SHINE Trial
Shorter Treatment for Minimal Tuberculosis (TB) in Children

Lisa Armitige, MD, PhD
August 31, 2023

A 4-Month Regimen for Non-Severe Tuberculosis in Children (based on the SHINE trial)
August 31, 2023
Webcast

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Lisa Armitige, MD, PhD has the following disclosures to make:

- No conflict of interests
- No relevant financial relationships with any commercial companies pertaining to this educational activity

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SHINE Trial

Shorter Treatment for Minimal Tuberculosis (TB) in Children

Lisa Armitige, MD, PhD
Assistant Medical Director
Heartland National TB Center

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Pediatric TB

- Tends to be paucibacillary, more challenging to diagnose
- US contact investigation activities have identified children earlier in the course of disease
- Similar to adult smear negative/culture negative disease
- Children don't tend to transmit disease, making them less of a threat to TB elimination

- TB treatment studies in children have lagged significantly behind those of adults
- Most treatment recommendations are based on adult data but adults have different disease presentation and metabolism

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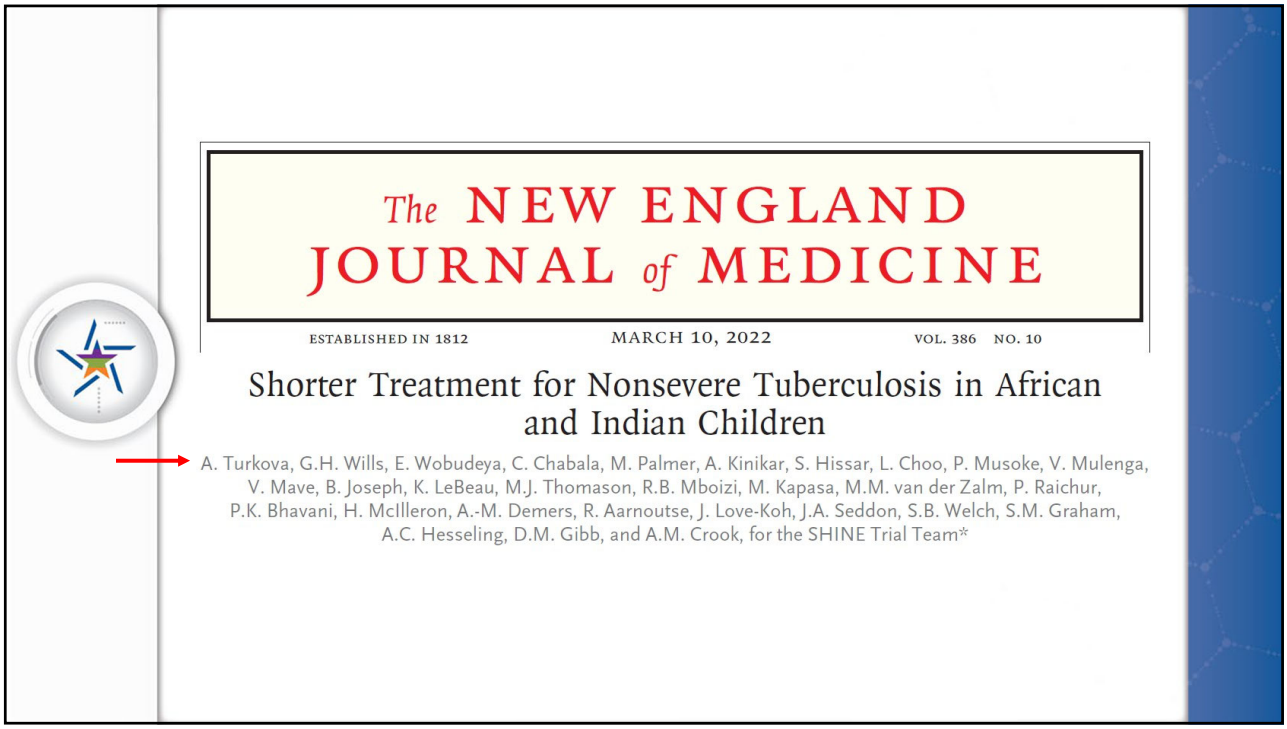
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Shorter Treatment for Nonsevere Tuberculosis in African and Indian Children
A. Turkova, G.H. Wills, E. Wobudeya, C. Chabala, M. Palmer, A. Kinikar, S. Hissar, L. Choo, P. Musoke, V. Mulenga, V. Mave, B. Joseph, K. LeBeau, M.J. Thomason, R.B. Mboizi, M. Kapasa, M.M. van der Zalm, P. Raichur, P.K. Bhavani, H. McIlleron, A.-M. Demers, R. Aarnoutse, J. Love-Koh, J.A. Seddon, S.B. Welch, S.M. Graham, A.C. Hesseling, D.M. Gibb, and A.M. Crook, for the SHINE Trial Team*

