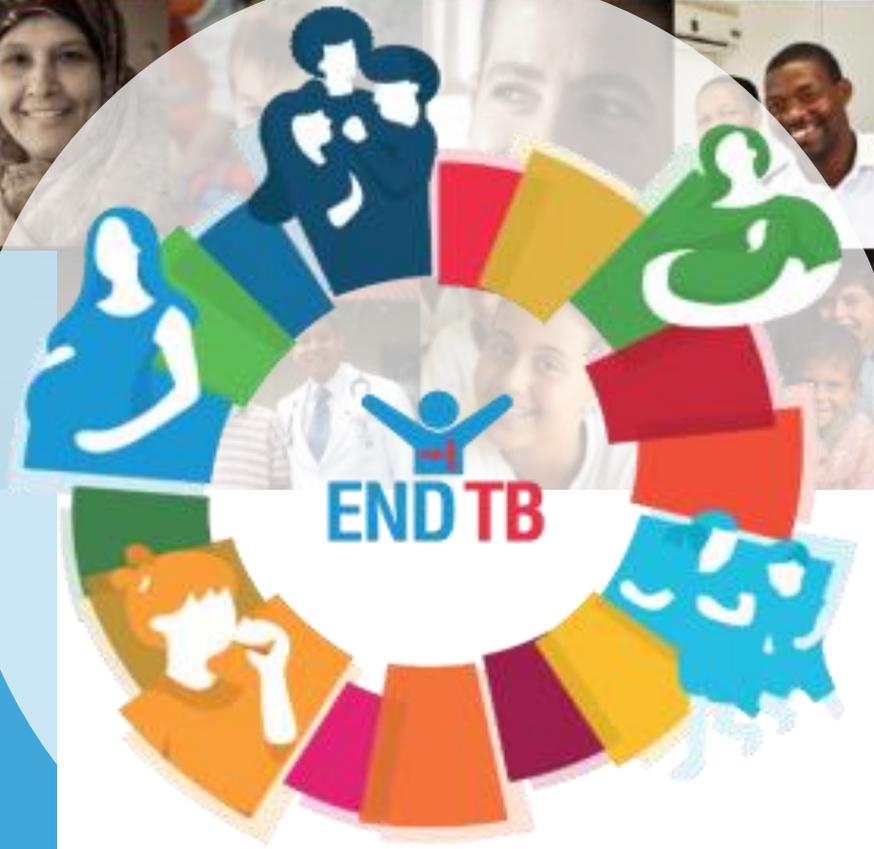




**WHO updates: latest epi data & development  
of new guidelines and operational handbook  
on the management of TB in children and  
adolescents**

**Annemieke Brands and Sabine Verkuil**

Annual meeting of the Child and Adolescent TB Working  
Group, 30 November 2021

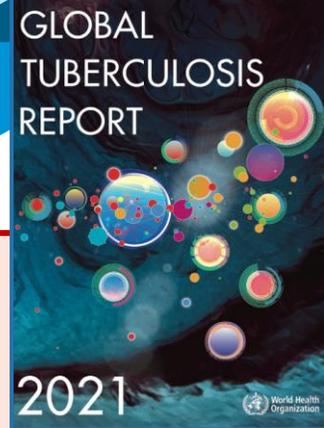


# Outline

- Update on data included and reported for the 2021 Global TB Report
- Guideline development
  - Key updates based on the rapid communication on the updated guidance on the management of TB in children and adolescents
  - Consolidation of recommendations
  - Consultations on classification of TB disease and dosing of bedaquiline, delamanid and the new TBM regimen
- Other updates
- Next steps



# 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**

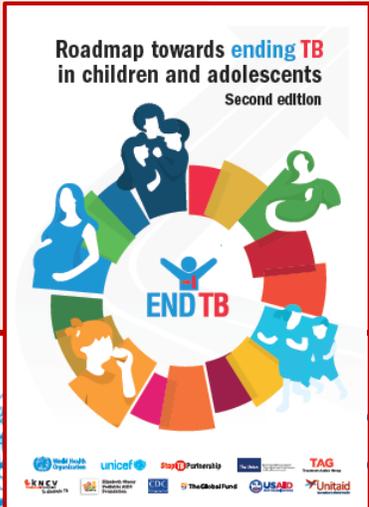
child (0-14) TB deaths in 2020

**80%** in children <5 years

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

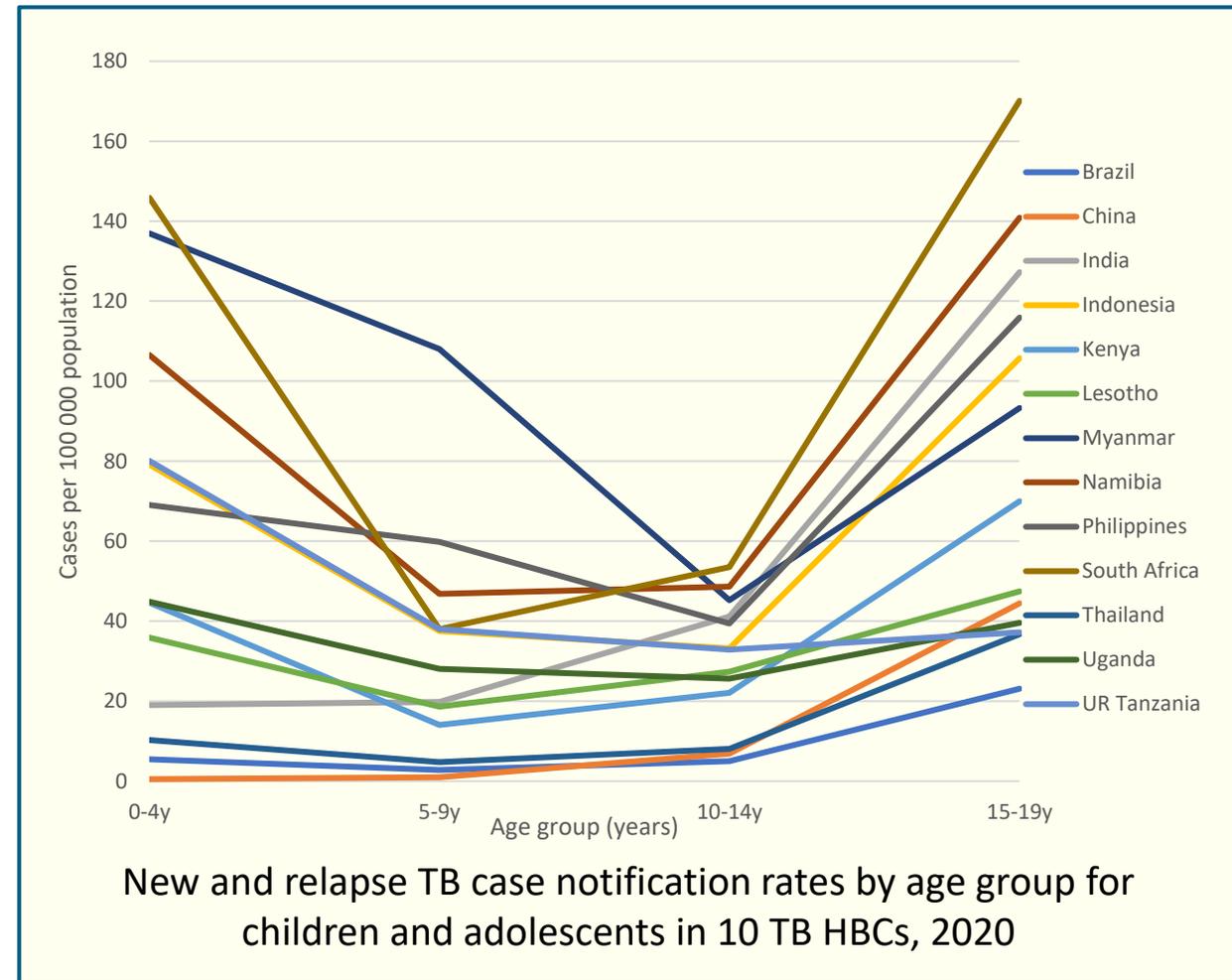
(Dodd et al, 2017a)

