Prevention and management of MDR-TB in children

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Every breath counts

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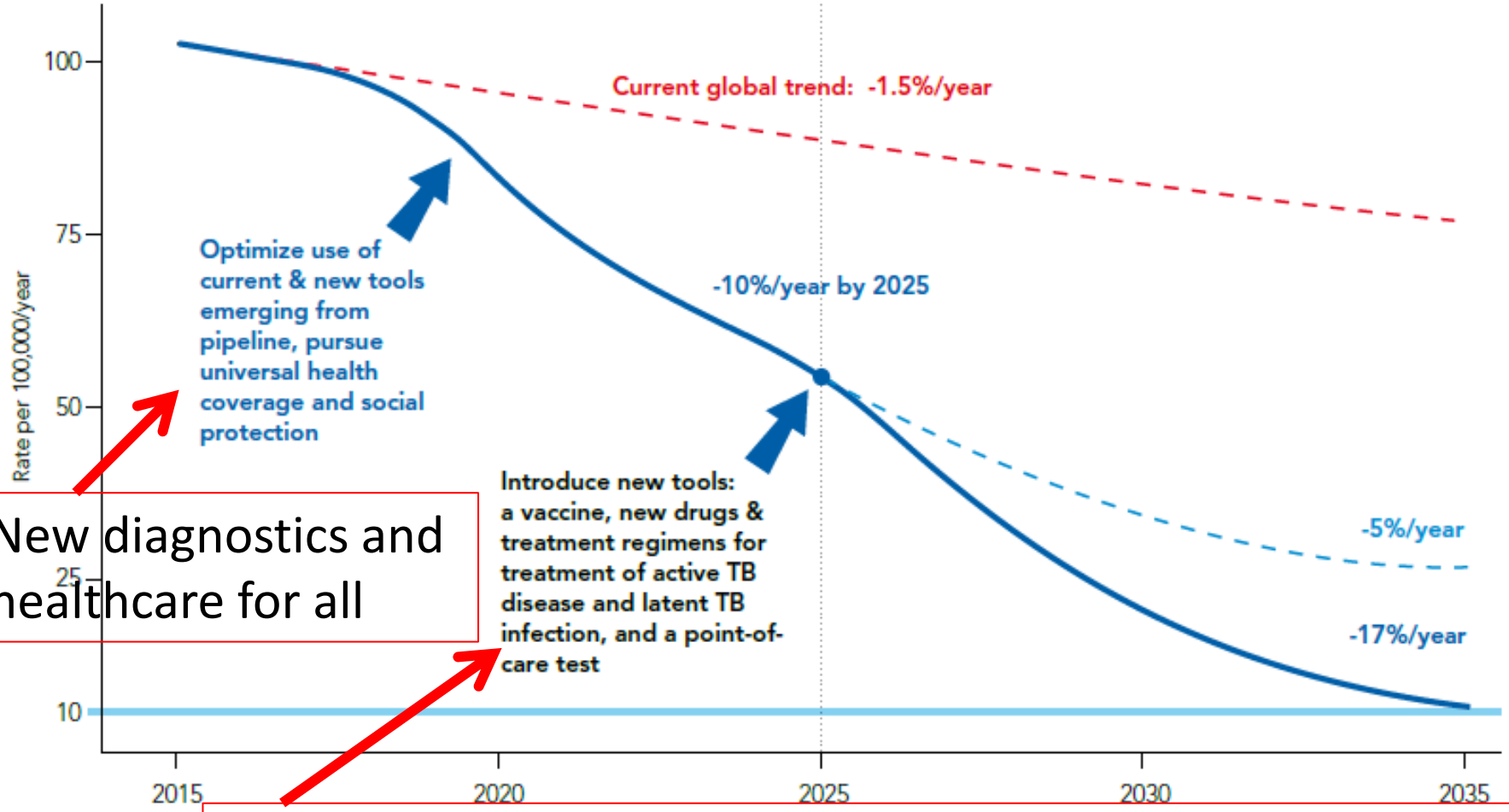
Introduction to Prevention

- Prevention of tuberculosis, including multidrug (MDR) and extensively drug-resistant tuberculosis (XDR-TB) is a top priority for global TB control
- Rapid detection and timely initiation of effective treatment is critical to rendering MDR/XDR-TB cases non-infectious
- Optimised infection control measures in hospitals and clinics are critical to protect other patients
- Among infected contacts, preventive therapy promises to reduce the risk of disease progression. This is supported by observational cohort studies

Fox GJ, Schaaf HS, et al. Preventing the spread of multidrug-resistant tuberculosis and protecting contacts of infectious cases. *Clin Microbiol Infect 2016*

Desired decline in global TB incidence rates to reach the 2035 targets



New diagnostics and healthcare for all

Including: **Vaccine**, **treatment of TB infection** and disease

Global priority indicators and targets for monitoring the implementation of the End TB Strategy

All countries should aim to reach these targets at the latest by 2025.

Treatment coverage

Number of people that developed TB, and were notified and treated, out of the total estimated number of incident cases in the same year (%).

≥ 90%

TB treatment success rate

Number of TB patients who were successfully treated out of all notified TB cases (%).

≥ 90%

Preventive treatment coverage

Number of people living with HIV and children who are contacts of cases who were started on preventive treatment for latent TB infection, out of all those eligible (%).

≥ 90%

TB affected households facing catastrophic costs

Number of TB patients and their households that experienced catastrophic costs due to TB, out of all TB patients (%)

0%

Uptake of new diagnostics and new drugs

Number of TB patients who were diagnosed using WHO-recommended rapid tests, out of all TB patients (%).