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SHINE
Are shorter treatments safe and effective?
SHINE trial
Anna Turkova
MRC Clinical Trials Unit at UCL
On behalf of the SHINE trial team
BAPT meeting
10 March 2022
Partners:
Funders:
Radboudumc
UCL
Medical Research Council
NIHR National Institute for Health Research
UKaid
wellcome
EDCTP
TB Alliance

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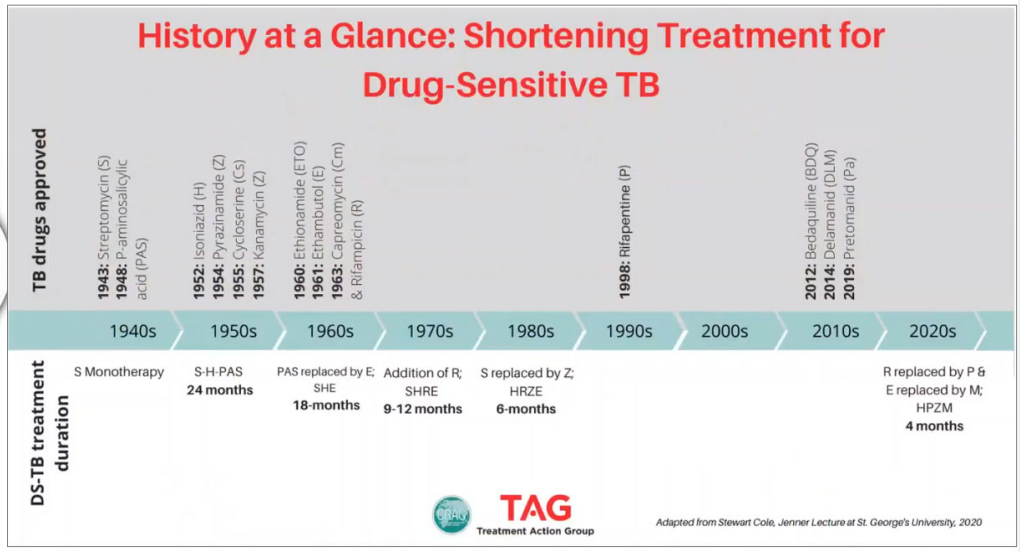

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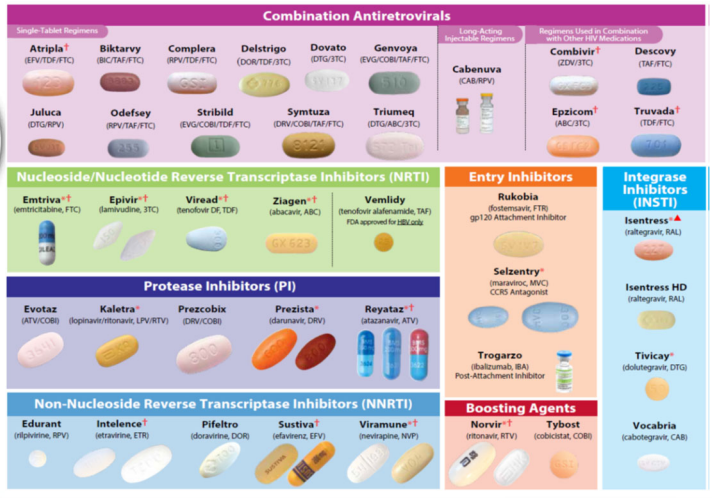
Medications for Treatment of HIV (since AZT in 1987)



