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Evidence Summaries

Intermittent versus daily therapy for treating tuberculosis in children: Summary of the evidence and implications for public health programmes

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ABSTRACT

A Cochrane systematic review summarized the evidence for the effects of intermittent versus daily short-course anti-tuberculosis (TB) treatment regimens (containing rifampicin in the intensive treatment phase) on cure rates, deaths, relapses, adherence, and adverse events in children with TB not known to have drug resistance. The review included four randomized controlled trials published between 1996 and 2000 and conducted in India (two trials), South Africa and Turkey that included 563 (465 evaluable) children aged five months to 15 years. Children were recruited from the community in one trial and from hospital clinics in the others; their HIV status was not reported. All trials used a combination of clinical and radiological criteria to diagnose childhood TB.

The four trials compared twice-weekly versus daily anti-TB regimens. No trials comparing thrice-weekly versus daily anti-TB regimens in children were identified. The review did not find significant differences between the intermittent twice-weekly and the daily treatment regimens in the proportions of children who were cured, who died, who relapsed over 12–30 months of follow-up, or who had treatment limiting adverse events. Adherence to the intermittent and daily treatments was also similar (87% and 84%). The trials were underpowered to detect significant differences in many of the outcomes, were at high risk of bias, and the regimens used in these trials were not the standard recommended regimens in use today. The review concluded that the evidence was in sufficient to “support or refute the use of intermittent twice- or thrice-weekly, short-course treatment regimens over daily short-course treatment in children with TB”. The review called for adequately powered, well conducted and reported randomized trials comparing intermittent versus daily regimens conducted in high TB-transmission settings to provide evidence to inform policy and practice.

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Table 1 – Intermittent (twice-weekly) short-course anti-TB regimens (six to nine months) compared to daily anti-TB regimens (six to 12 months) for treating TB in children: Summary of effects-follow-up 12 months to 30 months.

Outcomes	Illustrative comparative risks ^a (95% CI)		Relative risk (RR) (95% CI)	No of participants (studies)	Overall evidence quality
	Assumed risk	Corresponding risk			
	Daily short-course anti-TB regimens	Intermittent short-course anti-TB regimens			
Cure	836 Per 1000	844 Per 1000 (786–920)	RR 1.01 (0.94–1.1)	465 (4)	Very low (due to risk of bias, serious indirectness and serious imprecision)
Death from any cause	8 Per 1000	13 Per 1000 (2–75)	RR 1.52 (0.26–8.96)	213 (2) ^b	Very low (due to risk of bias, serious indirectness and serious imprecision)
Relapse	0 Per 1000	0 Per 1000 (0–0)	RR 3.68 (0.15–89.33)	214 (1) ^c	Very low (due to serious indirectness, and very serious imprecision)
Adherence	840 Per 1000	874 Per 1000 (815–932)	RR 1.04 (0.97–1.11)	458 (4)	Very low (due to risk of bias, serious indirectness and serious imprecision)
Treatment-limiting adverse events	15 Per 1000	6 Per 1000 (1–39)	RR 0.4 (0.06–2.6)	441 (4)	Very low (due to risk of bias, serious indirectness, and serious imprecision)

^a The basis for the assumed risk is the control group risk in single studies, and the median risk in the control group for pooled data. The corresponding risk (and its 95% CI) is based on the assumed risk in the control group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval.

^b Data for deaths are from two of the four trials; no deaths were reported in the other two trials.

^c Data for relapse are only from one trial as no confirmed relapses were reported in the other three trials over follow-up.