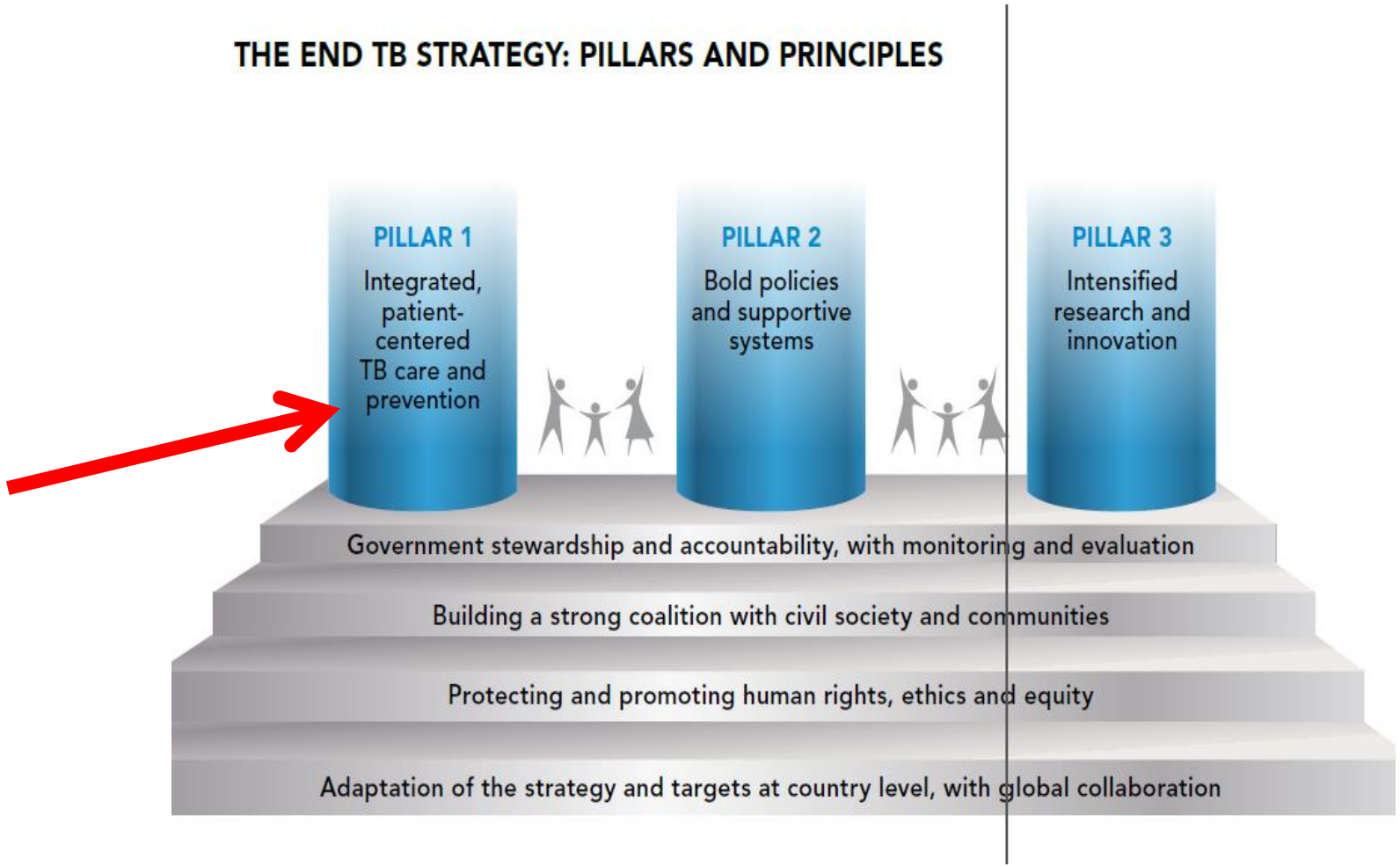
Number of TB patients who were treated with regimens including new TB drugs, out of those eligible for treatment with such drugs (%).

≥ 90%

THE END TB STRATEGY

World Health Organization

THE END TB STRATEGY: PILLARS AND PRINCIPLES



How pillar 1 works : Key components

A. Early diagnosis of TB including universal drug-susceptibility testing, and systematic screening of contacts and high-risk groups

B. Treatment of all people with TB including drug-resistant TB, and patient support

D. Preventive treatment of persons at high risk; and vaccination against TB

C. Collaborative TB/ HIV activities; and management of co-morbidities

Five (or 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

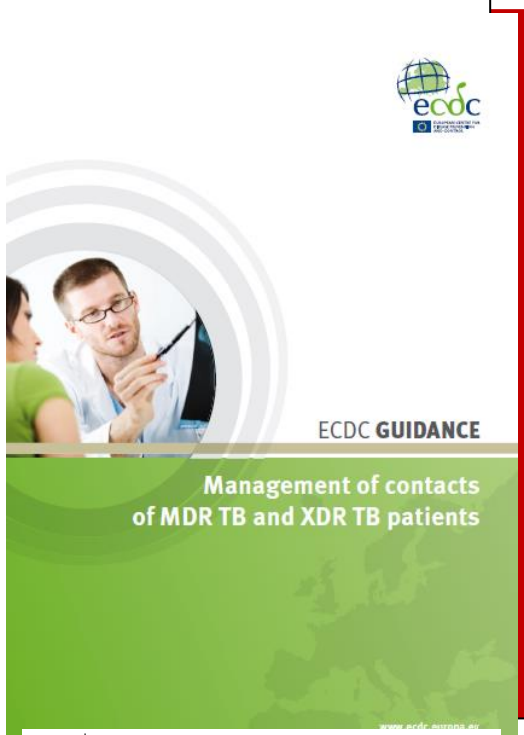
Child contacts of MDR-TB (1)

