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MAJOR ARTICLE

Comparative Effectiveness of Regimens for Drug-Susceptible Tuberculous Meningitis in Children and Adolescents: A Systematic Review and Aggregate-Level Data Meta-Analysis

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Background. Before August 2021, the only regimen recommended by the World Health Organization (WHO) to treat pediatric drug-susceptible tuberculous meningitis was a 12-month regimen consisting of isoniazid, rifampicin, ethambutol, and pyrazinamide (2HRZE/10HR). The comparative effectiveness of shorter regimens is unknown.

Methods. To inform a WHO guideline update, we undertook a systematic review and meta-analysis to evaluate outcomes from regimens of 6- to less than 12-months' duration that included, at a minimum, isoniazid, rifampicin, and pyrazinamide. We included studies that applied rigorous diagnostic criteria and reported outcomes for ≥10 children or adolescents. Using generalized linear mixed models, we estimated the random effects pooled proportions of patients with key outcomes.

Results. Of 7 included studies, none compared regimens head-to-head. Three studies (724 patients) used a 6-month intensive regimen, which includes isoniazid and rifampicin at higher doses, pyrazinamide, and ethionamide instead of ethambutol (6HRZEto). Outcomes for this versus the 12-month regimen (282 patients, 3 studies) were, respectively, as follows: death, 5.5% (95% confidence interval [CI], 2.1%–13.4%) vs 23.9% (95% CI, 17.5%–31.7%); treatment success (survival with or without sequelae), 94.6% (95% CI, 73.9%–99.1%) vs 75.4% (95% CI, 68.7%–81.1%); and neurological sequelae among survivors, 66.0% (95% CI, 55.3%–75.3%) vs 36.3% (95% CI, 30.1%–43.0%). Relapse did not occur among 148 patients followed-up for 2 years after completing the 6-month intensive regimen.

Conclusions. Our findings are limited by the small number of studies and substantial potential for confounding. Nonetheless, the 6HRZEto regimen was associated with high treatment success and is now recommended by WHO as an alternative to the 12-month regimen.

Keywords. neurological sequelae; treatment outcomes; tuberculosis; World Health Organization guidelines.

Tuberculous (TB) meningitis is associated with a 19.3% risk of death and 36.7% risk of neurological sequelae among surviving children and adolescents [1]. Despite poor outcomes, evidence to support current treatment approaches is limited. Before August 2021, the only regimen recommended by the World Health Organization (WHO) to treat pediatric drug-susceptible TB meningitis was a 12-month regimen, consisting of daily isoniazid, rifampicin, ethambutol, and pyrazinamide at standard doses for 2 months, followed by daily isoniazid and rifampicin for 10 months (2HRZE/10HR) [2, 3]. Regimens of less than 12 months' duration, which may facilitate treatment completion and reduce burdens on patients and healthcare systems, are routinely used in some settings based on expert opinion [4, 5], but their effectiveness compared to the 12-month regimen is unknown. A 2014 systematic review and meta-analysis of pediatric TB meningitis outcomes observed no associations between treatment duration and outcomes [1]. However, the meta-analysis included studies of outdated regimens, and it did not control for confounding [1]. Although a randomized controlled trial is underway to compare a 6-month regimen of isoniazid, rifampicin, pyrazinamide, and levofloxacin against

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the WHO recommended 12-month regimen, results are not expected for a few more years [6].

To inform an update of WHO guidance on TB meningitis treatment in children (ages 0–9 years) and adolescents (ages 10–19 years), we undertook a systematic review and meta-analysis of outcomes from regimens that included, at a minimum, isoniazid, rifampicin, and pyrazinamide, and were given for 6 to less than 12 months. We sought to determine whether the risks of death, loss to follow-up, treatment success, and neurological sequelae were different when a regimen of 6 to less than 12 months' duration was used, compared to the 12-month regimen.

METHODS

The protocol for this systematic review was registered on PROSPERO on April 12, 2021 (CRD 42021243817).

Search Strategy

An academic librarian (G.G.) adapted the search strategy used in a previous systematic review of pediatric TB meningitis outcomes [1] (Supplementary Text S1). Search terms included those related to the treatment of TB meningitis, children/adolescents, and outcomes. We ran the search on February 24, 2021, in PubMed, EMBASE Classic + EMBASE (Ovid), Web of Science Core Collection (Web of Science), BIOSIS Citation Index (Web of Science), Cochrane CENTRAL (Trials) (Cochrane Library), and LILACS (Global Index Medicus). We also considered unpublished studies/datasets proposed by the WHO Secretariat.

Screening and Data Abstraction

We screened studies in English, Spanish, French, Italian, Portuguese, Romanian, German, Chinese, Russian, and Ukrainian. Supplementary Text S2 provides detailed inclusion and exclusion criteria. In brief, we included studies that applied rigorous diagnostic criteria (see Supplementary Text S2) and reported our outcomes of interest for at least 10 children or adolescents treated with eligible regimens. Regimens had to include isoniazid, rifampicin, and pyrazinamide, with a treatment duration of 6 to less than 12 months. We excluded studies restricted to specific subsets of patients, such as those requiring shunt placement.

