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Emerging data on the management of MDR-TB exposure in children

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Disclosure:

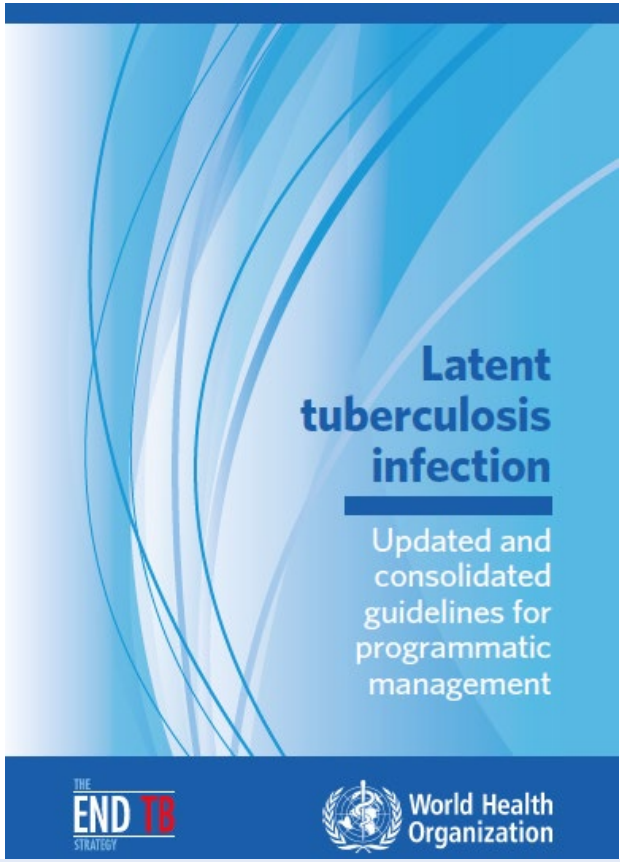
No relevant financial disclosures to report and no mention of off-label use of any medications or products

Overview

- Historical context for MDR-TB preventive therapy for children
- Emerging evidence – TB-CHAMP trial
- Practical implications

Historical approaches to preventive therapy for children exposed to MDR-TB

- Limited evidence available and lack of international consensus
  - Failure of INH or INH/RMP to prevent MDR-TB reported.
  - Fluoroquinolone-based preventive therapy possibly effective in small, observational studies – low quality evidence
- Varying guidance
  - Fluoroquinolone-based preventive therapy *versus* 2-3 drugs the isolate is susceptible to *versus* careful follow-up only
  - Duration?
  - Cape Town – 6 months hdINH, FQN, EMB



In selected high-risk household contacts of patients with multidrug-resistant tuberculosis, preventive treatment may be considered based on individualised risk assessment and a sound clinical justification. *(Conditional recommendation, very low-quality evidence.* ***New recommendation****)*

MDR preventive therapy for children: Weighing up risks and benefits

Factors favoring MDR-TB PT	Factors opposing MDR-TB PT
Young children at high risk of progressing to disease, including severe, life-threatening	Not high-quality evidence for efficacy
Challenge to diagnose DR-TB in children, and treatment is long, toxic, burdensome, costly	Not risk free (fluoroquinolones), especially concerning for well children
Current evidence for efficacy of PT is low quality, but suggests it works (see Policy Brief)	Costly to deliver at a programmatic level, esp in high-burden settings
~Safe	Poorly palatable drugs and formulations
Low risk of generating resistance	
Models suggest highly cost-effective	

Expert Consensus (2015)

- Individual risk assessment
- A fluoroquinolone-based regimen was highly recommended in high-risk contacts (children <5 years of age)
- **Randomized controlled trials are needed**

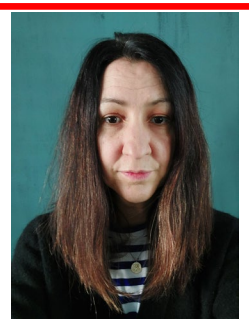
TB-CHAMP team

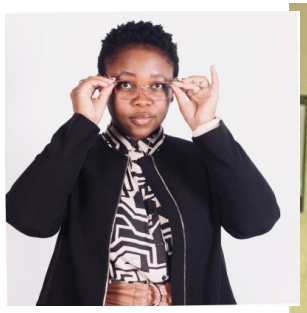
*slides from Anneke Hesseling with permission and minor adapations
