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



# Detailed age-disaggregated reporting

- 13 TB HBCs reported fully age disaggregated notifications: **Brazil, China, India, Indonesia, Kenya, Lesotho, Myanmar, Namibia, Philippines, South Africa, Thailand, Uganda, Tanzania**
- These 13 countries represent almost 54% of all notifications in the 0-14y age group
- Data on **adolescents aged 10-19 years** reported since 2020
  - Relatively high notification rates in older adolescents



# Treatment initiation in children with MDR/RR-TB

- Countries requested to report on the number of children/young ado's (0-14y) initiated on second-line treatment for MDR/RR-TB since 2020
- **79 countries** reported **at least 1 child** started on second-line treatment in 2020
- **6 countries** (India, Russian Federation, South Africa, Ukraine, Pakistan and Kazakhstan) reported **≥100 children** started on second-line treatment (81% of all cases) in 2019, but only 3 of these reported over 100 children in 2020
- Drop in number starting treatment in 2020
  - Impact of COVID-19 pandemic: 43% drop between 2019 and 2020
  - % of children among all patients: **2.5%**

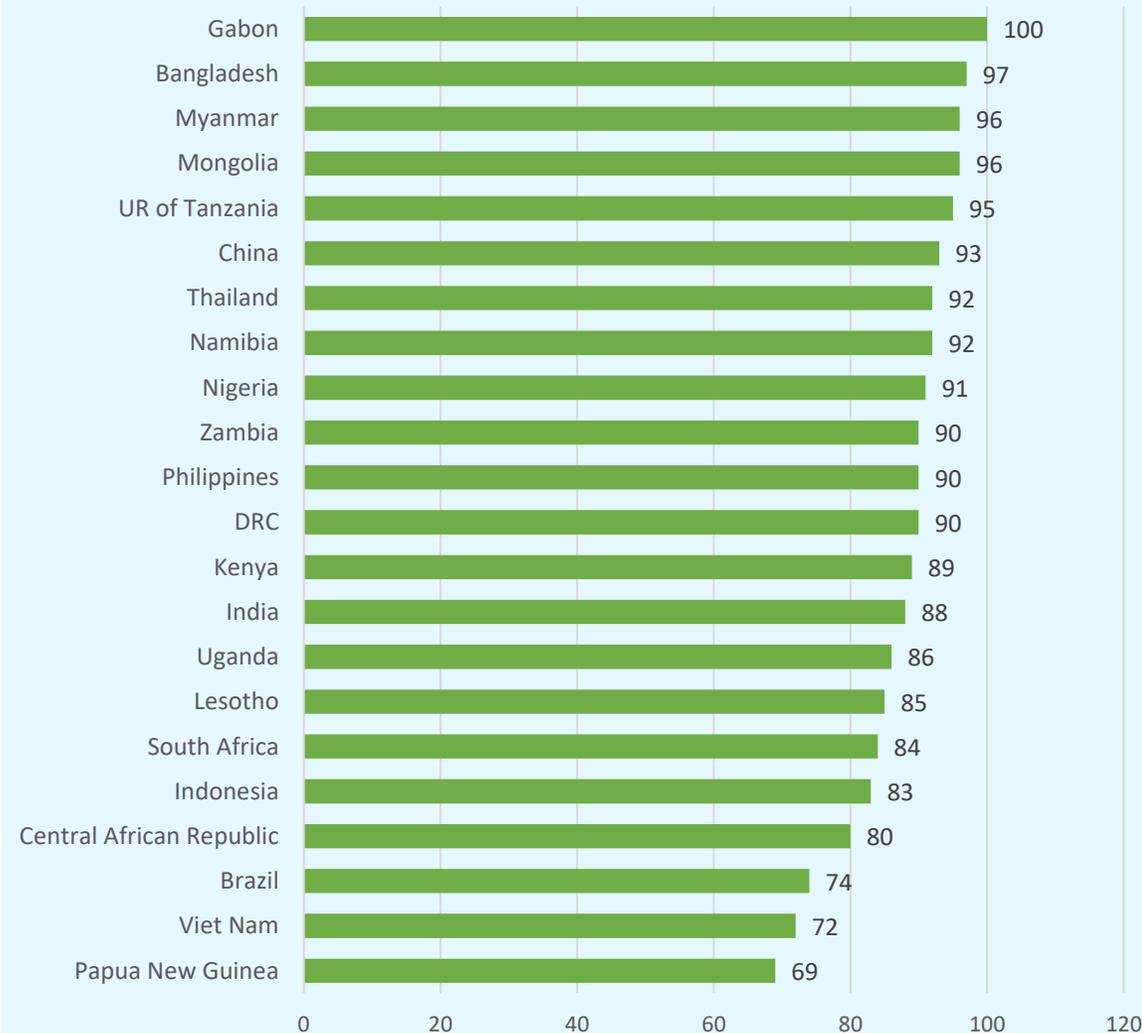
Country	Children initiated SLD (2019)	Children initiated SLD (2020)
<b>India</b>	<b>3360 (60%)</b>	<b>1844 (57%)</b>
Russian Federation	476	54
South Africa	332	162
Ukraine	161	115
Pakistan	110	76
Kazakhstan	100	75
<b>Global total</b>	<b>5588</b>	<b>3235</b>

