TBC multiresistente: nuovi farmaci e nuovi schemi terapeutici

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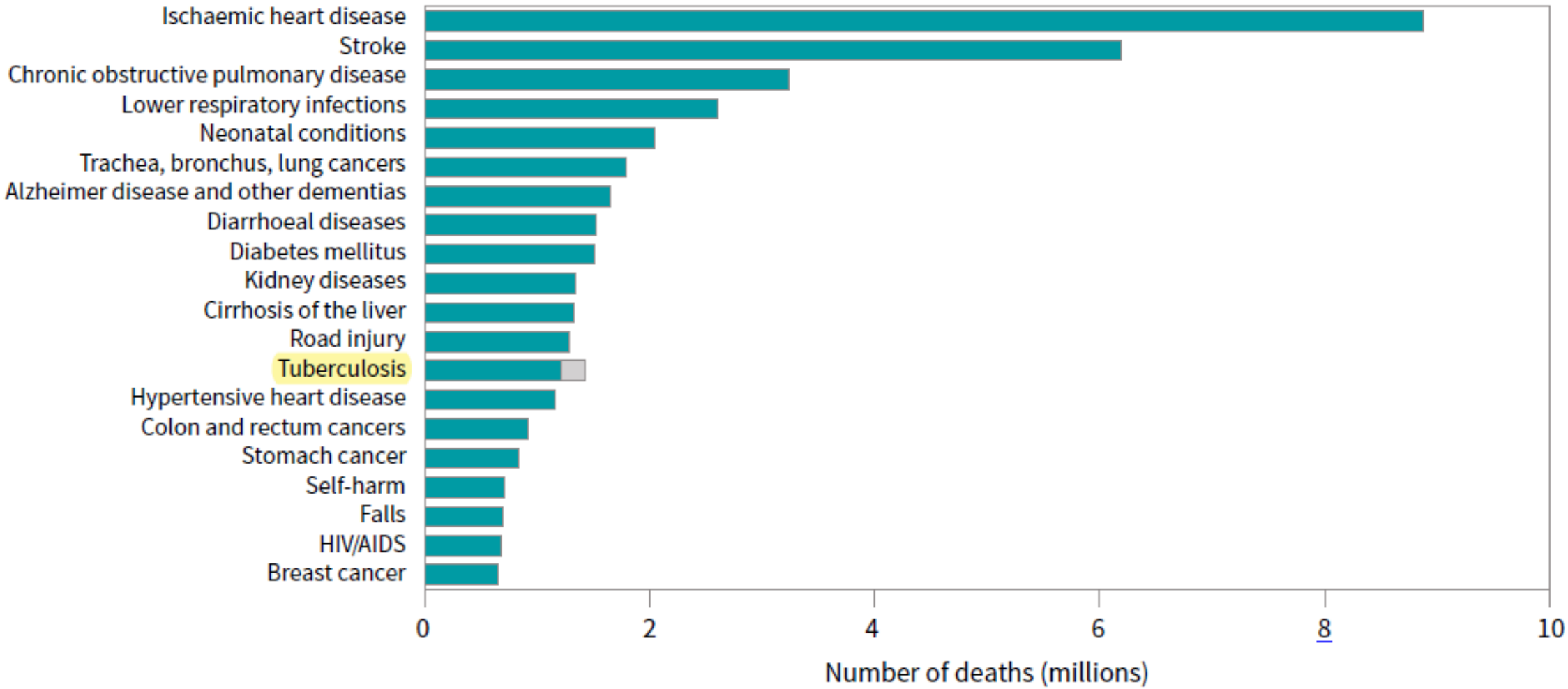
GLOBAL TUBERCULOSIS REPORT 2022

Tuberculosis (TB) is a communicable disease that is a major cause of ill health and one of the leading causes of death worldwide

Without treatment, the death rate from TB disease is high (about 50%).

Top causes of death worldwide in 2019[a,b]

