Tuberculosis Scientific Committee

ICAB Update
Anneke C. Hesseling
TBSC Chair
IMPAACT Annual Network Meeting
23 June 2021

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Overall TB Scientific Committee Goals

"Evaluate novel approaches for TB prevention, diagnosis and treatment in HIV-positive and negative infants, children, adolescents, and pregnant and postpartum women that will lead to optimal dosing and regimens, licensing and improved care."

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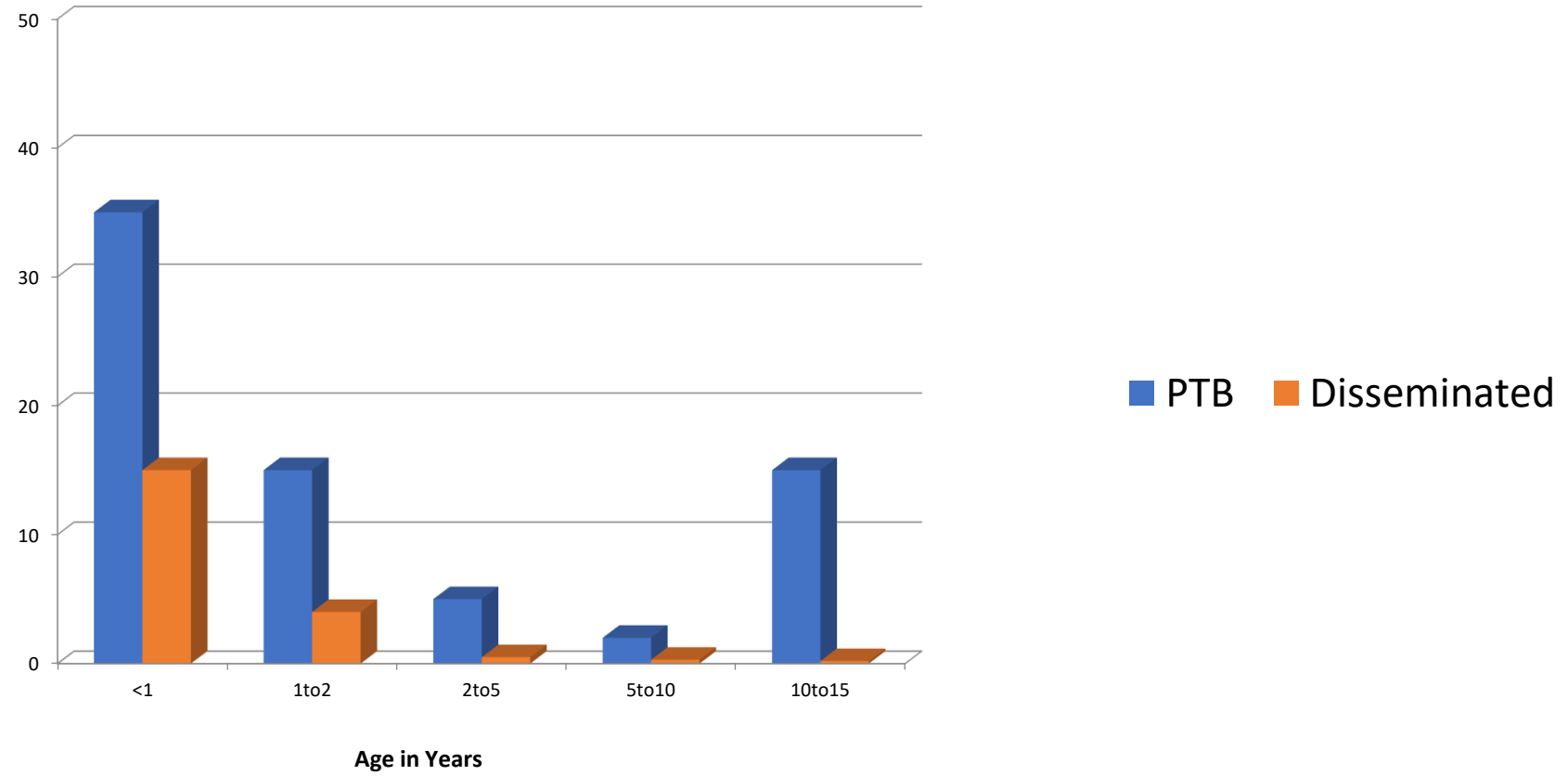
Age related risk of disease progression to TB: “natural history”

Disease Progression (Percent)



Marais et al. Int J Tuberc Lung Dis. 2004

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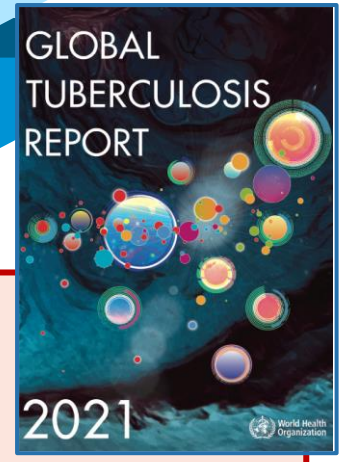
Global burden estimates (2021 Global TB report)