Families and trial participants, local health services
Stellenbosch: Anneke Hesseling, James Seddon, Simon Schaaf, Sue Purchase, Graeme Hoddinott, Anne-Marie Demers, Anthony Garcia-Prats, Andrew Whitelaw., Elize Batist, Samke Nyanathe
MRC CTU at UCL: Trinh Duong, Di Gibb, Jo Bridgen, Charlotte McGowan, Charlotte Layton
PHRU: Neil Martinson WHRI: Lee Fairlie.Think: Suzanne Staples Isanga Lethemba: Susan Ford, Francesca Conradie.
Economist: Tommie Wilkinson

TB-CHAMP: Tuberculosis Child Multidrug-Resistant Preventive Therapy Trial

Primary objective: To assess whether levofloxacin (LVX) given daily for 24 weeks **(15-20 mg/kg)** is ***efficacious*** to prevent TB in child household contacts of adults with MDR-TB

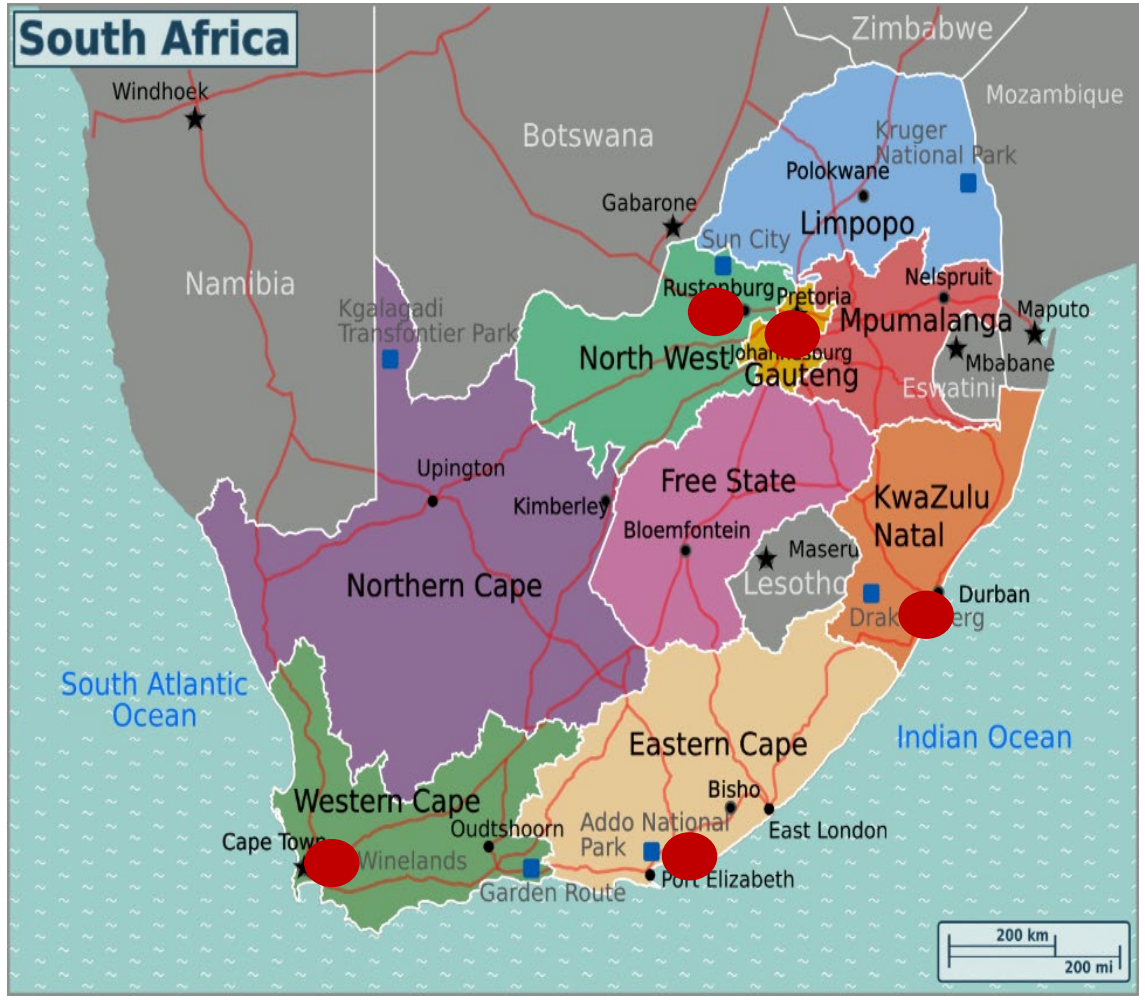
Secondary objectives

1. Does LVX have acceptable ***safety and tolerability*** in children?

Trial design

Design	Phase III, cluster randomised, double-blind placebo controlled, superiority trial
