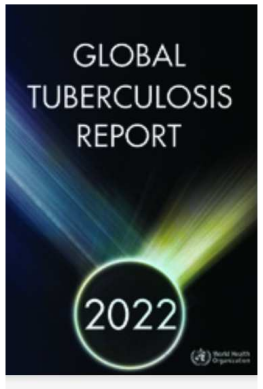
Mycobacterium tuberculosis MDR e XDR: i nuovi schemi di terapia

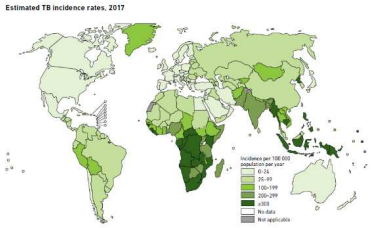
Alberto Matteelli

Clinic of Infectious Diseases - University of Brescia
WHO Collaborating Center for TB precention





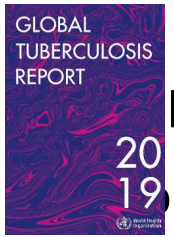
The Global Burden of TB, 2021



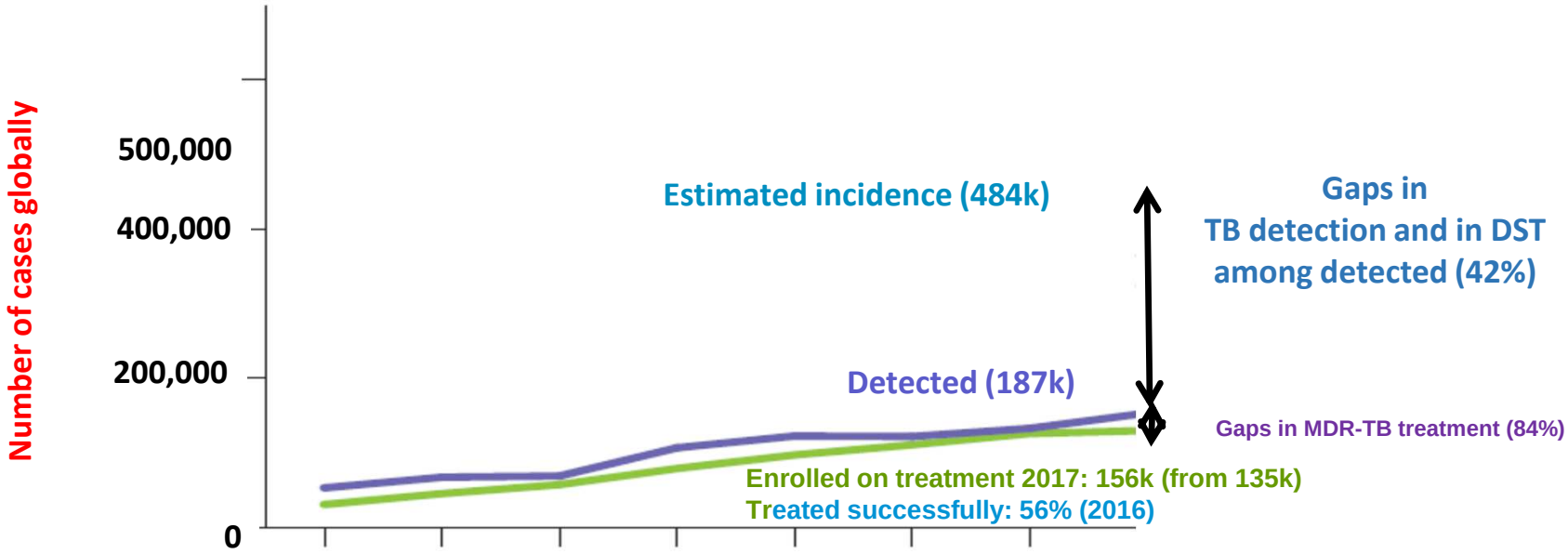
	Estimated number of cases	Estimated number of deaths
All forms of TB	10.6 million (127 per 100,000)	1.4 million*
Notified	6.4 million	
HIV-associated TB	0.7 million (6.7%)	187,000
Multidrug-resistant TB MDR/RR-TB	450,000	230,000
Latently infected	1.7 billion	

