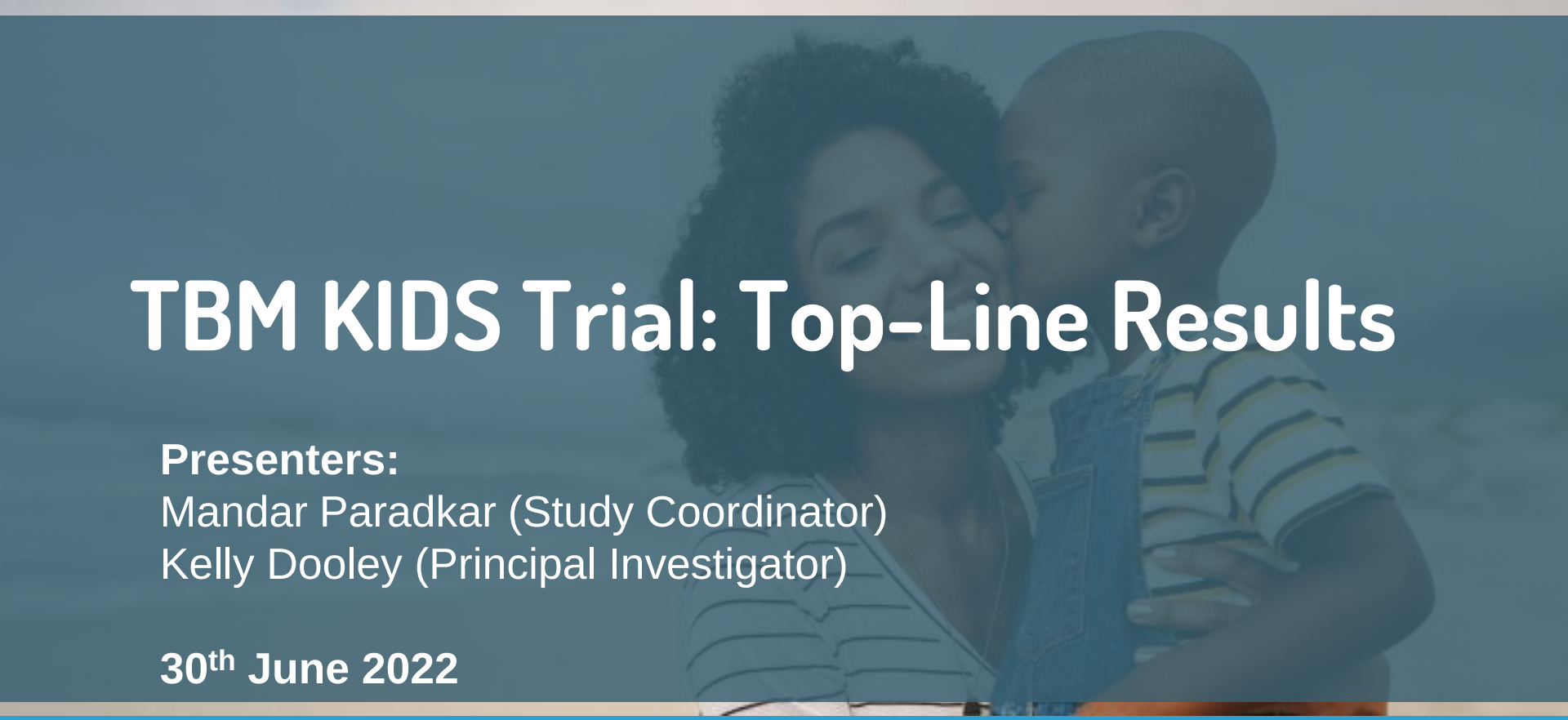

TBM KIDS Trial: Top-Line Results

Presenters:
Mandar Paradkar (Study Coordinator)
Kelly Dooley (Principal Investigator)

30th June 2022

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2

Clin Infect Dis. 2022 Mar 15;ciac208. doi: 10.1093/cid/ciac208. Online ahead of print.