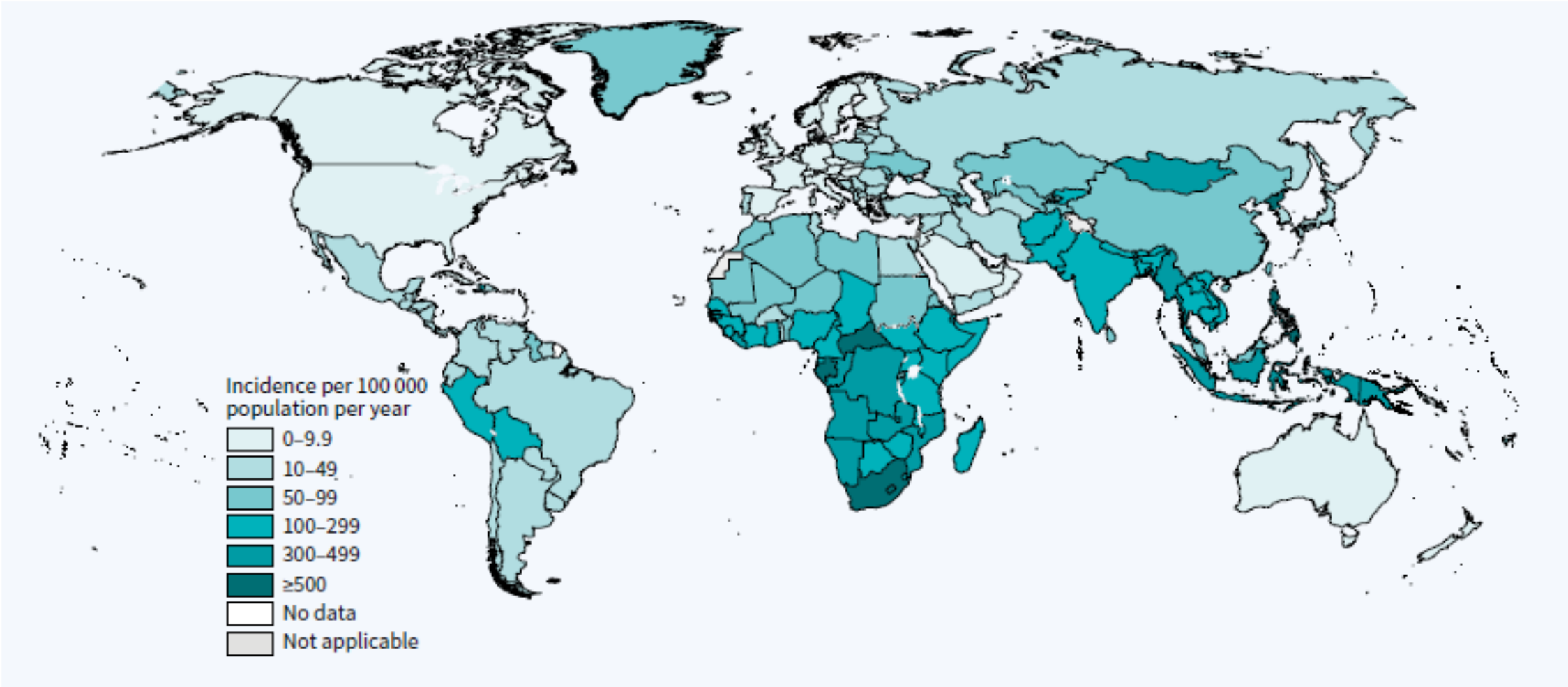
Deaths from TB among HIV-positive people are shown in grey.

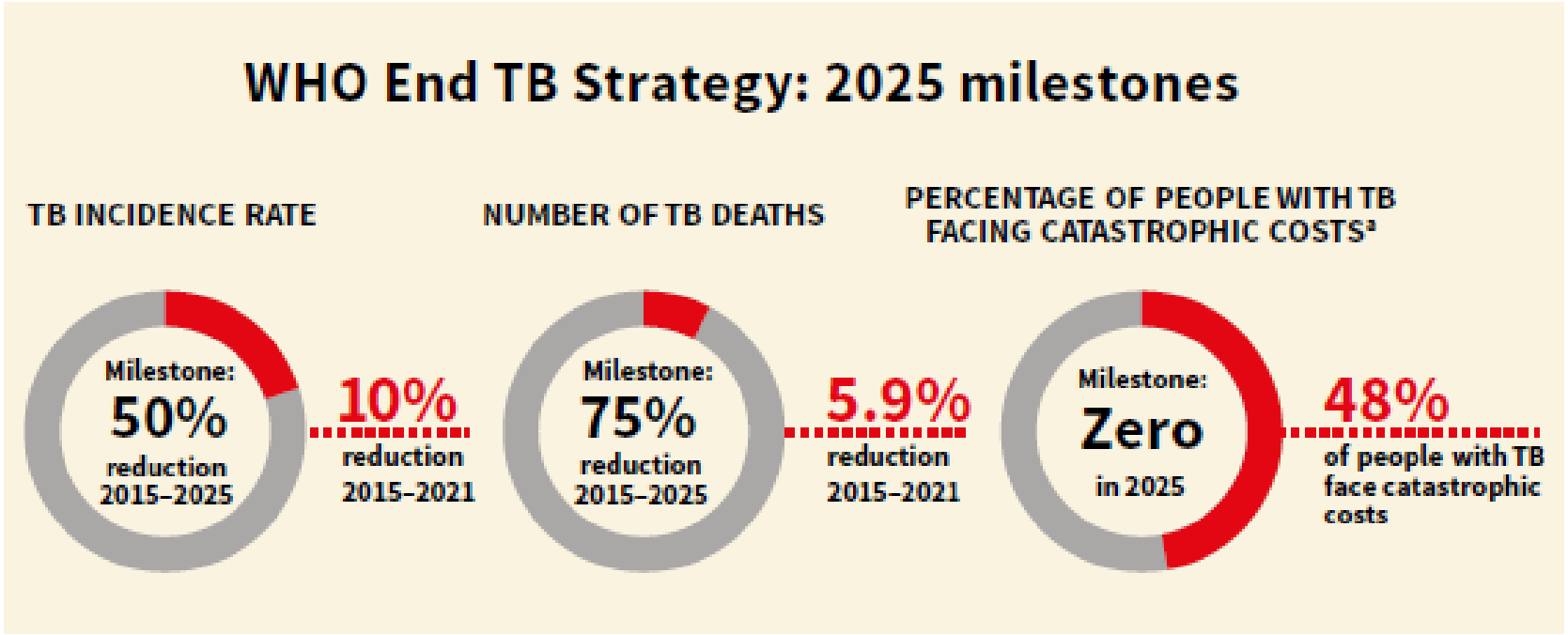


[a] This is the latest year for which estimates for all causes are currently available. See WHO estimates, available at https://www.who.int/data/gho/data/themes/mortality-and-global-health-estimates/ghe-leading-causes-of-death

[b] Deaths from TB among HIV-positive people are officially classified as deaths caused by HIV/AIDS in the International Classification of Diseases.

