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forward together · saam vorentoe · masiye phambili

MDR-TB preventive treatment considerations

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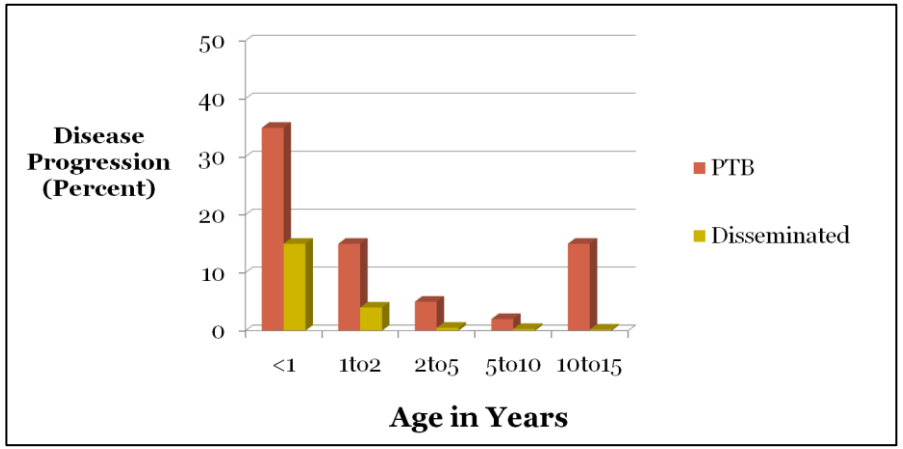
Every breath counts

Conflict of interest disclosure

X I have no Conflict of Interest to report.

Background

- 460,000 new cases of MDR-TB in 2017
- 25-32,000 MDR-TB paediatric cases estimated (2010)
- 2 million children infected with MDR-TB
- Current MDR-TB treatment long, toxic, expensive
- MDR-TB prevention is important but no evidence from randomised controlled trials



WHO Global TB Report 2018 , WHO LTBI Guidelines, 2018; Jenkins HE et al. Lancet 2014; Dodd PJ et al. Lancet Global Health 2014

Five (Six?) priority actions to address the global MDR-TB crisis

1. Prevent the development of drug resistance through high quality treatment of drug-susceptible TB
2. Expand rapid testing and detection of drug-resistant TB cases
3. Provide immediate access to effective treatment and proper care
4. Prevent transmission through infection control
5. Increase political commitment with financing
6. **Contact tracing and preventive therapy?**

WHO: Multidrug-resistant Tuberculosis 2014 Update

WHO Global TB Report 2018 refers to “universal access to TB prevention” but WHO guidelines on LTBI not strong support for MDR-TB preventive therapy

FIG. 2.4

Strategic priorities and targets for TB aligned with WHO's General Programme of Work

Achieve universal access to TB prevention, treatment and care services

TARGETS

- At least 40 million people with TB reached with care in the period 2018–2022, including 3.5 million children and 1.5 million people with drug-resistant TB
- At least 30 million people reached with TB prevention services in the period 2018–2022
- No TB-affected households facing catastrophic costs due to TB by 2020

Prevent TB as a public health threat and contribute to protecting populations from airborne infections

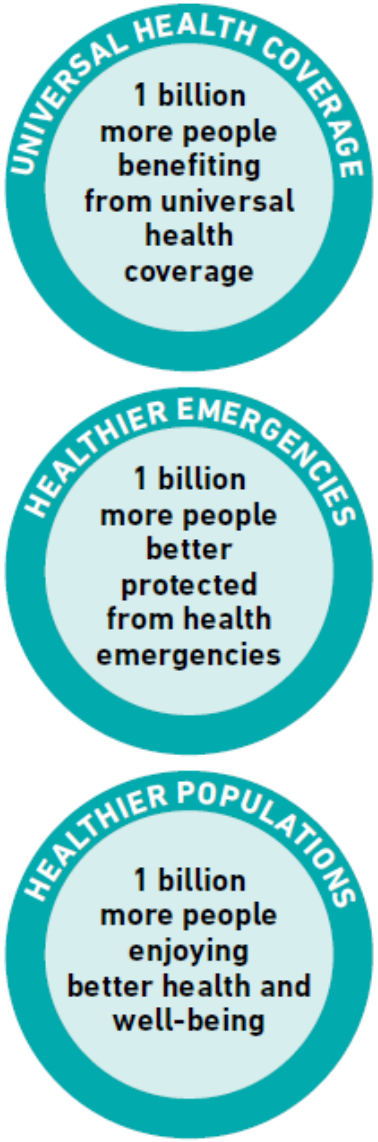
TARGET

- Increase treatment coverage for MDR-TB to 80% of estimated incidence by 2023

Protect populations and vulnerable groups from the social and economic impacts of TB infection and disease