Randomized Clinical Trial of High Dose Rifampicin with or without Levofloxacin versus Standard of Care for Paediatric Tuberculous Meningitis: The TBM-KIDS Trial

Mandar S Paradkar [1 2], D Bella Devaleenal [3], Tisungane Mvalo [4 5], Ana Arenivas [6], Kiran T Thakur [7], Lisa Wolf [8], Smita Nimkar [1 2], Sadaf Inamdar [1 2], Prathiksha Giridharan [3], Elilarasi Selladurai [9], Aarti Kinikar [1 10], Chhaya Valvi [1 10], Saltanat Khwaja [1 2], Daphne Gadama [4], Sarath Balaji [3], Krishna Yadav Kattagoni [3], Mythily Venkatesan [3], Radojka Savic [11], Soumya Swaminathan [12], Amita Gupta [8], Nikhil Gupte [1 2 8], Vidya Mave [1 2 8], Kelly E Dooley [8], TBM-KIDS Study Team

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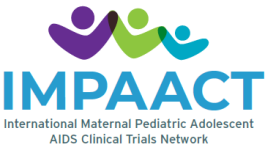
INTRODUCTION



Introduction

Children are at higher risk of disseminated/severe TB, especially TBM

Neurocognitive function may be affected (unique to children)

TBM regimens are based on drugs (& doses) effective for pulmonary TB but may have low penetration into brain and CSF (EMB, SM, RIF)

Adjusting dose or regimen composition can improve delivery of drug to site of disease and improve outcomes (in adults)

Modeling work to derive drug doses for children that would achieve target exposures associated with better TBM treatment response in adults.

TBM-KIDS was designed as the first randomized clinical trial of anti-microbial regimens for pediatric TBM

Savic RM et al. Clinical Pharmacology & Therapeutics. 2015

Objectives

- **Primary objective**
  - Assess the safety and pharmacokinetics (PK- plasma and CSF) of model-optimized doses of rifampicin with or without levofloxacin given to children as part of multidrug treatment for TBM

- **Secondary Objectives**
  - Effect of rifampicin concentrations on functional outcomes (Modified Rankin Scale)
  - Longitudinal neurocognitive outcomes (Mullen Scales of Early Learning)

METHODS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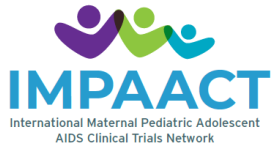
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Eligibility Criteria

Inclusion Criteria

- Weight ≥ 6 kg
- Age 6 months to 12 years
- Possible/Probable/definite TBM
- Consent of parent/guardian
- Can comply with study requirements

Exclusion Criteria

- TB treatment for > 10 days
- Exposure to or history of MDR-TB
- Intolerance/allergy to study drugs
- Death imminent within 24h
- Moderate to severe renal/liver dysfunction (Gr2 ALT, direct bili, Cr)
- HIV and taking PI or NVP
- Other trials in last 8 weeks
- Clinically important, active co morbid medical problem that would make participation undesirable

