

## **Annex 1 - Evidence summary tables**

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**RECOMMENDED DOSES FOR FIRST LINE MEDICINES, TAKING INTO ACCOUNT THE COMPARATIVE RISK OF HEPATOTOXICITY FOR INH, RMP AND PZA**

**When to start**

**Recommendations**

• Taking into account the comparative risk of drug-induced hepatotoxicity, the following doses are recommended for the treatment of pulmonary tuberculosis and tuberculous peripheral lymphadenitis:

Isoniazid (H) 10mg/kg (range 10-15 mg/kg); maximum dose 300mg/day  
Rifampicin (R) 15mg/kg (range 10-20 mg/kg); maximum dose 600 mg/day  
Pyrazinamide (P) (35mg/kg (range 30-40 mg/kg)  
Ethambutol (E) 20mg/kg (range 15-25 mg/kg)

**(Strong recommendation, moderate level of evidence)**

• Children living in settings with high HIV prevalence 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 H resistance settings should be treated with a four drug regimen (HRZE) for 2 months followed by a two drug regimen (HR) for 4 months at the following doses:

H - 10 mg/kg (range 10-15 mg/kg); maximum dose 300 mg/day  
R - 15 mg/kg (range 10-20 mg/kg); maximum dose: 600 mg/day  
Z - 35 mg/kg (30-40 mg/kg)  
E - 20 mg/kg (15-25 mg/kg)

**(Strong recommendation, moderate quality evidence)**

• Children with suspected or confirmed pulmonary tuberculosis or tuberculous peripheral lymphadenitis who live in a setting with a low HIV prevalence and/or low H resistance and children who are HIV negative can be treated with a three drug regimen (HRZ) for 2 months followed by a two drug (HR) regimen for 4 months at the following doses:

H - 10 mg/kg (range 10-15 mg/kg); maximum dose 300 mg/day  
R - 15 mg/kg (range 10-20 mg/kg); maximum dose: 600 mg/day  
Z - 35 mg/kg (30-40 mg/kg)

**(Strong recommendation, moderate level of evidence)**

**Domains and considerations**

**Quality of evidence**

• A review by Donald (2009)<sup>1</sup> searched the literature to find articles assessing antituberculosis drug-induced hepatotoxicity (ADIH) for three tuberculosis (TB) drugs – isoniazid (H), rifampicin (R) and pyrazinamide (P).

• Seventeen studies assessed hepatotoxicity of TB treatment in children. Five considered all or undefined types of TB, 6 considered pulmonary or extrapulmonary TB and 6 considered TB meningitis (table 1). There were 11 studies that assessed hepatotoxicity of TB prophylaxis in children (table 2). Study populations ranged in age from 0 to <21 years, with the study sample size ranging from 36 to 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

<sup>1</sup> Donald PR. 2009. Antituberculosis drug-induced hepatotoxicity in children: A literature review. (unpublished). Commissioned by WHO Department of Medicines, Access and Rational Use, Essential Medicines and Pharmaceutical Policies, WHO HQ Geneva.

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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.

•Conclusions of literature review

- Isoniazid doses of 5-15mg/kg alone or in the company of other drugs do not constitute an undue risk for the development of hepatotoxicity in children;
- Rifampicin has the capacity to precipitate INH hepatotoxicity; however the dosage of R did not appear to be a critical factor in this interaction.
- There is little evidence that PZA makes a significant contribution to ADIH.

The panel noted the absence of high quality evidence available to directly address the question of hepatotoxicity caused by the first line medicines for the treatment of tuberculosis in children.

However, the panel took account of:

- the long duration of clinical experience with these medicines for the treatment of TB in adults and children
- a relatively large quantity of low quality observational studies in a variety of settings and paediatric populations that show no evidence of increased toxicity with these doses of the medicines
- the potential risk of inefficacy of treatment if lower doses are used
- the risk of developing isoniazid resistance if low doses are used
- The relationship between mean inhibitory concentration (MIC) in adults and efficacy outcomes
- the development of metabolic pathways which increase the metabolism in young children
- the high likelihood of reporting bias which would over-report the occurrence of hepatotoxicity

**Uncertainty: YES, given low quality of the evidence and relative lack of paediatric evidence**

**Risks/benefits**

**Benefits**

- improved efficacy and decreased resistance, especially for fast acetylators of isoniazid

**Risks**

- development of isoniazid resistance if doses used are inadequate
- inefficacy of treatment if lower doses are used
- risk of drug-induced hepatotoxicity

**Benefits outweigh risks**

**Values and acceptability**

**In favour:**

- long duration of clinical experience with these medicines for the treatment of TB in adults and children
- observational studies in a variety of settings and paediatric populations show no evidence of increased toxicity with these doses of the medicines
- dose-dependent hepatotoxicity is very rare
- want to achieve the same systemic exposure in children as in adults

**Against:**

- there is some risk, but it is not clear exactly what it is based on the available evidence
- interpretation depends on your definition of hepatotoxicity and what level of toxicity you are

<p align="center"><b>RECOMMENDED DOSES FOR FIRST LINE MEDICINES, TAKING INTO ACCOUNT THE COMPARATIVE RISK OF HEPATOTOXICITY FOR INH, RMP AND PZA</b></p>
<p>willing to accept  <b>Uncertainty: YES, given lack of evidence</b></p>
<p><b>Cost</b></p> <ul style="list-style-type: none"> <li>• Cost was not considered an important issue due to the fact that the medicines are inexpensive and are often provided free of charge to countries by international agencies for national programmes</li> </ul> <p><b>Uncertainty: YES, given the lack of paediatric specific data and cost analyses.</b></p>
<p><b>Feasibility</b></p> <ul style="list-style-type: none"> <li>• currently no fixed dose combination drugs exist for the newly recommended dose strengths and regimens</li> </ul> <p><b>Uncertainty: No</b></p>
<p><b>Gaps, research needs, comments</b></p> <ul style="list-style-type: none"> <li>• While there is available data addressing, or including, assessment of hepatotoxicity of TB drugs, there is a relative lack of data specifically addressing hepatotoxicity in children</li> <li>• All types of hepatotoxicity are reported, but it was not clear which type is responsible for the majority of cases</li> <li>• There is a need for clear consistent definitions of hepatotoxicity</li> <li>• Urgent requirement for further research in this area, including a population PK study and pharmacovigilance</li> </ul>
<p><b>Final comment</b></p> <ul style="list-style-type: none"> <li>• Strong recommendation for treatment using new higher doses for children. Overall, there was not convincing data that the new higher recommended dosages would cause more hepatotoxicity 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.</li> </ul>

TB=tuberculosis; H=isoniazid; R=rifampicin; P=pyrazinamide

**Table 1: Hepatotoxicity – treatment for active disease**

Trial	Design	N/age	Treatment duration	Type of treatment	Hepatotoxicity definition	Outcome
<b>All or undefined types</b>						
Gendrel 1989	•OL	•47 •3 months-13 years, mean age 31.2 months	6 months	•INH/RMP doses INH 20mg/kg; RMP 25mg/kg •treatment active disease	NR	•30 patients (63.8%) had increase in aminotransferase levels •14 patients (29.2%) had aminotransferase >100IU/l •many patients were malnourished, with 68% of malnourished patients having elevated aminotransferase levels
Ohkawa 2002	•RR	•117 (99 analysed) •0-16 years	NR	•INH/RMP + PZA or SM or EMB or SM+PZA or EMB+PZA doses INH 4-10mg/kg; RMP 10-20mg/kg; SM 20-30mg/kg; EMB 15-20mg/kg; PZA 200-300mg/kg*see footnote •treatment active disease	•severe hepatotoxicity ALT or AST 5 times ULN	•8 patients (8.1%) developed severe hepatotoxicity •multivariate logistic regression analysis indicated that age (OR=143; 95% CI: 4.2 to 4934.9) and administration of PZA (OR=0.60; 95% CI: 0.39 to 0.90) had a significant contribution to development of hepatotoxicity •estimated probability of a patient at 1, 5 and 10 years developing hepatotoxicity when receiving PZA with RMP and INH would be 0.95, 0.72 and 0.16, respectively
Ormerod 1996	•RR	•267 •0-19 years	9-15 months	•child-specific regimens not provided, doses for children were INH 10mg/kg; RMP 10mg/kg; PZA 30mg/kg; EMB 15mg/kg •treatment active disease	•hepatitis defined as biochemically confirmed jaundice and/or elevation serum ALT >5 times pretreatment level	•hepatitis occurred in 2 patients (0.75%)
Padmini 1993	•OL	•83 •<12 years	6, 9 or 12 months	•6 INH/RMP •9 INH/RMP/SM or EMB •12 INH/RMP/SM/PZA Doses INH 15mg/kg; RMP 10-15mg/kg; PZA 20-40mg/kg; SM 40mg/kg; EMB 15-20mg/kg •treatment active disease	NR	•4 patients (4.8%) had transient hepatitis with clinical jaundice and serum bilirubin 2-4.5mg % and ALT elevation 4 times ULN. When INH and RMP doses were reduced to 10mg/kg the biochemical levels returned to normal
Parthasarathy 1986	•R, OL	•180	1 year	•2 RMP/SM/INH or 2	NR	•29 patients (16.1%) had hepatitis during first two months of therapy

Trial	Design	N/age	Treatment duration	Type of treatment	Hepatotoxicity definition	Outcome
		•1-12 years		RMP/SM/INH/PZA + 10 EMB/INH doses INH 20mg/kg in first 2 months then 12mg/kg; RMP 12mg/kg; SM 40mg/kg; PZA 30mg/kg; EMB 17.5mg/kg •treatment active disease		•137 patients continued to second phase of treatment (EMB/INH) and of these, jaundice was observed in 1 (0.7%)
<b>Pulmonary and/or extrapulmonary tuberculosis</b>						
Martinez-Roig 1986	•OL	•74 •4 months-15 years	9-18 months	•RMP/INH + SM for 1.5 months then EMB for 1.5 months doses RMP 10mg/kg; INH 7mg/kg; SM 25mg/kg; EMB 15mg/kg •treatment active disease	NR	•hepatotoxicity occurred in 27 (37%) of patients •5 patients (7%) had clinical manifestations
O'Brien 1983	•RR	•874 •<1-14 years	NR	•INH/RMP + SM or EMB or PAS or SM/EMB •INH + PAS or EMB or SM or PAS/SM or EMB/SM or EMB/PAS •INH Doses not provided for all drugs. For patients with hepatotoxicity, INH ranged from 8-17mg/kg and RMP 7-43mg/kg •treatment active disease	NR	•16 patients with hepatotoxicity (1.8%) •hepatotoxicity attributed to INH in 12 patient, RMP in 2 and INH+RMP in 2 •hepatotoxicity rate 3.2% with RMP and 0.5% with INH
Reis 1990	•OL	•117 •6 months-15 years	6 months	•6 RMP/INH doses RMP 15mg/kg; INH 10mg/kg •treatment active disease	NR	•increase of less than twice the initial levels in AST and ALT observed in 23 of 77 (29.9%) patients; levels returned to normal with continued treatment
Sanchez-Albisua 1997	•OL	•114 •6 months-15 years, mean	6 months	•2 INH/RMP/PZA + 4 INH/RMP doses INH 10mg/kg; RMP 15mg/kg; PZA 20-25mg/kg	•ALT >45u/L	•11 (19.6%) of those with normal hepatic enzymes before treatment showed increased ALT values with treatment •none of the 11 patients showed clinical signs of hepatotoxicity and

