Antimicrobial Management of Pediatric TBM

Tuberculosis Meningitis Workshop: Advancing Immunopathogenesis, Diagnosis, and Treatment

May 23, 2017

NIH, Bethesda, MD

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DIVISION OF
CLINICAL
PHARMACOLOGY

THE CENTER FOR TB RESEARCH
JOHNS HOPKINS UNIVERSITY

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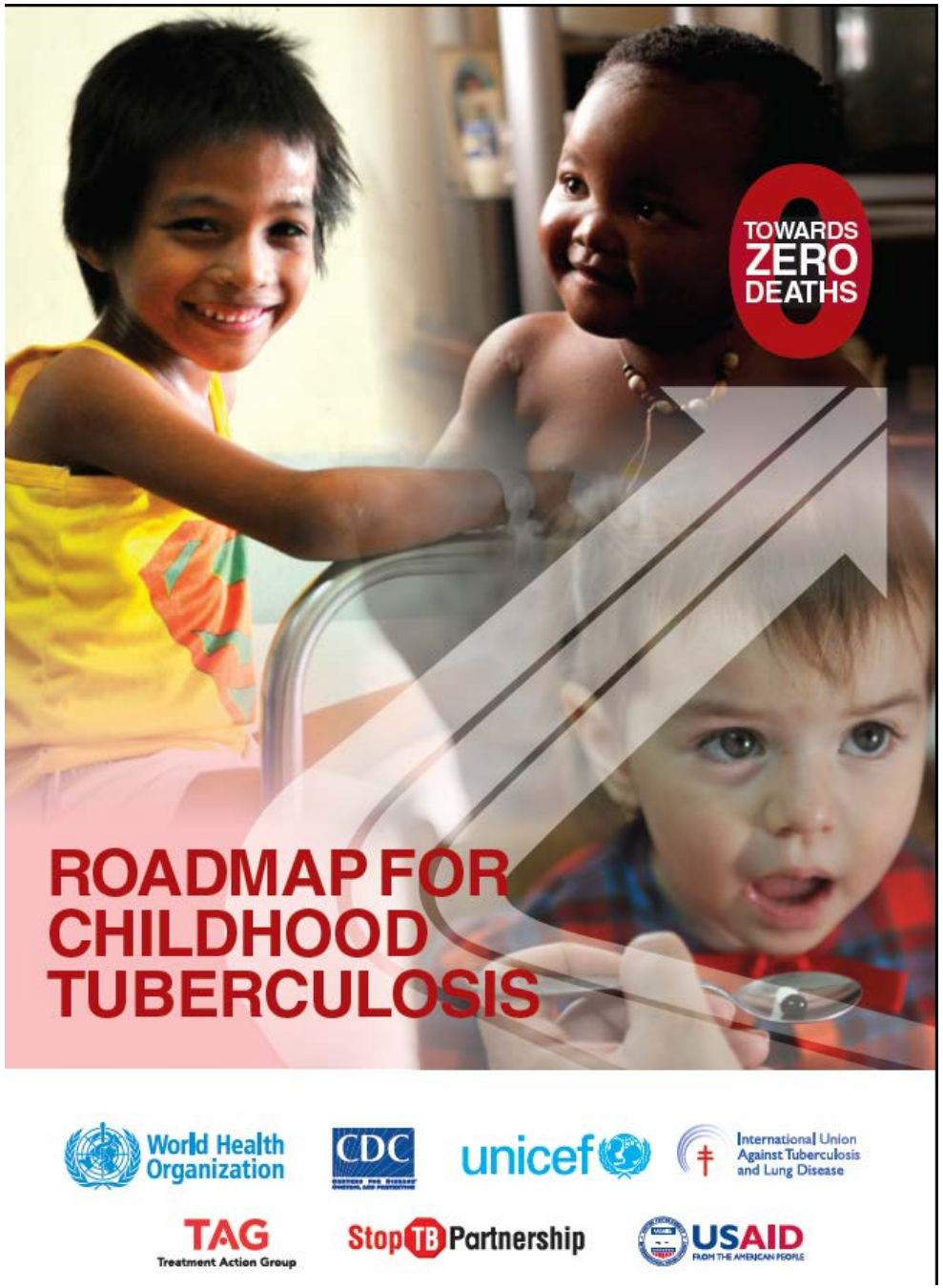
Childhood TB:
Towards Zero Deaths

- **"Childhood TB needs to be lifted out of the shadows"**
  - **Historical neglect**

- 1,000,000 cases in 2015

- >169,000 deaths from TB yearly (41K in children with HIV)



Pediatric TB ≠ Adult TB: What does pediatric TB *look like*?

It depends (on how old you are)!

Disease risk and presentation

Age (yrs)	No disease	Pulmonary dz	TBM/miliary dz
<1	50	30-40	10-20
1-2	70-80	10-15	2-5
2-5	95	5	0.5
5-10	98	2	<0.5
>10	80-90	10-20	<0.5

Pulmonary disease

Age (yrs)	Ghon/LN	Bronchial	Effusion	"Adult-type"
<1	X	X		
1-2	X	X		
2-5	X	X		
5-10	X	X	X	X
>10			X	X

Table 4. Average age-specific risk for disease development following primary infection (immune-competent children)*

*Adapted from Marais *et al* 2004 IJTLD.

The natural history of childhood intra-thoracic tuberculosis: a critical review of literature from the pre-chemotherapy era

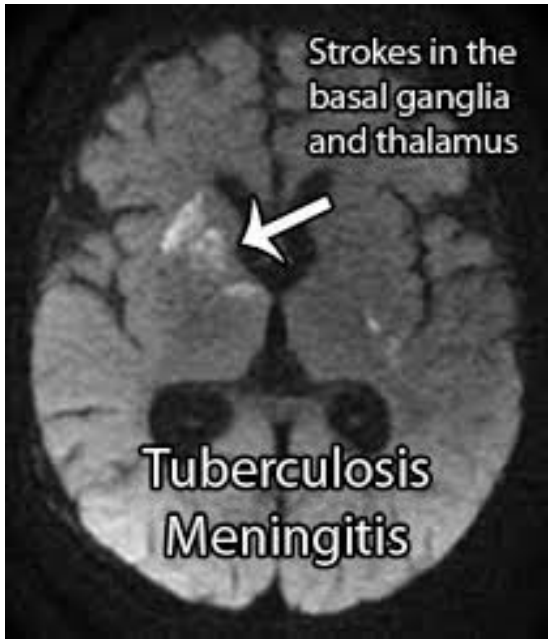
TBM: Epidemiology

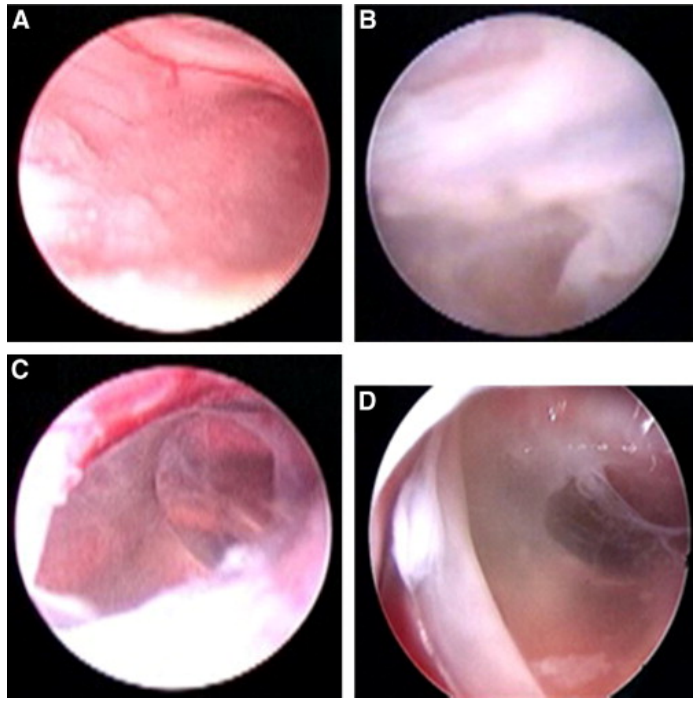
- Develops within one year of infection (**household contact**)
- Highest risk for severe disseminated disease like TBM: **< 3 years of age, HIV co-infection, malnutrition**
- Majority of children **present at late stage**:
  - Stage I (no focal neurologic signs, intact sensorium)
  - Stage II (disturbed consciousness or focal neurologic deficit)
  - Stage III (coma +/- focal neurologic deficits)

