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Impact of Levofloxacin on Non-Tuberculosis Clinical Outcomes in Young Children Receiving Preventive Treatment for MDR-TB

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Desmond Tutu TB Centre – Every breath counts

Stellenbosch University

Background

MDR-TB preventive treatment

- Young household contacts of MDR/RR-TB patients are at high risk of
  - ➢ TB infection
  - ➢ Progression to disease
- WHO now recommends 6 months of levofloxacin preventive treatment for MDR-TB contacts
- However, concerns remain regarding prolonged fluoroquinolone exposure

Evidence gap

- There are limited data describing the broader non-TB clinical effects of long-term levofloxacin use in young children

Problem statement/Rationale

- Programmatic scale-up of MDR-TB preventive therapy is increasing globally
- Existing studies have focused on
  - TB prevention efficacy
  - Serious adverse events
- Less is known about
  - growth outcomes
  - haematologic changes
  - intercurrent infections
  - antibiotic use
  - healthcare facility use
- Understanding these outcomes is essential to support clinician confidence, caregiver acceptance & policy implementation

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Problem statement/Rationale

Primary Objective

To evaluate the impact of levofloxacin preventive treatment on non-TB clinical outcomes among young child household contacts enrolled in the TB-CHAMP MDR-prevention trial

Specific objectives

To compare between levofloxacin and placebo groups:

- Growth trajectories
- Full blood count parameters
- Antibiotic prescriptions
- Infectious events
- Healthcare utilization

Methods

TB-CHAMP

- Cluster-randomized, double-blind, placebo-controlled
- Enrolled children between 2017 and 2022
- Compared levofloxacin daily × 24 weeks versus matching placebo