Title and abstract screening, full-text screening, and data abstraction were conducted independently by 2 investigators; disagreements were resolved by consensus or arbitration by a third investigator. We contacted study authors to ask for outcomes stratified by disease stage at diagnosis and other clarifying information, but we did not receive further data from the published studies of the 12-month regimen.

Risk of Bias Assessment

Given the lack of validated criteria for assessing the risk of bias in TB treatment studies, recent systematic reviews that have informed WHO TB guidelines have evaluated risk of bias in studies using tailored approaches informed by existing tools [7–9]. Similarly, we developed a checklist to assess 5 key sources of bias: (1) participant selection and loss to follow-up; (2) diagnostic uncertainty; (3) treatment allocation, including confounding by indication, and adherence; (4) assessment and reporting of treatment outcomes; and (5) potential confounding by age, human immunodeficiency virus (HIV) status, disease stage at diagnosis, and *Mycobacterium tuberculosis* resistance pattern (Supplementary Table S1). Each domain consisted of several subdomains relevant to pediatric TB meningitis. The risk of bias arising from each subdomain was judged to be low, high, or uncertain. Two investigators (1) independently applied the risk of bias tool to all included studies, (2) resolved discrepancies by discussion or consultation with a third investigator, and (3) summarized findings in a color-coded table. We did not generate an overall impression of bias for each study.

Statistical Analysis

Using generalized linear mixed models, we estimated the random effects pooled proportion and 95% confidence interval (CI) of patients with each of 5 outcomes: (1) death; (2) loss to follow-up; (3) treatment success, defined as the number of patients who completed treatment and were alive, with or without neurological sequelae; (4) neurological sequelae, defined as the number of survivors who completed treatment (ie, were not lost to follow-up) and developed neurological sequelae of any severity; and (5) survival without neurological sequelae. For neurological sequelae, the denominator was the number of patients who survived and completed treatment. For all other outcomes, the denominator was the total number of patients starting treatment.

We assessed between-study heterogeneity through visual inspection of forest plots. Because of the noncomparative nature of the studies, we did not pool measures of relative effect. Insufficient data precluded subgroup analyses (Supplementary Table S2). Analyses were performed using the *meta* package in R version 3.6.3 [10, 11].

Patient Consent Statement

As a systematic review and meta-analysis of aggregate-level data, this study did not require institutional board approval or patient consent.

RESULTS

From 1820 unique citations, we identified 130 studies for full-text screening. We also screened the 19 studies included in a prior systematic review [1] and 2 unpublished datasets identified by the WHO Secretariat [12]. One of those unpublished datasets has since been published [12]. Seven studies met inclusion criteria [12–17] (Supplementary Figure S1). Supplementary

Table S3 reports reasons why individual studies were excluded after full-text review.

Characteristics of Included Studies

Table 1 summarizes the characteristics of the included studies, all of which were cohort studies, and none of which performed head-to-head comparisons of the regimens of interest [12–17]. Of 837 patients who received regimens of less than 12 months' duration, 100 received an 8-month regimen in Vietnam (2HRZES/1HRZE/5HRE) [13], and 737 were treated at a single referral center in South Africa [14, 15]. Among the 737 patients in South Africa, 724 received the 6-month intensive ("Cape Town") regimen, which consisted of daily isoniazid, rifampicin, pyrazinamide, and ethionamide throughout treatment (6HRZEto). As detailed in Table 1, dosing of isoniazid and rifampicin was higher compared to the 12-month regimen. For an additional 13 patients with HIV, the intensive regimen was extended to 9 months (9HRZEto) [14]. Patients whose regimens were extended beyond 6 months for other reasons, including poor adherence, tuberculomas, and isoniazid monoresistance, were excluded. A total of 282 patients received the 12-month regimen. Two studies of the 12-month regimen were conducted in India [16, 17], while data for the third study that included the 12-month regimen were collected in various centers in Europe through the Pediatric Tuberculosis Network European Trials Group (ptbnet) [12].

Among cohorts that received regimens of less than 12 months' duration, the median age of patients ranged from 2.3 to 2.9 years. The median age of the ptbnet patients who received the 12-month regimen was 3.3 years; summary age data were not reported for the Indian cohorts. Children with HIV comprised 2.5% of patients who received the 6-month intensive regimen. Two of 3 cohorts that received regimens of 12 months' duration did not include patients with HIV [12, 16]. The ages of the 12 patients with HIV included in the third study of 12-month regimen, which combined adults and children, were not reported [17].

