Recruitment challenges and levofloxacin acceptability in the TB-CHAMP MDR-TB prevention trial

Dr Susan Purchase

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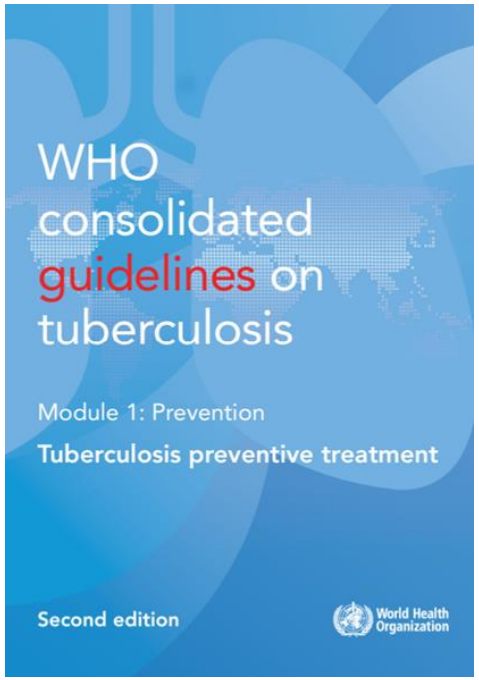
ANNUAL MEETING
2024

Introduction

- Modelling suggests that 2 million children globally are infected with MDR TB, with 50,000 progressing to TB disease each year
- Until very recently there was no evidence from randomized controlled trials re MDR TB prevention
- TB-CHAMP was a RCT designed to assess the efficacy of levofloxacin as preventive therapy in child HHCs of adults with MDR-TB
- Based on the results of TB-CHAMP (and V-QUIN), WHO now recommends 6 months of levofloxacin as TB preventive treatment in contacts exposed to RR-TB



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Recruitment challenges and solutions in TB-CHAMP

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Challenges in recruiting children to a multidrug-resistant TB prevention trial

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Introduction

- Recruiting to RCTs is often challenging: 20-45% of all trials fail to meet planned sample size
- Consequences of poor recruitment: reduced statistical power, need for supplemental funding, trial abandonment and delayed identification of life-saving interventions
- Recruiting challenges on CHAMP led to severe funding challenges - could easily have derailed this important trial

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Methods

- Data was collected between September 2017 and July 2019
- TB-CHAMP was being conducted at 3 diverse research sites in South Africa
- Adult MDR-TB index patients were identified from lab extracts and referrals, then traced by recruiting team.
- Each site had its own recruiting plan and team structure

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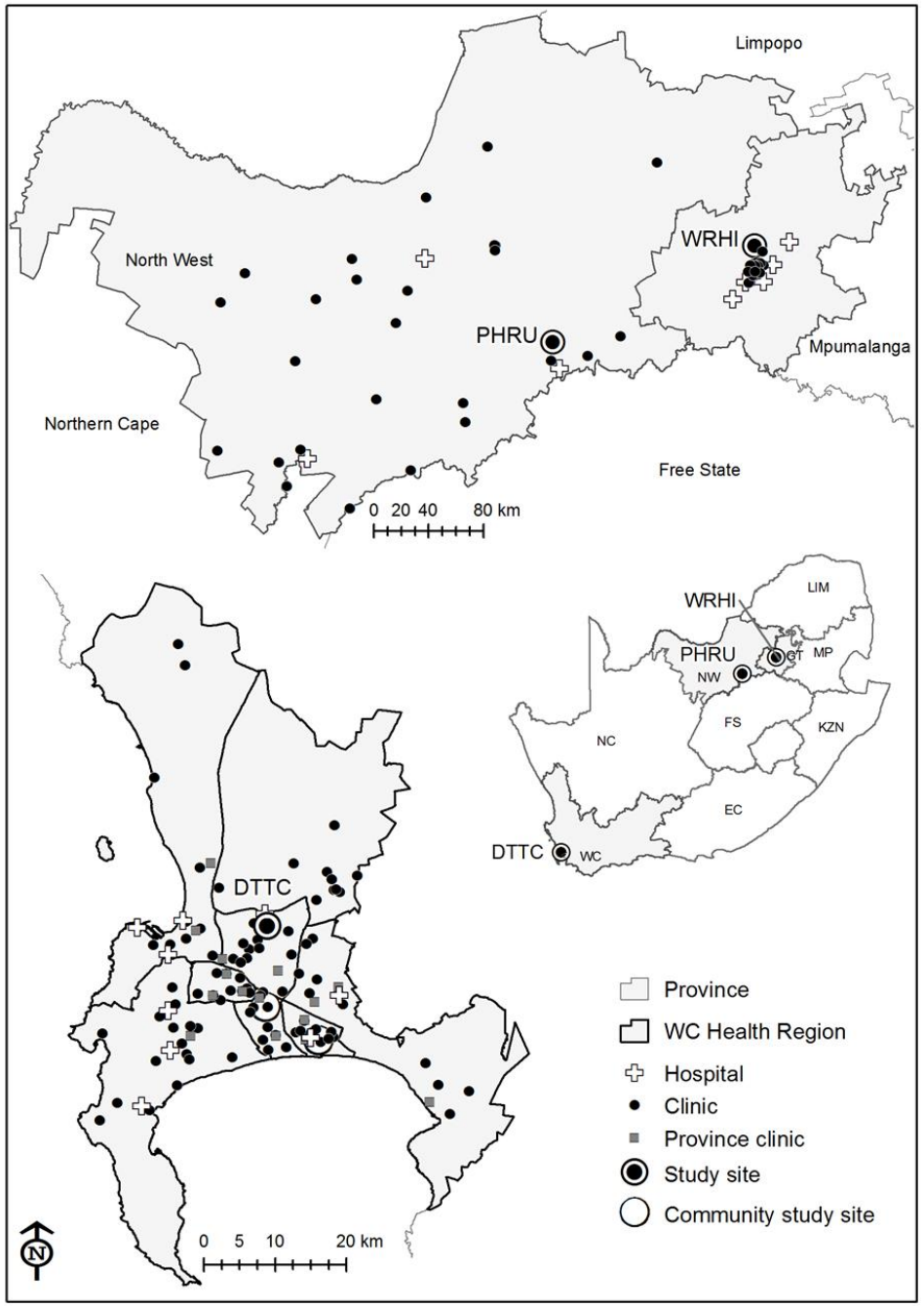
Location of South African sites conducting the TB-CHAMP study, and clinics where sites recruit



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Methods

- Recruitment process originally tracked using logs and online spreadsheets - later a dedicated recruiting platform “Mobilize” was developed
- Data for consort diagram: Drawn from logs, Mobilize, and trial database
- Data to elucidate challenges/solutions: Came from weekly site meetings, team calls, questionnaires completed by study staff, diaries, in-person full-team workshops & brain-storming sessions

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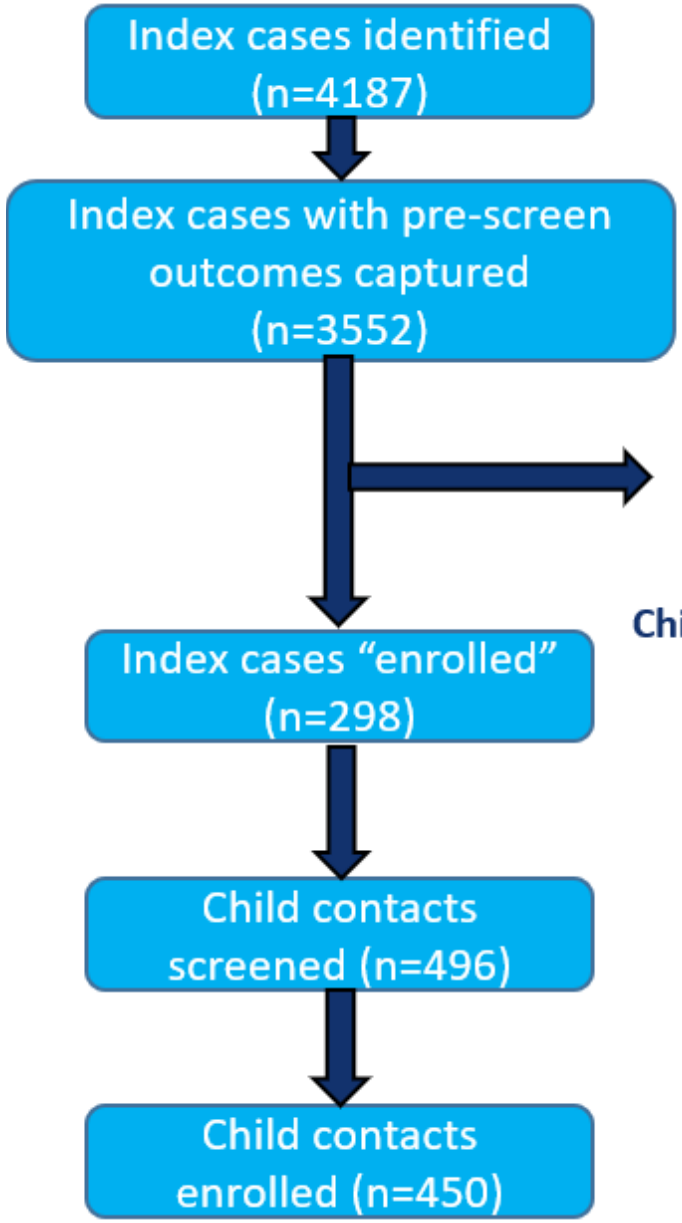
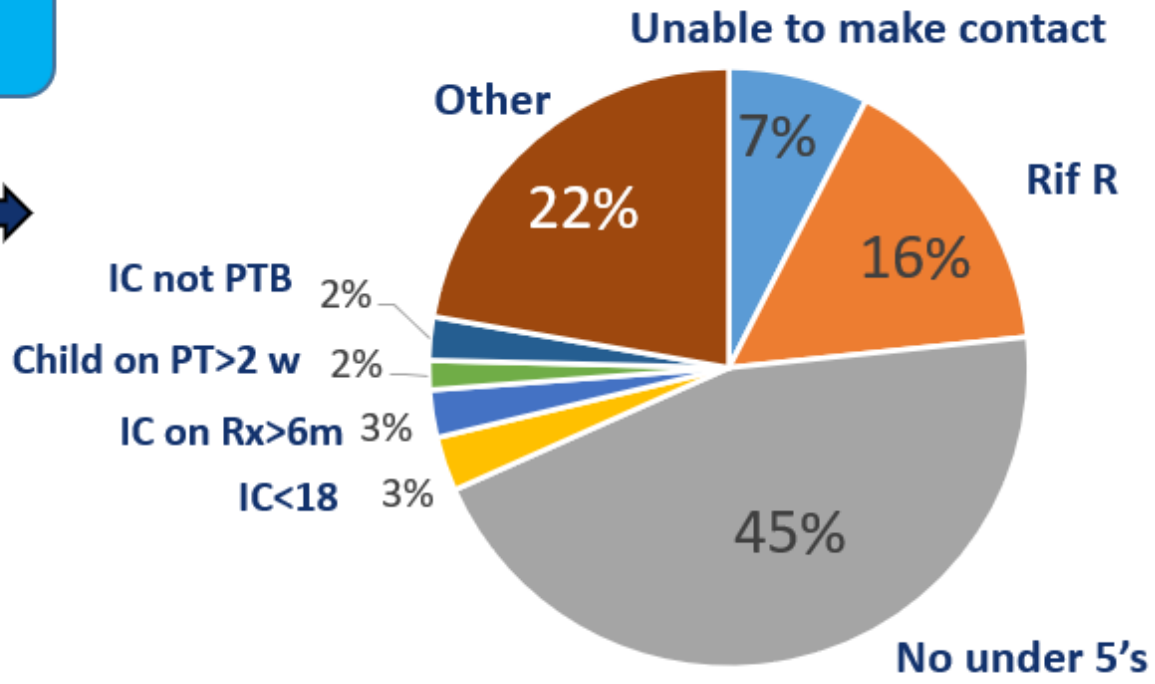
Results

