mg/kg (range 15–25 mg/kg).

Dr Donald introduced his review, outlined the methodology, and presented his draft recommendations.

The studies on the pharmacokinetics of pyrazinamide, isoniazid and rifampacin are summarized below, along with the meeting recommendations.

Key findings and recommendations

Pyrazinamide

Current dose recommendation

The current WHO recommendation is 25 mg/kg (range 20-30). Current approved labeling according to the FDA is 15-30 mg/kg.

Current dosage forms

Marketed dosage forms	Products prequalified by WHO	Products available through GDF
400 mg tablet or capsule	400 mg tablet (Cadila, Macleods)	150 mg tablet (Lupin)
500 mg tablet or capsule		

[1] Donald PR, Maher D, Maritz JS, Qazi S. Ethambutol dosage for the treatment of children: literature review and recommendations. *Bull Int Union Tuberc Lung Dis* 2006; 10(12):1318-30.

Summary of evidence discussed

See Annex 1 for studies reviewed.

Indication/target use

PRZ is used in children of all ages with TB, in combination with other anti-TB medications. The PK properties and metabolic pathways for pyrazinamide are known in adults, but have not been quantitatively described in children.

Seven potentially relevant (English language) citations were retrieved, of which five contained pharmacokinetic data from approximately 150 children aged 1 to 14 years, published from 1987 to 2008. Sampling processes and assay methods vary across studies, and the dosage form, method of administration as well as dosage regimens are not consistently described. *The panel recommended that if at all possible, additional information about these issues be sought from the authors.* In general the overall quality of PK evidence is low. However, the limited information available would suggest that, to achieve plasma concentrations in children comparable to those in adults that are associated with efficacy, the current recommended dosage needs to be increased. There is very little evidence, if any, of dose related toxicity in children. Efficacy and safety data are available in children but need to be formally summarized.

The panel noted in particular that despite widespread use in children aged 0-3 months of age, there is a lack of evidence to guide specific dosing recommendations in this age group. The consensus of the panel was that in current clinical practice, doses of 30 mg/kg per day are frequently used.

The panel recommends that the dose of PZ in children above 3 months of age should be 35 mg/kg (range 30-40) per day. The maximum daily dose should not exceed the recommended adult daily dose. If data are accessible, further analysis of the IPD from recent PK studies may increase the confidence in this recommendation.

The panel noted that the current dosage forms do not provide appropriate flexibility for accurately administering the recommended dose to children of a range of weights, based on considerations of currently available dosage forms (listed) above. Specifically, the current liquid form is suitable for a 5-9 kg child but for children > 10 kg, may require 10 mL per dose or more to achieve target doses. The 150mg scored or dispersible tablet could be used for 5 kg children. The 400 mg tablet could be used for 10 kg children and two 400 mg tablets could be used for 20 kg children.

Research needs

The following research priorities were identified:

- review of any existing data in children 0-3 months
- further modelling of PK data from existing studies

Isoniazid

Current dose recommendation

The current WHO recommendation is 5 mg/kg (range 4-6) for both adults and children. Current approved labeling according to the FDA is 10-15 mg/kg or 10-20 mg/kg.

Current dosage forms

Marketed dosage forms	Products prequalified by WHO	Products available through GDF
100 mg tablet or capsule	300 mg tablet (Macleods)	100 mg tablet (Cadila, Lupin, Macleods)
300 mg tablet or capsule	100 mg tablet (Macleods)	50 mg tablet (Lupin, Macleods)

Summary of evidence discussed

See Annex 2 for studies reviewed.

Indication/target use

INH is used in children from the newborn period onwards, for treatment of active disease and latent TB infection (also referred to as prophylaxis). In treatment it is used in combination regimens; in prophylaxis it is used as single treatment. The PK properties of INH have been extensively studied and metabolism has been characterized according to acetylator phenotype and genotype in some instances.

Efficacy and safety data are available but need to be formally summarized. Although hepatoxicity of INH is well described, anecdotally it seems to be less frequent in children even at higher doses but this needs further review.

Thirty-five (English language) citations were identified containing data from approximately 7300 children aged 3 months to 14 years, published from 1956 to 2005. As noted for PZ, studies are reported poorly in general, but the extent of data available provides sufficient information about plasma concentrations in children that can be compared to those in adults. A relationship between exposure and efficacy has been established. On the basis of these data, even in homozygous slow acetylators, the recommended dose of INH should be increased. There is very little evidence, if any, of dose related toxicity in children. An additional consideration is the public health importance of reducing the risk of developing isoniazid resistance, which is more likely to occur with lower plasma concentrations.

Use of isoniazid for the treatment of latent TB infection (prophylaxis) was considered and it was noted that doses of 5mg/kg per day have been shown to be effective for this purpose. However, in making its recommendation the panel took account of the public health issues related to resistance, as noted above, and the wide therapeutic margin of safety for isoniazid. Noting the value of consistent dosage recommendations for implementation of treatment regimens at the programmatic level, on balance, the panel decided that the dose used for treatment of latent TB infection (prophylaxis) should be the same as that used for treatment.