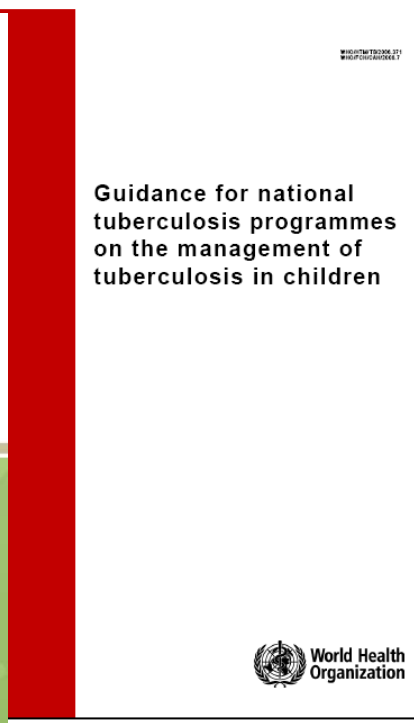
- In children, the term “TB infection” instead of LTBI is preferred, as they are usually recently infected and could still be in the phase of progression to disease
- The majority (90%) of infected children who will develop disease will progress to disease within 12 months – almost all in 2 years
- Biomarkers 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.

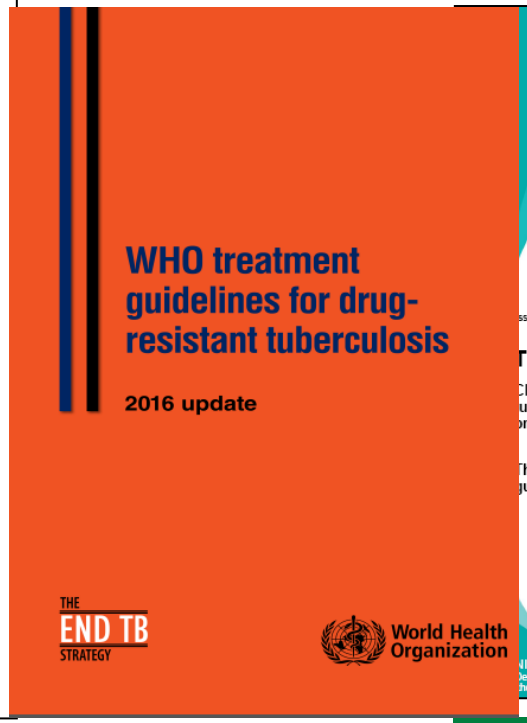
  Shah NS et al. Yield of contact investigations in households of patients with drug-resistant tuberculosis: systematic review and meta-analysis. CID 2014;58:381-91

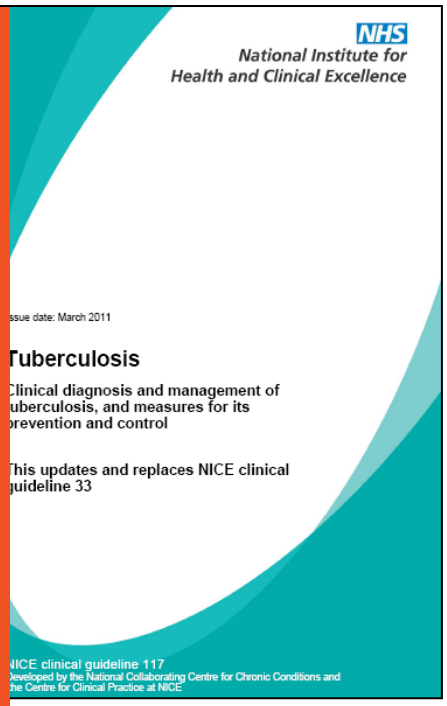
Child contacts of MDR-TB (2)

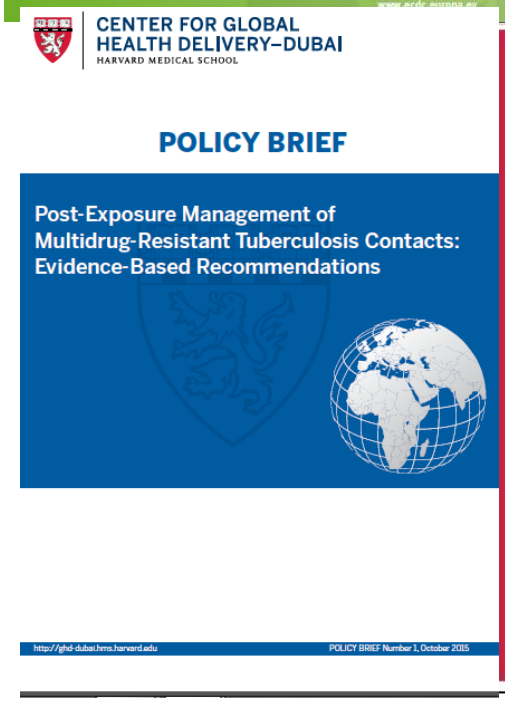
- Strain concordance of household members with DR-TB is high in child contacts <5 years with 75-88% concordance
- No RCTs have been done to evaluate preventive therapy for MDR-TB contacts
- However, a number of prospective observational studies (some unpublished) have shown the potential of preventive treatment in preventing MDR-TB
- Despite this, the debate on the management of MDR-TB contacts is ongoing
- If then prevention is so important, why are we not "putting our money where our mouths are"?