CONSORT diagram
Number of adult MDR-TB index cases pre-screened and screened
Number of children screened and enrolled

Note: 9.3 MDR index cases screened for every child enrolled





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PARTICIPANT CHALLENGES AND SOLUTIONS

CHALLENGE	POSSIBLE SOLUTIONS	IMPLEMENTED?
Index case and caregiver		
Difficult to contact/locate (lack of contact details, migration, work schedule, illness, hospitalisation, imprisonment)	Meet index case at clinic, drive together to home. Record multiple contact details. Work outside normal office hours. Obtain permissions to recruit in hospitals.	Yes
Illness (making consenting difficult), death	Be prepared to take consent in hospital, over multiple days. Allow relative of deceased index case to consent.	Yes
Substance abuse (drugs, alcohol)	Be prepared to visit home on multiple occasions, especially early morning.	Yes
Mistrust regarding research studies	Well trained recruiters from local communities to take consent. Active Community Advisory Board.	Yes
Stigma, fear of rejection/eviction	Recruiters to discuss stigma at first contact. Use of unmarked cars and clothing. Option to use own transport to get to study site.	Intermittently
Child		
In foster care due to illness/hospitalisation of caregiver - unable to attend study visits	Take consent from parent/legal guardian. Arrange transport for child and foster parent for follow-up visits.	Yes
Caregiver		
No legal confirmation of guardianship	Assist family to obtain guardianship	Yes
Second parent refuses consent	Try to involve both parents in consent process	Yes

PARTICIPANT CHALLENGES AND SOLUTIONS

CHALLENGE	POSSIBLE SOLUTIONS	IMPLEMENTED?
Index case and caregiver		
D…tact d… illness, hospitalisation, imprisonment)	recruit in hospitals …ltiple …missions to	Yes
I… d…	…llow	Yes
S…	…arly	Yes
M…	…t. Active Community Advisory Board.	Yes
S…	… cars and	Intermittently
C…		
I… illness/hospitalisation of caregiver - unable to attend study visits	…r child and foster parent for follow-up visits.	Yes
Caregiver		
No legal confirmation of guardianship	Assist family to obtain guardianship	Yes
Second parent refuses consent	Try to involve both parents in consent process	Yes

Challenges

Difficult to contact (lack of contact details, migration, work schedule, illness)

Stigma, fear of rejection/eviction

Possible solutions

Meet index case at central point - drive together to find home. Record multiple contact details. Work outside normal office hours. Hospital visits.

Discuss at first contact. Unmarked vehicles and clothing.

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STUDY TEAM/RESOURCE CHALLENGES AND SOLUTIONS

CHALLENGE	POSSIBLE SOLUTIONS	IMPLEMENTED?
Short staffed, especially drivers	Budget carefully for support staff. Train drivers as recruiters.	Over time
Lack of recruitment tracking system	Start study with good electronic recruitment tracking system. Does not need to be complex.	Over time
Dual roles (as recruiter and research assistant)	Carefully structure team and clarify roles - preferable to have dedicated recruiting team	Over time
Lack of team leadership, clearly defined team structure	Recruitment team leader key hire - motivated individual with good administrative, interpersonal skills	Over time
Communication between team members, multiple facilities, and study sites	User friendly recruitment tracking system. WhatsApp groups. Phones, data, airtime to all team members. Dedicated study phone per study site. Good internet connection at study sites.	Over time
High staff turnover	Protocols/material in place for rapid training of new staff.	Over time
Trial fatigue	Clear targets. Staff incentives (meals, social events, small gifts).	Over time

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Dual ro … assista …	Care … ave dedi …	Over time
Lack o … defined	Recr … with goo …	Over time
Comm … membe … study s …	Use … ups. Pho … udy pho … sites.	Over time
High st …	Prot …	Over time
Trial fatigue	Clear targets. Staff incentives (meals, social events, small gifts).	Over time

Challenges	Possible solutions
Short staffed (especially drivers)	Budget carefully for additional support staff Multiple roles
Lack of good recruitment tracking system	Start study with customised electronic system
Lack of team leadership	Recruiting team leader is key hire

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STUDY DESIGN & SETTING CHALLENGES AND SOLUTIONS

CHALLENGE	POSSIBLE SOLUTIONS	IMPLEMENTED?
Randomised, placebo-controlled trial	Carefully explain rationale in simple language. Meet regularly with routine health care team to discuss study rationale.	Yes
Prevention trial	Carefully explain benefits of prevention.	Yes
Long follow-up period	Explain rationale for follow-up period and stress that follow-up in routine care would be similar length.	Yes
Time-consuming consent process	Use of recruiters to consent. Drivers function as recruiters.	Yes
Dual written consent (index case and caregiver) needed	Use of recruiters to consent. Drivers function as recruiters.	Yes
Index case criteria (adult, MDR-TB, diagnosed from sputum during last 6 months, rifampicin mono-resistance excluded)	Data extract from laboratory very useful to identify newly diagnosed pulmonary TB adult index cases. Careful follow-up and tracking to exclude rifampicin mono-susceptibility.	Yes
Child inclusion criteria (under 5, close household contact, preventive therapy < 2 weeks)	Plan for large recruiting area. Attempt to enrol children as soon as possible after index case is diagnosed.	Over time
Potential duplication of work with routine care	Develop and pilot good communication tools between study and routine care	Over time
Long waiting times during study visits	Optimise clinic flow with available resources. Participant appointments in different time slots. Doctors start day by writing scripts to avoid pharmacy delays.	Over time
Migrant population - moving regularly between homes, suburbs, provinces	Constantly update contact details. Anticipate multiple attempts to make contact.	Yes
Poor communities (homes difficult to locate, poorly educated participants, co-morbidities, substance abuse)	Make use of local knowledge, employ staff from local communities, simple language in study material	Yes
Violent communities	Staff safety is paramount: Recruiters work in pairs, drivers accompany recruiters to homes, drivers with advanced driving skills, avoid potential hot spots.	Yes
Over researched communities	Ensure excellent synergy and co-operation with other researchers in the area	Mostly
Large recruiting area, numerous clinics	Budget appropriately for transport costs	Over time
Health care worker concerns regarding study design	Face to face contact sessions with health care workers, and well as presentations at clinical meetings, forums. Ready availability of supporting study documentation - simple, widely distributed	Yes
Over-worked health care workers in routine care; few referrals	Ensure referral to study is not onerous, study decreases workload for healthcare workers. Promotional materials (mugs, pens, rulers) as reminders of study.	Yes
Rapid turnover of health care workers in routine care	Regular updates, posters in each clinic, be prepared to explain study at each clinic visit	As far as possible
Conflicting trials	Large recruiting area, develop synergies, cross-referral.	Yes
Hospitals and in-patients difficult to locate, often already discharged.	Track index cases to local clinics using address details; knowledge of local geography and referral patterns crucial.	Yes
Frequent unrest/strike action (cars mistaken for taxis)	Study vehicles to be clearly marked, using magnetic labelling (removable where stigma is a concern)	Yes