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Methodology

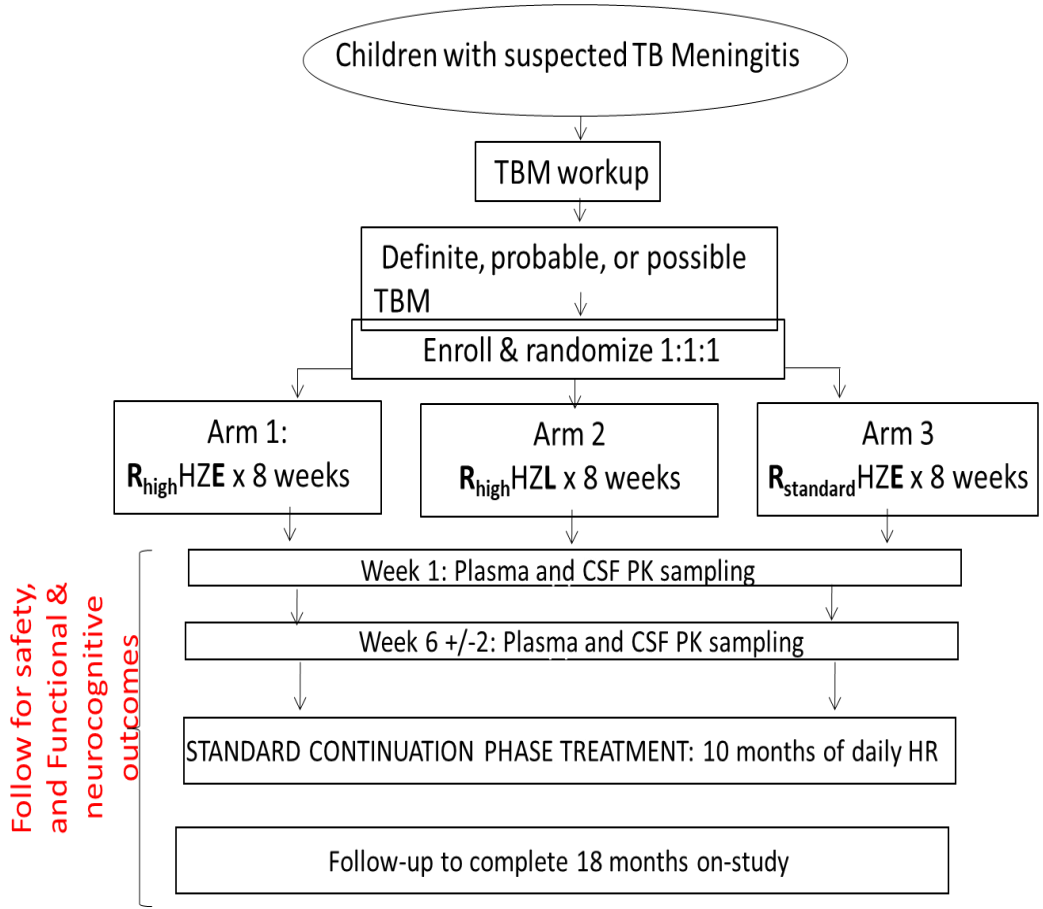
- **Design**: Phase I/II, open label PK, safety, efficacy in children with TBM

Sadaf Afrin

- **Study regimen**
  - Arm 1: high-dose RIF (R30HZE)
  - Arm 2: high-dose RIF plus levofloxacin (R30HZL)
  - Arm 3: standard WHO regimen (R15HZE)

- **Duration:** 12 months (2 months experimental treatment, then 10 months std. treatment)

Study flow chart



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Schedule of Evaluations

Week	Screen	Entry	Week 1 (+/-3 days)	Week 2 (+/- 2 days)	Week 4 (+/- 1 week)	Week 8 (+/- 1 week)	Week 16 (+/- 1 week)	Week 24 (+/- 2 weeks)	Week 36 (+/- 2 weeks)	Week 48 (+/- 2 weeks)	Week 72 (+/- 2 wk)
Month		**1**				**2**	**4**	**6**	**9**	**12[1]**	**18**
CLINICAL EVALUATIONS											
Staging of disease severity[3]		X									
Neurologic/functional status[3]		X				X		X		X	
Neurocognitive evaluation[3]		X				X				X	X
LABORATORY EVALUATIONS											
Hematology	X		X	X	X	X[4]					
Chemistries, including LFTs	X		X	X	X	X[4]					
TB diagnostics											
Chest X ray	X										
Head CT or MRI	X										
Lumbar puncture (protein, cell count differential, glucose)	X		X		X[5]						
CSF for gram stain, culture, GXP	X				X						
Pharmacology											
Intensive PK[9], plasma			X		X						
Sparse PK[9], plasma				X	X	X	X				
Sparse sampling PK[10], CSF			X		X						
DBS for INH acetylator status					X[11]						
Whole blood for LTA4H genotype			X[11]								
Specimen for storage											
Plasma		X		X		X					
Whole blood		X		X		X					
CSF[12]		X	X		X						