Pediatric TBM: Clinical consequences

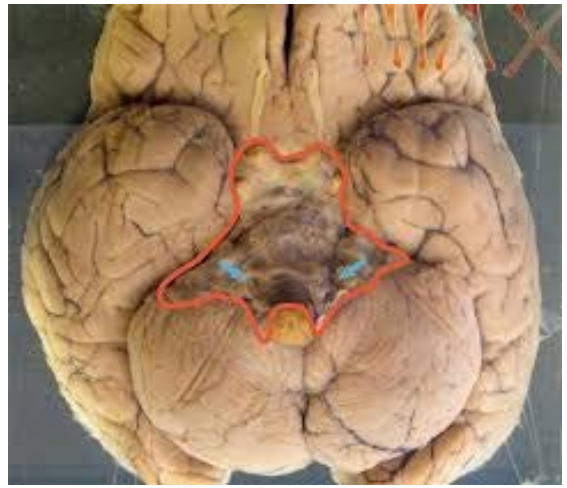
Catastrophic

- Dense meningeal exudate with adhesions (hydrocephalus, cranial nerve deficits)
- Obliterative vasculitis (strokes)
- Encephalitis/myelitis (reduced consciousness)





Figaji & Fieggen (2013) World Neurosurgery



Pediatric TB meningitis:
What does TBM do to the developing brain?

- Data are sparse: Cognitive and gross motor impairment, Behavioral difficulties, Emotional problems
  - Stage II and III TBM (N=554)
    - 6 months after treatment 58% with IQ deficit 50-80, 20% IQ deficit < 50

    Van Well (2009) Pediatrics
  - Stage I-III TBM (N=123 children, ages 12-56 months)
    - 6-9 months after treatment, mild intellectual handicap 38% severe 25%
  - Stage II and III TBM (N=74)
    - Behavioural disinhibitions as well as internalized emotional disorder

    Wait (2010) J Trop Ped

Long-term neurocognitive outcomes, impact on functioning in society not well characterized

Questions:

Science

- Is the disease *different* in children and adults
  - Pathophysiology, location of bacilli, outcomes?
- What, then, are we asking of our treatment?
  - Rapid kill, stop protein synthesis, kill ‘persisters’, prevent acquired resistance?
- How do we optimize drug delivery to sites of disease/construct a regimen?
  - Pick best CNS Multiparameter Optimization desirability score, IV formulation, hit hard early (prevent mortality), hit hard late (when BBB healed), intensive/continuation phase?
- Which drugs have highest likelihood of providing benefit? What outcomes are we interested in?
- Are there biomarkers that correlate with outcomes, Rx response?

Questions:

Logistics

- Whom to (pre)screen?
- Does the ‘research definition’ of probable TB work? Will Gene Xpert Ultra help?
- Drug doses across age/weight spectrum, formulations
- Is safety of drugs uniform across spectrum of disease? Handling stop/restart
- Is it remotely possible to enlarge a large pediatric TBM trial?

Treatment: Current “SOC”

Do TB Drugs get to the site of infection?

WHO recommends 2HRZE/10HR with R dose of 10-20 mg/kg for TBM

Drug	CSF:serum ratio*
Isoniazid	0.8-1.0
Rifampicin	0.04-0.11
Pyrazinamide	0.79-1.05
Ethambutol	Negligible (<MIC even with meningitis)
Ethionamide	Good
Fluoroquinolones	0.7-0.8

Pediatric TBM: What is SOC? (*it depends*)

	Drugs*	Rifampin dose	Frequency	Duration
Malawi	2HRZ**S**/10HR	10-17 mg/kg	Daily	12 months
India	$2H_3R_3Z_3\mathbf{E}_3$ (or HRZ**S**)/$10H_3R_3$	10-17 mg/kg	Thrice-weekly†	12 months
S Africa	6HRZ**Eth**	20 mg/kg	Daily	6 months
WHO	2HRZ**E**/10HR§	10-20 mg/kg	Daily	12 months

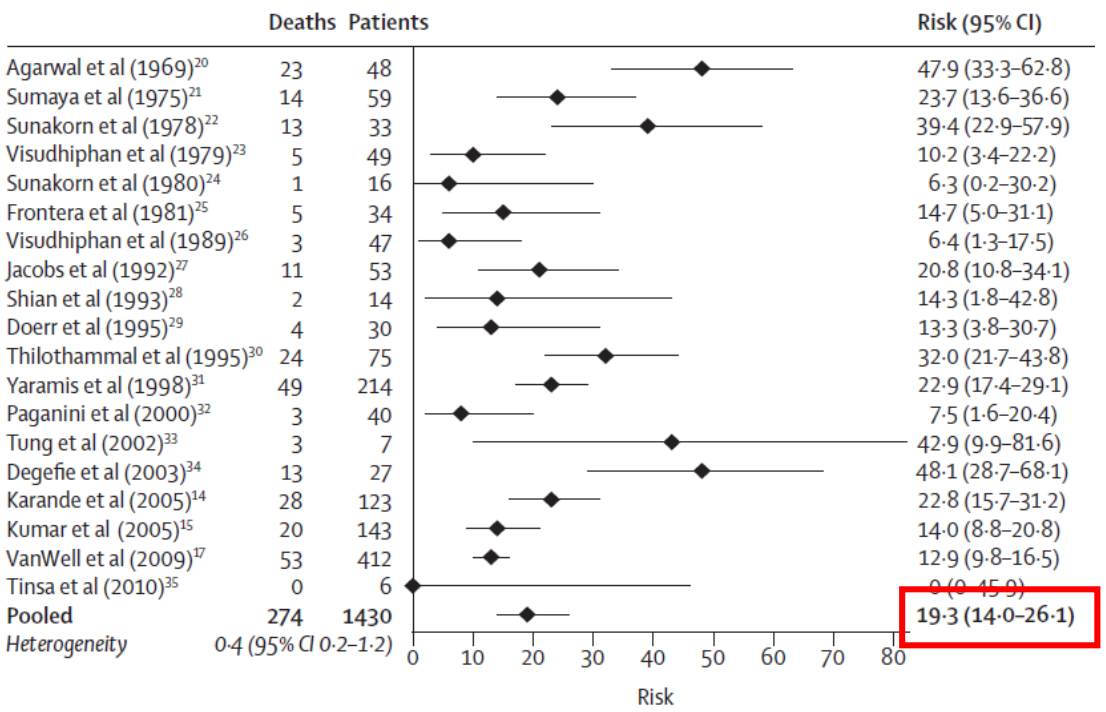
*Steroids (2 mg/kg/day prednisone or equivalent) are SOC everywhere
§Strong recommendation, low quality of evidence
†Changing to daily

