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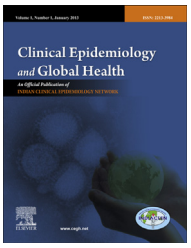

Evidence Summaries

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