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

(Dodd 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

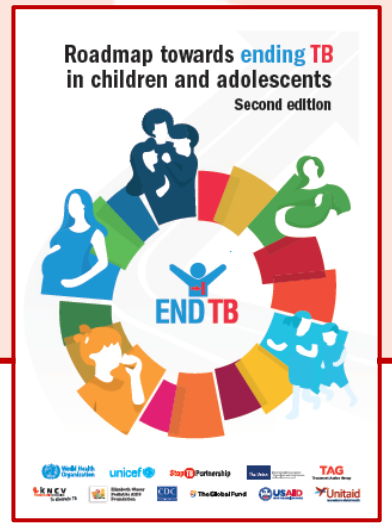
child (0-14) TB deaths in 2020

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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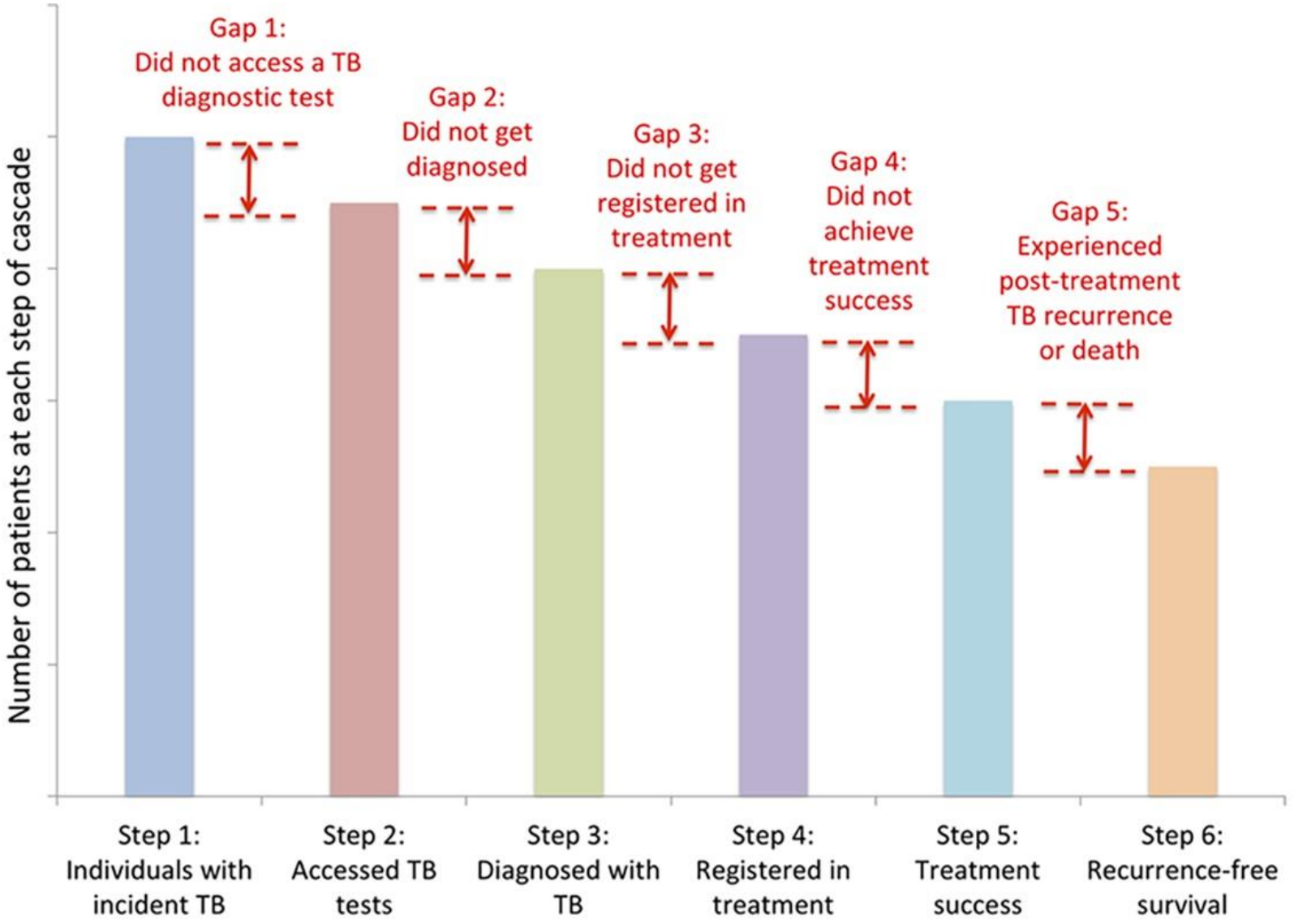
Prevention