TARGET

- Reduce TB deaths by 50% by 2023 compared with a baseline of 2018 (aligned to the End TB Strategy, but with baseline and target years that correspond to the GPW)



UN GENERAL ASSEMBLY HIGH-LEVEL MEETING ON ENDING TB - Declaration (Sept 2018)

25. Commit to prevent tuberculosis for those most at risk of falling ill through the rapid scale-up of access to testing for tuberculosis infection, according to the domestic situation, and provision of preventive treatment, with a focus on high burden countries, so that at least 30 million people, including 4 million children under five years of age, 20

26. Commit to overcome the global public health crisis of multidrug-resistant tuberculosis through actions for prevention, diagnosis, treatment and care, including: compliance with stewardship programmes to address the development of drug

Introduction: Infection/prevention

- MDR-TB in children is mainly through infection with MDR *M. tuberculosis strains* from infectious (adult) PTB cases
- Although AFB sputum smear-positive cases are more infectious than smear-negative/culture-positive cases, the latter is also infectious
- BCG does NOT provide good protection against infection and disease in children
- Starting adult source cases on TB Rx or separating the child from the source case could prevent ongoing transmission BUT does not mean the child does not need preventive Rx (may already be infected)

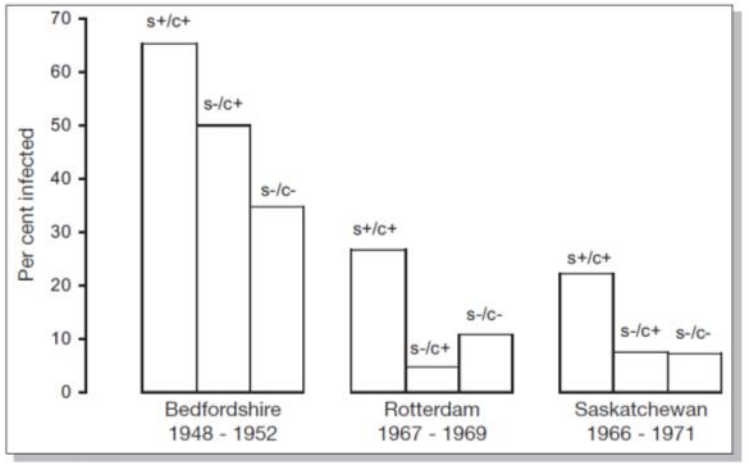
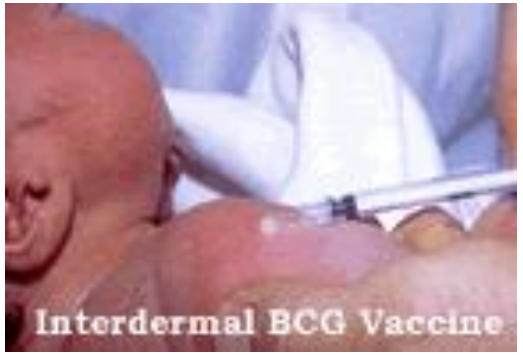


Figure 7. Infectiousness of pulmonary tuberculosis by bacteriologic status of source case. s+/c+ indicates smear- and culture-positive; s-/c+ indicates smear-negative, culture-positive; and s-/c- indicates negative on both smear and culture. Data from [29-31].



Rieder H. (The Union) Epidemiologic Basis of Tuberculosis Control - 1999

Child contacts of MDR-TB (1)

- The majority (90%) of infected children who will develop disease will progress to disease within 12 months – almost all in 2 years
- Biomarkers to determine which individuals have the highest risk of progression to TB disease are lacking
- The risk of TB disease among contacts exposed to MDR-TB is considerable. In a meta-analysis of 25 studies, 7.8% of household contacts of MDR-TB patients developed TB, most within three years.

