La gestione del paziente con MDR-TB
Ruolo dei centri di riferimento

29 Febbraio 2025

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StopTB Italia

SOMMARIO

- **DEFINIZIONI**
- **EPIDEMIOLOGIA (WHO REPORT 2024)**
- **DIAGNOSI**
- **TRATTAMENTO**
- **RUOLO DEI CENTRI DI RIFERIMENTO**

LA SCHIZOFRENIA SEMANTICA

RR

DR

MDR

XDR

XXDR

PREXDR

???

Definitions

- Drug-resistant tuberculosis (DR-TB) = bacilli are resistant to the drugs used to treat the infection
- Different types of DR-TB:
  - **Multi drug-resistant TB (MDR-TB/RR-TB)** – TB resistant to rifampicin and izoniazid
  - **Pre-Extensively drug-resistant tuberculosis (pre-XDR-TB)** – TB caused by Mycobacterium tuberculosis strains that fulfil the definition of MDR/RR-TB and that are also resistant to any fluoroquinolone
  - **Extensively drug-resistant tuberculosis (XDR-TB)-** – XDR-TB is MDR/RR-TB that is resistant to a fluoroquinolone and either bedaquiline or linezolid (or both).

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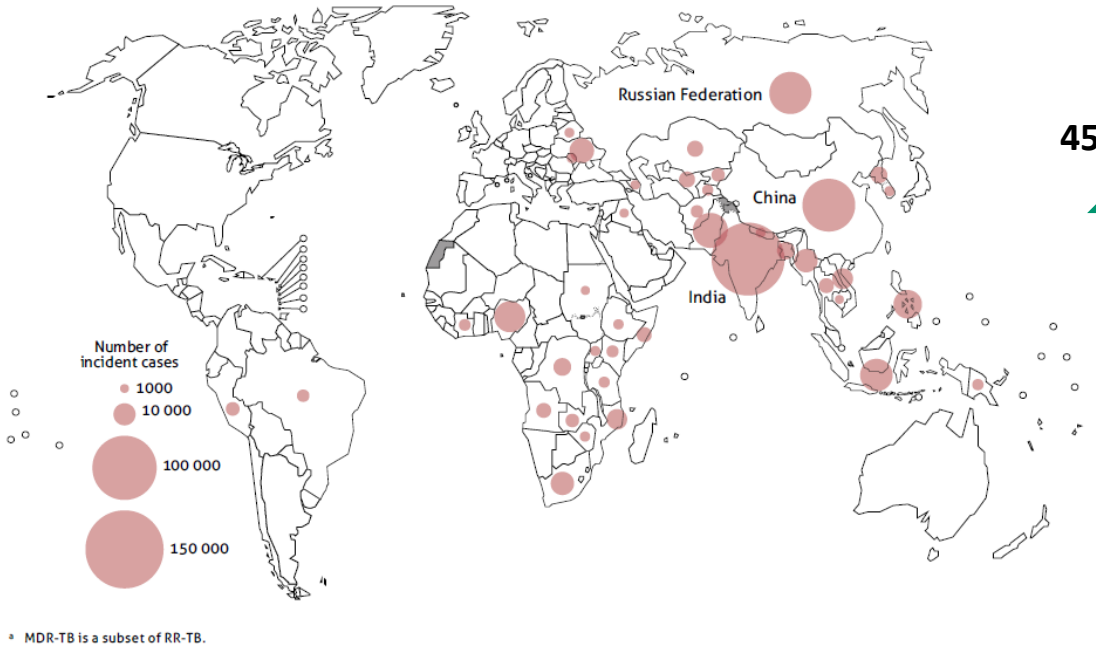
MDR/RR-TB: #cases

Estimated incidence of MDR/RR-TB[a] in 2018, for countries with at least 1000 incident cases



[a] MDR-TB is a subset of RR-TB.

