EVIDENCE-BASED CHILD HEALTH: A COCHRANE REVIEW JOURNAL
Evid.-Based Child Health **5**: 1566–1577 (2010)
Published online in Wiley Online Library (onlinelibrary.wiley.com). **DOI:** 10.1002/ebch.589

Beyond Randomized Trials – TB treatment in Children

Anna Ridge,[1]* Patti Whyte,[2] Malgosia Grzemska,[3] Peter Donald[4] and Suzanne Hill[1]

[1]*Medicine Access and Rational Use, Department of Essential Medicines and Pharmaceutical Policies, World Health Organization, Geneva, Switzerland*
[2]*1110 Joan Avenue, Dromana, Victoria, Australia 3936*
[3]*Tuberculosis, Operations and Coordination, Stop TB Department, World Health Organization, Geneva, Switzerland*
[4]*Department of Paediatrics and Child Health and Division of Molecular Biology and Human Genetics and the MRC Centre for Molecular and Cellular Biology, DST/NRF Centre of Excellence for Biomedical TB Research, Faculty of Health Sciences, University of Stellenbosch and Tygerberg Children's Hospital, Stellenbosch, South Africa*

Introduction

Tuberculosis (TB) represents a major cause of morbidity and mortality in the paediatric population. Of the estimated 8.3 million new tuberculosis cases diagnosed worldwide in 2000, 884,019 (11%) were children (1). Due to the difficulty of establishing an accurate diagnosis of tuberculosis in children, exact figures are difficult to calculate. In endemic areas their contribution to disease burden has been estimated to be up to 14% (2).

The impact of TB is particularly devastating in young children as they are more likely than adults to develop TB disease following exposure to the bacterium *Mycobacterium tuberculosis*, are at increased risk for severe disease, including disseminated and meningeal TB and have disproportionately higher rates of morbidity and mortality (3–5). It is well recognized that for treatment of TB in adults, proper dosages and duration of treatment are key to reducing the risk of progression from latent to active TB disease, achieving high rates of cure and preventing development of drug-resistant disease. The same should be true for the treatment of TB in children.

The WHO guideline for national TB programmes in children was first published in 2006 (6). This publication included revised recommendations on the use of ethambutol in children, following a review of efficacy and safety (7). The amended daily dose of ethambutol for children of all ages was 20 mg/kg, with a range of 15–25 mg/kg. The previously recommended daily dose of ethanbutol for children varied from 15 mg/kg (without range) to 15–20 mg/kg and 20 mg/kg (range 15–25 mg/kg), with advice not to use in children <5 years of age. In undertaking that review, two issues were highlighted: first, that children metabolize TB medicines differently than do adults, and second, that there was evidence available to inform dosage recommendations about these 'old' drugs. Neither of these findings are new but the systematic consideration of the findings to inform WHO recommendations was important.

*Correspondence to: Anna Ridge, Medicine Access and Rational Use, Department of Essential Medicines and Pharmaceutical Policies, World Health Organization, Geneva, Switzerland. E-mail: ridgea@who.int

To update the WHO 2006 recommendations for the treatment of TB in children, a series of literature reviews of clinical studies were carried out. As there are very few randomized trials of TB treatment in children, it was decided to include observational and pharmacokinetic studies to inform treatment decisions and ensure that all available evidence was considered. This overview provides a summary of the reviews and key issues encountered when using the data to develop recommendations. The new WHO Guidelines for the treatment of TB in children can be found at: http://whqlibdoc.who.int/publications/2010/9789241500449_eng.pdf and/or http://www.stoptb.org/wg/dots_expansion/childhoodtb/assets/documents/GuidelinesFinal%209Nov2010.pdf

Methods

Guideline scope

The guideline revision was carried out according to the process for developing WHO guidelines (8). The key questions that were the basis of the guideline scope were:

Pulmonary tuberculosis

- What are the optimal doses of isoniazid, rifampicin and pyrazinamide, taking into account the comparative risk of hepatotoxicity, for the treatment of pulmonary TB in children?
- Should children with suspected or confirmed pulmonary TB or tuberculous lymphadenopathy be treated with intermittent regimens (meaning drugs are given 2 or 3 days per week instead of daily)?
- Should infants 0–3 months with suspected or confirmed pulmonary TB be treated with the new optimal doses of isoniazid, rifampicin and pyrazinamide that are recommended for older children?
- Should streptomycin be used as part of first-line treatment regimens for children with pulmonary TB or TB peripheral lymphadenopathy?

Extra-pulmonary tuberculosis

- What should be the recommended treatment regimen for TB meningitis in children?

- What should be the recommended treatment regimen for osteo-articular TB in children?.

Each question was the basis of a comprehensive review of the literature.

Search strategy

A preliminary literature search identified no Cochrane reviews of TB treatment in children, one published systematic review and five randomized trials of treatment of TB. It was therefore decided that the reviews should include pharmacokinetic studies of isoniazid, rifampicin and pyrazinamide in children as well as observational studies and case reports of TB treatment where relevant.

Full search methods are described in each review (9–12). However, the general approach is described below.

