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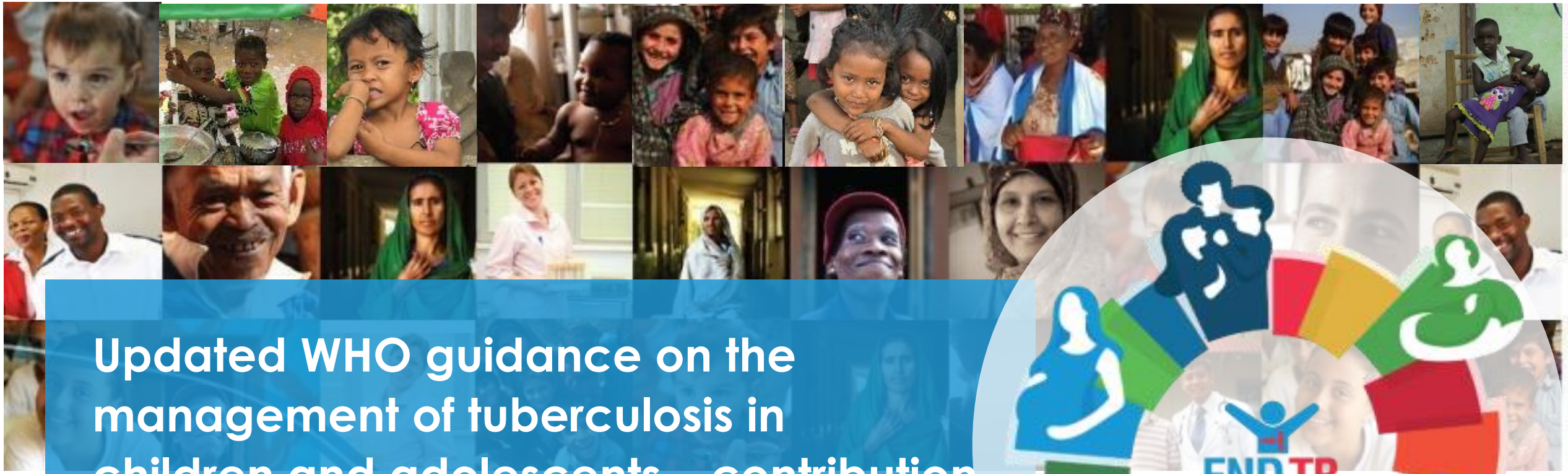

Updated WHO guidance on the management of tuberculosis in children and adolescents – contribution of data from IMPAACT

Sabine Verkuijl,
WHO Global Tuberculosis Programme

IMPAACT Network Annual Meeting, 28 June 2022

END TB

Outline

- Historical overview
- Epidemiology of TB in children and adolescents and main programmatic gaps
- Brief overview of new guidelines and operational handbook
- Focus on new recommendation on the use of bedaquiline in children with MDR/RR-TB and role of data from IMPAACT P1108
  - Historical context on use of bedaquiline
  - Evidence reviewed by the GDG
  - Dosing guidance meeting
  - Importance of child-friendly formulations
- Remaining research gaps
- Conclusions

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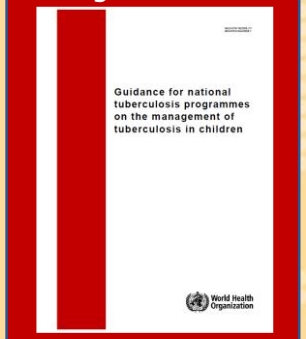
Historical overview

Unitaid paediatric DR-TB project (BENEFIT Kids, Stellenbosch)

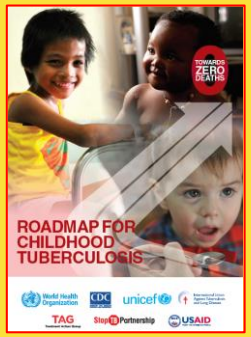
STEP-TB project (first-line child-friendly FDCs)

2006 — First WHO guidance



2008 — First call to action, Stockholm

2010 — First Roadmap towards zero deaths

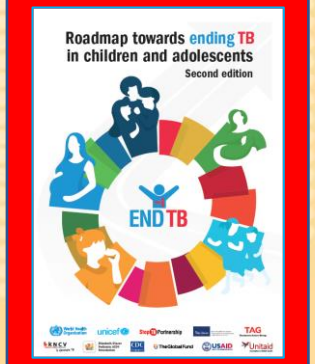


2011 — Childhood TB consultation for the African region

2012 — Global consultation on childhood TB for EMR, SEAR, WPR

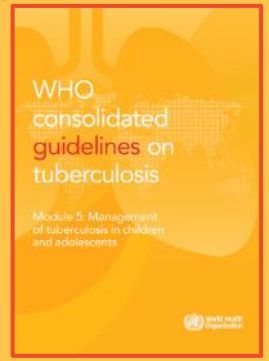
2013 — Childhood TB integration meeting

2014 — Second Roadmap towards ending TB

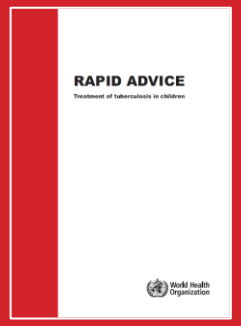


2015 — 1st paediatric anti-TB drug optimization (PADO-TB1) meeting

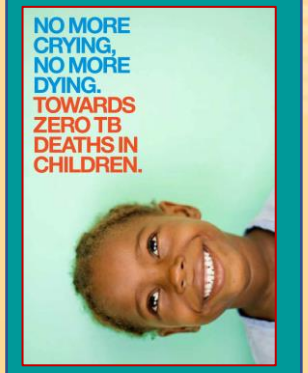
2016 — Consolidated guidelines and operational handbook



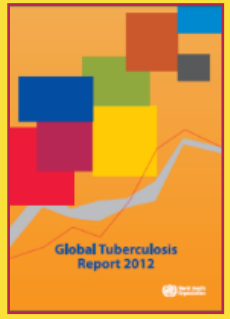
2017 — WHO rapid advice – treatment of TB in children



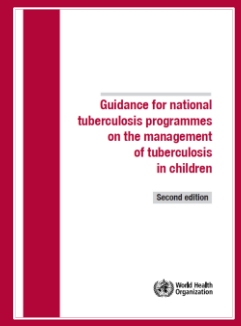
2018 — NO MORE CRYING, NO MORE DYING. TOWARDS ZERO TB DEATHS IN CHILDREN.