Study Design

Secondary analysis of TB-CHAMP

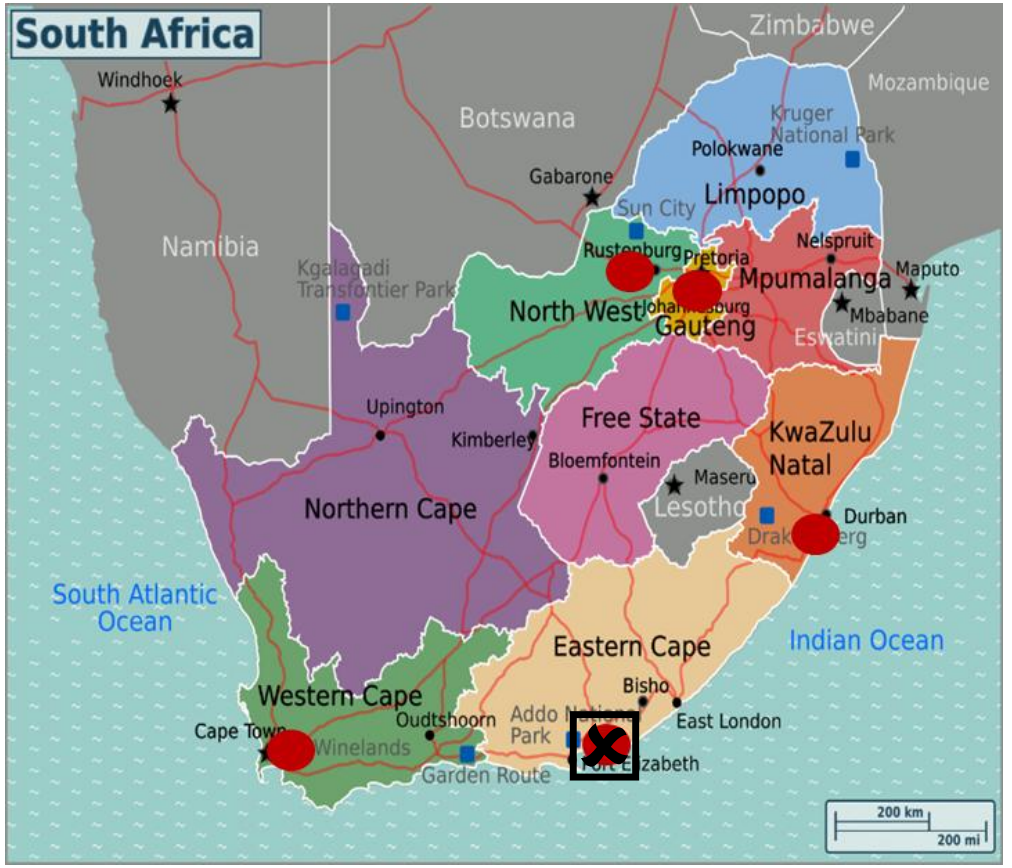
Participants

- Household contacts of MDR-TB patients
- <5 years

Setting

Four South African sites

- Western Cape, Gauteng, Northwest Province, KwaZulu-Natal



