Updated WHO MDR-TB treatment guidelines and the use of new drugs in children

Annual meeting of the
Childhood TB subgroup
Liverpool, UK, 26 October 2016

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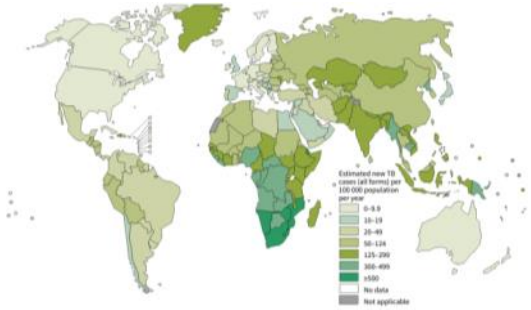
Outline

- Latest epidemiological data
- Existing guidelines
- 2016 update of the DR-TB treatment guidelines
- New recommendations for treatment of RR-TB and MDR-TB in children
- Delamanid guideline for use in children and adolescents
- Research gaps
- Conclusions

The Global Burden of TB - 2015



	Estimated number of cases	Estimated number of deaths
All forms of TB	**10,4** million • 1 million Children (10%)	**1.8** million* • 210,000 children (170,000 HIV negative and 40,000 HIV-positive)
HIV-associated TB	**1.2** million (11%)	**390,000**
Multidrug-resistant TB	**480,000** +100,000 RR cases	**190,000**

Childhood TB: MDRTB estimates

Dodd P., Sismanidis B., Seddon J., Lancet Inf Dis, 21 June 2016:

Global burden of drug-resistant tuberculosis in children: a mathematical modelling study

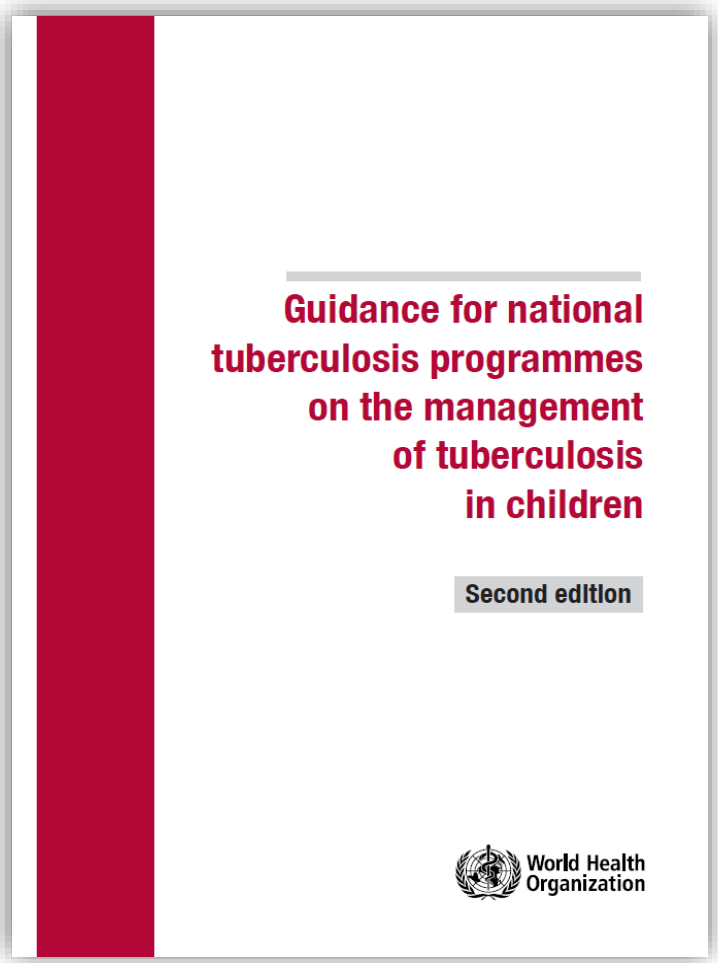
- It is estimated that over 67 million children are infected with TB and therefore at risk of developing disease in the future;
  - 5 mln with INH resistance; 2 mln with MDR; 100,000 with XDR
- **Every year 25,000 children develop MDRTB and 1200 XDR TB**

MDR-TB in children

- MDR-TB in children is mainly the result of transmission of a strain of *M. tuberculosis* that is **MDR from an adult source case**, and therefore often not suspected unless a history of contact with an adult pulmonary MDR-TB case is known.

- Referral to a specialist is advised for treatment.