2019 — 1st set of global burden estimates



2020 — WHO childhood TB guidance 2nd ed.



2021 — Childhood TB subgroup status changed to full Working Group, adolescent focus added

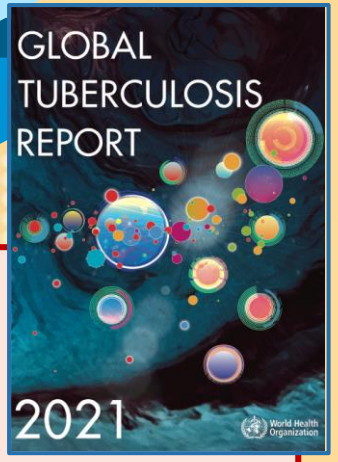
2022 — UNICEF/WHO joint statement on the FDCs

Global consultation on ending TB in children and adolescents for EMR, SEAR, WPR

Regional consultation on ending TB in children and adolescents for the African region (tbc)

Unitaid paediatric TB projects (CaP-TB. TB-Speed)

Global burden estimates (2021 Global TB report)



TB among all ages

9.9 million

TB patients in 2020

1.5 million

TB deaths in 2020

1.3m in HIV-uninfected
215k in PLHIV

7.5 million

children (0–14) infected with TB each year

et al, 2014)

1.09 million

children (0-14 years) developed TB in 2020

47.5% <5 years olds

727 000 adolescents

(10–19 year-olds) developed TB in 2012

(Snow et al, 2018)

226 000

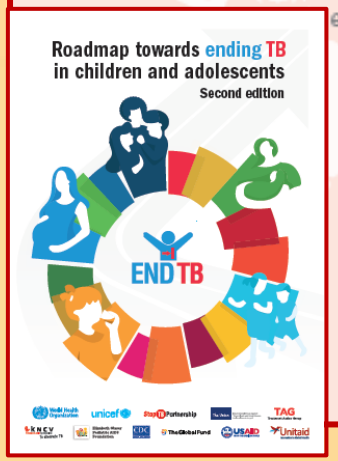
child (0-14) TB deaths in 2020

80% in children <5 years

96% of deaths in children who did not access TB treatment

21 000 (9%) deaths among children living with HIV

(Dodd et al, 2017a)



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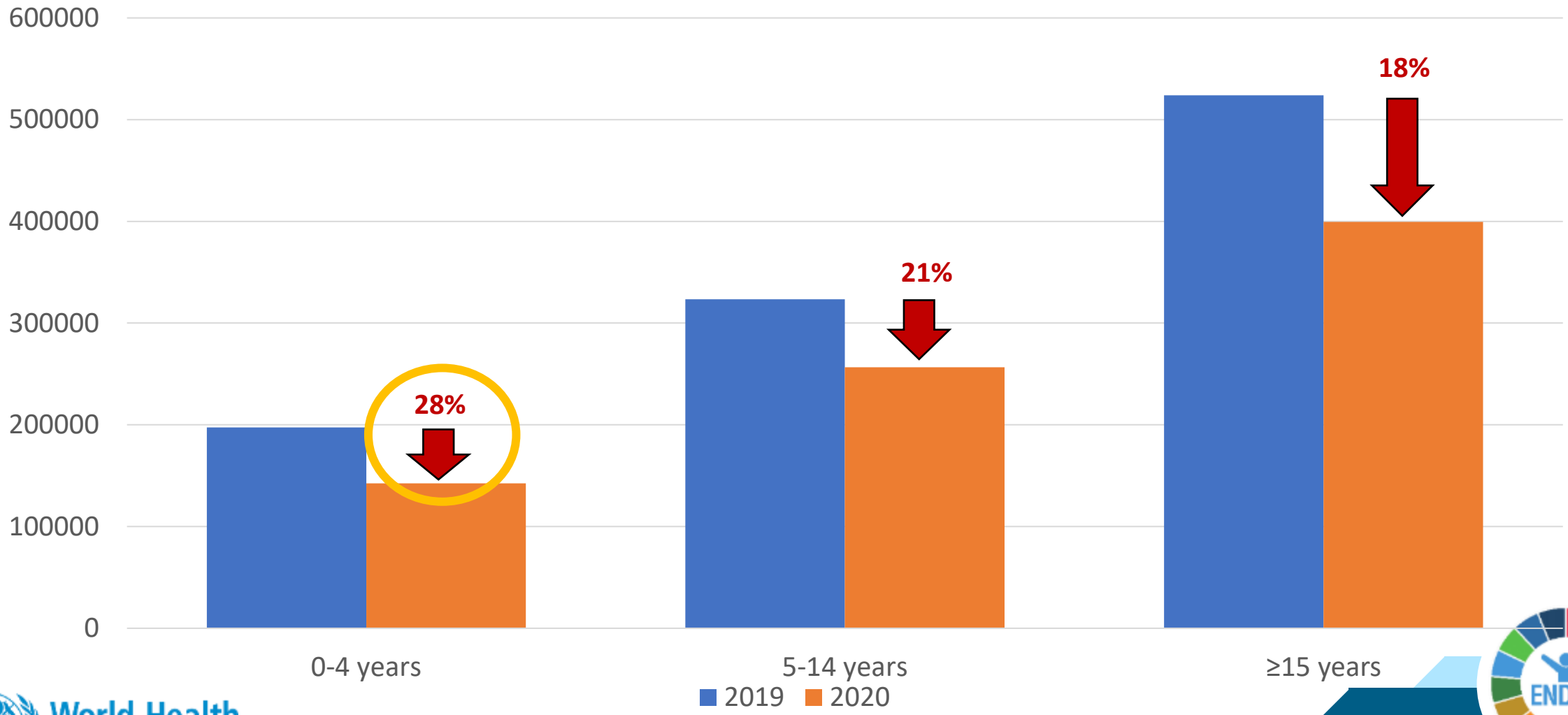
Impact of COVID-19 on TB notifications in <15years



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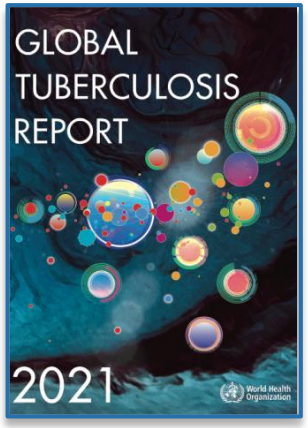
Treatment initiation in children with MDR/RR-TB