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Challenges

Possible solutions

Health care worker concerns re study design

Multiple contact sessions with routine service health care workers, widely distributed supporting material

Poor, often unstable or violent communities

Make use of local knowledge, employ local staff, staff safety paramount – work in pairs, marked vehicles

Child criteria – few under 5s

Recruit over wide geographic area from multiple facilities

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Conclusions and Recommendations

- Recruiting young children to a placebo-controlled MDR-TB prevention trial was particularly challenging
- Recommendations:
  - Invest considerable time and resources in a detailed and careful recruiting plan
  - Budget carefully – anticipate considerable expenditure to work safely, effectively and sensitively in communities
  - Cross-training of staff - train recruiters to consent participants and drivers to recruit
  - Invest resources in developing a recruiting tracking system

Acceptability of a novel levofloxacin dispersible tablet formulation in young children exposed to MDR-TB

Acceptability of a Novel Levofloxacin Dispersible Tablet Formulation in Young Children Exposed to Multidrug-resistant Tuberculosis

Susan E. Purchase, MD, Anthony J. Garcia-Prats, MD,* Petra De Koker, MSc,* Heather R. Draper, MSc,* Muhammad Osman, MD,* James A. Seddon, PhD,*† H. Simon Schaaf, MD,* and Anneke C. Hesseling, PhD**

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Introduction

- A 100-mg dispersible taste-masked child-friendly levofloxacin formulation was developed by Macleods Pharmaceuticals, for possible use in TB-CHAMP
- An open-label PK lead-in study took place in Cape Town, before TB-CHAMP, to characterize the pharmacokinetics and safety of this novel formulation
- This sub-study investigated the acceptability of this novel formulation in the children on the PK study

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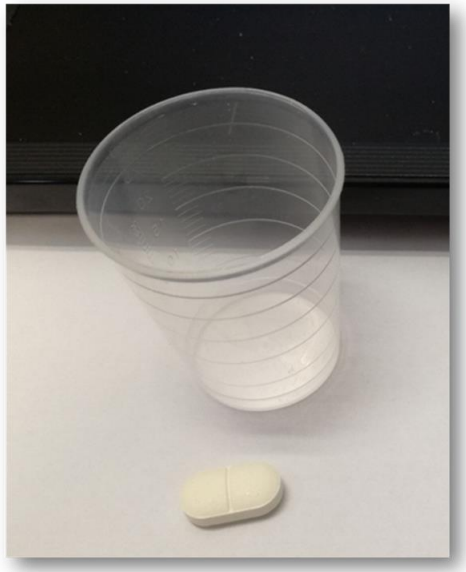
Methods

- Levofloxacin 100 mg tablets administered once daily by caregivers to children, for 7-14 days.
- Tablets administered whole, crushed or dissolved
- A Likert scale palatability/acceptability questionnaire was administered to all caregivers on last day of levofloxacin administration.
- In situ household observations and interviews with patients and caregivers conducted



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Results: Questionnaire

- **27** children enrolled, **11** (40%) girls, median age **25** (IQR 9.5 – 31.5) months
- All caregivers reported that the tablet **dissolved easily**
- All caregivers were happy with the drug **volume**

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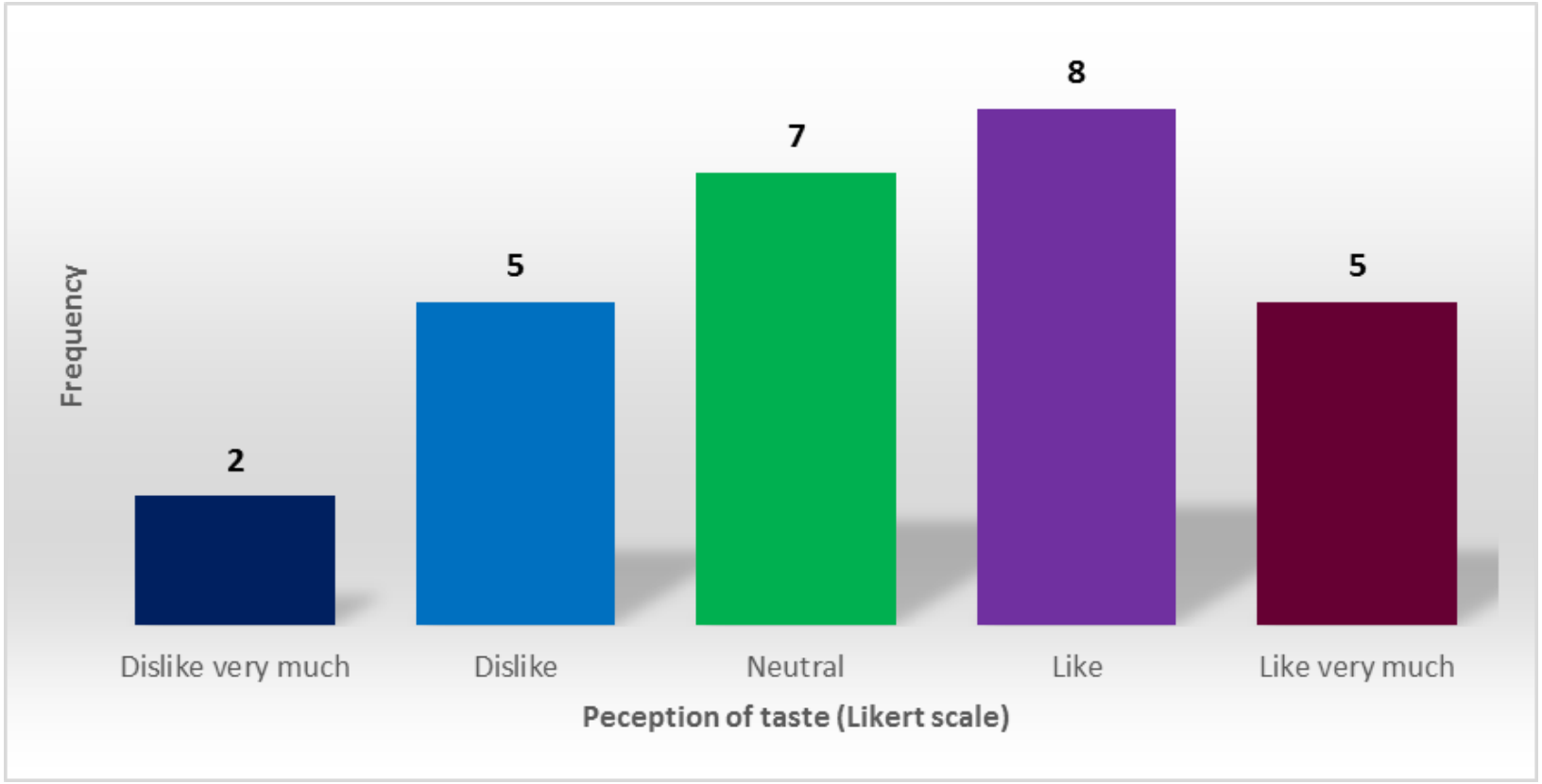
Caregiver's perceptions of palatability



13/27 (48%) of caregivers felt that their children liked/really liked the taste of the tablets. Only 7/27 (26%) disliked the taste.