1. The evidence

A Cochrane systematic review identified four randomized trials from high-TB burden countries randomizing 563 children aged five months to 15 years, whose HIV status was not known and who were not known to be resistant to anti-TB drugs. The trials evaluated four different twice-weekly short-course anti-tuberculosis (TB) regimes given for six nine months, or to daily anti-TB regimens given for six to 12 months, and with follow-up for 12–30 months. Pooled data from the trials indicated that:

- Twice-weekly anti-TB treatment regimens may not significantly differ from daily anti-TB treatment regimens in the number of patients cured (84% in each regimen; four trials, 465 children).
- Twice-weekly anti-TB treatment regimens may not significantly differ from daily anti-TB treatment regimens in the number of patients who died (1% versus 0.8%; two trials, 213 participants).
- Twice-weekly anti-TB treatment regimens may not significantly differ from daily anti-TB treatment regimens in the number of patients who relapsed (one relapse in one of the four trials, 214 participants).
- Reported adherence to treatment was similar (87% versus 84%; four trials, 458 children).
- Twice-weekly anti-TB treatment regimens may not significantly differ from daily anti-TB treatment regimens in the number of patients who had treatment limiting adverse events (0.6% versus 1.5%; four trials, 441 participants). No child developed serious adverse events in the four trials, and other adverse events were infrequent and transient.

- The trials were underpowered to detect significant differences for most outcomes, had limitations in design, and used non-standard treatments; hence there is uncertainty regarding the comparative efficacy of twice-weekly versus daily treatment regimens.
- The review did not find trials comparing the more commonly used thrice-weekly anti-TB short-course regimen with the daily treatment regimen.

Review on which this evidence summary is based: Bose A, Kalita S, Rose W, Tharyan P. Intermittent versus daily therapy for treating tuberculosis in children. Cochrane Database of Systematic Reviews 2014, Issue 1. Art. No.: CD007953. <http://dx.doi.org/10.1002/14651858.CD007953.pub2>

This evidence summary presents an overview of the findings and the implications for low- and middle-income countries. For further details, please read the latest version of the full review that can be downloaded, free of charge (through various funded provisions) in most parts of the world, from the Cochrane Database of Systematic Reviews that is published in *The Cochrane Library* (www.thecochranelibrary.com).

2. Why is this question important?

- Childhood tuberculosis (TB) is a neglected global public health problem. It is estimated that around 75% of the global incidence of childhood TB occurs in 22 high-burden countries, and that India and China, the countries with the

highest TB burden, contribute nearly 40% of the global incidence of TB annually.

- Childhood TB is largely sputum smear-negative, and the diagnosis of childhood TB is difficult because of the lack of specificity of diagnostic criteria. These result in underestimation of prevalence, as well as the possibility that around 15%–20% of the children diagnosed in high-incidence communities may not have TB.
- Short treatment courses with rifampicin-containing anti-TB drugs given daily for six-months cure over 90% of infected children, but poor adherence reduces treatment success.
- Intermittent, short-course anti-TB regimens, given two or three times a week under direct observation, were associated with the reduced need for hospitalization and higher adherence in observational studies; but how they compare with daily treatment in relation to cure is unclear.
- The rationale for intermittent dosing was based on *in vitro* observations that following interruption of treatment with anti-TB drugs, growth of *M. tuberculosis* takes some days to resume, thereby suggesting that short interruptions would be possible before resuming treatment. This interval is decided by the shortest time taken for resumption of bacterial activity after drug cessation that varies with anti-TB drugs, and is shortest for rifampicin at two to three days.
- Current international and national recommendations differ on the use of intermittent regimens to treat TB in children. Current evidence-based guidance from the World Health Organization (WHO) on the treatment of paediatric TB¹ recommends against using intermittent regimens (twice- or

thrice-weekly) in children with suspected or confirmed pulmonary TB or tuberculous peripheral lymphadenitis living in settings with a high HIV prevalence (or with confirmed HIV infection). The WHO guidance suggests that thrice-weekly regimens can be considered only during the continuation phase of treatment for children known to be HIV-uninfected and living in settings with well-established DOTS; thus only partially-intermittent thrice weekly regimens are recommended, and fully-intermittent schedules (without initial daily treatment for two months) are not currently recommended for children with TB. The American Thoracic Society, along with the Centers for Disease Control and Prevention (CDC), recommend a daily or twice-weekly regimen.² Current Indian guidelines recommend thrice-weekly intermittent therapy given by DOTS in both the intensive phase and the continuation phase.^{3,4}

3. What did the systematic review seek and what did the review find?

Review objectives: To compare the efficacy and safety of intermittent, short-course anti-TB treatment regimens (twice- or thrice-weekly) with daily short-course anti-TB treatment regimens in treating childhood TB.