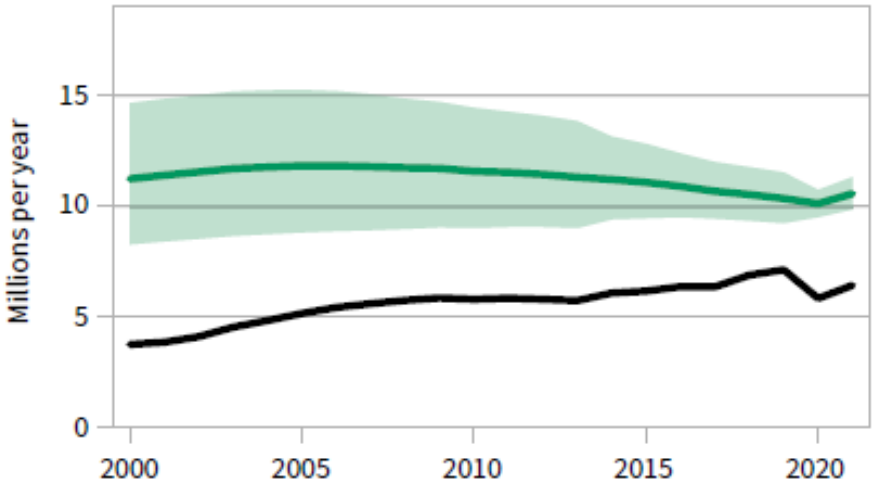
Estimated TB incidence rates, 2021





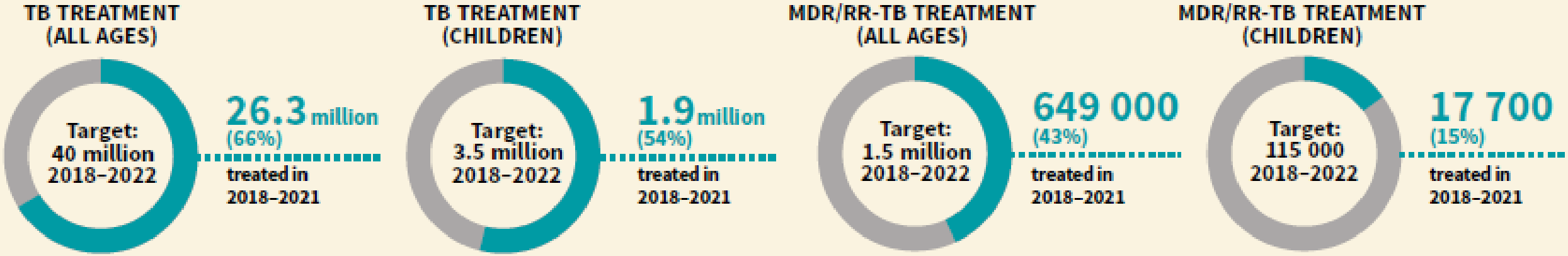
The **COVID-19** pandemic continues to have a damaging impact on access to TB diagnosis and treatment and the burden of TB disease. Progress made in the years up to 2019 has slowed, stalled or reversed, and global TB targets are off track.

Global trends in notifications of people newly diagnosed with TB (black) and the estimated number of incident TB cases (green), 2000–2021



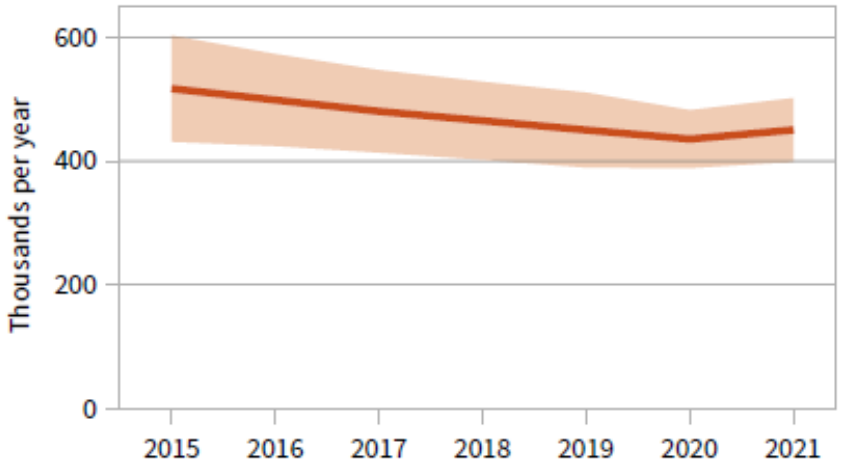
Reductions in the reported number of people diagnosed with TB in 2020 and 2021 suggest that the number of people with undiagnosed and untreated TB has grown, resulting first in an increased number of TB deaths (in 2021, there were an estimated 1.6 million of death, was up from best estimates of 1.5 million in 2020 and 1.4 million in 2019) and more community transmission of infection and then, with some lag-time, increased numbers of people developing TB.