	MDR/RR-TB (all ages)	MDR/RR-TB (0-14y)	% children among all MDR/RR-TB
2018	156 205	3 398	2.2%
2019	177 099	5 588	3.2%
2020	128 338	3 235	2.5%

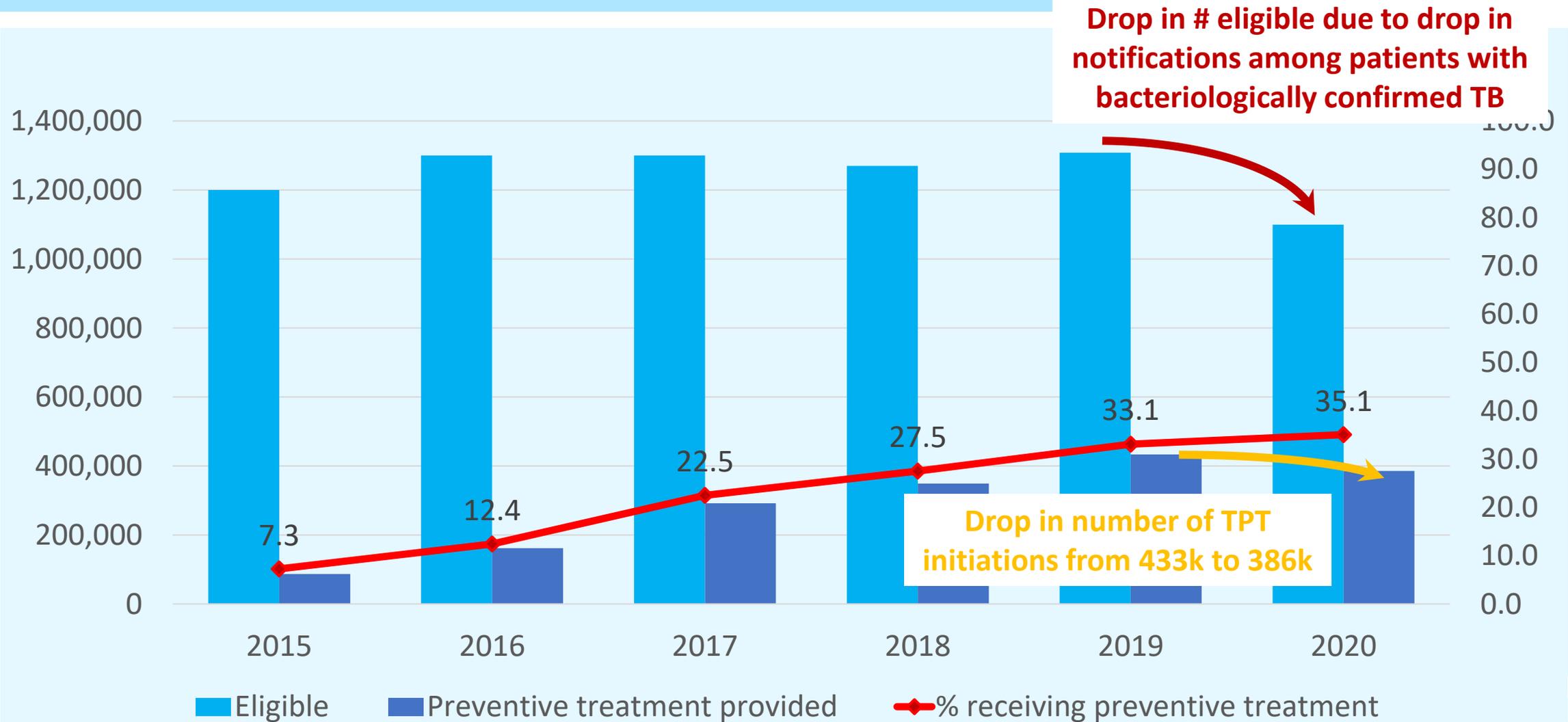
# Treatment success rates in children 0-14y

- 130 (of 215) countries reported treatment success rate in children and young adolescents (0-14y) for the 2019 cohort
- 22 (of the 30) TB HBCs reported (N=387 360 or 74% of total notifications in 0-14y in 2019)
- Overall: **87.6%** treatment success (range 69-100%)

Treatment success rate (%), children (0-14y) in 22 TB HBCs, N=387 360



# Trends in provision of TPT to eligible <5 contacts



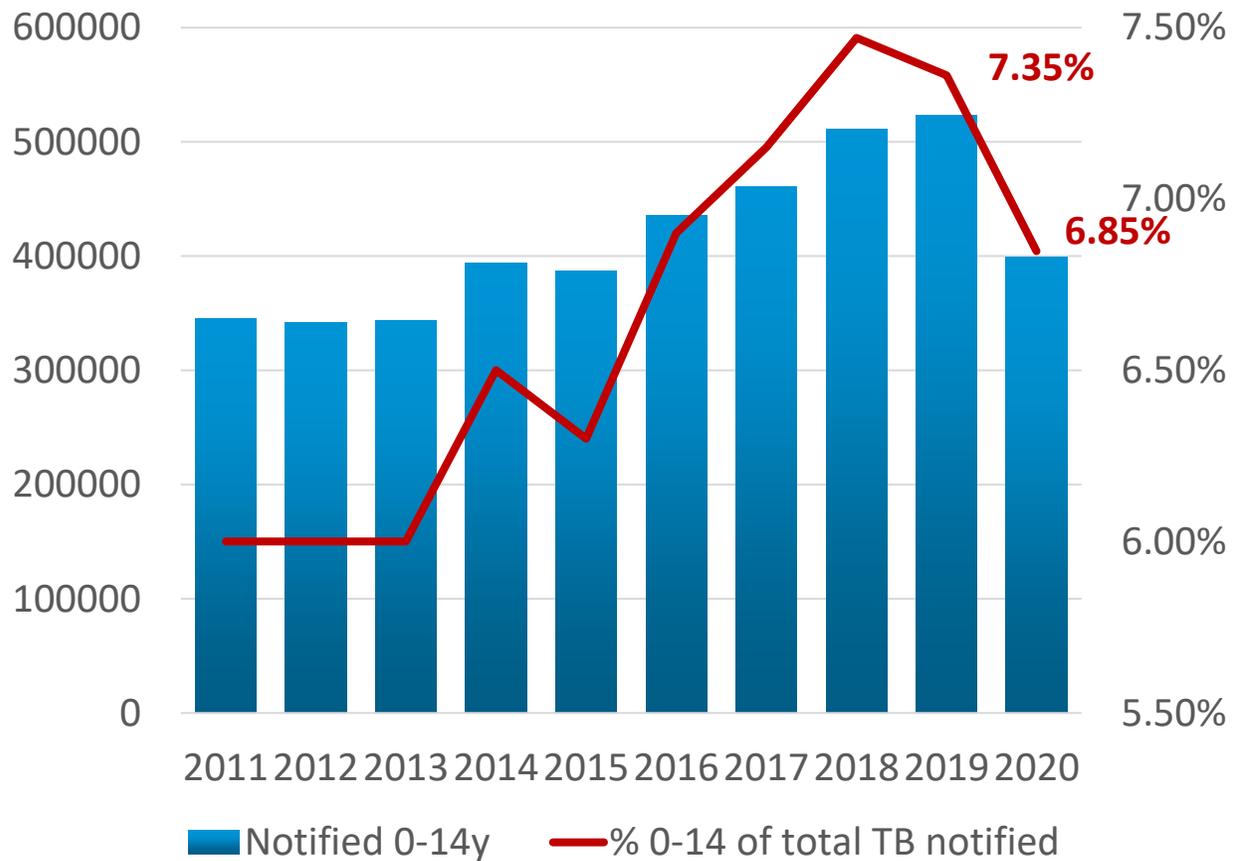
Drop in # eligible due to drop in notifications among patients with bacteriologically confirmed TB