To identify relevant studies, a combination of the following electronic databases were used: Cochrane Controlled Trials Register, Cochrane Database of Systematic Reviews and MEDLINE/PubMed (1950 to present). No language limits were placed on the searches. French, German, Italian and Spanish papers were reviewed if accompanied by an English abstract. Searches were limited to children $\leq$18 years unless otherwise specified. Search terms tailored to each specific topic were:

1. **Pharmacokinetic review:** (isoniazid OR rifampicin OR pyrazinamide) AND childhood AND (pharmacokinetics OR pharmacodynamics).
2. **Antituberculosis drug-induced hepatotoxicity:** (hepatotoxicity OR hepatitis OR liver injury) AND (antituberculosis treatment OR chemoprophylaxis OR chemotherapy OR isoniazid OR rifampin OR rifampicin OR pyrazinamide) AND (childhood OR children OR paediatric).
3. **Safety and efficacy of medicines for TB preventive therapy and treatment in neonates:** (isoniazid OR ethambutol OR pyrazinamide OR rifampin) AND (tuberculosis OR tuberculosis multidrug-resistant). Search limited to 'All infant: birth–23 months'
4. **Intermittent treatment in children:** Drug administration schedule AND (isoniazid OR ethambutol OR pyrazinamide OR rifampin) AND (tuberculosis OR tuberculosis, multidrug-resistant) AND (drug intermittent therapy OR drug intermittent dosage).
5. **Streptomycin in the treatment of uncomplicated pulmonary TB in children:** tuberculosis pulmonary AND streptomycin AND (children OR pediatric OR paediatric)
6. **Chemotherapy of tuberculous meningitis in children:** (tuberculous meningitis OR CNS) AND (isoniazid OR rifampin OR rifampicin OR pyrazinamide OR streptomycin) AND (treatment OR chemotherapy)
7. **Chemotherapy of osteo-articular TB in children**: (tuberculosis of the spine OR tuberculous osteomyelitis OR bone tuberculosis OR joint tuberculosis) AND (treatment OR chemotherapy)

For each review, references were cross-checked and experts in the field contacted for possible unpublished data. To assess clinical efficacy, all intervention studies (with or without a control group) were included. Studies reporting treatment outcomes in children and adults were included in the chemotherapy reviews for tuberculous meningitis, osteo-articular TB and tuberculous lymphadenopathy. For safety data, all study designs were considered eligible for inclusion, including randomized controlled trials (RCT), quasi-RCTs, case-control studies, case reports and case series describing different drug dosages and different schedules.

Results

Figure 1 show the overall numbers of citations retrieved. The summary of studies finally included in the review and used for developing recommendations is in Table 1. The overall body of evidence comprised 5 RCTs and 131 observational studies.

Pharmacokinetics reviews

Thirty-five studies were identified reporting data for isoniazid from approximately 7300 children aged 3 months to 14 years, published from 1956–2005. Five studies reported pharmacokinetic data for pyrazinamide from approximately 150 children aged 1–14 years published from 1987 to 2008 and 15 studies reported PK data for rifampicin from approximately 347 children aged <3 days to 14 years, published from 1969–1997 (see Table S1 in the Supporting Information, available from the online version of this article).

Sampling processes and assay methods varied across the studies. The dosage form of the products used, the method of administration, as well as dosage regimens were not consistently described. The use of microbiological analysis methods, which measure active metabolites, further confounded the interpretation of many of the rifampicin studies. In general, the quality of the evidence was poor. Out of 35 studies reporting results for isoniazid, 16 studies did not report the age range of the participants and 19 studies did not report the assay method used. However, for each medicine sufficient information about plasma concentrations in children could be compared to those in adults and a relationship between exposure and efficacy could be established.

In one comparative PK study between adults and children, children required higher mg/kg doses to ensure plasma concentrations equivalent to those in adults (13). On the basis of the available pharmacokinetic data, and taking into account the public health importance of reducing the risk of developing isoniazid resistance which is more likely to