Shah NS et al. Yield of contact investigations in households of patients with drug-resistant tuberculosis: systematic review and meta-analysis. CID 2014;58:381-91

Golla *et al. BMC Infectious Diseases* (2017) 17:593
DOI 10.1186/s12879-017-2668-2

BMC Infectious Diseases

RESEARCH ARTICLE Open Access

The impact of drug resistance on the risk of tuberculosis infection and disease in child household contacts: a cross sectional study

Vera Golla[1], Kathryn Snow[2], Anna M. Mandalakas[3], H. Simon Schaaf[1], Karen Du Preez[1], Anneke C. Hesseling[1*] and James A. Seddon[1,4*]

Results: Of 538 children included, 312 had DS-TB and 226 had MDR-TB exposure. 107 children with DS-TB exposure had TB infection (34.3%) vs. 101 (44.7%) of children with MDR-TB exposure (adjusted Odds Ratio [aOR]: 2.05; 95% confidence interval [CI]: 1.34–3.12). A total of 15 (6.6%) MDR-TB vs. 27 (8.7%) DS-TB child contacts had TB disease at enrolment (aOR: 0.43; 95% CI: 0.19–0.97).

Conclusions: Our results suggest a higher risk of TB infection in child contacts with household MDR-TB vs. DS-TB exposure, but a lower risk of TB disease. Although potentially affected by residual confounding or selection bias, our results are consistent with the hypothesis of impaired virulence in MDR-TB strains in this setting.

However, there remains a significant risk for development of disease in child contacts of infectious MDR-TB cases

Child contacts of MDR-TB (2)

- Strain concordance of household members with DR-TB is high in child contacts <5 years with 75-88% concordance
- No RCTs have been completed evaluating preventive therapy for MDR-TB contacts
- However, a number of prospective observational studies (some unpublished) have shown the potential of preventive treatment in preventing MDR-TB
- Despite this, the debate on the management of MDR-TB contacts is ongoing

Rationale for preventive treatment

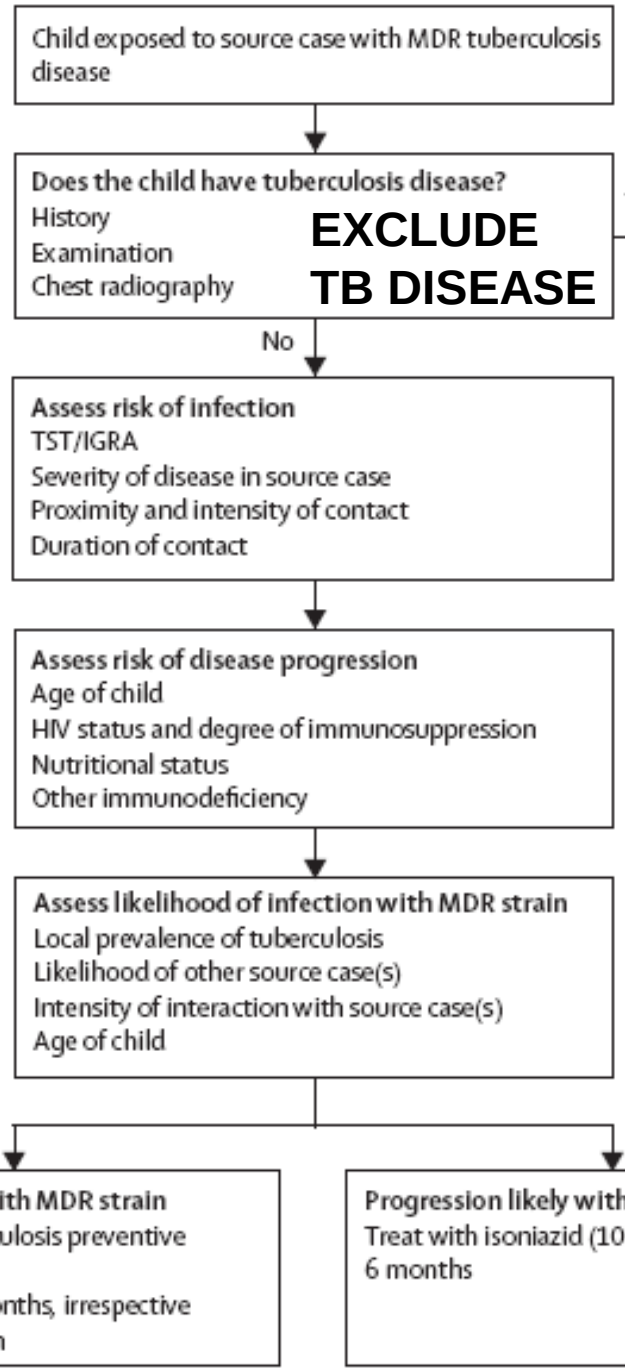
- Prophylactic treatment is given after exposure to prevent TB infection, and treatment given after TB infection is intended to prevent progression to TB disease.
- Preventive treatment includes both these situations
- To provide preventive treatment
  - contact with a source case and risk of infection needs to be established and
  - TB disease should have been excluded