Pediatric TBM: Treatment Outcomes

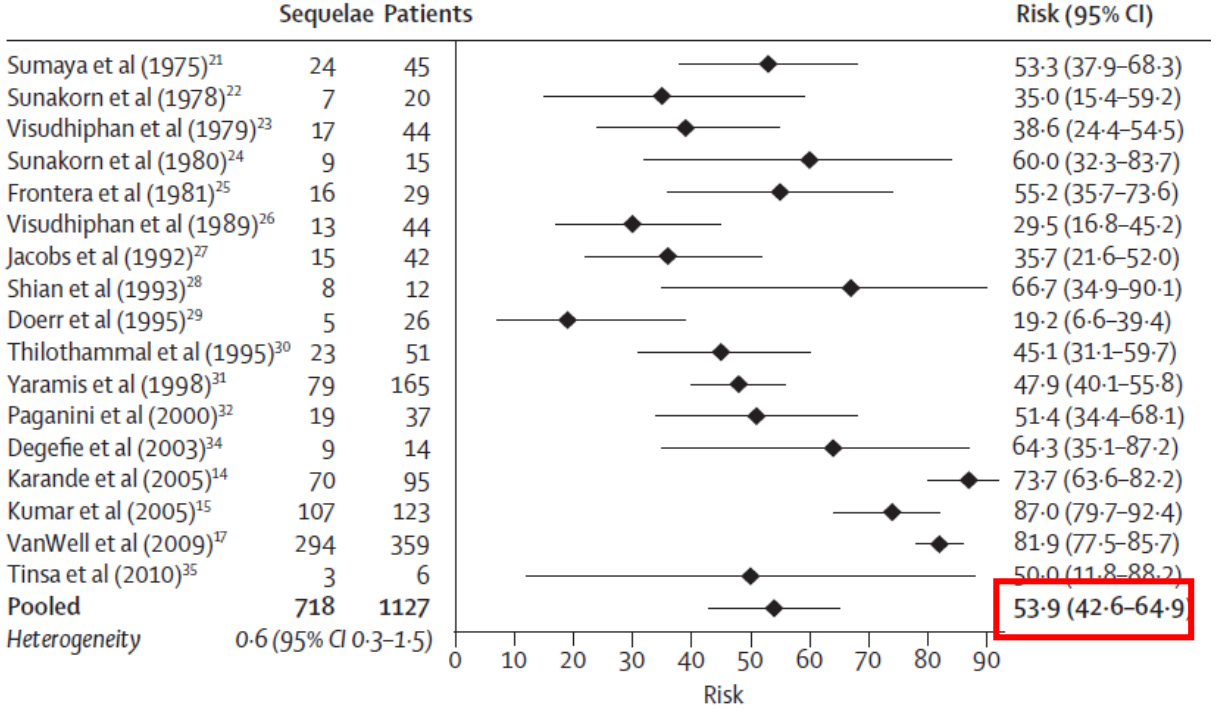
Treatment outcomes of childhood tuberculous meningitis: a systematic review and meta-analysis

Silvia S Chiang, Faiz Ahmad Khan*, Meredith B Milstein, Arielle W Tolman, Andrea Benedetti, Jeffrey R Starke, Mercedes C Becerra*

A Risk of death



B Risk of neurological sequelae among survivors



27 Different Regimens, no RCT

Lancet ID 2014

Revised WHO dosing for children-

Are we achieving target plasma concentrations?

Drug	Revised dose	2-hour target	Mean concentration	% achieving target
Isoniazid	10-15 mg/kg	3 mcg/mL	4.5 mcg/mL	65%
Rifampicin	10-15 mg/kg	8 mcg/mL	2.9 mcg/mL	6%
Pyrazinamide	30-40 mg/kg	20 mcg/mL	23 mcg/mL	55%
Ethambutol	15-25 mg/kg	2 mcg/mL	1.1 mcg/mL	15%

PHATISA Study (n=23, Durban, SA): Hiruy et al JAC doi:10.1093/jac/dku478

TBM: Rifampin prevents death

Long-term Mortality of Patients With Tuberculous Meningitis in New York City: A Cohort Study

Christopher Vinnard,[1] Liza King,[2] Sonal Munsiff,[3] Aldo Crossa,[2] Kentaro Iwata,[4] Jotam Pasipanodya,[5] Douglas Proops,[2] and Shama Ahuja[2]

[1]Public Health Research Institute, New Jersey Medical School, Newark, New Jersey, [2]New York City Department of Health and Mental Hygiene, Bureau of Tuberculosis Control, Queens, and [3]University of Rochester School of Medicine and Dentistry, New York; [4]Division of Infectious Disease Therapeutics, Kobe University, Japan; and [5]Center for Infectious Disease Research and Experimental Therapeutics, Baylor University, Dallas, Texas

Results. Among 257 TBM patients without rifampin-resistant isolates, isoniazid resistance was associated with mortality after the first 60 days of treatment when controlling for age and HIV infection (adjusted hazard ratio, 1.94 [95% confidence interval, 1.08–3.94]). Death occurred before completion of antituberculosis therapy in 63 of 67 TBM patients (94%) with rifampin-resistant disease.

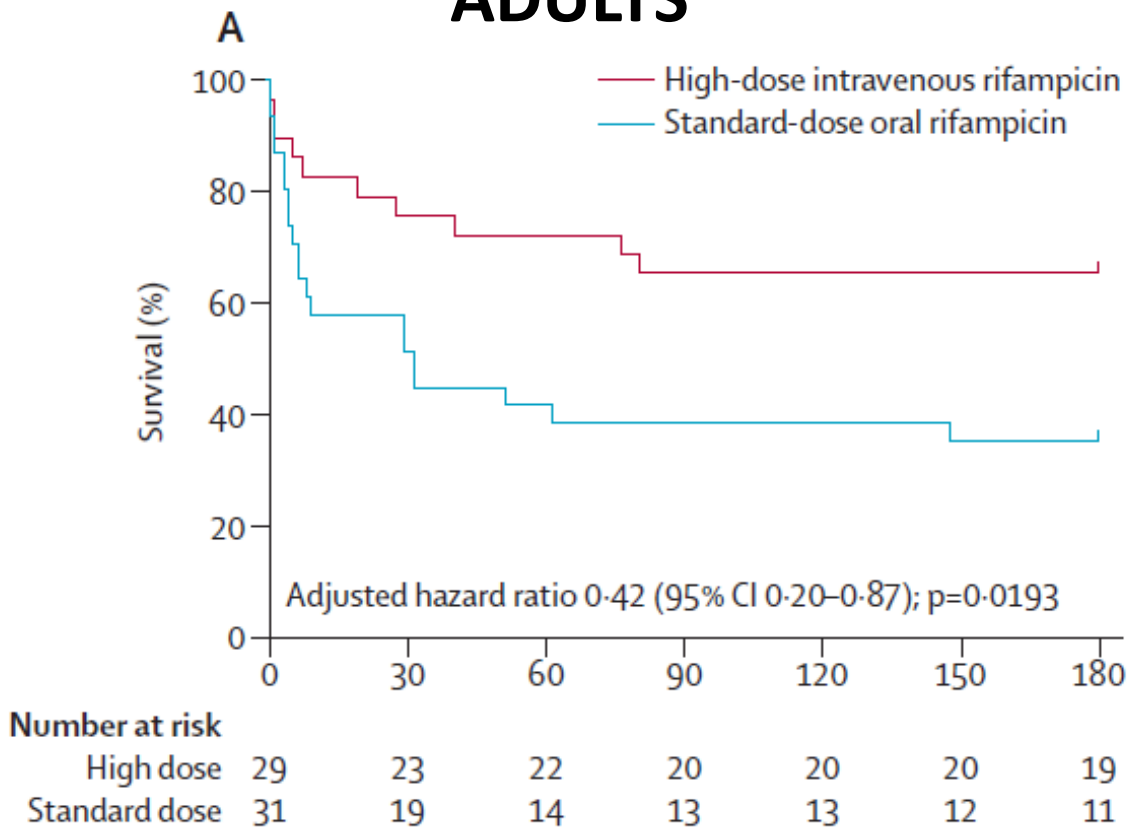
See also Tho et al AAC 2012 HIV-associated TBM.
INH resistance increased risk death 1.78-fold MDR-TBM uniformly fatal

CID 2017

Can we do better?