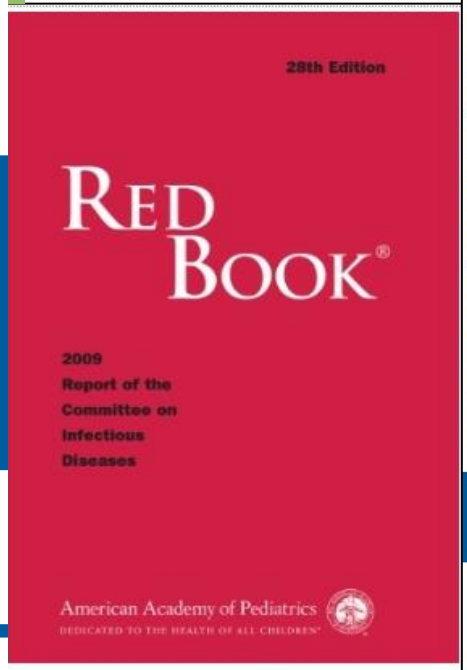

ecdc
ECDC GUIDANCE
Management of contacts
of MDR TB and XDR TB patients


Guidance for national
tuberculosis programmes
on the management of
tuberculosis in children
World Health
Organization


WHO treatment
guidelines for drug-
resistant tuberculosis
2016 update
THE
END TB
STRATEGY
World Health
Organization


NHS
National Institute for
Health and Clinical Excellence
Tuberculosis
Clinical diagnosis and management of
tuberculosis, and measures for its
prevention and control
This updates and replaces NICE clinical
guideline 33
NICE clinical guideline 117


CENTER FOR GLOBAL
HEALTH DELIVERY–DUBAI
HARVARD MEDICAL SCHOOL
POLICY BRIEF
Post-Exposure Management of
Multidrug-Resistant Tuberculosis Contacts:
Evidence-Based Recommendations
http://ghd-dubai.hms.harvard.edu
POLICY BRIEF Number 1, October 2015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2009
Report of the
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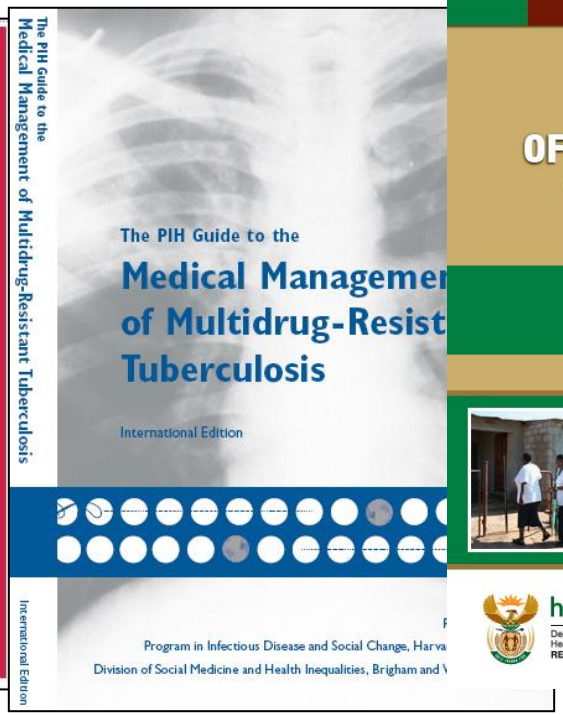
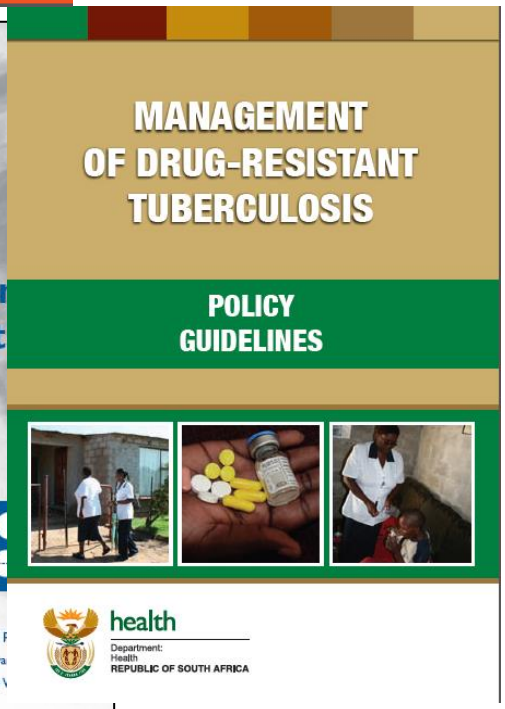
American Academy of Pediatrics
DEDICATED TO THE HEALTH OF ALL CHILDREN


The PIH Guide to the
Medical Management of Multidrug-Resistant Tuberculosis
International Edition


MANAGEMENT
OF DRUG-RESISTANT
TUBERCULOSIS
POLICY
GUIDELINES
health
Department:
Health
REPUBLIC OF SOUTH AFRICA

CENTER FOR GLOBAL HEALTH DELIVERY–DUBAI
HARVARD MEDICAL SCHOOL

POLICY BRIEF

Post-Exposure Management of Multidrug-Resistant Tuberculosis Contacts: Evidence-Based Recommendations

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.

Challenge: To prevent MDR/XDR-TB

- This policy brief followed from a meeting of >50 TB practitioners from 19 countries on MDR-TB prevention
- The current evidence base includes at least ten observational studies (published and unpublished – all were presented), including >600 contacts treated for presumed MDR-TB infection – high rate of success
- The group felt strongly that the time for MDR-TB preventive treatment has come
- Fluoroquinolone-based preventive regimen preferred
- However – RCTs to confirm efficacy should go ahead
- Prevention of XDR-TB remains a problem – new drugs?