Target Population	Children who are household contacts of adult MDR-TB cases • 0-4 years regardless of IGRA or HIV status • 5-17 years (IGRA or HIV+); included in version 3.0 protocol (Sept 2021)
Intervention	LVX (15-20 mg/kg) vs. placebo daily for 24 weeks
Randomisation	Households randomised 1:1 to either LVX or placebo (stratified by site); all eligible children in the household treated with the same intervention
Primary endpoint	Confirmed or unconfirmed TB by 48 weeks
Target sample size	1009 contacts (~505 households) 80% power; 2-sided 5% type 1 error Assumed **60%** LVX efficacy, reducing TB incidence from **7% to 2.8%**; 10% LTFU

Setting: South Africa: 5 diverse sites, 6 provinces



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Wits Reproductive Health and HIV Institute, Shandukani Research Centre, Wits Health Consortium

Tuberculosis & HIV Investigative Network, Pietermaritzburg and Durban, KwaZulu Natal

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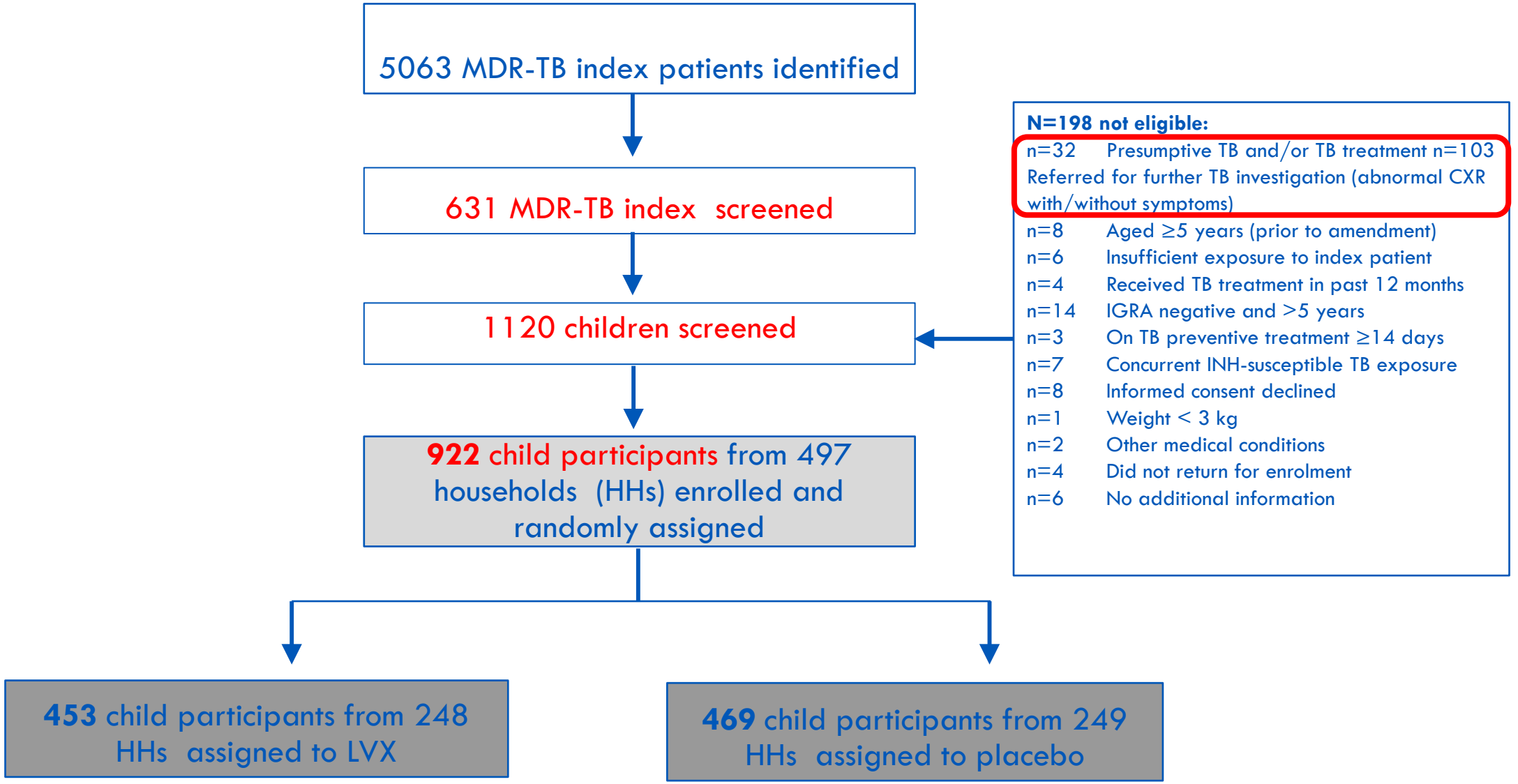
Overview of enrolment, randomization and analysis of child MDR-TB household contacts