The panel noted in particular that despite widespread use in children aged 0-3 months of age, there is a lack of evidence to guide specific dosing recommendations in this group. The consensus of the panel was that in current clinical practice, doses of 10-15 mg/kg per day are frequently used in this group.

The panel recommends that the dose of isoniazid in children above 3 months of age for treatment or prophylaxis (treatment of latent TB infection) should be 10 mg/kg (range 10-15) per day. The maximum daily dose should not exceed the recommended adult daily dose.

The panel noted that the current dosage forms would allow accurate treatment of children from 5 kg up, but with heavier children needing to take multiple tablets.

Rifampicin

Current dose recommendation

The current WHO recommendation is 10 mg/kg per day (range 8-12), including for intermittent doses. Current approved labeling according to the FDA is 10-20 mg/kg.

Current dosage forms

Marketed dosage forms	Products prequalified by WHO	Products available through GDF
150 mg tablet or capsule	(available as FDC only)	(available as FDC only)
300 mg capsule		
300 mg tablet or capsule		
20 mg/mL syrup		

Summary of evidence discussed

See Annex 3 for studies reviewed.

Indication/target use

RMP is used in children of all ages with TB, in combination with other anti-TB medications. The PK properties and metabolic pathways for rifampicin are well described in adults, and have been studied in children.

Eighteen potentially relevant citations were reviewed, of which eleven contained pharmacokinetic data from approximately 250 children aged 23 days to 14 years, published from 1969 to 1997. Sampling processes and assay methods vary across studies, and the dosage form, method of administration as well as dosage regimens are not consistently described. In the case of rifampicin, there are known potential problems with pharmaceutical manufacturing and product quality that mean this lack of reporting complicates interpretation of the study findings.[2] In general the overall quality of PK evidence is low, and the use of microbiological analysis methods which measure active metabolites further

[2] Panchagnula R, Agrawal S. Biopharmaceutic and pharmacokinetic aspects of variable bioavailability of rifampicin. *Int J Pharm.* 2004 Mar 1;271(1-2):1-4.

confounds the interpretation of many early studies. However, the information available would suggest that, to achieve plasma concentrations, efficacy relationships have been established. Most of the available PK data was based on single-dose studies. Rifampicin is known as a very potent inducer of drug metabolism, including its own metabolism. No quantitative data is available on the induction in children. However, theoretically it can be assumed that the effect of induction in children would probably be less or equal to that in adults.

If children are to attain plasma drug concentrations comparable to those concentrations in adults that are associated with efficacy, the current recommended dosage needs to be increased. Experience with rifapentine suggests that higher dosages are required to obtain similar plasma concentrations in young patients compared with those achieved in adults. Evidence of dose related toxicity in children needs to be further examined. Efficacy and safety data are available in children, but as for the other drugs, need to be formally summarized.

The panel noted in particular that, despite widespread use in children aged 0-3 months of age, there is a lack of evidence to guide specific dosing recommendations in this group. The consensus of the panel was that in current clinical practice, doses of 10-20 mg/kg per day are frequently used in this group.

The panel recommends that the dose of RMP in children above 3 months of age should be 15 mg/kg (range 10-20) per day. Dosages at the higher ranges may be preferable for children under 10 kilograms, and children with HIV infection or malnutrition. The maximum daily dose should not exceed the recommended adult daily dose.

The panel noted that the current dosage forms do not provide appropriate flexibility for accurately administering the recommended dose to children of a range of weights. Based on considerations of currently available dosage forms (listed) above, a 150 mg tablet could be used for 10 kg children and a 300 mg tablet could be used for 20 kg children. The participants noted that these tablets are not scored and cannot be fractured, and that titration is possible across weight ranges. The meeting also noted that GDF does not distribute RMP as a single product and that the market for it seems limited.

Research needs

- data in children 0-3 months
- further modelling of PK data from existing studies

Fixed-dose combinations:

Current combinations:

Product	Dosage form	Manufacturer	Source
Isoniazid 150 mg/Rifampicin 150 mg	tablet or capsule		∞
Isoniazid 100 mg/Rifampicin 150 mg	tablet or capsule		∞
Isoniazid 150 mg/Rifampicin 300 mg	tablet or capsule	Sandoz	∞*
Isoniazid 75 mg/Rifampicin 150 mg	tablet or capsule	Lupin, Sandoz, Macleods	∞*
Isoniazid 75 mg/Rifampicin 150 mg/Ethambutol 275 mg	tablet or capsule		∞
Isoniazid 75 mg/Pyrazinamide 400 mg/Rifampicin 150 mg	tablet or capsule		∞
Isoniazid 75 mg/Pyrazinamide 400mg/Rifampicin 150mg/Ethambutol 275mg	tablet	Macleods, Wyeth, Lupin, Sandoz	*
Isoniazid 30 mg/Pyrazinamide 150 mg/Rifampicin 60 mg	tablet or capsule dispersible	Macleods, Sandoz	∞ ±
Isoniazid 30 mg/Rifampicin 60 mg	tablet or capsule dispersible	Macleods, Sandoz	∞ ±
Isoniazid 150 mg/Ethambutol 400 mg	tablet	Macleods	*
Isoniazid 60 mg/Rifampicin 60 mg	tablet or capsule dispersible	Macleods, Sandoz	∞ ±