The individual risk assessment should take into consideration the following:

- TB contact's (child's) risk for progression to TB disease (age, immune status)
- Infectiousness of the source case AND the closeness and duration of contact with the source case
- Whether there is one or more source cases
- The DST pattern(s) of the source case(s)
- The risk for adverse events upon initiating preventive therapy

Decision algorithm for assessing child contacts of MDR-TB

Management of children exposed to multidrug-resistant *Mycobacterium tuberculosis*.
Seddon JA et al.
Lancet Infect Dis 2012



EXPOSED TO MDR-TB ?

RISK OF INFECTION?

RISK OF DISEASE PROGRESSION?

MDR-TB STRAIN OR OTHER?

High risk MDR-TB
Preventive Rx & follow-up

DS-TB risk?
PT for DS-TB

How to investigate contacts

Clinical assessment:

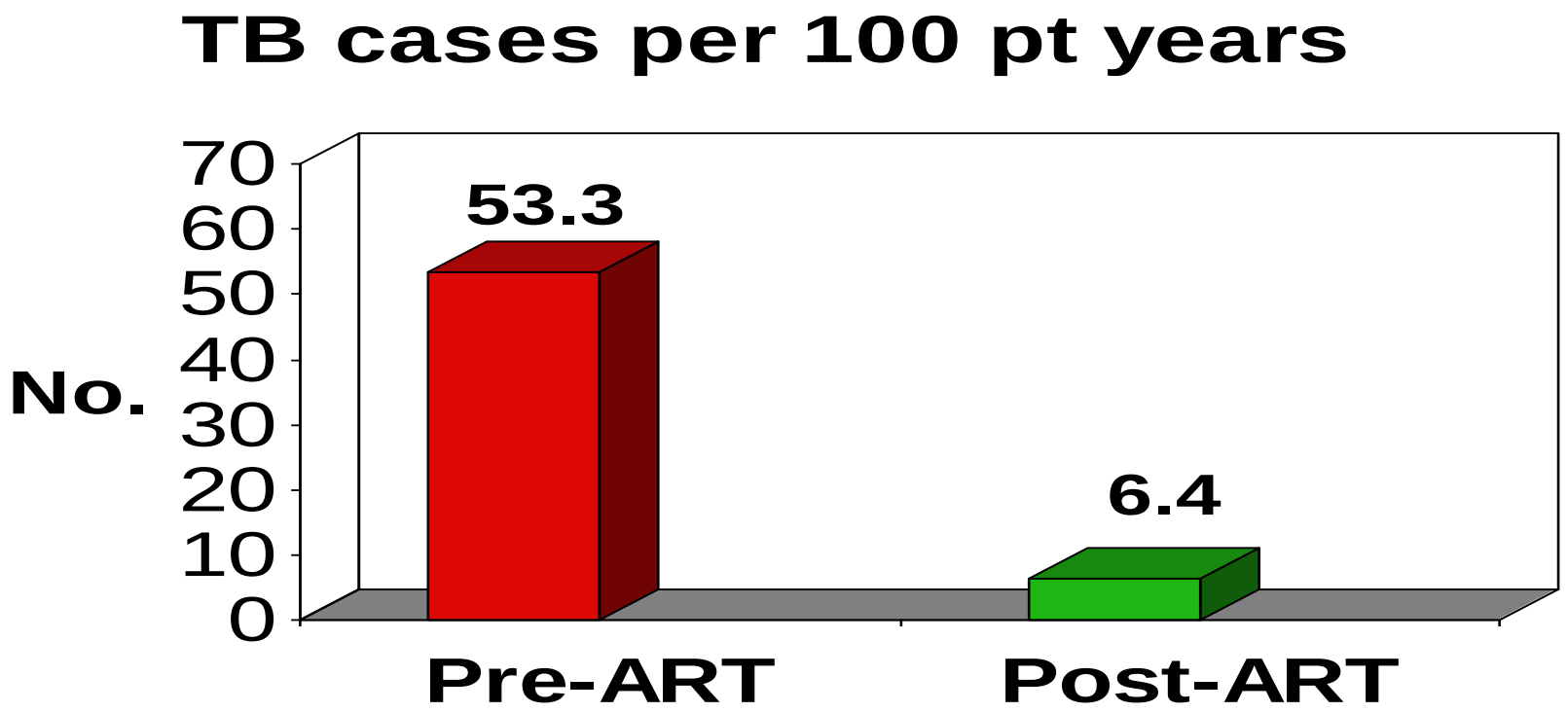
- History (Symptoms – not only chronic symptoms; closeness and duration of contact; DST of source case's isolate)
- Clinical examination (PTB/EPTB)