- Reporting on # of children <15 y initiated on second-line treatment for MDR/RR-TB since 2020
- **6 countries** (see table on top right) reported **≥100 children** started on treatment (81% of all cases) in 2019



- Drop in numbers starting treatment in 2020
  - Drop compared to 2019:
    - 42% in children <15; 27% in adults >15
  - % of children among all patients: **2.5%**
  - Estimated treatment coverage (based on modelling data): **10%**

Country	Children initiated SLD (2019)	Children initiated SLD (2020)
India	**3360 (60%)**	**1844 (57%)**
Russian Federation	476	54
South Africa	332	162
Ukraine	161	115
Pakistan	110	76
Kazakhstan	100	75
Global total	**5588**	**3235**

	MDR/RR-TB (all ages)	MDR/RR-TB (0-14y)	% children among all MDR/RR-TB	% of estimated annual burden in children*
2018	156 205	3 398	2.2%	10.6%
2019	177 099	5 588	3.2%	17.5%
2020	128 338	3 235	2.5%	10.1%

* Estimated annual burden 32 000 (Dodd, 2016; Jenkins, 2018)

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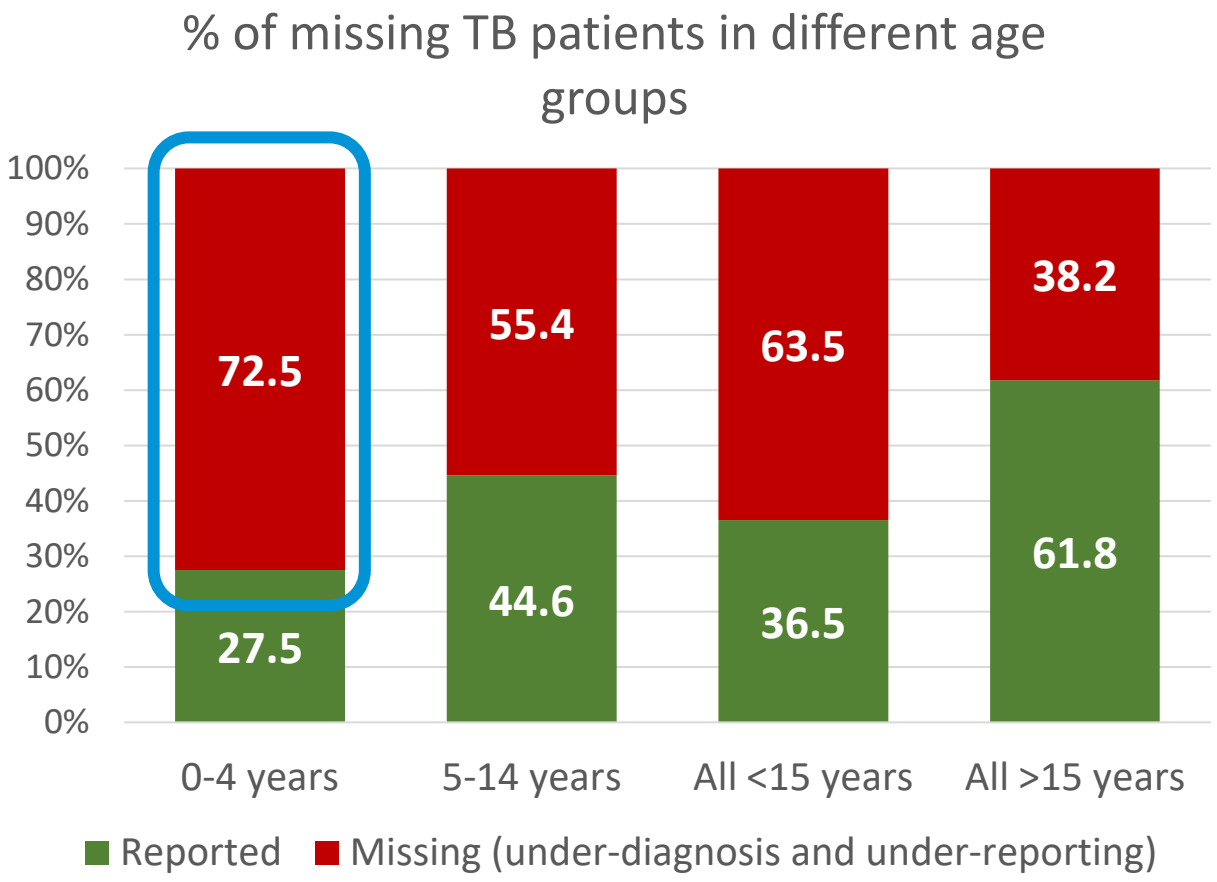
The case detection and prevention gaps

The case detection gap



The prevention gap

In 2020, **almost two thirds** of 1.1 million eligible contacts <5 years* did **NOT access TB preventive treatment (TPT)**

* Estimated number of eligible children was reduced due to lower notifications of bacteriologically confirmed patients in 2020
No data collected on TPT for DR-TB