* = Prequalified by WHO
± = Available through GDF
∞ = Listed in International Drug Price Indicator Guide

After much deliberation as to the best fixed dose combinations (FDCs), the meeting participants recommended that existing formulations were not optimal. It was concluded that ideally, both a three and a four-drug tablet would be necessary but that a three-drug combination constitutes the first priority, with the possibility of adding ethambutol as a separate tablet if needed. More specifically, the meeting decided on the following ideal formulation: Isoniazid 100 mg/Pyrazinamide 350 mg/Rifampicin 200 mg/(Ethambutol 200 mg). From a biopharmaceutical perspective, the ideal formulation would be readily dispersible and scored to a sufficient depth to allow accurate splitting of the tablet while maintaining the integrity of the final dosage form.

It would then be possible for a half tablet to be used for a 5 kg child, one tablet for a 10 kg child, 1.5 tablets for a 20 kg child and two tablets for a 30 kg child.

Next steps and outstanding issues

Guideline revision process

The recommendations from this technical meeting will be discussed at the TB Guidelines meeting later in 2008. A decision by the STB Department will be made as to whether the treatment guidelines for children will be further updated as a separate process.

To confirm the recommendations, a number of topics were identified as needing urgent evidence reviews:

1. A summary of the evidence from clinical trials on the use of first-line TB drugs for the treatment of children, including a review of safety and adverse reactions.

2. Further development of recommendations on whether the current dosage forms, specifically the FDC products, can be used appropriately in children of various ages and weights, particularly in younger age groups. The following table provides an estimate of plasma concentrations that could be achieved with the currently available formulations (Isoniazid 30 mg/Pyrazinamide 150 mg/Rifampicin 60 mg/; Isoniazid 30 mg/Rifampicin 60 mg and Isoniazid 60 mg/Rifampicin 60 mg) in children weighing 5, 6, 7, 8 and 9 kg. As shown, the 60 mg dose of rifampicin in the currently available formulations would be appropriate only for children of 5 and 6 kg who have a strain of M. tuberculosis that has an MIC of 1.0. With a more sensitive organism (MIC 0.1), it would be possible for the 60 mg RMP dose to be effective for the entire 5 to 9 kg weight band. Children weighing more than 9 kg would need to take multiple tablets of this combination.

Weight (kg)	Dose (mg/kg)	Cmax at 2 hr (mg/L)	% of Q24hr dose interval where C > MIC (of 1 mg/L)
5	12	9.0	39.1
6	10	7.5	36.8
7	8.6	6.4	35
8	7.5	5.6	33.3
9	6.7	5	32

Outstanding issues for further research:

Several topics were identified as needing further investigation and clinical trials:

Key priorities, possible to commence immediately pending funding:

1. Individual patient data analysis of the PK data on PZA from the published literature with modelling of population PK data if possible.
2. Review of any existing data on use of first-line TB medicines in children 0-3 months.
3. Review of existing data on the use of intermittent dose treatment regimens in children.
4. Review of evidence on the treatment of tuberculous meningitis in children.
5. Review of evidence on the treatment of HIV/TB co-infection in children although currently the available evidence suggests that there is no need to adjust the doses for untreated HIV infected and malnourished children.
6. Review of evidence of the effect of malnutrition on the efficacy and safety of first-line medicines for TB in children.

Additional topics

1. Interaction of existing dosage forms with foods/liquids commonly used as mixers to administer medicines to children
2. Development of a guide on recommended/acceptable methods to administer medicines to children
3. Pharmacoanthropologic study of medication administration to children in different cultures
4. Studies (using optimal formulations) on the induction of drug metabolism caused by rifampicin in children, particularly newborns.

In addition, the meeting suggested that further clinical trials in children with TB are clearly needed, particularly if new products can be developed in new dosage forms that are more suitable than the exciting products. Clinical trials are especially needed to test whether the assumptions made by the meeting's participants on the basis of available pharmacokinetic data hold up to expectations, especially regarding drug side effects.

Update of WHO Model List of Essential Medicines for Children

The meeting report will be presented to the next meeting of the Subcommittee on Essential Medicines for Children, to inform their review of the current medicines listed for paediatric first-line treatment of TB.