WHO Guidance on the management of TB in children - 2nd edition 2014: treatment



Annex 3 – **Management of drug-resistant TB in children**

- Do not add a drug to a failing regimen.
- Treat the child **according to the drug susceptibility pattern (and using the treatment history) of the source case's** *M. tuberculosis* strain if an isolate from the child is not available.
- Use at least four drugs certain to be effective.
- Use **daily treatment only**; directly observed therapy is essential.

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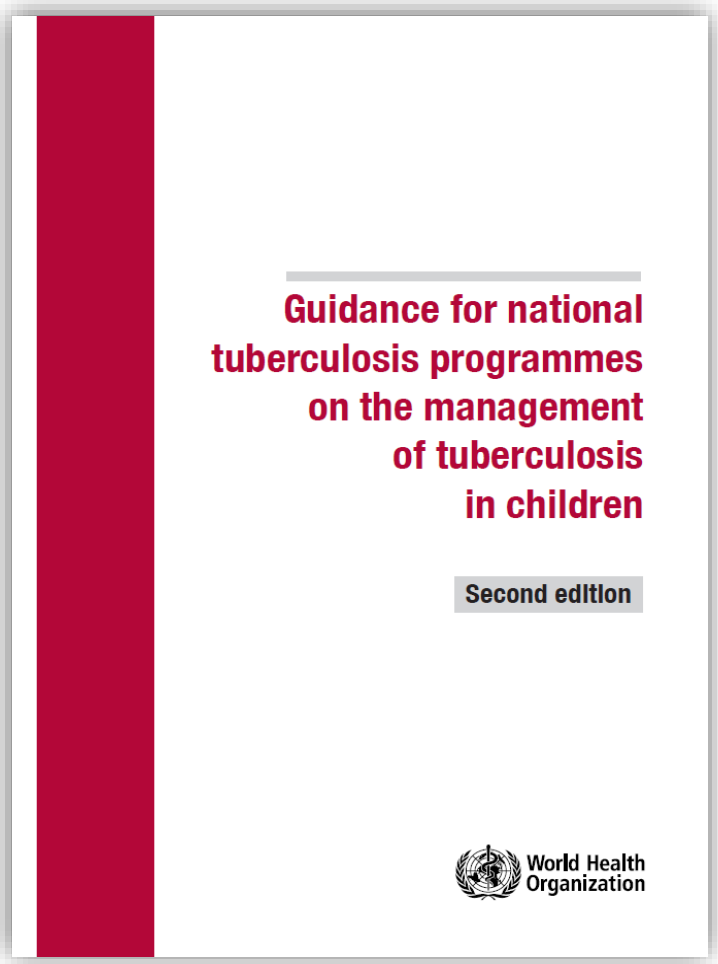
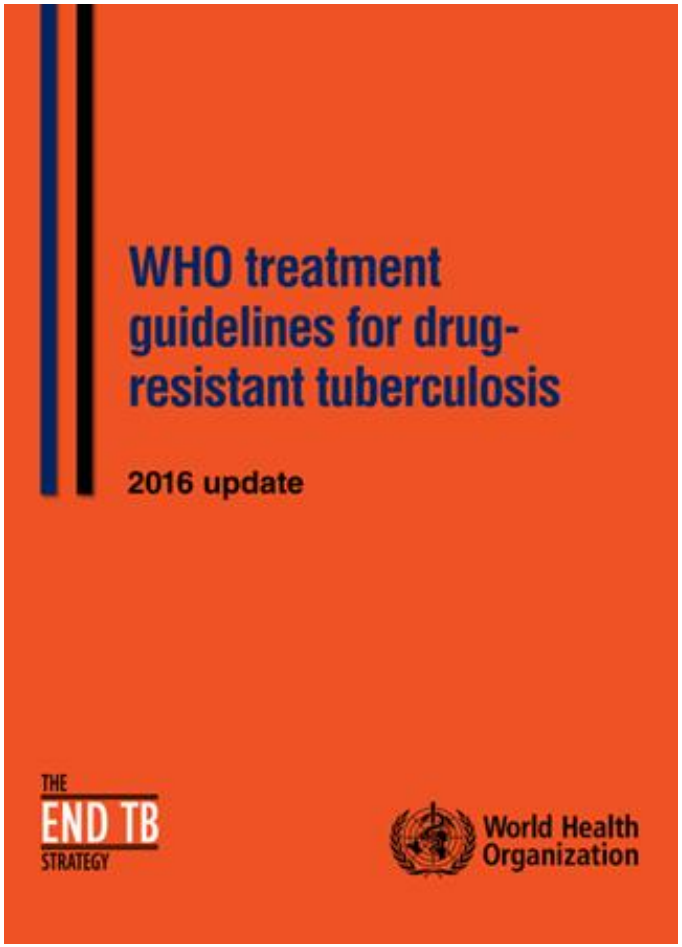
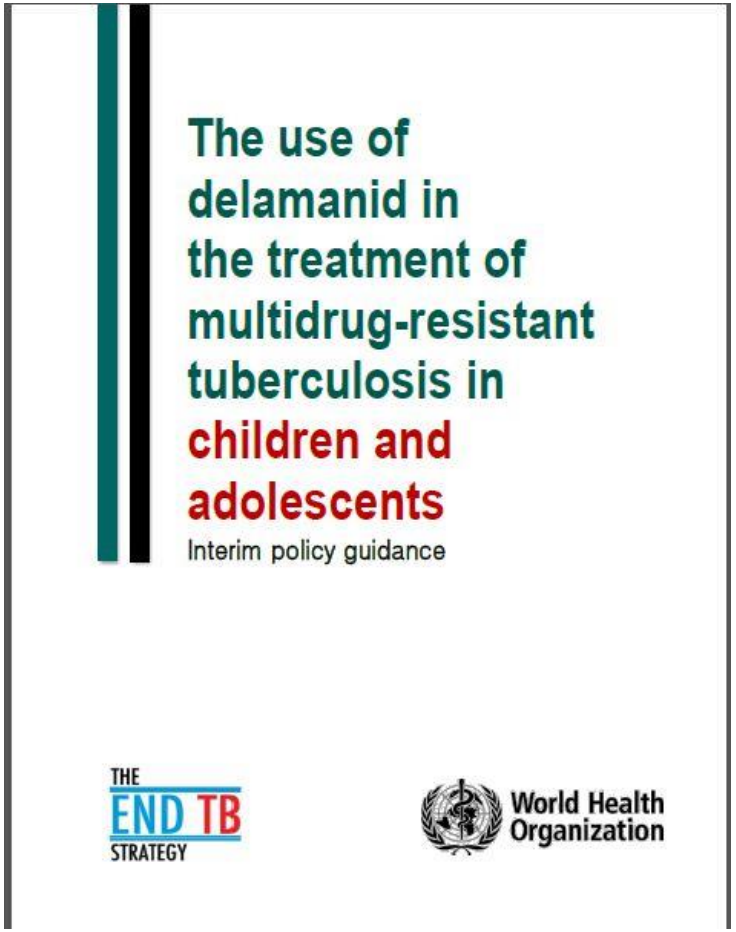