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Trial Design for SHINE

- Multicenter, open-label, parallel-group, non-inferiority, randomized controlled, two-arm trial
- Comparing a 4-month vs the standard 6-month regimen
- Used fixed-dose, combination dispersible tablets
  - mg/kg: INH 10 (7-15), rifampin 15 (10-20), EMB 20 (15-25), PZA 35 (30-40)
- Endpoint: favorable outcome; TB-free survival at 72 weeks
- Margin of Inferiority set at 6%

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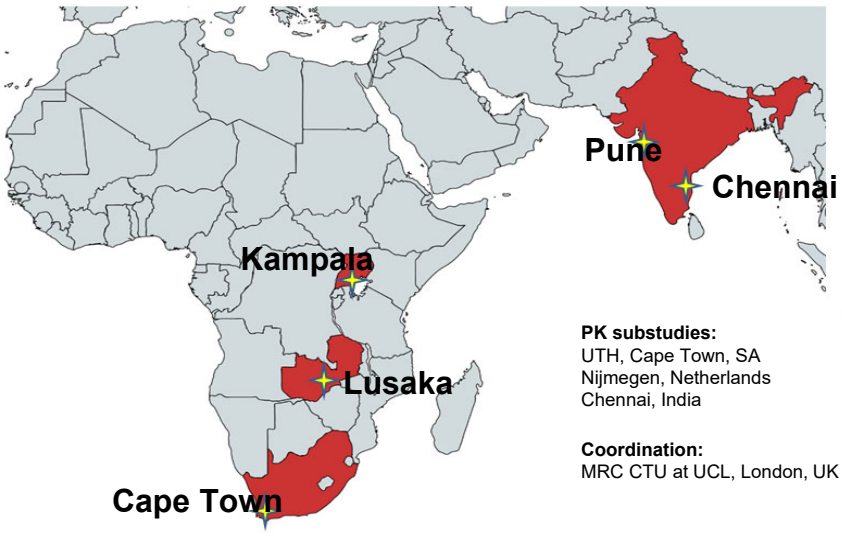
SHINE clinical sites



PK substudies:
UTH, Cape Town, SA
Nijmegen, Netherlands
Chennai, India

Coordination:
MRC CTU at UCL, London, UK

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Inclusion Criterion

- Age 0-16 years
- Weight ≥ 3kg.
- Clinician has decided to treat with standard first-line regimen
- Symptomatic but non-severe TB including:
  - extrathoracic lymph node TB; intra-thoracic uncomplicated (hilar) lymph node TB
  - minimal or no parenchymal abnormality on CXR
  - smear negative on gastric aspirate/other respiratory sample

Note: GeneXpert may be positive or negative and a negative GeneXpert can be used as a substitute for a negative smear;
culture of respiratory sample may be positive or negative;
lymph node aspirate may be smear/culture/GeneXpert positive or negative)

- Not treated for previous TB unless successfully treated > 2 years since last completed treatment
- Known (or pending confirmation of) HIV status; HIV-infected or HIV-uninfected
- Willing and likely to adhere to 72 weeks follow up
- Informed written consent from the parent/legal caregiver(s) and assent in children
- Home address accessible for visiting and intending to remain within the recruitment area

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Exclusion Criterion

1. Smear-positive respiratory sample TB
   (note: smear-positive peripheral lymph node sample is allowed)
2. Premature (<37 weeks) **and** aged under 3 months
3. Miliary TB, spinal TB, TB meningitis, osteoarticular TB, abdominal TB, congenital TB
4. Pre-existing non-tuberculous disease likely to prejudice the response to, or assessment of, treatment e.g. liver or kidney disease, peripheral neuropathy, cavitation
5. Any known contraindication to taking anti-TB drugs
6. Known contact with drug resistant adult source case (including mono- resistant TB)
7. Known drug resistance in the child
8. Severely sick
9. Pregnancy

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Methods

Children aged < 16 years with minimal (non-severe) TB (n = 1,200)