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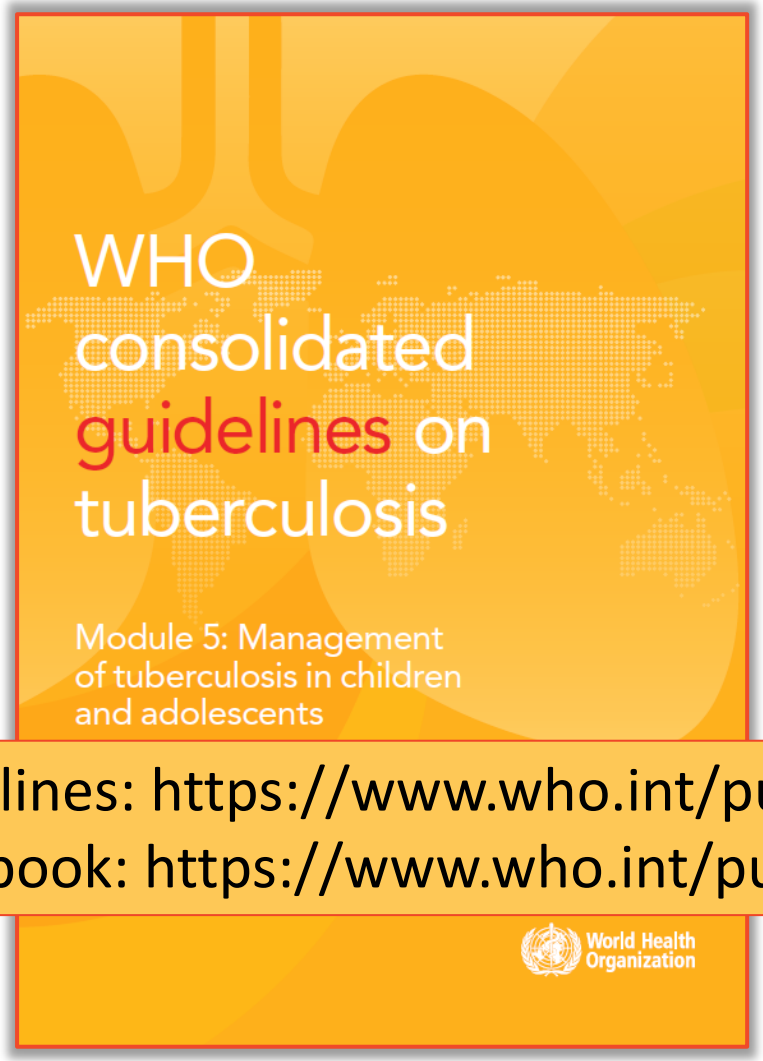
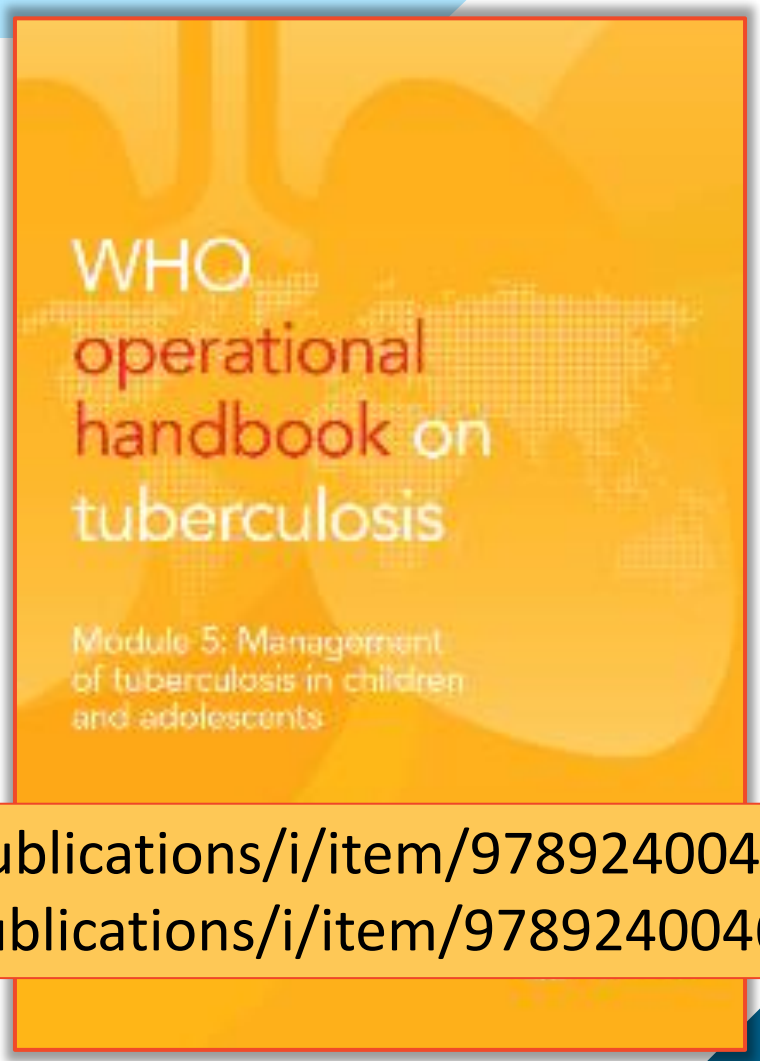
WHO consolidated guidelines and operational handbook on the management of TB in children and adolescents





Guidelines: https://www.who.int/publications/i/item/9789240046764
Handbook: https://www.who.int/publications/i/item/9789240046832

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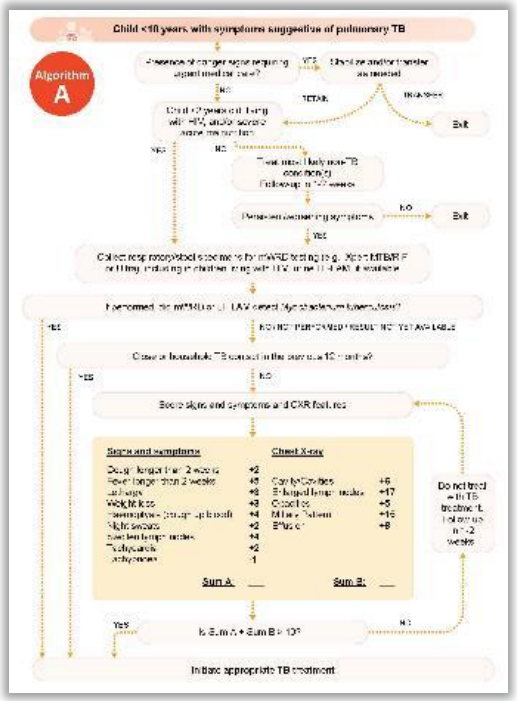
Summary of new recommendations – diagnostic approaches

In children with signs and symptoms of pulmonary TB, **Xpert Ultra** should be used as the initial diagnostic test for TB and detection of rifampicin resistance on sputum, nasopharyngeal aspirate, **gastric aspirate or stool**, rather than smear microscopy/culture and DST

*(**UPDATED**: strong recommendation, moderate certainty of evidence for test accuracy in stool and gastric aspirate; low certainty of evidence for test accuracy in sputum; very low certainty of evidence for test accuracy in nasopharyngeal aspirate)*

In children with presumptive pulmonary TB attending health care facilities, **integrated treatment decision algorithms** may be used to diagnose pulmonary TB

*(**NEW INTERIM** conditional recommendation, very low certainty of evidence)*



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Shorter treatment duration in children with non-severe TB

In children and adolescents between 3 months and 16 years of age with non-severe TB (without suspicion/evidence of MDR/RR-TB), a 4-month treatment regimen (2HRZ(E)/2HR) should be used.