** Excluding deaths attributed to HIV/TB*

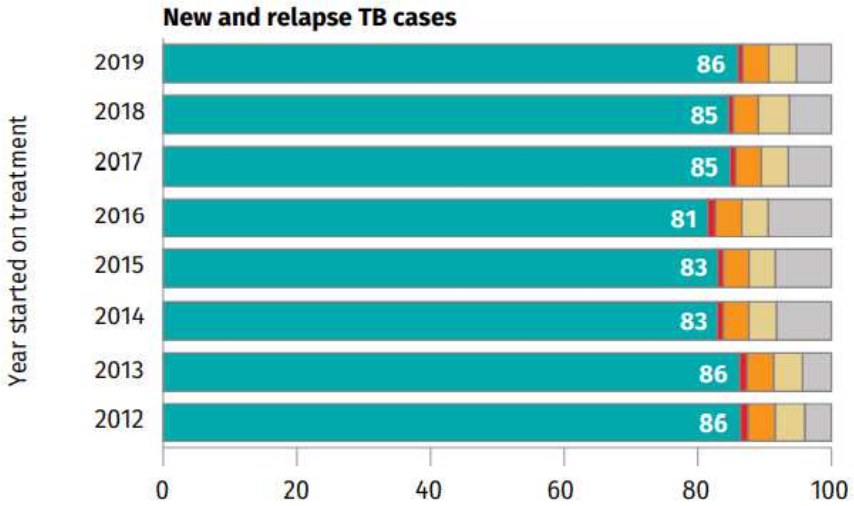
Source: WHO Global Report, 2021

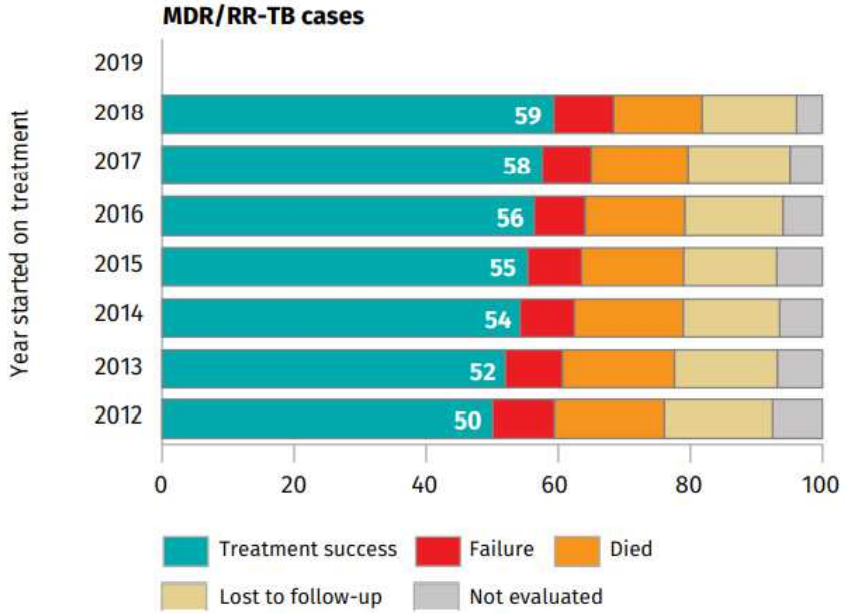


rug-resistant TB:
, diagnosed and treated, and gaps



Treatment outcomes for new and relapse TB cases, new and relapse HIV-positive TB cases, and MDR/RR-TB cases, globally,a 2012–2019





Definition of resistance in TB

1. isoniazid-resistant TB
2. RR-TB and **MDR-TB**
3. pre-extensively drug-resistant TB (pre-XDR-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.

A clinical case

- A Pakistani female of 28 years is diagnosed with pulmonary TB by a strain resistant to rifampin and isoniazid, sensitive to other drugs.

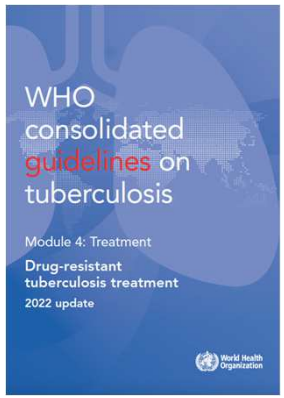
What is your preferred treatment regimen in this case?

BPaLM – 6 mesi

- **B**edaquilina: 400 mg/die per 2 settimane → 200 mg trisettimanale per 24 settimane
- **P**retom**a**nid: 200 mg/die per 26 settimane
- **L**inezolid: 600 mg/die per 26 settimane
- **M**oxifloxacin: 400 mg/die per 26 settimane

5 cp/die





WHO guidelines 2022

1. The 6-month bedaquiline, pretomanid, linezolid and moxifloxacin (BPaLM) regimen for MDR/RR-TB and pre-XDR-TB (a)

1.1 WHO suggests the use of the 6-month treatment regimen composed of bedaquiline, pretomanid, linezolid (600 mg) and moxifloxacin (BPaLM) rather than 9-month or longer (18-month) regimens in MDR/RR-TB patients.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 5, 2020 VOL. 382 NO. 10

Treatment of Highly Drug-Resistant Pulmonary Tuberculosis

Francesca Conradie, M.B., B.Ch., Andreas H. Diacon, M.D., Nosipho Ngubane, M.B., B.Ch.,

- **Methods**
- Open-label, single-group study in three South African sites. **(The NIX TB trial)**
- We evaluated the safety and efficacy of the drug combination for 26 weeks in patients with XDR-TB or MDR-TB that was not responsive to treatment or for which a second-line regimen had been discontinued because of side effects.
- The primary end point was the incidence of an unfavorable outcome, defined as treatment failure (bacteriologic or clinical) or relapse at 6 months of follow-up

Results

109 patients enrolled and included in the evaluation of efficacy and safety end points.