	What did the review authors search for?	What did the review find?
Types of studies	Randomized controlled trials (RCTs) and quasi-RCTs.	Four RCTs published between 1996 and 2000 met the review's inclusion criteria. One trial randomized children by households but did not report the proportions in each arm that were cluster-randomized and individually randomized. In the other three trials, the unit of randomization was the individual. Of 44 excluded studies, 13 were RCTs, of which 10 did not fulfil inclusion criteria, while three trials included adults and children but disaggregated data for children were not available from the reports or the authors of the trials. No ongoing trials were identified and no studies were reported as awaiting assessment for inclusion in the review.
Setting	Any setting	Two trials were conducted in India, and one each in South Africa and in Turkey. Two trials recruited children attending outpatient clinics of general hospitals, one recruited from the community, while in the fourth trial, the children were hospitalized for the first two weeks.
Participants	Children aged 15 years or younger diagnosed as having TB in category 1, 2, or 3 according to the WHO diagnostic categories. Excluded were trials of children diagnosed under category 4 (multiple-drug resistant TB) by the WHO.	The four included trials recruited boys and girls with ages ranging from five months to 15 years. Their HIV status was not reported. All trials used a combination of clinical and radiological criteria (parenchymal or mediastinal lymph nodes in chest radiograph) to diagnose childhood TB; the trials used additional explicit criteria for diagnosis that are similar to currently used criteria for the diagnosis of childhood TB. All trials excluded children with primary complex and included the spectrum of childhood TB covered in the WHO

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	What did the review authors search for?	What did the review find?
Interventions	<p>1. Twice-weekly short-course anti-TB chemotherapy.</p> <p>2. Thrice-weekly short-course anti-TB chemotherapy.</p> <p>Control</p> <p>1. Daily short-course anti-TB chemotherapy. For both arms, all regimens had to contain rifampicin for the intensive phase of treatment. The total duration of treatment should ideally have been six months, but should not have exceeded one year. Short course treatment regimens, where daily dosing was used for the first two months, were considered daily treatment, even if this was followed by intermittent treatment thereafter, since daily dosing in the intensive phase of treatment is considered critical for treatment success.</p>	<p>Classification 1, 2, or 3, except the South African trial that excluded children with extra-pulmonary TB. Previous treatment for TB was an exclusion criterion in two of the studies and most of the children in the four trials were newly diagnosed with TB.</p> <p>No trials of thrice-weekly versus daily treatment regimens were identified.</p> <p>The four trials included in the review compared four different twice-weekly short-course anti-TB regimens with daily short-course anti-TB regimens.</p> <p>The twice-weekly regimens compared with daily anti-TB regimens were:</p> <p>1) Partially-intermittent treatment versus daily treatment (Turkey 1996): Streptomycin, rifampicin, isoniazid daily for two weeks, followed by intermittent treatment for 8.5 months with twice-weekly isoniazid and rifampicin) (N = 18) versus daily treatment with streptomycin daily for 40 days followed by daily rifampicin for nine months and isoniazid to 12 months (N = 18).</p> <p>2) Fully-intermittent treatment (six months) versus daily treatment for two months plus intermittent treatment for four months (India 1990): Isoniazid, rifampicin, and pyrazinamide given twice-weekly for two months followed by isoniazid and rifampicin twice-weekly for four months (N = 37) versus isoniazid, rifampicin and pyrazinamide daily for two months, followed by isoniazid and rifampicin twice-weekly for four months (N = 39);</p> <p>3) Fully intermittent (six months) versus daily treatment (nine months) regimen (India 1998): Isoniazid, rifampicin, and pyrazinamide thrice-weekly for two months, followed by INH and rifampicin twice-weekly for four months (N = 69) versus isoniazid and rifampicin daily for nine months (N = 68).</p> <p>4) Fully intermittent (six months) versus daily treatment (six months) regimen (South Africa 2000): Isoniazid, rifampicin and pyrazinamide twice-weekly for six months (N = 153 randomized, 96 given treatment) versus isoniazid, rifampicin and pyrazinamide (five days a week) for six months (N = 161 randomized, 118 given treatment).</p>
Outcomes	<p>Primary outcomes</p> <p>Cure as defined by the trial authors and including the following:</p>	<p>Primary outcomes</p> <p>The four trials reported data for cure that were defined in different ways. The trial from Turkey (1996) used clinical</p>