DOI: 10.1002/ebch.589

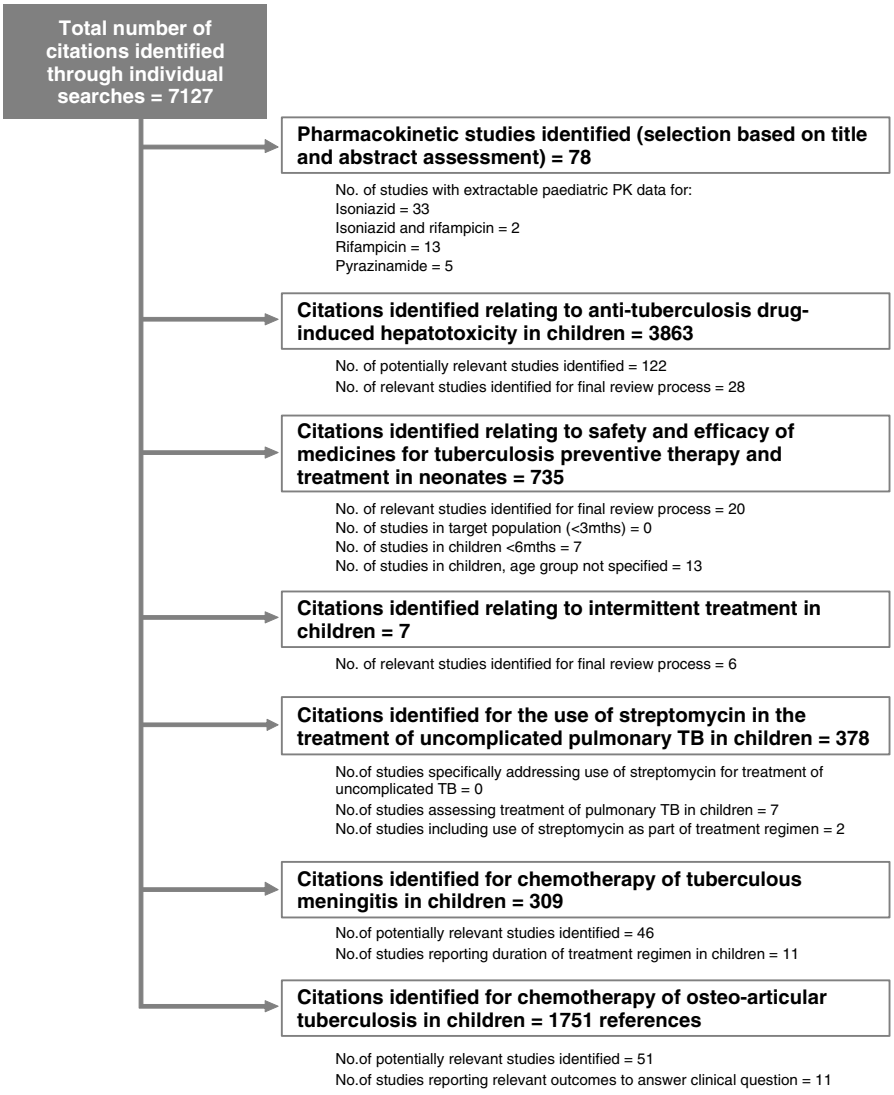

Figure 1. Flow diagram for selected studies

occur with lower plasma concentrations, the review indicated that the dosage of INH for use in children should be increased to 10 mg/kg (range 5–15 mg/kg) per day, even in homozygous slow acetylators. The wide range for INH arises from two variables, age and genotype. For an adult, a dosage of 3 mg/kg in an homozygous NAT2 slow acetylator will give the same INH exposure as approximately 9 mg/kg in a homozygous rapid acetylator. In adults, it is possible to use a standard dosage with a limited range (5 mg/kg, range 4–6 mg/kg) because INH has a very wide therapeutic margin. However, in children further differences arise from the age related changes in drug metabolism which lead to younger children getting higher mg/kg dosages. In India most individuals are slow acetylators of INH; in Japan nearly 90% are homozygous rapid acetylators, therefore international recommendations must take into account these considerable differences in INH metabolism across the world.

Pharmacokinetic data for pyrazinamide indicated that mean dosages of PZA >30 mg/kg in children >5 years of age resulted in peak plasma concentrations and AUC_{0-24} comparable to those reported in adults receiving a similar PZA dose. Results from two studies that included children ≤4 years indicated that a dosage <30 mg/kg would result in a significant proportion of younger children not reaching the desired plasma concentrations of PZA (14–15). Findings of the review indicated that the daily dosing of PZA for children older than 3 months should be 35 mg/kg (range 30–40).

Based on the results from the 14 studies measuring rifampicin plasma concentrations in children and compared to those of adults, the pharmacokinetic review suggested that the dose of rifampicin for children above 3 months of age should be 15 mg/kg (range 10–20 mg/kg) per day.

Overall, the review of the pharmacokinetics of isoniazid, pyrazinamide and rifampicin in children demonstrated that children needed higher doses on a mg/kg basis of these medicines than currently recommended in WHO treatment guideline to achieve similar concentrations as those known to be effective

DOI: 10.1002/ebch.589

Table I. Summary of available evidence for pharmacokinetic review and clinical questions

	Number of studies	Study design	Patient population/N	Intervention[a]	Outcomes
Pharmacokinetic studies					
Isoniazid	• 35	• Observational	• Age ranging from 3 months to 14 years • Sample size ranging from 1 to 2750	• INH ranging from 1.25 mg/kg to 20 mg/kg • INH 15 mg/kg/RMP 15 mg/kg • INH 10 mg/kg/RPM 12 mg/kg • INH 20 mg/kg/RMP 12 mg/kg • INH 5 mg/kg/RMP 10 mg/kg/PZA 30 mg/kg • INH 20 mg/kg/RMP 20 mg/kg/SM 40 mg/kg	• Serum concentration • Cerebrospinal fluid concentration
Pyrazinamide	• 5	• Observational	• Age ranging from 1 year to 14 years • Sample size ranging from 10 to 34	• RMP ranging from 7.5 mg/kg to 25 mg7kg • RMP 12 mg/kg/INH 20 mg/kg	• Serum concentration • Cerebrospinal fluid concentration
Rifampicin	• 15	• Observational	• Age ranging from <3 days to 14 years •sample size ranging from 5 to 94	• PZA ranging from 15 mg/kg to 35 mg/kg • PZA 30 mg/kg/INH 5–10 mg/kg/RMP 10–15 mg/kg	• Serum concentration • Cerebrospinal fluid concentration
Clinical questions					
Hepatotoxicity	• Treatment active disease $n = 17$	Active disease • 5 retrospective reviews, 12 open-label studies	Active disease • Age ranging from 3 months to 19 years • Sample size ranging from 36 to 874	Active disease • INH 10–20 mg/kg/RMP 10–25 mg/kg • INH 4–10 mg/kg/RMP 10–20 mg/kg + PZA 200–300 mg/kg	• Occurrence of hepatotoxicity (defined in 5 of 17 active treatment studies and 7 of 11 prophylaxis studies)