Post TB health

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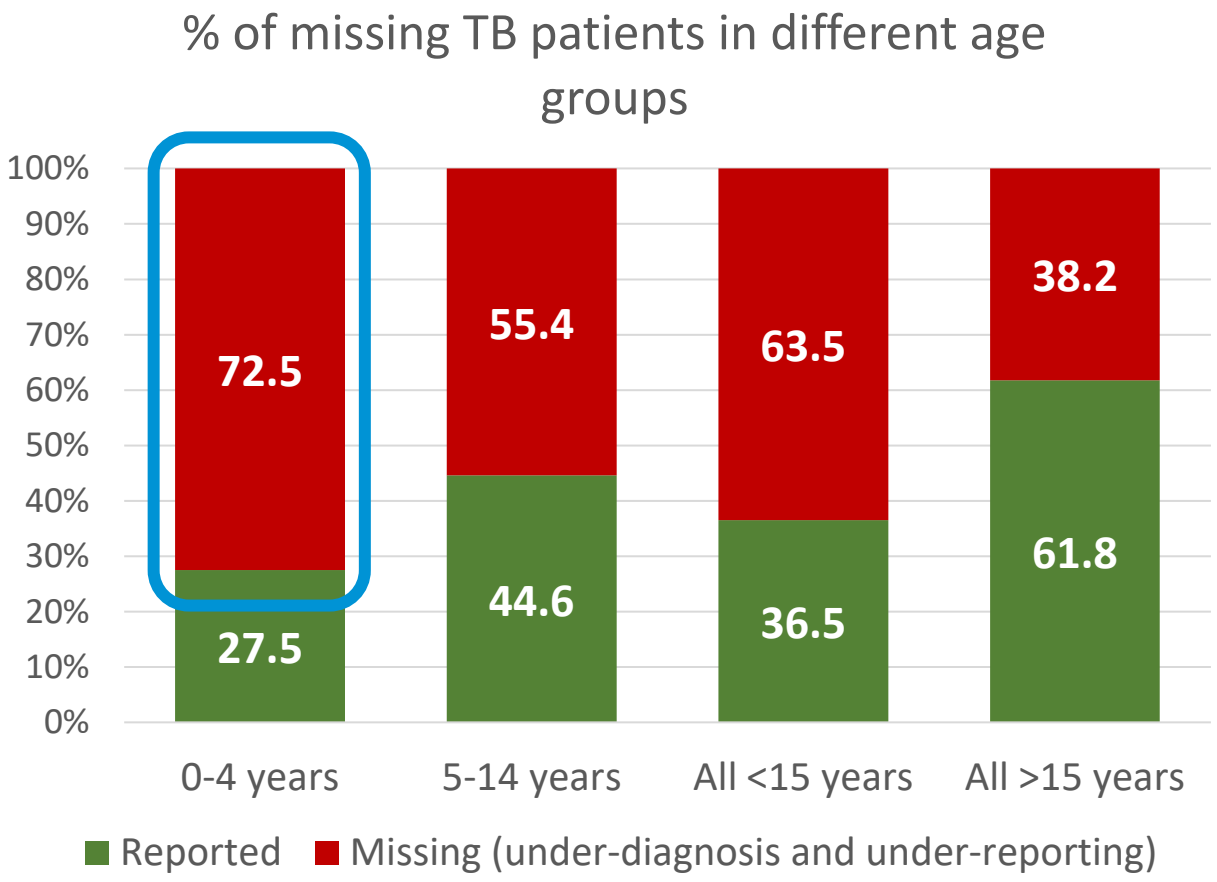
The case detection and prevention gaps