Sample size (2° analysis)

- 839 children
  - 405 levofloxacin
  - 434 placebo

Methods: Analysis

Outcomes Assessed

Growth
- Weight-for-age z-score
- Height-for-age z-score

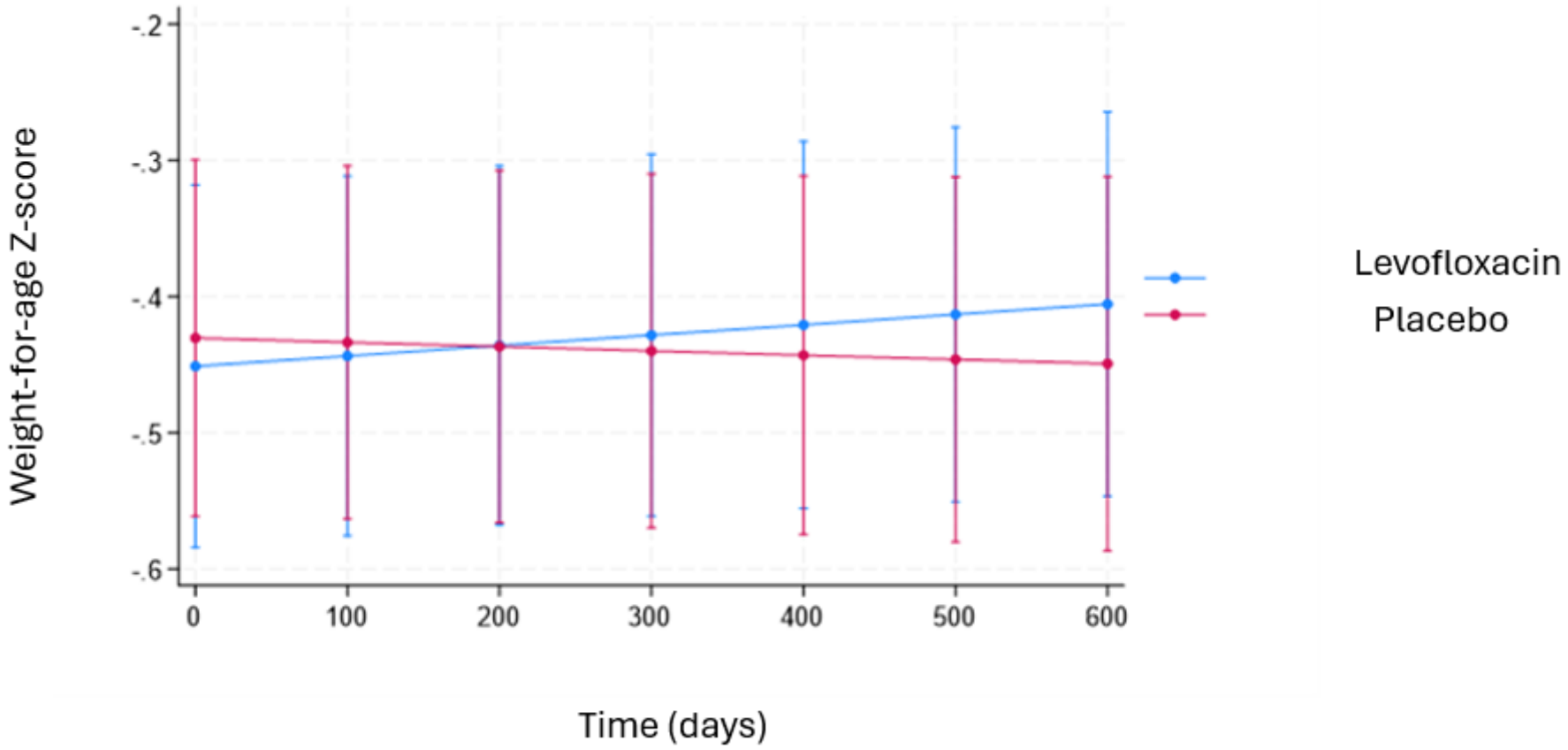
Laboratory
- Haemoglobin
- White cell count
- Platelets