• Prophylaxis $n = 11$	Prophylaxis • 6 retrospective reviews, 1 review, 3 open-label studies, 1 randomized controlled trial	Prophylaxis • Age ranging from 3 months to <21 years • Sample size ranging from 39 to 2473	• INH 5–15 mg/kg/RMP 10–15 mg/kg/SM 20–40 mg/kg or EMB 15–20 mg/kg • INH 10–12 mg/kg/RMP 10–12 mg/kg/PZA 30–35 mg/kg • INH 20 mg/kg/RMP 20 mg/kg/PZA 40 mg/kg/ETH 20 mg/kg Prophylaxis • INH 10–15 mg/kg • RMP10 mg/kg • INH 10 mg/kg/RMP 10 mg/kg/PYR 10 mg/kg • RMP 10 mg/kg/PZA 25 • Intermittent (twice weekly): 2mos SM 20 mg/kg/INH 15 mg/kg/RMP 15 mg/kg followed by 8.5mos INH 15 mg/kg/RMP 15 mg/kg Daily: 40 days SM 20 mg/kg/INH 15 mg/kg/RMP 15 mg/kg followed by 9mos INH 15 mg/kg/RMP 15 mg/kg and then 3mos INH 15 mg/kg mg/kg

Table I. (*Continued*)

	Number of studies	Study design	Patient population/N	Intervention[a]	Outcomes
Intermittent therapy	• 6 studies in paediatric patients	• 4 randomized controlled trials, 1 retrospective review, 1 prospective study	• Age ranging from 6 months to 17 years • Sample size ranging from 35 to 213	• Intermittent (thrice weekly): 2mos INH 15 mg/kg/RMP 12 mg/kg/PZA 45 mg/kg followed by 4mos INH 15 mg/kg/RMP 12 mg/kg twice weekly Daily: 9mos INH 6 mg/kg/RMP 12 mg/kg, • Intermittent (twice weekly): 2mos INH 20–30 mg/kg/RMP 10–15 mg/kg/PZA 50–60 mg/kg followed by 4mos INH 20–30 mg/kg/RMP 10–15 mg/kg Daily: 2mos INH 10–15 mg/kg/RMP 10–15 mg/kg/PZA 20–30 mg/kg followed by 4mos INH 10–15 mg/kg/RMP 10–15 mg/kg, • Intermittent (twice weekly): 2mos INH 15 mg/kg/RMP 15 mg/kg/PZA 55 mg/kg followed by 4mos INH 15 mg/kg/RMP 15 mg/kg Daily: 6mos INH 10 mg/kg/RMP 10 mg/kg/PZA 25 mg/kg 5 days a week, • INH 10–15 mg/kg/RMP 10–15 mg/kg/SM 30 mg/kg daily for 15 days, followed by similar doses of INH and RMP twice weekly for 8.5 mos or same regimen without SM • Wk 1–2(daily treatment): INH 10–15 mg/kg/RMP 10–20 mg/kg/PZA 20–40 mg/kg Wk 3–8(twice weekly): INH 20–40 mg/kg/RMP 10–20 mg/kg/PZA 50–70 Wk 9–24 (twice weekly): INH 20–40 mg/kg/RMP 10–20 mg/kg	• Cure, adherence, relapse, adverse events

Children <3 months	• None <3 months	<6 months of age	<6 months of age	<6 months of age	• Clearance symptoms, death, sequelae, adverse events, development of TB in prophylactic studies
	• 7 studies including children <6 months	• 2 cohort studies, 1 case report, 1 case series, 2 open–label studies, 1 retrospective review	• Age ranging from 0 to 15 years	• INH10–20 mg/kg/RMP 10–20 mg/kg	• Majority of studies reported outcomes using descriptive statistics
	• 13 studies with paediatric population, number <3 or <6 months unknown	unknown if children <6 months	• Number of children <6 months ranging from 1 to 15 across studies	• INH 5 mg/kg/RMP 20 mg/kg/EMB 15 mg/kg or PZA 20 mg/kg	
		• 3 observational studies, 1 prospective study, 1 cohort study, 4 retrospective reviews, 2 randomized controlled trials, 1 survey, 1 open–label study	unknown if children <6 months	• INH 10–15 mg/kg/RMP 10–15 mg/kg/SM 30 mg/kg	
			• Age ranging 6 months to 15 years	• INH 10 mg/kg/RMP 10 mg/kg/PZA 20 mg/kg/SM 20 mg/kg	
			• Total 497 children aged <1 year	INH 5–10 mg/kg/RMP 10 mg/kg/PZA 25 mg/kg	
Streptomycin for uncomplicated pulmonary TB	• None specifically addressing use of SM for uncomplicated pulmonary TB in children	• 1 systematic review, 2 retrospective reviews, 2 reviews, 1 open-label study, 1 randomized controlled trial	• Age ranging from <11 years to 17 years	• INH 15 mg/kg/SM 40 mg/kg/EMB 25 mg/kg	• Response to therapy
	• 7 studies assessing treatment of pulmonary TB		• Sample size ranging from 140 to 1098	• SM included in only 2 studies (Kansoy 1996 and Gubkina 2009)	