Clinical assessment alone is sufficient to decide whether contact is well or symptomatic (developing countries)

If available:

- TST (IGRA) – but even if TST/IGRA is negative and exposure has been confirmed, preventive Rx is indicated – reassess after 2-3 months?
- CXR (for diagnosis of disease) – or other imaging/tests
- If DR-TB suspected and contact is symptomatic or has abnormal CXR – specimens culture/DST before starting Rx

HIV: Impact of ART on child TB



- Retrospective study at Tygerberg Hospital (2003-2005)
- 136 episodes TB in 290 children
- Pre-ART - 9m period before ART initiation
- ART is essential in prevention of TB in HIV-infected children

Walters et.al. BMC Pediatrics 2008

Observational studies that started to change opinions

CDC - Chuuk study, Micronesia

- Contacts of 2 source cases: strain (A) resistant to HRZES; strain (B) resistant to HREto
- Evaluation of MDR-TB contacts: 15 had MDR-TB disease, 5 had DS-TB, and 119 had LTBI with positive TST.
- LTBI contacts were offered preventive Rx. 15 of the 119 cases refused, preventive Rx was initiated in 104 contacts
- A FQN-based regimen was used: FQN alone or in combination with Eto (strain A) or E (strain B) with DOT for 12 months
- Of the 104 who started on MDR preventive Rx (93 completed) – none developed TB disease
- 3 of 15 who refused preventive therapy developed MDR-TB disease (P = 0.002)

Preventive Therapy for Child Contacts of Multidrug-Resistant Tuberculosis: A Prospective Cohort Study. Seddon/Schaaf et al. CID 2013

Risk factors:
- Young age
- Multiple source cases
- HIV-positive status
- Poor adherence to prevention

Table 6. Assessment of Risk Factors for Poor Outcome (Death or Incident Tuberculosis Disease) in Children Exposed to Multidrug-Resistant Tuberculosis and Treated With a Preventive Therapy Regimen (N = 186)

Risk Factor	No. of Events	Years of Observation	Incidence Rate With 95% CI (Events per 1000 py)	Rate Ratio (95% CI)	*P* Value
Age					
>12 mo	2	175.5	11.4 (1.4–41.1)	1.0	
0–12 mo	5	43.5	114.9 (37.3–268.2)	10.1 (1.65–105.8)	.009
Sex					
Female	3	95.6	31.4 (6.5–91.7)	1.0	
Male	4	123.4	32.4 (8.8–83.0)	1.03 (.17–7.05)	1.00
TST					
Negative	4	132.1	30.3 (8.3–77.5)	1.0	
Positive	2	84.8	23.6 (2.9–85.2)	0.78 (.07–5.43)	1.00
Source cases					
Single	2	152.4	13.1 (3.28–52.5)	1.0	
Multiple	5	56.4	88.6 (36.9–213.0)	6.75 (1.11–70.9)	.036
HIV status					
Negative	5	201.5	24.8 (8.1–579.1)	1.0	
Positive	2	7.6	263.8 (31.9–950.6)	10.6 (1.01–64.9)	.049
Adherence					
Good	2	164.3	12.2 (1.5–44.0)	1.0	. . .
Poor	5	54.8	91.3 (29.6–212.9)	7.50 (1.23–78.7)	.026
Type of delivery					
DOT	0	31.5	0 (0–117.1)	. . .	. . .
Other	7	187.6	37.3 (15.0–76.8)	. . .	.68

Abbreviations: CI, confidence interval; DOT, daily observed therapy; HIV, human immunodeficiency virus; py, person-years; TST, tuberculin skin test.