Drop in number of TPT initiations from 433k to 386k

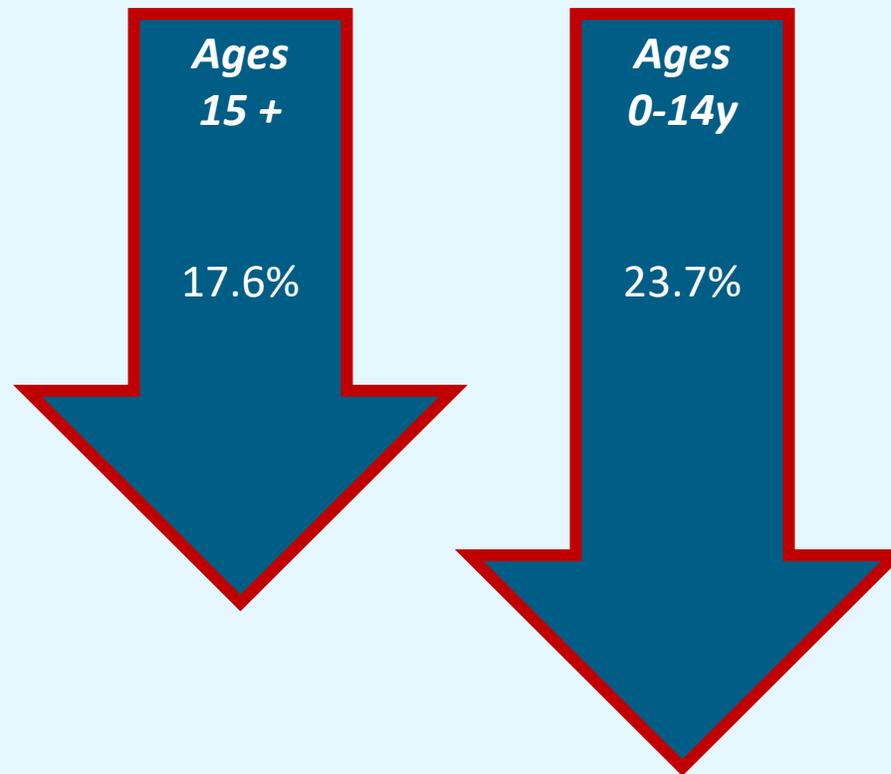


# Impact of COVID on TB notifications in 2020

Trends in case detection in children (<15y)



Drop in notifications: 2020 compared to 2019

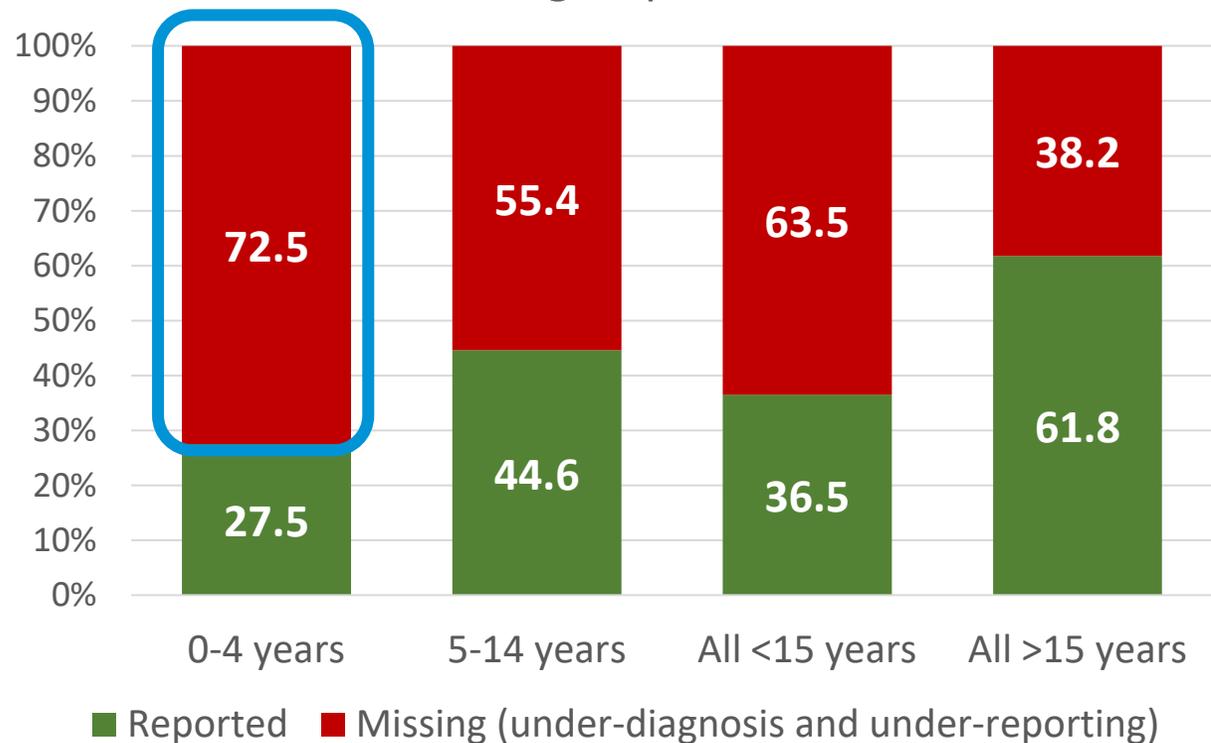


Notifications 2019: Total: 7 120 320; 15+: 6 596 500; 0-14y: 523 820  
 Notifications 2020: Total: 5 834 188; 15+: 5 434 671; 0-14y: 399 517