Trial	Design	N/age	Treatment duration	Type of treatment	Hepatotoxicity definition	Outcome
		age 4.5 years		•treatment active disease		treatment was not interrupted
Seth 1989	•OL	•66 •1.5-13 years	6 months	•INH/RMP doses INH 10mg/kg; RMP 12mg/kg •treatment active disease	NR	•no patients (either rapid or slow acetylators) developed signs of hepatotoxicity
Tsakalidis 1992	•OL	•36 •8 months-12 years, mean age 5.5 years	6 months	•2 INH/RMP/PZA + 4 INH/RMP doses INH 10-12mg/kg; RMP 10-12mg/kg; PZA 30-35mg/kg •treatment active disease	NR	•5 patients (13.9%) had rise on serum transaminase and uric acid values •3 patients (8.3%) had elevated serum transaminase •liver enzymes returned to normal within 2 months without treatment modification
<b>Tuberculosis meningitis</b>						
Donald 1987	•OL	•56 •5-144 months, median age 22 months	8 weeks	•INH/RMP/PZA/ETH doses INH 20mg/kg; RMP 20mg/kg; PZA 40mg/kg; ETH 15mg/kg •treatment active disease	•normal ALT <53 U/L; normal AST <40 U/L; normal GGT <50 U/L	•increased bilirubin in 1 patient (125 mmol/L) •of 33 patients observed for 8 weeks, 5 (15%) had normal LFTs •6 patients (18%) had normal AST, 9 (28%) had normal ALT, 14 (42%) had normal GGT throughout observation, but proportion with normal values increased toward end of 8 week period
Donald 1998	•OL	•95 •stage II median age 17 months; stage II median age 38 months and stage I median age 37 months	6 months	•INH/RMP/PZA/ETH doses INH 20mg/kg; RMP 20mg/kg; PZA 40mg/kg; ETH 20mg/kg •treatment active disease	NR	•10 patients (11%) had mildly elevated bilirubin (median concentration 33mmol/L) •1 patient (1%) severely clinically jaundiced was shown to have hepatitis A •13 patients (14%) had mild transient elevation in ALT or AST. In all cases treatment was not stopped and values returned to normal
Faella 2006	•RR	•32 •0-14 years	12-18 months	•2 INH/RMP/SM + 10-18 INH/RMP doses INH 5mg/kg; RMP 10mg/kg; SM 20mg/kg •EMB/PZA given to 10 patients, doses not provided	NR	•3 (9.4%) patients had cytolytic hepatitis with ALT levels 3 times greater than normal, and had INH dose reduced

Trial	Design	N/age	Treatment duration	Type of treatment	Hepatotoxicity definition	Outcome
Ramachandran 1980	•OL	•76 •1-12 years	1 year	•2 RMP/INH/SM + SM/EMB/INH 4 + 6 INH/SM doses INH 12-20mg/kg; RMP 12mg/kg; SM 40mg/kg; EMB 17.5mg/kg •treatment active disease	NR	•11 of 22 children (50%) given INH 20mg/kg developed clinical jaundice •8 of 40 children (20%) given INH 12mg/kg developed clinical jaundice
Tsagaropoulou-Stinga 1985	•OL	•44 •4-14 years, mean age 4.5 years	NR	•INH/RMP doses INH 15-20mg/kg; RMP 15mg/kg •treatment active disease	ALT >100 units	•36 patients (82%) had hepatotoxic reaction (ALT >100 units) during treatment 15 of the 36 patients had jaundice •no correlation between ALT values and duration of therapy •in 22 of 36 patients liver function returned to normal without alteration of drug regimen
Visudhipan 1989	•RR	•51 •7 months-14 years	1 year	••INH/RMP doses INH 10-15mg/kg; RMP 15mg/kg	NR	•4 patients (7.8%) had elevated ALT and AST •Alt and AST levels decreased in 3 of 4 patients who had RMP dose decreased to 10mg/kg

TB=tuberculosis; NA= not available; NR=not reported; R=randomised; DB=double-blind; OL=open-label; RR=retrospective review; Rev=review; PK=pharmacokinetic; MC=multicentre; INH=isoniazid; RMP=rifampicin; EMB=ethambutol; ETH=ethionamide; SM=streptomycin; PZA=pyrazinamide; PAS=para-aminosalicylic acid; PYR=pyridoxine; ALT=alanine aminotransferase; AST=aspartate aminotransferase; LFT=liver function test; GGT=γ-glutamyl transferase; LTBI=latent tuberculosis infection; ULN=upper limit of normal

\*NB. PZA dose as presented in the publication. This may be an error, with dose more likely to be 20-30mg/kg. Although maybe not – as the paper also said max dose <1000mg/kg/day.

**Table 2: Hepatotoxicity - prophylaxis**

Trial	Design	N/age	Treatment duration	Type of treatment	Hepatotoxicity definition	Outcome
Byrd 1979	•OL	•0-9 years: 19 •10-19 years: 44	1 year	•INH dose NR •prophylaxis	•AST 100IU/ml (5 times normal)	•no children discontinued due to elevated AST; no other child-specific results reported
Dash 1980	•RR	•644 •<15 years	1 year	•INH dose NR •prophylaxis	NR	•4 patients (0.6%) had possible hepatic event and no patients had probable hepatic event •no cases of elevated ALT or AST reported
Kopanoff 1978	•RR	•2473 •<20 years	1 year	•INH dose NR •prophylaxis	•probable hepatitis defined as AST >250 Karmen units or AST <250 Karmen units but ALT >AST and negative HBsAg and other causes of hepatitis not apparent	•case rate of hepatitis was 0 cases per 1000 persons
Lobue 2003	•RR	•1277 •0-14 years	6 or 9 months	•INH dose NR •prophylaxis LTBI	•elevation transaminases >3 times normal in presence of symptoms compatible with liver injury or transaminases >5 times normal in absence of symptoms	•incidence of hepatotoxicity 0% in 0-14 year olds
Nakajo 1989	•RR	•564 •3 months-18 years, mean age 8 years	1 year	•INH 10mg/kg •prophylaxis in children with TB infection	•elevation in ALT or AST >100 IU/L with or without elevation in serum bilirubin	•1/564 (0.18%) with ALT/AST >100 IU/L and discontinued INH •39 children (6.9%) with signs or symptoms of hepatotoxicity, however all continued INH
Ormerod 1987	•RR	•339 Age NR	6 or 9 months	•INH/RMP/PYR doses INH 10mg/kg; RMP 10mg/kg; PYR 10mg/kg •prophylaxis	NR	•paper reports that no cases of obvious liver function abnormalities observed
Palusci 1995	•RR	•39 •6 months-18 years, mean age 12.7 years	NR	•INH, dose NR •prophylaxis in children with TB infection	NR	•11 of 39 (3.5%) had symptoms suggestive of hepatitis and 1 had transaminase elevation •2 of remaining 28 children (7.1%) had elevated LFTs
Rapp	•OL	•116	NR	•INH 10-15mg/kg	•normal AST defined as AST <92 IU for	•5 patients had abnormal AST levels, but these

Trial	Design	N/age	Treatment duration	Type of treatment	Hepatotoxicity definition	Outcome
1978		•<21 years (upper age only defined as >10 and <21 years)		•prophylaxis of children with TB infection	children 6-12 months; <76 IU for 1-5 years; <64 IU for 5-16 years; <40 IU for >16 years	returned to normal and paper states no evidence of hepatotoxicity observed
Spyridis 2007	•R	•926 •<15 years	•9 vs. 4 vs. 3 months	•INH 10mg/kg •INH10mg/kg + RMP 10mg/kg •prophylaxis for LBTI	NR, however transient rise considered to be ≤3 times ULN	•in 200 patients treated with INH 10mg/kg 12 (6%) had transient rise in liver enzymes •of 650 children treated with INH+RMP 8 (1.2%) had transient increase in liver enzymes
Tortajado 2005	•R, OL, MC	•61 •1-19 years	6 months INH versus 2 months RMP/PZA	•6 INH vs. 2 RMP/PZA doses INH 5mg/kg; RMP 10mg/kg; PZA 25mg/kg •prophylaxis for LTBI	•ALT/AST ≥5 times ULN (grade 3)	•no cases of grade 3 hepatotoxicity in children <20 years, however trial was halted due to greater than expected hepatotoxicity with RMP/PZA in adults (10% compared to 2.5% with INH)
Villarino 1997	•OL	•157 •high school age	6 months	•RMP 10mg/kg •prophylaxis	NR	•4 patients (2.5%) had ALT 2 times ULN

TB=tuberculosis; NA= not available; NR=not reported; R=randomised; DB=double-blind; OL=open-label; RR=retrospective review; Rev=review; PK=pharmacokinetic; MC=multicentre; INH=isoniazid; RMP=rifampicin; EMB=ethambutol; ETH=ethionamide; SM=streptomycin; PZA=pyrazinamide; PAS=para-aminosalicylic acid; PYR=pyridoxine; ALT=alanine aminotransferase; AST=aspartate aminotransferase; LFT=liver function test; GGT=γ-glutamyl transferase; LTBI=latent tuberculosis infection; ULN=upper limit of normal

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### Table 1. Hepatotoxicity - treatment for active disease

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**Table 2. Hepatotoxicity - prophylaxis.**

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<b>Use of intermittent regimens for the treatment of TB in children</b>
<b>Which treatment regimen</b>
<p><b>Recommendations</b></p> <ul style="list-style-type: none"> <li>• 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). <b>(Strong recommendation, low to moderate evidence against the use of intermittent treatment in children)</b></li> <li>• In the continuation phase of treatment, in settings with well established directly observed therapy, thrice weekly regimens might be considered for children known to be HIV uninfected. <b>(Weak recommendation, very low quality evidence for use of intermittent treatment in children in specific settings)</b></li> </ul>
<b>Domains and considerations</b>
<p><b>Quality of evidence</b></p> <ul style="list-style-type: none"> <li>• Six studies assessed the effectiveness of intermittent therapies in children (Table 1). 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 (Ramachandran et al. 1998); the intermittent arm included the use of pyrazinamide with isoniazid and rifampicin, while the daily arm only included isoniazid and rifampicin.</li> <li>• Four of the RCTs (466 children) were included in a published meta-analysis (Menon et al. 2010) 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).</li> <li>• There were no high quality studies of thrice weekly intermittent treatment regimens in children.</li> <li>• There were no data pertaining to the use of intermittent therapy for the treatment of TB in HIV positive children.</li> </ul> <p><b>Uncertainty: YES, given the low quality of evidence assessing the use of intermittent regimens in children</b></p>
<p><b>Risks/benefits</b></p> <p><b>Benefits</b></p> <ul style="list-style-type: none"> <li>• Limited evidence of benefits</li> <li>• In some regions and countries thrice weekly intermittent regimens have been successfully used 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).</li> </ul> <p><b>Risks</b></p> <ul style="list-style-type: none"> <li>• The metabolism of these medicines in children makes it more likely that intermittent treatment regimens may result in inadequate exposure to the medicines, therefore increasing the risk of inefficacy. This is supported by evidence from adult studies where adult patients using intermittent therapy have a higher risk of treatment failure and developing multidrug resistant TB.</li> </ul> <p><b>Uncertainty: YES, given lack of conclusive evidence for the use of intermittent regimens in children</b></p>
<p><b>Values and acceptability</b></p>