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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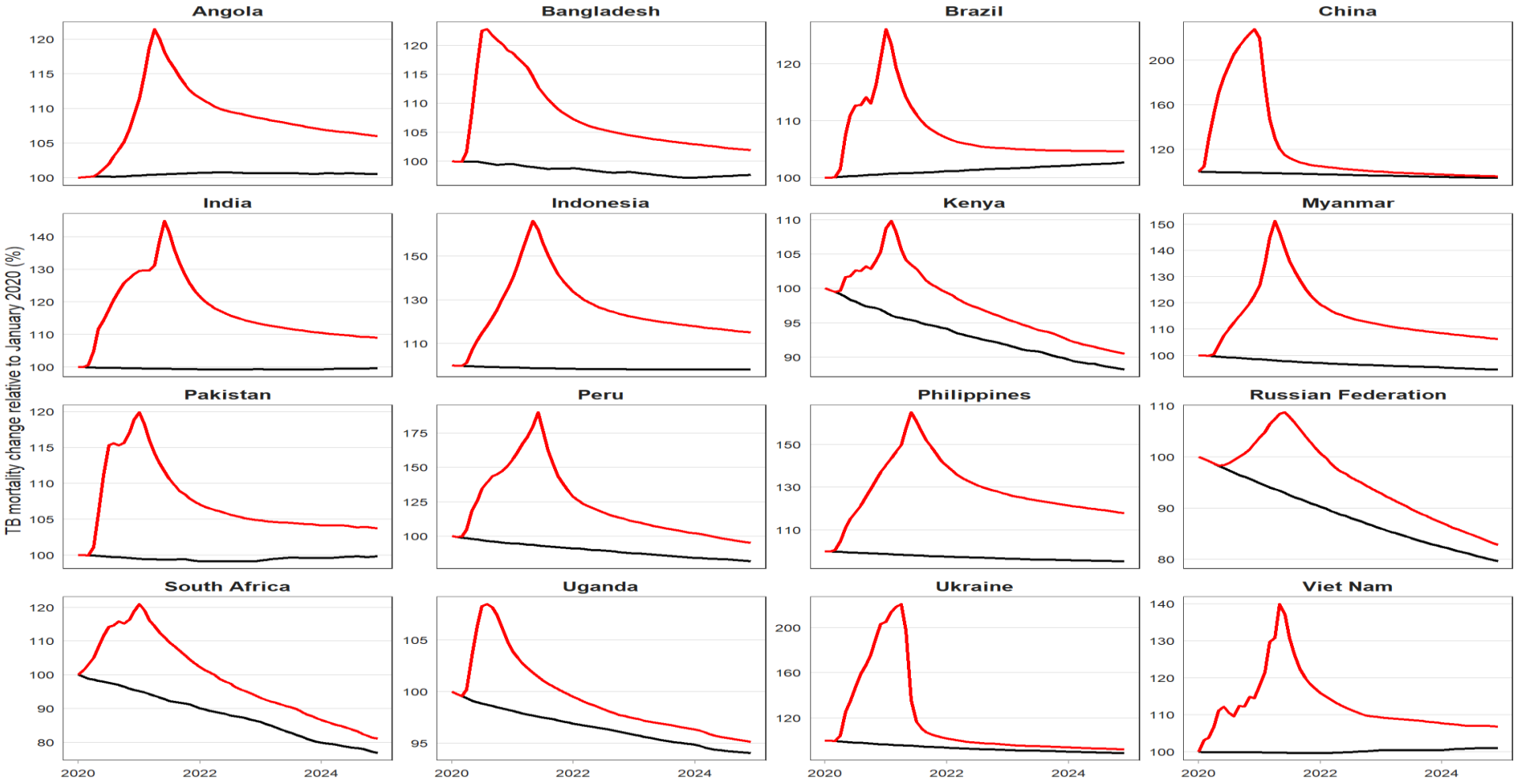
Update, October 2021

Estimated impact of the COVID-19 pandemic on TB mortality for 16 selected countries, up to 2025