DOI: 10.1002/ebch.589

Table I. (*Continued*)

Treatment regimens for tuberculosis meningitis	• 11 studies in paediatric patients	• 4 retrospective reviews, 3 open-label non-randomized studies, 1 open-label randomized study, 1 randomized controlled trial	• Age ranging from 2 months to <14 years	• INH 20 mg/kg/SM 30–50 mg/kg/RMP 10–15 mg/kg	• Death, sequelae
			• Sample size ranging from 30 to 199	• INH 20 mg/kg/PAS 200–300 mg/kg/SM 30–50 mg/kg • INH 10–15 mg/kg/RMP 15 mg/kg • INH 20 mg/kg/RMP 20 mg/kg/PZA 40 mg/kg/ETH 20 mg/kg+thalidomide or • INH 20 mg/kg/RMP 20 mg/kg/PZA 40 mg/kg/ETH 20 mg/kgplacebo • INH 10–15 mg/kg/RMP 15–20 mg/kg/SM 20–25 mg/kg or PZA 25–35 mg/kg • INH 15 mg/kg/SM 40 mg/kg/EMB 25 mg/kg • RMP 20 mg/kg/SM 40 mg/kg/EMB 25 mg/kg • INH 15 mg/kg/RMP 20 mg/kg/PZA 30 mg/kg/SM 40 mg/kg	• Majority of studies reported outcomes using descriptive statistics
Treatment regimens osteo-articular TB	• 11 studies in paediatric patients	• 6 retrospective reviews, 4 case series, 1 unknown design	• Age ranging from 10 months to 18 years • Sample size ranging from 4 to 150	• INH 5–20 mg/kg • RMP 10–30 mg/kg • PZA 20–35 mg/kg • SM 15–30 mg/kg • EMB 15 mg/kg • PAS 200 mg/kg	• Relapse • All studies reported outcomes using descriptive statistics

[a] interventions listed provide range of doses used for each drug across studies.
EMB=ethambutol; ETH=ethionamide; INH=isoniazid; PAS=para-aminosalicylic acid; PK=pharmacokinetic; PYR=pyridoxine; PZA=pyrazinamide; RMP=rifampicin; SM=streptomycin; TB=tuberculosis

in adults. The new recommended doses are for use in daily regimens.

Evidence reviews for clinical questions

What is the risk of hepatotoxicity with higher doses of isoniazid, rifampicin and pyrazinamide for the treatment of pulmonary TB?

Seventeen studies assessed hepatotoxicity of TB treatment. Five considered all or undefined types of TB, six considered pulmonary or extrapulmonary TB and six considered TB meningitis (see Table S2 in the Supporting Information, available from the online version of this article). There were 11 studies that assessed hepatotoxicity of TB prophylaxis (see Table S3 in the Supporting Information, available from the online version of this article). Study populations ranged in age from 0 to <21 years, with the study sample size ranging from 36–2473, although the majority of studies had <100 patients. The data from different studies using different drug dosages were difficult to compare because of a lack of unified definitions of hepatotoxicity and differences in duration of treatment and drug combinations used. Overall, the quality of the studies was low, given the inconsistency in reporting and definition of hepatotoxicity and the risk of confounding and bias with the observational nature of most studies.

In most of the reported cases, hepatotoxicity was either transient or there was no data to determine whether it persisted, and possible confounding factors like malnutrition, acetylator status or poor adherence were not adequately considered. It was noted that due to probable publication bias, occurrence of hepatoxicity in the paediatric population may have been over reported. Overall, there was not convincing data that the new higher recommended dosages would cause more hepatoxicity reactions than the previously recommended dosages, while there was evidence from pharmacokinetic studies that using the previously recommended lower drug dosages, minimum inhibitory concentrations (MIC) may not be reached in children.

Should children with suspected or confirmed pulmonary TB or tuberculous lymphadenopathy be treated with intermittent regimens?

Six studies assessed the effectiveness of intermittent therapies in children (see Table S4 in the Supporting Information, available from the online version of this article). The quality of the RCTs was low due to lack of reporting of the method of randomization, allocation concealment, and blinding. One study that concluded there was no difference between daily and intermittent treatment regimens had not compared identical regimens (16); the intermittent arm included the use of pyrazinamide with isoniazid and rifampicin, while the daily arm only included isoniazid and rifampicin. Four of the RCTs (466 children) were included in a published meta-analysis (17). The results of the pooled estimates of effect suggested that children receiving twice weekly intermittent therapy were less likely to be cured than those receiving daily therapy (per protocol analysis: OR 0.27, 96% CI 0.15–0.51; intention to treat analysis: OR 0.66; 95% CI 0.23–1.84). There were no data pertaining to the use of intermittent therapy for the treatment of TB in HIV positive children.