<b>Use of intermittent regimens for the treatment of TB in children</b>
<p><b>In favour:</b></p> <ul style="list-style-type: none"> <li>• Do not want children to be excluded from well established directly observed therapy programmes in countries with a low prevalence of HIV</li> </ul> <p><b>Against:</b></p> <ul style="list-style-type: none"> <li>• Inefficacy of treatment if twice weekly intermittent regimens are used</li> </ul> <p><b>Uncertainty: YES, given lack of evidence</b></p>
<p><b>Cost</b></p> <ul style="list-style-type: none"> <li>• There are no data available assessing the cost–effectiveness of the use of intermittent treatment regimens for tuberculosis in children. It may not be appropriate to apply results of cost-effectiveness analyses in adult populations to children, given that the factors that impact on cost-effectiveness, such as treatment efficacy and safety and relative cost, are likely to differ between adults and children.</li> </ul> <p><b>Uncertainty: YES, given lack of data and uncertainty regarding applicability of results from other populations.</b></p>
<p><b>Feasibility</b></p> <ul style="list-style-type: none"> <li>• Current evidence does not strongly support intermittent regimens for the treatment of TB in children</li> </ul> <p><b>Uncertainty: YES, given lack of evidence</b></p>
<p><b>Gaps, research needs, comments</b></p> <ul style="list-style-type: none"> <li>• There are no high quality randomised controlled trials assessing thrice weekly treatment regimens for the treatment of TB in children.</li> </ul>
<p><b>Final comment</b></p> <ul style="list-style-type: none"> <li>• The panel 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.</li> </ul>

**Table 1. Summary of evidence for use of intermittent regimens in children**

Citation	Study Design/location	Participants Number and age	Intervention (drugs used in mg/kg)	Follow-up	Results	Adverse events
Kansoy et al. 1996	RCT, Turkey	35 Mean age 7.6 years	<b>Intermittent (twice weekly):</b> n=18, 2m SHR / 8.5m HR S 20; H 15; R 15 <b>Daily:</b> n=15, 40d SHR / 9m HR / 3m H S 20; H 15; R 15	12 months	<b>Cure:</b> Intermittent 100% (18/18) Daily 100% (15/15) <b>Adherence:</b> Information not available <b>Relapse:</b> 0	Transaminitis (n=1)
Ramachandran et al. 1998	RCT, Chennai, India	141 56% < 5 years	<b>Intermittent (thrice/twice weekly):</b> n=69, 2m HRZ thrice weekly followed by 4m HR twice weekly H 15; R 12; Z 45 <b>Daily:</b> n=68, 9m HR H 6; R 12	60 months	<b>Cure:</b> Intermittent 48% (33/69) Daily 60% (41/68) <b>Adherence:</b> Information not available <b>Relapse:</b> 1 in daily group	Jaundice (n=3)
Kumar et al. 1990	RCT, Chandigarh, India	76 1-15 years	<b>Intermittent (twice weekly):</b> n=37, 2m HRZ / 4m HR H 20-30; R 10-15; Z 50-60 <b>Daily:</b> n=39, 2m HRZ / 4m HR H 10-15; R 10-15; Z 20-30	24 months	<b>Cure:</b> Intermittent 97% (31/32) Daily 100% (31/31) <b>Adherence:</b> Information not available <b>Relapse:</b> 0	No serious adverse effects reported. Vomiting (n=6); Joint pains (n=2)

Citation	Study Design/location	Participants Number and age	Intervention (drugs used in mg/kg)	Follow-up	Results	Adverse events
Te Water Naude et al. 2000	Open RCT, South Africa	213 Mean 2.1 years	<b>Intermittent (twice weekly):</b> n=95, 2m HRZ / 4m HR H 15; R 15; Z 55 <b>Daily:</b> n=118, 6m HRZ five days a week H 10; R 10; Z 25	30 months	<b>Cure:</b> Intermittent 89% (85/95) Daily 97% (114/118) <b>Adherence:</b> Intermittent 79% vs. Daily 77% <b>Relapse:</b> 1 in intermittent group	Vomiting reported in intermittent group in children receiving Z at dosage of 62.5mg/kg. Resolved when dose reduced to Z 55mg/kg
Göçmen et al. 1993	Retrospective review, Turkey	130 Aged 6 mths to 17 years	<b>110 children received:</b> H 10-15; R 10-15; S 30 daily for 15 days, followed by similar doses of H and R twice weekly for 8.5 mths. <b>20 children received:</b> same regimen without streptomycin	1 yr to 14.5 yrs	<b>Cure:</b> 100%; 84% clinical recovery within 1st mth; 20% radiological recovery within 1st 3mths and completed at 1yr <b>Adherence:</b> Intermittent 79% vs. Daily 77% <b>Relapse:</b> 1 case 18 mths after treatment completion	No serious adverse effects reported. Transient increase in liver enzymes (n=1)
Al-Dossary et al. 2002	Prospective study, USA	185 Aged 5 mths to 17 yrs	<b>Wk 1-2(daily treatment):</b> H 10-15; R 10-20; Z 20-40 <b>Wk 3-8(twice weekly):</b> H 20-40; R 10-20; Z 50-70 <b>Wk 9-24 (twice weekly):</b> H 20-40; R 10-20	Not stated	<b>Cure:</b> 37% had complete resolution of disease at the end of treatment <b>Adherence:</b> 16 cases had poor adherence <b>Relapse:</b> 1 case; 4 yrs after treatment completion	Vomiting and skin rash (n=2). Gastrointestinal disturbances (n=9)

## References

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<b>TREATMENT OF TB IN INFANTS (0 - 3 MONTHS OF AGE)</b>
<b>Which treatment regimen</b>
<p><b>Recommendations</b></p> <ul style="list-style-type: none"> <li>• Infants (0-3 months of age) with suspected or confirmed pulmonary tuberculosis or tuberculosis peripheral lymphadenitis in settings with high HIV prevalence and/or high isoniazid resistance or extensive pulmonary disease living in low HIV prevalent or low H resistance settings should be promptly treated with a four drug (HRZE) regimen for 2 months followed by a two drug (HR) regimen for 4 months at the following doses:  H 10 mg/kg (range 10-15 mg/kg); maximum dose: 300 mg/day  R 15 mg/kg (range 10-20 mg/kg); maximum dose: 600 mg/day  Z 35 mg/kg (30-40 mg/kg)  E 20 mg/kg (15-25 mg/kg)</li> </ul> <p><b>(Strong recommendation, low quality evidence)</b></p> <ul style="list-style-type: none"> <li>• Infants (0-3 months of age) with suspected or confirmed pulmonary tuberculosis or tuberculosis peripheral lymphadenitis in a setting with a low HIV prevalence and/or low H resistance and infants aged 0-3 months who are HIV negative can be treated with a three drug regimen (HRZ) for 2 months followed by a two drug (HR) regimen for 4 months at the following doses :  H 10mg/kg (range 10 15 mg/kg); maximum dose: 300 mg/day  R 15mg/kg (range 10-20 mg/kg), maximum dose: 600 mg/day  Z (35mg/kg (range 30-40 mg/kg)</li> </ul> <p><b>(Strong recommendation, low quality evidence)</b></p>
<b>Domains and considerations</b>
<p><b>Quality of evidence</b></p> <ul style="list-style-type: none"> <li>• There are no data specifically addressing the treatment of TB in children &lt;3 months old.</li> <li>• A recent systematic review by Di Mario et al (2009)<sup>2</sup> sought to establish the dosages for tuberculosis prophylaxis in neonates, i.e. children aged 0 to 6 months, and for intermittent treatment in children up to 12 years of age. A total of 22 studies were included in the review, of which two were randomised controlled trials, four were observational studies, four were retrospective reviews, four were cohort studies, two were case reports, one was a prospective study and one was a survey. Of these 22 studies, only 7 included children &lt;6 months old, while 15 included older patients.</li> <li>• Due to heterogeneity amongst the studies, the authors did not perform any meta-analyses of the available data. The authors concluded that there are too few studies, with too much heterogeneity, due to setting, population enrolled, stage of disease and dose, duration and type of drug used, to draw any firm conclusions regarding treatment of neonates. The authors also comment that if higher doses are required to reach adequate bioavailability, as suggested by recent pharmacokinetic data, then the adverse event profiles of the drugs should be properly assessed with data coming from a variety of settings given the high inter-patient variability.</li> <li>• Brief summaries of the studies identified in the Di Mario et al (2009) review are provided in Table 1 below, highlighting the age of included patients. Overall, the available evidence is of very low quality, with no studies directly addressing the &lt;3 month old population and very few studies addressing the population aged up to 6 months. The studies addressing this young population are generally non-comparative and have small sample sizes, with the number of patients in each study aged &lt;6 months usually less than 10.</li> </ul>

<sup>2</sup> Di Mario et al. 2009. TB drugs in children: a systematic review of efficacy and safety of 4 standard drugs - isoniazid; rifampicin; pyrazinamide; ethambutol. (unpublished). Commissioned by WHO Department of Medicines, Access and Rational Use, Essential Medicines and Pharmaceutical Policies, WHO HQ Geneva.

## TREATMENT OF TB IN INFANTS (0 - 3 MONTHS OF AGE)

•The lack of comparative data, the range of doses used and the lack of data in the relevant population suggest that there is currently no strong evidence base for treatment recommendations for children aged 0 to 3 months. The data presented in the tables below represents the available evidence and should be interpreted with caution given the lack of data in patients <3 months old, the potential for bias and the inherent heterogeneity.

**Uncertainty: YES, given lack of evidence assessing treatment regimens in 0 to 3 month old patients as well as heterogeneity, imprecision and indirectness in the available evidence for dosing.**

### Risks/benefits

#### Benefits

• reduction of risk of under-treatment and mortality in this age group by prompt treatment at adequate doses (mortality in this age group is 30-40%)

#### Risks

• neonates are known to have a slow elimination of any substance. The elimination of substances increases at 3 months of age. There is therefore a theoretical risk of overdosing in children less than 3 months of age

**Uncertainty: YES, given lack of conclusive evidence for both efficacy and safety in the neonate population**

### Values and acceptability

#### In favour:

- the importance of treating TB as a severe infectious disease
- the importance of commencing treatment with an effective treatment regimen
- the need for simplified treatment instructions for programs dealing with these children

#### Against:

- due to the absence of PK, efficacy and safety data, the exact dose for children < 3 months old cannot be given

**Uncertainty: YES, given lack of evidence**

**TREATMENT OF TB IN INFANTS (0 - 3 MONTHS OF AGE)**

**Cost**

• There are no data available assessing the cost-effectiveness of TB treatment regimens in children aged 0 to 3 months. This is reasonable given lack of data for this patient population. It may not be appropriate to apply results of cost-effectiveness analyses in adult populations to this younger population, given that the factors that impact on cost-effectiveness, such as treatment efficacy and safety and relative cost, are likely to differ between adults and children.