RCTs for MDR Preventive Therapy

- Three randomised controlled trials are planned to evaluate the effectiveness of preventive therapy for infected MDR-TB contacts:

Study	Regimen	MDR-TB contacts/ sites
V-QUIN	Levofloxacin vs Placebo	Adults & children – Viet Nam
TB-CHAMP	Levofloxacin vs Placebo	Children <5 years – South Africa
PHOENIx	Delamanid vs isoniazid	Adults and children – International (multi)

Conclusions

- MDR preventive Rx could be effective in preventing MDR-TB in children
- There is an urgent need to address this issue in a randomised controlled trial(s)
- Single drug preventive Rx with a fluoroquinolone (e.g. levofloxacin) is considered (RCTs planned)
- What about XDR-TB contact? Careful follow-up and possibly high-dose INH (no evidence) – 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.

Managing MDR-TB in Children

Introductory comments:

- We are in a time of “RAPID” change ☺
- As clinicians treating children with MDR-TB it is both EXITING and CONFUSING times
- There are many “new” developments/changes that we need to take into consideration when managing MDR-TB in children
- HOWEVER – we need to adhere to (stick to) the basic principles of good TB treatment

What is “new” in MDR-TB management?

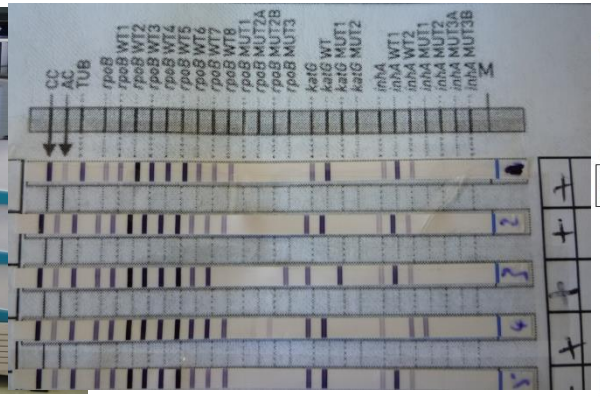
- New “rapid” diagnostics
- New data on doses of “old” anti-TB drugs (PK data)
- New drugs – repurposed and true novel drugs
- New (WHO) drug group classification
- New regimens
- New adverse effects to consider
- New ideas of
  - treatment shortening regimens
  - preventive therapy regimens
- Last, but not least
  - new patients identified
  - new health care workers managing MDR-TB in children

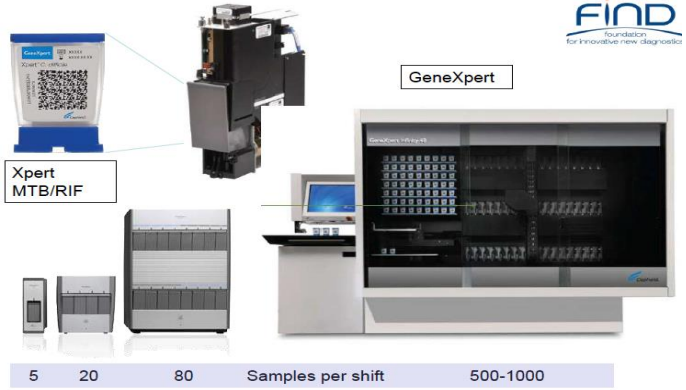
New “rapid” diagnostics

- Xpert MTB/RIF has taken many developing countries with a high TB burden by storm, however it has its limitations and problems
- Xpert Ultra – promising to be more sensitive, and using new technology, seems to be on its way
- In cultured isolates, line probe assay (LPA) mainly has been used for drug susceptibility testing (DST) for first-line drugs INH and RIF
- With the new Shorter MDR-TB regimen there is a need for rapid second-line DST and second-line LPA has now been approved by WHO (GenoType MTBDR*sl*) – however, phenotypic (culture-based) DST still required

Culture (and LPA) vs. Xpert MTB/RIF

Characteristic	Culture and DST	Xpert MTB/RIF
Speed	Slow (2-6 weeks) LPA DST – 1-2 days	Rapid (2 hours – capacity limit)
Positive yield	30-70%	60-70% of culture-POS cases
Detection threshold	10-100 cfu/ml	130-150 cfu/ml (Xpert-ULTRA 10-100?)
DST	Any drug DST/LPA	Only RIF DST
Specimens	Any type	Resp specimens, increasing number of other specimens