UN high-level meeting on TB: treatment targets



Global trend in the estimated number of incident cases of MDR/RR-TB, 2015–2021

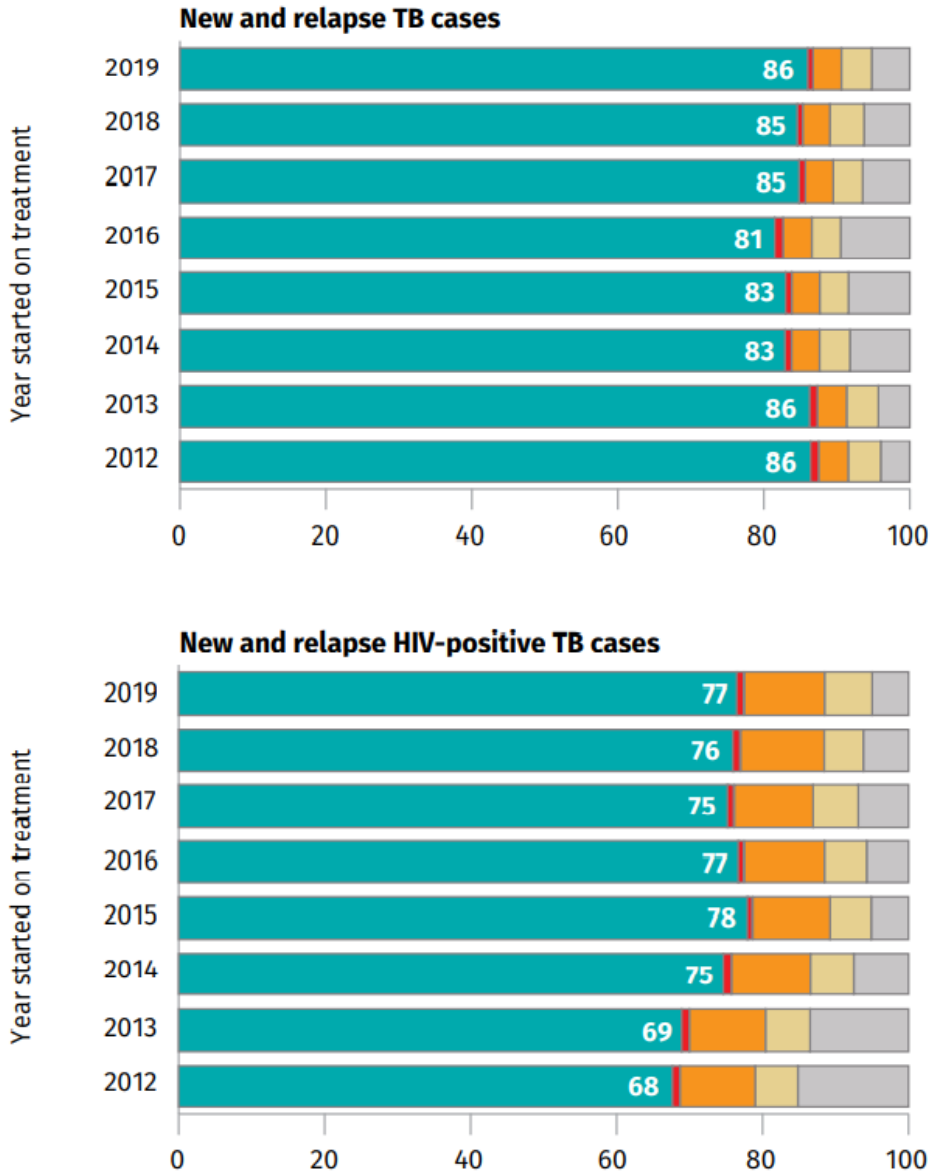
The shaded area represents the 95% uncertainty interval.

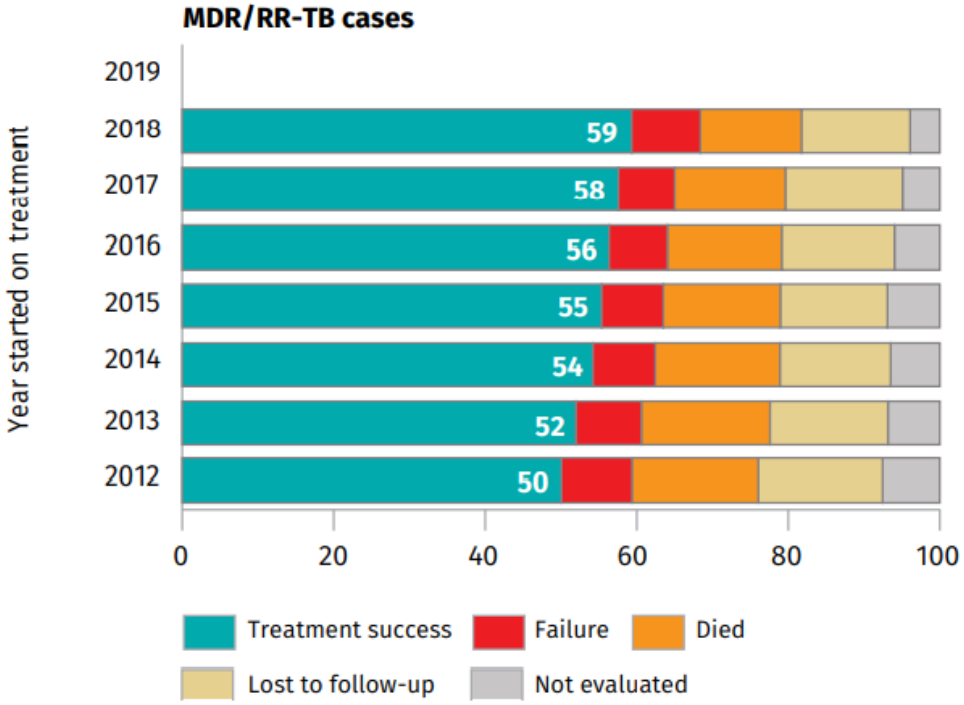


Globally, the estimated number of people who developed MDR-TB or RR –TB each year was relatively stable between 2015 and 2020, but it grew in 2021. There were an estimated 450 000 incident cases in 2021, up 3.1% from 437 000 in 2020, with <200000 cases diagnosed.