Clinical outcomes
- Infectious events
- Antibiotic use
- Clinic visits and hospitalization

Statistical Analysis

- Growth and haem analyses: Linear mixed-effects regression
- Heath facility visits, antibiotics and infections: IRR estimates using Poisson regression
- Adjusted for
  - household clustering
  - site stratification
  - repeated measures

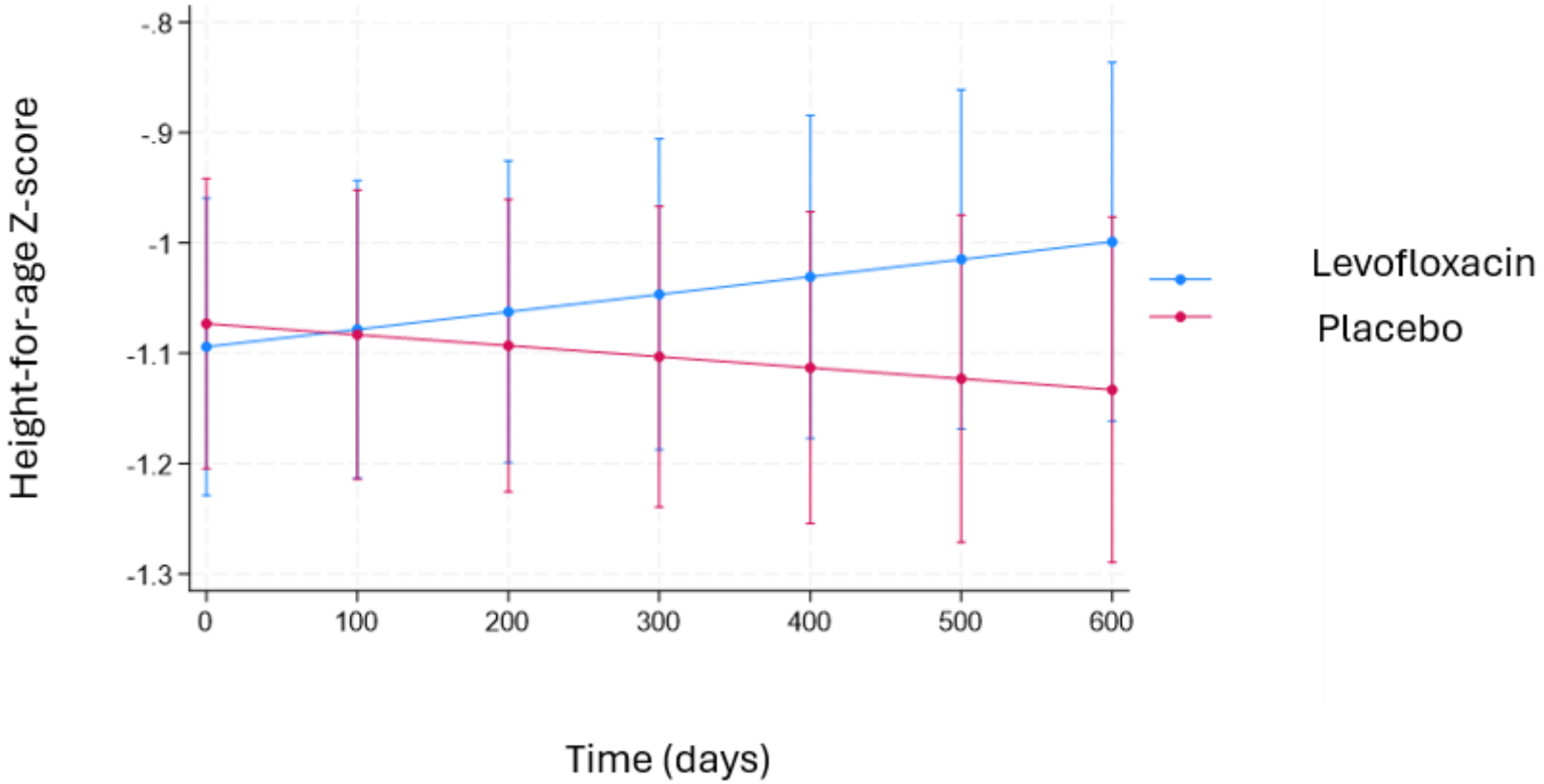
Results: Growth



Weight-for-age

- No significant difference between groups
- Interaction: p = 0.183

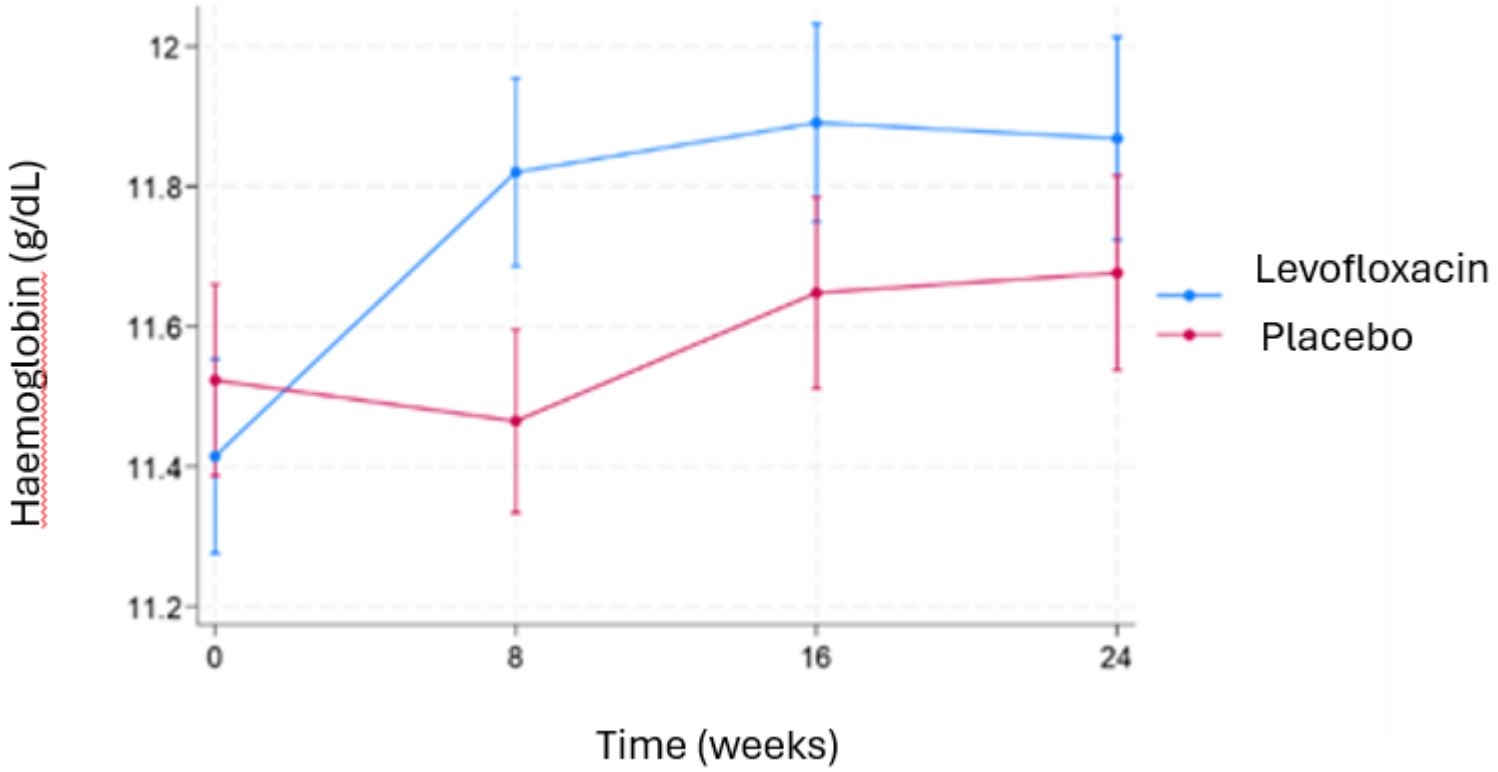
Results: Growth



Height-for-age

- Slightly improved trajectory in levofloxacin arm
- Significant interaction: p = 0.028