Neurologic Evaluations

- **Neurological and functional outcomes**
  - Modified Rankin Scale for disability assessment
    - Grade 0-6
    - Entry, 8 weeks, 24 weeks and 52 weeks

Kiran Thakur

- **Neurocognitive Assessment**
  - Mullen Scale of Early Learning
    - Children From 6 months to 6 years of age
    - Gross Motor, Fine Motor, Visual Reception, Receptive Language and Expressive Language
      Entry, Week 8, Week 52

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Smita Nimkar et al. , *Journal of Tropical Pediatrics*, 2021,

Modified Rankin Score

Score	Meaning
0	No symptoms
1	No significant disability, despite symptoms, able to perform all duties and activities
2	Slight disability; Unable to perform all previous activities but able to look after own affairs without assistance
3	Moderate disability; requires some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent, and requires constant nursing care and attention
6	Death

RESULTS


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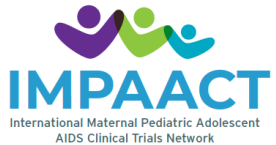
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TBM KIDS Trial Sites

March 2017 – December 2019

Pune, India
Chennai, India
Lilongwe, Malawi
Baltimore, USA

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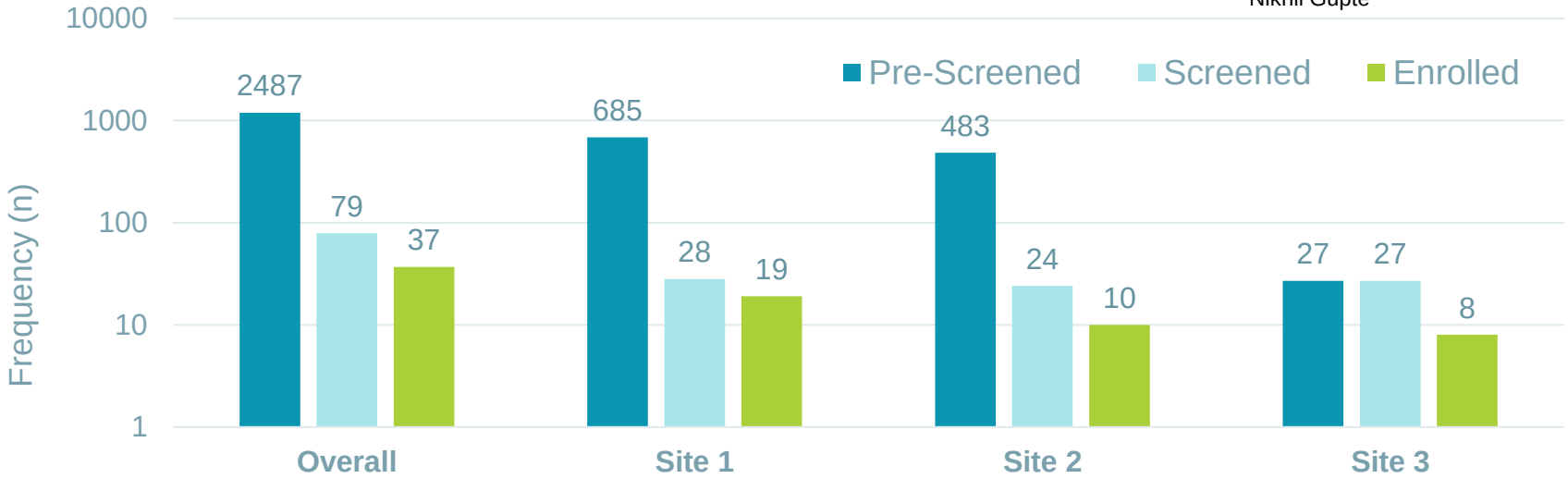
Recruitment

Nikhil Gupte



Mandar Paradkar

Bella Devaleenal D.