Improving *antimicrobial treatment* for TBM:
Higher-dose IV rifampin in adults

ADULTS



	Deaths	Univariable	Multivariable
Oral rifampicin 450 mg (n=31)	20 (65%)	1·00	1·00
Intravenous rifampicin 600 mg (n=29)	10 (34%)	0·42 (0·20–0·91)†	0·42 (0·20–0·91)†
No moxifloxacin (n=22)	10 (45%)	1·00	1·00
Moxifloxacin 400 mg (n=19)	8 (42%)	0·74 (0·29–1·89)§	0·76 (0·30–1·94)§
Moxifloxacin 800 mg (n=19)	12 (63%)	1·40 (0·60–3·25)§	1·27 (0·53–3·02)§
HIV positive (n=7)	4 (57%)	..	1·80 (0·59–5·53)
Glasgow Coma Scale at baseline	..	..	0·82 (0·68–0·99)

	600 mg, intravenous (n=26)	450 mg, oral (n=26)
Plasma		
AUC_{0-6} (mg.h/L)	78·7 (71·0–87·3)	26·0 (19·0–35·6)
C_{max} (mg/L)	22·1 (19·9–24·6)	6·3 (4·9–8·3)
C_{max} (≥8 mg/L)	26 (100%)	13 (50%)
T_{max} (h; median, range)	2 (1– 2)	2 (1–6)
CSF		
C_{max} (mg/L)§	0·60 (0·46–0·78)	0·21 (0·16–0·27)

n.b. MIC for RIF against MTB: 0.25

Rx for 14 days

Ruslami *et al.* (2013) Lancet ID 13: 27.

Drug-Sensitive pulmonary TB:
The Role of Individual Drugs

INH:	Early **bactericidal** activity, rapid reduction in organism burden
Rifampin:	Unique **sterilizing** activity against "persisters", key contributor to cure without relapse
Pyrazinamide:	Sterilizing activity in **acidic environments** over the first 2 months, allowing for shortening of treatment
Ethambutol:	**Prevents resistance** to other antibiotics

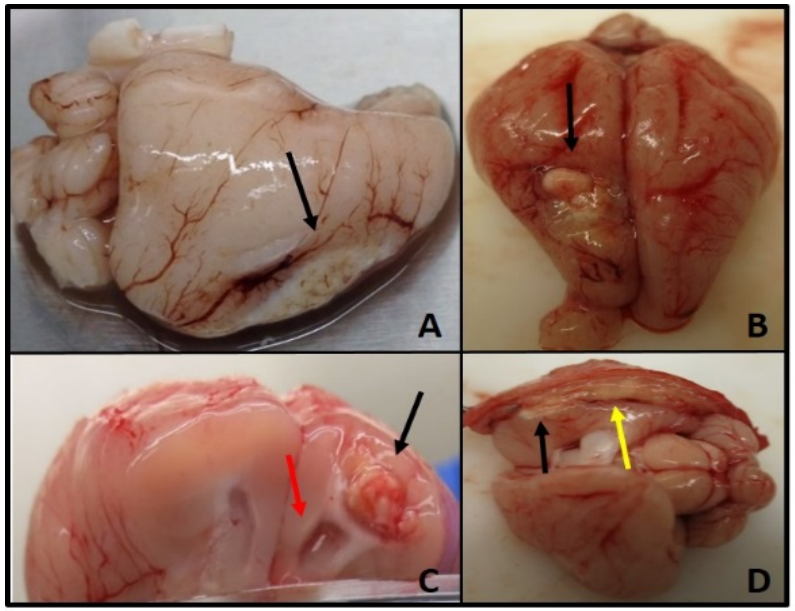
Drugs that may help

Drug	Supportive evidence	Pediatric gaps
Linezolid	CSF:plasma AUC ratio of 0.77 Faster GCS recovery with this drug in one study	PK-toxicity
Levofloxacin	Effective in INH-R TB in Vietnam trial	Dose, PK-safety
High-dose/IV rifampicin	13 mg/kg IV (=25-30 mg/kg PO) Indonesia	Formulation, dose by age/weight
Ethionamide	Stellenbosch experience	
Cycloserine	It makes you crazy	
Aminoglycosides	Good CSF levels when BBB inflamed	

Absence/paucity of data

Rifabutin, delamanid, (bedaquiline), clofazimine, pretomanid, sutezolid…

CNS-TB: How about animal model testing first?



Tucker *et al.*
Dis Model Mech 2016

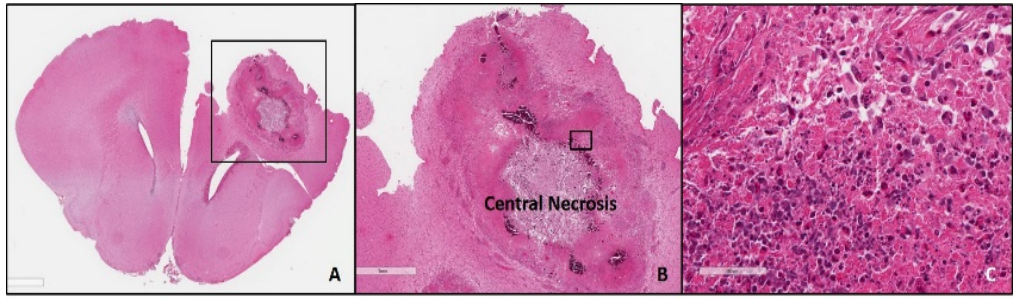


Fig. 2 Tuberculoma from Fig. 1C. H&E stain of brain section, 5µm. **A:** 10x magnification showing localization of tuberculoma to one hemisphere. Large black box around tubercuoma magnified to 20x in **(B)**. **B:** Central necrosis of tuberculoma with small black box at rim magnified to 40x in **(C)**. **C:** Dense cellular rim of tuberculoma.