Drug-resistant TB (DR-TB) continues to be a public health threat

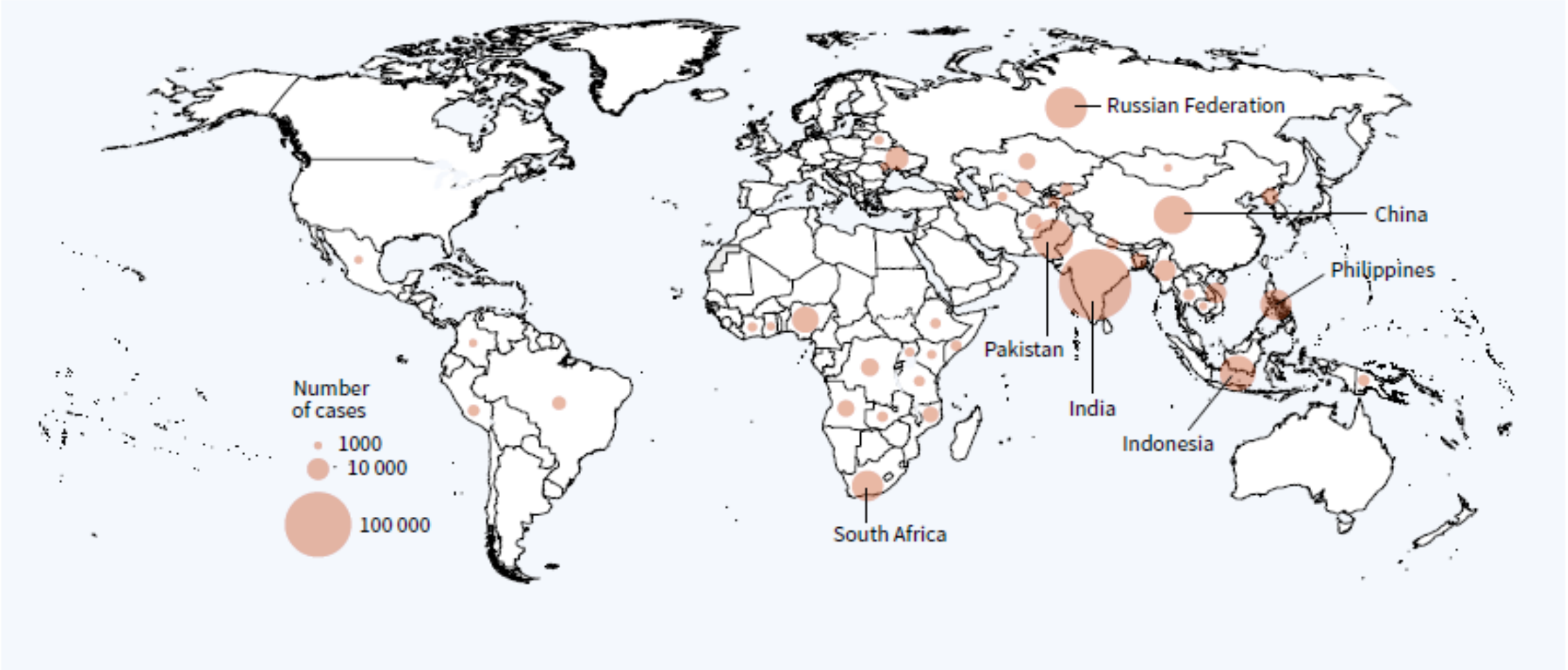
Treatment outcomes, globally, 2012–2019





Estimated incidence of MDR/RR-TB in 2021, for countries with at least 1000 incident cases

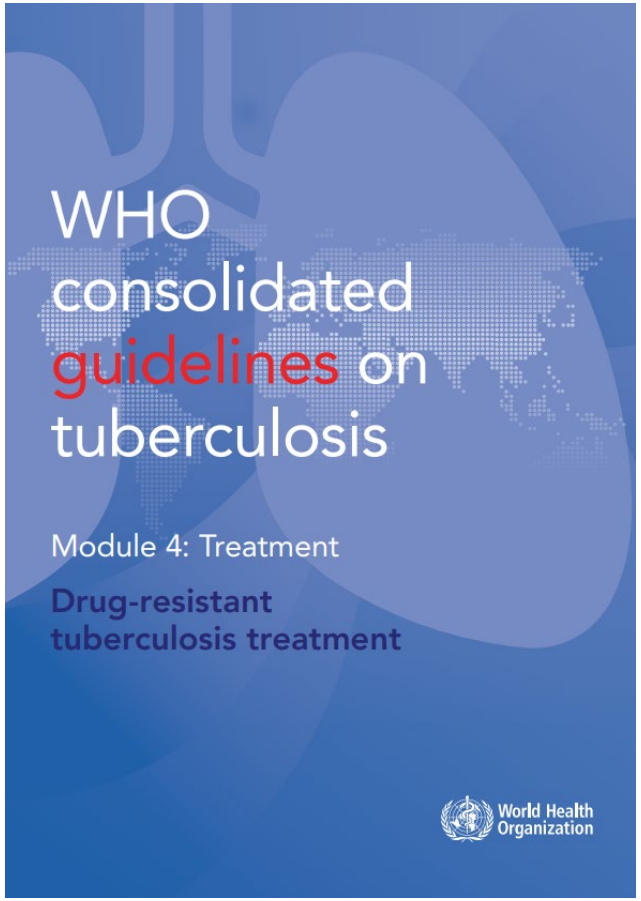
The seven countries with the highest burden in terms of numbers of MDR/RR-TB cases, and that accounted for two thirds of global MDR/RR-TB cases in 2021, are labelled.