98 patients (**90%; 95% confidence interval, 83 to 95) had a favorable outcome**.

The linezolid toxic effects of peripheral neuropathy (occurring in 81% of patients) and myelosuppression (48%), were manageable, often leading to dose reductions or interruptions in treatment with linezolid

The Ze Nix TB trial 2022

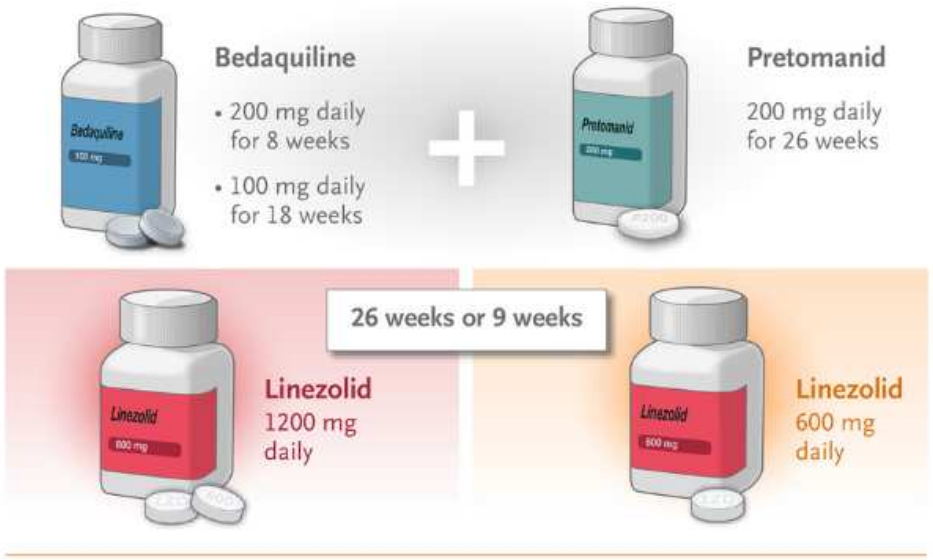
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

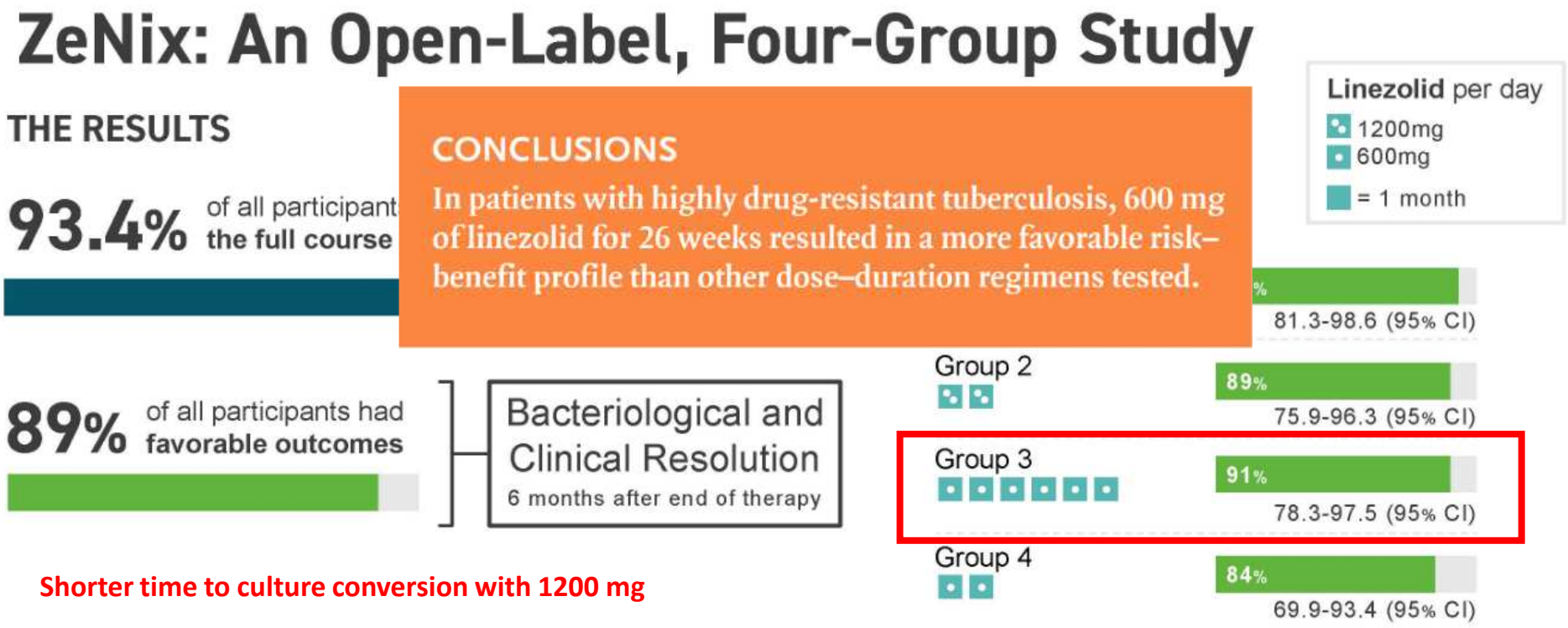
Bedaquiline–Pretomanid–Linezolid Regimens for Drug-Resistant Tuberculosis