**Uncertainty: YES, given lack of data and uncertainty regarding applicability of results from other populations.**

**Feasibility**

• due to the absence of PK, efficacy and safety data, the exact dose for children < 3 months old cannot be given

**Uncertainty: YES, given lack of evidence**

**Gaps, research needs, comments**

- The panel noted the very limited systematic clinical data describing treatment and outcomes of the treatment of TB in this age group
- PK studies in children less than 3 months of age

**Final comment**

• Treatment may require dose adjustment to take into account the affect of age and development on drug disposition (absorption, distribution, metabolism and excretion) and possible toxicity in very young infants. This should be done by a clinician experienced in the management of paediatric tuberculosis

**Table 1: Summary of studies including children aged 0 to 6 months of age**

Study	Design/location	Patient population	Number in target population (0 to 6 months) <sup>a</sup>	Drug(s)	Outcomes
<b>Studies with children &lt; 6 months of age</b>					
Abernathy 1983	<ul style="list-style-type: none"> <li>•cohort study</li> <li>•short-term treatment of TB</li> <li>•USA</li> </ul>	<ul style="list-style-type: none"> <li>•50 children aged 4 months to 15 years with TB</li> </ul>	<ul style="list-style-type: none"> <li>•6 children &lt;6 months of age</li> <li>•none &lt;3 months of age</li> </ul>	<ul style="list-style-type: none"> <li>•RMP 10-20mg/kg + INH 10-20mg/kg for one month followed by RMP 10-20mg/kg and INH 20-40mg/kg twice weekly for 8 months</li> </ul>	<ul style="list-style-type: none"> <li>•symptoms cleared in 1 to 2 months, sputum cultures converted to negative in 1 to 2 months, extrapulmonary disease disappeared, and pulmonary infiltrates cleared.</li> <li>•one child excluded due to drug toxicity</li> </ul>
Dubus 1994	<ul style="list-style-type: none"> <li>•case series</li> <li>•France</li> </ul>	<ul style="list-style-type: none"> <li>•6 children mean age 8 months</li> </ul>	3	<ul style="list-style-type: none"> <li>•initial treatment with 3 or 4 of INH 5mg/kg + RMP 20mg/kg + EMB 15mg/kg or PZA 20mg/kg followed by INH and RMP at doses listed for 13 months.</li> </ul>	<ul style="list-style-type: none"> <li>•all children cured without sequelae</li> <li>•one child developed cytotoxic hepatitis</li> </ul>
Jacobs 1992	<ul style="list-style-type: none"> <li>•open-label study assessing treatment of TBM</li> </ul>	<ul style="list-style-type: none"> <li>•53 children aged 0 to &gt;5 years</li> </ul>	8	<p>Does used were:</p> <ul style="list-style-type: none"> <li>•INH 15mg/kg</li> <li>•RMP 20mg/kg</li> <li>•PZA 30mg/kg</li> <li>•SM 40mg/kg</li> <li>•EMB 25mg/kg in following regimens:</li> <li>•INH/SM/EMB for 2 months then INH/EMB for 10 months (A)</li> <li>•INH/RMP/SM for 2 months then INH/RMP for 7 months (B)</li> <li>•INH/RMP/PZA/SM for 2 months followed by INH/RMP for 4 months (C)</li> </ul>	<p>Comparing regimens A+C combined versus regimen C:</p> <ul style="list-style-type: none"> <li>•total adverse outcomes OR=1.38; 95% CI: 1.38, 464.00; p=0.0018);</li> <li>•mortality OR=5.43; 95% CI: 0.78, 35.80; p=0.08;</li> <li>•sequelae OR=21.52; 95% CI: 1.07, 432.20; p=0.0048)</li> </ul>

<b>Study</b>	<b>Design/location</b>	<b>Patient population</b>	<b>Number in target population (0 to 6 months)<sup>a</sup></b>	<b>Drug(s)</b>	<b>Outcomes</b>
Kiper 1998	<ul style="list-style-type: none"> <li>•cohort study</li> <li>•Turkey</li> </ul>	<ul style="list-style-type: none"> <li>•15 children median age 4.68 months</li> </ul>	15	<ul style="list-style-type: none"> <li>•INH 10-15mg/kg+RMP 10-15mg/kg+SM 30mg/kg for 15 days followed by INH 10-15mg/kg+RMP 10-15mg/kg for 8.5 months</li> <li>•6 children received the above regimen and 9 children received similar regimen without SM</li> </ul>	<ul style="list-style-type: none"> <li>•clinical improvement in all children within 15 to 30 days, radiological improvement in 3 to 6 months</li> <li>•moderately elevated serum levels of liver enzymes in 3 children, which returned to normal when RMP dose reduced to 5mg/kg</li> </ul>
Kobayashi 2002	<ul style="list-style-type: none"> <li>•case report</li> <li>•Japan</li> </ul>	<ul style="list-style-type: none"> <li>•1 child 15 days old</li> </ul>	1	<ul style="list-style-type: none"> <li>•INH 10mg/kg + RMP 10mg/kg + PZA 20mg/kg + SM 20mg/kg + vitamin B6 daily for 2 month</li> <li>•at 4 months of age treatment changed to SM 20mg/kg twice weekly and RMP 10mg/day daily</li> </ul>	<ul style="list-style-type: none"> <li>•good response without any sequelae within 1 year from discharge</li> <li>•at 4 months child developed signs of cerebral hypertension and was diagnosed with cerebral haemorrhage and vitamin K deficiency</li> </ul>
Sneag 2007	<ul style="list-style-type: none"> <li>•retrospective review of medical records</li> <li>•prophylaxis for MDR-TB</li> <li>•South Africa</li> </ul>	<ul style="list-style-type: none"> <li>•5 children median age 0.4 years</li> <li>•one child 13.3 years</li> <li>•one child HIV positive</li> <li>•all exposed to MDR-TB contacts</li> </ul>	4	<ul style="list-style-type: none"> <li>•INH 10mg/kg/day for 14 months</li> <li>•INH 5mg/kg/day for 3 months from birth then INH/RMP/PZA 5/10/25 mg/kg/day for 2 months</li> <li>•INH/RMP/PZA 5/10/25 mg/kg/day from age 1 for 3 months</li> <li>•INH/RMP 10/10mg/kg/day from birth for 3 months</li> <li>•INH/RMP/PZA 5/10/25 mg/kg/day from birth for 2 months</li> </ul>	<ul style="list-style-type: none"> <li>•all treatment regimens were inadequate in preventing MDR-TB in children exposed to MDR-TB contacts</li> <li>•all patients were eventually treated with high dose H (15-20mg/day) plus Z/E/Eth/ofloxacin and amikacin. Four children became culture-negative within 3 months</li> </ul>
Stewart 1976	<ul style="list-style-type: none"> <li>•open-label prophylactic use of</li> </ul>	<ul style="list-style-type: none"> <li>•82 infants</li> </ul>	82	<ul style="list-style-type: none"> <li>•INH 8mg/kg for 8 weeks</li> </ul>	<ul style="list-style-type: none"> <li>•no infants developed tuberculosis</li> </ul>

Study	Design/location	Patient population	Number in target population (0 to 6 months) <sup>a</sup>	Drug(s)	Outcomes
	isoniazid following exposure to TB case •UK				
<b>Unknown if children &lt;6 months</b>					
Biddulph 1990	•prospective study •Papua New Guinea	•639 children	•unknown, with 48 children aged <1 year	•2 months INH 10-15mg/kg+RMP 10-15mg/kg+SM 20-30mg/kg+PZA 25-35mg/kg followed by 4 months twice weekly INH 15-20mg/kg+RMP 10-15mg/kg	•12 children died, 145 defaulted and 373 completed treatment •12 children developed rash •7 children relapsed
Donald 1998	•observational study •South Africa	•95 children	•unknown	•INH 20mg/kg+RMP 20mg/kg+PZA 40mg/kg+Eth 20mg/kg	•10 children in Stage III and 3 in Stage II died before completion of therapy •13 children developed mild transient elevation of liver enzymes that did not require treatment change •authors conclude young children can be safely treated with high doses of anti-TB drugs for 6 months
Gendrel 1989	•cohort study •assessment of hepatotoxicity of INH+RMP in children with TB •Gabon	•47 children with mean age 31.2 months	•not known	•ING 5-20mg/kg/RMP 6-25mg/kg+E 20mg/kg for 2 months then INH/RMP at same dosage for 4 months	•8 of 10 children who received ING >15mg/kg developed hepatic toxicity •63.8% had increase in liver enzyme levels at least during treatment, usually within first month •children with more severe malnutrition more likely to develop hepatic toxicity
Gocmen 1993	•retrospective review	•130 children	•unknown	•110 children received INH	•cure rate 100%

<b>Study</b>	<b>Design/location</b>	<b>Patient population</b>	<b>Number in target population (0 to 6 months)<sup>a</sup></b>	<b>Drug(s)</b>	<b>Outcomes</b>
	of short-course intermittent chemotherapy in children with TB •Turkey	aged 6 months to 17 years	•16 children (12%) aged 0 to 1 year	10-15mg/kg+RMP 10-15mg/kg+SM 30mg/kg daily for 15 days, followed by INH+RMP at same dosage twice weekly for 8.5 months •20 children received same regimen without SM	•one case of relapse after 18 months •increase in liver enzymes in one case (<1%)
Hsu 1984	•observational study HSU	•294 children	•unknown	•for prophylaxis INH 6-10mg/kg+PAS 200mg/kg •for treatment INH+PAS with SM for 1-2 months in early phase of treatment (doses unspecified)	•only 8 children developed active TB •for treatment, all children recovered completely
Mount 1961	•randomized controlled trial	•2570 children	•244 children <1 year but unknown how many <6 months	•INH 4-6mg/kg •placebo •12 month treatment	•36 treated with INH and 52 treated with placebo had adverse pulmonary changes •6 patients in INH group and 33 in placebo group developed extrapulmonary complications
O'Brien 1983	•retrospective review assessing hepatotoxic reactions •USA	•874 children 0 to 14 years of age	•108 children <1 year of age, unknown how many <6 months	•various regimens including INH+RMP plus SM, PAS or EMB or INH plus drugs other than RMP or INH alone. Doses were not reported.	•total of 68 adverse reactions reported with GI disturbance in 26 patients, hepatotoxicity in 16 patients and rash/itching in 14 patients. •Hepatotoxic reactions were attributed to INH, RMP and both INH+RMP, with 14/430 (3.3%) of children receiving INH+RMP having a hepatotoxic reaction •INH dose did not appear to be a predictor of hepatotoxic reactions
Ormerod 1998	•survey •UK	•605 children	•unknown	•INH 10mg/kg + RMP 10mg/kg	•prophylactic chemotherapy reduced proportion of paediatric

<b>Study</b>	<b>Design/location</b>	<b>Patient population</b>	<b>Number in target population (0 to 6 months)<sup>a</sup></b>	<b>Drug(s)</b>	<b>Outcomes</b>
					<p>notifications within a few years of introduction</p> <ul style="list-style-type: none"> <li>reduction in duration of prophylaxis to 4 and 3 months showed no increase in proportion of notifications</li> </ul>
Reis 1990	<ul style="list-style-type: none"> <li>cohort study</li> <li>Brazil</li> </ul>	117 children aged 6 months to 15 years	•none	•INH 10mg/kg+RMP 15mg/kg	<ul style="list-style-type: none"> <li>excellent clinical/radiologic response in all patients</li> <li>no relapses occurred during follow-up</li> <li>3 patients had side effects which disappeared after reduction of doses to 5-10mg/kg</li> </ul>
Sanchez-Albuisa 1997	<ul style="list-style-type: none"> <li>open-label study of tolerance of short course PZA</li> <li>Spain</li> </ul>	•114 children aged 6 months to 15 years	•none	•INH 10mg/kg+RMP 15mg/kg+PZA 20-25mg/kg for 2 months followed by INH/RMP at same doses for 4 months	<ul style="list-style-type: none"> <li>adverse effects mild in all cases; no signs of clinical hepatotoxicity</li> <li>increase in uric acid concentration in 92.2% of patients but no adverse effects associated with such</li> </ul>
Schaaf 2002	<ul style="list-style-type: none"> <li>observational study assessing chemoprophylaxis in children with household contact with adults with MDR-TB</li> <li>South Africa</li> </ul>	•125 children median age 28 months	•unknown	•range of prophylaxis and treatment regimens including INH, PZA, Eth, EMB; dose not reported	<ul style="list-style-type: none"> <li>2 of 41 (5%) who received prophylaxis developed TB</li> <li>all children who developed TB were clinically and radiologically cured after 30 months follow-up</li> </ul>
Te Water Naude 2000	<ul style="list-style-type: none"> <li>open-label randomised trial comparing intermittent twice weekly treatment and daily treatment</li> </ul>	•213 children median age 25.9 months	•unknown	<ul style="list-style-type: none"> <li>intermittent twice weekly INH 15mg/kg+RMP 15mg/kg+PZA 55mg/kg</li> <li>daily group INH 10mg/kg_RMP 10mg/kg+PZA 25mg/kg</li> </ul>	<ul style="list-style-type: none"> <li>no differences between groups for treatment outcome score one child in twice weekly group considered a relapse</li> <li>no significant side effects documented</li> </ul>