# The case detection and prevention gaps remain...

## The case detection gap

% of missing TB patients in different age groups



## The prevention gap

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



WHO recommends TB prevention including:

- ✓ Preventive therapy
- ✓ Infection control measures
- ✓ BCG vaccination

In the 158 countries for which data on BCG coverage are available, 120 reported coverage of at least 90% in 2017

\* 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

# Progress against UNGA HLM targets



UNITED NATIONS  
HIGH-LEVEL MEETING ON THE  
FIGHT TO END TUBERCULOSIS  
26 SEPTEMBER 2018, UNHQ, NEW YORK

## Case detection and treatment

1 433 000 children notified with TB 2018 - 2020

41% of the 2022 target (3.5m)

12 220 children started on second-line treatment  
for MDR/RR-TB 2018 - 2020

10.6% of the 2022 target (115 000)

## Provision of TB preventive treatment

1.2 million contacts < 5y initiated on TPT  
2018 - 2020

29% of the 2022 target (4m)

320 000 contacts ≥5y initiated on TPT  
2018 - 2020

1.6% of the 2022 target (20m)

7.2 million PLHIV initiated on TPT  
2018 - 2020

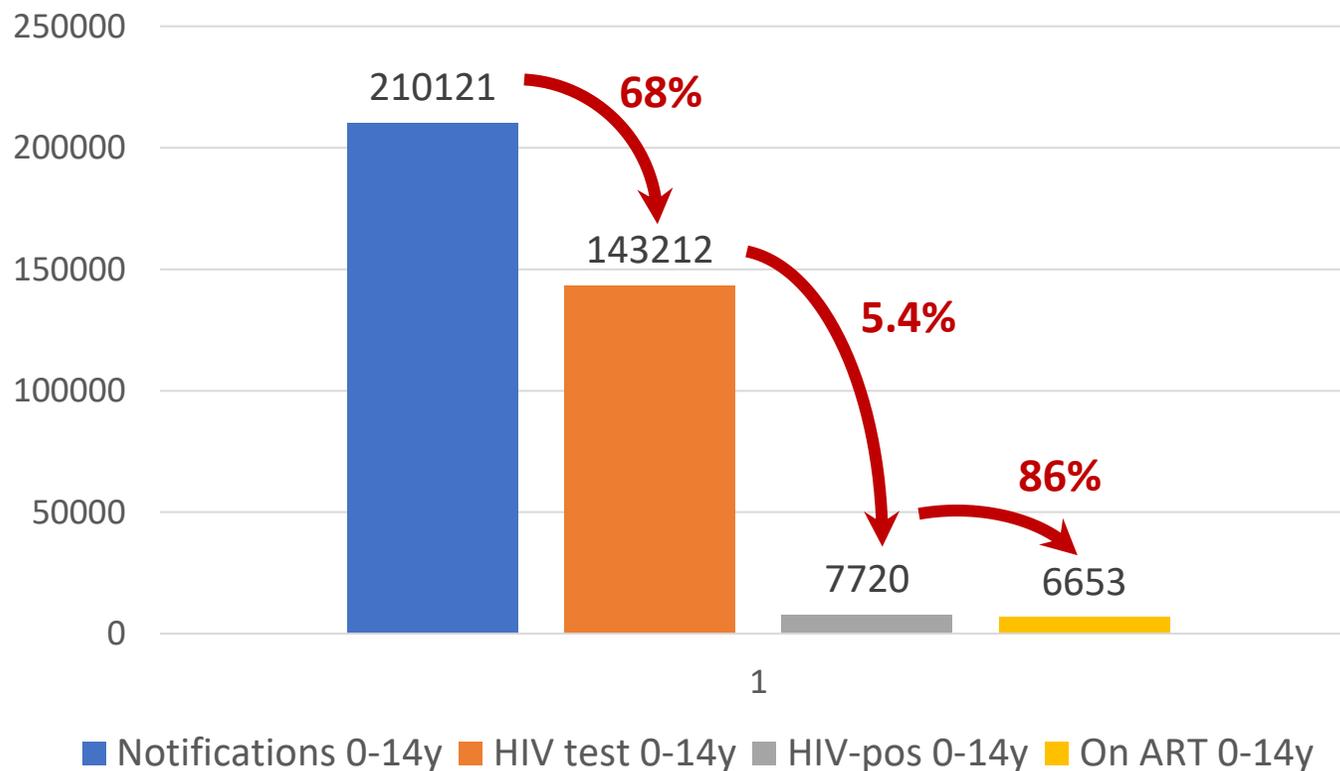
>100% of the 2022 target (6m)



# TB/HIV co-infection

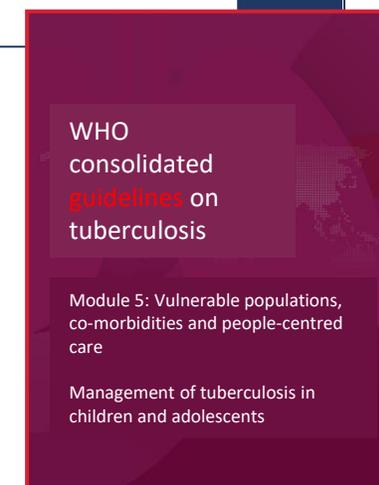
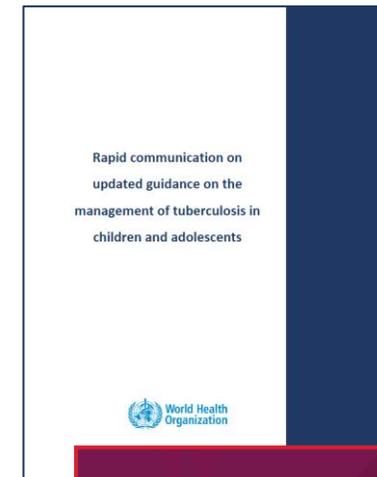
- WHO requested data on TB/HIV in children/young adolescents for the 1<sup>st</sup> time for the 2021 Global TB Report, in line with the commitments of the Rome Action Plan on Paediatric HIV & TB<sup>1</sup>
- 38 countries reported TB/HIV data in 0-14 years, including 16 TB/HIV HBCs, in 2020
  - 16 TB/HIV HBCs covered 98% of all testing
- Data reported:
  - # TB patients notified who have an HIV test result recorded
  - # TB patients tested for HIV who tested HIV-positive
  - # TB/HIV co-infected patients on ART