F. Conradie, T.R. Bagdasaryan, S. Borisov, P. Howell, L. Mikiashvili, N. Ngubane, A. Samoilova, S. Skornykova, E. Tudor, E. Variava, P. Yablonskiy, D. Everitt, G.H. Wills, E. Sun, M. Olugbosi, E. Egizi, M. Li, A. Holsta, J. Timm, A. Bateson, A.M. Crook, S.M. Fabiane, R. Hunt, T.D. McHugh, C.D. Tweed, S. Foraida, C.M. Mendel, and M. Spigelman, for the ZeNix Trial Team*

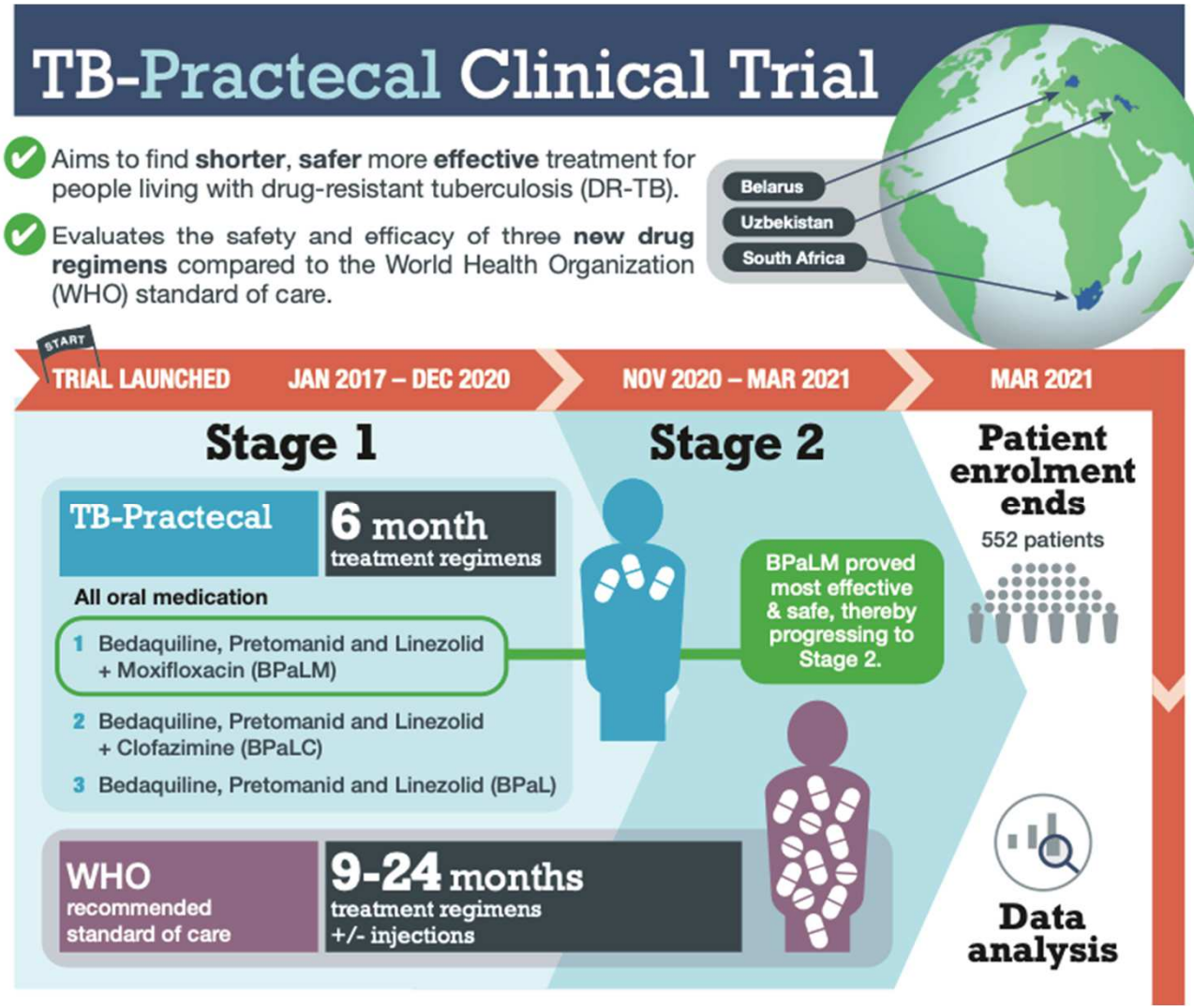
September 1, 2022
N Engl J Med 2022; 387:810-823
DOI: 10.1056/NEJMoa2119430