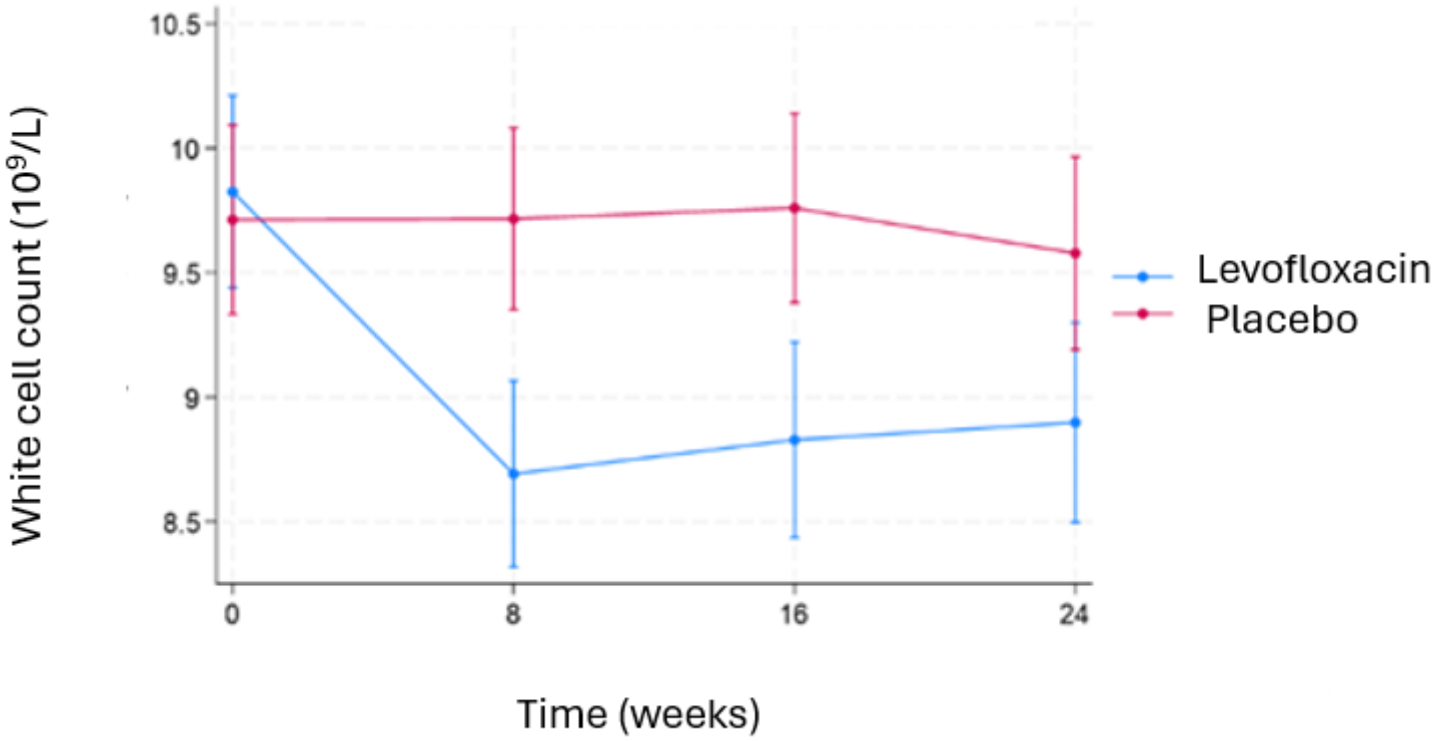
Results: Haematological outcomes



Haemoglobin

- Increased in levofloxacin group (+0.30 g/dL by week 24)
- Intervention effect: $p < 0.0001$