TB/HIV care cascade in 16 TB/HIV HBCs



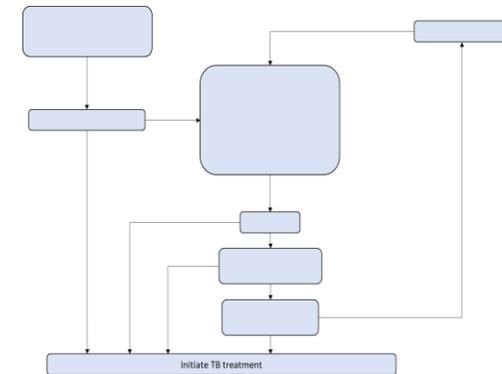
# Development of updated guidelines on the management of TB in children and adolescents

- GDG meeting held in May/June 2021
- Evidence reviewed on the following PICO questions, using GRADE\* methodology:
  - Use of Xpert Ultra in gastric aspirate and stool specimens
  - Integrated treatment decision algorithms
  - Treatment shortening in children with non-severe TB
  - In children with MDR/RR-TB: Use of bedaquiline in children under 6 and delamanid in children under 3 years
  - Short intensive treatment regimen for TBM
  - Models of care for case detection and provision of TPT (decentralized and family-centred, integrated approaches)
- **Rapid communication** published in August 2021
- Internal/external review, submission to WHO GRC on 19 November
- **Consolidated guidelines** with **operational handbook** expected in the next months



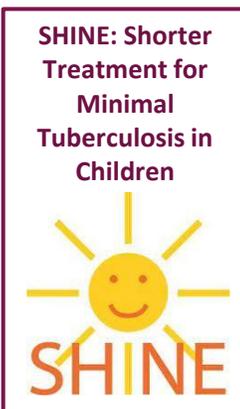
# TB diagnostic approaches in children – key updates

- In children with signs and symptoms of pulmonary TB, **Xpert MTB/ RIF Ultra in gastric aspirate or stool specimens** should be used as the initial diagnostic test for TB and the detection of rifampicin resistance, rather than smear microscopy/culture and phenotypic drug susceptibility testing (DST)
  - In addition to sputum or NPA specimens, already recommended for Xpert Ultra testing, in the same population
  - Both Xpert MTB/RIF and Ultra now recommended on all paediatric specimens
- In children with presumptive pulmonary TB, **treatment decision algorithms** may be used to diagnose pulmonary TB
  - Bacteriological confirmation needs to be sought whenever possible, using available and recommended diagnostic tests and appropriate paediatric specimens – especially in children with a high likelihood of DR-TB
  - Newly developed treatment decision algorithms for different settings with detailed practical guidance on their use will be included in the operational handbook to be published alongside the guidelines.
- Consolidation of existing recommendations on rapid diagnostics for TB detection, including for EPTB, detection of resistance to first- and second-line drugs (e.g. Xpert MTB/Rif, Ultra, LAMP, LF-LAM, FL/SL LPA, low/moderate/high complexity NAAT)



# Treatment for drug-susceptible TB – key updates

- Evidence from the SHINE trial reviewed by the GDG:
  - Main finding: 4-month treatment non-inferior to the 6-month regimen (consistent across all key analyses - including age groups, HIV status, type of TB and adherence)
- In children and adolescents (3 months to 16 years) with non-severe, presumed drug-susceptible TB, a 4-month regimen (2HRZ(E)/2HR) should be used rather than the standard 6-month regimen (2HRZ(E)/4HR).
  - Important implementation considerations were noted to determine eligibility for the shorter treatment regimen and will be described in the consolidated guidelines and in the operational handbook.
- Consolidation of new recommendation based on review of data from TBTC study 31/ACTG A5349 (to be included in updated guidelines on DS-TB treatment): Patients aged 12 years and older with drug-susceptible pulmonary TB, may receive a 4-month regimen of isoniazid, rifapentine, moxifloxacin and pyrazinamide.



Rapid communications:

Child and adolescent TB: <https://apps.who.int/iris/bitstream/handle/10665/344382/9789240033450-eng.pdf>

Drug-susceptible TB: <https://apps.who.int/iris/rest/bitstreams/1350979/retrieve>

# Treatment of TB meningitis in children and adolescents

- TBM: most serious, second most common form of EPTB; poor outcomes, even with treatment
- Current recommendation: 2HRZE/10HR (Based on 2009 literature review, non-randomized, non-comparative studies, not entered into GRADE)
- Systematic review and meta-analysis to compare the effectiveness of a shorter intensive regimen (6HRZEto, with slightly higher H and R dosing) vs WHO recommended regimen
  - Shorter intensive regimen: lower death rates, and higher successful treatment rates, but a high proportion of survivors with neurological sequelae
- Key update: 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 an alternative option to the **12-month regimen (2HRZE/10HR)**.

WHO  
consolidated  
guidelines on  
tuberculosis

Module 5: Vulnerable  
populations, co-morbidities and  
people-centred care

Management of tuberculosis in  
children and adolescents

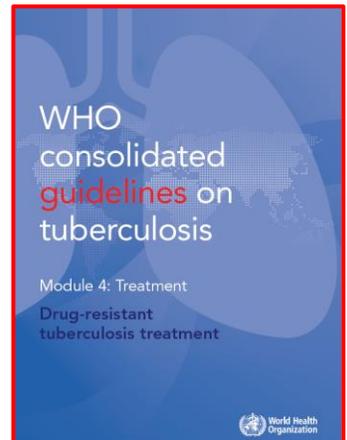
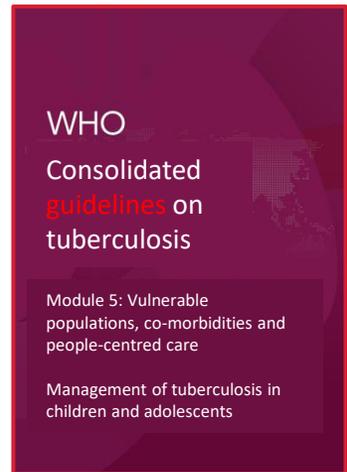
Guidance for national  
tuberculosis programmes  
on the management  
of tuberculosis  
in children

Second edition



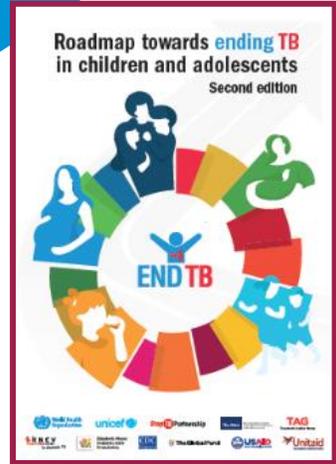
# Treatment of DR-TB in children – key updates