Should infants 0–3 months with suspected or confirmed pulmonary TB be treated with the higher doses of isoniazid, rifampicin and pyrazinamide?

There were no studies of treatment of TB in children <3 months old, but out of 20 studies identified, seven included data for children <6 months old. They were generally non-comparative and had small sample sizes, often less than 10 (see Table S5 in the Supporting Information, available from the online version of this article).

Should streptomycin be used as part of first-line treatment regimens for children with pulmonary TB or tuberculous peripheral lymphadenopathy?

No studies were identified that specifically addressed the use of streptomycin for the treatment of uncomplicated pulmonary TB in children. However, two studies included the use of streptomycin as part of the treatment regimen (18–19) but the impact of its use compared to other treatments could not be evaluated (see Table S6 in the Supporting Information, available from the online version of this article).

What should be the recommended treatment regimen for TB meningitis in children?

Forty-six potentially relevant studies addressing efficacy of different drug regimens and dosages for the management of TBM were identified. Of these, 25 reported paediatric data and 21 reported data for both adults and children. The majority were non-randomized, non-comparative studies. The quality of the studies ranged from low to very low, with the study designs open to a number of sources of bias given lack of randomization, lack of blinding, as well as lack of comparators. No clear conclusions could be drawn from the efficacy studies, given they differed widely in terms of design, drugs used and patient populations. Of the 46 efficacy studies, 11 studies were identified that reported treatment regimens including rifampicin for the treatment of TB meningitis in children. In order to determine optimal treatment duration, the 11 studies were assessed to determine whether 9 month regimens were more effective than 6 or 12 month regimens. In the 11 studies, duration of treatment ranged from 6 months to 2 years. There were no studies that reported clinical outcomes for a duration of treatment of 9 months and only one study used a treatment duration of 6 months. The majority used treatment regimens of at least 12 months (see Table S7 in the Supporting Information, available from the online version of this article).

What should be the recommended treatment regimen for osteo-articular TB in children?

Fifty-one potentially relevant citations were retrieved of which only 11 contained paediatric specific data. Sample sizes ranged from 4–150. Seven of the studies had less than 25 participants. None of

DOI: 10.1002/ebch.589

the studies were randomized, double-blind comparative studies. The studies focused on the outcome of 'no relapse', although the duration of follow up was often not reported. The quality of the studies ranged from low to very low, with the study designs open to a number of sources of bias given lack of randomization, lack of blinding as well as lack of comparators. Treatment regimens generally lasted for 12 months and most of the regimens included INH and RMP (see Table S8 in the Supporting Information, available from the online version of this article).

Discussion

In carrying out these reviews, we have found that although there may be a lack of high quality randomized controlled trials on which to base treatment recommendations, there is an extensive literature describing the treatment of TB in children. However, for some questions, there were no studies, such as treatment for infants aged less than 3 months and the use of streptomycin for the treatment of uncomplicated pulmonary TB in children. While we found a total of 7127 publications, only 136 could be used to directly address the issues relevant to the process of developing recommendations. These recommendations are summarized in Table 2.

One of the limitations of this process has been the difficulty of ensuring a systematic retrieval of all relevant literature. Observational studies generally are less easy to retrieve through systematic search strategies, as the methods for undertaking systematic reviews have generally focused on search strategies to retrieve all randomized trials. While these methods have been well established, the *Cochrane Collaboration* and others are yet to develop similarly rigorous methods for ensuring retrieval of all relevant studies. In this work, we have therefore had to rely on cascade searching as well as expert knowledge of relevant cohort studies. We are aware of the potential biases introduced by this approach but in the field of paediatric medicines particularly, we believe that attempting to retrieve at least the majority of observational data better informs treatment recommendations than not doing so. Including observational studies can increase the confidence in the effect of the intervention and may provide important information about the feasibility of the intervention in resource-poor settings, notwithstanding the increased risk of bias and possible overestimation of the size of the effect (20).

The selection of an appropriate drug dose for a neonate, infant, children or adolescent requires an understanding of the basic pharmacokinetic and pharmacodynamic properties of the compound (21). Developmental changes in physiology produce many