Annex 1: Summary of evidence on pyrazinamide

	Authors	Analysis Method	Single Dose?	Dose mg/kg	Age or Weight	n
1.	Magdorf 1987	Mass fragmentography	Not stated	34 children received 30; 21 children received only PZA and 13 received INH (5-10) and RMP (10-15)	1-14 yrs	34
2.	Donald et al 1988	HPLC	Not stated	40	Not stated	13
3.	Le Bourgeois et al 1989	Not stated	Not stated	Mean 23.3	Not stated	43
4.	Roy et al 1999	Spectrophotometry	Not stated	35	6-12 yrs (16-34kg)	10
5.	Zhu et al 2002	Gas chromatography assay	Established	25	21 children had mean age 4 yrs; 2 others were described with adults	23
6.	Graham et al 2006	HPLC	Not stated	Mean 33	Mean 5.7 yrs (Mean 14.3 kg weight)	27
7.	Gupta et al 2008	Spectrophotometry	Single	15 and 25	5-12 yrs	20

Annex 1 references:

1. **Magdorf K**. Intensiv-Anfangsbehandelung bei der Kindertuberkulose unter besonderer Berücksichtigung des pyrazinamids. *Intensivbehandelung* **1987**; 12:99-102.
2. **Donald PR**, Seifart HI. Cerebrospinal fluid pyrazinamide concentrations in children with tuberculous meningitis. *Pediatr Infect Dis J* **1988**; 7:469-71.
3. **le Bourgeois M**, de Blic, Paupe J, Scheinmann P. Good tolerance of pyrazinamide in children with pulmonary tuberculosis. *Arch Dis Child* **1989**; 64:177-8.
4. **Roy V**, Tekur U, Chopra K. Pharmacokinetics of pyrazinamide in children suffereing from pulmonary tuberculosis. *Int J Tuberc Lung Dis* **1999**; 3:133-7.
5. **Zhu M**, Starke JR, Burman WJ, et al. Population pharmacokinetic modeling of pyrazinamide in children and adults with tuberculosis. *Pharmacother* **2002**; 22:686-95.
6. **Graham SM**, Bell DJ, Nyirongo S, Hartkoorn R, Ward SA, Molyneux EM. Low levels of pyrazinamide and ethambutol in children with tuberculosis and impact of age, nutritional status and human immunodeficiency virus infection. *Antimicrob Agents Chemother* **2006**; 50:407-13.
7. **Gupta P**, Roy V, Sethi GR, Mishra TK. Pyrazinamide blood concentrations in children suffering from tuberculosis: a comparative study at two doses. *Brit J Clin Pharmacol* **2008**; 65:423-7.

Annex 2: Summary of evidence on isoniazid

	Authors	Analysis Method	Single Dose?	Dose mg/kg	Age	n
1.	Debré 1956	Not stated	Not stated	10 w/ children >2yrs old; 20 with children <2 yrs old Meningitis: 20 in older children and 30-40 in younger children	Not stated	Not stated
2.	Cocchi 1956	Not stated	Not stated	10-15	Not stated	Not stated
3.	Lincoln et al 1956	Not stated	Not stated	4 at first and then 20 once child diagnosed with meningitis	3.5 yrs	1
4.	U.S. Public Health Service 1957	Not stated	Not stated	4-6	Not stated	2750
5.	Lanier et al 1958	Microbiological assay	Not stated	12 children received 4; 45 children received 7-9 (Not clear)	Not stated	12+45+21 children 300 adults (Not clear)
6.	Levy et al 1960	Not stated	Not stated	8	103 children < 7yrs	169
7.	Bartmann et al 1961	Not stated	Not stated	Recommend 200	Not stated	Not stated
8.	Mount et al 1961	Bioassay	Not stated	4-6 but test dose of 8	Not stated	770
9.	Simane et al 1961	Not stated	Not stated	10	1-12 yrs	48
10.	Lupasco et al 1965	Not stated	Not stated	Suggest 10	<10yrs	96
11.	Comstock et al 1969	Not stated	Not stated	Two groups: 1.25 and 5	Not stated	1701
12.	Akabani et al 1977	Fluorometry/ spectrophotometry	Not stated	10	Not stated	12
13.	Stevenson 1977	Not stated	Not stated	Not stated	Not stated	Not stated
14.	Llorens et al 1978	Method of Maher et al 1957	Not stated	Three groups: RMP 15; INH 15; RMP15/INH 15	<3yrs	30
15.	Buchanan et al 1979	Not stated	Not stated	Not stated	Not stated	7
16.	Advenier et al 1981	Not stated	Not stated	Not stated	0.5-17yrs	134
17.	Olson et al 1981	Spectrophotometry	Not stated	5.8-20	1.5-15yrs	6
18.	Bouveret et al 1983	Fluorometry	Not stated	10	Mean 6.4 (±4.5) years	186