*(**NEW:** Strong recommendation, moderate certainty of evidence)*

- Recommendation informed by SHINE trial
- Multi-centre, open-label, parallel-group, non-inferiority, randomized, controlled, two-arm trial comparing 4-month versus the standard 6-month treatment durations in children < 16 years of age with symptomatic non-severe TB
- Non-inferiority of the 4-month regimen consistent across all intention-to-treat, per-protocol and key secondary analyses
- Including 2 IMPAACT sites (DTTC, Pune)

SHINE: Shorter Treatment for Minimal Tuberculosis in Children

World Health Organization

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Treatment of TB meningitis in children and adolescents

In children and adolescents with bacteriologically confirmed or clinically diagnosed TB meningitis (without suspicion or evidence of MDR/RR-TB), a 6-month intensive regimen (6HRZEto) may be used as alternative option to the 12-month regimen (2HRZE/10HR)

*(**NEW:** conditional recommendation, very low certainty of the evidence)*

- Short intensive (high dose) regimen used in South Africa for decades
- Meta-analysis:
  - Shorter intensive regimen: lower death rates, and higher successful treatment rates, but higher proportion of survivors with neurological sequelae
  - Very low certainty data – not favouring one regimen over the other

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New recommendations on DR-TB treatment

- **In children with MDR/RR-TB aged below 6 years, an all-oral treatment regimen containing bedaquiline may be used**
- In children with MDR/RR-TB aged below 3 years, delamanid may be used as part of longer regimens

(NEW: both conditional recommendations, very low certainty of the evidence)

These recommendations make it possible to build all oral regimens for children of all ages

- In TB high burden settings, **i) decentralized models of care and ii) family-centred, integrated models of care** may be used to deliver TB services to children and adolescents with signs and symptoms of TB and/or those exposed to TB

*(**NEW**: both conditional recommendations, very low certainty evidence)*

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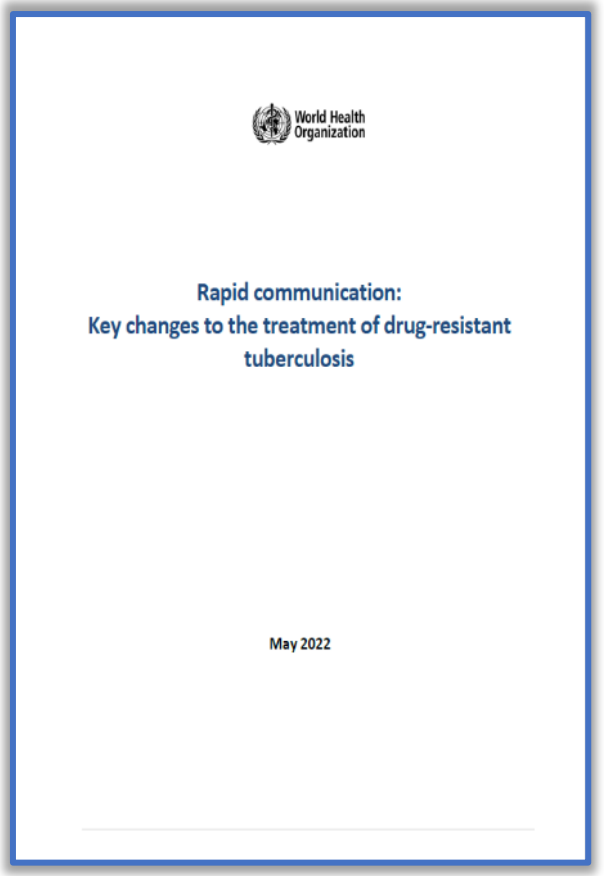
Rapid communication DR-TB (May 2022)

- **6-month BPaLM** (bedaquiline, pretomanid, linezolid (600mg), moxifloxacin) may be used programmatically (≥15y)
  - BPaL if fluoroquinolone resistant

- **9-month, all-oral, bedaquiline-containing regimens** are preferred over longer (>18 months) regimens in adults and children with MDR/RR-TB
  - 2 months of linezolid as alternative to 4 months of ethionamide
  - 4-6 Bdq [6]-Lfx [Mfx]-Lzd [2]-E-Z-H^h-Cfz / 5 Lfx [Mfx]-Cfz-Z-E *or*
  - 4-6 Bdq [6]-Lfx [Mfx]-Eto-E-Z-H^h-Cfz / 5 Lfx [Mfx]-Cfz-Z-E