Definition of resistance in TB

1. isoniazid-resistant TB
2. RR-TB and **MDR-TB**: resistance to rifampicin and isoniazid
3. **pre-XDR-TB** (pre-extensively drug-resistant TB): resistant to rifampicin and any fluoroquinolone (a class of second-line anti-TB drug)
4. **XDR-TB**: resistant to rifampicin, plus any fluoroquinolone, plus at least one of the drugs bedaquiline and linezolid

Detection of drug resistance requires bacteriological confirmation of TB and testing for drug resistance using rapid molecular tests, culture methods or sequencing technologies. Treatment requires a course of second-line drugs.



SHORTER REGIMEN

A shorter all-oral bedaquiline-containing regimen of **9–12 months** duration is recommended in eligible patients with confirmed multidrug- or rifampicin resistant tuberculosis (**MDR/RR-TB**) who have not been exposed to treatment with second-line TB medicines used in this regimen for more than 1 month, and in whom resistance to fluoroquinolones has been excluded.

(Conditional recommendation, very low certainty in the evidence)

- no resistance or suspected ineffectiveness of a medicine in the shorter regimen (except isoniazid resistance)
- no exposure to previous treatment with second-line medicines in the regimen for more than 1 month (unless susceptibility to these medicines is confirmed)
- no extensive TB disease and no severe extrapulmonary TB
- not pregnant
- children 6 years old and above

INITIAL PHASE for 4 months (with the possibility of extending to 6 months if the patient remains sputum smear positive at the end of 4 months) with:

- bedaquiline (is used for 6 months)
- levofloxacin/moxifloxacin
- clofazimine
- ethionamide
- ethambutol
- isoniazid (high dose)
- pyrazinamide

CONTINUATION PHASE for 5 months with:

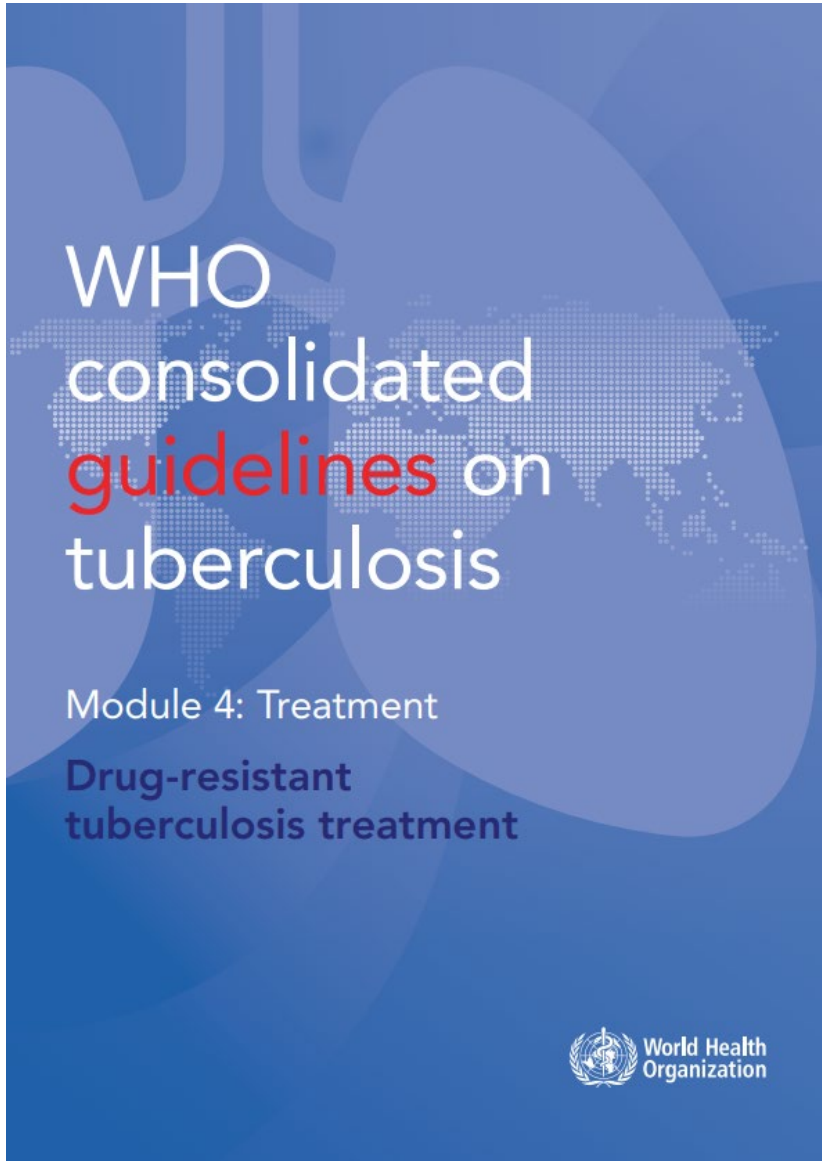
- levofloxacin/moxifloxacin
- clofazimine
- ethambutol
- pyrazinamide

All medicines were taken once a day on all days of the week, except for bedaquiline, which was taken every day for the first 2 weeks, followed by three times a week in the remaining 22 weeks.

Table 3.1. Grouping of medicines recommended for use in longer MDR-TB regimens[a]

Groups and steps	Medicine	Abbreviation
Group A: Include all three medicines	Levofloxacin *or* moxifloxacin	Lfx Mfx
	Bedaquiline[b,c]	Bdq
	Linezolid[d]	Lzd
Group B: Add one or both medicines	Clofazimine	Cfz
	Cycloserine *or* terizidone	Cs Trd
Group C: Add to complete the regimen and when medicines from Groups A and B cannot be used	Ethambutol	E
	Delamanid[e]	Dlm
	Pyrazinamide[f]	Z
	Imipenem–cilastatin *or* meropenem[g]	Ipm–Cln Mpm
	Amikacin (*or* streptomycin)[h]	Am (S)
	Ethionamide *or* prothionamide[i]	Eto Pto
	P-aminosalicylic acid[i]	PAS

LONGER REGIMEN



All three Group A agents and at least one Group B agent should be included to ensure that treatment starts with at least **four** TB agents likely to be effective.