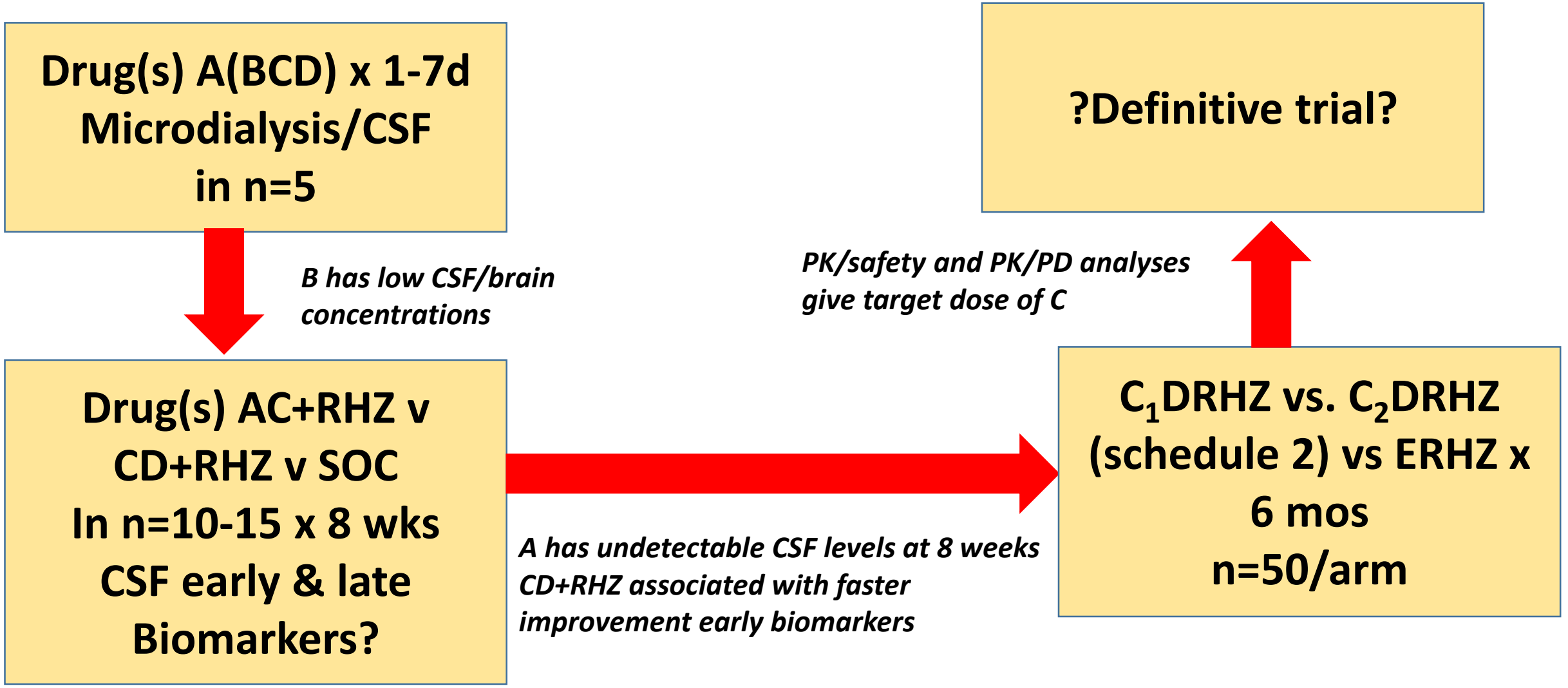
Drug concentrations plasma ≠ lumbar CSF ≠ ventricular CSF ≠ brain

	Patient 1
Plasma 2h	25000 ng/ml
Plasma 4h	10000 ng/ml
CSF (V) 4h	1250 ng/ml
MD Fluid 2h	220 ng/ml
MD Fluid 4h	150 ng/ml

	Rabbit 1
Plasma 1h	2540 ng/ml
Plasma 2h	1750 ng/ml
Plasma 5h	290 ng/ml
CSF (V) 5h	BLQ
brain 5h	29 ng/g

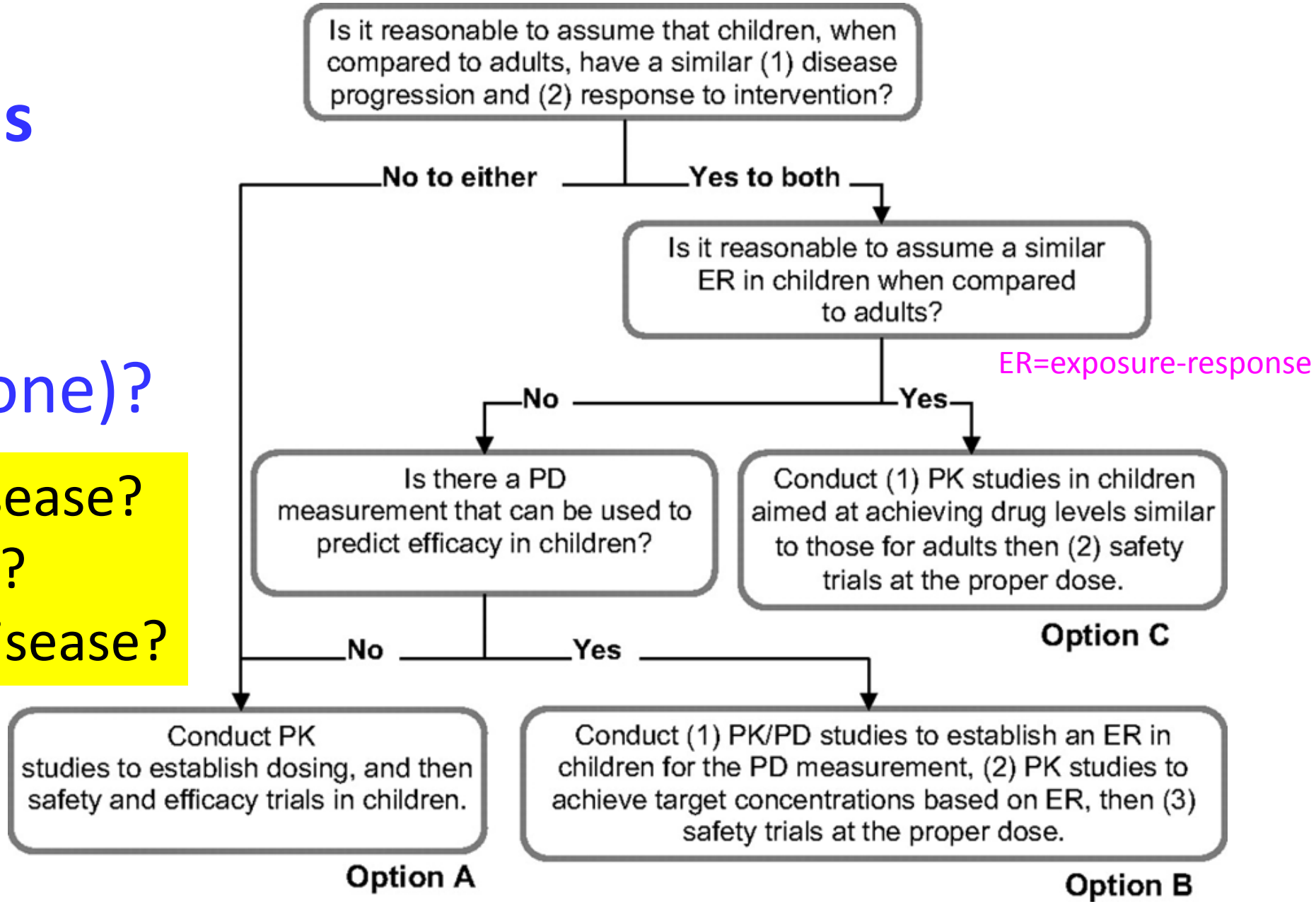
Figaji, Tucker, unpublished

Or, at the very least, staged, step-wise testing
(ABCD hypothetical drugs, made-up scenarios)



When are **efficacy trials** required for children (vs. PK/safety alone)?