- **Counsel the child's caregiver** at every visit, to provide support, advice about adverse events and the importance of compliance and completion of treatment.
- **Follow-up** is essential: clinical, radiological and bacteriological (mycobacterial culture for any child who had bacteriologically confirmed disease at diagnosis).
- With correct dosing, **few long-term adverse events** are seen with any of the more toxic second line drugs in children.

2016 WHO guidelines on the management of drug resistant TB





WHO guidelines for the treatment of drug-resistant tuberculosis. 2016 update

Key changes

- A shorter MDR-TB treatment regimen is recommended for RR-/MDR-TB patients (under several conditions)
- The design of conventional MDR-TB regimens uses a different regrouping of second-line medicines
- **Recommended treatment of children with RR-/MDR-TB** based on a first-ever meta-analysis of individual-level paediatric patient data for treatment outcomes
- Recommendation on partial lung resection surgery

Shorter MDR-TB regimen (1)

In patients (adults and children) with

- rifampicin-resistant TB or MDR-TB,
- who have not been previously treated with second-line drugs and
- in whom resistance to fluoroquinolones and second-line injectable agents has been excluded or is considered highly unlikely

a shorter MDR-TB regimen of **9–12 months** may be used instead of a conventional regimen

- Conditional recommendation – very low quality of evidence

Shorter MDR-TB regimen (2)

Main remarks

- Standardized regimen; limited modifications are possible
- 4-6 Km-Mfx-Pto-Cfz-Z-$H_{high\text{-}dose}$-E / 5 Mfx-Cfz-Z-E
- Recommendation applies to adults, **children**, PLHIV
- Ideally, patients are tested for resistance to fluoroquinolones and second-line injectable drugs; not recommended in case of 2nd line drug resistance, extrapulmonary disease and pregnancy

Shorter MDR-TB regimen (2)

Main remarks

- Lowered costs (<US$1,000 in drug costs/patient)
- Monitoring for effectiveness, relapse, and harms (active TB drug safety monitoring and management (aDSM)) applies
- Trials expected to provide high-certainty evidence