Baseline characteristics of randomised child participants (N=922)

N		LVX 453 (100%)	Placebo 469 (100%)	Overall 922 (100%)
Female		240 (53%)	228 (49%)	468 (51%)
	Median (IQR) years	3.0 (1.4, 4.3)	2.6 (1.3, 4.1)	2.8 (1.3, 4.2)
Age	<1	85 (19%)	83 (18%)	168 (18%)
	1-<3	140 (31%)	175 (37%)	315 (34%)
	3-<5	180 (40%)	176 (38%)	356 (39%)
	5-<10	18 (4%)	17 (4%)	35 (4%)
	10-<15	20 (4%)	13 (3%)	33 (4%)
	15-<18	10 (2%)	5 (1%)	15 (2%)
BCG vaccinated		423 (94%)	442 (95%)	865 (94%)
HIV-positive		10 (2%)	9 (2%)	19 (2%)
HIV-exposed uninfected		153 (34%)	160 (34%)	313 (34%)
Currently on TB preventive treatment		9 (2%)	6 (1%)	15 (2%)
Weight-for-age Z score, median (IQR)		-0.4 (-1.2,0.3)	-0.4 (-1.2,0.4)	-0.4 (-1.2,0.3)

Baseline IGRA status: randomised child participants

		LVX (n=405)	Placebo (n=434)	Total (n=839)
Age <5 years				
IGRA status	Negative	294 (74%)	334 (80%)	628 (77%)
	Positive	89 (23%)	74 (18%)	163 (20%)
	Indeterminate	12 (3%)	12 (3%)	24 (3%)
	N missing	10	14	24

* Children/adolescents aged 5-17 years were required to be IGRA-positive or living with HIV to be eligible