Table II. Summary of recommendations

1. Taking into account the risk of drug-induced hepatotoxicity the following doses are recommended for the treatment of tuberculosis in children:
Isoniazid (INH)—10 mg/kg (range 10–15 mg/kg); maximum dose 300 mg/day
Rifampicin (RMP)—15 mg/kg (range 10–20 mg/kg); maximum dose: 600 mg/day
Pyrazinamide (PZA) - 35 mg/kg (30–40 mg/kg)
Ethambutol (EMB)—20 mg/kg (15–25 mg/kg)
2. Children living in settings with high HIV prevalence[1] and/or high isoniazid resistance, with suspected or confirmed pulmonary tuberculosis or peripheral lymphadenitis, or children with extensive pulmonary disease living in low HIV prevalent or low INH resistance settings should be treated with a four drug regimen (INH/RMP/PZA/EMB) for 2 months followed by a two drug regimen (INH/RMP) for 4 months at the same doses as above assuming susceptibility to both drugs seems likely
3. Children with suspected or confirmed pulmonary tuberculosis or tuberculous peripheral lymphadenitis who live in a setting with a low HIV prevalence and/or low INH resistance and children who are HIV negative can be treated with a three drug regimen (INH/RMP/PZA) for 2 months followed by a two drug (INH/RMP) regimen for 4 months at the same doses as above assuming susceptibility to both drugs seems likely
4. Children with suspected or confirmed pulmonary tuberculosis or tuberculous peripheral lymphadenitis living in settings with high HIV prevalence (or with confirmed HIV infection) should not be treated with intermittent regimens (i.e. twice or thrice weekly doses) In the continuation phase[2] of treatment, in settings with well established directly observed therapy, thrice weekly regimens can be considered for children known to be HIV uninfected.
5. Infants (0–3 months of age) with suspected or confirmed pulmonary tuberculosis or tuberculous peripheral lymphadenitis should be promptly treated with the new higher dose treatment regimens as described above. Treatment may require dose adjustment to take into account the affect of age and possible toxicity in young infants. This should be done by a clinician experienced in the management of paediatric tuberculosis
6. Streptomycin should not be used as part of first line treatment regimens for children with pulmonary tuberculosis or tuberculous peripheral lymphadenitis.
7. Children with suspected or confirmed tuberculous meningitis should be treated with a four drug regimen (INH/RMP/PZA/EMB) for 2 months, followed by a two drug regimen (INH/RMP) for 10 months; the total duration of treatment being 12 months. The doses recommend for the treatment of tuberculous meningitis are the same as those for pulmonary TB.
8. Children with suspected or confirmed osteo-articular tuberculosis should be treated with a four drug regimen (INH/RMP/PZA/EMB) for 2 months followed by a two drug regimen (INH/RMP) for 10 months; the total duration of treatment being 12 months. The doses recommend for the treatment of osteo-articular tuberculosis are the same as those for pulmonary TB.

[1] Countries, subnational administrative units, or selected facilities, where the HIV prevalence among adult pregnant women is ≥1% or among TB patients is ≥5%.

[2] Tuberculosis treatment for pulmonary TB is divided into an initial (bactericidal) phase of 2 months with three or four medicines and a continuation (sterilizing) phase of 4 months with usually two medicines (INH and RMP).

DOI: 10.1002/ebch.589

age-related changes in absorption, distribution, metabolism and excretion of drugs that result in altered pharmacokinetics (22–23). The physiology of the gastrointestinal tract changes significantly in the first weeks of life and as a result, the rate at which most drugs are absorbed is slower in neonates and young infants than in older children. The time required to achieve maximal plasma levels is therefore prolonged in the very young (<3 months of age) (23–24). The relatively larger extracellular and total-body water spaces in neonates and young infants compared with adults, coupled with adipose stores that have a higher ratio of water to lipid, result in lower plasma levels of drugs when the drugs are administered based on weight alone (23–24). Clinical studies of drugs metabolized by the liver have consistently shown there is an age-dependent increase in plasma clearance in children younger than 10 years when compared with adults and as a result, relatively higher weight-based dosing is required in this population (22). Applying these principles to the available information about TB medicines in children, it is clear that previous treatment recommendations have resulted in probable under dosing of medicines for TB treatment in children.

The importance of treating TB in children effectively and the need for simplified treatment instructions for programs dealing with children were taken into account during the formulation of the treatment recommendations. With regards to the use of intermittent treatment regimens, it was noted that some regions and countries have successfully used thrice weekly intermittent regimens in their directly observed therapy programmes for the treatment of tuberculosis in adults and children. Recommending changing the well established practice may result in excluding children from directly observed therapy (DOT). However, it was highlighted that this should only be considered in settings with a low HIV prevalence and a well established DOT programme.

The research needs in the field of TB in children are substantial. During the guideline development process, the areas where the evidence was insufficient or inadequate were highlighted and the following research needs were identified:

- A randomized trial of different lengths of treatment of tuberculous meningitis;
- A large population pharmacokinetics study of all four first line medicines at the newly recommended doses, including in children with HIV;
- High quality observational studies to evaluate the risk of hepatotoxicity of isoniazid at the increased dose of 10 mg/kg;
- Pharmacokinetic studies in infants of rifampicin, isoniazid and pyrazinamide.

It is hoped that this review will act as a stimulus to researchers and funding agencies to encourage, plan and support randomized controlled studies in the field of childhood TB. In view of the importance of pharmacogenetics in the host and potential genetic differences in *Mycobacterium tuberculosis* populations, such studies should, where possible, be multicentre and enroll children over a spectrum of ages. It is particularly disturbing that very few studies have addressed the treatment and follow-up of children suffering from the various extra-pulmonary forms of TB. More than 20 years after the introduction of short-course chemotherapy, and more than 60 years after the first randomized controlled trials of treatment in adults, there is still uncertainty as to the optimal duration of therapy for tuberculous meningitis and osteoarticular TB.