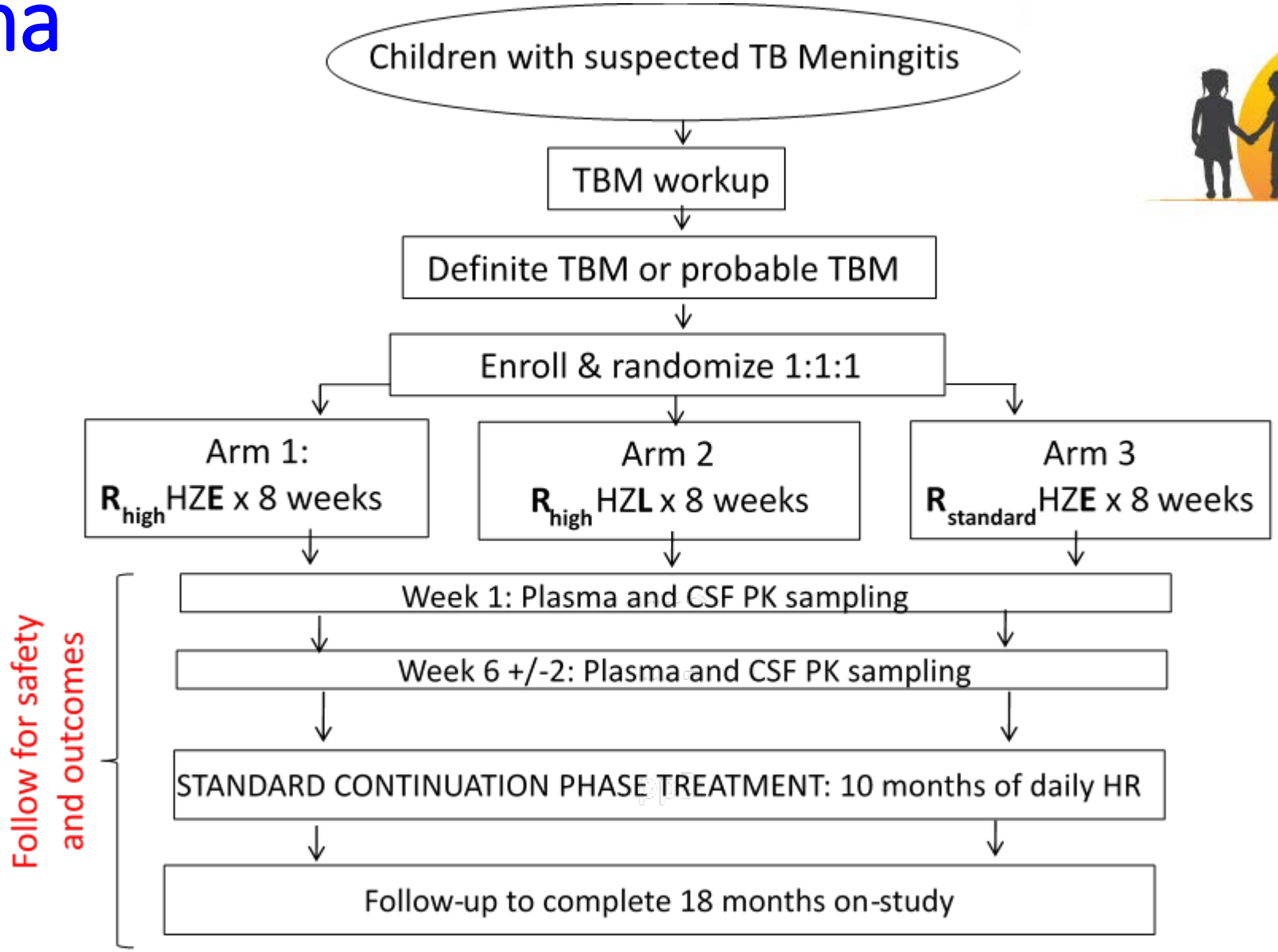
Non-severe disease?
Severe disease?
LTBI-> active disease?



Slide, modified, from FDA

Why this is very challenging

Schema


Children with suspected TB Meningitis
TBM workup
Definite TBM or probable TBM
Enroll & randomize 1:1:1
Arm 1:
R_{high}HZE x 8 weeks
Arm 2
R_{high}HZL x 8 weeks
Arm 3
$R_{standard}$HZE x 8 weeks
Week 1: Plasma and CSF PK sampling
Week 6 +/-2: Plasma and CSF PK sampling
STANDARD CONTINUATION PHASE TREATMENT: 10 months of daily HR
Follow-up to complete 18 months on-study
Follow for safety and outcomes

Dosing/formulation

Arm 2: $R_{hi}HZL$

R= 30 mg/kg

H= 10 (7-15) mg/kg

Z= 35 (30-40) mg/kg

L= 15 mg/kg (<2yo)

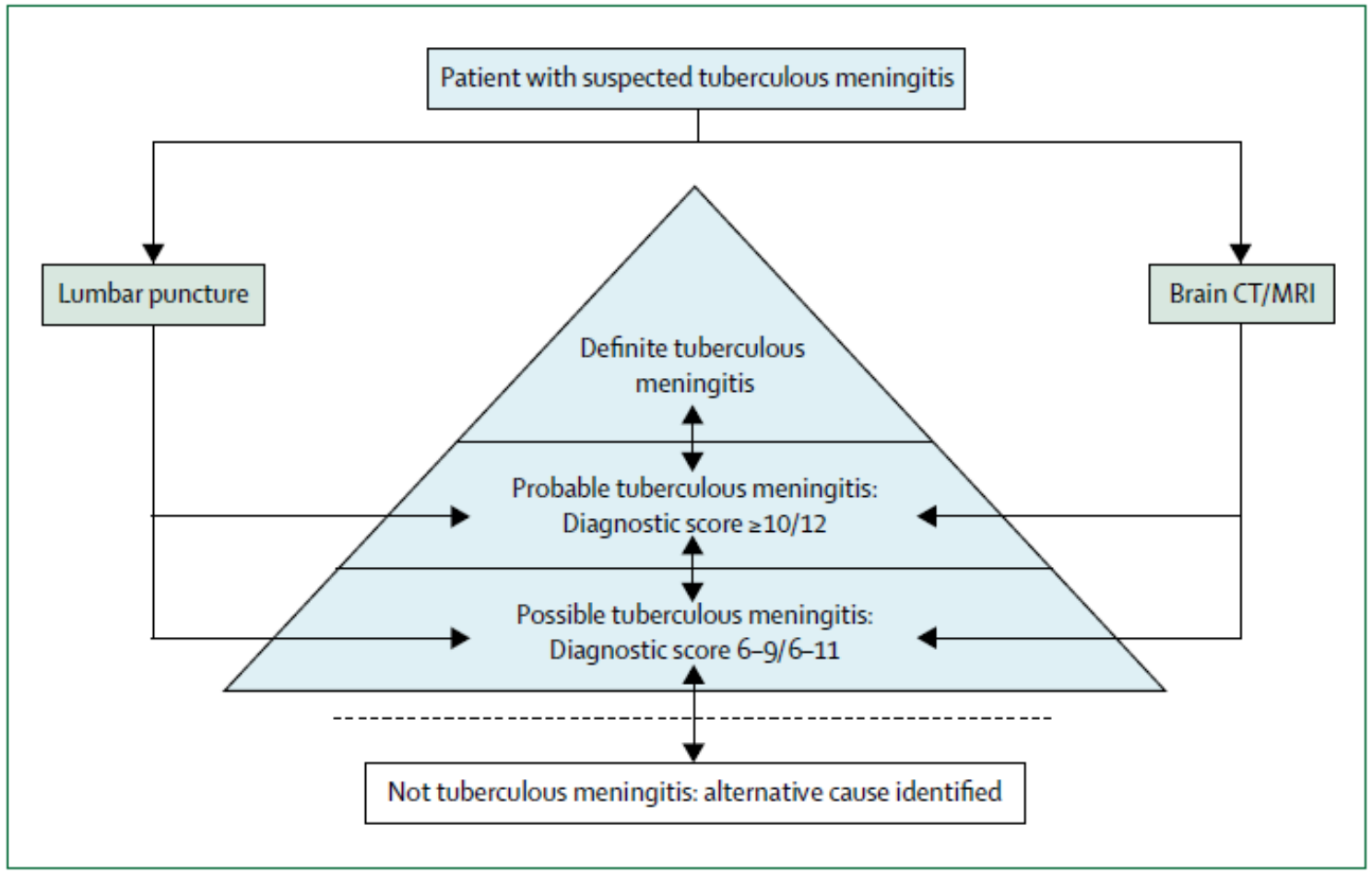
20 mg/kg (>2yo)

RHZ FDC ratio: 75/50/150

FDC PLUS Rifampicin 20mg/mL suspension used to supplement						
weight in kg	Dose @ 30mg/kg	Desired dose in mg	FTC provides in mg	Additional mg needed	suspension 20mg/mL	#mL required
7	30	210	75	135	20	6.8
8	30	240	150	90	20	4.5
9	30	270	150	120	20	6.0
10	30	300	150	150	20	7.5

This is just one of the four drugs….