Patients who received the 6-month intensive or 12-month regimens were staged at diagnosis using the original or modified British Medical Research Council (MRC) staging system [12, 14–16]. One study of the 12-month regimen did not report stage [17]. The Vietnam study used the MRC classification for patients 5 years or older and the Blantyre coma scale for patients younger than 5 years [13]. Of the 724 patients who received the 6-month intensive regimen, 36 (5.0%) presented in stage 1, 401 (55.4%) presented in stage 2, and 287 (39.6%) presented in stage 3. Of the 282 patients who received the 12-month regimen, 28 (9.9%) presented in stage 1, 67 (23.8%) presented in stage 2, and 49 (17.4%) presented in stage 3; stage was not reported for 138 (48.9%) patients. Fifty-nine percent of the patients in the Vietnamese cohort were diagnosed in stage 1 (Table 1).

Supplementary Tables S4 and S5 summarize additional patient characteristics.

Risk of Bias in Included Studies

Figure 1 presents the results of the risk of bias assessment. All studies of regimens of 6 to less than 12 months' duration had low risks of selection bias because they included all consecutive patients meeting eligibility criteria and had few losses to follow-up [13–15]. However, studies of the 12-month regimen had high or unclear risk of selection bias because they did not enroll consecutive patients [12, 17] or did not provide information on sampling approaches [16]. Risk of bias related to diagnostic uncertainty was uncommon because all studies applied prespecified diagnostic criteria, which, in all but 1 study, included cerebrospinal fluid (CSF) assays and/or central nervous system imaging.

Risk of bias related to treatment allocation was unclear for 5 studies because reasons for regimen choices were unreported [12, 13, 15–17]. Risk of bias related to treatment allocation was low for 2 cohorts that received the 6-month intensive regimen because the reasons for extending therapy beyond 6 months were explained, and we were able to exclude those patients from the meta-analysis [14]. Treatment adherence, which may have impacted effectiveness, was reported in only 1 unpublished dataset from South Africa. Steroid use was inconsistent in the largest cohort that received the 6-month intensive regimen [15] and was not reported in one cohort that received the 12-month regimen [17].

Risk of bias related to treatment outcome reporting was high for one study of the 6-month intensive regimen because over 10% of patients were missing outcomes [15]. For the unpublished study of the 12-month regimen, there was uncertain risk of bias related to ascertainment of neurological sequelae, which were not standardized across the 9 study sites [12]. Risk of bias related to adverse events was unclear in 4 studies due to a lack of data [12, 13, 15, 16].

Confounding was the domain with the highest concern for bias. Outcomes were not reported for age subgroups, thus hindering assessment of age-related differences. Two studies of the 12-month regimen did not disaggregate outcomes by disease stage [16, 17], the best-known predictor of outcome. Finally, most studies provided limited details regarding efforts to exclude drug-resistant cases. No study reported the resistance profiles of presumed source cases. In 3 cohorts that received the 6-month intensive regimen, drug susceptibility testing was conducted in fewer than a third of patients [14, 15]. The remaining studies did not report susceptibility testing [12, 13, 16, 17].

Treatment Outcomes

All studies reported mortality, treatment success, and neurological sequelae among survivors. All but 1 study reported loss to

Table 1. Main Characteristics of Studies Reporting on the Effectiveness of Regimens to Treat Drug-Susceptible Tuberculous Meningitis in Children and Adolescents

Study Reference	Study Design	Location	Years of Enrollment	Duration of Follow-up	Number of Patients	Treatment Regimen	Patients Receiving Steroids	Patient Characteristics: Age	Patient Characteristics: Female [n (%)]	Patient Characteristics: HIV Status	Patient Characteristics: Disease Stage (n per Stage)[b]
Intervention Regimens[a]											
Bang et al [13]	PC	Ho Chi Minh City, Vietnam	2009–2011	8 months	100	2HRZES/1HRZE/5HRE: H 5 mg/kg, R 10 mg/kg, Z 25 mg/kg, E 15 mg/kg, S 15 mg/kg	All	Median: 2.7 years (IQR 0.9–6.9 years) Range: 0.2–15 years	44 (44.0)	4/96 HIV-positive	59 stage 1; 23 stage 2; 18 stage 3
van Toorn et al [14]	PC	Western Cape, South Africa	2006–2009	≥2 years after treatment completion	135	6HRZEto: H 20 mg/kg, R 20 mg/kg, Z 40 mg/kg, Eto 20 mg/kg	All	Median: 2.9 years (IQR 1.5–7 years) Range: 0.2–14 years	72 (53.3)	6/135 HIV-positive	16 stage 1; 68 stage 2; 51 stage 3
					13	9HRZEto: H 20 mg/kg, R 20 mg/kg, Z 40 mg/kg, Eto 20 mg/kg	All	Median: 5.5 years (IQR 2.2–7.4 years) Range: 0.8–11 years	3 (23.1)	All HIV-positive	2 stage 1; 8 stage 2; 3 stage 3
van Well et al [15]	RC	Western Cape, South Africa	1985–2005	6 months	554	6HRZEto: H 20 mg/kg, R 20 mg/kg, Z 40 mg/kg, Eto 20 mg/kg	63%	Median: 2.3 years (IQR 1.3–4.2 years) Range: 0.2–15 years	263 (47.5)	8/213 HIV-positive	14 stage 1; 318 stage 2; 222 stage 3
Solomons et al (unpublished)	RC	Western Cape, South Africa	2011–2014	6 months	35	6HRZEto: H 20 mg/kg, R 20 mg/kg, Z 40 mg/kg, Eto 20 mg/kg	All	Median: 2.5 years (IQR 1.3–3.7 years) Range: 0.4–6.8 years	16 (45.7)	3/35 HIV-positive	6 stage 1; 15 stage 2; 14 stage 3
Comparator (WHO) Regimen[a]											
Dhawan et al [16]	PC	India	2010–2013	12 months after hospital discharge	130	2HRZE/10HR: H 10 mg/kg, R 15–20 mg/kg, Z 35–40 mg/kg, E 20–25 mg/kg	All	NR	50 (38.5)	All HIV-negative	26 stage 1; 56 stage 2; 48 stage 3
Gupta et al [17]	PC	Delhi, India	2012–2014	12 months	138	2HRZE/10HR: H 10–20 mg/kg, R 10–20 mg/kg, Z 30–35 mg/kg, E 15–20 mg/kg	NR	<18 years	NR	NR[c]	NR
Thee et al [12]	RC	Europe (multiple countries)	2009–2016	12 months	14	2HRZE/10HR: H 9.8 (5.8–12.1) mg/kg, R 11.8 (10.1–14.5) mg/kg, Z 28.8 (25.0–31.3) mg/kg, E 19.2 (17.0–20.1) mg/kg[d]	All	Median: 3.3 years Range: 1–16 years	5 (35.7)	All HIV-negative	2 stage 1; 11 stage 2; 1 stage 3

