Comparative effectiveness of regimens for drug-susceptible tuberculous meningitis in children and adolescents: a systematic review and aggregate-level meta-analysis

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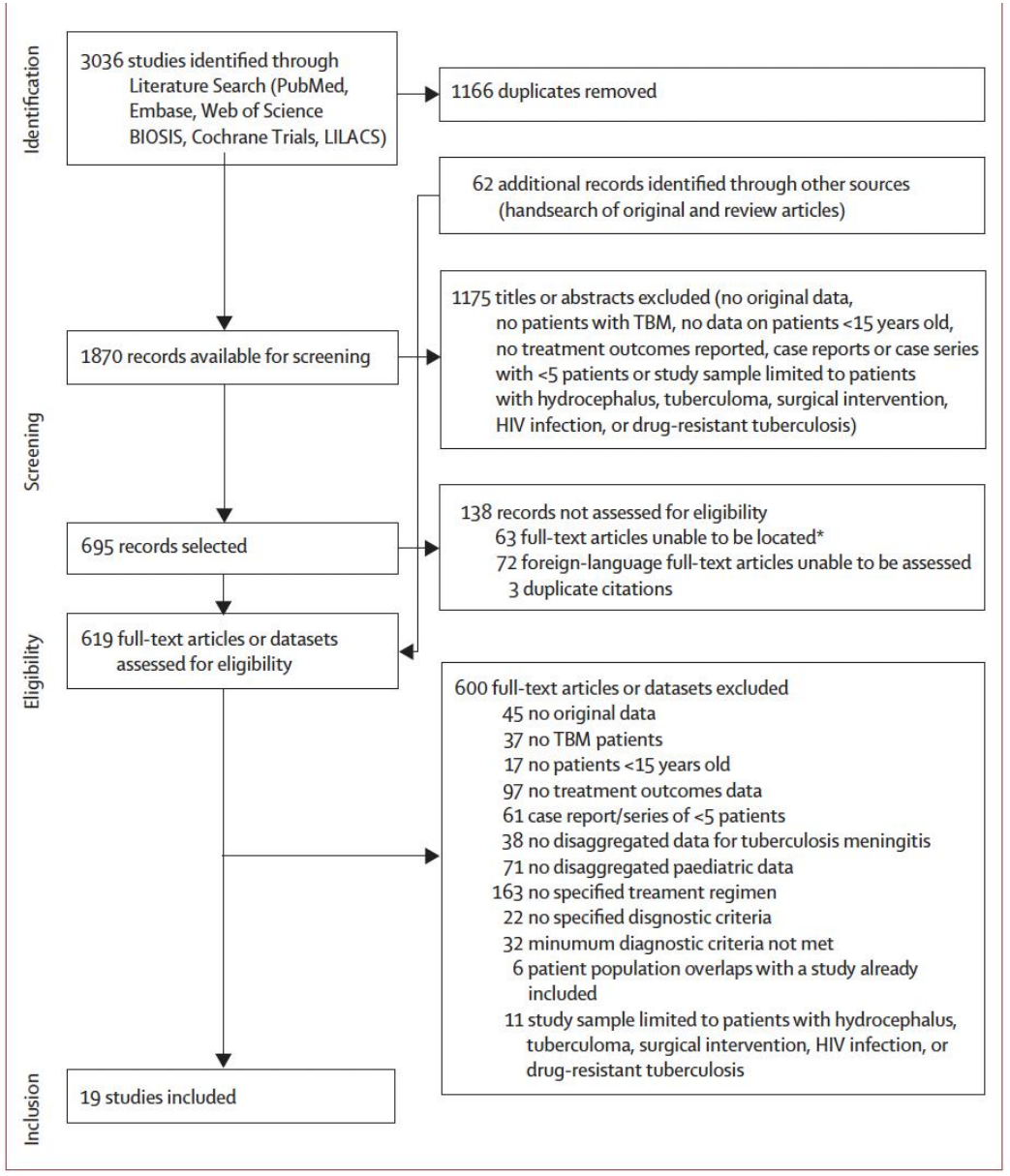
Background & Objectives