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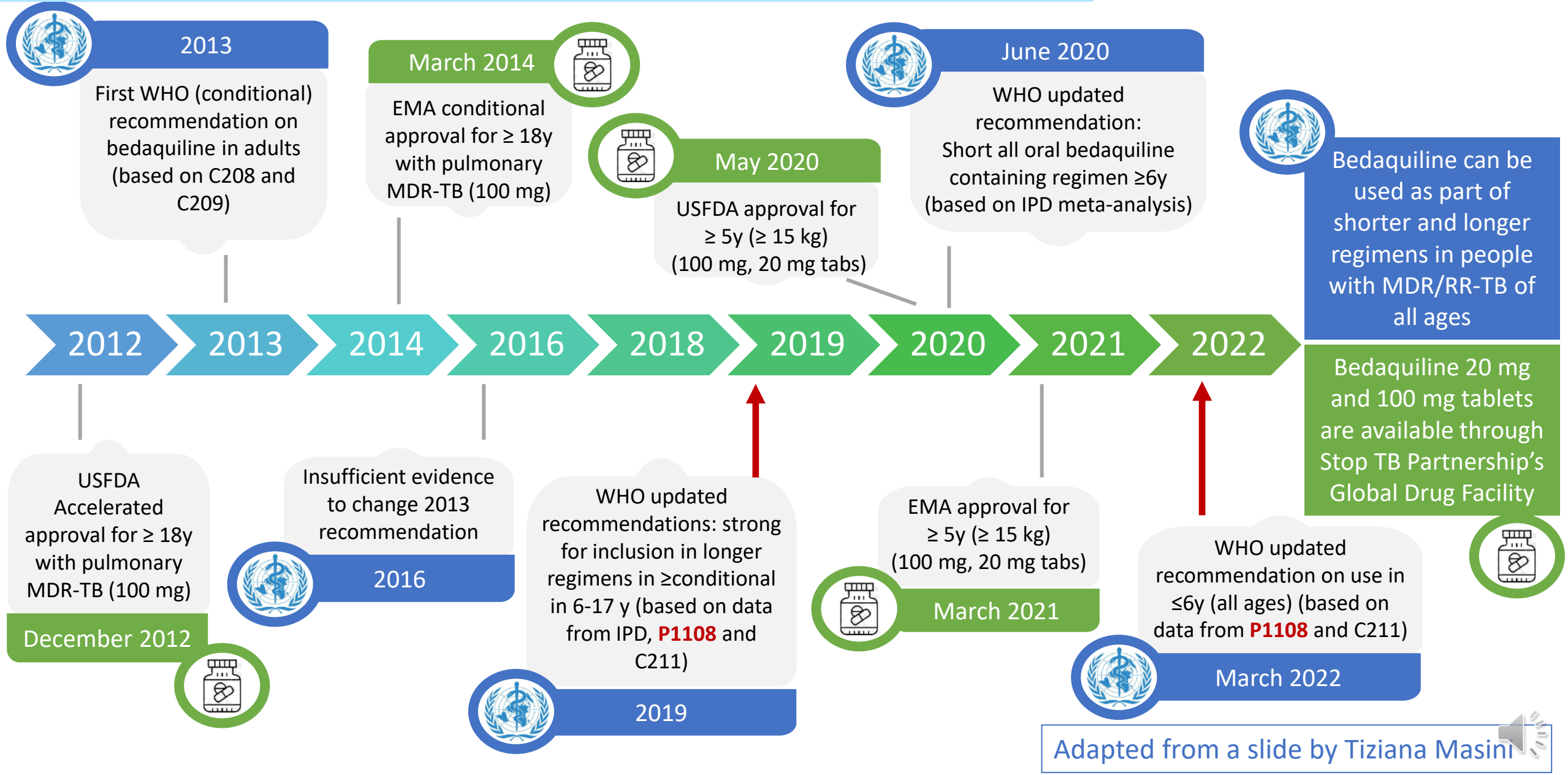
https://apps.who.int/iris/rest/bitstreams/1420701/retrieve

END TB

Historical context: BDQ recommendations and regulatory approvals



Adapted from a slide by Tiziana Masini

Evidence on BDQ presented to the WHO GDG

Data reviewed:

- Data from **IMPAACT P1108 (children aged 0-18)**, Janssen TMC207-C211 (children aged 5-18) and paediatric DR-TB IPD

Findings (trials)

- Small sample size of children below 6 years (N=12 from IMPAACT P1108)
  - All PK and safety data from P1108 available at the time used
  - Efficacy extrapolated from adults
- No cardiac safety signals distinct from adults
- PopPK models from both studies suggest adult drug exposures can be achieved in most children

IMPAACT P1108: phase I/II dose finding **modified age de-escalation** study to evaluate the PK, safety and tolerability of BDQ in children with MDR-TB with and without HIV

Janssen TMC207-C211: phase II, open-label, single-arm study to evaluate the PK, safety, tolerability and anti-mycobacterial activity of BDQ in children and adolescents 0–17 years with MDR-TB

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Evidence (paediatric DR-TB IPD): BENEFIT-Kids

- 24,231 records, majority from **India and South Africa**; ~20,000 used for matched analysis of treatment outcomes (>15 countries)
- BDQ significantly associated with **shorter treatment duration** and **lower injectable use**
- High overall treatment success
- IPD overall: majority **confirmed DR-TB** and a **high % of adolescents** suggesting many young children with MDR/RR-TB not yet routinely diagnosed and treated

World Health Organization
Unitaid
BENEFIT Kids
DESMOND TUTU TB CENTRE · SENTRUM · IZIKO
Every breath counts
Stellenbosch UNIVERSITY IYUNIVESITHI UNIVERSITEIT
END TB

Expert consultation on dosing for new recommendations

- Separate process to develop dosing strategy
- Interim dosing guidance based on available data using population PK modeling and simulation tools
  - Individual data from P1108, C211 and MDR-PK2
  - **P1108**: data shared from cohorts 2 and 3, additional data shared since GDG (N=17); all data sharing governed by a CDA. Only data in children < 2 years.
- Combined age-and weight-based approach in children <6y
- 20 mg dispersible formulation preferred, but 100 mg adult formulation can be used (pill burden, availability)
- Pharmacometric on BDQ and DLM led by Elin Svensson

Group	Medicine	Weight-based daily dose[b]	Formulations (mg/mL, as applicable)	3 to <5 kg	5 to <7 kg	7 to <10 kg
	Bedaquiline	-	20 mg dt[e]	0 to <3 months: 1.5 od for 2 weeks; then 0.5 od M/W/F for 22 weeks ≥ 3 months: 3 od for 2 weeks; then 1 od M/W/F for 22 weeks		0 to <3 months: 1.5 od for 2 weeks; then 0.5 od M/W/F for 22 weeks 3 to <6 months: 3 od for 2 weeks; then 1 od M/W/F for 22 weeks ≥ 6 months: 4 od for 2 weeks; then 2 od M/W/F for 22 weeks
		-	100 mg tab[e]	0 to <3 months: 3 mL od for 2 weeks; then 1 mL od M/W/F for 22 weeks[c] ≥ 3 months: 6 mL od for 2 weeks; then 2 mL od M/W/F for 22 weeks[c]		0 to <3 months: 3 mL od for 2 weeks; then 1 mL od M/W/F for 22 weeks[c] 3 to <6 months: 6 mL od for 2 weeks; then 2 mL od M/W/F for 22 weeks[c] ≥ 6 months: 8 mL od for 2 weeks; then 4 mL od M/W/F for 22 weeks[c]