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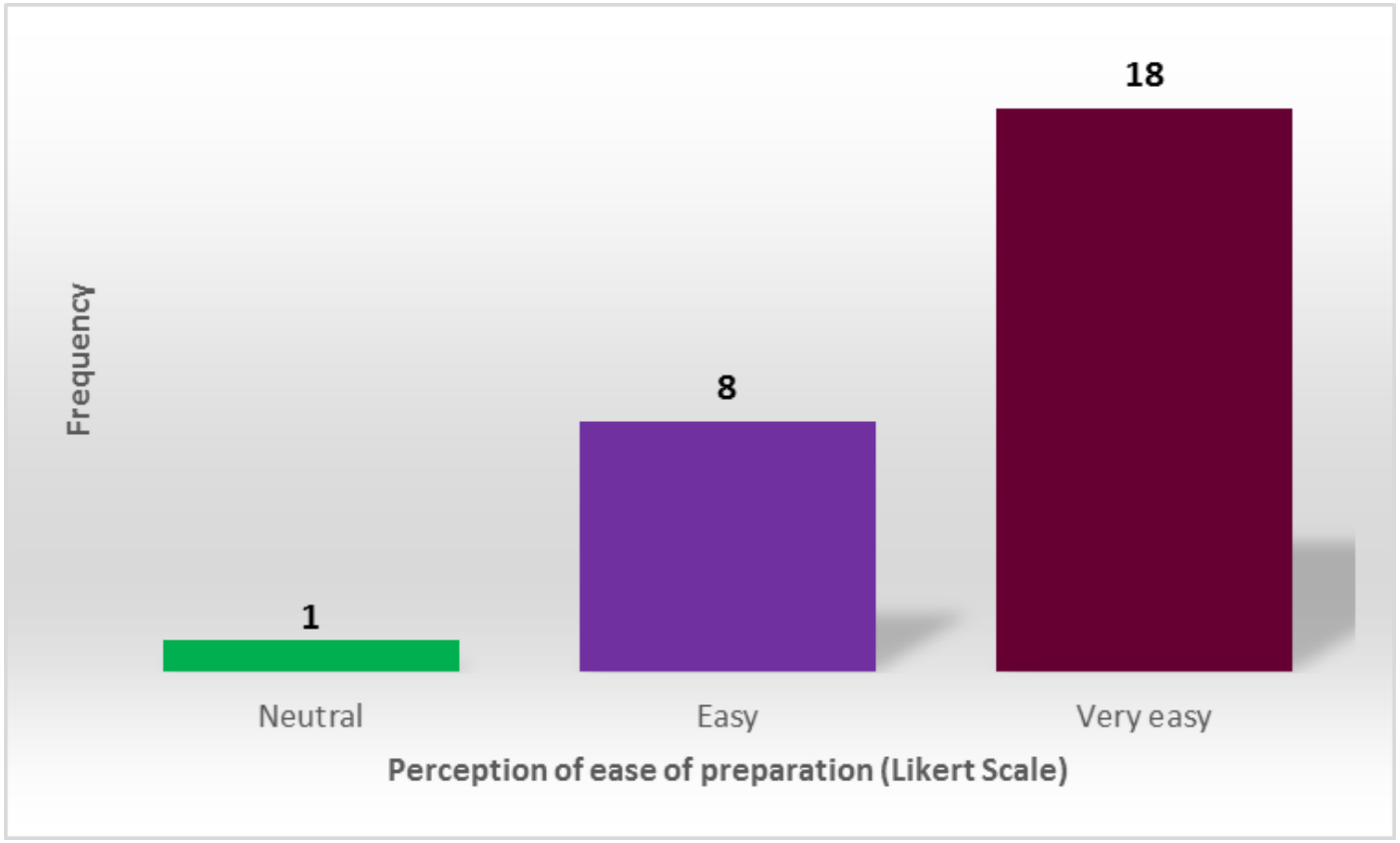
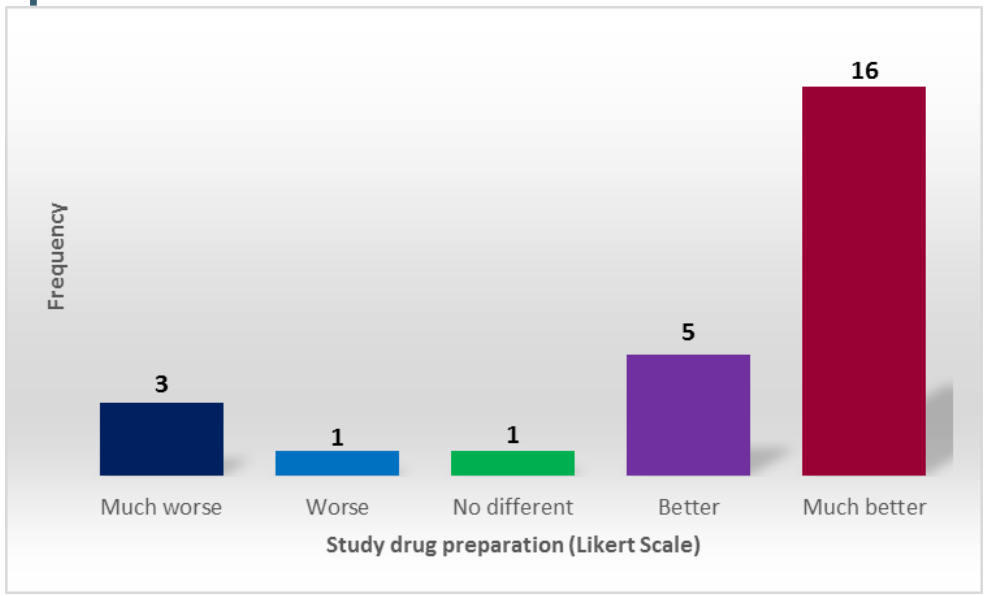
Caregiver's perceptions of ease of preparation



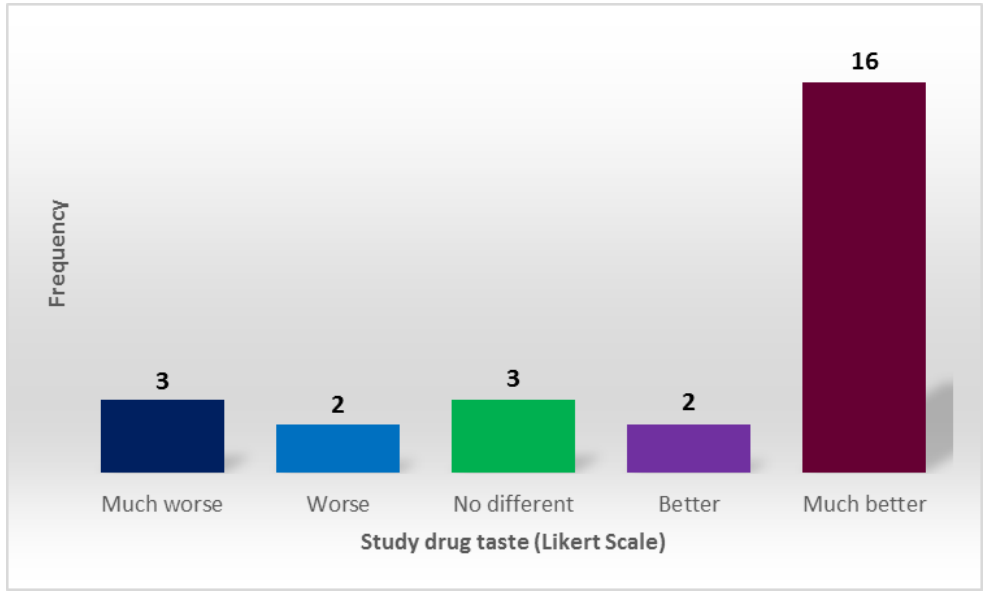
26/27 (96%) of caregivers indicated that the preparation of doses was easy/very easy.

Caregiver's comparison of study drug preparation with preparation of previous TB medication



22/26 (85%) felt that preparation of the new formulation was easier/much easier than preparation of previous regimen.

Caregiver's comparison of study drug taste with taste of previous TB medication



18/26 (81%) felt that taste of the new formulation was equivalent/better/much better than taste of their previous regimen.

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Results: Household interviews and observations

- Caregivers adopted various strategies to facilitate treatment administration
  - e.g. concealing treatment in food, praise, bribery, distraction, threats, reducing volume of water used
- Many caregivers very relieved by relative ease of administering the new formulation
- Children's reactions to new formulation varied - one child spat out the medication, while this little girl said…

Conclusions

- Good acceptability and palatability in young children taking a novel dispersible paediatric levofloxacin formulation.
- Caregivers adopt various innovative methods to ease treatment administration and improve acceptability.

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Acceptability of an adult levofloxacin formulation in children on MDR-TB preventive treatment: A quantitative analysis

Introduction

- PK-lead in work showed much higher bioavailability of dispersible formulation that was anticipated
- Decision made to use adult 250mg levofloxacin formulation for TB-CHAMP
- Adult formulations are affordable and widely used for TB treatment and prevention

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Aims

- To explore the **acceptability** of the 250mg formulation and taste-matched placebo over time
- To characterize **administration** methods used in children
- To assess the **relationship** between characteristics of children at baseline (age, gender, site, HIV exposure, chronic illness), and longitudinal acceptability
- To assess the impact of acceptability on **adherence**

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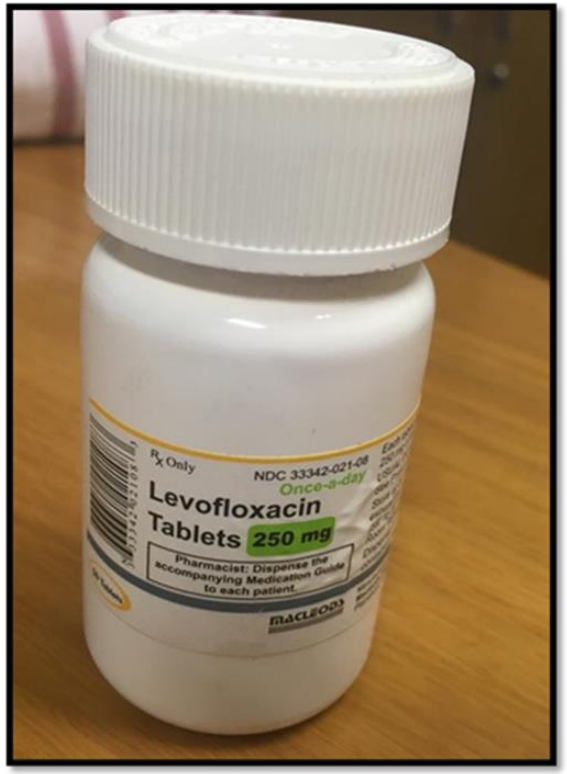
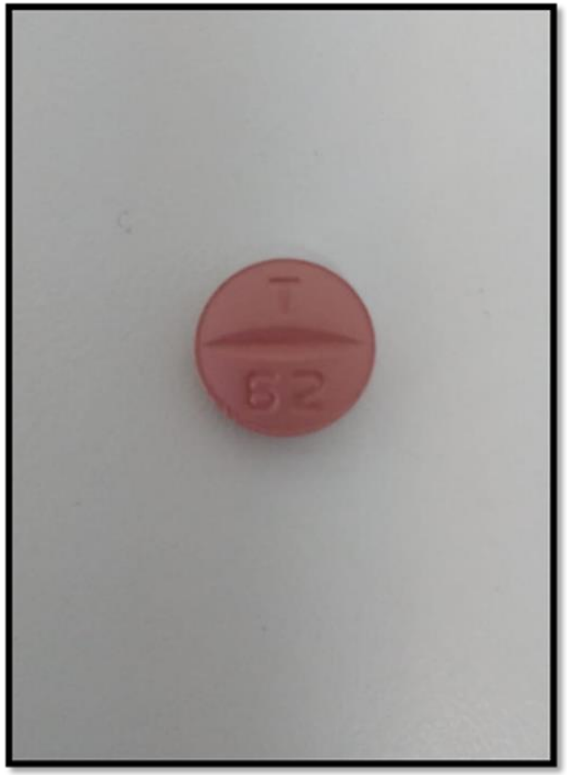
Methods

Study drug

- Study medications were manufactured by Macleods as 250 mg levofloxacin or matched levofloxacin-placebo
- Initial dosing was at the study site; subsequent doses were given by caregivers at home.
- Poor adherence was defined as participants having taken <80% of prescribed study treatment doses.