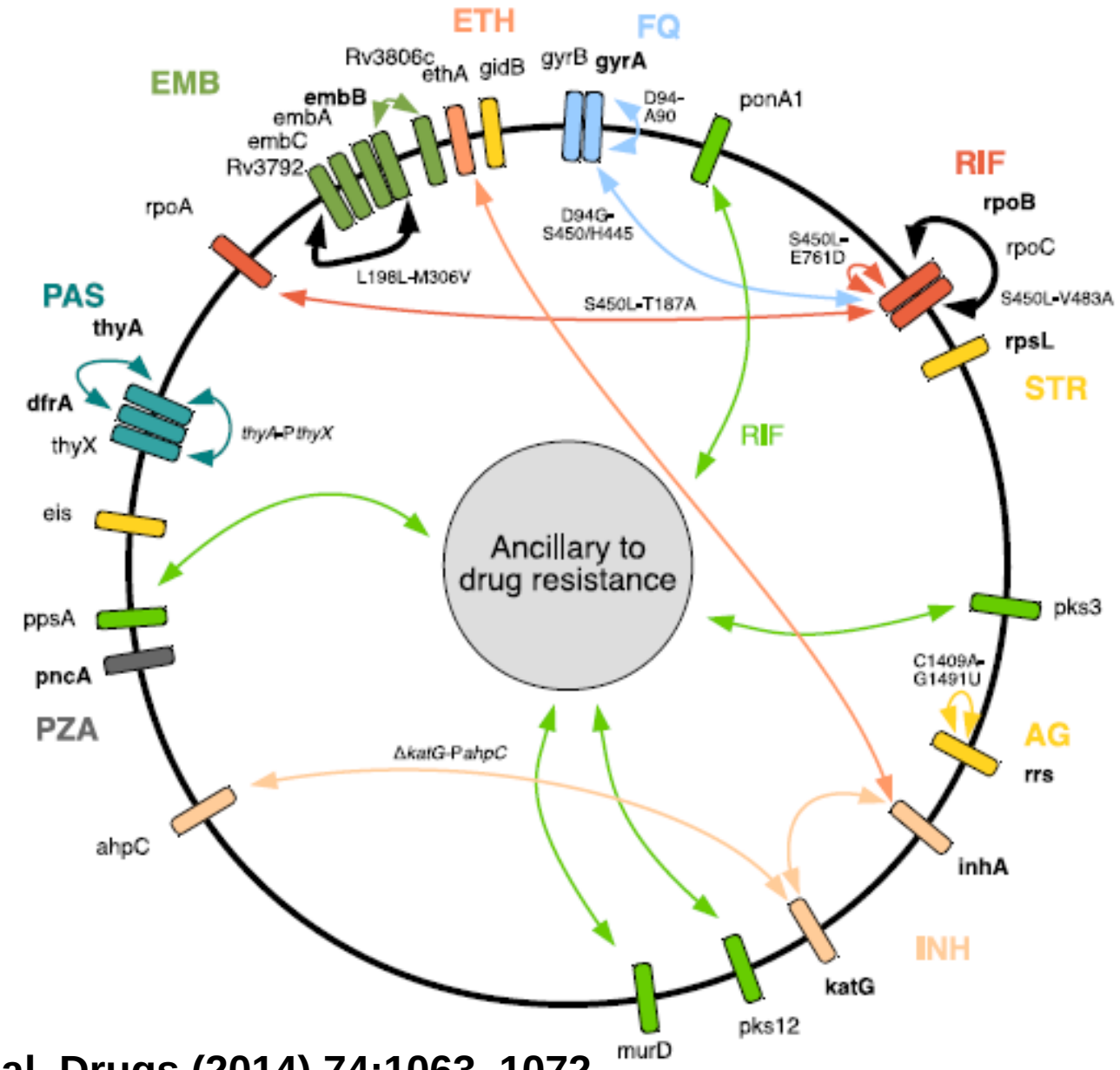




WHOLE GENOME SEQUENCING AND DRUG RESISTANCE GENE DISCOVERY

"…there has been significant interest and effort in using WGS to characterise drug-resistant *M. tuberculosis* isolates … to shed light on …drug resistance. An interesting observation … is that there are over 100 genetic loci that seem to be associated with drug resistance. This has led to the suggestion that drug resistance may be more complex than previously realised. Besides the conventional drug resistance gene mutations …, there are many other mutations that may collectively contribute to the drug resistance phenotype."

Zhang Y, Yew WW. Mechanisms of drug resistance in Mycobacterium tuberculosis: update 2015. Int J Tuberc Lung Dis 2015:19:1276–1289



A. Trauner et al. Drugs (2014) 74:1063–1072

New (PK) data on doses of "old" drugs

AAC Journals.ASM.org

Pharmacokinetics and Safety of Ofloxacin in Children with Drug-Resistant Tuberculosis

Anthony J. Garcia-Prats,[a] Heather R. Draper,[a] Stephanie Thee,[a,b] Kelly E. Dooley,[c] Helen M. McIlleron,[d] James A. Seddon,[e] Lubbe Wiesner,[d] Sandra Castel,[d] H. Simon Schaaf,[a] Anneke C. Hesseling[a]

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Oct. 2011, p. 4594–4600
0066-4804/11/$12.00 doi:10.1128/AAC.00379-11

Pharmacokinetics of Ethionamide in Children[▽]

S. Thee,[1,2]* H. I. Seifart,[3] B. Rosenkranz,[3] A. C. Hesseling,[2] K. Magdorf,[1] P. R. Donald,[2] and H. S. Schaaf[2]

Journal of Antimicrobial Chemotherapy

AAC Journals.ASM.org

Pharmacokinetics of Ofloxacin and Levofloxacin for Prevent Treatment of Multidrug-Resistant Tuberculosis in Children

S. Thee,[a,b] A. J. Garcia-Prats,[a] H. M. McIlleron,[c] L. Wiesner,[c] S. Castel,[c] J. Norman,[c] H. R. Draper,[a] P. L. van der Me A. C. Hesseling,[a] H. S. Schaaf[a]

J Antimicrob Chemother 2015; **70**: 1798–1803
doi:10.1093/jac/dkv039 Advance Access publication 10 March 2015

Pharmacokinetics of anti-TB drugs in Malawian children: reconsidering the role of ethambutol

R. Mlotha[1], D. Waterhouse[2], F. Dzinjalamala[3], A. Ardrey[2], E. Molyneux[1], G. R. Davies[4]* and S. Ward[3]

Journal of Tropical Pediatrics Advance Access published November 21, 2012
JOURNAL OF TROPICAL PEDIATRICS, 2012

Pharmacokinetics and Safety of Moxifloxacin in Children With Multidrug-Resistant Tuberculosis

Stephanie Thee,[1,2] Anthony J. Garcia-Prats,[1] Heather R. Draper,[1] Helen M. McIlleron,[3] Lubbe Wiesner,[3] Sandra Castel,[3] Simon Schaaf,[1,a] and Anneke C. Hesseling[1,a]

Para-Aminosalicylic Acid Plasma Concentrations in Children in Comparison with Adults after Receiving a Granular Slow-Release Preparation

by A. C. Liwa,[1] H. S. Schaaf,[2] B. Rosenkranz,[1] H. I. Seifart,[1] A. H. Diacon,[3] *and* P. R. Donald[2]

Pediatr Infect Dis J. 2016 Apr;35(4):414-21. doi: 10.1097/INF.0000000000001022.

