Adverse events of first-line therapy for pediatric tuberculosis: A systematic review and meta-analysis

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Background

In 2010, the World Health Organization (WHO) increased the recommended doses of first-line tuberculosis (TB) medications for children.[1]

Review question: Is higher WHO 2010 TB drug dosing associated with a change in adverse events (AEs) compared to lower doses in children with TB disease?

Objectives: 1) Determine the proportion of children experiencing AEs during first-line TB therapy, 2) Compare AEs for WHO 2010 and pre-WHO 2010 dosing.

Please scan for our **PROSPERO protocol:**

Methods

Population: Children ≦19 years old with TB disease receiving first-line drugs. Excluded: drug-resistance, latent TB infection, relapsed TB, and non-first line regimens.

Intervention & comparison: WHO 2010 dosing (mg/kg/day) of ≥3 drugs dosed at: H 10-15, R 10-20, Z 30-40, E 15-25 vs. HRZE at any lower dose.

Primary outcome: Proportion with any AE.

Secondary outcomes: Drug-related adverse effects, mild/severe AE (CTCAE v5.0), hepatotoxicity, vision change, and other AEs.

Search strategy: MEDLINE, Ovid, Embase, Cochrane Central Register of Controlled Trials, Scopus, ClinicalTrials.gov, and Global Index Medicus were searched without date restrictions on March 23 and July 23, 2024.

Risk of bias: Assessed with Joanna Briggs Institute tools, RoB-2, or ROBINS-I based on study type.

Analysis: We performed a meta-analysis of proportions to generate pooled proportions of AEs.

References

1. Ridge A, Grzemska M, Hill S, Gie R. Rapid advice: Treatment of tuberculosis in children. World Health Organization, 2010.

Results

40 studies included
(33 cohorts, 4 randomized trials, 2 case series, 1 case-control)

Table 1: Pooled proportions of AEs for participants with known dosing.

	All studies (N=5,021)	Pre-WHO 2010 (N=1,381) Proportion (95% CI)	WHO 2010 (N=2,863) Proportion (95% CI)	p-value
Any AE	682	8 (4-15)	26 (18-34)	0.001
Drug-related adverse effect	401	2 (0-5)	10 (4-18)	0.004
Change in therapy due to AE	56	3 (0-9)	2 (0-7)	0.82
Severe AE	88	0 (0-2)	2 (0-5)	0.04
Hepatotoxicity	252	5 (1-11)	9 (4-15)	0.23
Drug-related hepatotoxicity	39	0 (0-1)	0 (0-1)	0.2
Change in therapy due to hepatotoxicity	39	0 (0-3)	1 (0-6)	0.1
Gastrointestinal AE	59	2 (0-6)	14 (3-28)	0.009
Vision change	9	0 (0-1)	0 (0-5)	0.2

Figure 1: Forest plot of the pooled proportion of any AE.

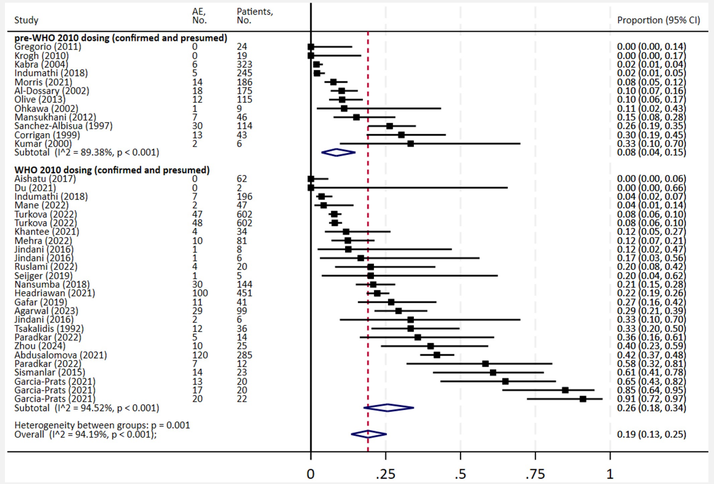
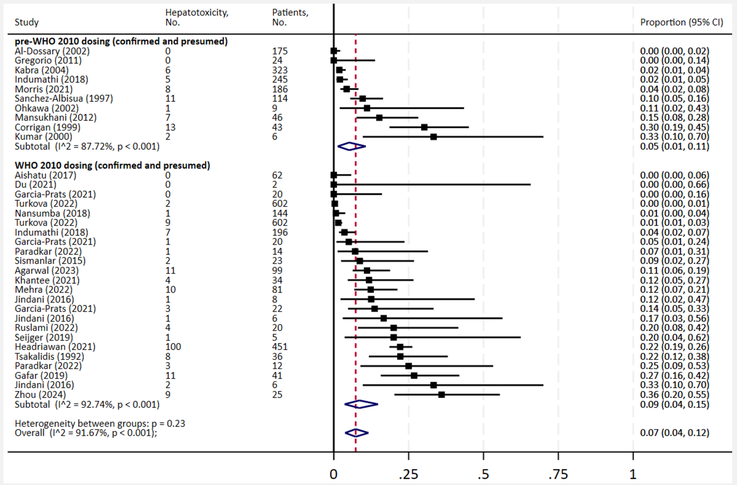


Figure 2: Forest plot of the pooled proportion of hepatotoxicity.



Conclusions

WHO 2010 dosing was associated with a significant increase in AEs, severe AEs, and drug-related adverse effects.

Hepatoxicity did not significantly change between dosing regimens; while not statistically significant, the 4% absolute increase in WHO-2010 dosing may be clinically important and became statistically significant in several subgroups.

Further dose escalation should be done cautiously and with careful monitoring.

Findings are limited by high between-study heterogeneity and low study quality.