GROUP A Fluoroquinolones		Levofloxacin Moxifloxacin Gatifloxacin
GROUP B Second-line injectable agents		Amikacin Capreomycin Kanamycin (Streptomycin)
GROUP C Other Core Second-line Agents		Ethionamide / Prothionamide Cycloserine / Terizidone Linezolid Clofazimine
GROUP D Add-on agents *(not core MDR-TB regimen components)*	**D1**	Pyrazinamide Ethambutol High-dose isoniazid
	D2	Bedaquiline Delamanid
	D3	*p*-aminosalicylic acid Imipenem-Cilastatin Meropenem Amoxicillin-Clavulanate (Thioacetazone)

Recommendation on longer MDR-TB regimen (1)

In patients with rifampicin-resistant TB or MDR-TB, *a regimen with at least five effective TB medicines* during the intensive phase is recommended, *including pyrazinamide and* four core second-line TB medicines – *one chosen from Group A, one from Group B, and at least two from Group C*

Group A =
levofloxacin;
moxifloxacin;
gatifloxacin

Group B =
amikacin,
capreomycin,
kanamycin,
(streptomycin)

Group C =
ethionamide/
prothionamide,
cycloserine/
terizidone, linezolid,
clofazimine

Recommendation on longer MDR-TB regimen (1)

- If the minimum number of five effective TB medicines cannot be composed as given above, an ***agent from Group D2 and other agents from Group D3 may be added to bring the total to five***

- the regimen may be further strengthened with high-dose isoniazid and/or ethambutol

Group D2
bedaquiline, delamanid
Group D3
p-aminosalicylic acid, imipenem–cilastatin, meropenem, amoxicillin–clavulanate, (thioacetazone)

Choosing the treatment regimen for RR-/MDR-TB

- Confirmed resistance or suspected ineffectiveness to a medicine in the shorter MDR-TB regimen (except isoniazid resistance)?
- Exposure to ≥1 second-line medicines in the shorter MDR-TB regimen for >1 month?
- Intolerance to ≥1 medicines in the shorter MDR-TB regimen or risk of toxicity (e.g. drug-drug interactions)?
- Pregnancy?
- Extrapulmonary disease?
- At least one medicine in the shorter MDR-TB regimen not available?

NO

Shorter MDR-TB regimen

FAILING REGIMEN, DRUG INTOLERANCE, RETURN AFTER INTERRUPTION >2 MONTHS, EMERGENCE OF ANY EXCLUSION CRITERION

YES

Longer MDR-TB regimens

Delamanid

- Children (6 – 11 years) - 50 mg – 2x /day for 6 months and
- Adolescents (12-17 years) – 100mg 2x /day for 6 months in adolescents aged 12 to 17
  - may be added to a <u>WHO recommended longer MDR-TB treatment regimen</u>

- (*conditional recommendation, very low confidence in estimates of effects*)

Delamanid (2)

- Patients with additional resistance or intolerance to fluoroquinolones or second line injectable drugs
- Patients with extended lesions, advanced disease and others deemed at higher baseline risk for poor outcomes
- Patients with XDR-TB

Delamanid (3)

- Excludes paediatric cases with reported QTc prolongation (greater than 500msec);
- Paediatric patients with HIV co-infection were excluded from the analysed studies; drug has not been tested in patients with extra-pulmonary MDR-TB
- Studies are underway, currently there are no data on the effect of delamanid in children younger than 6 years of age and weighting under 20 kg.

Bedaquiline

- No data available on the use of BDQ in children (patients younger than 18 years),

- Janssen BDQ compassionate use programme excluded paediatric patients

Research gaps

- Need for more randomised control studies, especially involving new drugs and regimens (adults and children)
- Inclusion of children and separate reporting of outcomes
- Identification of factors which determine the optimal duration of treatment for children
- PK studies to determine optimal drug dosing and safety
- Improved diagnostics and DST methods for children
- **Studies on preventive chemotherapy for children in contact with MDR-TB**

Conclusions

- MDR-TB in children recognized and guidelines available
- Finally evidence based recommendations for treatment of RR-TB and MDR-TB in children

BUT

- **Need for more data, especially on the use of new drugs and new regimens**

AND

- **Evidence needed to promote preventive chemotherapy for children in contact with a confirmed MDR TB in the household**

Acknowledgements

Annemieke Brands and Ernesto Jaramillo

Thank you for your attention to childhood TB !

http://www.who.int/tb/areas-of-work/children/en/