<b>Study</b>	<b>Design/location</b>	<b>Patient population</b>	<b>Number in target population (0 to 6 months)<sup>a</sup></b>	<b>Drug(s)</b>	<b>Outcomes</b>
	South Africa				
Vallejo 1994	<ul style="list-style-type: none"> <li>retrospective review medical records</li> <li>USA</li> </ul>	<ul style="list-style-type: none"> <li>47 children &lt;12 months of age</li> </ul>	<ul style="list-style-type: none"> <li>unknown</li> </ul>	<ul style="list-style-type: none"> <li>infants with thoracic disease received INH 10-15mg/kg+RMP 10-20mg/kg for 9-12 months with PZA 25-35mg/kg added in first two months</li> <li>patients with meningitis, tuberculoma or disseminated TB received INH 10-15mg/kg+RMP 10-20mg/kg for 9-12 months with PZA 25-35mg/kg+SM 20-25mg/kg for first 2 months</li> <li>PZA 25-35mg/kg+Smtwice weekly directly observed therapy given to 18 infants with INH 20-25mg/kg+RMP 10-20mg/kg+PZA 50-70mg/kg</li> </ul>	<ul style="list-style-type: none"> <li>all infants completed therapy, which was well-tolerated</li> <li>PZA 25-35mg/kg+Smno relapse in 6 months to 7 years of follow-up</li> <li>one patient developed hepatotoxicity associated with INH</li> </ul>
Visudhiphan 1975	<ul style="list-style-type: none"> <li>retrospective control group comparing standard treatment and RMP for treatment of tuberculosis meningitis</li> <li>Thailand</li> </ul>	<ul style="list-style-type: none"> <li>33 children &lt;15 years of age</li> </ul>	<ul style="list-style-type: none"> <li>unknown, with 6 children aged &lt;1 year</li> </ul>	<ul style="list-style-type: none"> <li>standard SM 20-240mg/kg+PAS 250mg/kg+INH 20mg/kg</li> <li>RMP group INH 20mg/kg+RMP 15mg/kg</li> </ul>	<ul style="list-style-type: none"> <li>of 20 patients given INH+RMP, 19 survived and one died</li> <li>for 13 patients receiving standard treatment, 9 survived and 4 dead</li> </ul>
Zar 2007	<ul style="list-style-type: none"> <li>randomized, double-blind trial comparing INH and placebo both given with co-trimoxazole in children with HIV</li> </ul>	<ul style="list-style-type: none"> <li>263 children aged ≥8 weeks with HIV</li> <li>median age 24.7 months</li> </ul>	<ul style="list-style-type: none"> <li>unknown</li> <li>77 children (29%) aged &lt;12 months</li> </ul>	<ul style="list-style-type: none"> <li>INH 10mg/kg +co-trimoxazole (trimethoprim 5mg/kg) daily or three times weekly</li> <li>placebo + co-trimoxazole (trimethoprim 5mg/kg) daily or</li> </ul>	<ul style="list-style-type: none"> <li>incidence of TB in children &lt;12 months 0/35 (0%) in INH group vs 0/42 (0%) in placebo group</li> <li>mortality in children &lt;12 months 7/35 (20.0%) in INH group vs 13/42 (30.9%) in placebo group</li> </ul>

Study	Design/location	Patient population	Number in target population (0 to 6 months) <sup>a</sup>	Drug(s)	Outcomes
	<ul style="list-style-type: none"> <li>•assessing impact of INH prophylaxis on mortality and incidence of TB</li> <li>•South Africa</li> </ul>			three times weekly	HR=0.43 (95% CI: 0.17, 1.09) <ul style="list-style-type: none"> <li>•for all patients there was a statistically significant advantage for INH group compared to placebo for incidence of TB (HR=0.28; 95% CI: 0.10, 0.78) and mortality (HR=0.46; 95% CI: 0.22, 0.95)</li> <li>•Grade 3 or 4 toxicity in overall population 4% in INH group vs 6.1% in placebo group</li> </ul>

<sup>a</sup> this refers to the target population in the Di Mario et al (2009) review; there were no articles available addressing TB treatment in patients aged 0 to 3 months.

TB=tuberculosis; MDR-TB=multidrug-resistant tuberculosis; ING=isoniazid; RMP=rifampicin; PAS=para-aminosalicylic acid; PZA=pyrazinamide; EMB=ethambutol; SM=streptomycin

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<b>STREPTOMYCIN IN THE TREATMENT OF UNCOMPLICATED PULMONARY TB IN CHILDREN</b>
<b>When to use</b>
<p><b>Recommendations</b></p> <ul style="list-style-type: none"> <li>• Streptomycin should not be used as part of first line treatment regimens for children with pulmonary tuberculosis or tuberculous peripheral lymphadenitis <b>(Strong recommendation, moderate quality evidence)</b></li> </ul>
<b>Domains and considerations</b>
<p><b>Quality of evidence</b></p> <ul style="list-style-type: none"> <li>• A literature search was conducted to identify publications addressing the use of streptomycin in the treatment of uncomplicated pulmonary TB in children. Medline and EMBASE were searched using the search terms 'tuberculosis pulmonary, streptomycin, children or pediatric or paediatric'.</li> <li>• No studies were identified that specifically addressed the use of streptomycin for the treatment of uncomplicated pulmonary TB in children. Articles were found that discussed streptomycin for the treatment of pulmonary TB in children, as well as articles addressing use of streptomycin to treat tuberculosis (either undefined type or 'primary') in children, and the treatment of pulmonary TB in adults including streptomycin. There were also studies that compared different courses of therapy for the treatment of TB in children, including streptomycin, with the majority of patients having pulmonary TB. The studies are summarized in Table 1.</li> <li>• The articles dating from the 1950s describing the use of streptomycin in childhood TB could not be sourced, therefore the quality of these trials could not be determined. However, given the date of the trials they are not likely to be randomized, blinded comparative trials. There was also a 1972 study comparing streptomycin plus isoniazid to isoniazid and thiacetazone in children with primary pulmonary tuberculosis (Gupta and Law, 1972), however this article could also not be sourced.</li> <li>• There are two articles addressing the treatment of children with TB which included the use of streptomycin. <ul style="list-style-type: none"> <li>• Kansoy et al (1996) compared intermittent short course chemotherapy of SM, RMP and INH for two weeks followed by INH and RMP twice weekly for 8.5 months for pulmonary TB with conventional chemotherapy consisting of SM for 40 days, RMP for 9 months and INH for 12 months. At six months of therapy response to treatment was complete in both groups.</li> <li>• The Kansoy trial is included in a systematic review (Menon et al. 2010) which compared the effectiveness of intermittent with daily chemotherapy in childhood tuberculosis. The review located four trials with a total of 466 patients, of which 439 had pulmonary TB. Only the Kansoy trial used streptomycin. This review concluded that twice weekly intermittent short course chemotherapy is less likely to cure TB in children compared to daily therapy. The review did not specifically address the role or impact of streptomycin.</li> </ul> </li> <li>• For the available trials, none directly addressed the use of streptomycin for uncomplicated pulmonary TB in children, instead they focussed on type of regimen used (e.g. intermittent versus daily treatment). A recent review (Marais et al., 2006) discussed childhood pulmonary TB in regard to diagnosis, treatment, HIV infection and drug resistance. The review recommended streptomycin as a second line drug at a dose of 20-40mg/kg (for disseminated miliary disease), but provided no further dosing or treatment regimen details, nor was the source of the recommended dose provided. The Marais review did note that streptomycin is limited by poor cerebrospinal fluid penetration and intramuscular administration.</li> </ul> <p><b>Uncertainty: YES, given lack of evidence</b></p>
<p><b>Risks/benefits</b></p> <p><b>Benefits</b></p> <ul style="list-style-type: none"> <li>• limited evidence of benefits</li> </ul>

<b>STREPTOMYCIN IN THE TREATMENT OF UNCOMPLICATED PULMONARY TB IN CHILDREN</b>
<p><b>Risks</b></p> <ul style="list-style-type: none"> <li>•potential for inappropriate dosing as well as adverse events, especially ototoxicity</li> </ul> <p><b>Uncertainty: YES, given lack of evidence</b></p>
<p><b>Values and acceptability</b></p> <p><b>Against:</b></p> <ul style="list-style-type: none"> <li>• problems with injection based treatment regimens</li> <li>• ototoxicity associated with use of streptomycin</li> <li>• availability of safe and effective oral alternatives which can be used as first line medicines</li> </ul> <p><b>Uncertainty: YES, given lack of evidence</b></p>
<p><b>Cost</b></p> <ul style="list-style-type: none"> <li>•There are no data available assessing the cost–effectiveness of streptomycin for the treatment of uncomplicated pulmonary TB in children</li> </ul> <p><b>Uncertainty: YES, given lack of evidence</b></p>
<p><b>Feasibility</b></p> <ul style="list-style-type: none"> <li>• streptomycin is already used in the treatment of tuberculosis; however additional paediatric-specific research would clarify use</li> </ul> <p><b>Uncertainty: YES, given lack of evidence</b></p>
<p><b>Gaps, research needs, comments</b></p> <ul style="list-style-type: none"> <li>•There is a considerable lack of evidence addressing the use of streptomycin in children with uncomplicated pulmonary TB. However, randomized controlled trials assessing its efficacy and safety in comparison with other drugs may not be warranted given the availability of safe, effective and oral alternatives which can be used as first line medicines</li> </ul>
<p><b>Final comment</b></p> <ul style="list-style-type: none"> <li>• Streptomycin should not be used as part of first line treatment regimens for children with pulmonary tuberculosis. The panel noted the low to moderate quality evidence of efficacy of streptomycin and took into account the risk of toxicity associated with the use of streptomycin, the problems with injection based treatment regimens and the availability of safer, more effective and oral alternatives</li> </ul>

TB=tuberculosis; INH=isoniazid; RMP=rifampicin; SM=streptomycin

**Table 1: Summary of articles addressing streptomycin and childhood TB and articles addressing pulmonary TB and children**

<b>Trial</b>	<b>Title</b>	<b>Design</b>	<b>Details</b>
<b>Streptomycin and children</b>			
Censi 1951	•Streptomycin therapy of pulmonary tuberculosis in children (Italian)	NA	NA
Fruhaufowa 1952	•Results of streptomycin and paraaminosalicylic acid therapy of tuberculosis in children (Polish)	NA	NA
Gupta 1972	•A controlled study on progressive primary pulmonary tuberculosis in children treated for one year with dual drugs: streptomycin and isoniazid versus isoniazid and thiacetazone	NA	NA
Halikowski 1953	•Significance of streptomycin in the treatment of tuberculosis in children; streptomycin in pulmonary tuberculosis in infants (Polish)	NA	NA
Krukowska 1952	•Streptomycin in the treatment of tuberculosis in children; streptomycin therapy of primary and postprimary pulmonary tuberculosis not including miliary tuberculosis (Polish)	NA	NA
Lowys 1951	•Streptomycin therapy of pulmonary tuberculosis in children (except miliary forms) (French)	NA	NA
McEney 1953	•A five year study of tuberculous children treated with streptomycin	NA	NA
Padula 1952	•Results of streptomycin and PAS therapy of pulmonary tuberculosis in children (Italian)	NA	NA
Ticinese 1953	•Streptomycin therapy of tuberculosis in children (Argentinian)	NA	NA
Wilkowa 1951	•Ocular changes in children with pulmonary tuberculosis treated with streptomycin (Polish)	NA	NA
<b>Pulmonary TB and children</b>			
Brinza 2007	•Difficulties in the treatment of pulmonary tuberculosis in children (Romanian)	•retrospective review of 254 children with pulmonary TB assessing treatment course, side effects and assessment of cases at end of treatment	•abstract does not mention streptomycin, although the majority of patients received 4 or 3-drug regimens, so streptomycin may have been used
Gubkina 2009	•Estimation of the possibilities of using unified chemotherapy regimens in new cases of pulmonary tuberculosis in old-age children and adolescents (Russian)	•review of children aged 13 to 17 with pulmonary TB	•streptomycin was included in treatment regimens along with INH, RMP, PZA and EMB, however no result specific to streptomycin were provided.