Tisungane Mvalo

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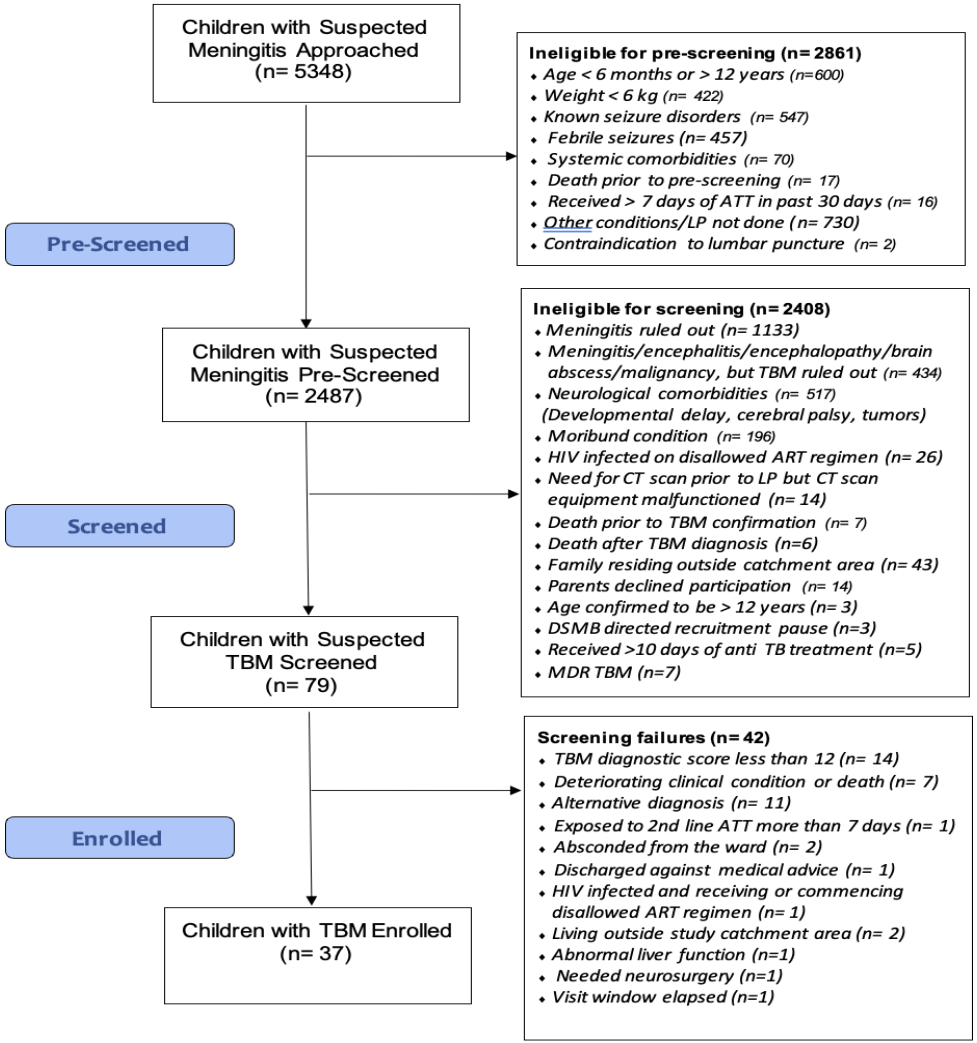
Consort Diagram