Randomise (1:1)

4-Month Regimen (n = 600)

Intensive phase: 8 weeks HRZ(E)

Continuation phase: 8 weeks HR

Follow-up phase: 56 weeks post-treatment

TOTAL FOLLOW-UP 72 WEEKS

6-Month Regimen (n = 600)

Intensive phase: 8 weeks HRZ(E)

Continuation phase: 16 weeks HR

Follow-up phase: 48 weeks post-treatment

TOTAL FOLLOW-UP 72 WEEKS

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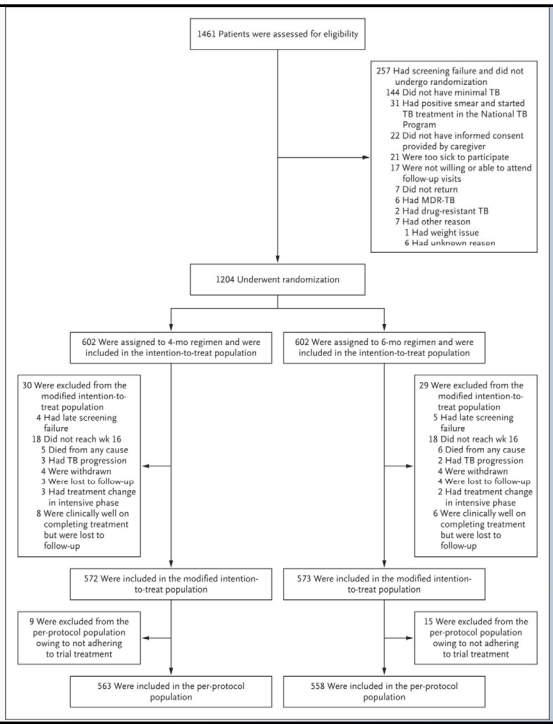
Randomization and Treatment of the Patients.



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Demographic and Clinical Characteristics of the Participants at Baseline.

Table 1. Demographic and Clinical Characteristics of the Participants at Baseline.*

Characteristic	4-Month Treatment (N=602)	6-Month Treatment (N=602)	Total (N=1204)
Age			
Median (interquartile range) — yr	3.4 (1.5 to 6.9)	3.5 (1.5 to 7.1)	3.5 (1.5 to 7.0)
Range	2 mo to 15 yr	2 mo to 15 yr	2 mo to 15 yr
Female sex — no. (%)	297 (49)	286 (48)	583 (48)
Site country — no. (%)			
Uganda	188 (31)	188 (31)	376 (31)
Zambia	183 (30)	181 (30)	364 (30)
South Africa	156 (26)	159 (26)	315 (26)
India	75 (12)	74 (12)	149 (12)
HIV-positive status — no. (%)	65 (11)	62 (10)	127 (11)
WHO weight band — no. (%)			
3–3.9 kg	0	3 (<1)	3 (<1)
4–7.9 kg	86 (14)	92 (15)	178 (15)
8–11.9 kg	162 (27)	152 (25)	314 (26)
12–15.9 kg	126 (21)	116 (19)	242 (20)
16–24.9 kg	142 (24)	153 (25)	295 (25)
≥25 kg	86 (14)	86 (14)	172 (14)
Clinical presentation — no. (%)			
Respiratory tuberculosis	398 (66)	406 (67)	804 (67)
Mixed respiratory and peripheral lymph-node tuberculosis	182 (30)	171 (28)	353 (29)
Peripheral lymph-node tuberculosis	19 (3)	21 (3)	40 (3)
Other†	3 (<1)	4 (1)	7 (1)
M. tuberculosis culture and Xpert MTB/RIF testing results — no. (%)‡			
All positive results	85 (14)	80 (13)	165 (14)
Tuberculosis culture–positive only	40 (7)	40 (7)	80 (7)
Xpert MTB/RIF–positive only	14 (2)	5 (1)	19 (2)
Tuberculosis culture–positive and Xpert MTB/RIF–positive	31 (5)	35 (6)	66 (5)

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Primary endpoints

SHINE

Primary efficacy outcome:

Unfavourable status

- TB treatment failure*
- TB recurrence
- Death of any cause by 72 weeks
- On-treatment loss-to-follow-up

Primary safety outcome:

Grade 3-5 adverse events on treatment

* Include treatment extensions beyond replacement of missed doses, TB treatment drug changes or restarts due to suspected treatment failure

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Analysis populations and sample size assumptions

Analysis populations

Modified ITT (mITT) = All randomised excluding:
- Late screening failures
- Did not reach week 16
- Completed treatment, well, lost before week 72

Per-Protocol (PP) = mITT excluding:
- Non-adherent to allocated treatment, using "80-120%" rule*

Intent-to-treat (ITT) = All randomised

Trial powered on
Key secondary analysis
- children adjudicated to have TB at baseline by an independent expert committee blinded to randomised arm (assumed 80% of all children)

Sample size
6% non-inferiority margin
8% unfavourable events in control arm
10% lost to follow-up
90% power, 5% 2-sided significance

*80% of daily doses within 120% of allocated treatment duration

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Retention and adherence to randomised duration

95% in 4m arm and 93% in 6m arm adhered to prescribed duration of treatment

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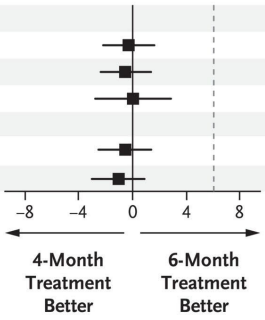
Unadjusted Analysis of the Primary Efficacy and Key Secondary Outcomes in the Trial Populations.

	No. of Patients	4-Month Treatment	6-Month Treatment	Risk Difference (95% CI)
		no. of participants with event/total no. (%)		6% *percentage points*
Primary outcome				
Modified intention-to-treat population	1145	16/572 (3)	18/573 (3)	−0.3 (−2.3 to 1.6)
Per-protocol population	1121	14/563 (2)	17/558 (3)	−0.6 (−2.5 to 1.4)
Intention-to-treat population	1204	44/602 (7)	44/602 (7)	0 (−2.9 to 2.9)
Key secondary outcome				
Modified intention-to-treat population	910	10/450 (2)	13/460 (3)	−0.6 (−2.6 to 1.4)
Per-protocol population	895	8/445 (2)	13/450 (3)	−1.1 (−3.1 to 0.9)



Turkova A et al. N Engl J Med2022;386:911-922

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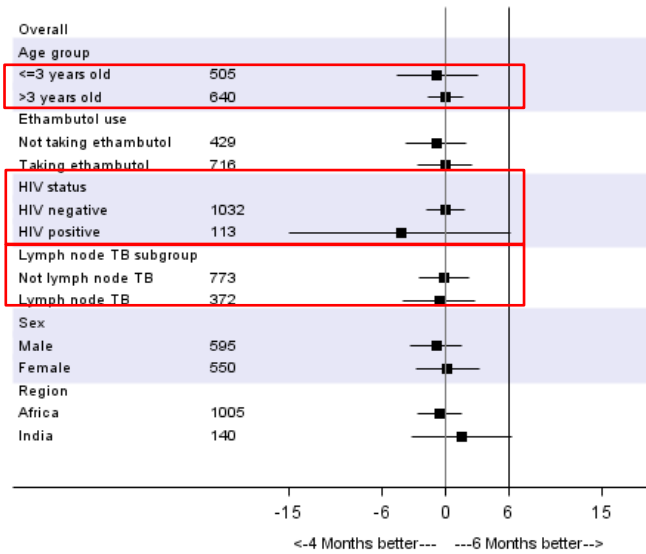
Efficacy outcomes by subgroup (mITT)

SHINE trial results - Primary efficacy analyses by subgroup (mITT)