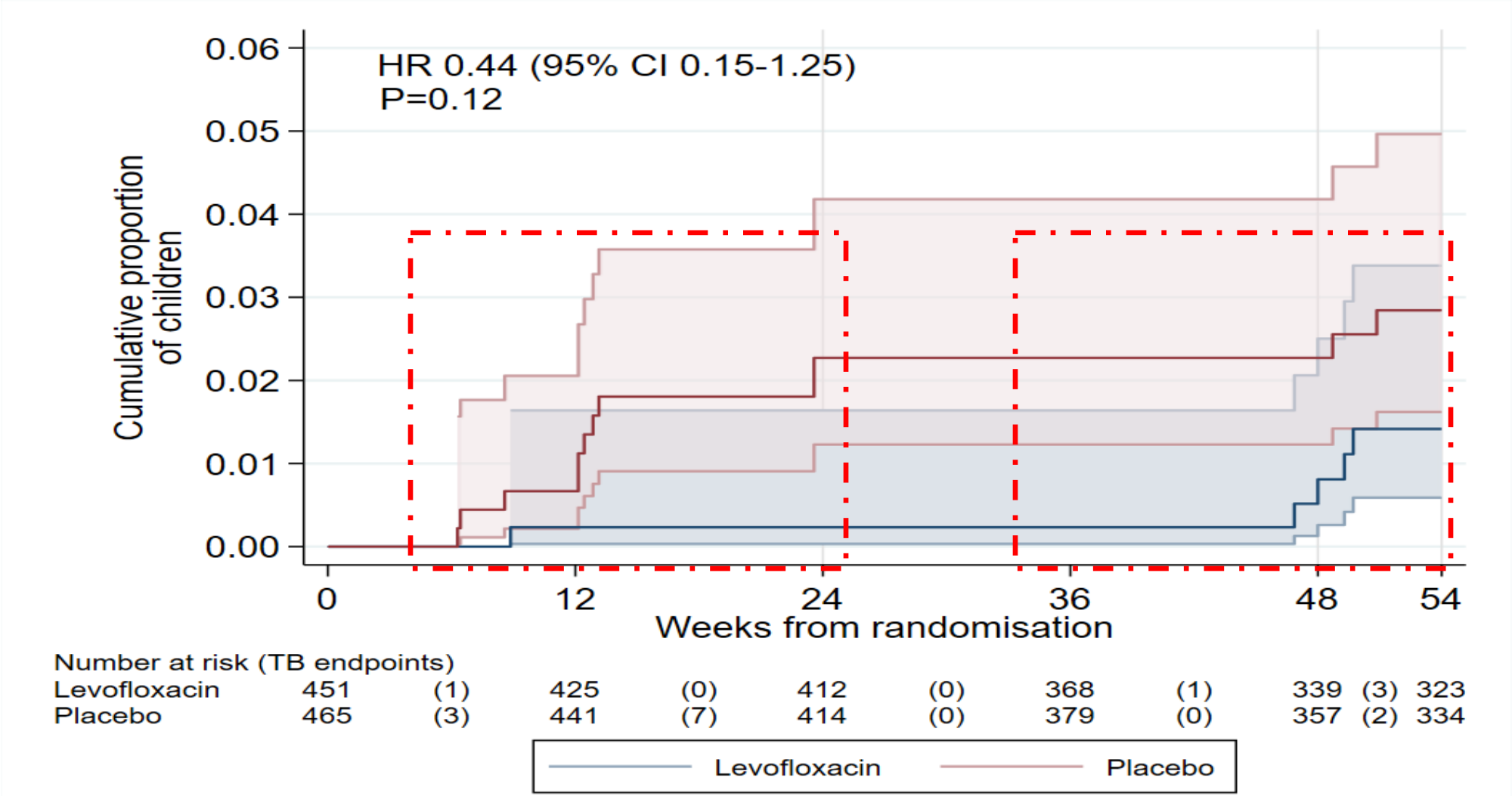
Primary efficacy analysis- mITT population

	LVX (n=451)	Placebo (n=465)	Total (n=916)
Participants with TB endpoint by 48 weeks*	**5 (1.1%)**	**12 (2.6%)**	**17**
Confirmed TB	3	7	10
Unconfirmed TB	2	5	7
Hazard ratio (95% CI), LVX vs placebo$	**0.44 (0.15-1.25)**		
P-value	**0.121**		

* Allowing for pre-defined ±6 weeks window at study visit at 48 weeks.