<b>Trial</b>	<b>Title</b>	<b>Design</b>	<b>Details</b>
Kansoy 1996	<ul style="list-style-type: none"> <li>•Superiority of intermittent short course chemotherapy in childhood pulmonary tuberculosis</li> </ul>	<ul style="list-style-type: none"> <li>•open-label comparison of intermittent short-course therapy consisting of SM, RMP and INH daily for 2 weeks followed by INH and RMP twice weekly for 8.5 months with conventional therapy of SM for 40 days, RMP for 9 months and INH for 12 months.</li> </ul>	<ul style="list-style-type: none"> <li>•at 6 months of therapy response to treatment was complete in both groups.</li> <li>•Authors conclude that a short course, intermittent therapy against pulmonary tuberculosis provides a safe alternative to the conventional, one-year duration chemotherapy</li> </ul>
Marais 2006	<ul style="list-style-type: none"> <li>•Childhood pulmonary tuberculosis. Old wisdom and new challenges</li> </ul>	<ul style="list-style-type: none"> <li>•review of the diagnosis, treatment, HIV infection and drug resistance in childhood pulmonary TB</li> </ul>	<ul style="list-style-type: none"> <li>•streptomycin recommended as second line treatment at dose of 20-40mg/kg for disseminated miliary disease. No further details provided.</li> <li>•review notes that streptomycin is limited by poor CSF penetration a intramuscular administration</li> </ul>
Menon 2010	<ul style="list-style-type: none"> <li>•Intermittent or daily short course chemotherapy for tuberculosis in children: Meta-analysis of randomised controlled trials</li> </ul>	<ul style="list-style-type: none"> <li>•systematic review and meta-analysis of trials comparing intermittent and short course chemotherapy for TB in children</li> </ul>	<ul style="list-style-type: none"> <li>•review included 4 trials, of these only one (Kansoy et al., 1996)used streptomycin</li> <li>•439 of 466 patients in the trials had pulmonary TB</li> <li>•authors conclude that twice weekly intermittent short course therapy is less likely to cure TB in children as compared to daily therapy.</li> </ul>
Shurygin 2009	<ul style="list-style-type: none"> <li>•The efficiency of ultraviolet autologous blood irradiation (UVABI) used in the complex therapy of infiltrative pulmonary tuberculosis in children and adolescents (Russian)</li> </ul>	<ul style="list-style-type: none"> <li>•randomized controlled trial comparing patients who received UVABI and those who did not</li> </ul>	<ul style="list-style-type: none"> <li>•no mention of streptomycin</li> </ul>
Sharma 2008	<ul style="list-style-type: none"> <li>•The DOTS strategy for treatment of paediatric pulmonary tuberculosis in South Delhi, India</li> </ul>	<ul style="list-style-type: none"> <li>•retrospective review of 1098 children with pulmonary TB.</li> </ul>	<ul style="list-style-type: none"> <li>•average age 11.2 years</li> <li>•authors conclude DOTS appears to be highly efficacious</li> </ul>

NA=not available; SM=streptomycin; INH=isoniazid; RMP=rifampicin; EMB=ethambutol

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<b>EVIDENCE BASE FOR TREATMENT REGIMENS FOR TB MENINGITIS IN CHILDREN</b>
<b>What treatment regimen</b>
<p><b>Recommendations</b></p> <ul style="list-style-type: none"> <li>• Children with suspected or confirmed tuberculosis meningitis should be treated for with a four drug regimen (HRZE) for 2 months, followed by a two drug regimen for 10 months; the total duration of treatment being 12 months. The dose recommended for the treatment of tuberculosis meningitis are the same as those described for pulmonary TB <ul style="list-style-type: none"> <li>H 10 mg/kg (range 10-15 mg/kg); maximum dose: 300mg/day</li> <li>R 15 mg/kg (range 10-20 mg/kg); maximum dose: 600 mg/day</li> <li>Z 35 mg/kg (30-40 mg/kg)</li> <li>E 20 mg/kg (15-25 mg/kg)</li> </ul> </li> </ul> <p><b>(Strong recommendation, low quality evidence)</b></p>
<b>Domains and considerations</b>
<p><b>Quality of evidence</b></p> <ul style="list-style-type: none"> <li>•A literature review by Donald (2009)<sup>3</sup> assessed the chemotherapy of TB meningitis (TBM) in children in order to make recommendations for the optimal chemotherapeutic management of TBM.</li> <li>•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.</li> <li>•Out of the 46 efficacy studies, 11 studies were identified that reported treatment regimens including rifampicin for the treatment of TB meningitis in children (Table 1). 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.</li> <li>•None of the studies from the Donald (2009) review were entered into GRADE, given the lack of comparative data.</li> <li>•The panel noted that although there are many observational studies of treatment of children with TBM, they are of very low quality. The panel also noted the existence of a number of treatment guidelines (American Thoracic Society and British Thoracic Society) that recommend longer durations of treatment, up to 2 years in some cases.</li> </ul> <p><b>Uncertainty: YES, given low quality of the evidence and relative lack of paediatric evidence.</b></p>
<p><b>Risks/benefits</b></p> <p><b>Benefits</b></p> <ul style="list-style-type: none"> <li>•effective treatment, with the risk of adverse events and development of drug resistance minimized.</li> </ul>

<sup>3</sup> Donald PR. 2009. The chemotherapy of tuberculous meningitis in children. A literature review. (submitted for publication). Commissioned by WHO Department of Medicines, Access and Rational Use, Essential Medicines and Pharmaceutical Policies, WHO HQ Geneva.

<b>EVIDENCE BASE FOR TREATMENT REGIMENS FOR TB MENINGITIS IN CHILDREN</b>
<p><b>Risks</b></p> <ul style="list-style-type: none"> <li>• inappropriate treatment regimens and dosing</li> </ul> <p><b>Risks outweigh benefits given lack of evidence in paediatric population</b></p>
<p><b>Values and acceptability</b></p> <p><b>In favour:</b></p> <ul style="list-style-type: none"> <li>• based on the severity of morbidity and mortality with this disease prompt treatment for a long duration is warranted</li> </ul> <p><b>Uncertainty: YES</b></p>
<p><b>Cost</b></p> <ul style="list-style-type: none"> <li>• there are no studies of cost or cost-effectiveness in TBM in children. Given the relative lack of efficacy and safety data, this is expected. Caution should be used when considering costs and cost-effectiveness for other types of TB and other populations, as results may not be generalizable.</li> </ul> <p><b>Uncertainty: YES, given the lack of paediatric specific data and cost analyses.</b></p>
<p><b>Feasibility</b></p> <ul style="list-style-type: none"> <li>• current evidence does not strongly support current treatment regimens</li> </ul> <p><b>Uncertainty: YES</b></p>
<p><b>Gaps, research needs, comments</b></p> <ul style="list-style-type: none"> <li>• the available evidence assessing the efficacy and safety of TBM treatment regimens is limited and of poor design.</li> <li>• a randomised trial of different lengths of treatment of tuberculous meningitis</li> </ul>
<p><b>Final comment</b></p> <ul style="list-style-type: none"> <li>• doses should be at least those recommended above and use of the maximum recommended range should be considered given the uncertain penetration of the medicines into the CNS</li> </ul>

**TBM=tuberculosis meningitis; INH=isoniazid; RMP=rifampicin; PZA=pyrazinamide; EMB=ethambutol; MDR-TB=multidrug resistant tuberculosis; CNS=central nervous system**

**Table 1: Summary of studies that included rifampicin in the treatment regimen for treatment of TB meningitis in children**

Trial	Design	Treatment	N	Outcomes
Donald 1998	•open-label non-randomized study of intensive short course treatment	•6 months INH/RMP/PZA/ETH doses INH 20mg/kg; RMP 20mg/kg; PZA 40mg/kg; ETH 20mg/kg	•Stage 1 - 4 •Stage II – 52 •Stage III – 39	•10 Stage III patients (25.6%) died before completion of therapy and 2 Stage III patients (5.1%) died after discharge •3 Stage II patients (5.8%) died before completion of therapy •12 of 29 (41.4%) Stage III survivors had major motor defects •10 of 49 (20.4%) Stage II survivors had major motor defects
Faella 2006	•retrospective review	•2 months INH/RMP/SM + 10-18 months INH/RMP doses INH 5mg/kg; RMP 10mg/kg; SM 20mg/kg •EMB/PZA given to 10 patients, doses not provided	•Stage 1 - 5 •Stage II – 10 •Stage III – 17	•4 deaths (12.5%), all in Stage II patients •6 patients (18.8%) had one or more serious sequelae •3 (9.4%) patients had cytolytic hepatitis with ALT levels 3 times greater than normal, and had INH dose reduced
Farinha 2000	•retrospective review	•2 year course of INH/RMP plus initial 3 months of SM + 20 doses intrathecal or intraventricular SM. Doses not provided •2 months INH/RMP/PZA/SM or EMB + 10 months INH/RMP. Doses not provided	•Stage 1 - 2 •Stage II – 10 •Stage III – 21 •tuberculoma - 5	•5 patients (13% of overall sample) died; all were stage III (23.8%) •19 (50%) either died or developed permanent sequelae •11 of 14 in Stage III (78%) and 3 of 10 (30%) in Stage II developed neurological sequelae
Humphries 1990	•retrospective review	•all patients received INH (mean duration 23.8 months) •84% SM (5.5 months) •85% ETH (19 months) •84% RMP (11.6 months) •47% EMB (14.4 months) •44% PZA (11.9 months) doses not provided	•Stage 1 - 49 •Stage II – 78 •Stage III – 72	•in Stage II, 1 patient died (1.3%), 7 (9.0%) had mild, 6 (7.7%) had moderate and 3 (3.8%) had severe neurological sequelae •in Stage III, 12 patients died (16.7%), 4 (5.6%) had mild, 18 (25.0%) had moderate and 23 (31.9%) had severe neurological sequelae
Jacobs 1992	•open-label, non-randomized study of intensive short course treatment	•2 INH/SM/EMB + 10 INH/EMB or 2 RMP/SM/EMB + 10 RMP/EMB (regimen A) •2 INH.RMP/SM + 7 INH/RMP (regimen B) •2 INH/RMP/PZA/SM + 4 INH/RMP (regimen C) doses: INH 15mg/kg; SM 40mg/kg; RMP 20mg/kg; EMB 25mg/kg; PZA 30mg/kg	•Stage 1 - 8 •Stage II – 29 •Stage III – 16	•there were 11 deaths overall (20.8%) •in Stage III there were 8 deaths (50%), 3 in patients using regimens A or B and 5 in patients using regimen C •in survivors, 19 patients had sequelae •2 patients in Stage III had sequelae (25% of survivors) •results for regimens A and B combined