Subgroup	N	4 months	6 months	Risk difference (95% CI)
Overall				
Age group				
<=3 years old	505	12 (5)	14 (6)	-0.8 (-4.6 to 3.1)
>3 years old	640	4 (1)	4 (1)	0 (-1.7 to 1.7)
Ethambutol use				
Not taking ethambutol	429	4 (2)	6 (3)	-0.9 (-3.8 to 2)
Taking ethambutol	716	12 (3)	12 (3)	0 (-2.7 to 2.6)
HIV status				
HIV negative	1032	12 (2)	12 (2)	0 (-1.8 to 1.9)
HIV positive	113	4 (7)	6 (11)	-4.3 (-14.9 to 6.2)
Lymph node TB subgroup				
Not lymph node TB	773	11 (3)	12 (3)	-0.2 (-2.6 to 2.2)
Lymph node TB	372	5 (3)	6 (3)	-0.6 (-4.1 to 2.8)
Sex				
Male	595	6 (2)	9 (3)	-0.9 (-3.4 to 1.6)
Female	550	10 (4)	9 (3)	0.2 (-2.8 to 3.3)
Region				
Africa	1005	14 (3)	17 (3)	-0.6 (-2.7 to 1.5)
India	140	2 (3)	1 (1)	1.5 (-3.3 to 6.3)



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Primary Safety Outcome, Serious Adverse Events, Deaths, Adverse Drug Reactions, and Suspected Bacterial Infections Leading to Hospitalization.

Table 3. Primary Safety Outcome, Serious Adverse Events, Deaths, Adverse Drug Reactions, and Suspected Bacterial Infections Leading to Hospitalization.*

Event	4-Month Treatment (N = 602)	6-Month Treatment (N = 602)	Total (N = 1204)
Primary safety outcome — no. of events	49	66	115
No. of participants with ≥1 event (%)†	47 (8)	48 (8)	95 (8)
At ≤4 mo			
No. of adverse events of grade ≥3	35	52	87
No. of participants with ≥1 event (%)	33 (5)	40 (7)	73 (6)
At >4 mo			
No. of adverse events of grade ≥3	14	14	28
No. of participants with ≥1 event (%)	14 (2)	12 (2)	26 (2)
Serious adverse event — no. of events	88	104	192
No. of participants with ≥1 serious adverse event (%)†	75 (12)	75 (12)	150 (12)
At ≤4 mo			
No. of serious adverse events	35	50	85
No. of participants with ≥1 serious adverse event (%)	33 (5)	40 (7)	73 (6)
At >4 mo			
No. of serious adverse events	53	54	107
No. of participants with ≥1 serious adverse event (%)	47 (8)	44 (7)	91 (8)
Death — no. (%)	12 (2)	19 (3)	31 (3)
At ≤4 mo			
No. of deaths (%)	5 (1)	6 (1)	11 (1)
No. of deaths considered to be related to tuberculosis (%)	3 (<1)	2 (<1)	5 (<1)
At >4 mo			
No. of deaths (%)	7 (1)	13 (2)	20 (2)
No. of deaths considered to be related to tuberculosis (%)	2 (<1)	6 (1)	8 (1)
Adverse drug reaction — no. of participants (%)‡	6 (1)	11 (2)	17 (1)
Bacterial infection leading to hospitalization — no. of events	40	40	80
No. of participants with ≥1 event (%)	36 (6)	30 (5)	66 (5)

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Deaths in SHINE

SHINE

Deaths in SHINE, overall	**31/1204 (2%)**
Children with HIV	**13/127 (10%)**
Deaths considered related to TB	13
Pneumonia	6
Epilepsy/ convulsions	2
Septicaemia	1
Acute respiratory failure	1
Chronic diarrhoea	1
Congestive heart failure	1
Suspected pulmonary TB	1

Context: mortality in children <5 years in general population

India	35 per 1000 (4%)
South Africa	31 per 1000 (3%)
Uganda	41 per 1000 (4%)
Zambia	57 per 1000 (6%)

UNICEF. Under five mortality 2020 https://data.unicef.org/topic/child-survival/under-five-mortality/

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Primary Efficacy Analysis (Modified Intention-to-Treat Population).