Macleods Pharmaceuticals (Mumbai, India)
Levofloxacin and taste-matched placebo

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Methods

Data collection

- Acceptability questionnaires administered at baseline and then monthly
- Questionnaires consisted of
  - 6 items soliciting ranked responses regarding **acceptability**
  - 14 questions soliciting categorical responses regarding **study drug administration**
  - 2 questions asking whether the caregiver needed to **force/coerce** the child to take the study drug
- 5-point Likert scale was used to grade acceptability domains

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Methods

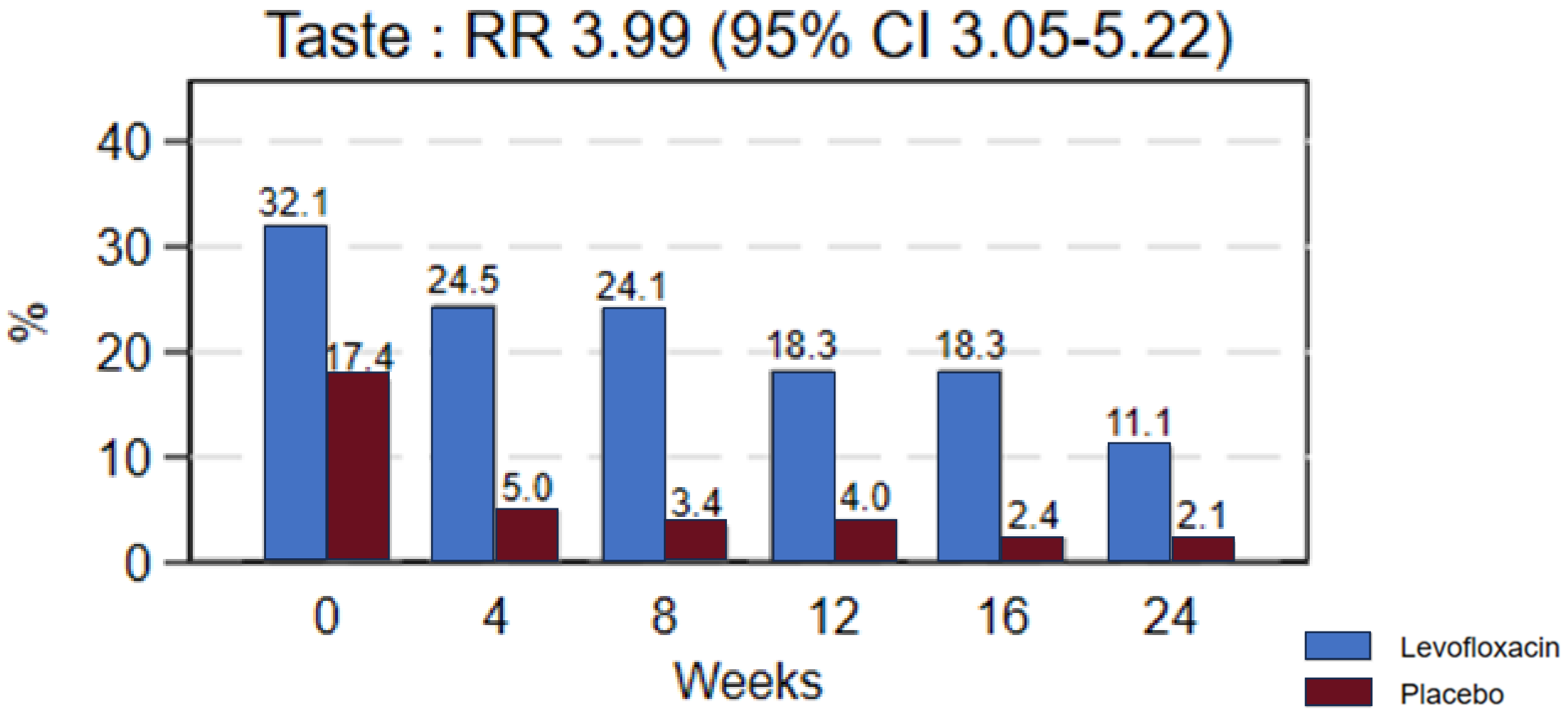
Analysis

- Binary outcomes were generated from the 5-point Likert scale; composite outcomes were generated which included participants with poor acceptability in any of the 6 domains
- Acceptability was compared between levofloxacin and placebo arms, and over time
- Modified Poisson regression was used to estimate RR and CIs

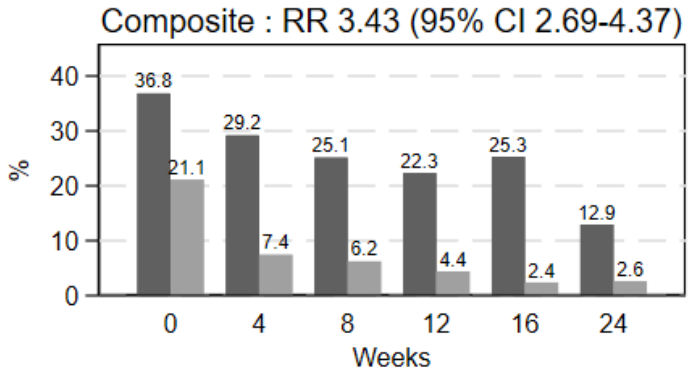
Results

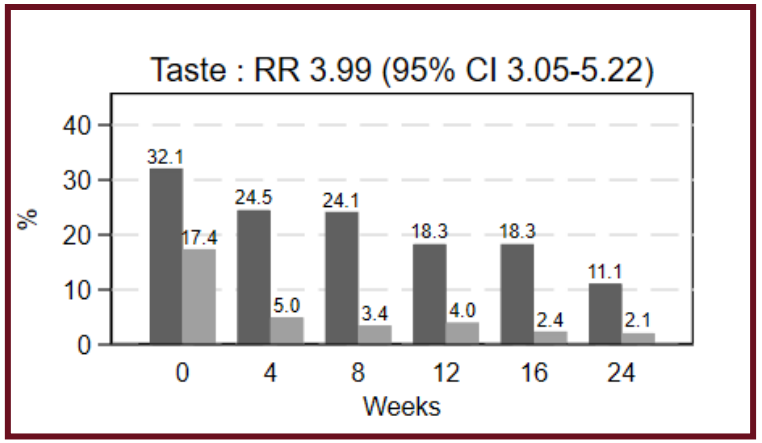
		Levofloxacin	Placebo	Total
N children randomised+	N	452 (100%)	468 (100%)	920 (100%)
Gender	Female	240 (53%)	226 (48%)	466 (51%)
Age (years)	Median	3.0	2.6	2.8
	IQR	1.4, 4.3	1.3, 4.1	1.4, 4.2
	Range	0.1, 17.9	0.1, 17.4	0.1, 17.9
HIV status	Positive#	10 (2%)	9 (2%)	19 (2%)
	HIV-exposed uninfected	153 (34%)	160 (34%)	313 (34%)
	HIV-unexposed	287 (64%)	297 (64%)	584 (64%)
	N missing	2	2	4
BCG vaccination status	No	28 (6%)	25 (5%)	53 (6%)
	Yes	422 (94%)	441 (95%)	863 (94%)
	N missing	2	2	4
Previously received any tuberculosis treatment	Yes	10 (2%)	8 (2%)	18 (2%)
Currently on tuberculosis preventive treatment	Yes	9 (2%)	6 (1%)	15 (2%)
Weight-for-age Z score	N	452	468	920
	Median	-0.4	-0.4	-0.4
	IQR	-1.2, 0.3	-1.2, 0.4	-1.2, 0.3
	Range	-7.2, 4.2	-6.2, 5.1	-7.2, 5.1
Height-for-age Z score	N	452	468	920
	Median	-0.9	-0.9	-0.9
	IQR	-1.6, -0.1	-1.8, -0.2	-1.7, -0.2
	Range	-6.8, 8.8	-6.1, 3.3	-6.8, 8.8

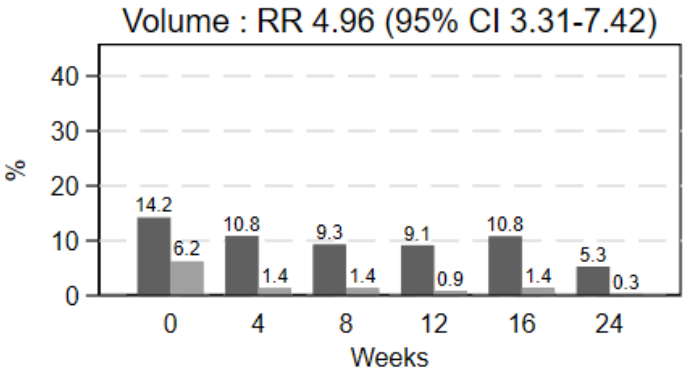
Baseline characteristics of child participants in the TB-CHAMP tuberculosis prevention trial