Childhood TB Meningitis

- Second most common form of extrapulmonary TB
- Higher risk in infants and toddlers
- Deadliest, most debilitating form of TB
  - Deaths: **19.3% (14.0 – 26.1)**
  - Neurological sequelae among survivors: **53.9% (42.6 – 64.9)**
  - Probability of survival without sequelae: **36.7% (27.9 – 46.4)**



Lancet Infect Dis. 2014:14(10): 947-57

Challenges

- **Low quality evidence** to guide regimen design

- **Previous WHO recommendation (2010)**:

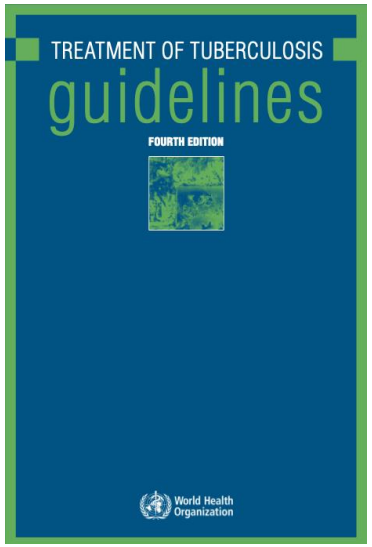
  2HRZE/10HR → *"strong recommendation, low-quality evidence"*

  - Literature review of 46 studies (21 exclusively pediatric) by Donald PR et al
  - Studies mostly non-randomized, non-comparative; differed in design, drugs, populations
  - Most reported regimens ≥12 months
  - Only study reported shorter regimen (Cape Town regimen)

- **2014 SR-MA**: too many variations in drugs and doses to compare regimens (27 different regimens)

- **Clinical trials**: none published to date, many challenges

No better evidence for TB meningitis treatment in adults



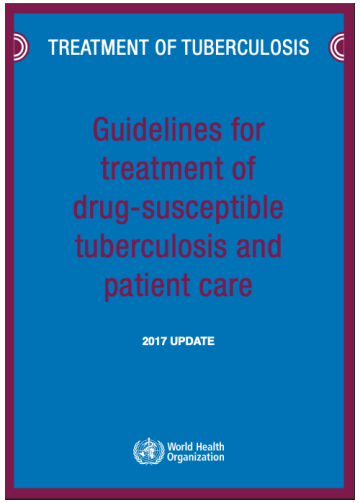
WHO Guidelines 2010:

- **Same regimen for pulmonary and extrapulmonary** TB. i.e. 2HRZE/4HR.
- Some experts recommend **9–12 months of treatment for TB meningitis** given the serious risk of disability and mortality.
- In TB meningitis, ethambutol should be replaced by **streptomycin**.
- **Optimal duration** of treatment yet **to be investigated.**

WHO Guidelines 2017:

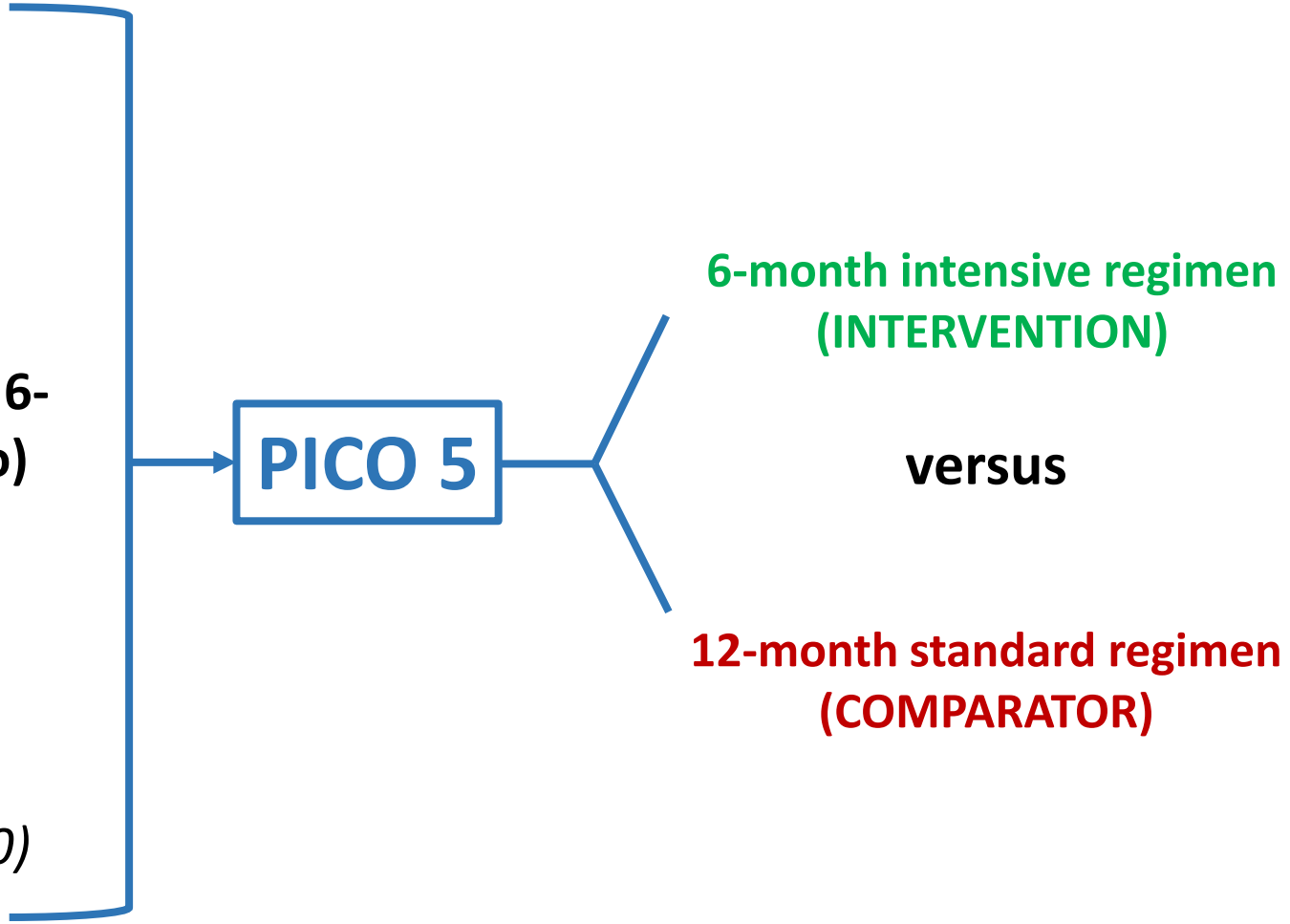
- In patients with TB meningitis, an **initial adjuvant corticosteroid therapy** with dexamethasone or prednisolone **tapered over 6-8 weeks should be used**

(Strong recommendation, moderate certainty in the evidence)



Developments since 2014

- **More published observational studies** using **WHO regimen** or variation
- **More data** from South Africa using **6-month intensive regimen (6HRZEto)**
- **More standardized reporting**, including use of standardized case definitions / diagnostic criteria *(Marais et al. Lancet Infect Dis 2010)*



PICO Question

*In **children** (<10 years old) **and adolescents** (10-19 years old) with microbiologically confirmed or clinically diagnosed **rifampin-susceptible tuberculous meningitis (TB meningitis), should a 6-month intensive regimen, compared to the current 12-month regimen*** that conforms to WHO guideline be used?