Trial	Design	Treatment	N	Outcomes
Rahajoe 1979	<ul style="list-style-type: none"> <li>randomized, open-label study of treatment with INH, RMP and SM</li> </ul>	<ul style="list-style-type: none"> <li>INH/SM/RMP</li> <li>INH/PAS/SM</li> <li>Doses INH 20mg/kg; SM 30-50mg/kg; RMP 10-15mg/kg; PAS 200-300mg/kg</li> <li>INH for 18 months, SM for 1 month in group 1 or 3 months in group 2, RMP for 6 months and PAS for 12 months</li> </ul>	<ul style="list-style-type: none"> <li>Stage 1 - 0</li> <li>Stage II - 14</li> <li>Stage III - 27</li> </ul>	<ul style="list-style-type: none"> <li>6 patients treated with INH/SM/RMP died, all Stage III</li> <li>7 patients treated with INH/SM/RMP had neurological sequelae, all Stage III cases</li> <li>5 patients treated with INH/PAS/SM died, with 4 of 5 being Stage III cases</li> <li>11 patients treated with INH/PAS/SM had neurological sequelae, 9 were Stage III cases and 2 were Stage II</li> </ul>
Ramachandran 1989	<ul style="list-style-type: none"> <li>retrospective review of long-term follow-up of 3 open-label, non-randomised studies</li> </ul>	<ul style="list-style-type: none"> <li>3 regimens used, all had INH/SM/RMP with or without PZA for 2 months + INH/EMB for 10 months</li> <li>doses not reported</li> </ul>	<ul style="list-style-type: none"> <li>119 (Stage not provided)</li> </ul>	<ul style="list-style-type: none"> <li>17 (14.3%) died at end of 1 year treatment</li> <li>of remaining 102, 3 (2.9%) had severe sequelae, 32 (31.4%) had moderate sequelae and 15 (14.7%) had mild sequelae</li> </ul>
Schoeman 2004	<ul style="list-style-type: none"> <li>randomized, double-blind trial comparing thalidomide and placebo in addition to INH/RMP/PZA/ETH</li> </ul>	<ul style="list-style-type: none"> <li>INH/RMP/PZA/ETH + patients randomized to thalidomide or placebo</li> <li>doses INH 20mg/kg; RMP 20mg/kg; PZA 40mg/kg; ETH 20mg/kg</li> <li>treatment duration not stated, although some 6 month results are provided</li> </ul>	<ul style="list-style-type: none"> <li>Stage 1 - 0</li> <li>Stage II - 34</li> <li>Stage III - 13</li> </ul>	<ul style="list-style-type: none"> <li>trial stopped early due to adverse events and deaths associated with thalidomide</li> <li>4 deaths, all Stage III patients (30.8%) receiving thalidomide</li> </ul>
Visudhiphan 1989	<ul style="list-style-type: none"> <li>open-label, non-randomized study of treatment using INH and RMP</li> </ul>	<ul style="list-style-type: none"> <li>12 months INH/RMP doses INH 10-15mg/kg; RMP 15mg/kg</li> </ul>	<ul style="list-style-type: none"> <li>Stage 1 - 5</li> <li>Stage II - 25</li> <li>Stage III - 21</li> <li>4 lost to follow-up so 47 analysed</li> </ul>	<ul style="list-style-type: none"> <li>3 deaths (6.4% of overall sample), all patients were in Stage III (14.3%)</li> <li>neurologic deficits in 13 (27.7% overall), 5 in Stage II (20.0%) and 8 in Stage 3 (38.1%)</li> </ul>
Waeker 1990	<ul style="list-style-type: none"> <li>retrospective review of medical records</li> </ul>	<ul style="list-style-type: none"> <li>INH used in all patients, RMP in 26 (86.7%), EMB in 16 (53.3%), SM in 11 (36.7%), PZA in 2 (6.7%)</li> <li>treatment duration and doses not provided</li> </ul>	<ul style="list-style-type: none"> <li>Stage 1 - 3</li> <li>Stage II - 10</li> <li>Stage III - 17</li> </ul>	<ul style="list-style-type: none"> <li>1 death in a Stage III patient (5.9%)</li> <li>in Stage III 15 had major sequelae (88.2%)</li> <li>in Stage II 5 had major sequelae (50%) and 2 had minor sequelae (20%)</li> </ul>
Yaramis 1998	<ul style="list-style-type: none"> <li>retrospective review</li> </ul>	<ul style="list-style-type: none"> <li>INH/RMP for 12 months, with SM or PZA also used in first 2 months</li> <li>Doses INH 10-15mg/kg; RMP 15-20mg/kg; SM 20-25mg/kg; PZA 25-35mg/kg</li> </ul>	<ul style="list-style-type: none"> <li>Stage 1 - 22</li> <li>Stage II - 120</li> <li>Stage III - 72</li> </ul>	<ul style="list-style-type: none"> <li>49 deaths overall (22.9%)</li> <li>14 deaths (11.7%) in Stage II patients and 31 (25.8%) with developmental sequelae</li> <li>35 deaths (48.6%) in Stage III patients and 27 (37.5%) with developmental sequelae</li> </ul>

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<b>EVIDENCE BASE FOR TREATMENT REGIMENS FOR OSTEO-ARTICULAR TB IN CHILDREN</b>
<b>Treatment regimen</b>
<p><b>Recommendations</b></p> <ul style="list-style-type: none"> <li>• Children with suspected or confirmed osteo-articular tuberculosis should be treated with a four drug regimen (HRZE) for 2 months followed by a two drug regimen (HR) 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 described for pulmonary TB. <ul style="list-style-type: none"> <li>H 10 mg/kg (range 10-15 mg/kg); maximum dose 300 mg/day</li> <li>R 15 mg/kg (range 10-20 mg/kg); maximum dose 600 mg/day</li> <li>P 35 mg/kg (30-40 mg/kg)</li> <li>E 20 mg/kg (15-25 mg/kg)</li> </ul> </li> </ul> <p><b>(Strong recommendation, low quality evidence)</b></p>
<b>Domains and considerations</b>
<p><b>Quality of evidence</b></p> <ul style="list-style-type: none"> <li>•A review by Donald (2010)<sup>4</sup> assessed the literature relating to osteo-articular TB with the aim of making recommendations for chemotherapy of the disease in children.</li> <li>•Fifty-one potentially relevant citations were retrieved of which only 11 contained paediatric specific data. Sample sizes ranged from 4 to150. Seven of the studies had less than 25 participants. None of 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.</li> <li>•None of the studies included in the Donald (2010) review were entered into GRADE, given the lack of comparative data.</li> <li>•A summary of the trials including paediatric patients only is provided in Table 1 below. The trials including both adults and children are not provided as the majority do not provide results separately for adults and children, and it may not be appropriate to assume results can be applied to children.</li> </ul> <p><b>Uncertainty: YES, given low quality of the evidence, relative lack of paediatric evidence and lack of appropriate analyses of available data.</b></p>
<p><b>Risks/benefits</b></p> <p><b>Benefits</b></p> <ul style="list-style-type: none"> <li>• effective treatment, with the risk of adverse events and development of drug resistance minimized</li> </ul> <p><b>Risks</b></p> <ul style="list-style-type: none"> <li>• inappropriate treatment regimens and dosing</li> </ul> <p><b>Risks outweigh benefits given lack of evidence in paediatric population</b></p>

<sup>4</sup> Donald PR. 2009. The chemotherapy of osteo-articular tuberculosis in children. A literature review. (unpublished). Commissioned by WHO Department of Medicines, Access and Rational Use, Essential Medicines and Pharmaceutical Policies, WHO HQ Geneva.

**EVIDENCE BASE FOR TREATMENT REGIMENS  
FOR OSTEO-ARTICULAR TB IN CHILDREN**

**Values and acceptability**

**In favour:**

- pharmacological arguments support the longer duration of treatment for infections of bones and joints
- no evidence of increased risk of toxicity associated with increased duration of treatment

**Against:**

- evidence is low quality

**Uncertainty: YES, given lack of evidence**

**Cost**

• There are no studies of cost or cost-effectiveness in osteo-articular TB in children. Given the relative lack of efficacy and safety data, this is expected. Caution should be used when considering costs and cost-effectiveness for other types of TB and other populations, as results may not be generalizable.

**Uncertainty: YES, given the lack of paediatric specific data and cost analyses.**

**Feasibility**

- current evidence does not strongly support recommended treatment regimens

**Uncertainty: YES, given lack of evidence**

**Gaps, research needs, comments**

• There are no randomised controlled trials assessing different treatment regimens for osteo-articular TB in children. The available evidence includes differing populations and treatments and is open to a number of sources of bias. Consequently, the use of RCTs to address research questions would allow more definitive conclusions to be drawn and would allow for improved consideration of the relationship between treatment and outcome.

**Final comment**

• The panel noted that although the evidence is of low quality, the treatment regimens used in children were generally given for at least 12 months duration and the studies reported 'no relapse' as the main outcome, although the duration of follow-up was often poorly reported. The panel took into account the pharmacological arguments to support the longer duration of treatment for infections of bones and joints and the lack of evidence to indicate an increased risk of toxicity associated with increased duration of treatment, and the difficulty of determining cure in patients treated for osteo-articular TB.

**Table 1: Summary of paediatric studies of osteo-articular TB treatment**

<b>Study</b>	<b>Design</b>	<b>Patients</b>	<b>Drug(s)</b>	<b>Treatment duration</b>	<b>Outcomes</b>
Agrawal 2008	•review surgical treatment of tuberculous osteomyelitis	•7 children aged 4 to 18 years with TB of the rib	•INH 5mg/kg •RMP 10-15mg/kg •PZA 25mg/kg •EMB 15mg/kg	•12 months	•surgical excision in all cases •no relapse in 5-8 years follow-up
Altman 1996	•review of use of chemotherapy and anterior/posterior spinal fusion	•6 children with severe spinal TB	•INH, RMP and PAS, doses not provided	•12 months	•follow-up of 9.5 to 13.7 years with no relapse
Bailey 1972	•retrospective review	•100 children 18 months to 10 years of age •Pott's disease	•INH 5-10mg/kg •SM 20mg/kg (6 months) •PAS 200mg/kg	At least 18 months	•94% had complete 'working capacity' and 6% had partial working capacity •no mention of relapse
Govender 2007	•retrospective review of clinical and radiographic outcome of children treated operatively and non-operatively	•58 children with cervical spine TB, with age ranging from 1.9 to 14 years	•INH 5-10mg/kg •RMP 10-20mg/kg •PZA 25mg/kg •EMB 15mg/kg	•12 months	•no relapses recorded
Hakimi 2008	•review of 4 cases of tuberculous osteomyelitis	•4 children aged 10 to 16 months with TB disease of knee, ankle, wrist	•INH, RMP, EMB and PZA followed by INH and RMP	•INH, RMP, EMB and PZA for nine months followed by INH and RMP for 7 months	•satisfactory radiological recovery within 6 months
Kalra 2007	•review of patients with tubercular atlantoaxial dislocation, treated with surgery and chemotherapy	•17 children with atlanto-axial TB, aged from 5 to 16 years	•INH 10-20mg/kg •RMP 10-20mg/kg •PZA 20-35mg/kg •EMB 15mg/kg	•PZA for 3 months, EMB for 12 months, RMP and INH for 18 months	•no relapses recorded
MRC 1973	•unknown design •comparison of bed	•150 children with spinal TB	•INH 10mg/kg •SM 30mg/kg	18 months	•spinal TB could be managed without

Study	Design	Patients	Drug(s)	Treatment duration	Outcomes
	rest with ambulant outpatient treatment in patients receiving chemotherapy		•PAS 200mg/kg		admission to hospital for bed rest
Papavasiliou + Petropoulos 1981	<ul style="list-style-type: none"> <li>•report on cases of bone and joint TB</li> <li>•surgical curettage plus chemotherapy followed by immobilization in plaster</li> </ul>	•10 children with bone and joint TB aged 18-30 months	<ul style="list-style-type: none"> <li>•INH 5mg/kg</li> <li>•RMP 30mg/kg</li> <li>•SM 15mg/kg</li> </ul>	6 months (SM for 6 weeks)	•no relapse recorded during at least 2 years follow-up
Rasool 1994	•report of cases of cystic tuberculosis of bone	•13 children mean age 5 years	•doses not provided	•INH 12 months; RMP 6 months; PZA 12 months	<ul style="list-style-type: none"> <li>•healing in all cases</li> <li>•no relapses reported</li> </ul>
Shih 1997	<ul style="list-style-type: none"> <li>•report of 24 cases of long bone TB</li> <li>•biopsy, curettage and chemotherapy provided</li> </ul>	•24 children with long bone TB	<ul style="list-style-type: none"> <li>•INH 10-20mg/kg</li> <li>•RMP 10-20mg/kg</li> </ul>	•6 months	•follow-up to 32 months, no relapses
Singh 1992	•review of cases	•104 children with osteo-articular TB	<ul style="list-style-type: none"> <li>•INH 5mg/kg</li> <li>•RMP 10mg/kg</li> <li>•EMB 15mg/kg</li> </ul>	•INH 18 months; RMP 6 months; EMB 12 months	<ul style="list-style-type: none"> <li>•clinical/radiological disease healing from 12-14 months n 74% of patients</li> <li>•no recurrence</li> </ul>