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Baseline Characteristics

Baseline characteristics	Overall N = 37	Arm R_{high}HZE 12	Arm R_{high}HZL 11	Arm R_{std}HZE 14
Age (mo), Median (IQR)	72 (22 -98)	56 (16 – 100)	57 (29 – 125)	72 (22 – 91)
Female, n (%)	14 (38%)	4 (33%)	5 (45%)	5 (36%)
Weight (kg), Median (IQR)	11 (6.9 – 21.0)	18.1 (10.4 – 22.0)	11.0 (1.0 – 21.0)	8.7 (6.9 – 20.0)
Head CT				
Normal	7 (19%)	3 (25%)	1 (9%)	3 (21%)
Abnormal	26 (70%)	7 (58%)	10 (91%)	9 (64%)
Not Done	4 (11%)	2 (17%)	0	2 (14%)
CSF lab tests				
WBC	59 (7 – 140)	99 (6 – 360)	35 (0 – 68)	70 (20 - 140)
Lymphocytes	85 (25 – 98)	90 (65 – 97)	57 (40 – 90)	75 (25 – 98)
Glucose	45 (25 – 68)	45 (19 – 68)	38 (25 – 70)	49 (25 – 68)
Total Protein	109 (48 – 211)	131 (62 – 311)	90 (50 – 152)	105 (38 – 141)
Baseline Modified Rankin	3 (1 – 4)	4 (1 – 5)	1 (1 – 4)	2 (1 – 5)
Stage				
I	18 (49%)	3 (25%)	8 (73%)	7 (50%)
IIA	10 (27%)	5 (42%)	2 (18%)	3 (21%)
IIB	6 (16%)	2 (17%)	1 (9%)	3 (21%)
III	3 (8%)	2 (17%)	0	1 (7%)

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Clinical Presentation

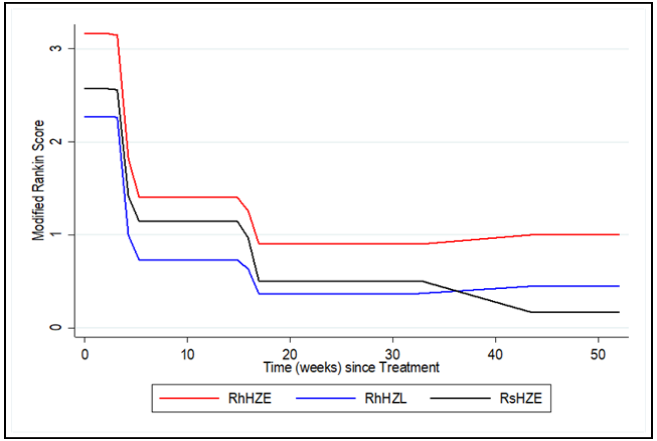
Symptoms	n (%)	Symptoms	n (%)
Reduced playfulness	31 (84)	Vomiting	13 (35)
Lethargy	25 (88)	Focal neurological deficits	11 (30)
Fever	21 (57)		
Irritability	18 (49)	Seizures	7 (19)
Neck stiffness	17 (46)	Abdominal pain	4 (11)
Weight loss	18 (43)	Cough	4 (11)
Altered Consciousness	14 (38)	Diarrhea	3 (8)
Headache	13 (35)	Night sweats	3 (8)

Safety

	% children with* N = 37	Arm R_{high}HZE N = 12	Arm R_{high}HZL N = 11	Arm R_{std}HZE N = 14	P-value
Grade ≥3 AE	18 (49%)	7 (58%)	6 (55%)	5 (36%)	0.50

- 6 early treatment discontinuation, 4 in R_{high}HZE arm (3 for toxicity), 1 in R_{high}HZL (toxicity), 1 in R_{std}HZE (disallowed med)
- 2/4 early discontinuations due to toxicity were during *intensive phase* (during experimental therapy)
- 1 death, in R_{high}HZE arm (all the other children completed the study)

Functional Outcomes (MRS)



Rankin Score	Arm 1 R_{hi}HZE	Arm 2 R_{hi}HZL	Arm 3 R_{std}HZE
Entry	4 (1 – 5)	1 (1 – 4)	2 (1 – 5)
Week 8	1 (0 – 3)	0 (0 – 1)	0 (0 – 2)
Week 24	0 (0 – 1)	0 (0 – 0)	0 (0 – 1)
Week 52	0 (0 – 2)	0 (0 – 0)	0 (0 – 0)