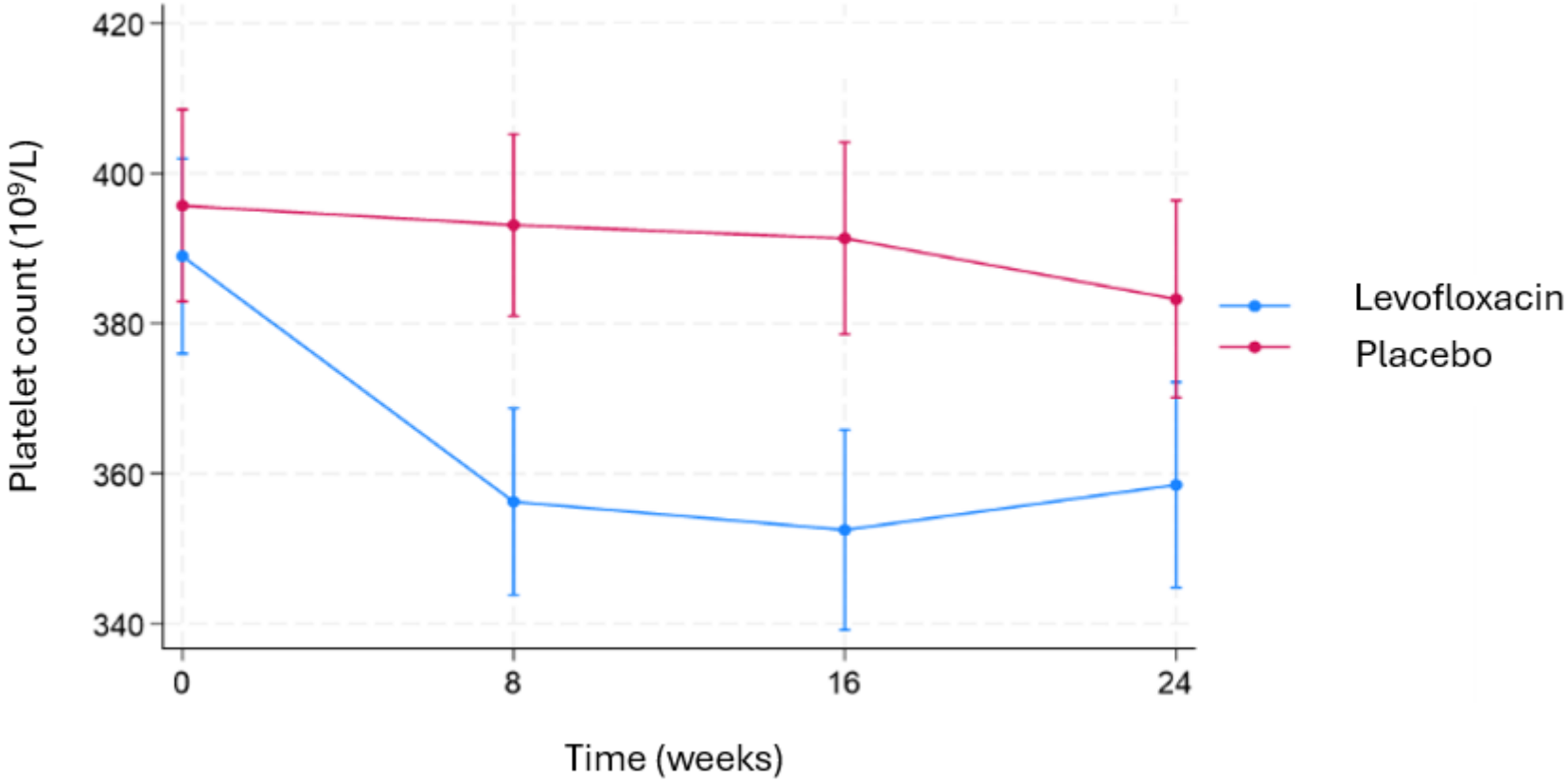
Results: Haematological outcomes



White cell count

- Mild reduction in levofloxacin arm (−0.79 × 10^9/L by week 24)
- Intervention effect: p = 0.0001

Results: Haematological outcomes



Platelet count

- Mild reduction in levofloxacin arm (-18 x 10^9/L g/dL by week 24)
- Intervention effect: p = 0.013

Results: Healthcare visits and antibiotic use

- No difference in incidence of hospitalisation or clinic visits
- Decreased incidence of and duration of antibiotic use in the levofloxacin arm

Effect of study arm on healthcare visits and antibiotic use in children enrolled in the TB-CHAMP trial

Outcome	Effect estimate (levofloxacin vs placebo)	95% CI	p-value
Hospitalizations	IRR = 1.05	0.31 – 3.58	0.937
Clinic visits	IRR = 0.91	0.67 – 1.24	0.554
Number of antibiotic prescriptions	IRR = 0.77	0.59 – 1.00	0.046
Total days of antibiotics	IRR = 0.77	0.60 – 0.99	0.039

Results: Infections

Infection category	Number events: Levofloxacin arm (N=405)	Number events: Placebo arm (N=434)	IRR	95% Confidence interval	p-value
Presumed bacterial events, potentially treatable by levofloxacin					
Conjunctivitis	2	6	0,36	0.07-1.86	0,22
Fever	9	13	0,74	0.29-1.86	0,52
Gastroenteritis	28	31	0,96	0.53-1.74	0,90
Acute diarrhoea	25	26	1,02	0.56-1.86	0,94
Bronchitis	4	9	0,47	0.14-1.62	0,23
Chest infection	67	71	1,02	0.56-1.85	0,94
Pneumonia	5	5	1,08	0.32-3.61	0,91
Folliculitis	2	4	0,55	0.10-2.92	0,48
Impetigo	7	13	0,57	0.21-1.51	0,26
Otitis media	10	13	0,83	0.36-1.92	0,66
Pharyngitis	3	8	0,4	0.10-1.62	0,20
Sinusitis	1	12	0,09	0.01-0.72	0,024
Upper respiratory tract infection	156	241	0,69	0.55-0.87	0,002
Tonsillitis	15	15	1.07	0.50-2.31	0.86
Potentially treatable by Levofloxacin*	337	477	0.76	0.61-0.93	0.008
Fungal events					
Oral candida	4	7	0,61	0.17-2.20	0,45
Tinea	45	47	1,03	0.66-1.39	0,87
Total Fungal*	49	55	0,96	0.78-1.80	0,83

- Fewer infections in levo arm
- Significant reductions in sinusitis and URTIs
- No differences in fungal events

Comparison of infectious events in children receiving levofloxacin versus placebo over 24 weeks

Conclusions

First randomised study comparing long-term levofloxacin vs placebo on non-TB outcomes in young children