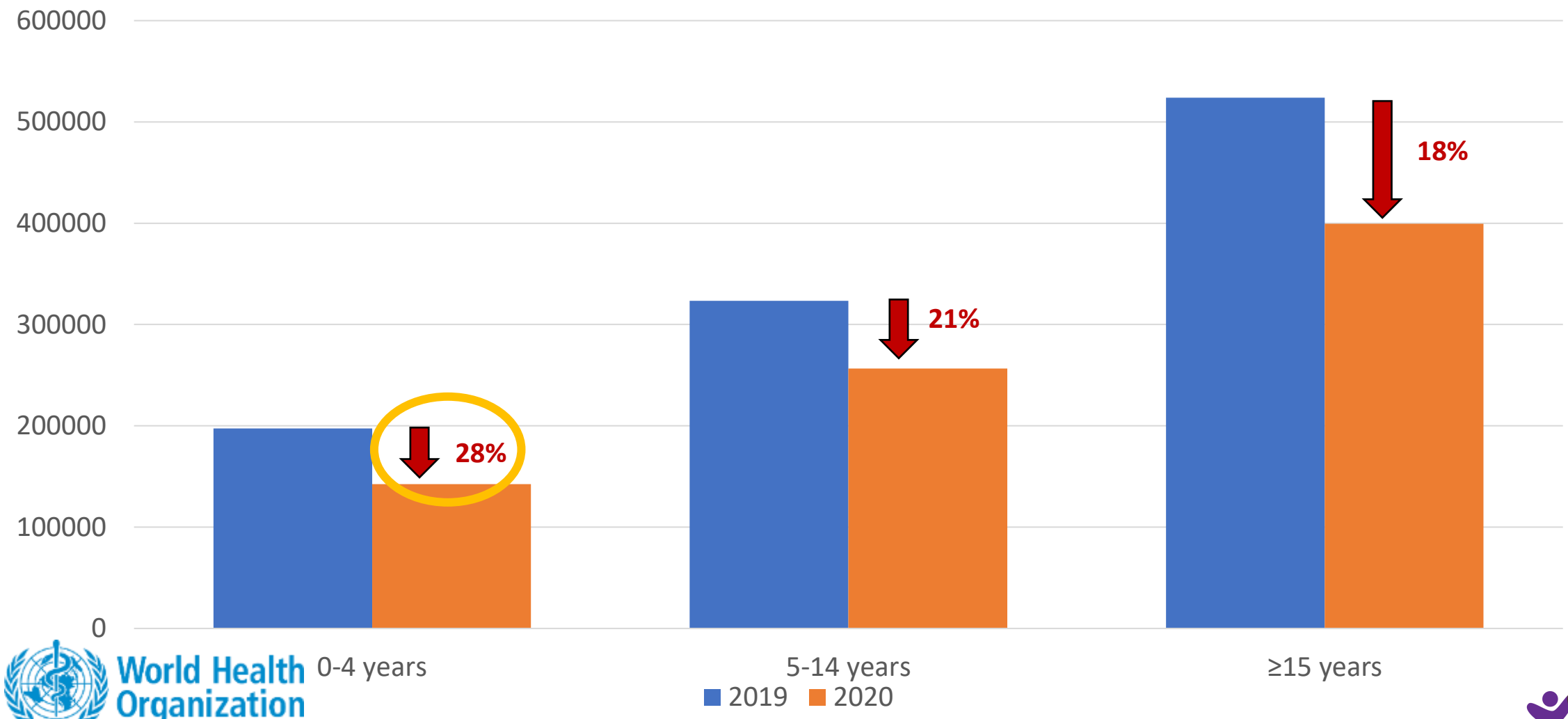
Standardized TB mortality rate (including HIV)[a]. The black line indicates the baseline assuming no COVID-19 disruptions, and the red line is the modelled impact.