$ Hazard ratio estimated adjusting for site, age group and allowing for household clustering.

Tuberculosis disease by 48-week visit in child household contacts by treatment arm

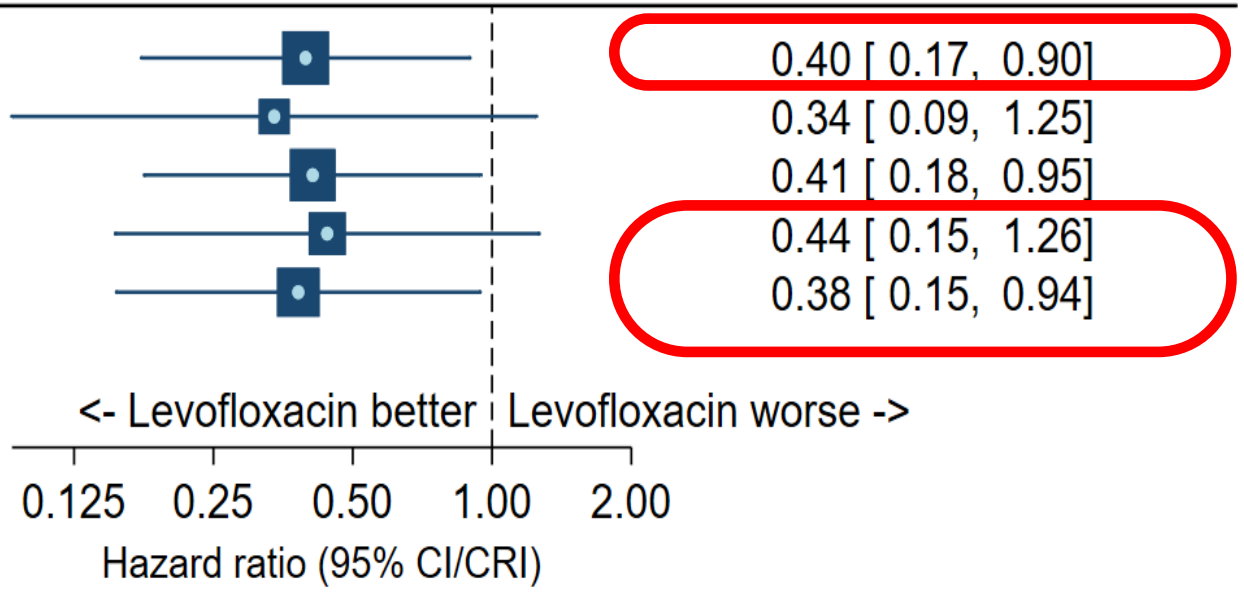


* Allowing for pre-defined ±6 weeks window at study visit at 48 weeks. Test for non-proportional hazards p-value = 0.106

Estimated treatment effect of levofloxacin on time to TB disease by 54 weeks: results from TB-CHAMP and V-QUIN

V-QUIN

Analyses	Levofloxacin n with endpoint / N	Placebo n with endpoint / N	Hazard ratio with 95% CI/CRI
Overall estimate: IPD meta-analysis	8 / 1474	21 / 1483	0.40 [0.17, 0.90]
V-QUIN: standard analysis	3 / 1023	9 / 1018	0.34 [0.09, 1.25]
V-QUIN: Bayesian analysis*	3 / 1021	9 / 1015	0.41 [0.18, 0.95]
TB-CHAMP: standard analysis	5 / 451	12 / 465	0.44 [0.15, 1.26]
TB-CHAMP: Bayesian analysis*	5 / 448	12 / 464	0.38 [0.15, 0.94]



* Treatment effect in V-QUIN was estimated while "borrowing" information from TB-CHAMP, and vice versa; allows levofloxacin efficacy to differ between the study populations, and increases power compared to corresponding standalone analyses of each study. IPD = individual patient data; CI = confidence interval; CRI= credibility interval (for Bayesian results)