	Authors	Analysis Method	Single Dose?	Dose mg/kg	Age	n
19.	Cheminat et al 1983	Not stated	Not stated	1.64-13.3	Not stated	204
20.	Beltran et al 1986	Not stated	Not stated	INH 5, RMP 10 and PZA 30	"14" yrs (but could be error: <14)	112
21.	Kergueris et al 1986	Fluorometry	Not stated	5	16 were ≤15yrs	458
22.	Notterman et al 1986	Spectrophoto fluorometry	Not stated	INH 20, RMP 20 and SM 40 (in apple sauce)	8 months	1
	"	Same as above	Not stated	Same as above	12 and 18 yrs	2
23.	Steensma et al 1986	Not stated	Not stated	4-8 (Mean dose 5.1)	Not stated	45
24.	Eriksson et al 1988	Spectro-photometry	Not stated	10	6 months-12 yrs	41
25.	Seth et al 1990	HPLC	Not stated	10	0-13 yrs	70
26.	Pariente-Khayat et al 1991	Not stated	Not stated	Not stated	8-447 days (children with variety of conditions)	54 with variety of conditions and 5 with Pierre-Robin syndrome
27.	Donald et al 1992	HPLC	Not stated	10 and 20	Not stated	38
28.	Seth et al 1992	Not stated	Not stated	INH 10 and RMP 12	Not stated	Not stated
29.	Seth et al 1993	Spectro-fluorometry assay	Not stated	10	1-13yrs	94
30.	Seth et al 1994	HPLC	Not stated	INH 20 and RMP 12	1-13yrs	20
31.	Seifart et al 1995	Not stated	Not stated	20	Not stated	13
32.	Roy et al 1996	Spectro-photometry	Not stated	2 groups: received 5 or 10	6-12	20
33.	Rey et al 1998	Not stated	Not stated	10	Not stated	61
34.	Rey et al 2001	HPLC	Single	10	Not stated	34
35.	Schaaf et al 2005	HPLC	Not stated	10	Mean 3.8yrs	64

Annex 2 references:

1. **Debré R**, Brissaud HE. Present method and results of treatment of tuberculous meningitis. *Am Rev Tuberc* **1956**; 74 (suppl):221-4.
2. **Cocchi C**. Cortisone and corticotrophin in the treatment of tuberculosis in infancy and childhood. *Am Rev Tuberc* **1956**; 74 (suppl):209-16.
3. **Lincoln EM**, Lythcott GI. Tuberculous meningitis developing in the course of isoniazid therapy. *Am Rev Tuberc* **1956**; 73:940-3.
4. **United States Public Health Service**. Prophylactic effects of isoniazid on primary tuberculosis in children. *Am Rev Tuberc* **1957**; 76:942-63.
5. **Lanier VS**, Russel WF, Heaton A, Robinson A. Concentrations of active isoniazid in serum and cerebrospinal fluid of patients with tuberculosis treated with isoniazid. *Pediatrics* **1958**; 21:910-4.
6. **Levy D**, Russel WF, Middlebrook G. Importance of individualization of chemotherapy in childhood tuberculosis. *Am J Dis Child* **1960**; 100:695-6.
7. **Bartmann K**, Massmann W. Experimentelle Untersuchungen zur Dosierung von INH. *Beitr Klin Tuberk* **1961**; 124:310-9.
8. **Mount FW**, Anastasiades AA, Schnack GA. Control study of biologically active isoniazid in serum of children with primary tuberculosis *Am Rev Respir Dis* **1961**; 83:173-83.
9. **Simane Z**, Kraus P, Roter Z, Wagner J. INH Stoffwechsel bei Kindern. *Bietr Klin Tuberk* **1961**; 123:161-5.
10. **Lupasco I**, Algeorge G, Ghiu-Cipeanu V. Taux d'isoniazide actif dans le sérum des enfants tuberculeux. *Poumon Coeur* **1965**; 21:1105-14.
11. **Comstock GW**, Hammes LM, Pio A. Isoniazid prophylaxis in Alaskan boarding schools. *Am Rev Respir Dis* **1969**; 100:773-9.
12. **Akabani Y**, Bolme P, Lindblad BS, Rahimtoola RJ. Control of streptomycin and isoniazid in malnourished children treated for tuberculosis *Acta Paediatr Scand* **1977**; 66:237-40.
13. **Stevenson I**. Factors influencing antipyrine elimination. *Br J Clin Pharmacol* **1977**; 4:261-5.
14. **Llorens,** Serrano RJ, Sanchez R. Pharmacodynamic interference between rifampicin and isoniazid. *Chemotherapy* **1978**; 24:97-103.
15. **Buchanan N,** Eyberg C, Davis MD. Isoniazid pharmacokinetics in kwashiorkor. *S Afr Med J* **1979**; 56:299-300.
16. **Advenier C**, Saint-Aubin A, Scheinmann P, Paupe J. Pharmacocinétique de l'isoniazide chez l'enfant. *Rev Fr Mal Resp* **1981**; 9:365-74.
17. **Olson WA**, Pruitt AW, Dayton PG. Plasma concentrations of isoniazid in children with tuberculous infections. *Pediatrics* **1981**; 67:876-8.
18. **Bouveret JP,** Hanoteau J, Gerbeaux J, Houin G, Tillement JP. Variations de l'indice d'inactivation de l'isoniazide au cours des traitements antituberculeux chez l'enfant. *Archiv Fr Pediatr* **1983**; 40: 615-9.
19. **Cheminat J-C**, Paire M, Lavarenne J, Ducarrouge C, Molina C. Intérêt de la détermination de l'INH plasmatique au cours du traitement antituberculeux. *Rev Fr Mal Resp* **1983**; 11:867-73.
20. **Beltran ORP**, Pelosi F, Budani H, et al. The treatment of child tuberculosis with isoniazid (H), rifampicin (R) and pyrazinamide (Z). *Bull Internat Union Tuberc* **1986**; 61:17 (A020).
21. **Kergueris MF**, Bourin M, Larousse C. Pharmacokinetics of isoniazid: influence of age. *Eur J Clin Pharmacol* **1986**; 30:335-40.
22. **Notterman DA**, Nardi M, Saslow JG. Effect of dose formulation of isoniazid in two young children. *Pediatrics* **1986**; 77:850-2.
23. **Steensma JT,** Nosent G. INH dosage in children. *Bull Internat Union Tuberc* **1986**; 61:110.
24. **Eriksson M**, Bolme P, Habte D, Paalzow L. INH and streptomycin in Ethiopian children with tuberculosis and different nutritional status. *Acta Paediatr Scand* **1988**; 77:890-4.
25. **Seth V**, Beotra A, Semwal OP, Mukopahya S. Monitoring of serum rifampicin and isoniazid levels in childhood tuberculosis. *Am Rev Respir Dis* **1990**; 141(suppl): A 337.