World Health Organization

END TB

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



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Access to TB and HIV care and research during the COVID era

- Delayed health care seeking behavior
  - Anxiety to get COVID at hospital
  - Lockdown/ messaging “stay home”
- Decreased focus of health services
  - Overburdened health services
  - Overlapping symptoms
  - Fear to collect respiratory samples
- Decreased laboratory services
  - Overburdened system
  - Supply chain/ Xpert platform
- Reduced access to child health services,

clinical research, delay of much-needed data resulting

delayed and decreased access

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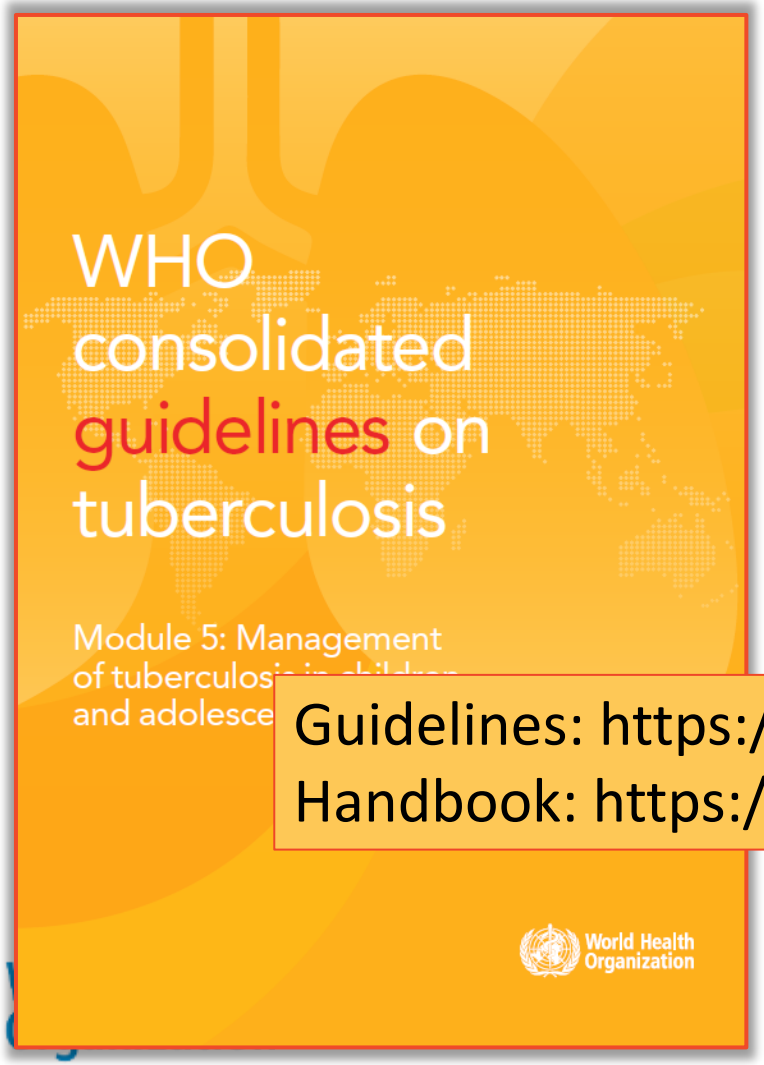
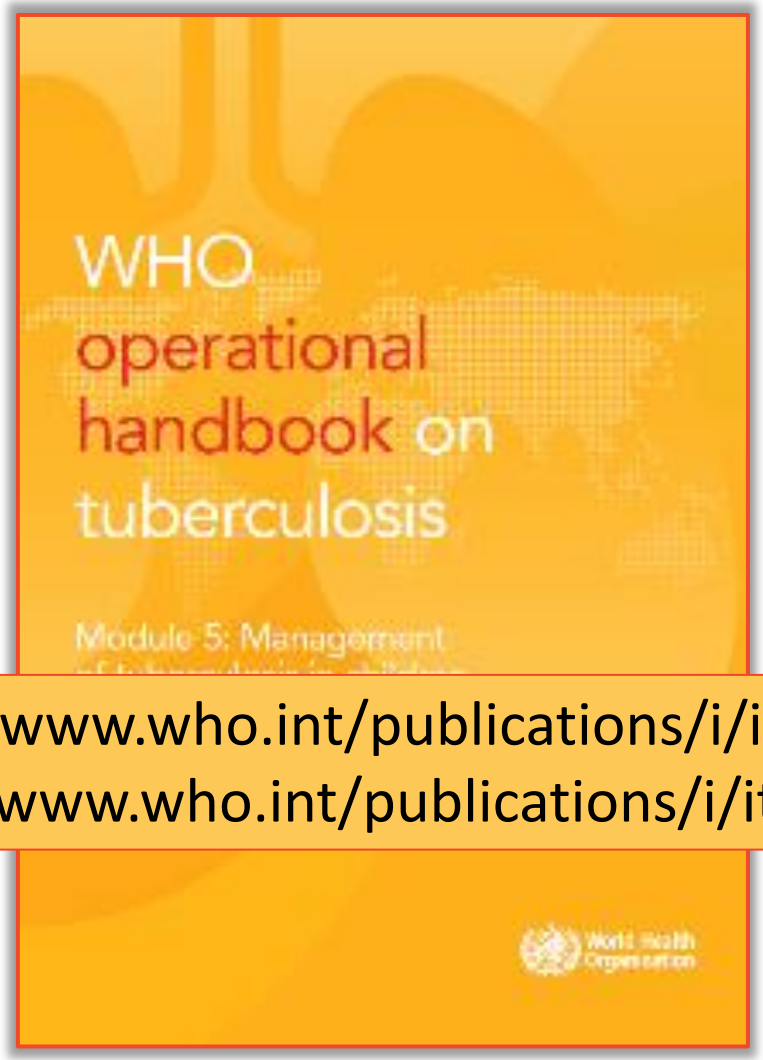
WHO consolidated guidelines and operational handbook on the management of TB in children and adolescents