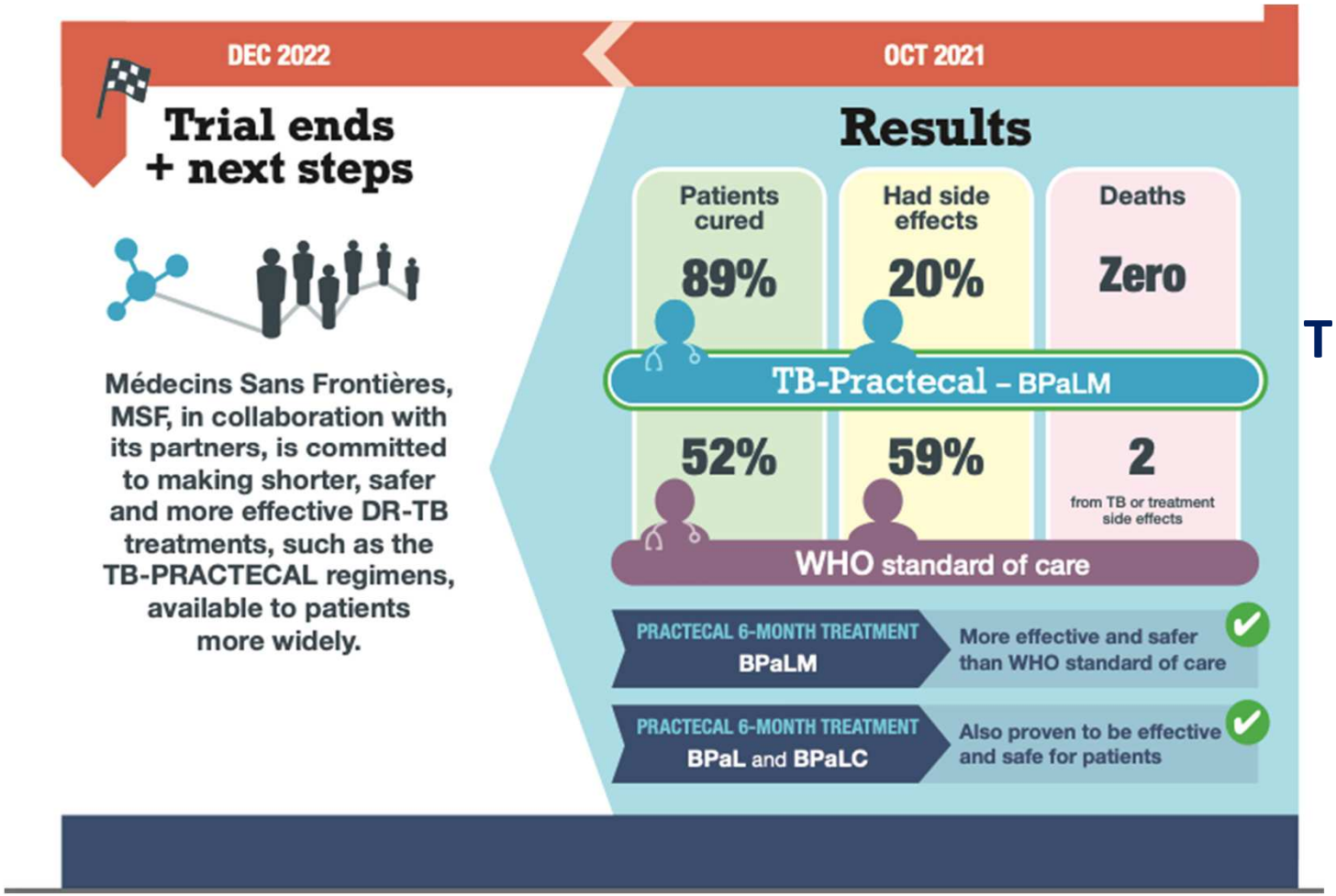
The Ze Nix TB trial 2022



Shorter time to culture conversion with 1200 mg



The practecal TB trial 2022



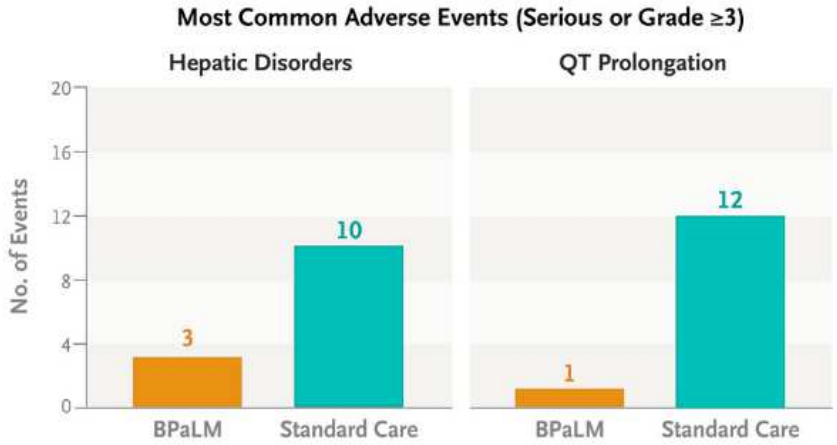
The practecal TB trial 2022

A 24-Week, All-Oral Regimen for Rifampin-Resistant Tuberculosis

The NEW ENGLAND JOURNAL of MEDICINE

Nyang'wa B-T et al. DOI: 10.1056/NEJMoa2117166

December 22, 2022
N Engl J Med 2022; 387:2331-2343
DOI: 10.1056/NEJMoa2117166



CONCLUSIONS

In patients with rifampin-resistant tuberculosis, a 24-week, all-oral BPaLM regimen was noninferior to the standard-care regimen with respect to unfavorable outcomes, and it had a better safety profile.

Hospital isolation

- B.M. 29 years old, born in Peru, married, no children
- Diagnosed with smear positive pulmonary XDR-TB (wife with similar disease, hospitalized in same room)
- Treatment with the only available effective drugs: linezolid, pretomanid, clofazimine
- Needs to work to send money back home

When would you allow them to re-enter the community?

Standard or individualized treatment?

The WHO strongly encourage a standardized approach to the treatment of tuberculosis and, particularly, MDR-TB

Do you believe this applies to well-off counties like Italy ?



Standard or individualized treatment?

Would you use BPaLM in a patients with TB caused by MTB resistant to rifampicin and isoniazid only?

Would And resistant to rifampicin only?

Starting an MDR-TB treatment

- You admit a patient with pulmonary disease
- The sputum smear results positive
- The X-pert MTB test demonstrate resistance to rifampicin

Is this information enough to start a TB regimen?