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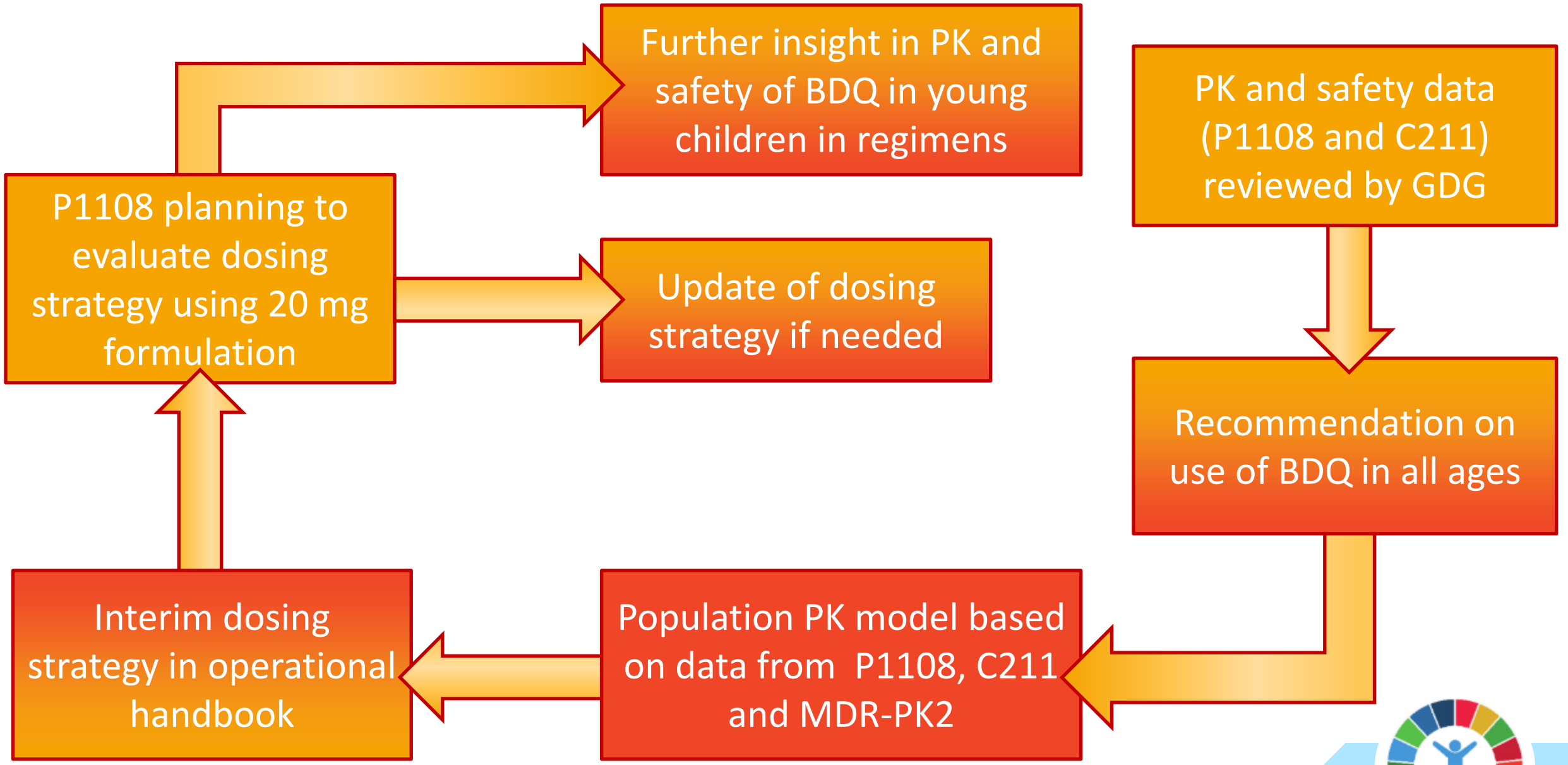

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Importance of formulations

- Child-friendly formulations critical to support implementation of new recommendations and dosing
- Formulations needed beyond DR-TB (TPT, new shorter DS-TB regimen, possible future higher dosing e.g. rifampicin)
  - WHO-led PADO-TB process prioritizes formulations for development in short, medium and longer term
  - Good quality, palatable, dispersible, scored, flexible formulations (multiple indications)
  - Generic moxifloxacin, linezolid, new taste masked formulations: BENEFIT-Kids

https://www.who.int/publications/m/item/statement-on-the-use-of-child-friendly-fixed-dose-combinations-for-the-treatment-of-tb-in-children

World Health Organization

BENEFIT Kids

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Remaining research gaps

DR-TB treatment

- Ideal regimen (duration, composition) for children with FQ susceptible and FQ resistant DR-TB
  - 6-9 months
  - Covering full disease spectrum, HIV; bacteriologically confirmed and clinically diagnosed (majority)
  - Once daily dosing pragmatic strategy
  - Additional data needed on BDQ PK and safety using new dosing guidance – clinical trials, extended PV
  - Acceptability, cost of regimens
- Pretomanid (BPaL or BPaLM) – PK and safety data in <14 years
  - Single dose PK study (girls only) starting 2022: IMPAACT 2034
  - Substitute pretomanid with delamanid in the interim?

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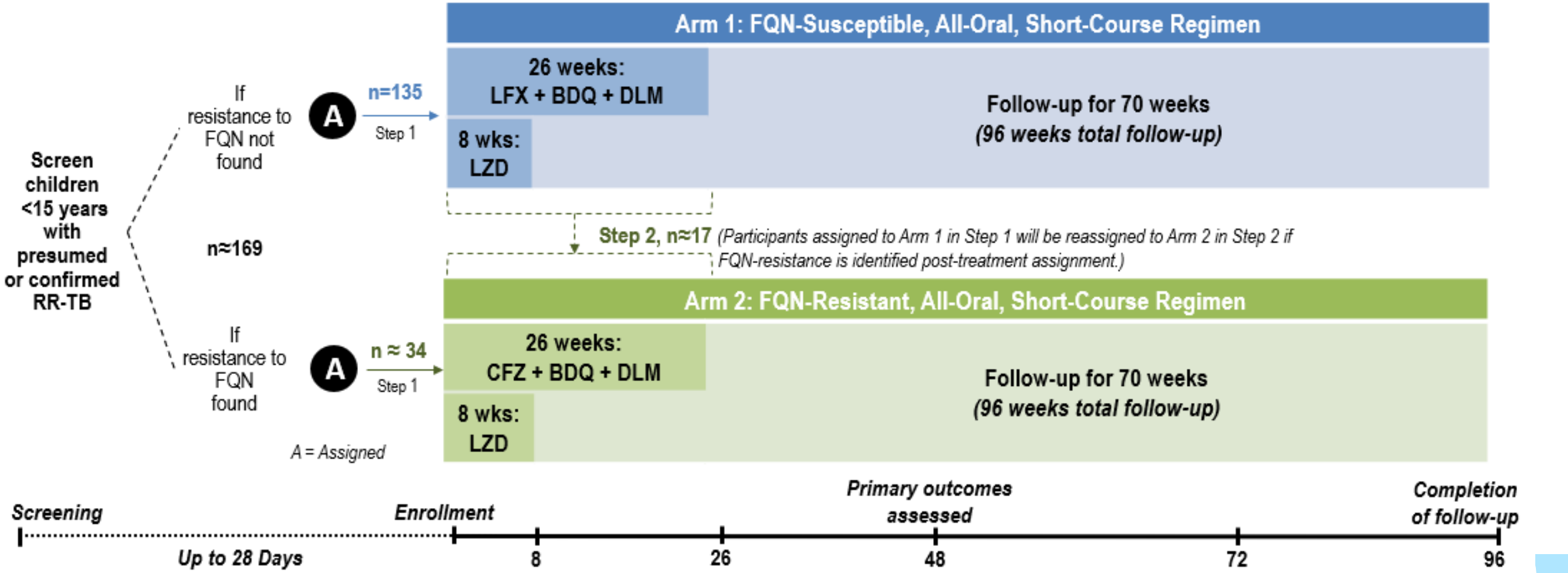
IMPAACT 2020: Phase II Study of Shortened Oral Treatment for MDR-TB in Children (SMaRT Kids)