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

Development of updated guidelines
on the management of TB in children and adolescents

- GDG meeting held in May/June 2021
- Evidence reviewed on the following PICO questions, using GRADE* methodology:
  1. **Use of Xpert Ultra in gastric aspirate and stool specimens**
  2. **Integrated treatment decision algorithms**
  3. **Treatment shortening in children with non-severe TB**
  4. **In children with MDR/RR-TB: Use of bedaquiline in children under 6 and delamanid in children under 3 years**
  5. **Short intensive treatment regimen for TBM**
  6. **Models of care for case detection and provision of TPT (decentralized and family-centred, integrated approaches)**
- **Rapid communication** published in August 2021
- **Consolidated guidelines** with **operational handbook** released 21 March 2022

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

Organization

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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 under 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

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Use of bedaquiline and delamanid in children

- **In children with MDR/RR-TB aged below 6 years, an all-oral treatment regimen containing bedaquiline may be used: data from P1108**
- **In children with MDR/RR-TB aged below 3 years, delamanid may be used as part of longer regimens**

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

Remarks:

- *Applies to and complements current WHO recommendations on shorter and longer regimens that contain bedaquiline*
- *Complements the current WHO recommendation on longer regimens that contain delamanid*

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

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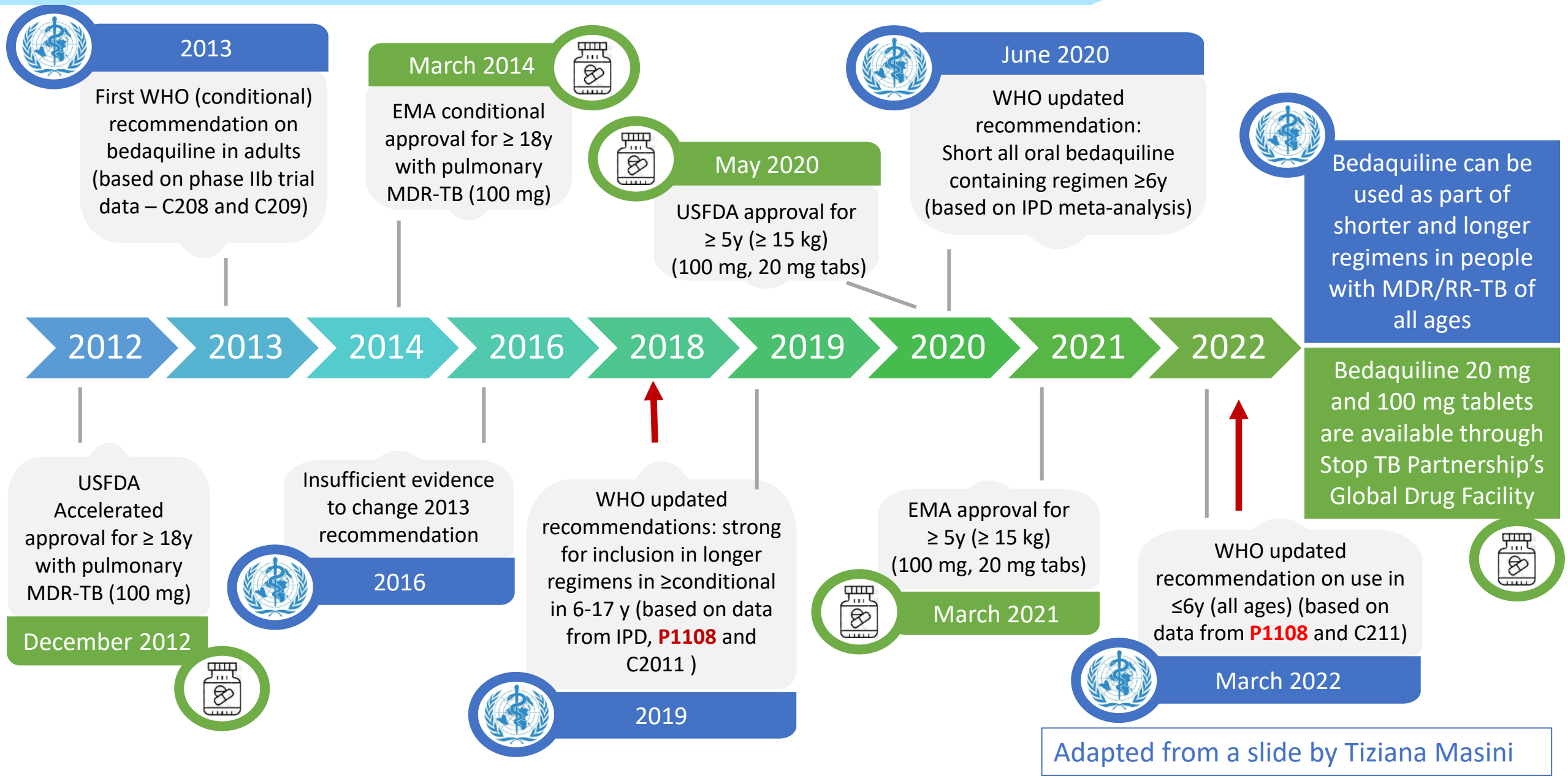
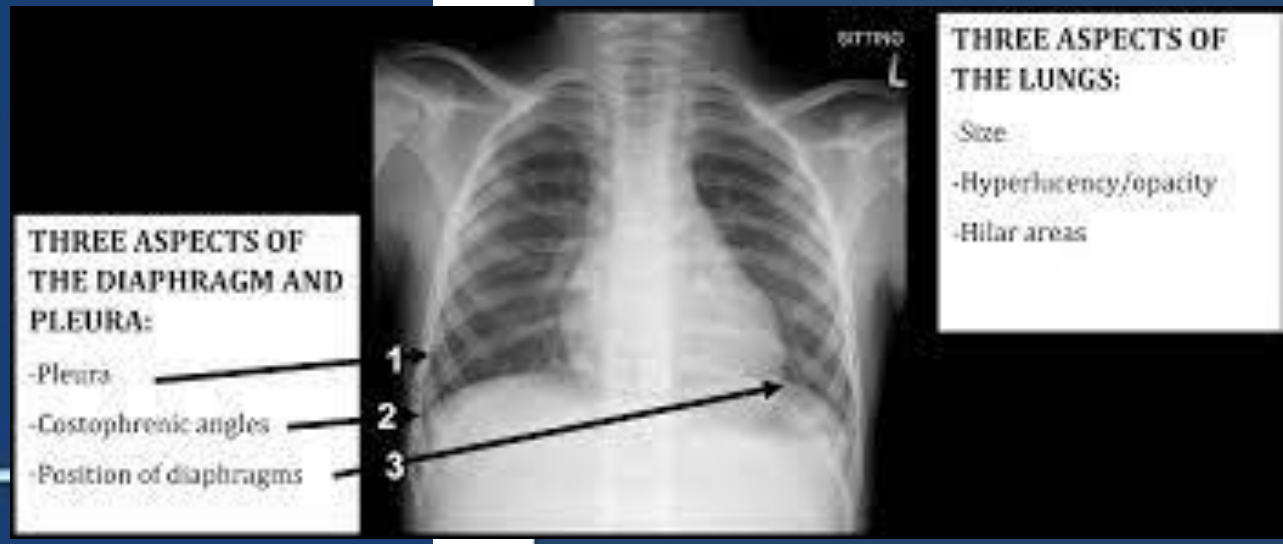
Historical context: BDQ recommendations and regulatory approvals



Adapted from a slide by Tiziana Masini

DIAGNOSTIC CXR ATLAS FOR TUBERCULOSIS IN CHILDREN

A guide to chest X-ray interpretation



Second Edition
2022

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)
  - Investment and more initiatives needed