Many opinions published on preventive therapy in MDR-TB contacts

Seddon JA, Fred D, Amanullah F, Schaaf HS, Starke JR, Keshavjee S, Burzynski J, Furin JJ, Swaminathan S, Becerra MC. (2015)
Post-exposure management of multidrug-resistant tuberculosis contacts: evidence-based recommendations.
Policy Brief No. 1. Dubai, United Arab Emirates: Harvard Medical School
Center for Global Health Delivery–Dubai.


Journal of Clinical Tuberculosis and Other Mycobacterial Diseases 1 (2015) 1–12

Contents lists available at ScienceDirect

Journal of Clinical Tuberculosis and Other Mycobacterial Diseases

journal homepage: www.elsevier.com/locate/jctube

How to manage children who have come into contact with patients affected by tuberculosis

Laura Lancella[a], Andrea Lo Vecchio[b], Elena Chiappini[c], Marina Tadolini[d], Daniela Cirillo[e], Enrico Tortoli[e], Maurizio de Martino[c], Alfredo Guarino[b], Nicola Principi[f], Alberto Villani[a], Susanna Esposito[f,*], Luisa Galli[c], for the Italian Pediatric TB Study Group[1]

Published in final edited form as:
Clin Infect Dis. 2017 June 15; 64(12): 1670–1677. doi:10.1093/cid/cix208.

Systematic Review, Meta-analysis, and Cost-effectiveness of Treatment of Latent Tuberculosis to Reduce Progression to Multidrug-Resistant Tuberculosis

Suzanne M. Marks, **Sundari R. Mase**, and **Sapna Bamrah Morris**
Division of Tuberculosis Elimination, Centers for Disease Control and Prevention, Atlanta, Georgia

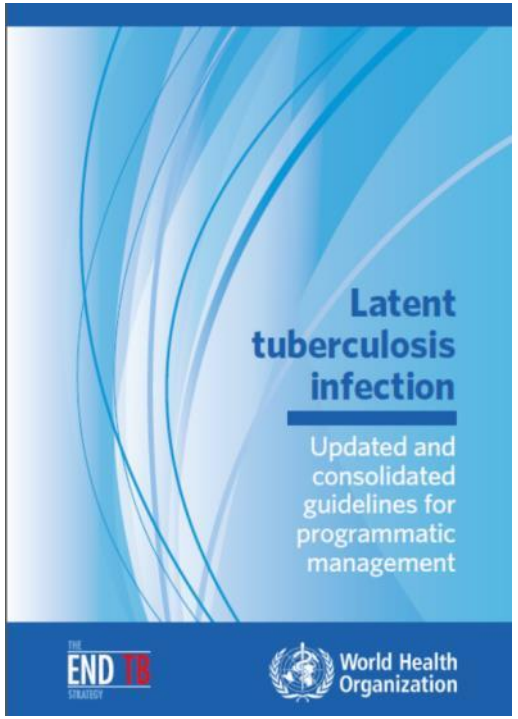
Results: …. The estimated MDR-TB incidence reduction was 90% (9%–99%) using data from 5 comparison studies. We found…high treatment discontinuation rates due to adverse effects in persons taking pyrazinamide-containing regimens. Cost-effectiveness was greatest using a fluoroquinolone/ethambutol combination regimen.
Conclusions—Few studies met inclusion criteria, therefore results should be cautiously interpreted.