Outcome Variable	Randomized Treatment	Multivariable Analysis		Interpretation
		Estimated Diff (95% CI)	P-value	
Ordinal (OR) Multilevel ordered logistic random effects model	R_{15}HZE	Ref	-	Odds of having lower MRS than higher with SOC as the referent
	R_{30}HZE	3.31 (0.17– 63.8)	0.43	
	R_{30}HZL	1.52 (0.06 – 36.9)	0.80	

Smita Nimkar

Neurocognitive Outcomes over 12 months

Ana Arenivas

Outcome Variable	Arm	Univariable Analysis (95% CI)	P-value	Multivariable Analysis (95% CI)	P-value	Interpretation
Visual Perception	$R_{15}HZE$	Ref	-	Ref	-	Average score was higher by 2 points among children receiving $R_{30}HZE$
	$R_{30}HZE$	1.96 (-5.65 , 9.57)	0.61	3.56 (-2.72, 9.83)	0.27	
	$R_{30}HZL$	0.45 (-7.13, 8.03)	0.91	-2.83 (-9.77, 4.10)	0.42	
Fine motor	$R_{15}HZE$	Ref	-	Ref	-	Average score higher by 11 points among children receiving $R_{30}HZE$.
	$R_{30}HZE$	10.7 (3.19, 18.28)	0.005	12.0 (5.46, 18.5)	0.01	
	$R_{30}HZL$	5.20 (-2.39, 12.8)	0.18	2.40 (-4.82, 9.62)	0.52	

Adjusted for age, gender, MRS

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Neurocognitive Outcomes over 12 months

Outcome Variable	Arm	Univariable Analysis		Multivariable Analysis		Interpretation
		Estimated Diff (95% CI)	P-value	Estimated Diff (95% CI)	P-value	
Receptive Language	R_{15}HZE R_{30}HZE R_{30}HZL	Ref 11.78 (3.61, 20.0) 4.80 (-3.36, 13.0)	- 0.005 0.25	Ref 12.2 (5.87, 18.5) 1.30 (-5.68, 8.28)	- P < 0.01 0.72	Average score was higher by 12 points among children receiving R_{30}HZE
Expressive Language	R_{15}HZE R_{30}HZE R_{30}HZL	Ref 13.2 (1.4 – 24.9) 7.2 (-4.4, 18.8)	 0.03 0.22	Ref 14.9 (4.45, 25.28) 2.64 (-8.45, 13.7)	- 0.01 0.64	Average score for was higher by 13 points among children receiving R_{30}HZE

Adjusted for age, gender, MRS

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CONCLUSION


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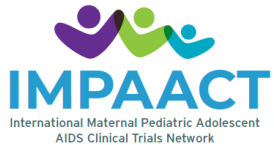
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Summary

- Pediatric TBM clinical trials are very hard to recruit, we did not meet enrollment targets
- Trend towards higher risk of grade ≥3 AEs in the higher-dose rifampicin arms (but NS, and many occurred during continuation phase (SOC) or likely due to disease)
- Functional status overall high by 8 weeks, in all arms (no significant difference)

Summary continued..

- Statistically significantly better fine motor, expressive, and receptive language neurocognitive outcomes in the R_{30}HZE arm (what would otherwise be an undetected or seemingly invisible disability)
- Results seem to align with those from adult studies (no detectable effect of fluoroquinolone when isoniazid is present; some clinical benefit of higher-dose RIF)
- Final analyses, including PK-PD assessments pending

Other publications from TBM KIDS Trial

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INT J TUBERC LUNG DIS 23(10):1082–1089

http://dx.doi.org/10.5588/ijtld.18.0786

Challenges in conducting trials for pediatric tuberculous meningitis: lessons from the field