26. **Pariente-Khayat A**, Pons G, Rey E, et al. Caffeine acetylator phenotyping during maturation in infants. *Pediatr Res* **1991**; 29:492-5.
27. **Donald PR**, Gent WL, Seifart HI, Lamprecht JH, Parkin DP. Cerebrospinal fluid Isoniazid concentrations in children with tuberculous meningitis: the influence of dosage and acetylation status. *Pediatrics* **1992**; 89: 247-50.
28. **Seth V**, Beotra A, Bagga A, Seth S. Drug therapy in malnutrition. *Indian Pediatr* **1992**; 29:1341-6.
29. **Seth V**, Beotra A, Seth SD, Semwal OP, Kabra S, Jain Y, Mukhopadhya S. Serum concentrations of rifampicin and isoniazid in tuberculosis. *Indian Pediatr* **1993**; 30: 1091-8.
30. **Seth V**, Seth SD, Beotra A, Semwal OP, D'monty V, Mukhopadya S. Isoniazid and acetylisoniazid kinetics in serum and urine in pulmonary primary complex with intermittent regimen. *Indian Pediatr* **1994**; 31:279-85.
31. **Seifart HI**, Donald PR, de Villiers JN, Parkin DP, van Jaarsveld PP. Isoniazid elimination kinetics in children with protein-energy/malnutrition treated for tuberculous meningitis with a four-component antimicrobial regimen. *Ann Trop Paediatr* **1995**; 15: 249-54.
32. **Roy V**, Tekur U, Chopra K. Pharmacokinetics of isoniazid in pulmonary tuberculosis - a comparative study at two dose levels. *Indian Pediatr* **1996**; 33:287-91.
33. **Rey E**, Pons G, Crémier O, et al. Isoniazid dose adjustment in a pediatric population. *Ther Drug Monitor* **1998**; 20:50-5.
34. **Rey E**, Gendrel D, Treluyer JM, et al. Isoniazid pharmacokinetics in children according to actylator phenotype. *Fund Clin Pharmacol* **2001**; 15:355-9.
35. **Schaaf HS**, Parkin DP, Seifart HI, et al. Isoniazid pharmacokinetics in children treated for respiratory tuberculosis. *Arch Dis Child* **2005;** 90: 614-8.

Annex 3: Summary of evidence on rifampicin

Rifampicin maximum serum concentration (Cmax) in children following a single oral dose.