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

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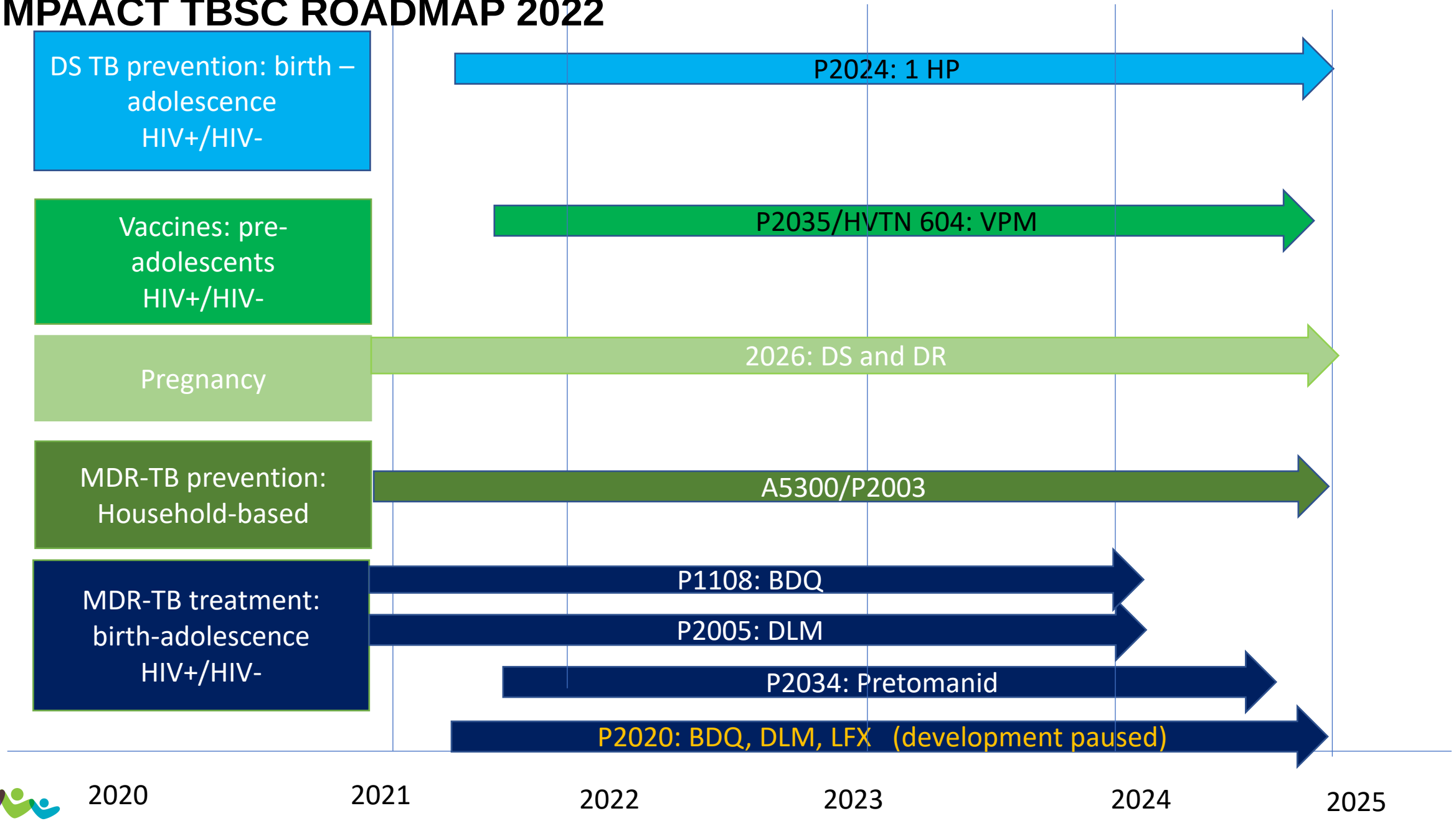
IMPAACT TBSC ROADMAP 2022



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TB Protocols in development

2035	Phase I/II Study of the Safety and Immunogenicity of **VPM1002 Vaccination or BCG Re-Vaccination** against Tuberculosis in South African Pre-Adolescents Living with and without HIV
2034	Phase I Study of PK, Safety, & Acceptability of **Pretomanid** in Children with Rifampicin-Resistant TB
2024	Phase I/II Dose Finding, Safety, and Tolerability Study of **Daily Rifapentine Combined with Isoniazid (1HP)** for Tuberculosis Prevention in Children 2 to <13 years of age with and without HIV
2020?	All oral once daily MDR TB treatment regimen in infants, children and adolescents (BDQ, DLM, LFX, Linezolid)

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Sabine Verkuil , Kerri Vinery, Tiziana Masini, Annemieke Brands, WHO Global TB Program
Simon Schaaf
Sharon Nachman, IMPAACT
DTTC CAB

THANK YOU!

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