Abbreviations: E, ethambutol; Eto, ethionamide; H, isoniazid; HIV, human immunodeficiency virus; IQR, interquartile range; NR, not reported; PC, prospective cohort; RC, retrospective cohort; R, rifampin; SD, standard deviation; S, streptomycin; WHO, World Health Organization; Z, pyrazinamide.

[a]Regimens of 6 to <12 months' duration were classified as "intervention," whereas 12-month regimens were classified as "comparator" (WHO).

[b]Disease stage was defined in accordance with the British Medical Research Council scale in all studies; however, children younger than 5 years in Bang et al [13] were staged as per the Blantyre Coma Scale.

[c]The study included both adults and children; 12 HIV-positive individuals were included in the entire cohort but their age distribution was not reported.

[d]Reported doses are the median (25th and 75th percentile) doses given for each drug.

Study	Risk of bias related to participant selection and loss to follow-up			Risk of bias related to diagnostic uncertainty		Risk of bias related to treatment			Risk of bias related to outcomes				Risk of bias related to confounding			
	Recruitment strategy	LTFU during treatment	LTFU post-treatment	Use of predefined diagnostic criteria	CSF findings or imaging compatibility with TBM	Potential for confounding by indication	Missed treatment doses	Proper use of steroids as adjunctive treatment	Mortality data	Neurological sequelae outcome data	Ascertainment of neurological sequelae	Ascertainment of adverse events	Stratification by age subgroup	Stratification by HIV status	Stratification by TBM stage	Exclusion of resistant cases
Bang et al 2016	Low	Low	Low	Low	Low	Unclear	Unclear	Low	Low	Low	Low*	Unclear	Low	Low**	Low	High
van Toorn et al 2014	Low	Low	Low	Low	Low	Low	Unclear	Low	Low	Low	Low*	Low	High	Low	Low	Low
van Well et al 2009	Low	Low	Low	Low	Low	Unclear	Unclear	Low	High	High	Low	Unclear	High	Low	Low	Unclear
Solomons et al (unpublished)	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	High	Low	Low	Low
Dhawan et al 2016	Unclear	Low	Low	Low	Low	Unclear	Unclear	Low	Low	Low	Low	Unclear	High	Low	High	Unclear
Gupta et al 2017	High	Low	Low	Low	Unclear	Unclear	Unclear	Unclear	Low	Low	Low	Low	High	Low**	High	Unclear
Thee et al 2022	High	Low	Unclear	Low	Low	Unclear	Unclear	Low	Low	Low	Unclear	Unclear	Low	Low	Low	Unclear

Figure 1. Summary results of risk of bias assessment of 7 reporting on the effectiveness of regimens to treat drug-susceptible tuberculous meningitis in children and adolescents. *, Neurological sequelae were ascertained through both clinical exam and reports from patients/caregivers. **, Although stratum-specific data were not available, this was considered of limited concern given the very small number of human immunodeficiency virus (HIV)-positive patients included in the cohort. CSF, cerebrospinal fluid; LTFU, loss to follow-up; TBM, tuberculous meningitis.

follow-up [12–16]. Only 1 study from South Africa reported relapse [14].

All studies of the 6-month intensive regimen stratified death and neurological sequelae by stage at diagnosis. No studies stratified outcomes by age, sex, nutritional status, isoniazid susceptibility pattern, microbiological confirmation, or complications (Supplementary Table S2).