Authors	Dose (mg/kg)	age	n	Cmax (μg/ml)
Kofman et al 1969	20	-	3	21.9
"	15	-	3	11.7
"	20	-	3	11.2
"	20	-	3	9.6
Bergamini et al 1970	20	8-12 months	14	10.2
	10	8-12 months	14	3.7
Acocella et al 1970	10	4-18 months	12	3.5
Hussels et al 1973	10	2-<6 years	7	4.5
"	10	2-<6 years	7	6.5
"	10	6-10 years	11	5.3
"	10	6-10 years	11	7.1
"	10	10-14 years	9	5.4
"	10	10-14 years	9	6.6
McCracken et al 1980)	10 Suspension	6-58 months	21	9.2
«	10 Suspension in apple sauce	6-58 months	12	6.2
«	10 Powder in apple sauce	6-58 months	5	8.8
Tan et al 1993	10	Mean 23 days	4	2.8

Rifampicin maximum serum concentration (Cmax) in children established on rifampicin.

Authors	Dose (mg/kg)	age	n	Cmax (μg/ml)
Kofman et al 1969	20	-	1	9.6
De La Roy et al 1974	15	2months-5 years	20	5.2
Seth et al 1992	12	1-13 years	15 Normal nutrition	3.0
«	12	«	30 Malnutrition	3.3
«	12	«	10 Malnutrition	3.4
Seth et al 1993	12	1-13 years	29 Primary Complex	3.9
«	«	«	5 Progresssive Primary TB	3.4
«	«	«	5 Tuberculous meningitis	3.9
Mahajan et al 1997	10	6 months-10 years	10	3.8
«	7.5	«	10	2.2

Annex 3 references:

Table 1:

1. **Kofman I**, Galimberti H, Mara R. Niveles séricos y urinarios de rifampicina en niňos. *El Dia Méd* **1969**; 41:477-9.
2. **Bergamini N**, Matnardi L, Rosaschino F. Tassi ematici eliminazione urinaria di rifampicina nei lattanti. *Aggiorn Pediat* **1970**; 21:191-7.
3. **Acocella G,** Buniva G, Flauto U, Nicolis FB. Absorption and elimination of the antibiotic rifampicin in newborns and children. Proc 6th Int Congress of Chemotherapy; Tokyo 1969, Vol 2: *Univ Tokyo Press.* Tokyo **1970;** 755-60.
4. **Hussels H,** Kroening U, Magdorf K. Ethambutol and rifampicin serum levels in children: second report on the combined administration of ethambutol and rifampicin. *Pneumonologie* **1973**; 149:31-8.
5. **McCracken GH**, Ginsburg CM, Zweighaft TC, Clahsen J. Pharmacokinetics of rifampin in infants and children: relevance to prophylaxis against *Haemophilus influenzae* type B disease. *Pediatrics* **1980**; 66:17-21.
6. **Tan TQ**, Mason EO, Ou C-N, Kaplan SL. Use of intravenous rifampin in neonates with persistent staphylococcal bacteraemia. *Antimicrob Agents Chemother* **1993**; 37: 2401-2406.

Table 2:

1. **Kofman I**, Galimberti H, Mara R. Niveles séricos y urinarios de rifampicina en niňos. *El Dia Méd* **1969**; 41:477-9.
2. **De Rautlin de la Roy Y,** Hoppeler A, Creusot G, Bruault AM. Taux de rifampicine dans le sérum et le liquide céphalo-racidiene chez l'enfant. *Arch France Péd* 1**974**; 31: 477-88.
3. **Seth V**, Beotra A, Bagga A, Seth S. Drug therapy in malnutrition. *Indian Pediatr* **1992**; 29:1341-6.
4. **Seth V**, Beotra A, Seth SD, Semwal OP, Kabra S, Jain Y, Mukhopadhya S. Serum concentrations of rifampicin and isoniazid in tuberculosis. *Indian Pediatr* **1993**; 30:1091-8.
5. **Mahajan M**, Rohatgi D, Talwar V, Patni SK, Mahajan P, Agarwal DS. Serum and cerebrospinal fluid concentrations of rifampicin at two dose levels in children with tuberculous meningitis. *J Commun Dis* **1997**; 29:269-74.

Annex 4: Meeting agenda and presentations

Day 1
Chairperson: Mr Robert Matiru

Tuesday, 8 July		
09.00 -09.15	Welcoming remarks	Dr Hans V. Hogerzeil Director, STB Director, CAH
09.15 - 09.30	Introductions Declaration of Interests	Chair
09.30 -10.00	Objectives of the meeting	WHO
10.00 - 10.30	Background information • current recommendations on the first line TB medicines for children • current products • summary of ethambutol review	Malgosia Grzemska Robert Matiru Shamim Qazi
10.30 - 11.00	Overview of review	Peter Donald
11.00-11.30	*Coffee*	
11.30 -13.00	Pyrazinamide • summary of evidence • pharmacokinetics / clinical pharmacology • recommendations	Peter Donald Stephen Spielberg -
13.00-14.00	*lunch*	
14.00-15.30	Isoniazid • summary of evidence • pharmacokinetics / clinical pharmacology	Peter Donald Kalle Hoppu
15.30-15.45	*Coffee*	
15.45-16.45	Isoniazid • recommendations	
16.45 - 17.00	Summing up and close	