Consensus research definition



"Probable TB" could reasonably be used for clinical trials, but reduced sensitivity for Stage I TBM may be a concern

Points based on:

- Clinical criteria
- CSF criteria
- Cerebral imaging criteria
- Evidence of TB elsewhere
- Exclusion of alternative diagnoses

How does it perform?

- "Probable TB" sensitivity 86%, spec 100% for culture-confirmed TBM
- "Possible TB" sensitivity 100%, specificity 56%

Marais *et al.* (2010) Lancet ID; Solomons (2014) CID (n=254)

Total children admitted to SGH and underwent CSF (23rd Feb 2017-18th May 2017) = 83

Reasons for not prescreening (A-B = 33)

1. *Age < 6 months = 13*
2. *Weight < 6 kg = 6*
3. *Febrile seizures/known seizure disorder with history not suggestive of TBM = 11*
4. *Received > 7 days of AKT in past 30 days = 2*
5. *Death soon after admission prior to CSF= 1*

Prescreened (CSF collected as a study procedure) = 50

Reasons for not screening (Prescreen failure, B-C = 47)

1. *Meningitis ruled out on CSF = 31*
   a) *Seizure disorder/ Febrile convulsion = 9*
   b) *Metabolic disease = 1*
   c) *Hypo calcemic seizure = 1*
   d) *Hepatic Encephalopathy = 1*
   e) *Other febrile illnesses = 19*
2. *Meningitis but TBM ruled out = 12*
   a) *Viral meningoencephalitis = 9*
   b) *Bacterial meningitis = 2*
   c) *Brain abcess = 1*
3. *Suspected TBM but death before confirmation = 2*
4. *Family was planning to migrate out of state = 1 (AFB smear and genexpert negative, but MGIT later showed confirmed TBM after 2 weeks of AKT)*
5. *Age > 12 years (confirmed after prescreening) = 1*

Screened (Full study consenting and screening procedures apart from CSF) = 3

Reasons for non-enrollment (Screen failure, C-D= 1)

1. *Discharge against advice followed by death = 1*

Enrolled in the study = 2
(Both are diagnosed as probable meningitis)

One site's experience…

Managing toxicity

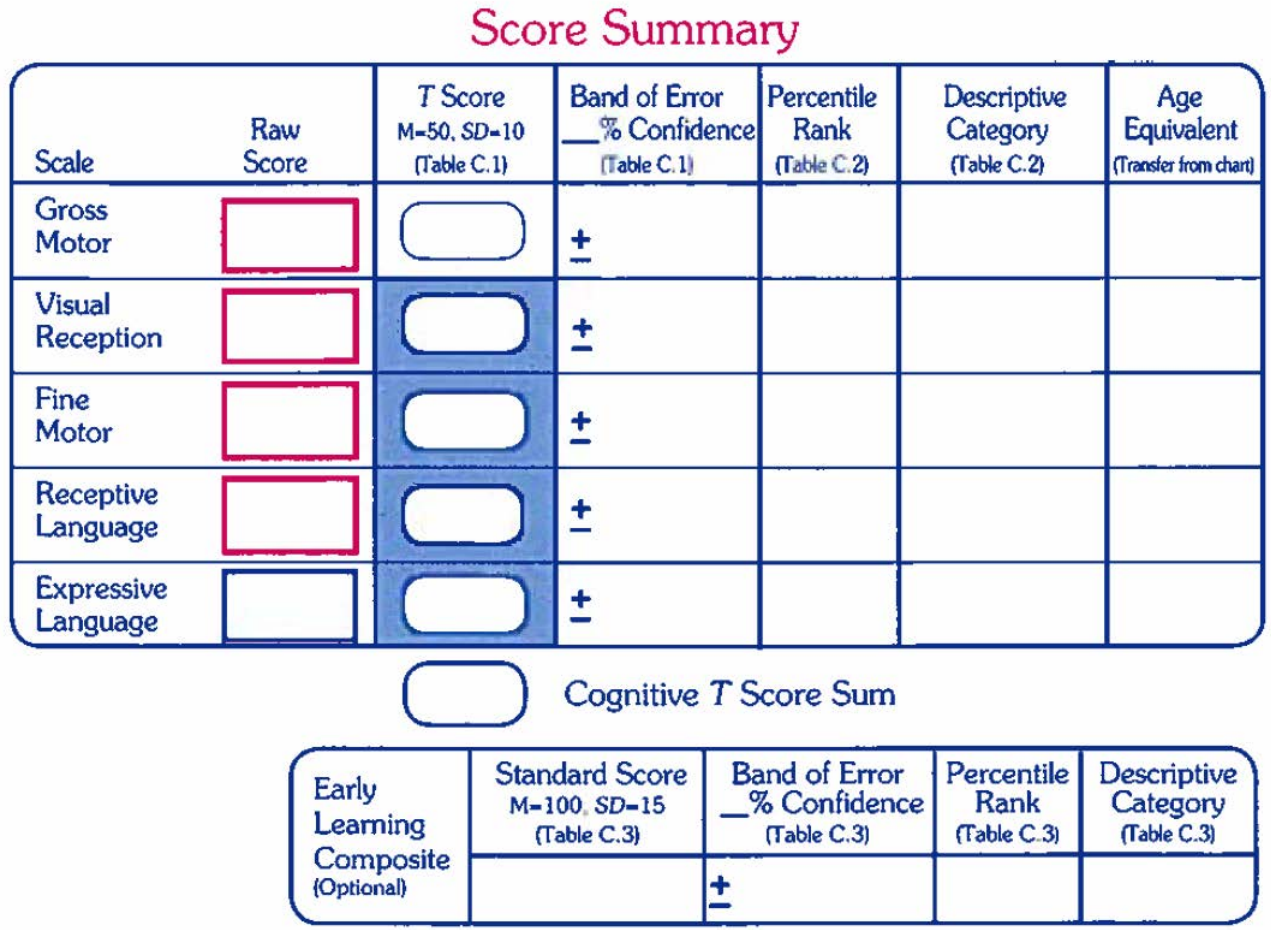
- Some scenarios
- How then to analyze the data

Resources (to share)

Measuring *functional* outcomes: Modified Rankin Scale for children

Score	Description
0	No symptoms at all
1	No significant disabilities despite symptoms in clinical examination; age appropriate behaviour and further development
2	Slight disability; unable to carry out all previous activities, but same independence as other age- and sex-matched children (no reduction of levels on the gross motor function scale)
3	Moderate disability; requiring some help, but able to walk without assistance; in younger patients adequate motor development despite mild functional impairment (reduction of one level on the gross motor function scale)
4	Moderately severe disability; unable to walk without assistance; in younger patients reduction of at least 2 levels on the gross motor function scale
5	Severe disability; bedridden, requiring constant nursing care and attention
6	Dead

Measuring *neurocognitive* outcomes:
Mullen Scales of Early Learning



Score Summary

Scale	Raw Score	*T* Score M=50, *SD*=10 (Table C.1)	Band of Error __% Confidence (Table C.1)	Percentile Rank (Table C.2)	Descriptive Category (Table C.2)	Age Equivalent (Transfer from chart)
Gross Motor			±			
Visual Reception			±			
Fine Motor			±			
Receptive Language			±			
Expressive Language			±			