One cohort of 13 patients with HIV who received a 9-month intensive regimen in South Africa and another cohort of 100 patients who received an 8-month regimen in Vietnam were excluded from meta-analysis [13, 14]. The proportions of patients who received the 9-month intensive regimen that died (1) were lost to follow-up, (2) were successfully treated, and (3) had neurological sequelae fell within the 95% CIs of those proportions in the cohorts that received the 6-month intensive regimen. Likewise, outcomes for patients who received the 8-month regimen were similar to those of the cohorts that received the 12-month regimen (Tables 2 and 3).

Compared to the 12-month regimen, the 6-month intensive regimen was associated with a lower proportion of death, similar proportion of loss to follow-up, and higher proportions of treatment success and neurological sequelae. Death ranged from 0% to 9.6%, with a pooled proportion of 5.5% (95% CI, 2.1%–13.4%) for the 6-month intensive regimen, and from 7.1% to 30.0%, with a pooled proportion of 23.9% (95% CI, 17.5%–31.7%) for the 12-month regimen (Table 2 and Figure 2). Heterogeneity was limited for the 6-month intensive regimen but substantial for the 12-month regimen.

No patients were lost to follow-up in 2 of 3 cohorts that received the 6-month intensive regimen [14]; 11.9% of patients were lost to follow-up in the third cohort [15]. Two of three studies of the 12-month regimen reported loss to follow-up [12, 16], which occurred in 0% and 7.1% of patients (Table 2 and Figure 2). The pooled proportions of loss to follow-up were 0.3% (95% CI, .0%–51.3%) and 0.6% (95% CI, .0%–24.1%) for the 6-month intensive and 12-month regimens, respectively.

Treatment success ranged from 78.5% to 100.0%, with a pooled proportion of 94.6% (95% CI, 73.9–99.1) for the 6-month intensive regimen, and from 70% to 85.7%, with a pooled proportion of 75.4% (95% CI, 68.7–81.1) for the 12-month regimen (Table 2 and Figure 2). Heterogeneity was moderate for the 6-month intensive regimen but minimal for the 12-month regimen.

Neurological sequelae were defined and assessed differently between study sites (Table 3). Fifty to 66.7% of survivors successfully treated with the 6-month intensive regimen had neurological sequelae, mostly mild. Among survivors successfully treated with the 12-month regimen, 31.9%–50.0% had neurological sequelae. In one study from India, 17 of 29 (58.6%) patients with sequelae had mild sequelae [16]. The other studies of the 12-month regimen did not report severity. The pooled proportions of survivors who completed treatment and had neurological sequelae were 66.0% (95% CI, 55.3%–75.3%) and 36.3% (95% CI, 30.1%–43.0%) for the 6-month intensive regimen and the 12-month regimen, respectively (Figure 2). Heterogeneity was substantial for both regimens.

The proportion of patients who completed treatment and survived without sequelae was 20.0%–43.0%, with a pooled proportion of 29.9% (95% CI, 20.4%–41.4%) for the 6-month intensive regimen; among those who received the 12-month regimen, the proportions ranged from 42.9% to 48.6% (Supplementary Table S6), with a pooled proportion of 47.9% (95% CI, 42.1%–53.7%). Heterogeneity was moderate for the 6-month intensive regimen and limited for the 12-month regimens.

Only 1 study reported relapse. Among 148 patients who received the 6-month intensive regimen, none relapsed within 2 years posttreatment [14].

Adverse Events

Only 3 studies reported drug-related adverse events [13, 14, 16]. Hepatotoxicity was the most frequently reported event (Supplementary Table S7). In one study of the 6-month

Table 2. Proportions of Death, Loss to Follow-up, and Treatment Success Across Studies Reporting on the Effectiveness of Regimens to Treat Drug-Susceptible Tuberculous Meningitis in Children and Adolescents