At least **three** agents are included for the rest of treatment if bedaquiline is stopped.

If only one or two Group A agents are used, both Group B agents are to be included.

If the regimen cannot be composed with agents from Groups A and B alone, Group C agents are added to complete it.

(Conditional recommendation, very low certainty in the estimates of effect)

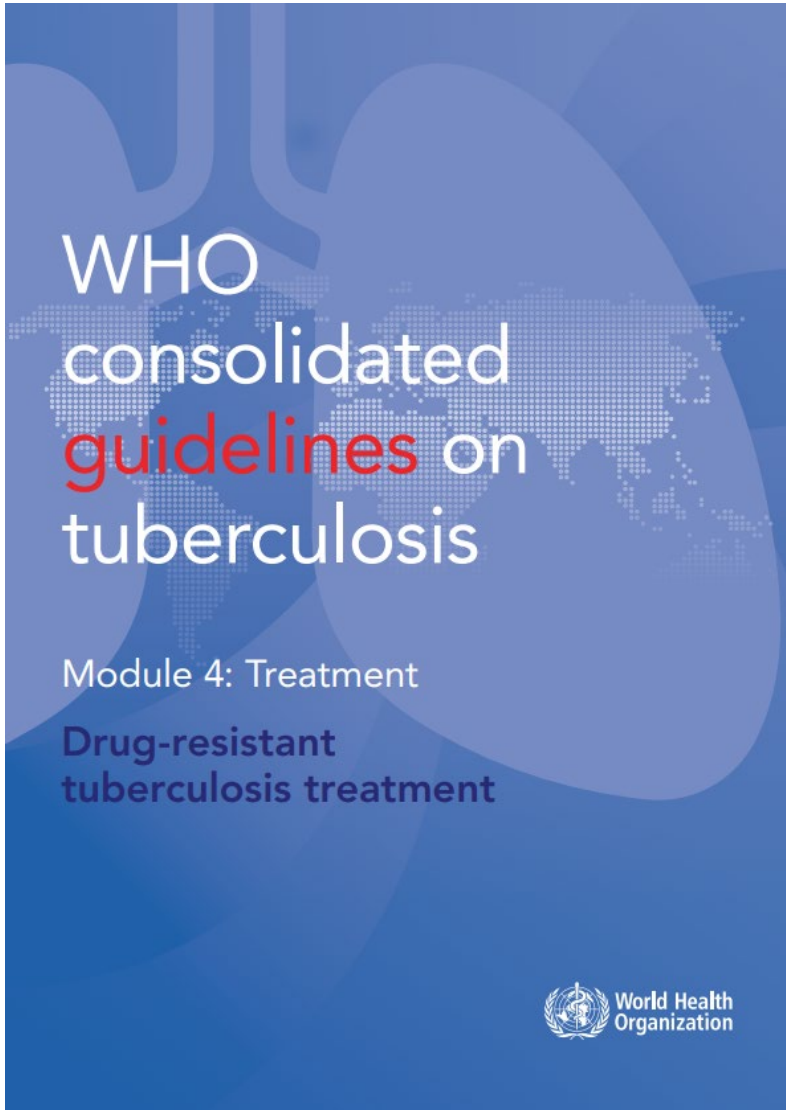
INITIAL PHASE for 6 months with:
- bedaquiline
- levofloxacin/moxifloxacin
- linezolid
- clofazimina/cicloserina

CONTINUATION PHASE for 12 months with:
- levofloxacin/moxifloxacin
- linezolid
- clofazimine/cicloserina

A total treatment duration of 18–20 months is suggested for most patients; it may be modified according to the patient's response to therapy.

All medicines were taken with food, once a day on all days of the week, except for bedaquiline, which was taken every day for the first 2 weeks, followed by three times a week in the remaining 22 weeks.

- **RR-MDR** TB
- **pre-XDR** and **XDR** TB (individualized regimen)
- extensive TB disease
- severe extrapulmonary TB
- pregnant
- children 6 years
- complex resistance pattern
- intolerance or contraindications to drugs of shorten regimen
- shorten regimen discontinuation after one month of therapy for more than 2 months



BPaL REGIMEN

A **6-9 month** bedaquiline, pretomanid and linezolid (1200 mg/die) regimen for MDR-TB with also resistant to fluorochinolones (**pre-XDR**).

May be used under operational research conditions in patients who have either had no previous exposure to bedaquiline and linezolid or have been exposed for no more than 2 weeks.

(Conditional recommendation, very low certainty in the estimates of effect)

If the sputum culture after 4 months is positive, patients can receive an additional 3 months of treatment (total 9 months).

Is possible interrupt temporarily interrupted for a maximum of 35 consecutive days.

- no extrapulmonary TB
- not pregnant
- children 14 years old and above

Rapid communication (May 2022): Key changes to the treatment of drug-resistant tuberculosis

World Health Organization

Some new regimens have recently been tested in trials or used programmatically:

TB-PRACTECAL TRIAL: open-label, randomised, controlled, phase II/III non-inferiority evaluating the safety and efficacy of 24-week regimens containing bedaquiline and pretomanid to treat rifampicin-resistant tuberculosis. Conducted in Uzbekistan, South Africa and Belarus.