- Children usually tolerate second-line treatment well, with favourable treatment outcomes
- Data reviewed:
  - BDQ: Data from TMC207-C211 (children aged 5-18) and IMPAACT P1108 (children aged 0-18)
  - DLM: Phase I PK/safety/tolerability study and corresponding extension study (protocols 242-12-232 and 233); cohorts 1 (12-17 years), 2 (6-11 years), 3 (3-5 years) and 4 (0-2 years) for both protocols
  - Both: Paediatric DR-TB IPD (24,231 records, majority from India and South Africa; just under 20,000 used for matched analysis of treatment outcomes)
- **UPDATE: In children of all ages with MDR/RR-TB, an all-oral treatment regimen containing bedaquiline may be used**
  - as part of the shorter, all oral BDQ regimen (conditionally recommended by WHO in 2020) or as part of longer treatment regimens
- **UPDATE: In children of all ages with MDR/RR-TB, delamanid may be used as part of longer treatment regimens**

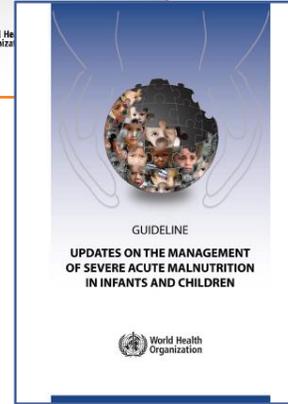
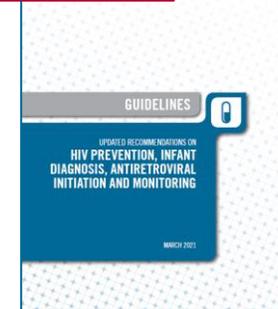
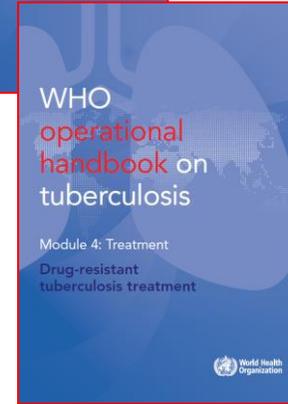
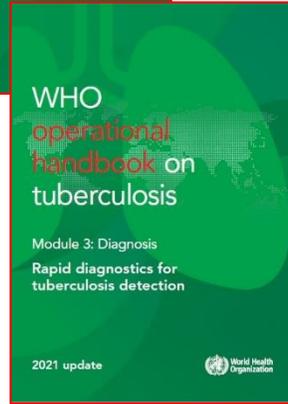
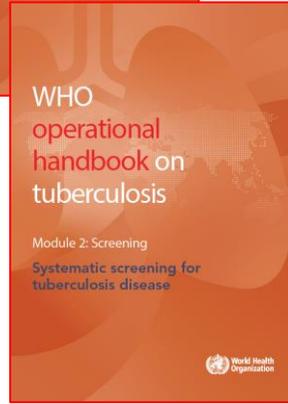
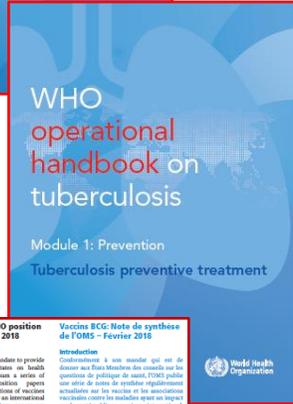
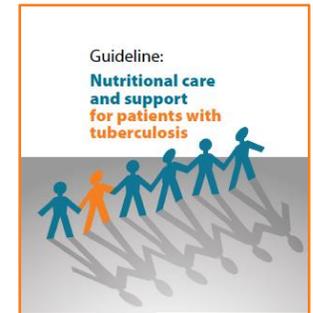
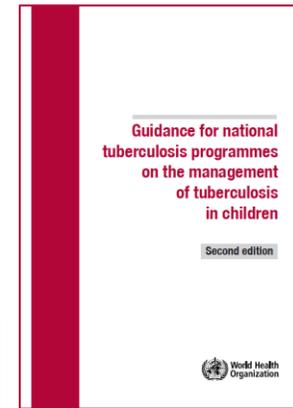
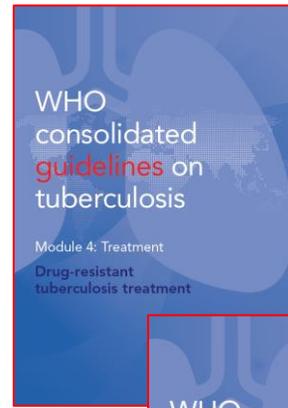
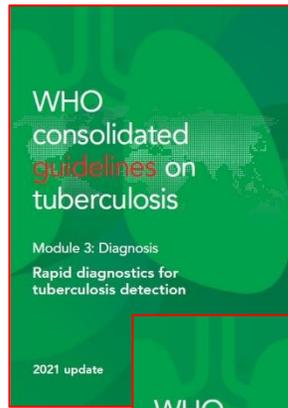
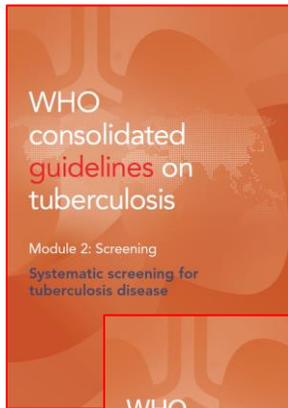
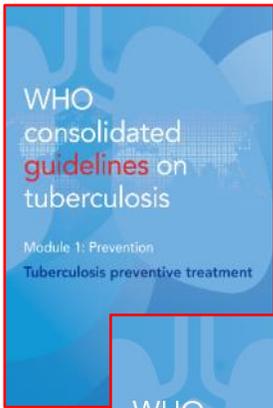


# Models of care for case detection and provision of TB preventive treatment in children and adolescents

- Paediatric TB services often highly centralized, with limited capacity at PHC level, leading to missed opportunities for contact tracing, TB prevention, TB detection, care and management
- Decentralization and family-centred, integrated care: one of 10 key actions in **2018 Roadmap Towards Ending TB in Children and Adolescents**.
- **Systematic review:**
  - Impact of combined health facility and community approaches on the number of children and adolescents diagnosed with TB; of decentralized services on levels of TPT initiation.
  - Impact of different types of service integration on TB case notifications in children and adolescents; of socio-economic support for families affected by TB on TPT coverage/completion among children and adolescents.
- **Key update:** In high TB burden settings, decentralized and family-centred, integrated services may be implemented to improve TB case detection and the uptake of TB preventive treatment.
  - In this context, decentralized services do not replace centralized or specialized child and adolescent TB services, rather, they complement them.