Study	Regimen	Number Started on Treatment		Number (%) Lost to Follow-up		Number (%) of Deaths by End of Treatment		Number (%) of Patients With Treatment Success[a]	
Bang et al [13]	2HRZES/1HRZE/5HRE	100	Stage 1: 59 Stage 2: 23 Stage 3: 18	4 (4.0) All patients lost to follow-up were in stage 1		15 (15.0) 14/15 deaths occurred <45 days of diagnosis	Stage 1: 1 (1.7) Stage 2: 4 (17.4) Stage 3: 10 (55.6)	81 (81.0)	Stage 1: 91.5% Stage 2: 82.6% Stage 3: 44.4%
van Toorn et al [14]	6HRZEto	135	Stage 1: 16 Stage 2: 68 Stage 3: 51	0		6 (4.4) All deaths occurred <8 days of treatment initiation in patients who were moribund at presentation	Stage 1: 0 (0) Stage 2: 0 (0) Stage 3: 6 (11.8)	129 (95.6)	Stage 1: 100% Stage 2: 100% Stage 3: 82.5%
	9HRZEto	13 (all HIV-pos)	Stage 1: 2 Stage 2: 8 Stage 3: 3	0		1 (7.7) Patient in stage 3		12 (92.3)	Stage 1:100% Stage 2: 100% Stage 3: 33.3%
van Well et al [15]	6HRZEto	554	Stage 1: 14 Stage 2: 318 Stage 3: 222	66[b] (11.9)	Stage 1: 1 (7.1) Stage 2: 17 (5.3) Stage 3: 48 (21.6)	53 (9.6)	Stage 1: 0 (0) Stage 2: 11 (3.5) Stage 3: 42 (18.9)	435 (78.5)	Stage 1: 92.9% Stage 2: 91.2% Stage 3: 59.5%
Solomons et al (unpublished)	6HRZEto	35	Stage 1: 6 Stage 2: 15 Stage 3: 14	0		0		35 (100)	Stage 1: 100% Stage 2: 100% Stage 3: 100%
Dhawan et al [16]	2HRZE/10HR	130	Stage 1: 26 Stage 2: 56 Stage 3: 48	0		39 (30.0) -38/39 deaths occurred during hospitalization (early phase of treatment), and 1/39 occurred 2 months after hospital discharge -Stage-specific outcomes not reported, but stage 3 was strongest risk factor for mortality		91 (70.0)	Stage not reported
Gupta et al [17]	2HRZE/10HR	138	Stage not reported	Not reported[b]		29 (21.0) No further details provided		109 (79.0)	Stage not reported
Thee et al [12]	2HRZE/10HR	14	Stage 1: 2 Stage 2: 11 Stage 3: 1	1 (7.1) Patient lost to follow-up was in stage 2		1 (7.1) Patient in stage 3		12 (85.7)	Stage 1: 100% Stage 2: 90.9% Stage 3: 0

Abbreviations: d, day; E, ethambutol; Eto, ethionamide; H, isoniazid; HIV, human immunodeficiency virus; pos, positive; R, rifampicin; Z, pyrazinamide.

[a]Treatment success was defined as the number of patients who were still alive, with or without sequelae, and had completed treatment.

[b]This includes 53 patients who were likely alive and had completed treatment, but whose outcome was not recorded and whose neurological status was not assessed.

Table 3. Neurological Sequelae Among Survivors Across Studies Reporting on the Effectiveness of Regimens to Treat Drug-Susceptible Tuberculous Meningitis in Children and Adolescents

Study	Regimen	Definition of Neurological Outcomes	Number Alive at End of Treatment		Number (%) With Neurological Sequelae	
Bang et al [13]	2HRZES/1HRZE/5HRE	Severe or intermediate disability (not further specified)	81	Stage 1: 54 Stage 2: 19 Stage 3: 8	27 (33.3) Moderate: 21 (25.9) Severe: 6 (7.4)	Stage 1: 11 (20.4) Stage 2: 10 (52.6) Stage 3: 6 (75.0)
van Toorn et al [14]	6HRZEto	Mild sequelae: • mild intellectual impairment, • hemiparesis • impaired vision and/or hearing Severe sequelae: • severe intellectual impairment, • quadriparesis, • blindness and/or deafness.	129	Stage 1: 16 Stage 2: 68 Stage 3: 45	71 (55.0) Mild: 49 (38.0) Severe: 22 (17.1)	Stage 1: 1 (6.3) Stage 2: 27 (39.7) Stage 3: 43 (95.6)
	9HRZEto		12	Stage 1: 2 Stage 2: 8 Stage 3: 2	6 (50.0) Mild: 3 (25.0) Severe: 3 (25.0)	Stage 1: 1 (50.0) Stage 2: 3 (37.5) Stage 3: 2 (100)
van Well et al [15]	6HRZEto		435	Stage 1: 13 Stage 2: 290 Stage 3: 132	294 (66.7) Mild: 217 (49.9) Severe: 77 (17.7)	Stage 1: 2 (15.4) Stage 2: 182 (62.8) Stage 3: 110 (83.3)
Solomons et al (unpublished)	6HRZEto		35	Stage 1: 6 Stage 2: 15 Stage 3: 14	28 (80.0)	Stage 1: 3 (50.0) Stage 2: 13 (86.7) Stage 3: 12 (85.7)
Dhawan et al [16]	2HRZE/10HR	Mild/moderate/severe disability, coma, or vegetative state	91	Not disaggregated by stage, but stage 3 was the strongest risk factor for poor neurological outcome	29 (31.9) Mild: 17 (18.1) Moderate: 5 (5.5) Severe: 4 (4.4) Coma or vegetative state: 3 (3.3)	
Gupta et al [17]	2HRZE/10HR	Altered sensorium, cranial nerve palsy, extrapyramidal movements, focal neurological deficit, mental retardation, optic atrophy, and/or tone abnormalities	109	Not disaggregated by stage	42 (38.5) No further details provided	
Thee et al [12]	2HRZE/10HR	Coma, paresis, spasticity, cranial nerve palsy, seizures, hydrocephalus, hypothalamic or pituitary dysfunction, developmental delay, impairment of speech, hearing, or vision	12	Stage 1: 2 Stage 2: 10 Stage 3: 0	6 (50.0)	Stage 1: 0 Stage 2: 6 (60.0) Stage 3: 0