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	What did the review authors search for?	What did the review find?
	<ul style="list-style-type: none"> • Negative sputum test (if appropriate); • Weight gain; • Resolution of symptoms and signs within one month after completion of treatment. These may include, but are not confined to: Fever or cough, Decrease in size of the lymph nodes, and Resolution of the chest X-ray findings. <p>Secondary outcomes</p> <ol style="list-style-type: none"> 1. Death from any cause during treatment or within one year after the completion of treatment. 2. Relapse: defined as re-emergence of signs and symptoms of TB within 12 months after stopping treatment. 3. Adherence to treatment: defined as the proportion of children who are not defaulters (a defaulter being a child whose treatment was interrupted for two consecutive months or more). <p>Adverse events</p> <ol style="list-style-type: none"> 1. Serious adverse effects: as defined by the trial authors and based on clinical or laboratory findings, or both. 2. Treatment-limiting adverse events: adverse effects during treatment requiring interruption or alteration of the treatment regimen. 3. Other adverse effects: including skin rash, nausea or vomiting, diarrhoea, epigastric pain, fatigue or malaise, dizziness, headache, fever or chills, arthralgia, peripheral neuropathy, anorexia or weight loss, insomnia, and pruritus. 	<p>and radiological assessments and weight gain to monitor children for clinical improvement. One trial from India (1990) provided explicit criteria to define general improvement (afebrile, improved appetite, weight gain); and for marked, moderate, and poor improvement for pulmonary TB, with poor improvement defined as no significant general improvement, no radiological clearance, and increase in the size of pulmonary lesions or the appearance of new lesions. The other trial from India (1998) monitored resolution of radiological lesions to evaluate treatment response and the review authors used the proportions with complete resolution as well as those with general improvement but with residual lesions to define cure. The South African trial (2000) did not report the proportions in the treatment groups considered to be responders, but presented scores for those assessed at different time points from 3 to 30 months as median scores (with ranges) on a composite score of four domains (parental assessment, clinical assessment, weight gain, and chest radiograph), with each scored from –1 (worse); 0 (no better); +1 (better); +2 (much better). The combined scores ranged from –4 to +8. In the trial any patient with a score of four or more at six months was considered as better or improved on all four domains; and those scoring eight were considered free of clinical and radiological evidence of TB. The Cochrane review authors interpreted the proportions ‘cured’ as all those who scored four or more at the six month assessment and used the lower limit of the range of scores to determine the proportions cured among those assessed, and confirmed this interpretation with the first author of the South African trial.</p> <p>Secondary outcomes</p> <p>All trials reported relapse and adherence, though they were defined and assessed in different ways.</p> <p>Adverse events</p> <p>The two Indian trials reported deaths. The four included trials reported serious adverse events, again assessed in different ways. Non-serious adverse events were poorly reported and it was unclear if they were systematically ascertained.</p>
Date of the last search:	30 May 2013	
Funding sources:	Christian Medical College, Vellore, Tamil Nadu, India; South Asian Cochrane Network & Centre, Vellore, Tamil Nadu, India; South Asian Network for Chronic Diseases, Public Health Foundation of India, New Delhi, India; UKAid: Department for International Development (DFID), UK, through a grant in aid of low- and middle-income countries to the Effective Healthcare Research Consortium (Paul Garner, Liverpool School of Tropical Medicine, UK); Indian Council of Medical Research, New Delhi India via a grant to the Prof BV Moses and ICMR Centre for Evidence-Informed Healthcare at CMC Vellore, that hosts the South Asian Cochrane Centre.	
What were the effects of twice-weekly versus daily short-course anti-TB treatments in children with TB?	<p>Primary outcome: The review pooled data from the trials using intention to treat analysis, where those lost to follow-up before being judged treatment responders, and those who required extended treatment after the allocated treatment duration were considered not cured. Intermittent and daily treatments consistently cured similar proportions of children (85% versus 83%; RR 1.01, 95% CI 0.94 to 1.10, four trials, 465 children; very low quality evidence). In pre-stated sensitivity analysis of evaluable children judged cured (excluding drop-outs) the pooled estimate again did not significantly differ between daily treatments versus intermittent treatments (four trials, 441 children). In additional sensitivity analysis, excluding the South African trial that was at high risk of selection bias, and also had data unadjusted for clustering, the pooled effect estimates continued to show no</p>	(continued on next page)