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Study schema courtesy Anneke Hesseling

Remaining research gaps

Diagnosis

- Better diagnostic tools (point-of-care tests), computer-aided detection in children, biomarkers
- External validation of treatment decision algorithms (including for DR-TB)

Prevention

- Shorter child-friendly TPT regimens
- DR-TB prevention (PHOENIx: A5300/P2003)

Treatment: DS TB

- Further shortening of treatment for DS-TB?

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Conclusions

- Significant progress made in child and adolescent TB evidence and care
- **Major gaps** remain - investment in paediatric TB R&D and building trial capacity to generate high-quality evidence to inform guidelines is critical
- Ongoing significant contributions of **IMPAACT** to global guidance on the prevention and treatment of TB in children and adolescents with and without HIV
- Important research gaps remain around **ideal treatment regimen** for children with MDR/RR-TB
- Better options for TB treatment and prevention available – translation into access
  - Child-friendly **rifapentine and rifampicin** formulations are high priorities
  - Efforts needed to **increase case detection** and reporting

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END TB

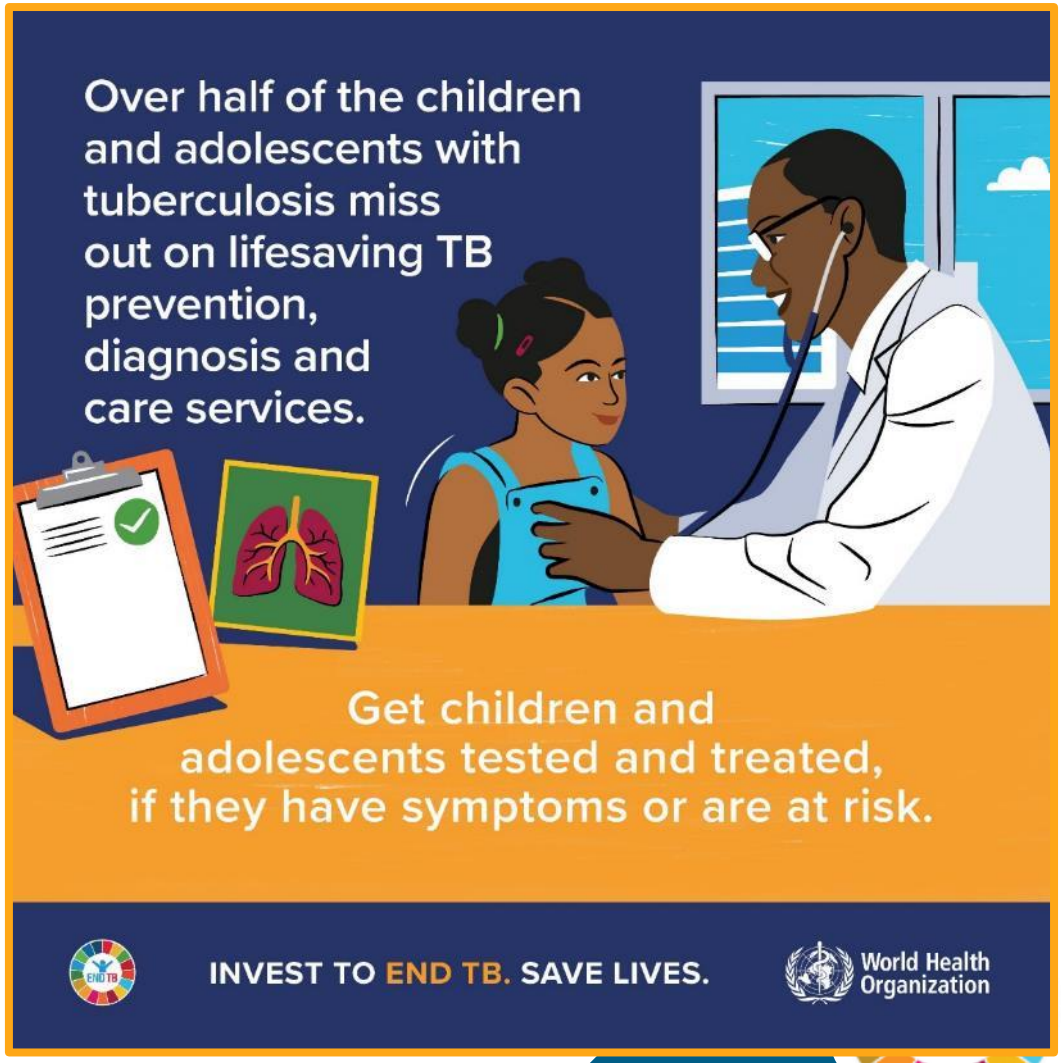
Acknowledgements and thanks

- Tereza Kasaeva, Farai Mavhunga, Kerri Viney, Annemieke Brands, Tiziana Masini and other colleagues from the WHO Global TB Programme

- IMPAACT: Anneke Hesseling, Anthony Garcia-Prats, Simon Schaaf,, Elin Svensson, Patrick Jean-Philippe

- BENEFIT-Kids: Stellenbosch University

Thank you for your attention!



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