Methods

Search & selection of studies

SEARCH

- Updated from 2014 SR&MA
- Key terms for “TB meningitis”, “children/adolescents” and “outcomes”
- 6 databases
- Launched on Feb 24, 2021
- Unpublished studies

SCREENING PROCESS

- Pre-specified protocol with detailed inclusion/exclusion criteria
- 2 independent reviewers performed title/abstract screening, full-text screening, data extraction and quality assessment
- Discrepancies solved by discussion or arbitration by a third researcher
- Standardized data collection form

INCLUSION CRITERIA

- Design: cohort studies, clinical trials
- Language: English, French, Chinese, German, Italian, Portuguese, Russian, Spanish, Turkish, Ukrainian
- Population: children (<10 y.o.) and adolescents (10-19 y.o.) with TBM defined as per prespecified criteria
- Treatment: available details with respect to at least composition and duration
  - SHORTER REGIMENS → 6-month intensive regimens or 6 to <12 months regimens of various forms
  - STANDARD REGIMEN → 2HRZE/10HR
- Outcomes: at least death and/or neurologic sequelae at the end of treatment

EXCLUSION CRITERIA

- No patients <15 y.o. or pediatric data not disaggregated
- No TBM cases included (or disaggregated)
- Diagnostic criteria for TBM not reported
- Treatment details not specified
- Outcome data not reported
- Ineligible regimen:
  - RIF not included
  - ≥12-month regimens other than WHO regimen
  - Intermittent regimens
  - Non-intensive short regimens (e.g. 2HRZE/4HR)
- Population restricted to patients with complications
- Sample size <10 patients
- Duplicate data

Risk of bias assessment

Tailored checklist covering key domains:

1. Bias related to participant selection & loss to follow-up
2. Bias related to diagnostic uncertainty
3. Bias related to treatment allocation
4. Bias related to outcomes
   - death
   - neurologic sequelae
5. Bias related to confounding
   - age
   - HIV status
   - disease stage
   - drug-resistance