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significant difference between intermittent and daily treatment regimens for children cured (RR 1.02; 95% CI 0.93 to 1.12; three trials, 352 children).

Secondary outcomes: Intermittent treatments did not differ significantly from daily treatments in the proportions that died due to any cause (four trials, 460 children; *very low quality evidence*), though only the two Indian trials reported any mortality due to TB (three in the intermittent treatment arm and two in the daily treatment arm). Only one confirmed relapse among 449 evaluated children (with intermittent treatment) was reported over 24 months of follow-up in one trial from South Africa (*very low quality evidence*). Adherence rates (defined and assessed in different ways) did not differ significantly with intermittent treatment or with daily treatment (87% versus 84%; RR 1.04, 95% CI 0.97 to 1.11; four trials, 458 children; *very low quality evidence*).

Adverse events: None of the participants in the four trials were reported to have developed serious adverse events. Adverse events requiring interruption of treatment were not significantly different with both schedules (four trials, 441 children; *very low quality evidence*). These events were transient hepatic toxicity in three children in two trials that required alterations in trial medication till resolution of symptoms and liver functions tests had normalized. Among other adverse events, two trials reported transient episodes of vomiting and mild joint pains in the initial period. (See Table 1 for a summary of findings for important outcomes linked to the overall quality of the evidence)

What were the conclusions of the review?

This Cochrane review concluded that: “Trials conducted to date are insufficient to support or refute the use of intermittent twice- or thrice-weekly, short-course treatment regimens over daily short-course treatment in children with TB. Further randomized trials conducted in high TB-transmission settings will help inform policy and practice”.

What were the assessments of the overall quality of the evidence?

The review authors assessed the overall quality of evidence for outcomes considered important for clinical decisions using the GRADE approach (Table 1). In this approach, evidence from randomized controlled studies is initially graded as high and downgraded by one or two levels on five domains, after full consideration of: any limitations in the design of the studies, the directness (or applicability) of the evidence, the consistency, and precision of the results, and the possibility of publication bias. This results in an assessment of the quality of a body of evidence as *high*, *moderate*, *low*, or *very low*. A GRADE quality level of ‘*high*’ reflects confidence that the true effect lies close to that of the estimate of the effect for an outcome, and that further research is unlikely to alter these results. A judgement of ‘*moderate*’ quality indicates that the true effect is likely to be close to the estimate of the effect, but acknowledges the possibility that it is substantially different, and that further studies could alter the estimates. ‘*Low*’ and ‘*very low*’ quality evidence limit our confidence in the effect estimate. The evidence for the overall quality of the evidence for intermittent short-course versus daily anti-TB treatments from the four included trials was judged *very low* for all outcomes (Table 1).