If so, which regimen?

If not, what would you need more?

Starting an MDR-TB treatment

- You admit a patient with cerebral lesions
- The cerebrospinal fluid is positive for rifampicin-resistnt M.tuberculosis at X-pert examination

WhichTB regimen would you start?

Patient management

- A patient with MDR-TB has been started with BPaLM.
- After two months of treatment she develops nausea and her transaminasis levels rise to 7 times the normal level

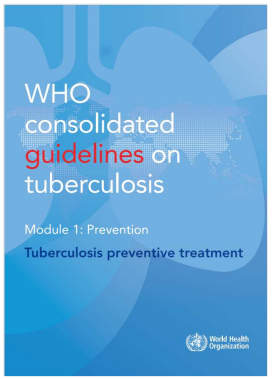
How do you manage this situation ?

A clinical case (1)

- The index case is a Pakistani female of 28 years, diagnosed with pulmonary TB by a strain resistant to rifampin and isoniazid, sensitive to other drugs.
- The couple has a one year old boy, in good health, with a normal chest Xray, and a Mantoux test with a reaction of 7 mm

What management do you suggest for the boy ?

2020: the first WHO guidance
(but data from 2018)

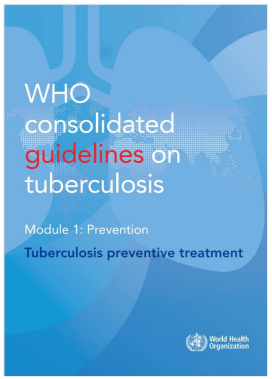


<u>Lack of RCT evidence.</u>

One cohort of 119 contacts with LTBI:
- 104 initiated fluoroquinolone based PT, 93 (89%) completed, none TB cases;
Vs.
- 15 (20%) refused treatment and 3 (20%) developed MDR-TB
(OR 0.02, 95% CI 0.00; 0.39) (36).

Bamrah S, et al. Int J Tuberc Lung Dis. 2014 Aug 1;18(8):912–8

2020: the first WHO guidance
(but data from 2018)

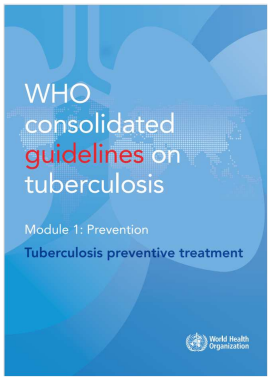


<u>Lack of RCT evidence</u>

One cohort of 105 contacts with LTBI:
Confirmed or probable TB developed in 2 of 41 (4.9%) children receiving tailored PT
Vs.
13 of 64 (20.3%) children who did not receive PT
(OR 0.2, 95% CI 0.04; 0.94).