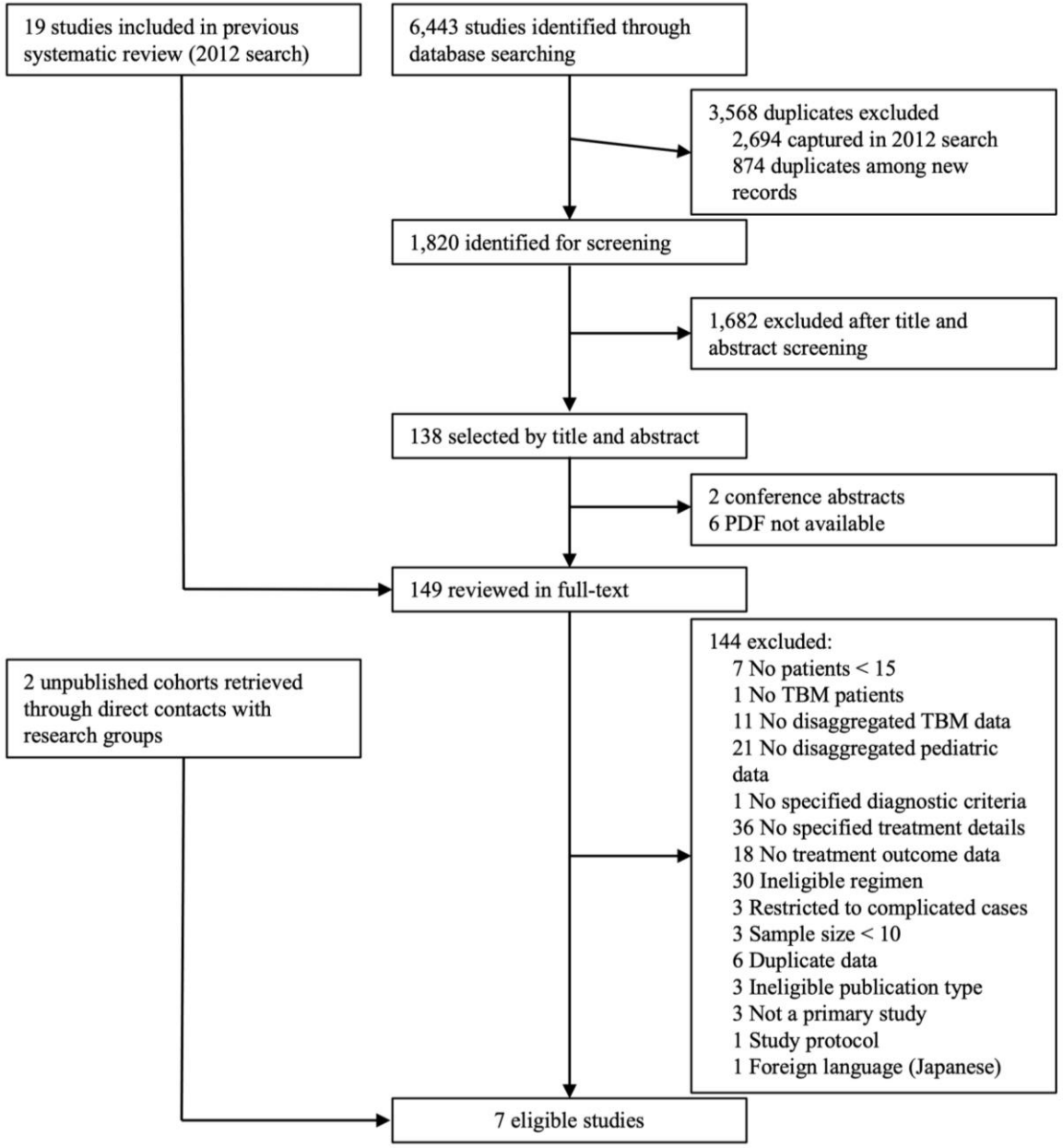
Data analysis

- Pooled proportions estimated across studies and within regimens through aggregate-level **meta-analysis using generalized linear mixed models**
  - Death by end of treatment
  - Loss to follow-up
  - Treatment success (= known alive by end of treatment)
  - Neurological sequelae (among survivors)
  - Probability of survival without neurological sequelae (among those starting treatment)

- **Challenges** → small number of studies and high between-study heterogeneity

- Subgroup analyses planned but not feasible due to lack of data

Results



7 studies included

- 4 on regimens 6 to <12 mo
  - 3 published
  - 1 unpublished
- 3 on standard 12-mo regimen
  - 2 published
  - 1 unpublished

Studies on regimens of 6 to <12 months' duration

Reference	Study type and setting	Regimen	Patient characteristics	Major outcomes	Bias concerns
van Toorn 2014	PC South Africa 2006-2009	6HRZEto + steroids	135 HIV-uninfected children. Median age: 2.9 years TBM stage: 16 stage 1; 68 stage 2; 51 stage 3.	- Deaths: 6 (4.4%), all <8 days of treatment initiation. - No relapses during 2-year post-treatment FUP. - TS: 129 (95.6%). - NS: 71/129 (55.0%).	Unknown adherence; confounding by age.
van Well 2009	RC South Africa 1985-2005	6HRZEto + steroids	554 children of whom 2013 with known HIV status and 8 HIV-infected. Median age: 5.5 years TBM stage: 14 stage 1; 318 stage 2; 222 stage 3.	- Deaths: 53 (9.6%), mostly in stage 3 patients. - TS: 435 (78.5%). - NS: 294/435 (66.7%).	Confounding by indication; unknown adherence; >10% patients had missing outcome data; confounding by age.
Solomons (unpublished)	RC South Africa 2011-2014	6HRZEto + steroids (63% of patients)	35 children (3/35 HIV-infected). Median age: 2.5 years TBM stage: 6 stage 1; 15 stage 2; 14 stage 3.	- Deaths: none. - TS: 35 (100%). - NS: 28/35 (80.0%).	Confounding by age.
Bang 2016	PC Vietnam 2009-2011	2HRZES/1HRZE/ 5HRE + steroids	100 children (4/96 HIV-infected). Median age: 2.7 years TBM stage: 59 stage 1; 23 stage 2; 18 stage 3.	- Deaths: 15 (15.0%), 93.3% <45 days of diagnosis. - TS: 81 (81.0%). - NS: 27/81 (33.3%).	Confounding by indication; unknown adherence; potential inclusion of drug-resistant cases.