Strengths and limitations of the review

The review followed the standard methods used in Cochrane Reviews and no important limitations were detected. The review excluded three trials that met inclusion criteria because data on children were not presented separately from that of adults, and could not be obtained from the authors. The review summarized the data from these excluded trials and concluded that two used comparisons not strictly relevant to the review. The third trial also used drug combinations not currently recommended but the results in children and adults in the trial were consistent with the results of the review. Although the included trials used different definitions for the diagnosis of childhood TB, they concur with current methods used in clinical practice to diagnose TB in children. All trials excluded children with primary complex and all but one included the spectrum of childhood TB covered in the WHO Classification 1, 2, or 3. The doses of anti-TB drugs used were comparable to current recommendations, but the treatment regimens used in all of the trials were not similar to current recommendations for the treatment of childhood TB. Moreover, only four RCTs addressing the review’s objectives were identified, and no RCTs comparing the commonly used thrice-weekly treatment regimens with daily treatment were found. None of the trials reported the HIV-status of the children randomized. There view authors acknowledged that these lacunae in the body of evidence limit the conclusions that can be drawn regarding the effects of intermittent dosing versus daily short-course anti-TB treatment, in HIV-negative or HIV-positive children with TB.

Did the results and conclusions of the review differ from other reviews on this topic?

The current evidence-based guidance from the WHO on the treatment of paediatric TB¹ recommends only partially-intermittent thrice-weekly regimens (daily treatment for two months and intermittent treatment only in the continuation phase of four months) for children known to be HIV uninfected, living in settings with low HIV prevalence and with well-established DOTS programmes. The revised guidelines of the Indian Academy of Pediatrics³ also recommend thrice-weekly anti-TB treatment. The National TB Control Programme of India⁴ recommends thrice-weekly treatment in the intensive treatment and continuation phases. However, the Cochrane review not find any RCTs of thrice-weekly fully-intermittent or partially-intermittent treatment regimens versus daily or twice-weekly, intermittent anti-TB treatment regimens. This WHO’s evidence-based guidance¹ was largely influenced by a meta-analysis (5) that was published while the Cochrane review was in progress. This meta-analysis also included only the four trials included in the Cochrane review. The results of the pooled effect estimates in the meta-analysis indicated that children receiving twice-

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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; four trials, 466 children), though the results were not statistically significant in intention-to-treat analysis (OR 0.66; 95% CI 0.23–1.84). The Cochrane review did not find any significant differences in cure rates between intermittent and daily therapy in intention to treat and per protocol analysis of the same four trials. The Cochrane review offers reasons for the differences in the results of the review and that of the meta-analysis⁵:

1. The meta-analysis used odds ratios while the Cochrane review used risk ratios to compare cure rates. When event rates are common (risk is more than ~20%), odds ratios and risk ratios differ in their magnitude and precision (with odds ratios often over-estimating effects).

2. The meta-analysis and the Cochrane review interpreted primary data from two trials differently:

a. In the primary per-protocol analysis in the meta-analysis⁵, the data for the nine children from the 1998 Indian trial⁶ who required extended treatment after six months were included among those cured. The meta-analysis also reported that when only those in this trial who did not need extended treatment were considered cured in sensitivity analysis, the pooled analysis did not reveal

statistically significant differences between the two arms (OR 0.53, 95% CI 0.23–1.21). However, the meta-analysis opted to present the statistically significant results of per-protocol analyses over the statistically non-significant results obtained with intention-to-treat analyses, and also did not consider the results of the sensitivity analysis using different definitions for those cured in framing conclusions. The Cochrane review defined cure in accordance with international

recommendations¹ as resolution of symptoms and signs within one month after completion of treatment, and did not include those children in the Indian trial⁶ who required extended treatment as among those cured in intention-to-treat and in per-protocol analyses. These analyses did not differ in indicating no significant difference in cure rates between the anti-TB treatment regimens. b. The meta-analysis mistook treatment completion rates reported in the South African trial⁷ for cure rates and used this data revealing daily treatment superior to be superior to intermittent treatment in pooled analysis. The Cochrane review authors confirmed with the first author of the South African trial their interpretations of the actual cure rates derived from the reported median scores (with ranges) of the composite outcomes used. These cure rates did not differ between twice-weekly and daily short course treatments.

c. The meta-analysis noted that the trials, as assessed using the Jadad Scale, were mostly of poor quality but did not link this assessment to the assertion that twice-weekly anti-TB treatments were less likely to cure TB than daily treatment. The Cochrane review used the GRADE approach to link the numerical effect estimates for each outcome to the confidence placed in these estimates in drawing conclusions. These conclusions reflected uncertainty in the comparative effects of intermittent short-course versus daily short-course treatment in childhood TB; with no convincing evidence to indicate that daily short-course anti-TB treatment is superior to intermittent short-course anti-TB treatment in children with TB.