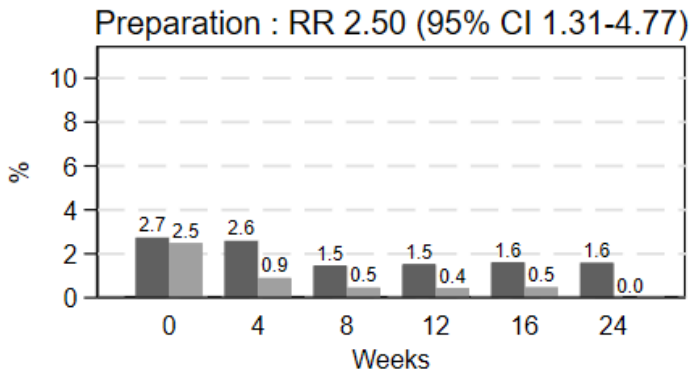


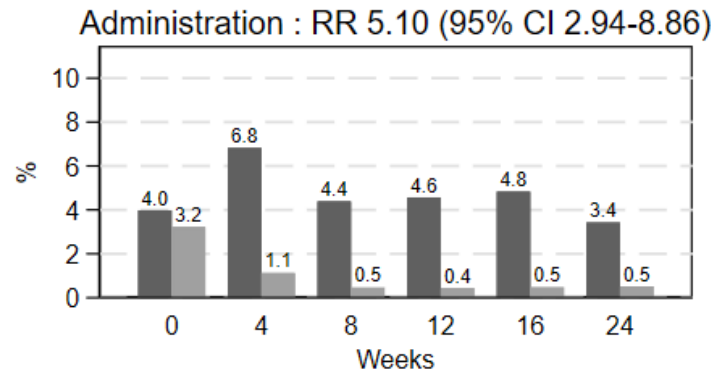
Percentage of children receiving levofloxacin/matched placebo with poor taste acceptability scores by week of study visit

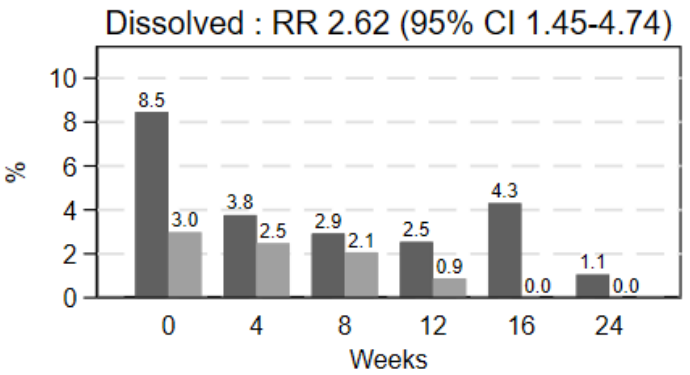

Composite : RR 3.43 (95% CI 2.69-4.37)
%
Weeks
0 4 8 12 16 24
0 10 20 30 40
36.8 21.1
29.2 7.4
25.1 6.2
22.3 4.4
25.3 2.4
12.9 2.6

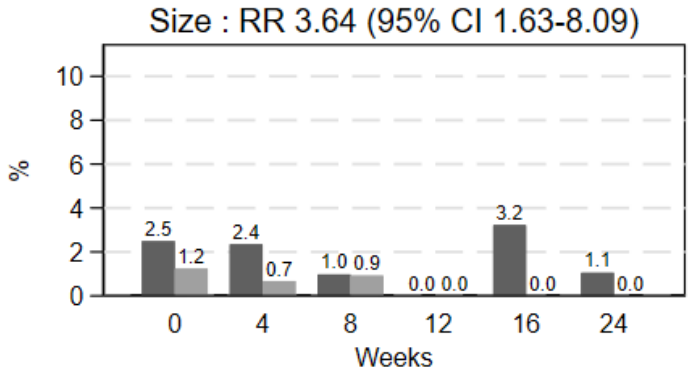

Taste : RR 3.99 (95% CI 3.05-5.22)
%
Weeks
0 4 8 12 16 24
0 10 20 30 40
32.1 17.4
24.5 5.0
24.1 3.4
18.3 4.0
18.3 2.4
11.1 2.1

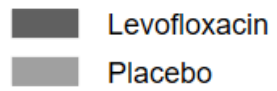

Volume : RR 4.96 (95% CI 3.31-7.42)
%
Weeks
0 4 8 12 16 24
0 10 20 30 40
14.2 6.2
10.8 1.4
9.3 1.4
9.1 0.9
10.8 1.4
5.3 0.3


Preparation : RR 2.50 (95% CI 1.31-4.77)
%
Weeks
0 4 8 12 16 24
0 2 4 6 8 10
2.7 2.5
2.6 0.9
1.5 0.5
1.5 0.4
1.6 0.5
1.6 0.0


Administration : RR 5.10 (95% CI 2.94-8.86)
%
Weeks
0 4 8 12 16 24
0 2 4 6 8 10
4.0 3.2
6.8 1.1
4.4 0.5
4.6 0.4
4.8 0.5
3.4 0.5


Dissolved : RR 2.62 (95% CI 1.45-4.74)
%
Weeks
0 4 8 12 16 24
0 2 4 6 8 10
8.5 3.0
3.8 2.5
2.9 2.1
2.5 0.9
4.3 0.0
1.1 0.0


Size : RR 3.64 (95% CI 1.63-8.09)
%
Weeks
0 4 8 12 16 24
0 2 4 6 8 10
2.5 1.2
2.4 0.7
1.0 0.9
0.0 0.0
3.2 0.0
1.1 0.0


Levofloxacin
Placebo

Factors		Levofloxacin		Placebo		Overall	
		RR (95% CI)	P	RR (95% CI)	P	RR (95% CI)	P
Gender	Male	1		1		1	
	Female	1.19 (0.97,1.46)	0.104	0.89 (0.66,1.21	0.468	1.09 (0.92,1.29)	0.310
Age	<1 year	1		1		1	
	1 to <3 years	1.11 (0.87,1.42)		1.41 (0.91,2.18		1.18 (0.95,1.46)	
	3 to <5 years	0.79 (0.60,1.02)		0.90 (0.58,1.41		0.81 (0.64,1.02)	
	≥5 years	0.45 (0.29,0.71)	P<0.001	0.96 (0.43,2.13	0.039	0.55 (0.36,0.83)	P<0.001
Site*	Site 1*	1		1		1	
	Site 2	1.26 (0.94,1.69)		0.77 (0.42,1.44		1.09 (0.84,1.43)	
	Site 3	0.81 (0.56,1.16)		0.83 (0.42,1.63		0.82 (0.58,1.15)	
	Site 5	1.23 (0.69,2.21)	0.125	0.00 (0.00,0.00	P<0.001	0.86 (0.47,1.56)	0.441
HIV exposure status	No	1		1		1	
	Yes	0.96 (0.76,1.19)	0.687	0.70 (0.46,1.09	0.112	0.87 (0.72,1.07)	0.182
Significant chronic illness	No	1		1		1	
	Yes	1.23 (0.86,1.76)	0.263	1.23 (0.72,2.09	0.456	1.23 (0.91,1.66)	0.187

Association of poor acceptability with demographic & clinical characteristics by study treatment arm and over time

		Week 0	Week 4	Week 8	Week 12	Week 16	Week 24
Tablet swallowed whole with liquid	Levofloxacin	134/402 (33.3%)	133/425 (31.3%)	145/410 (35.4%)	59/197 (29.9%)	68/186 (36.6%)	158/378 (41.8%)
	Placebo	134/403 (33.3%)	170/444 (38.3%)	196/435 (45.1%)	93/227 (41.0%)	100/211 (47.4%)	191/386 (49.5%)
Tablet swallowed halved with liquid	Levofloxacin	59/402 (14.7%)	55/425 (12.9%)	50/410 (12.2%)	14/197 (7.1%)	23/186 (12.4%)	51/377 (13.5%)
	Placebo	63/403 (15.6%)	65/444 (14.6%)	55/435 (12.6%)	30/227 (13.2%)	33/211 (15.6%)	52/386 (13.5%)
Tablet crushed	Levofloxacin	126/401 (31.4%)	167/424 (39.4%)	162/408 (39.7%)	82/195 (42.1%)	73/185 (39.5%)	138/375 (36.8%)
	Placebo	97/400 (24.2%)	104/444 (23.4%)	94/430 (21.9%)	60/223 (26.9%)	46/209 (22.0%)	80/384 (20.8%)
Tablet softened (“dissolved”) in a liquid solution	Levofloxacin	225/402 (56.0%)	210/424 (49.5%)	178/410 (43.4%)	90/197 (45.7%)	73/186 (39.2%)	143/378 (37.8%)
	Placebo	228/403 (56.6%)	219/444 (49.3%)	199/435 (45.7%)	103/226 (45.6%)	84/210 (40.0%)	166/384 (43.2%)
Child was restrained or forced	Levofloxacin	72/401 (18.0%)	81/424 (19.1%)	71/410 (17.3%)	33/197 (16.8%)	26/186 (14.0%)	47/378 (12.4%)
	Placebo	64/403 (15.9%)	15/443 (3.4%)	13/435 (3.0%)	2/227 (0.9%)	3/211 (1.4%)	6/386 (1.6%)
Child was bribed or coerced	Levofloxacin	39/401 (9.7%)	65/424 (15.3%)	58/410 (14.1%)	25/197 (12.7%)	22/186 (11.8%)	40/378 (10.6%)
	Placebo	45/403 (11.2%)	20/443 (4.5%)	16/435 (3.7%)	11/227 (4.8%)	9/211 (4.3%)	6/386 (1.6%)
Composite score for tablet swallowed whole or halved with liquid	Levofloxacin	156/402 (38.8%)	156/425 (36.7%)	162/410 (39.5%)	68/197 (34.5%)	77/186 (41.4%)	172/378 (45.5%)
	Placebo	158/403 (39.2%)	193/444 (43.5%)	212/435 (48.7%)	105/227 (46.3%)	109/211 (51.7%)	210/386 (54.4%)
Composite score if child was restrained/forced or bribed/coerced	Levofloxacin	83/401 (20.7%)	100/424 (23.6%)	94/410 (22.9%)	43/197 (21.8%)	39/186 (21.0%)	62/378 (16.4%)
	Placebo	83/403 (20.6%)	27/443 (6.1%)	20/435 (4.6%)	11/227 (4.8%)	11/211 (5.2%)	11/386 (2.8%)