724 patients started on treatment

Excluded from meta-analysis

NS, Neurologic sequelae; PC, Prospective cohort; RC, Retrospective cohort; TBM, TB meningitis; TS, Treatment success

Studies on standard 12-month regimen

Reference	Study type and setting	Regimen	Patient characteristics	Major outcomes	Bias concerns
Dhawan 2016	PC India 2010-2013	2HRZE/10HR + steroids	130 HIV-uninfected children (age unspecified). TBM stage: 26 stage 1; 56 stage 2; 48 stage 3.	- Deaths: 39 (30.0%), mostly associated with stage 3 and occurring shortly after treatment initiation. - TS: 91 (70.0%) - NS: 29/91 (31.9%).	Patient sampling; confounding by indication; unknown adherence; confounding by age and stage.
Gupta 2017	PC India 2012-2014	2HRZE/10HR [adjunctive treatment unknown]	138 children aged <18 years.‡ TBM stage not reported.	- Deaths: 29 (21.0%) – details not reported. - TS: 109 (79.0%) - NS: 42/109 (38.5%).	Patient sampling; confounding by indication; adherence and adjunctive treatment unknown; confounding by age and stage.
Thee (unpublished from ptbnet)	RC Europe (multiple countries) 2009-2016	2HRZE/10HR + steroids	14 HIV-uninfected children. Median age: 3.3 years. TBM stage: 2 stage 1; 11 stage 2; 1 stage 3.	- Deaths: 1 (7.1%) in stage 3. - TS: 12 (85.7%). - NS: 6/12 (50.0%).	Patient sampling; confounding by indication; unknown adherence; non-standardized approach to assess NS.

282 patients started on treatment

NS, Neurologic sequelae; PC, Prospective cohort; TBM, TB meningitis; TS, Treatment success

Meta-analysis findings: 6HRZEto vs. 2HRZE/10HR

Outcome	Intervention: 6HRZEto				Comparator: 2HRZE/10HR			
	No. studies	n/N	Pooled proportion (95% CI)		No. studies	n/N	Pooled proportion (95% CI)	
			Random-effects model	Fixed-effects model			Random-effects model	Fixed-effects model
Death	3	59/724	0.06 (0.02-0.13)	0.08 (0.06-0.10)	3	68/282	0.24 (0.18-0.32)	0.24 (0.20-0.30)
Loss to follow-up	3	66/724	0.0 (0.0-0.51)	0.09 (0.07-0.11)	2	1/144	0.01 (0.0-0.24)	0.01 (0.0-0.05)
Treatment success	3	599/724	0.95 (0.74-0.99)	0.83 (0.80-0.85)	3	212/282	0.75 (0.69-0.81)	0.75 (0.70-0.80)
Neurological sequelae	3	393/599	0.66 (0.55-0.75)	0.66 (0.62-0.69)	3	77/212	0.36 (0.30-0.43)	0..36 (0.30-0.43)
Survival without neurological sequelae	3	206/724	0.30 (0.20-0.41)	0.28 (0.25-0.32)	3	135/282	0.48 (0.42-0.54)	0.48 (0.42-0.54)

Proportion of deaths by end of treatment: 6HRZEto vs. 2HRZE/10HR

Outcome	Intervention: 6HRZEto				Comparator: 2HRZE/10HR			
	No. studies	n/N	Pooled proportion (95% CI)		No. studies	n/N	Pooled proportion (95% CI)	
			Random-effects model	Fixed-effects model			Random-effects model	Fixed-effects model
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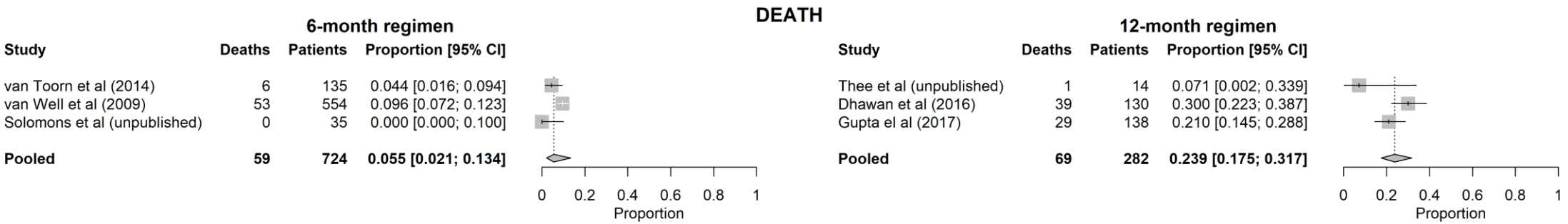