# Consolidation of recommendations from other guidelines



**BCG vaccines: WHO position paper – February 2018**

**Vaccins BCG: Note de synthèse de l'OMS – Février 2018**

**Introduction**

In accordance with its mandate to provide guidance to Member States on health policy matters, WHO issues a series of regularly updated position papers on vaccines and combinations of vaccines against disease that have an international public health impact. These papers are concerned primarily with the use of vaccines in large-scale national immunisation programmes. They summarise essential background information on diseases and vaccines and conclude with the current WHO position on the use of vaccine candidates.

**Background**

Conformément à son mandat qui est de donner aux États membres des conseils sur les questions de politique de santé, l'OMS publie une série de notes de synthèse régulièrement actualisées sur les vaccins et les associations vaccinales contre les maladies ayant un impact sur la santé publique au niveau international. Ces notes portent essentiellement sur l'utilisation des vaccins dans le cadre de programmes nationaux de vaccination à grande échelle. Elles résument les informations essentielles sur les maladies et les vaccins et présentent en conclusion la position actuelle de l'OMS concernant l'utilisation des vaccins dans le contexte mondial.

Ces notes sont destinées aux décideurs politiques et aux membres du personnel de l'OMS, aux érudits et, notamment, aux membres du Groupe stratégique consultatif d'experts sur la vaccination (GACE) de l'OMS, l'organisme scientifique principal pour l'évaluation de nouvelles stratégies de vaccination. Elles résument les informations essentielles sur les maladies et les vaccins et présentent en conclusion la position actuelle de l'OMS concernant l'utilisation des vaccins dans le contexte mondial.

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The papers are reviewed by external experts and WHO staff, and reviewed and endorsed by the WHO Strategic Advisory Group of Experts (SAGE) on Immunisation. (http://www.who.int/immunization/sage) The GACE methodology is used to systematically assess the quality of the available evidence. The SAGE decision-making process is reflected in the evidence-to-recommendation tables at the beginning of the processes followed. This position paper is available at [http://www.who.int/immunization/policy/vaccines\\_position\\_papers/vaccine\\_paper\\_position.pdf](http://www.who.int/immunization/policy/vaccines_position_papers/vaccine_paper_position.pdf)

The position papers are intended for use mainly by national public health officials and managers of immunisation programmes. They may also be of interest to international funding agencies, vaccine health professionals, researchers, health policy-makers, consumers, the scientific media, and the general public.

This position paper replaces the 2004 WHO position paper on Bacillus Calmette-Guérin (BCG) vaccine and the 2007 WHO

WHO, 2018. 27-28.

**WHO TB Module 1: Prevention - Tuberculosis preventive treatment (2020)**

**WHO TB Module 2: Screening - Systematic screening for tuberculosis detection (2021)**

**BCG position paper (2018)**

**WHO TB Module 3: Diagnosis – Rapid diagnostics for tuberculosis detection (2021)**

**WHO TB Module 4: Treatment - Drug-resistant tuberculosis treatment (2020)**

**Treatment – Drug-susceptible tuberculosis treatment (in progress)**

**WHO guidance for national TB programmes on the management of TB in children (2014)**

**WHO HIV guidelines (2016, 2018, 2021)**

**WHO nutritional care and support for patients with TB (2013)**

**Updates on the management of SAM in infants and children (2013)**

# Follow-up consultations (Sept/Oct. 2021)

- **Expert Consultation on classification of intrathoracic TB disease in children under 10 years**
  - Intrathoracic lymph node TB disease currently classified as extra-pulmonary TB
  - Ben Marais prepared background documentation including the historical perspective and rationale, and a motivation to update the classification from a pathophysiological, clinical, and surveillance perspective
  - Conclusions and updates be provided in the guidelines and operational handbook, as well as upcoming Global guidance on TB surveillance
- **Expert consultation on dosing of bedaquiline and delamanid and the short intensive treatment regimen for TB meningitis**
  - Background documentation prepared by Elin Svensson (bdq and dlm) and Kelly Dooley, Roeland Wasmann, Paolo Denti (TBM)
  - Review of latest evidence from PK studies, relevant pharmacometric simulations and implementation considerations on dosing for BDQ and DLM and for the TBM regimen to ensure that the new WHO recommendations can be implemented
  - Interim dosing strategies to be included in the operational handbook

# Other updates

- Publication of the **PADO-TB virtual review** report
- Update of the **WHO Prequalification Expression of Interest (EOI)**
  - Included 150 mg **scored** dispersible tablet for **rifapentine** (to ensure flexible dosing across indications and age groups for current and future needs) – 3HP, 1HP, DS-TB treatment
- Update of the **Global Fund Expert Review Panel EOI**
  - Inclusion of **rifapentine** 150mg dispersible tablet (scored)
- **Essential medicines list for children (EMLc) updates (October 2021)**
  - Inclusion of bedaquiline 20mg tablet and delamanid 25mg dispersible tablet

Report of the meeting to review the Paediatric Antituberculosis Drug Optimization priority list



World Health Organization  
Model List of Essential Medicines  
for Children

8th List  
(2021)



Updated WHO EMLc (8<sup>th</sup> list, 2021):  
<https://apps.who.int/iris/bitstream/handle/10665/345534/WHO-MHP-HPS-EML-2021.03-eng.pdf>

# Next steps at global level

- Release of updated and consolidated recommendations as the *WHO consolidated guidelines on tuberculosis: Module 5: Co-morbidities, vulnerable populations and people-centred care - Management of tuberculosis in children and adolescents* (early 2022).  
Translations into French, Spanish and Russian.
- Release of **operational handbook** with practical operational guidance  
e.g. on treatment decision algorithms; eligibility criteria for shorter treatment regimens for children with non-severe TB; building treatment regimens for children with MDR/RR-TB not eligible for shorter all-oral bdq regimens; updated dosing tables for second-line drugs, dosing strategy for short TBM regimen; examples of models of care from various settings; post-TB health; palliative care; TB and pneumonia; TB and malnutrition
- **Launch event** around World TB Day (to be confirmed)
- Dissemination of guidelines and handbook, through WHO webinars, WHO Knowledge Sharing Platform, global, regional and country meetings
- Development of **training materials** (2022)
- Second meeting of the Paediatric Anti-TB Drug Optimization group (**PADO-TB 2**, end 2022)
- Update of the 2018 **Roadmap** (2023)



WHO  
operational  
handbook on  
tuberculosis

Module 5: Vulnerable populations, co-morbidities and people-centred care

Management of tuberculosis in children and adolescents



# Acknowledgements

- Tereza Kasaeva, Farai Mavhunga, Kerri Viney, Tiziana Masini, and other colleagues at WHO Global Tuberculosis Programme
- GDG and ERG members, evidence reviewers, national TB programmes, WHO staff, technical and funding partners, community and civil society representatives, patients and their care-givers, as well as all others who contributed to the data to inform the update of the guidelines.



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