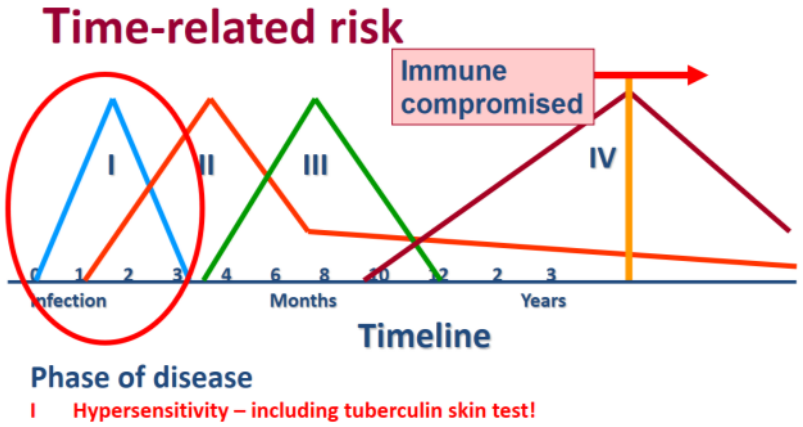
WHO 2018 Consolidated Guidelines for Programmatic Management of LTBI

- In high-risk HHCs of MDR TB patients, preventive treatment may be based on individualised risk assessment and sound clinical justification. *(New, Conditional recommendation, low quality of evidence)*

- Confirmation of infection with LTBI tests is required

- Recommendation must not affect RCTs of PT for MDR-TB HHCs on ethical grounds since these trials are critical given current limited evidence





What do guidelines agree on regarding management of MDR-TB contacts?

- Screening for excluding active disease is important (if disease, treat according to likely source case's DST pattern)
- Follow-up of exposed/infected individuals (especially people with high risk, such as children and immunocompromised patients) is essential (1-2 years)
- Although some older guidelines still do not recommend preventive therapy with second-line drugs, this opinion is definitely changing with more guideline agreeing on preventive therapy in at least high risk contacts
- Choice of regimens vary, but most guidelines agree that a fluoroquinolone should be included, with or without a second drug
- RCTs are needed to prove effectiveness of preventive regimens – preferably a single drug

SUMMARY OF ONGOING AND PLANNED MDR-TB PREVENTION TRIALS

	TB-CHAMP	V-QUIN	PHOENIx
Intervention	LVF vs. placebo daily for 6 months	LVF vs. placebo daily for 6 months	DLM vs. standard dose INH daily for 26 weeks
Target Population	<5 years regardless of IGRA or HIV status **Only study powered for efficacy in children**	• All ages • TST + • Children not yet treated	• HIV + • Children <5 years • TST/IGRA + >5 years
Sample size	778 Households 1556 contacts < 5 y	1326 Households 2785 contacts	1726 Households 3452 contacts
Sites	South Africa DTTC, Shandukani, PHRU Matlosana	Viet Nam NTP	ACTG & IMPAACT sites
Timelines	**Open; n=230 enrolled**	**Open ; 70% enrolled**	**Q1 2019**
Funder, PI	BMRC/Wellcome Trust/DFID, SA MRC SHIP; Hesseling MRC CTU at UCL	Australian MRC Fox, Nguyen SA NTP	DAIDS, ACTH/IMPAACT Churchyard, Gupta, Hesseling, Swindells