Day 2
Chairperson: Dr Suzanne Hill

Wednesday, 9 July		
09.00 - 09.15	Welcome	Chair
09.15 - 10.45	Rifampicin • summary of evidence • pharmacokinetics / clinical pharmacology	 Peter Donald Greg Kearns
10.45 - 11.00	*Coffee break*	
11.00 -12.00	Rifampicin recommendations	
12.00 - 13.00	Evidence for fixed dose combinations	
13.00 -14.00	*Lunch*	
14.00 - 15.30	Recommendations for fixed dose combinations	
15.30 - 16.00	*Coffee*	
16.00 - 17.00	Next steps Close	

Annex 5: List of participants

Temporary Advisers	
Dr Lisa Adams Assistant Professor, Department of Medicine Section of Infectious Disease and International Health Director, Dartmouth's Global Health Initiative Dartmouth Medical School 6048 Haldeman, Dartmouth College Hanover, NH 03755 USA Telephone: +1 603 646 2023 Fax: +1 603 646 2168 E-mail: lisa.v.adams@dartmouth.edu	**Dr Peter Roderick Donald** Department of Paediatrics and Child Health Faculty of Health Sciences Stellenbosch University, Francie van Zijl Drive Tygerberg 7505 South Africa Telephone: +27 21 938 9592 Fax: +27 21 938 9138 E-mail: prd@sun.ac.za
Dr Rohini Fernandopulle Senior Lecturer, Department of Pharmacology, Faculty of Medicine, University of Colombo, P.O. Box 271, Kynsey Road, Colombo 8 Sri Lanka Telephone: +94-1 695 300 ext 410 Fax: +94-1 691 581 E-mail: rohinifernandopulle@hotmail.com, rohini12@sltnet.lk	**Dr Robert Gie** Department of Paediatrics and Child Health Faculty of Health Sciences Stellenbosch University PO Box 19063, Tygerberg 7505 South Africa Telephone: +27 21 938 506 Fax: +27 21 938 138 E-mail: rpg1@sun.ac.za
Dr Kalle Hoppu, Director, Poison Information Centre Helsinki University Central Hospital PO Box 790 (Tukholmankatu 17), 00029 HUS Helsinki Finland Telephone: +358 9 471 74 788 Fax: 358 9 471 74 702 E-mail: kalle.hoppu@hus.fi	**Professor Cleotilde Hidalgo How** Professor, Department of Pharmacology & Toxicology, University of the Philippines (UP) College of Medicine, College of Medicine, UP Manila 547 Pedro Gil Street, Ermita, 1000, MM Philippines Telephone: +63 2 526 4248 Fax: +63 2 521 8251 E-mail: tellyhow@yahoo.com
Dr Thomas P. Kanyok Senior Program Officer, Global Health- Infectious Diseases Bill and Melinda Gates Foundation PO Box 23350 Seattle, WA 98102 USA Mobile: +1 206 604 8303 E-mail: Thomas.Kanyok@gatesfoundation.org	**Dr Gregory Kearns** Professor of Paediatrics and Pharmacology University of Missouri Kansas City (UMKC) 2401 Gillham Road, Kansas City MO 64108 USA Telephone: +1 816 234 3961 Fax: +1 816 855 1703 E-mail: gkearns@cmh.edu

Temporary Advisers	
Dr Stephen Spielberg Dean, Professor of Paediatrics Pharmacology and Toxicology Dartmouth Medical School, 1 Rope Ferry Rd. Hanover, NH 03755 USA Telephone: +1 603 650 1200 Fax: +1 603 650 1202 E-mail: Stephen.p.spielberg@dartmouth.edu	**Dr Jeffrey Starke** Texas Children's Hospital, MC 3-2371, 1102 Bates Street Houston, Texas 77030 USA Telephone: +1 713 873 3504 Fax: +1 713 873 3505 E-mail: jrstarke@texaschildrens.org
Dr Anita Zaidi Associate Professor Department of Paediatrics and Microbiology Aga Khan University, Stadium Road P. O. Box 3500, Karachi 74800 Pakistan Telephone: +92 21 486 4734 Fax: +92 21 493 4294 E-mail: anita.zaidi@aku.edu	

WHO Secretariat	
Dr Suzanne Hill Department of HSS/PSM/PAR hills@who.int	**Dr Hans Hogerzeil** Department of HSS/PSM hogerzeilh@who.int
Dr Malgosia Grzemska Department of HTM/STB/TBS grzemskam@who.int	**Dr Lulu Massa Muhe** Department of FCH/CAH/NCH muhel@who.int
Mr Robert H. Matiru Department of HTM/STB/TBP matirur@who.int	**Dr Shamim Ahmad Qazi** Department of HQ/DG/FCH/CAH/NCH qazis@who.int
Dr Mario Raviglione Department of HTM/STB raviglionem@who.int	