TB-CHAMP: Key safety outcomes among participatns receiving ≥1 study drug dose

	LVX (n=452)	Placebo (n=469)	Total
Grade ≥3 adverse events at least possibly associated with study drug			
Number of events	5	8	13
Participants with ≥1 event(s)	4 (0.9%)	8 (1.7%)	12
Arthritis/arthralgia/tendinopathy (any grade)			
Number of events	7	4	11
Participants with ≥1 event(s)	6 (1.3%)	4 (0.9%)	10
Permanently discontinued treatment due to an adverse event			
Participants (n)	6 (1.3%)	1 (0.2%)	7

Levofloxacin dose for TPT

- Recommended dose based on levo pop PK model, TB-CHAMP lead-in PK data, formulation effects
- Formulation
  - Disp tabs good acceptability, preferred by children, caregivers
  - TB-CHAMP used 250 mg tabs only
    - Acceptable and improved over time
    - PK of crushed tabs known and is okay
  - Suspension
- **Take home:** 15-20 mg/kg once daily OR **WHO weight banded levo doses for TPT**

Pharmacokinetics and Optimal Dosing of Levofloxacin in Children for Drug-Resistant Tuberculosis: An Individual Patient Data Meta-Analysis

Yasmine N. White,[1,a] Belen P. Solans,[1,2,a,@] Paolo Denti,[3] Louvina E. van der Laan,[3,4] H. Simon Schaaf,[4] Bryan Vonasek,[5] Amyn A. Malik,[6,7] Heather R. Draper,[4] Hamidah Hussain,[6,b] Anneke C. Hesseling,[4] Anthony J. Garcia-Prats,[4,5,c] and Radojka M. Savic[1,2,c]

Deriving Dosages for Levofloxacin Tuberculosis Preventive Treatment for Young People Exposed to Rifampicin-Resistant Tuberculosis

Belén P. Solans,[1,2,@] Ryo Miyakawa,[1,2,@] Maureen Shin,[1,2,@] Anneke C. Hesseling,[3] Yasmine White,[1,2,@] Tiziana Masini,[4,@] Avinash Kanchar,[4,@] Dennis Falzon,[4] and Radojka M. Savic[1,2,@]

	250 mg NDT			500 mg NDT			100 mg DT		
Weight Band	mg	mg/kg	No. of Tablets	mg	mg/kg	No. of Tablets	mg	mg/kg	No. of Tablets
3–5.9 kg, <3 m	62.5	11–21	1/4	…	…	…	**50**	**8–17**	**1/2**
3–5.9 kg, ≥3 m	125	21–42	1/2	…	…	…	**100**	**17–33**	**1**
6–9.9 kg, <6 m	125	13–21	1/2	…	…	…	**100**	**10–17**	**1**
6–9.9 kg, ≥6 m	250	25–41	1	…	…	…	**150**	**15–25**	**1 + 1/2**
10–14.9 kg	250	17–25	1	…	…	…	200	13–20	2
15–19.9 kg	375	19–25	1 + 1/2	…	…	…	250	13–17	2 + 1/2
20–24.9 kg	375	15–19	1 + 1/2	…	…	…	300	12–15	3
25–29.9 kg	**500**	**17–20**	**2**	**500**	**17–20**	**1**	350	12–14	3 + 1/2
30–34.9 kg	**500**	**14–17**	**2**	**500**	**14–17**	**1**	…	…	…
35–49.9 kg	**500**	**10–14**	**2**	**500**	**10–14**	**1**	…	…	…
≥50 kg	**750**	**<15**	**3**	**750**	**<15**	**1 + 1/2**	…	…	…

Conclusions

- **Levofloxacin efficacious**
  - LFZ administered to high-risk household contacts of MDR-TB results in ~60% reduction in incident TB among
- **LVX safe in children:**
  - Few Grade 3 events, arthritis/arthropathy events (no different than placebo)
- **Good acceptability, good treatment adherence**
- **Now recommended by the WHO with weight-banded dosing recommendations**
- **Standard approach for children with MDR-TB exposure in whom preventive therapy is indicated**
- Future evidence: PHOENIx Trial – Delamanid vs standard dose INH

Questions and Answers

Thank you