. Schaaf HS, et al. Pediatrics. 2002 May;109(5):765–71.

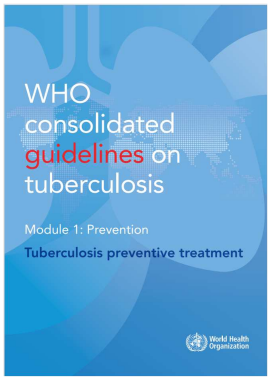
2020: the first WHO guidance
(but data from 2018)



Contacts of multidrug-resistant tuberculosis patients

7. In selected high-risk household contacts of patients with multidrug-resistant tuberculosis, preventive treatment may be considered based on individualized risk assessment and a sound clinical justification. *(Conditional recommendation, very low certainty in the estimates of effect)*

WHO consolidated guidelines on tuberculosis. Module 1: prevention – tuberculosis preventive treatment. Geneva: 2020



2020: the first WHO guidance
(but data from 2018)

<u>Individualized risk assessment</u>

Includes

- intensity of exposure,
- certainty of the source of disease,
- information on the drug resistance pattern of the source
- potential adverse drug reactions.

WHO consolidated guidelines on tuberculosis. Module 1: prevention – tuberculosis preventive treatment. Geneva: 2020

What next?

Ongoing randomized controlled trials

24 January 2023

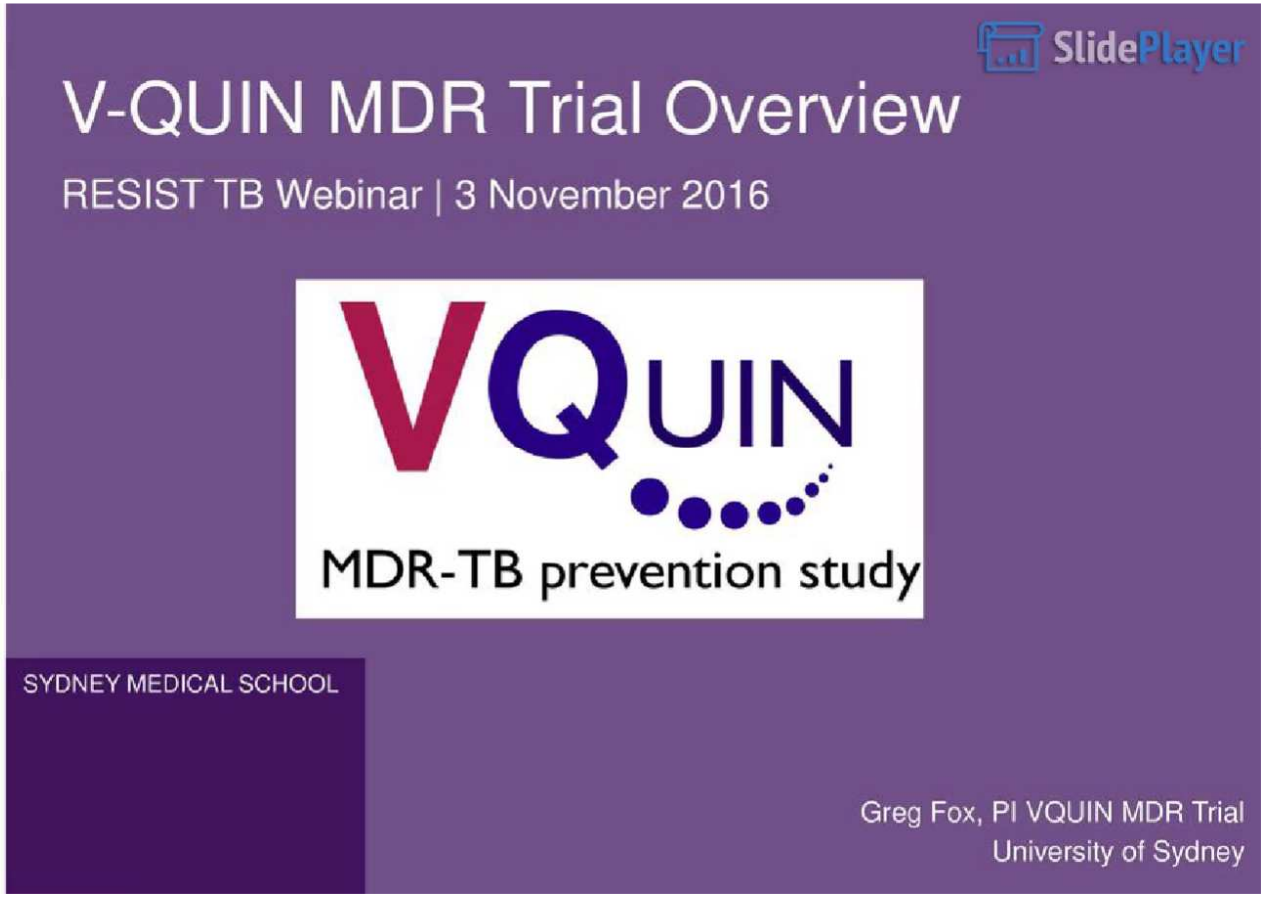


TB-CHAMP study comes to an end!