M. Paradkar,[1] D. B. Devaleenal,[2] T. Mvalo,[3,4] A. Arenivas,[5,6] K. T. Thakur,[7] S. Afrin,[1] P. Giridharan,[2] E. Selladurai,[8] A. Kinikar,[1,9] C. Valvi,[1,9] A. Gupta,[10] V. Mave,[1,9] K. E. Dooley[10]

[1]Byramjee Jeejeebhoy Government Medical College-Johns Hopkins Clinical Research Site, Pune, [2]National Institute for Research in Tuberculosis, Indian Council for Medical Research, Chennai, India; [3]University of North Carolina Project-Malawi, Lilongwe, Malawi; [4]Department of Pediatrics, School of Medicine, University of North Carolina at Chapel Hill, NC, [5]The Institute for Rehabilitation and Research Memorial Hermann, Department of Rehabilitation Psychology and Neuropsychology, Houston, TX, [6]Baylor College of Medicine, Department of Physical Medicine and Rehabilitation, Houston, TX, 7Department of Neurology, Columbia University College of Physicians and Surgeons, New York, NY, USA; [8]Institute of Child Health and Hospital for Children, Chennai, [9]BJ Government Medical College, Pune, India; [10]Johns Hopkins University School of Medicine, Baltimore, MD, USA

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Journal of Tropical Pediatrics, , 00, 1–9
doi: 10.1093/tropej/fmaa034
Original Paper

OXFORD

Mullen Scales of Early Learning Adaptation for Assessment of Indian Children and Application to Tuberculous Meningitis

Smita Nimkar

Ana Arenivas

Smita Nimkar, MSC[1,2], Suvarna Joshi, PhD[2,3], Aarti Kinikar, MD, MRCP[3], Chhaya Valvi, MD[3], D. Bella Devaleenal, MBBS, MPH[4], Kiran Thakur, MD[5], Manjushree Bendre, MSW[1], Saltanat Khwaja, MBBS, DCH[1], Mahesh Ithape, GNM[1], Krishna Kattagoni, MSC[4], Mandar Paradkar, DCH, MPH[1], Nikhil Gupte, PhD[6], Amita Gupta, MD, MHS[6], Nishi Suryavanshi, PhD[1], Vidya Mave, MD, MPH[1,6], Kelly E. Dooley, MD, PhD[6], *and* Ana Arenivas, PhD, MPH[7,8]

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TBM KIDS

Neeta Pradhan

› Int J Tuberc Lung Dis. 2022 Apr 1;26(4):317-325. doi: 10.5588/ijtld.21.0388.

Performance of Xpert ® MTB/RIF and Xpert ® Ultra for the diagnosis of tuberculous meningitis in children

N N Pradhan [1], M S Paradkar [1], A Kagal [2], C Valvi [2], A Kinikar [2], S Khwaja [3], R Dhage [3], J Chandane [3], M Ithape [3], M Bendre [3], R Madewar [3], V Nadgeri [3], A Nijampurkar [1], D Jain [3], N Gupte [4], A Gupta [5], V Mave [4], K E Dooley [5], K T Thakur [6]

Affiliations + expand

PMID: 35351236 DOI: 10.5588/ijtld.21.0388

Mandar Paradkar

Kiran Thakur

Bella Devaleenal D.

TBM KIDS

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Collaborative team

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BJ Government Medical College (BJMC) - Sassoon General Hospital	Pune, India
National Institute for Research in Tuberculosis - Institute of Child Health (ICH)	Chennai, India
UNC/Project Malawi - Kamuzu Central Hospital	Lilongwe, Malawi
Columbia University/New York Presbyterian	New York, USA
TIRR, Memorial Hermann/Baylor	Houston, USA
University of California at San Francisco (UCSF)	San Francisco, USA
University of Cape Town (UCT) analytical lab	Cape Town, S. Africa

Lisa Wolf, kept us all moving forward, together

Special thanks to our study participants and the clinical/faculty collaborators:
Aarti Kinikar, Chhaya Valvi, S Ezhilarasi, Daphne Gadama, Noel Mumba…

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THANKS!

Any questions?

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