Pharmacokinetics and Dosing of Levofloxacin in Children Treated for Active or Latent Multidrug-resistant Tuberculosis, Federated States of Micronesia and Republic of the Marshall Islands.

Mase SR[1], Jereb JA, Gonzalez D, Martin F, Daley CL, Fred D, Loeffler AM, Menon LR, Bamrah Morris S, Brostrom R, Chorba T, Peloquin CA.

WHO MDR-TB drug grs	Recommended doses	CSF penetration
Gr. A Fluoroquinolones		
Levofloxacin	15-20 mg/kg (higher?)	Moderate to
Moxifloxacin	10 mg/kg (PK studies)	good (60-80%)
Gr. B 2nd-line Inject	15-20 mg/g	Poor (<20%)
Km/Am/Cm		
Gr. C: Other core		
2nd-line drugs		
Ethionamide /Pto	15-20 mg/kg	Good
Cycloserine / Tzd	15-20 mg/kg	Good
Linezolid	<10 yrs: 10mg/kg bd	Good
	>10 yrs: 300-600mg/day	
Clofazimine	2-5 mg/kg; max 100mg	Poor
	(alternate day dosing?)	

MDR-TB drug groups	Recommended dose	CSF penetration
Group D: Add-ons		
D1: Pyrazinamide	30-40 mg/kg	Good
Ethambutol	20-25 mg/kg	Poor (<20%)
High-dose INH	15-20 mg/kg (400mg)	Good
D2: Bedaquiline	**>12 yrs >33kg as in adults**	Likely Poor
Delamanid	**>6yrs/>20kg - 50mg bd**	Likely Poor
	>12yrs/>35kg - 100mg bd	
D3: PAS	150-200 mg/kg/day	Poor – single dose for C_{max}
Amox/Clav used with imipenem /meropenem)	25-30mg/kg tds	Poor
	15-25mg/kg/dose x 6hrly	
	10-20mg/kg/dose x 8hrly	
	Latter both iv (no studies)	

New regimens

Basic Principles of MDR-TB treatment remain the same!

- Give 4 or more drugs to which the patient's isolate is susceptible and/or naïve. Number of effective drugs depends on extent of disease and availability of drugs
- Drugs in previously failed regimen likely not effective
- Be aware of the different drug groups and cross-resistance (and co-resistance) amongst these drugs
- 2nd-line drugs are generally more toxic than 1st-line drugs
- Follow-up: clinical, radiographic and by culture – decide on duration of treatment
- NEVER add one drug to a failing regimen

Building a regimen for MDR/XDR-TB

- Group A: A Fluoroquinolone – levofloxacin or moxifloxacin
- Group B: A 2nd-line injectable drug – kanamycin, amikacin or capreomycin (high rates of cross-resistance)
- Group C: Other core drugs in combination:
  - Ethionamide/Prothionamide (*inhA* mutation?)
  - Cycloserine/Terizidone
  - Clofazimine
  - Linezolid
- Group D1: Add-on drugs (not counted as effective drugs?)
  - high-dose INH (low-level INH resistance / *inhA* mutation)
  - pyrazinamide; ethambutol
- Group D2: New drugs: Delamanid; Bedaquiline
- Group D3: PAS; Amoxiclav plus Carbapenem