What further research is required?

The Cochrane review made two specific sets of recommendations for further research:

1. Adequately powered, multi-centre, multi-country, randomized, non-inferiority, pragmatic trials conducted in high TB-transmission settings, in low and middle-income countries that compare thrice-weekly, and daily short-course (six months) dosing, and use the currently recommended four drugs, in HIV-negative children are needed to help inform policy. Twice-weekly regimens are not as commonly used as thrice-weekly regimens and it would be important to establish the equivalence of thrice-weekly regimens before considering trials of twice-weekly anti-TB regimens. Thrice-weekly, fully-intermittent treatment versus partially-intermittent treatment (with initial daily dosing for the first two months) should also be evaluated in similar separate trials. The review also presented detailed suggestions regarding the design, conduct and reporting considerations for such trials.

2. The Cochrane review also called for national TB control programmes that treat children with TB routinely with intermittent regimens, to regularly report treatment success rates along with the criteria used to evaluate treatment success. These programmes should also report adherence rates, relapse rates, and rates of adverse events, in order to build the evidence base for programmatic success with intermittent regimens.

What are the implications of the review for public health?

The Cochrane review did not find evidence of high quality to support or refute the efficacy and safety of intermittent short-course anti-TB treatment in childhood TB. It concluded that intermittent and daily regimens may have similar effects in children with TB, but further research is required to confirm the observations in the review.

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Short-course treatments given daily or intermittently (twice- or thrice-weekly) over six months to one year are commonly used in national TB control programmes, and are based on treatment regimens in adults due to convenience in implementation. In a systematic review and meta-analysis of studies in adults, TB treatment outcomes were significantly worse with shorter duration of rifampicin, or with initial drug resistance to isoniazid, or streptomycin, or both.⁸ Treatment outcomes were similar with all intermittent schedules evaluated, but there was insufficient evidence to support administration of treatment twice-weekly throughout therapy.⁸ A Cochrane Review of fully-intermittent dosing with drugs for treating TB in adults also produced inconclusive results.⁹ Data from observational studies indicate that over 95% of childhood TB cases can be successfully treated with short-course treatments, but rates of successful treatment are often much lower in low-income countries, due to poorer compliance and low treatment completion rates, delayed diagnosis, wrong diagnoses, co-infection with HIV, poor absorption of anti-TB drugs in malnourished or HIV-infected children, and also due to drug resistance.¹⁰ The WHO also strongly recommends against using intermittent anti-TB treatment regimens in HIV-positive children. The potential for drug resistance with intermittent regimens is lower in children with TB as childhood TB mostly involves few bacilli, and few children with TB have cavitation (particularly among younger children) that can lead to treatment failure and drug resistance with intermittent treatment. It is also thought that children do not contribute to the transmission of drug-resistant TB. However, drug resistance in children reflects the community transmission of drug-resistant strains from adults, and reports demonstrating the potential for drug-resistant TB to be transmitted within families by infected children are a matter of concern. In the light of these uncertainties, the Cochrane review's call for the regular reporting of cure, adherence, relapse and rates of adverse events by national programmes that use intermittent short course anti-TB regimens will provide valuable updates of the benefits of intermittent treatment for childhood TB from programmatic evaluations to supplement data from future RCTs.

Declaration of interest

TDS is an editor with the Cochrane Infectious Diseases Group, but was not involved with the editorial process of this Cochrane review. PT is a one of the authors of this Cochrane review and a programme partner of the Effective Healthcare Research Consortium.

Conflicts of interest

All authors have none to declare.

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