The **6-month BPaLM** regimen, comprising bedaquiline, pretomanid, linezolid (**600 mg**) and moxifloxacin, may be used programmatically in place of 9-month or longer (>18 months) regimens, in patients (aged ≥15 years, not pregnant) **with MDR/RR-TB** (no extrapulmonary TB) who have not had previous exposure to bedaquiline, pretomanid and linezolid (defined as >1 month exposure).

Berry *et al. Trials (2022) 23:484* https://doi.org/10.1186/s13063-022-06331-8

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ZeNix trial: the participants, in **BPaL** regimen, were randomly assigned, in a 1:1:1:1 ratio, to one of the four linezolid regimens (either 1200 mg or 600 mg daily for either 26 weeks or 9 weeks).

Patients aged above 14 ys, not pregnant, not severe forms of extrapulmonary TB (e.g. TB meningitis).

The assessment of evidence suggested that the optimal dosing of linezolid is **600 mg** daily in **BPaL** regimen in patients with **pre-XDR**, with the possibility of dose reduction in the event of toxicity or poor tolerability.

N Engl J Med 2022;387:810-23

The evidence from the available studies suggests that these regimens may be used in eligible patients with MDR/RR-TB and pre-XDR-TB regardless of their HIV status.

Rapid communication (May 2022): Key changes to the treatment of drug-resistant tuberculosis

World Health Organization

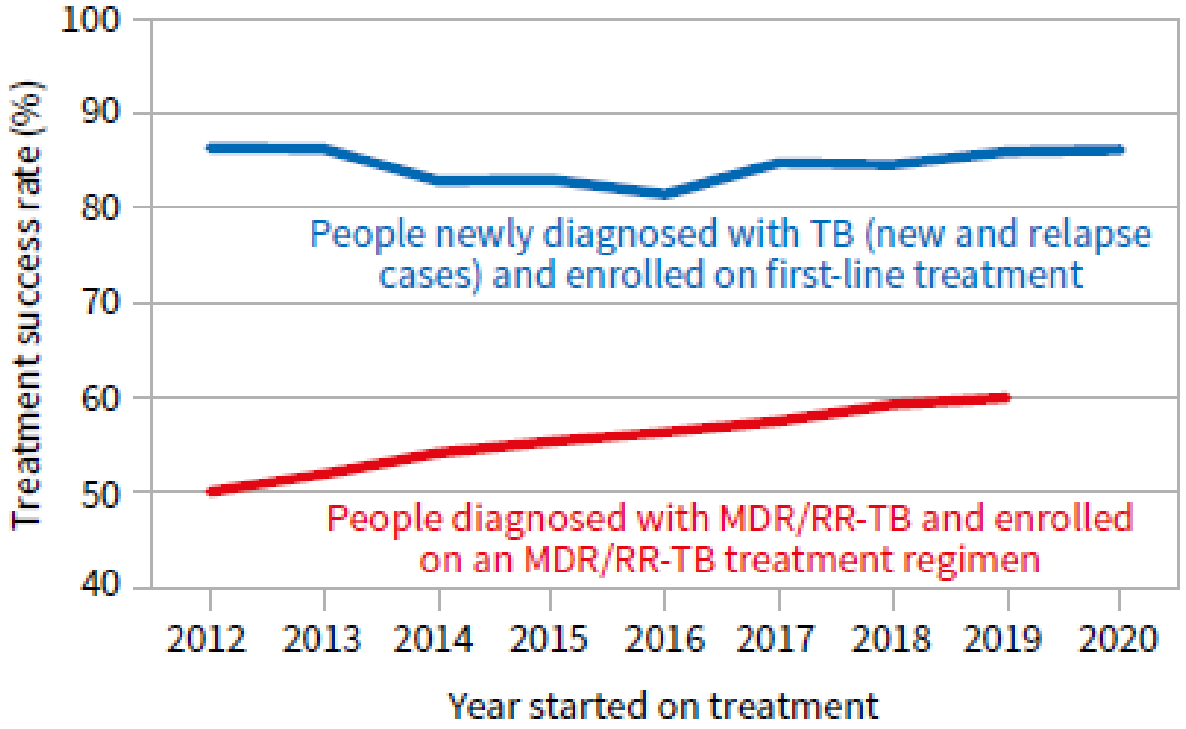
Some new regimens have recently been tested in trials or used programmatically:

NeXT study: this regimen has been used in South Africa since mid-2018

4-6 Bdq[6]-Lfx[Mfx]-**Lzd[2]-**E-Z-Hh-Cfz / 5 Lfx[Mfx]-Cfz-Z-E, with 2 months of linezolid (**600 mg**) replacing 4 months of ethionamide in patient with **MDR TB** (aged ≥ 6 years), without previous exposure to second-line treatment (including bedaquiline), without fluoroquinolone resistance and with no extensive pulmonary TB disease or severe extrapulmonary TB.

NExT-5001 NCT02454205

Global success rates for people treated for TB, 2012–2020[a]



Novel all-oral regimens for MDR/RR –TB and pre-XDR-TB can now reduce treatment duration to only 6 months, compared with older regimens lasting 20 months or more. WHO recommends expanded access to all-oral regimens, supported by counselling and monitoring for adverse events.

Dr Tedros Adhanom Ghebreyesus
Director-General
World Health Organization

“If the pandemic has taught us anything, it’s that with solidarity, determination, innovation and the equitable use of tools, we can overcome severe health threats. Let’s apply those lessons to tuberculosis. It is time to put a stop to this long-time killer. Working together, we can end TB.”

Grazie per l’attenzione