Abbreviations: E, ethambutol; Eto, ethionamide; H, isoniazid; NR, not reported; R, rifampicin; S, streptomycin.

intensive regimen, hepatotoxicity resolved after a change to a less hepatotoxic regimen and subsequent stepwise restarting of the original regimen [14]. In Vietnam, 2 patients developed drug-induced hepatotoxicity (defined per the WHO definition) and recovered after discontinuation of pyrazinamide [13, 18]. The remaining study did not explain the approach to managing hepatotoxicity [16].

DISCUSSION

In this systematic review and meta-analysis, we found that, compared to the 12-month regimen, the 6-month intensive regimen was associated with lower mortality, higher treatment success, and more frequent neurological sequelae among survivors. Loss to follow-up was similar between the regimens, but data on this outcome were incomplete. The cohort in Vietnam had similar outcomes as those that received the 12-month regimen [13]. Data were insufficient to compare adverse events. A key concern with shorter TB regimens is relapse; however, in one study of the 6-month intensive regimen, none of the 148 patients who were monitored for 2 years posttreatment relapsed [14]. Moreover, across studies and regimens, almost all deaths occurred in the early treatment phases. Taken together, these observations suggest that treatment success may depend more on early effective treatment than on regimen duration beyond 6 months.

These findings should be interpreted with caution. As highlighted in our risk of bias assessment, there was high potential