TB-CHAMP study

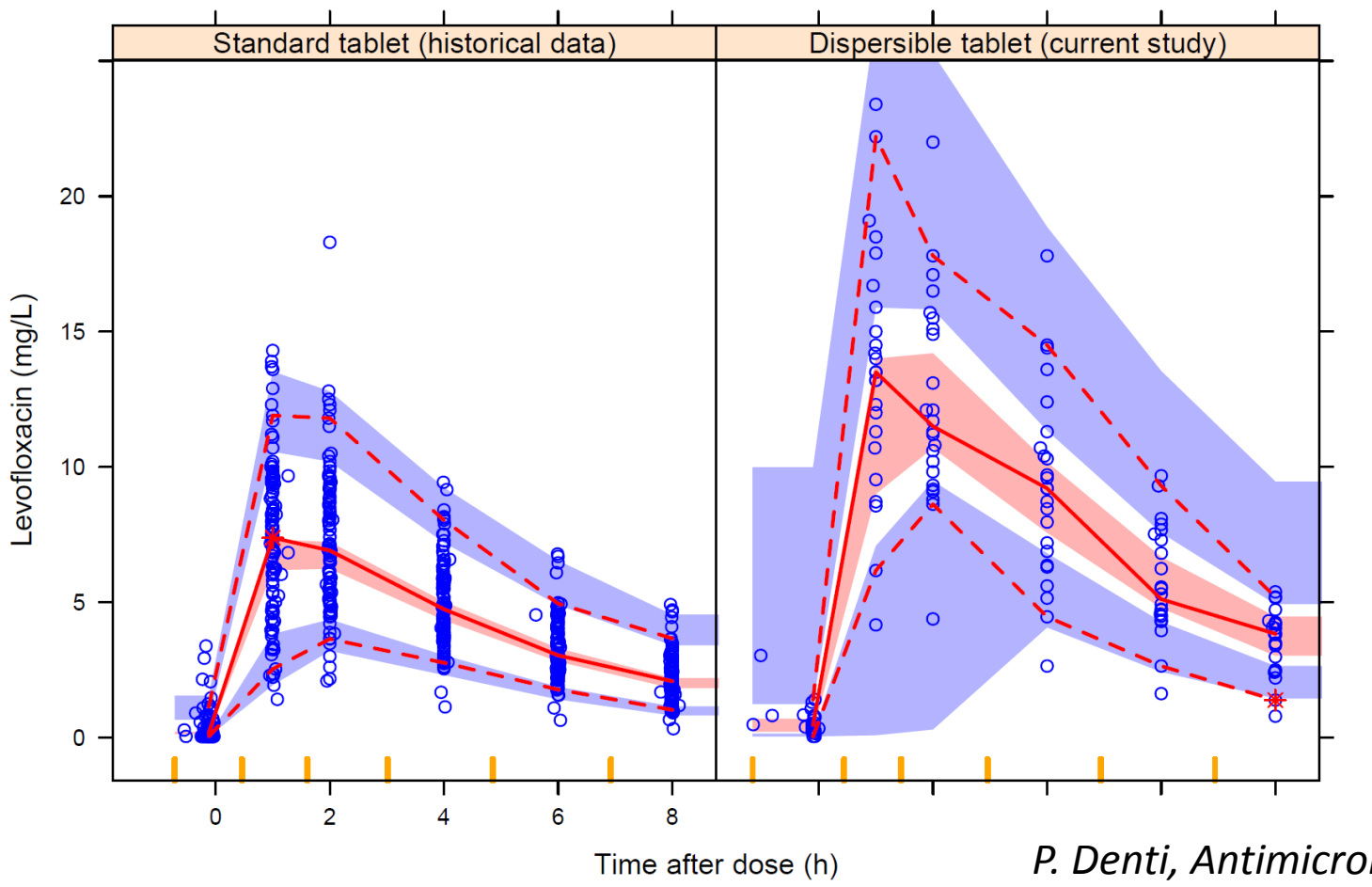
- Realized need for child-friendly levofloxacin formulation and with pharmaceutical company developed 100mg dispersible tablet (now WHO approved)
- Palatability and acceptability study was done in 27 children
- The dispersible tablet was found to be highly palatable and acceptable by children and their caregivers
  (S. Purchase et al, submitted)

- A lead-in pharmacokinetic study of this formulation was done in 24 children (median age 2.1 years, IQR 1.2, 2.7)

Levofloxacin 100 mg DT (TB-CHAMP lead-in PK)

N=109 children MDR treatment/prevention

N=24 children <5y with HH MDR-TB exposure



Using the same model, bioavailability is estimated to be 70% higher with the 100mg dispersible tablet compared to the Lfx 250mg adult formulation tablet

P. Denti, Antimicrobials and Therapy, 2018
A.J. Garcia-Prats, submitted

Conclusions

- MDR preventive therapy likely effective in preventing MDR-TB in children
- Randomised controlled trial(s) are ongoing – for choice of regimen, efficacy and safety
- Currently, single drug preventive therapy regimens with a fluoroquinolone (e.g. levofloxacin) or a novel drug is considered
- Child-friendly levofloxacin formulation for preventive therapy looks promising (acceptability, pharmacokinetics and safety)
- What about XDR-TB contacts? Careful follow-up and possibly a novel drug (delamanid) – treat as XDR-TB if TB develops
- In both MDR and XDR-TB regular clinical follow-up is indicated, but pendulum swinging towards preventive treatment.

- Financial Support: SA National Research Foundation, SA MRC, BMRC
- Acknowledgements: Anneke Hesseling, Tony Garcia-Prats, Sue Purchase, James Seddon and DTTC Team Stellenbosch University, Greg Fox from VQUIN study, Division of Pharmacology University of Cape Town