Table 2. Primary Efficacy Analysis (Modified Intention-to-Treat Population).*

Outcome	4-Month Treatment (N=572)	6-Month Treatment (N=573)	Difference (95% CI)	
			Adjusted Analysis†	Unadjusted Analysis
			percentage points	
Unfavorable status — no. (%)	16 (3)	18 (3)	−0.4 (−2.2 to 1.5)	−0.3 (−2.3 to 1.6)
Death from any cause after 4 mo	7 (1)	12 (2)		
Loss to follow-up after 4 mo but during treatment period	0‡	1 (<1)		
Treatment failure				
Tuberculosis recurrence	6 (1)	4 (1)		
Extension of treatment	2 (<1)	0		
Restart of treatment§	1 (<1)	1 (<1)		
Favorable status — no. (%)	556 (97)	555 (97)		

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Outcomes among children with 'severe TB' as adjudicated by Central radiology expert review

SHINE

- All children enrolled in the trial had non severe TB as judged by local site clinicians
- Overall, 71 children were adjudicated to have severe TB at the Central CXR review
- Of these, 16 (23%) were microbiologically confirmed (GeneXpert or Culture)
- 94% had favourable outcomes
  - ITT population in the whole trial – 93% had favourable outcomes

	4 Months N=34	6 Months N=37
Total number of unfavourable outcomes	**2**	**2**
Suspected TB	1	1
Death	1*	1**

*Solid tumour Week 28

**Pneumonia Week 67

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SHINE: Mantoux and IGRA results at screening

		4 Month	6 Month	Total
Randomised		602	602	1204
Mantoux test performed	No	141 (23)	136 (23)	277 (23)
	Yes	461 (77)	466 (77)	927 (77)
Mantoux result*, **	Negative	196 (43)	178 (38)	374 (40)
	Positive	265 (57)	288 (62)	553 (60)
IGRA (QuantiFERON) test performed	No	583 (97)	587 (98)	1170 (97)
	Yes	19 (3)	15 (2)	34 (3)
IGRA result	Negative	10 (53)	6 (40)	16 (47)
	Positive	9 (47)	8 (53)	17 (50)
	Test Error	0	1 (7)	1 (3)

* Mantoux Positive defined as ≥10mm diameter of induration if patient is HIV negative
or ≥5mm diameter of induration if patient is HIV positive

** % of those tested

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Caveats

- No standardized case definition – encouraged use of NIH criteria
- ~50% of the subjects were contacts to known cases
- TST/IGRA results not part of the case definition
- 3 blinded reviewers [retrospective]: 85% of cases likely TB; non-TB evenly distributed between the 2 regimens
- Positive AFB smear of the sputum was exclusionary but not a positive Xpert result
- Used pediatric fixed dose combination dispersible medications – not available in the U.S.
- Ethambutol use at the discretion of the local physician
- No DOT – all self-supervised therapy with pill counts at each visit

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Take Home points

- 4 months of treatment was non-inferior to 6 months of treatment for children with non-severe TB
- Non-inferiority/adverse effects were similar across all analysis performed
- Unfavorable outcomes were few (3% in each arm)
- Side effects, treatment abandonment and deaths were low in children treated for TB

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Implementation questions

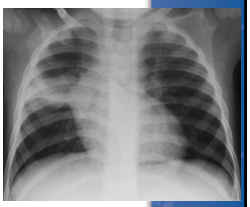
SHINE included children with **minimal TB**

Minimal TB = smear-negative + non-severe TB

TB severity in SHINE based on clinical examination and Chest X-ray:

Child clinically not severely sick

CXR: no cavities, infiltrate <1 lobe, no significant airway obstruction, no complicated pleural effusion, no miliary TB



Implementation solutions:

Settings with CXRs available:

The UNION Diagnostic CXR Atlas for Paediatric TB

Infographics

Computer-aided detection (CAD) for paediatric CXR reading

Settings with CXRs NOT widely available:

Consider referring children to health centres where CXRs are available

Investments to improve access to portable, digital CXRs

Implementation studies for presumptive pulmonary TB

TAG. An activist guide to shorter treatment for drug-sensitive TB. 2021 https://www.treatmentactiongroup.org/wp-content/uploads/2021/10/activists_guide_shorter_treatment_ds_tb_final.pdf

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Please add Questions
to the
Q&A box!