Administration of study treatment over time in children receiving levofloxacin 250 mg or placebo

Results: Administration

- Children taking levofloxacin were 5 x as likely to be forced/bribed to take treatment than those taking placebo
- Children aged 1 to < 3 years were >7 x more likely to be forced/bribed to take treatment than children > 5 years
- 65.6% of children aged 3-<5 years given levofloxacin were able to swallow tablets whole/halved at some point during the trial

Results: Adherence

- Adherence good in both arms – 87% in levo arm and 86% placebo arm took > 80% of prescribed doses

Acceptability outcome		Number of participants	Median proportion (IQR) of doses missed	Proportion of participants discontinuing treatment early	Proportion of participants with poor adherence (took < 80% of doses)	Risk ratio (95% CI)	P
Child/adolescent disliked very much/disliked the taste of medication	No	321	4 (1,10)	39 (12.1%)	35 (10.9%)	1	
	Yes	104	4.5 (2,12)	18 (17.3%)	16 (15.4%)	1.47 (0.81,2.65)	0.201
Caregiver found it very difficult/difficult to prepare of study medication	No	414	4 (2,11)	53 (12.8%)	47 (11.4%)	1	
	Yes	11	4 (1,60)	4 (36.4%)	4 (36.4%)	3.39 (1.53,7.52)	0.003
Caregiver found it very difficult/difficult to administer the doses	No	396	4 (1,10)	52 (13.1%)	46 (11.6%)	1	
	Yes	29	10.5 (3.5,18)	5 (17.2%)	5 (17.2%)	1.29 (0.53,3.14)	0.568

Acceptability at Week 4 and adherence in children receiving 250 mg levofloxacin or matched placebo

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Conclusions

- 250mg formulation had reasonable acceptability – only 25% reported poor acceptability by week 8, and 13% by week 24
- Acceptability improved over time
- Levofloxacin was less well-tolerated than placebo
- No clear relationship between acceptability (usability) and adherence
- Many children aged 3-<5 learnt to swallow whole/halved
- Poor acceptability was associated with being younger and being unable to swallow whole/halved

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Acceptability of an adult levofloxacin formulation in children on MDR-TB preventive treatment: A qualitative analysis

Holistic acceptability of an adult levofloxacin formulation in children and adolescents on a tuberculosis preventive treatment trial

Susan E. Purchase[1]*, Dillon T. Wademan[1], Nosibusiso L. Tshetu[1], Mohhadiah Rafique[1], Graeme Hoddinott[1], James A. Seddon[1,2], H. Simon Schaaf[1], Anneke C. Hesseling[1]

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Introduction

- Acceptability of drug treatment in children has been limited to assessing palatability and ease of administration
- However, **individual patient-related factors**, (co-morbidities, treatment adverse effects, and psychological responses) also impact acceptability
- Additional **broader socio-environmental factors** (stigmatisation, social determinants of health, poverty and poor functioning health systems) may also impact treatment acceptability

Methods

Toward a conceptual framework of the acceptability of tuberculosis treatment in children using a theory generative approach

Dillon T. Wademan[1]*, Megan Palmer[1], Susan Purchase[1], Marieke M. van der Zalm[1], Muhammad Osman[1,2], Anthony J. Garcia-Prats[1,3], James A. Seddon[1,4], H. Simon Schaaf[1], Anneke C. Hesseling[1], Ria Reis[5], Lindsey J. Reynolds[6,7], Graeme Hoddinott[1]

- Nested **qualitative evaluation** in a subset of children & caregivers at a **single** CHAMP site
- We used a case study, longitudinal design, comprising multiple interviews with each participant group over 6 months
- Interviews included verbal and activity-based probes, expressly used to facilitate children's active participation in the study
- Analytic themes were informed by Wademan et al.'s (2022) conceptual framework of TB treatment acceptability

Socio-behavioural scientist during interview with participant and caregiver

Activity-based probe used to explore concept of placebo

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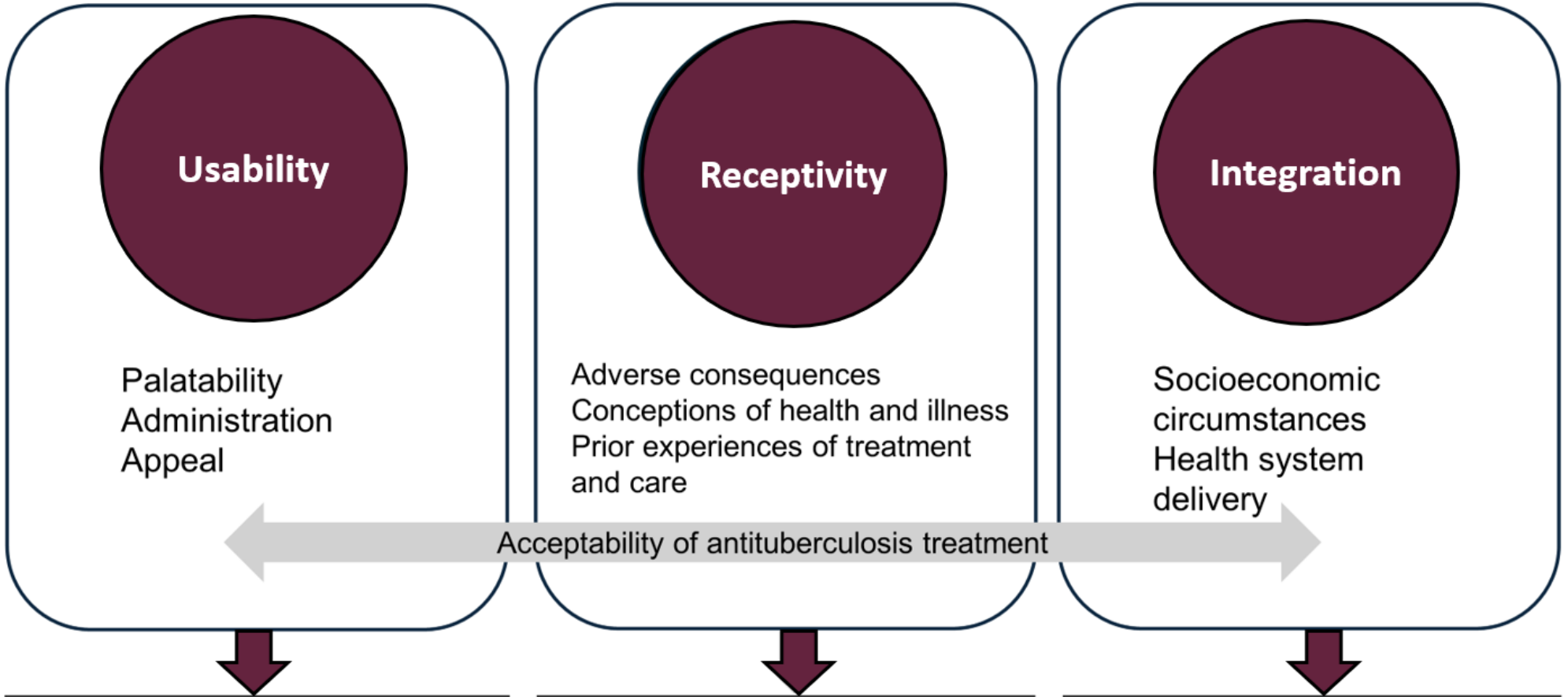
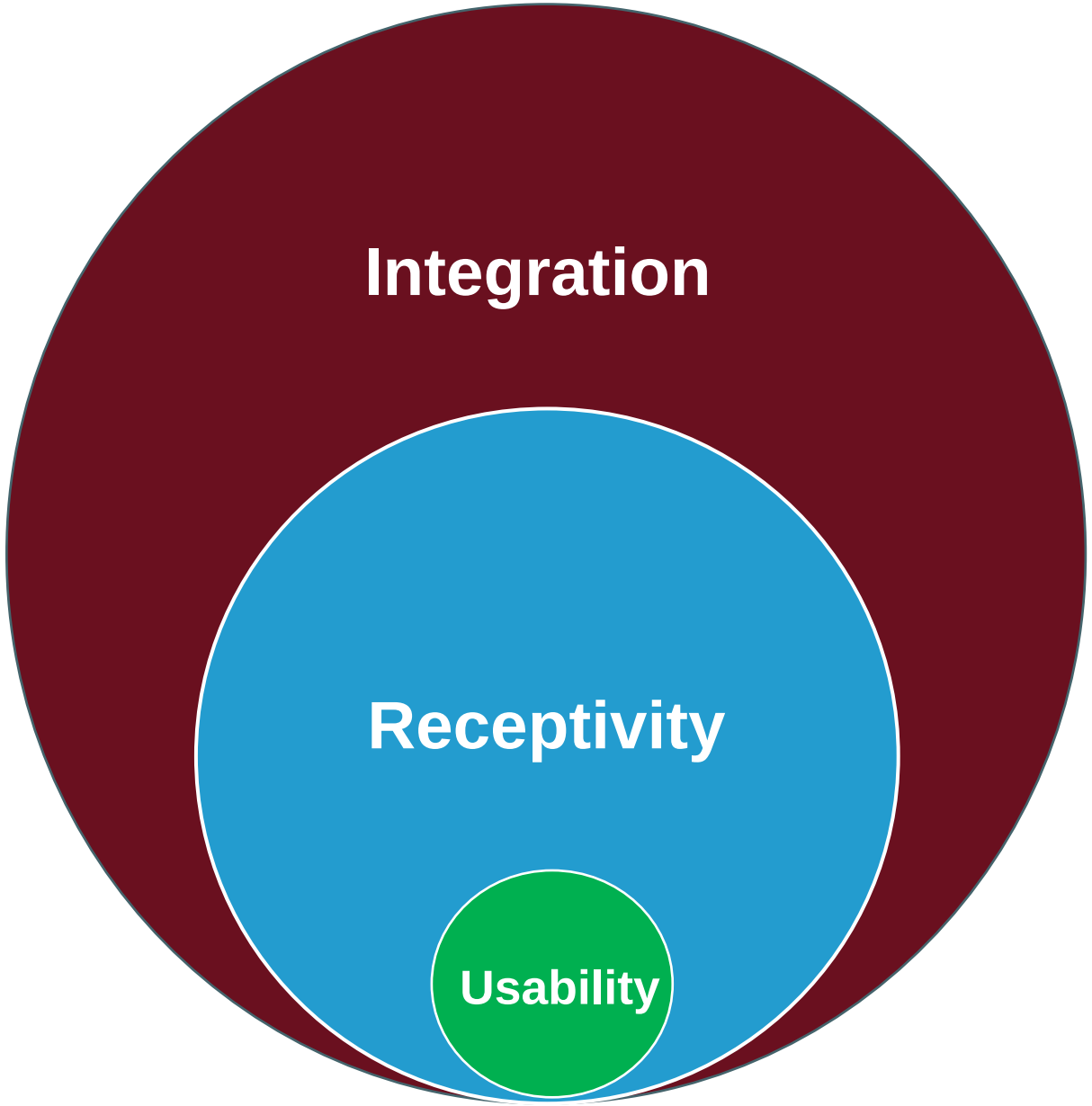
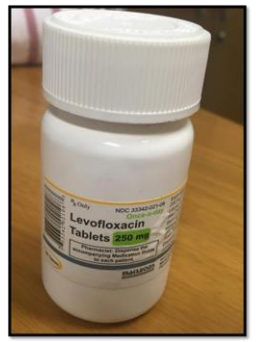
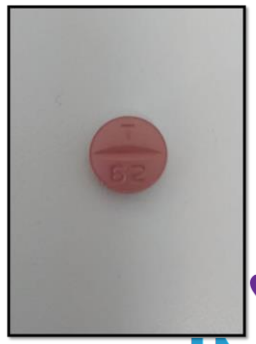
Wademan's conceptual framework of TB treatment acceptability