No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Certainty
6	Observational	Very serious	Serious	Very serious	Not serious	⨁◯◯◯ Very low

Proportion of lost to follow-up: 6HRZEto vs. 2HRZE/10HR

Outcome	Intervention: 6HRZEto				Comparator: 2HRZE/10HR			
	No. studies	n/N	Pooled proportion (95% CI)		No. studies	n/N	Pooled proportion (95% CI)	
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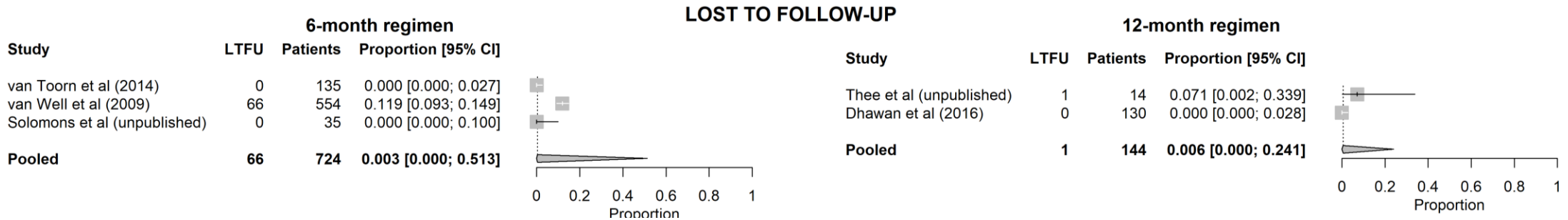

No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Certainty
5	Observational	Very serious	Serious	Very serious	Not serious	⨁◯◯◯ Very low

Proportion of treatment success: 6HRZEto vs. 2HRZE/10HR

Outcome	Intervention: 6HRZEto				Comparator: 2HRZE/10HR			
	No. studies	n/N	Pooled proportion (95% CI)		No. studies	n/N	Pooled proportion (95% CI)	
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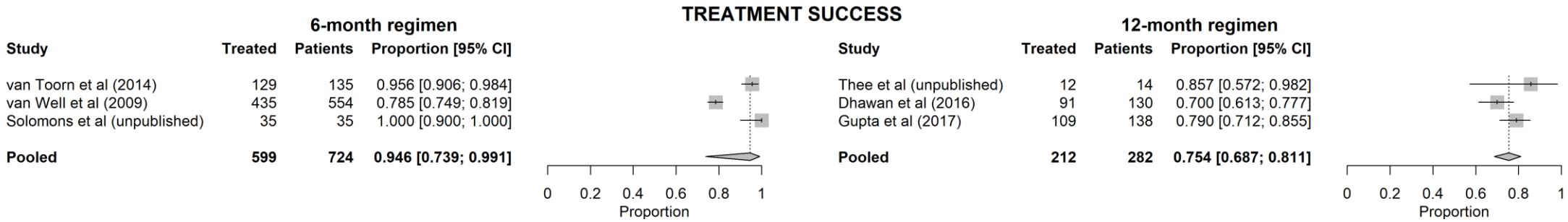
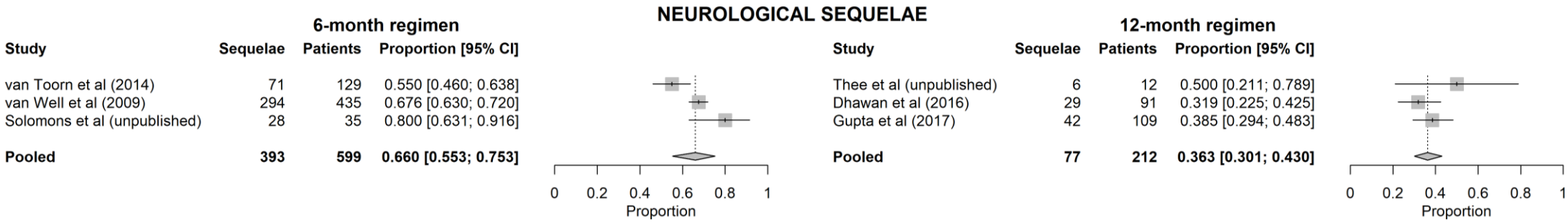