Note

AR, MG and SH are staff members of the World Health Organization. The authors alone are responsible for the views expressed in this publication and they do not necessarily represent the decisions, policy or views of the World Health Organization.

Authors' Contributions

All of the authors contributed to the writing of the manuscript.

Declaration of Interest

The authors declare that they have no competing interests.

References

1. Nelson LJ, Wells CD. Tuberculosis in children: considerations for children from developing countries. *Semin Paediatr Infect Dis* 2004; **15**: 150–154.
2. Marais BJ, Hesseling AC, Gie RP, Schaaf HS, Beyers N. The burden of childhood tuberculosis and the accuracy of routine surveillance data in high -burden setting. *Int J Lung Dis* 2006; **10**: 259–263.
3. Comstock GW, Livesay VT, Woolpert SF. The prognosis of a positive tuberculin reaction in childhood and adolescence. *Am J Epidemiol* 1974; **99**: 131–138.
4. Gedde-Dahl T. Tuberculosis infection in the light of tuberculin matriculation. *Am J Hyg* 1952; **56**: 139–214.
5. Marais BJ, Gie RP, Schaaf HS, Hesseling AC, Obihara CC, Starke JJ, Enarson DA, Donald PR, Beyers N. The natural history of disease of childhood intra-thoracic tuberculosis: a critical review of the pre-chemotherapy literature. *Int J Tuberc Lung Dis* 2004; **8**: 392–402.
6. WHO/HTM/TB/2006.371. Guidance for national tuberculosis programmes on the management of tuberculosis in children. WHO 2006. Available at: http://whqlibdoc.who.int/hq/2006/WHO_HTM_TB_2006.371_eng.pdf.
7. Donald PR, Maher D, Maritz JS, Qazi S. Ethambutol dosage for the treatment of children: literature review and recommendations. *Int J Tuberc Lung Dis* 2006; **10**: 1318–1330.
8. Schünemann HJ, Hill SR, Kakad M, Vist GE, Bellamy R, Stockman L, Wisløff TF, Del Mar C, Hayden F, *et al*. Transparent

DOI: 10.1002/ebch.589

Development of the WHO Rapid Advice Guidelines. *PLoS Medicine* 2007; **4**: e119.
9. Donald P. The chemotherapy of tuberculous lymphadenopathy in children. *Tuberculosis* (accepted for publication).
10. Donald P. Cerebrospinal fluid concentrations of antituberculosis agents in adults and children. *Tuberculosis* (submitted for publication).
11. Donald P. The chemotherapy of tuberculous meningitis in children and adults. *Tuberculosis* (submitted for publication).
12. Stefania C, Di Mario S, Lewinsohn D, Detjen A, Baronciani D, Magrini N, Richeldi L. Assessing evidence for currently used dosages of anti-tuberculosis drugs in children: a systematic review. *Am J Respiratory Critical Care Med* (submitted for publication).
13. 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**: 910–914.
14. Zhu M, Starke JR, Burman WJ, *et al*. Population pharmacokinetic modeling of pyrazinamide in children and adults with tuberculosis. *Pharmacother* 2002; **22**: 686–695.
15. 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**: 407–413.
16. Ramachandran P, Kripasankar AS, Duraipandian M. Short course chemotherapy for pulmonary tuberculosis in children. *Indian J Tuberc* 1998; **45**: 83–87.
17. Menon P, Lodha R, Sivanandan S, Kabra S. Intermittent or daily short course chemotherapy for tuberculosis in children: meta-analysis of randomized controlled trials. *Indian Pediatrics* 2010; **47**: 67–73.
18. Kansoy S, Kurta N, Akit S, Aksoylar S, Yaprak I, Çalayan S. Superiority of intermittent-short course chemotherapy in childhood pulmonary tuberculosis. *Turkish J Med Sci* 1996; **26**: 41–43.
19. Gubkina MF, Ershova NG. Estimation of the possibilities of using unified chemotherapy regimens in new cases of pulmonary tuberculosis in old-age children and adolescents (Russian). *Problemy Tuberkuleza I Boleznej Legkih* 2009; **1**: 33–36.
20. Schulz, K. F, *et al*. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *J Am Medic Assoc* 1995; **273**(5): 408–412.
21. Ritschel WA, Kearns GL. *Handbook of basic pharmacokinetics including clinical applications*, 6th edn. Washington, DC: American Pharmaceutical Association, 2004; 227–240.
22. Kearns GL, Abdel-Rahman SM, Alander SW, Blowey DL, Leeder JS, Kauffman RE. Developmental Pharmacology – drug disposition, action, and therapy in infants and children. *N Engl J Med* 2003; **349**: 1157–1167.
23. Bartelink IH, Rademaker CM, Schobben AF, van den Anker JN. Guidelines on paediatric dosing on the basis of developmental physiology and pharmacokinetic considerations. *Clin Pharmacokinet* 2006; **45**: 1077–1097.
24. Siber GR, Echeverria P, Smith AL, Paisley JW, Smith DH. Pharmacokinetics of gentamicin in children and adults. *J Infect Dis* 1975; **132**: 637–651.

DOI: 10.1002/ebch.589