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USABILILTY	RECEPTIVITY	INTEGRATION
Palatability When crushed or softened described as: "*Bitter" like "aloe"; "lemon", "paracetamol*"; "*dark chocolate*" When swallowed whole described as: "*Lekker*" (nice); "*no taste*"; "*Taste bad if you suck them*" **Administration** Process challenges: Crushed/softened in water for young children "*Takes about 20 minutes to dissolve*" Halving tablet is difficult Difficult to mask taste Needed to bribe Learnt to tolerate over time **Appeal** "*Feels grown up*" when taking treatment (7-year-old, watches other family member takes TB treatment) Smells bad Tablets are "*small*"	**Adverse consequences** ***- Physiological*** Variety of minor adverse effects (nausea, stomach cramps, dizziness, insomnia, increased appetite) Did not interfere with ability/willingness to administer drug ***- Psychological*** Little associative stigma, some internalized stigma. Caregivers use stigmatizing language towards index cases. **Conceptions of health and illness** Health requires regular water, fruit and veg and exercise TB a contagious, airborne, "*terrible*" illness MDR-TB "*a lot worse*", "*they say it sends you to your maker*" Strong belief that TB preventive therapy will prevent TB **Prior experiences of treatment and care** Most families have substantial experience of TB – anxious to prevent in children - "*as long as my child is going to be alright*" Little experience of preventive therapy in routine care	**Socioeconomic circumstances** Barriers: Most families struggling financially Isolation, depression Facilitators: Free transport, financial compensation "*I can buy food*"; helpful study staff "*They really care*" **Health system delivery** ***- Accessing care on study*** Barriers: Waiting times, blood draws, communication with drivers Facilitators: Accessible study sites, shorter waiting times (compared with routine care), sick certificates, convenient appointment times ***- Accessing care in routine health system*** Barriers: Loss of patient folders, long waiting times "*You sit there the whole day*", fear of contracting illness while waiting in queues, unavailability of certain medications, shortage of staff, unhelpful staff - "*they don't have passion*" Facilitators: None mentioned

USABILILTY

Palatability
When crushed or softened described as: "*Bitter" like "aloe"; "lemon", "paracetamol*"; "*dark chocolate*"
When swallowed whole described as: "*Lekker*" (nice); "*no taste*"; "*Taste bad if you suck them*"

Administration
Process challenges:
Crushed/softened in water for young children
"*Takes about 20 minutes to dissolve*"
Halving tablet is difficult
Difficult to mask taste
Needed to bribe
Learnt to tolerate over time

Appeal
"*Feels grown up*" when taking treatment (7-year-old, watches other family member takes TB treatment)
Smells bad
Tablets are "*small*"

Palatability
Crushed: "bitter" like "aloe", "paracetamol", "dark chocolate"
Whole: "Lekker (nice)", "taste bad if you suck them"

Administration
"Takes about 20 minutes to dissolve"
Halving tablet is difficult
Difficult to hide taste, need to bribe
Learnt to tolerate over time

Appeal
"Feels grown up" when taking treatment
Smells bad

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RECEPTIVITY

Adverse consequences
- Physiological
Variety of minor adverse effects (nausea, stomach cramps, dizziness, insomnia, increased appetite)
Did not interfere with ability/willingness to administer drug
- Psychological
Little associative stigma, some internalized stigma.
Caregivers use stigmatizing language towards index cases.

Conceptions of health and illness
Health requires regular water, fruit and veg and exercise
TB a contagious, airborne, "*terrible*" illness
MDR-TB "*a lot worse*", "*they say it sends you to your maker*"
Strong belief that TB preventive therapy will prevent TB

Prior experiences of treatment and care
Most families have substantial experience of TB – anxious to prevent in children - "*as long as my child is going to be alright*"
Little experience of preventive therapy in routine care

Adverse consequences

Physiological: Minor (nausea, cramps, dizziness, insomnia, increased appetite); did not interfere with willingness to give/take drug
Psychological: Little associative but some internalized stigma

Conceptions of health and illness

TB is contagious, airborne, "terrible"
MDR-TB is "a lot worse" "they says it sends you to your Maker"

Prior experiences of care and treatment

Most had substantial experience of TB – anxious to prevent in kids
Little experience of preventive therapy in routine care

INTEGRATION

Socioeconomic circumstances
Barriers: Most families struggling financially
Isolation, depression
Facilitators:
Free transport, financial compensation "*I can buy food*"; helpful study staff "*They really care*"

Health system delivery
- Accessing care on study
Barriers: Waiting times, blood draws, communication with drivers
Facilitators: Accessible study sites, shorter waiting times (compared with routine care), sick certificates, convenient appointment times
- Accessing care in routine health system
Barriers: Loss of patient folders, long waiting times "*You sit there the whole day*", fear of contracting illness while waiting in queues, unavailability of certain medications, shortage of staff, unhelpful staff - "*they don't have passion*"
Facilitators: None mentioned

Socioeconomic circumstances

Barriers: Financial, isolation, depression
Facilitators: Free transport, compensation "I can buy food", helpful study staff "they really care"

Health system delivery

On study:
Barriers: Waiting times, blood draws, communication with drivers
Facilitators: Accessible sites, shorter waiting times, sick certificates, convenient appt times

Routine care:
Barriers: "You sit there the whole day", loss of patient folders, fear of contracting illness in queues, unavailability of medication, unhelpful staff - "they don't have passion"
Facilitators: none mentioned

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Conclusions

- Older children found this formulation acceptable - disliked by younger children
- Better formulations will not address the challenging home circumstances that many families face
- Implementation models for MDR-TPT must interface with the financial and social circumstances of the child & caregiver

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TB-CHAMP team



















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PHRU: Neil Martinson WHRI: Lee Fairlie.Think: Suzanne Staples Isanga Lethemba: Susan Ford, Francesca Conradie.

Economist: Tommie Wilkinson

Thank you for listening