TB=tuberculosis; INH=isoniazid; RMP=rifampicin; PAS=para-aminosalicylic acid; PZA=pyrazinamide; EMB=ethambutol; SM=streptomycin

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<b>USE OF FLUOROQUINOLONES IN CHILDREN WITH MDR-TB</b>
<b>When to use</b>
<p><b>Recommendations</b></p> <ul style="list-style-type: none"> <li>• Children with proven or suspected pulmonary tuberculosis or TB meningitis caused by multiple drug resistant bacilli can be treated with a fluoroquinolone in the context of a well functioning MDR-TB programme and within an appropriate MDR-TB regimen. This should be done by a clinician experienced in the management of paediatric tuberculosis</li> </ul> <p><b>(Strong recommendation, very low quality evidence)</b></p>
<b>Domains and considerations</b>
<p><b>Quality of evidence</b></p> <ul style="list-style-type: none"> <li>• There are no randomized controlled trials, nor are there any non-randomized studies specifically assessing the efficacy and safety of fluoroquinolones (FQs) for the treatment of multi-drug resistant tuberculosis (MDR-TB) in children.</li> <li>• There is one US study (Feja et al., 2008) which assesses management of 20 paediatric patients (mean age 2.7 years) with MDR-TB in New York city. Fourteen (60%) of these patients were treated with FQs (ofloxacin, ciprofloxacin, levofloxacin). The paper does not provide any drug-specific efficacy or safety results, however there was no evidence that recurrent disease occurred amongst the patients. Only 11 patients had available adverse event data, and of these four (36%) experienced adverse events, but there are no details provided as to which drug(s) these patients were taking.</li> <li>• There is a 2008 Cochrane review (Ziganshina and Squire) which was up-to-date in 2007 and assessed the use of FQs for tuberculosis. None of the trials included in the review had paediatric patients. There is also a 2007 review of the use of FQ for the treatment of pulmonary TB, however none of the 15 studies which used FQs to treat MDR-TB included paediatric patients.</li> <li>• There are four publications addressing the safety of FQ in paediatric patients (Grady 2003; Chalumeau et al., 2003; Yee et al., 2002; Noel et al., 2007), as well as one review of FQs in infants and children (Schaad, 2005), however none of these papers consider the use of FQs in patients with MDR-TB. These are summarised in Table 1 below.</li> <li>• A review prepared for the Guideline group (Goldman and Kearns 2010)<sup>5</sup> summarised available data on use of FQ in children. The authors report the Mitnick et al (2008) retrospective review which assessed the use of FQs in extensively drug-resistant tuberculosis. There were no children included in the Mitnick review, with the average age of the patients greater than 30 years.</li> <li>• GRADE tables are provided for the Yee et al (2002) and Chalumeau et al (2003) studies (Table 2). Given the lack of comparative data in the relevant population (children with MDR-TB receiving FQ treatment) no other GRADE tables were produced for the papers described above.</li> <li>• Overall, the quality of evidence is very low, given study design, indirectness and inconsistency. Most studies did not report a significant association between FQ use and joint abnormalities, although Chalumeau et al (2003) reported a higher level of adverse events with FQ patients compared to controls receiving other antibiotics.</li> </ul> <p><b>Uncertainty: YES</b></p> <p><b>Risks/benefits</b></p>

<sup>5</sup> Goldman JA and Kearns GL. 2009. Fluoroquinolone use in paediatrics: focus on safety and place in therapy (unpublished). Commissioned by WHO Department of Medicines, Access and Rational Use, Essential Medicines and Pharmaceutical Policies, WHO HQ Geneva.

**USE OF FLUOROQUINOLONES IN CHILDREN WITH MDR-TB**

**Benefits**

- oral bioavailability and tissue penetration
- broad antimicrobial spectrum
- predictable concentration-effect relationships
- low incidence of development of microbial resistance

**Risks**

- potential for cartilage damage in paediatric patients, based on cartilage damage in juvenile animal models

**Uncertainty: YES, given lack of conclusive evidence for both efficacy and safety in the paediatric TB population**

**Values and acceptability**

**In favour:**

- potential for effectiveness in multidrug-resistant disease
- oral administration

**Against:**

- potential for adverse events
- lack of long term safety data in children
- misuse may lead to increased resistance

**Uncertainty: YES, given lack of evidence**

## USE OF FLUOROQUINOLONES IN CHILDREN WITH MDR-TB

### Cost

• There are no data available assessing the cost-effectiveness of FQs for the treatment of MDR-TB in paediatric patients. There is a 2002 study (Suarez et al) which assessed the cost-effectiveness of second-line TB drugs in a middle-income country (Peru). A total of 466 patients (5 less than 15 years of age) were included, 298 (87%) of which had MDR-TB. The mean cost per DALY gained was \$USD211.

**Uncertainty: YES, as the available data are not specific to paediatric patients, and also include patients with conditions other than MDR-TB.**

### Feasibility

- formulations are stable and available
- fluoroquinolones are registered for use in TB in some countries

**Uncertainty: YES, given lack of evidence**

### Gaps, research needs, comments

- There is a considerable lack of evidence addressing the use of FQs in paediatric patients with MDR-TB. As such, there is a need for randomised controlled trials addressing the use of these agents in the relevant population
- The panel noted the lack of long term safety data for the use of fluoroquinolones in children and the paucity of evidence for their use in the treatment of tuberculosis in children
- The panel considered indirect evidence from the treatment of cystic fibrosis and osteomyelitis which indicated that longer term use was not associated with an increased risk of joint abnormalities in children. Where arthralgia has been described in studies it has been completely reversible
- The panel took into account the pharmacological arguments for the use of fluoroquinolones, such as their good penetration of tissue and oral bioavailability and predictable pharmacokinetics in children
- Research needs include: RCTs comparing regimens including a fluoroquinolone to standard regimens in the context of MDR-TB; collection of long term safety data and validation of biomarkers for cartilage damage and studies to elicit their usefulness in the treatment of skeletal TB

### Final comment

- The panel reached a consensus that in the context of multi-drug resistant tuberculosis, the benefits of treatment outweighed the risks.

MDR-TB=multidrug resistant tuberculosis; FQ=fluoroquinolone

**Table 1: Summary of papers addressing safety of FQs in paediatric patients**

<b>Trial</b>	<b>Design</b>	<b>Outcomes</b>
Chalumeau 2003	<ul style="list-style-type: none"><li>•observational comparative cohort study comparing patients receiving systemic FQs and matched controls receiving other antibiotics</li></ul>	<ul style="list-style-type: none"><li>•rate of potential adverse events was higher in the FQ group OR=3.7; 95% CI: 1.9, 7.5), with musculoskeletal potential adverse events occurring more frequently in the FQ group (3.8%) compared to controls (0.4%).</li><li>•authors conclude that the higher rates of adverse events in the FQ group supports the American Academy of Pediatrics statement restricting off-label use of FQs in paediatric patients to second-line use in limited situations.</li></ul>
Grady 2005	<ul style="list-style-type: none"><li>•report of retrospective reviews and RCTs assessing the use of ciprofloxacin in children</li></ul>	<ul style="list-style-type: none"><li>•rate of arthralgia and quinolone-induced cartilage toxicity were low</li><li>•no differences in efficacy and safety between ciprofloxacin and the comparator drugs, and no evidence of joint toxicity</li></ul>
Noel 2007	<ul style="list-style-type: none"><li>•safety profile of 2,523 children treated with levofloxacin</li></ul>	<ul style="list-style-type: none"><li>•reports of musculo-skeletal events were higher in children treated with levofloxacin compared to those treated with non-FQ antibiotics. Five patients with musculoskeletal complaints underwent CT or MRI which failed to reveal any structural abnormalities, and there was no association between levofloxacin exposure and long-term joint abnormalities or growth impairment.</li></ul>
Schaad 2005	<ul style="list-style-type: none"><li>•literature review for quinolone-induced cartilage toxicity</li></ul>	<ul style="list-style-type: none"><li>• there was no unequivocal documentation of quinolone-induced arthropathy in patients as described in juvenile animals; clinical observations temporally related to quinolone use are reversible episodes of arthralgia that do not lead to long-term sequelae when treatment is discontinued; most joint complaints associated with quinolone use are coincidental and do not represent adverse effects.</li></ul>
Yee 2002	<ul style="list-style-type: none"><li>•retrospective observational study comparing children with a history of FQ use to those with exposure to azithromycin</li></ul>	<ul style="list-style-type: none"><li>• no statistically significant difference in the risk of tendon or joint disorders between the two groups</li></ul>

**Author(s):** P. Whyte

**Date:** 2010-03-20

**Question:** Should fluoroquinolones vs. other antibiotics be used in paediatric patients?<sup>1</sup>

**Settings:**

**Bibliography:** Yee 2002; Chalumeau 2003

**Table 2: Comparisons of FQs and other antibiotics in paediatric patients – adverse events**

Quality assessment							Summary of findings				Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients		Effect			
							fluoroquinolones	other antibiotics	Relative (95% CI)	Absolute		
<b>levofloxacin vs. azithromycin (tendon or joint disorders)</b>												
1 <sup>2</sup>	observational studies	serious <sup>3</sup>	no serious inconsistency	serious <sup>4</sup>	no serious imprecision	none	13/1593 (0.8%)	118/15073 (0.8%)	RR 1.04 (0.55 to 1.84)	0 more per 1000 (from 4 fewer to 7 more)	VERY LOW	IMPORTANT
<b>ciprofloxacin vs. control (tendon or joint disorders)</b>												
1 <sup>2</sup>	observational studies	serious <sup>3</sup>	no serious inconsistency	serious <sup>4</sup>	no serious imprecision	none	37/4531 (0.8%)	118/15073 (0.8%)	RR 1.04 (0.72 to 1.51)	0 more per 1000 (from 2 fewer to 4 more)	VERY LOW	IMPORTANT
<b>FQs vs. other antibiotics (potential adverse events)</b>												
1 <sup>5</sup>	observational studies	serious <sup>6</sup>	serious <sup>7</sup>	serious <sup>4</sup>	serious <sup>8</sup>	none	47/276 (17%)	13/237 (5.5%)	OR 3.7 (1.9 to 7.5)	122 more per 1000 (from 44 more to 248 more)	VERY LOW	IMPORTANT

<sup>1</sup> Given that all studies are non-randomized, non-blinded and do not include patients with MDR-TB, the quality of evidence is very low.

<sup>2</sup> Yee 2002

<sup>3</sup> Retrospective review of medical records, thus susceptible to bias given lack of randomization and blinding.

<sup>4</sup> The study did not include any patients with TB.

<sup>5</sup> Chalumeau 2003

<sup>6</sup> observational comparative cohort study assessing paediatric patients taking FQs or other antibiotics. There is risk of bias given lack of randomization and blinding.

<sup>7</sup> Results of this study, with significantly greater occurrence of adverse events in patients using FQs, is not consistent with most other observational studies, which report no differences between FQs and other antibiotics regarding occurrence of adverse events.

<sup>8</sup> Based on one trial only, with total number of events <300

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