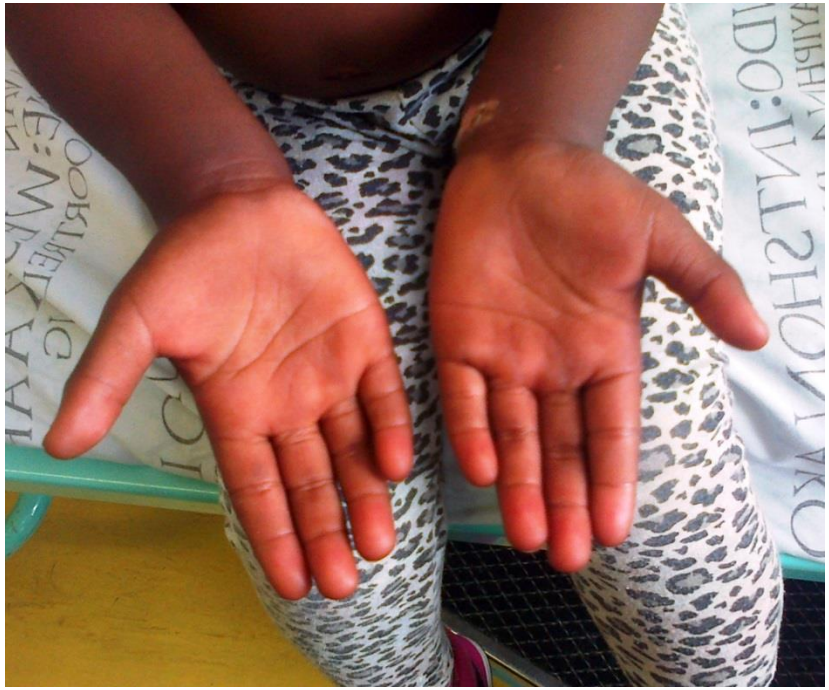
WHO new shorter regimen for RMR/MDR-TB

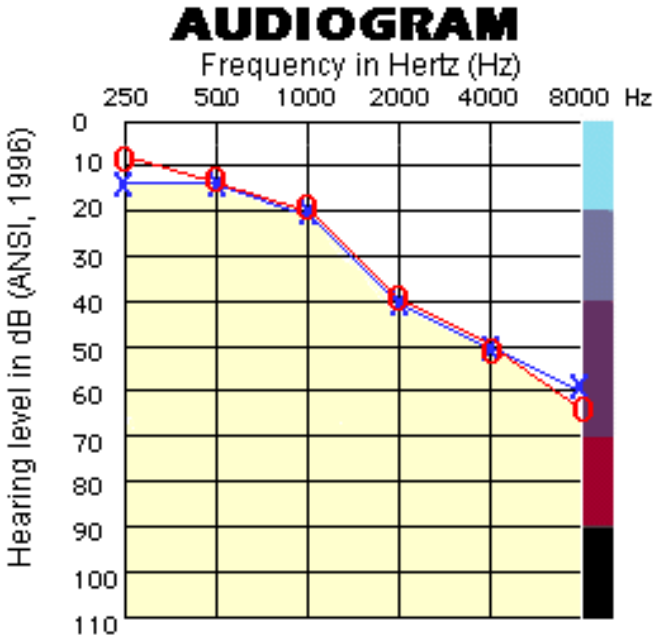
- ONLY for RMR-TB or strictly MDR-TB (INH+RIF resistance, no FQN/SLID resistance)
- 9-12 month regimen (response to treatment)
- 4-6 Km Mfx Cfz H-hd E Pto Z / 5-6 Mfx Cfz E Z
- What about children?
  - Lfx vs Mfx? – Mfx no child-friendly formulation
  - Cfz dose? – 50 or 100 mg gelcaps only – dosing?
  - Pto/Eto AND H-hd? Both or according to INH mutation?
  - Still injectable agent – Am better (MIC lower)?
  - Are 2 effective drugs in continuation phase sufficient? (high rates E & Z resistance). Few long-term follow-up observational studies of regimen

"New" Adverse Effects – Pharmacovigilance!

- **A**rthralgia/arthritis: FQNs/PZA/RFB
- **B**lood dyscrasias: INH/RIF/PZA/LZD/FQNs/PAS and more
- **C**entral nervous system toxicity: headache, drowsiness, seizures, weakness, insomnia, hallucinations: FQNs
- **D**epression/Psychosis: INH/ETO/TZD
- **E**ndocrine effects – hypothyroidism: PAS/ETO, gynaecomastia: ETO/INH
- **F**lu-like syndrome: RIF/RFB/PAS
- **G**IT disturbances – nausea, vomiting, abdominal pain, diarrhoea: Many! ETO/PAS/FQNs/CFZ/LZD/BDQ

Expert Opinion Drug Safety 2016 – Schaaf et al




AUDIOGRAM
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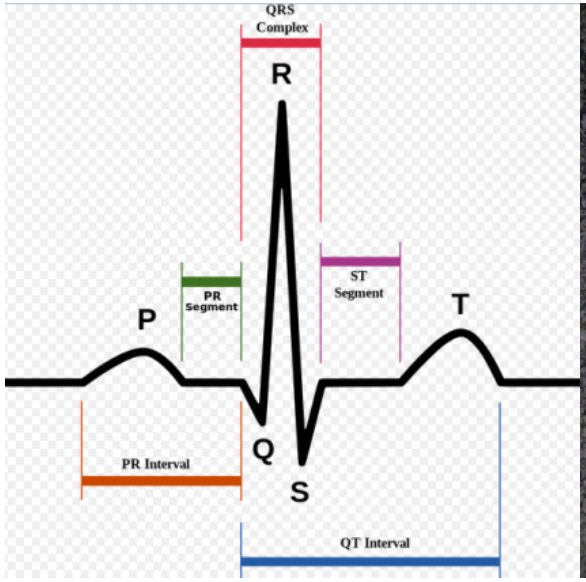
QRS Complex
R
PR Segment
ST Segment
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PR Interval
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QT Interval


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"New" Adverse Effects – Pharmacovigilance! (2)

- **H**earing impair/ototoxicity: AM/KM/CM
  Hair loss (alopecia): INH/ETO
- **I**diopathic intracranial pressure: FQNs
- **J**aundice/hepatotoxicity: PZA/INH/RIF/ETO/PAS/MFX
- **K**+ decrease: Electrolyte disturbance : CM/PAS
- **L**actic acidosis: LZD
- **M**yelosuppression: LZD
- **N**ephrotoxicity: AM/KM/CM/SM
- **O**ptic neuritis/vision disturbance/colour blindness: EMB/LZD/INH/ETO/PAS

Expert Opinion Drug Safety 2016 – Schaaf et al

"New" Adverse Effects – Pharmacovigilance! (3)

- **P**eripheral neuropathy: INH/ETO/LZD/TZD
  Pancreatitis: LZD
- **Q**Tc interval prolongation: FQN/CFZ/CLA/BDQ/DLM
- **R**ashes: PZA/FQNs/TZD/PAS and many other
- **S**kin discolouration – red skin: CFZ
- **T**endinitis/tendonopathy: FQNs
- **U**veitis: RFB
- **V**estibular toxicity: AM/KM/CM/SM

Expert Opinion Drug Safety 2016 – Schaaf et al

New ideas

- Injectable-free MDR-TB treatment regimen (already possible in non-severe disease – low organism load)
- Child-friendly formulations: get them AVAILABLE
- Short-course MDR-TB regimen (6 months) for MDR- and XDR-TB cases
  - we have a number of “new” bactericidal drugs (Lzd, Cfz, Dlm, Bdq, FQNs)
  - in adults already doing 6-month trial in XDR-TB cases
  - time for an efficacy trial in younger children
- Single-drug preventive therapy for MDR-TB contacts

Thank you!