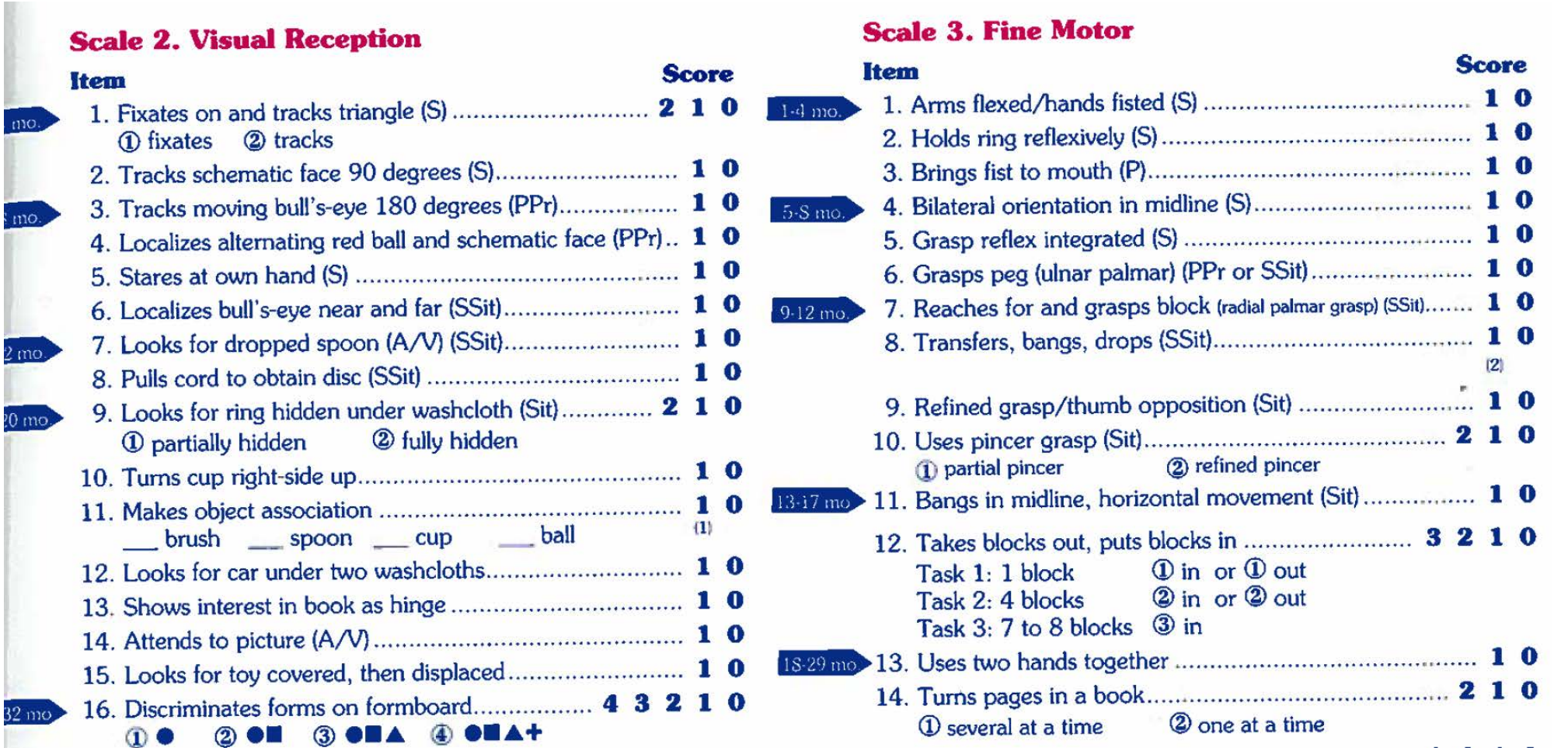
Cognitive *T* Score Sum

Early Learning Composite (Optional)	Standard Score M=100, *SD*=15 (Table C.3)	Band of Error __% Confidence (Table C.3)	Percentile Rank (Table C.3)	Descriptive Category (Table C.3)
		±		

Challenges:

- "Cultural fairness"
- Language
- Validation
- Very ill children
- Training
- Age range

Measuring *neurocognitive* outcomes:
Mullen Scales of Early Learning



Scale 2. Visual Reception

	Item	Score
mo.	1. Fixates on and tracks triangle (S) ① fixates ② tracks	2 1 0
	2. Tracks schematic face 90 degrees (S)	1 0
mo.	3. Tracks moving bull's-eye 180 degrees (PPr)	1 0
	4. Localizes alternating red ball and schematic face (PPr)	1 0
	5. Stares at own hand (S)	1 0
	6. Localizes bull's-eye near and far (SSit)	1 0
2 mo.	7. Looks for dropped spoon (A/V) (SSit)	1 0
	8. Pulls cord to obtain disc (SSit)	1 0
20 mo.	9. Looks for ring hidden under washcloth (Sit) ① partially hidden ② fully hidden	2 1 0
	10. Turns cup right-side up	1 0
	11. Makes object association ___ brush ___ spoon ___ cup ___ ball (1)	1 0
	12. Looks for car under two washcloths	1 0
	13. Shows interest in book as hinge	1 0
	14. Attends to picture (A/V)	1 0
	15. Looks for toy covered, then displaced	1 0
32 mo	16. Discriminates forms on formboard ① ● ② ●■ ③ ●■▲ ④ ●■▲+	4 3 2 1 0

Scale 3. Fine Motor

	Item	Score
1-4 mo.	1. Arms flexed/hands fisted (S)	1 0
	2. Holds ring reflexively (S)	1 0
	3. Brings fist to mouth (P)	1 0
5-8 mo.	4. Bilateral orientation in midline (S)	1 0
	5. Grasp reflex integrated (S)	1 0
	6. Grasps peg (ulnar palmar) (PPr or SSit)	1 0
9-12 mo.	7. Reaches for and grasps block (radial palmar grasp) (SSit)	1 0
	8. Transfers, bangs, drops (SSit) (2)	1 0
	9. Refined grasp/thumb opposition (Sit)	1 0
	10. Uses pincer grasp (Sit) ① partial pincer ② refined pincer	2 1 0
13-17 mo	11. Bangs in midline, horizontal movement (Sit)	1 0
	12. Takes blocks out, puts blocks in Task 1: 1 block ① in or ① out Task 2: 4 blocks ② in or ② out Task 3: 7 to 8 blocks ③ in	3 2 1 0
18-29 mo	13. Uses two hands together	1 0
	14. Turns pages in a book ① several at a time ② one at a time	2 1 0

Returning to Key Unanswered Questions:

- Is the disease *different* in children and adults?
  - Pathophysiology, location of bacilli, outcomes?
- Can Gene Xpert Ultra improve diagnostic accuracy in children?
- What are we asking of our treatment?
  - Rapid kill, stop protein synthesis, kill 'persisters', prevent acquired resistance?
- How can we use animal models and data from adult trials to derive most promising therapies to test in children?
- How do we optimize drug delivery to sites of disease/construct a regimen?
  - Pick best CNS Multiparameter Optimization desirability score, IV formulation, hit hard early (prevent mortality), hit hard late (when BBB healed), intensive/continuation phase?
- Are extent and rate of delivery into brain/CSF same across the age continuum?
- Which drugs have highest likelihood of providing benefit?
- Are there (CSF) biomarkers that can be used on trial level to discriminate among regimens?
- Can better antimicrobial therapy improve: mortality, functional outcome, neurocognitive outcomes?

Thank you.

TBM KIDS

NICHD: R01HD0774944

Collaborative team

- Johns Hopkins University — Baltimore, USA
- BJ Government Medical College (BJMC) — Pune, India
  - Sassoon General Hospital
- National Institute for Research in Tuberculosis — Chennai, India
  - Institute of Child Health (ICH)
- UNC/Project Malawi — Lilongwe, Malawi
  - Kamuzu Central Hospital
- University of California at San Francisco (UCSF) — San Francisco, USA
- University of Cape Town (UCT) analytical lab — Cape Town, S. Africa