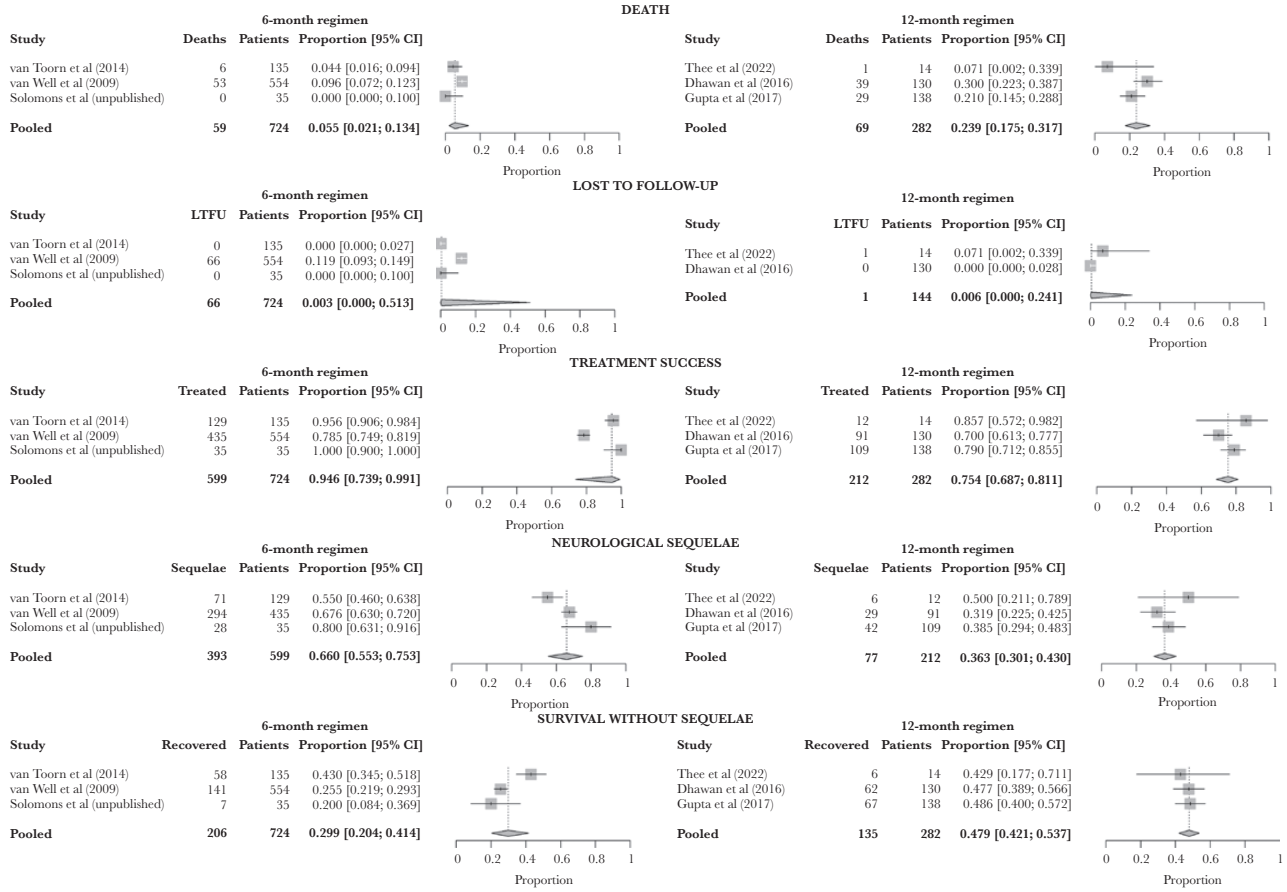

Figure 2. Forest plot of pooled proportions of death, loss to follow-up, treatment success, neurological sequelae, and survival without sequelae across 3 studies of 6-month intensive regimen (6HRZEto) and 3 studies of 12-month standard regimen (2HRZE/10HR). One study of the 12-month regimen (Gupta et al [17]) was excluded from analysis of loss to follow-up because it only included patients with complete follow-up period. In van Well et al [15], 53 of 66 patients who were counted as lost to follow-up were likely alive and had completed treatment, but their outcome was not recorded, and their neurological status could not be assessed. CI, confidence interval; LTFU, loss to follow-up.

for confounding by indication, disease stage at diagnosis, treatment adherence, and other patient characteristics. A range of antimicrobial doses were prescribed to patients who received the 12-month regimen, including within studies (Table 1). However, because outcomes were not disaggregated by dose, we could not evaluate for associations between these 2 variables. All data for the 6-month intensive regimen came from a single referral center in South Africa [14, 15], whereas most patients who received the 12-month regimen were treated in India [16, 17]. These distinct settings may lead to additional sources of confounding, including the following: time to diagnosis and treatment; the non-antimicrobial components of TB meningitis therapy, such as hydrocephalus management and steroid treatment; and perhaps even genetic differences in anti-TB drug metabolism [19, 20]. Finally, the lack of standardization of the assessment and categorization of neurological sequelae may account for differences in this outcome across sites.

The available data were insufficient to directly compare the effectiveness of pediatric TB meningitis regimens. Nevertheless, treatment success among patients who received the 6-month intensive regimen was 95%. The higher doses of isoniazid and rifampicin used in this regimen, together with the greater CSF penetration of ethionamide compared with ethambutol, may contribute to the effectiveness of the 6-month intensive regimen [21]. Rifampicin dosing may be particularly important for successful treatment [22]: data from adults with TB meningitis show an association between higher rifampicin concentrations and survival, and a small pediatric trial has shown improved neurocognitive function with doses of 30 mg/kg compared to the standard dose of 15 mg/kg [23, 24]. Nonpharmacological interventions also may have contributed to low mortality, but treatment success would not have been so high had the regimen been ineffective. Based on our findings, in August 2021, the WHO conditionally recommended the 6-month intensive regimen as an alternative to the 12-month regimen for treating TB meningitis in children and adolescents, for which a strong recommendation remains in place [3].

The current evidence base on pediatric TB meningitis treatment is limited. Despite an extensive search, we identified only 7 datasets meeting inclusion criteria. Few studies report

outcomes from the regimens of interest, and many studies—particularly those reporting on the 12-month regimen—have design limitations. Children and adolescents with TB meningitis often are managed in hospitals at the start of treatment and then transferred to outpatient clinics to complete therapy; most hospital-based studies do not collect data after discharge and, thus, do not report end-of-treatment outcomes. Some studies reported aggregated results from multiple regimens, including the 12-month regimen. Another limitation is inconsistent reporting of patient characteristics and treatment outcomes across studies. Currently, 2 clinical trials of pediatric TB meningitis regimens are underway [6, 25]. Although these interventional studies are important, they are challenging to carry out and subject to their own limitations; for instance, stricter enrollment criteria lead to highly selective participant populations [26].

Future studies on pediatric TB meningitis must improve upon limitations in the current literature. Collaboration across sites is critical to pediatric TB meningitis research. In addition, the implementation of standardized methods for the conduct and reporting of TB meningitis studies, as proposed by a group of experts in the field, would improve the evidence base and facilitate future meta-analyses [27]. These proposed standards include the following: the reporting of explicit indications for which deviations from the standard regimen occurred; the reporting of susceptibility patterns of patients' *M tuberculosis* strains, confirmed through testing, if available, or presumed based on the source case's susceptibility pattern; the stratification of outcomes by disease stage at diagnosis; and the application of standardized evaluations of neurological outcomes, adverse events, loss to follow-up, and relapse [28].

Finally, future research must address not only antimicrobial regimen composition, doses, and duration but also identify strategies for earlier diagnosis and treatment of TB meningitis; optimal anti-inflammatory therapies; and ways to prevent and treat paradoxical reactions, which may have devastating consequences for the patient [29]. Unless these limitations to pediatric TB meningitis research are addressed, too many children and adolescents will continue to succumb to or suffer long-term disability from this disease.

CONCLUSIONS

This meta-analysis of pediatric TB meningitis regimens is limited by the small number of studies that met inclusion criteria and substantial potential for confounding. Nonetheless, the 6-month intensive regimen was associated with high treatment success and is now recommended by the WHO as an alternative to the 12-month regimen.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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