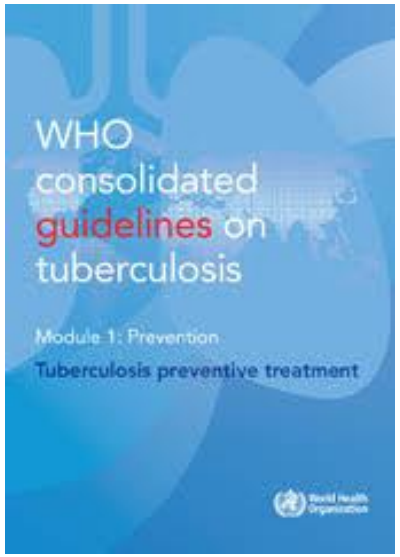
- **Growth**
  - ➢ Significant positive difference in height-for-age slope
- **Haematological effects**
  - ➢ Small ↑ Hb, ↓ WBC, plts; not clinically significant
- **Healthcare visits**
  - ➢ No difference in visit rates between arms
- **Antibiotic exposure**
  - ➢ Fewer prescriptions and shorter duration in levo groups
- **Infections**
  - ➢ Fewer overall infections in levo group; ↓ sinusitis and URTIs, no ↑ fungal

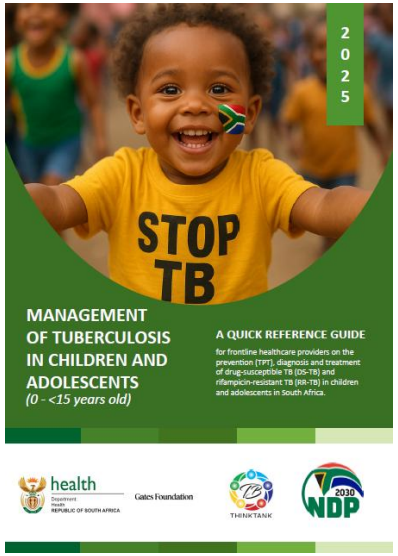
Conclusions

- **Possible mechanisms (hypothesized)**
  - Direct activity against respiratory pathogens
  - Anti-inflammatory/immunomodulatory effects (eg cytokine suppression)
- **Context**
  - Findings consistent with prior evidence showing no long-term harm to growth
  - Minor blood count changes likely clinically insignificant
  - No data in literature as to whether patients on long-terms antibiotics develop fewer infections or receive fewer antibiotics
  - Decreased antibiotic use, decreased infections, lack of difference in healthcare visits suggests no net harm

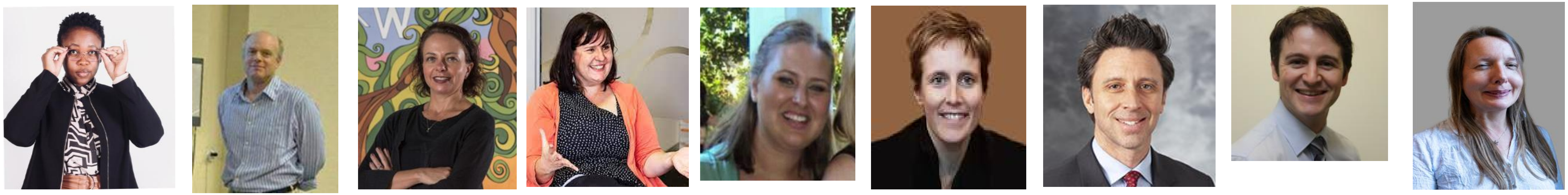
Conclusions

- **Overall conclusion**
  - ➢ Long term levofloxacin prophylaxis shows minimal adverse non-TB effects
  - ➢ May confer modest benefits in Hb levels, infection burden and antibiotic use
  - ➢ Findings provide important reassurance for programmes implementing WHO-recommended levofloxacin preventive treatment in children in SA and globally





TB-CHAMP team



Co-authors, funders, partners, local health services, trial participants and families

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Thank you for listening!

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