No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Certainty
5	Observational	Very serious	Serious	Very serious	Not serious	⨁◯◯◯ Very low

Proportion with neuro sequelae among survivors: 6HRZEto vs. 2HRZE/10HR

Outcome	Intervention: 6HRZEto				Comparator: 2HRZE/10HR			
	No. studies	n/N	Pooled proportion (95% CI)		No. studies	n/N	Pooled proportion (95% CI)	
			Random-effects model	Fixed-effects model			Random-effects model	Fixed-effects model
Neurological sequelae	3	393/599	0.66 (0.55-0.75)	0.66 (0.62-0.69)	3	77/212	0.36 (0.30-0.43)	0..36 (0.30-0.43)



No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Certainty
5	Observational	Very serious	Very serious	Very serious	Not serious	⨁◯◯◯ Very low

Probability of survival without neuro sequelae: 6HRZEto vs. 2HRZE/10HR

Outcome	Intervention: 6HRZEto				Comparator: 2HRZE/10HR			
	No. studies	n/N	Pooled proportion (95% CI)		No. studies	n/N	Pooled proportion (95% CI)	
			Random-effects model	Fixed-effects model			Random-effects model	Fixed-effects model
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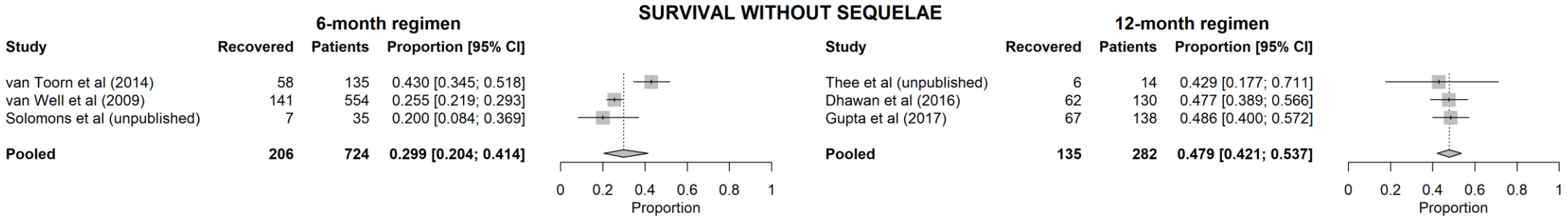

No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Certainty
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Concluding remarks

- Very few studies meet inclusion criteria to inform PICO 5 (treatment outcomes seldom reported from the regimens of interest, outcomes reported only at end of hospitalization)

- Key findings:
  - Mortality by end of treatment higher with **2HRZE/10HR** versus **6HRZEto**
  - Probability of survival without neurological sequelae slightly lower with 6HRZEto

- Great caution is advised in interpreting pooled estimates
  - Small number of studies
  - High potential for confounding by indication
  - Residual confounding
  - Between-study heterogeneity in assessment of neurological sequelae

- 6HRZEto has been used for almost 35 years in South Africa, with comparable results as observed with standard regimen.

  Note: no relapses observed in a subset of patients 2 years post treatment (van Toorn et al, 2014)

THANK YOU!

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