Trials of treatment for MDR TB infection

	TB-CHAMP
Intervention	LVF (paediatric dispersible tablet formulation) vs. placebo daily for 6 months
Design	Cluster randomized; superiority Community-based
Target Population	0-5 years of age regardless of TST or HIV status
Assumptions	LVF decreases incidence from 7 to 3.5%; 80% power
Sample size	788 HH 1565 contacts
Sites	South Africa

Study completed



	V-QUIN
Intervention	LVF vs placebo daily for 6 months
Design	Cluster randomized; superiority Community-based
Target Population	All ages (including infants < 6 mo), TST +
Assumptions	LVF decreases incidence by 70% from 3% untreated; 80% power
Sample size	1326 HH 2785 contacts
Sites	Viet Nam

A 32 years ole Peruvian man

- Arrives into Italy, presents with TB diagnosed in Peru. He had started treatment in Peru 9 months before, with undefined drugs.
- An M.tuberculosis isolate from respiratory secretions shows the following sensitivity test.
  - ✓ **Resistant** ro rifampicin, isoniaxid, pyrazinamide, fluorquinolones, bedaquiline clofazinime and etionamide
  - ✓ **sensitive** to linezolid, delamanid ethambutol, amikavine and meropenm / clavulanate

What regimen would you start ?

The wife of the Peruvian man

- Smear positive pulmonary TB
- The sensitivity pattern of the isolate differs because of sensitivity to bedaquiline

What regimen would you start ?

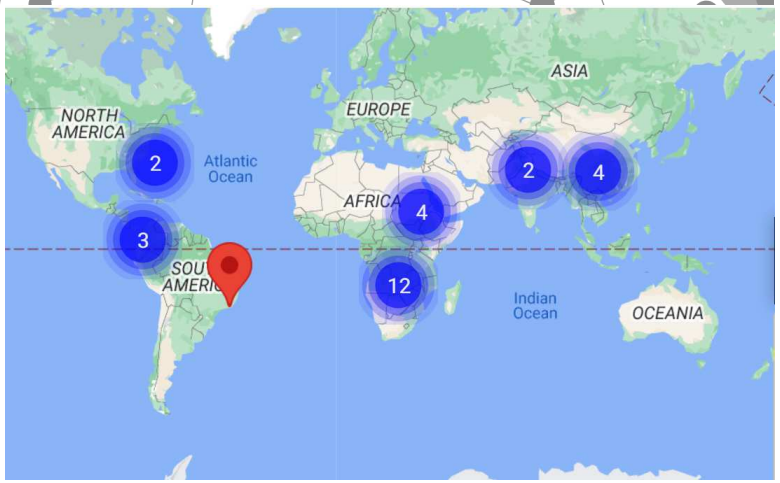
The 2.5 year old daughter of the couple

- No symptoms, good growth
- At the chest TC right upper lobe calcification in absence of signs of disease
- Gastric aspirate and stools negative for *M.tuberculosis* by Xpert MTB/Rif

What management do you suggest ?

A5300B/I2003B:Protecting Households On Exposure to Newly Diagnosed Index Multidrug-Resistant Tuberculosis Participants (PHOENIx)

ACTG/IMPAACT collaborative phase III, open-label, multicentre, international trial (NCT03568383).



The Phoenix trial

Aim: to evaluate the efficacy and safety of **delamanid** for TPT in **high-risk household contacts of MDR-TB**.

Recruiting: in 12 countries (Botswana, Brazil, Haiti, India, Kenya, Peru, Philippines, South Africa, Tanzania, Thailand, Uganda, Zimbabwe)

Treatment arm: 26 weeks of delamanid

Control arm: 26 weeks of isoniazid

Follow-up: 96 weeks post-randomization

Sample size: 5610 participants

Termination: 2026

Am J Respir Crit Care Med. 2022 Mar 1;205(5):570-579. doi: 10.1164/rccm.202012-4541OC.

Efficacy of Long-Acting Bedaquiline Regimens in a Mouse Model of Tuberculosis Preventive Therapy

Amit Kaushik [1], Nicole C Ammerman [1], Rokeya Tasneen [1], Sophie Lachau-Durand [2],

Long-acting formulation of bedaquiline demonstrated antituberculosis activity for up to 12 weeks after injection in a validated mouse model of preventive therapy.

- Two injections with 4 weeks of oral bedaquiline equivalent to
- daily isoniazid-rifapentine for 4 wk (control)