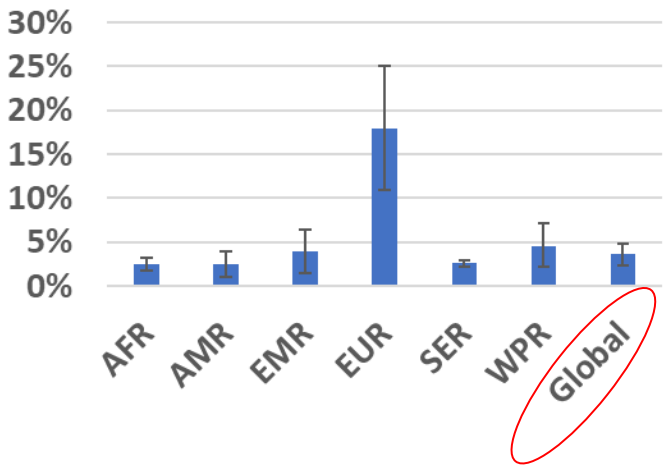
450 000 (399 000 - 501 000) new cases

3% since 2020

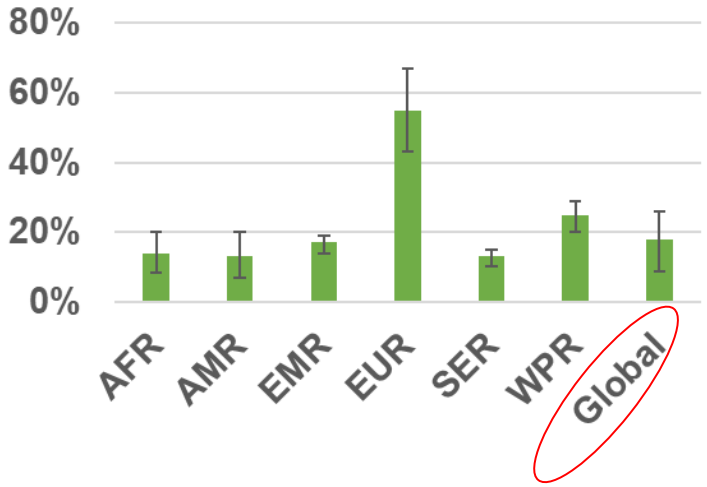
WHO Global TB Report 2022

Global MDR/RR-TB rates

ESTIMATED % OF NEW CASES WITH MDR/RR-TB

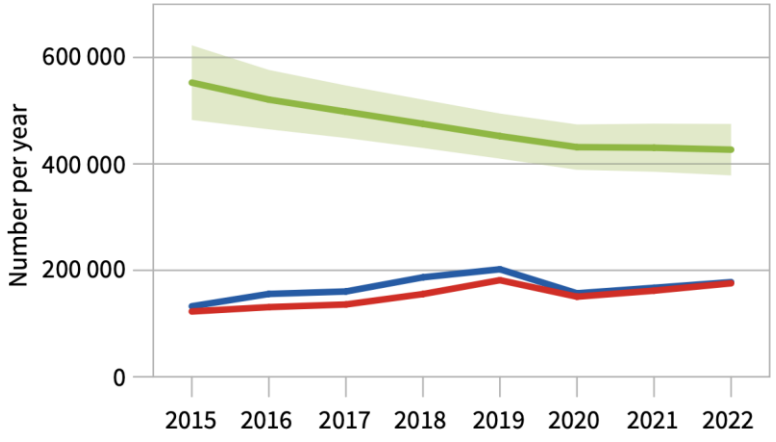


ESTIMATED % OF PREVIOUSLY TREATED CASES WITH MDR/ RR-TB

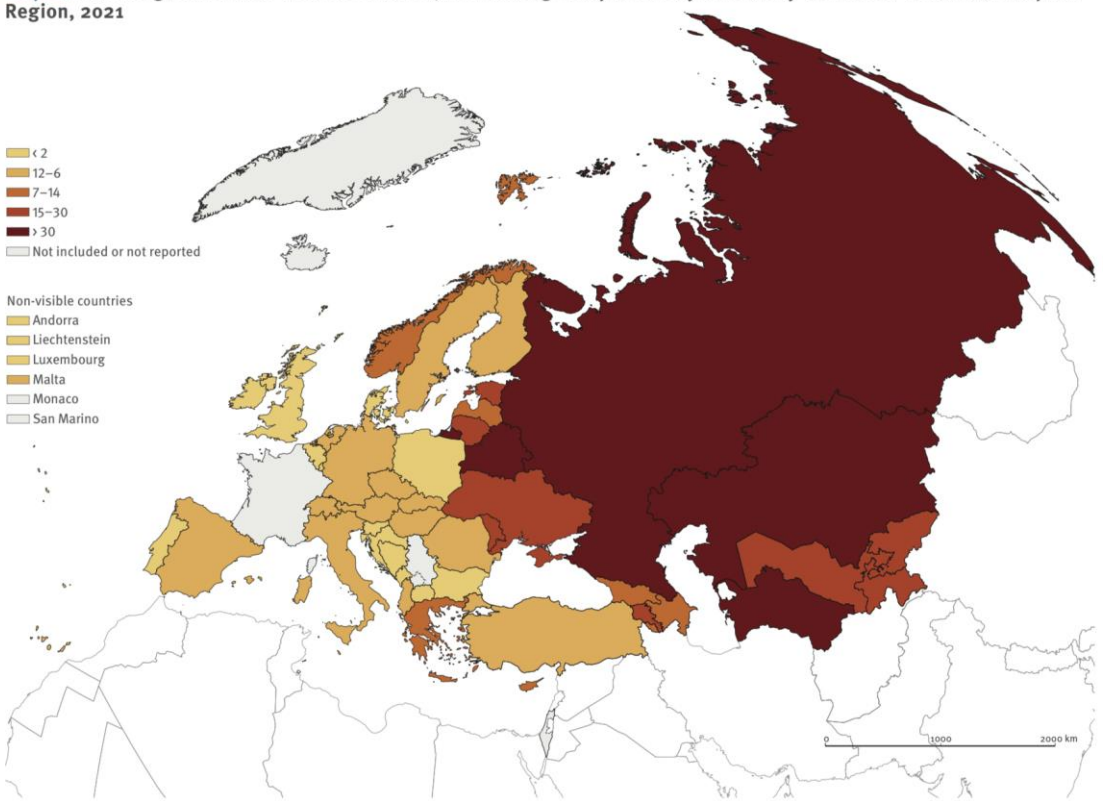


WHO Global TB Report 2022

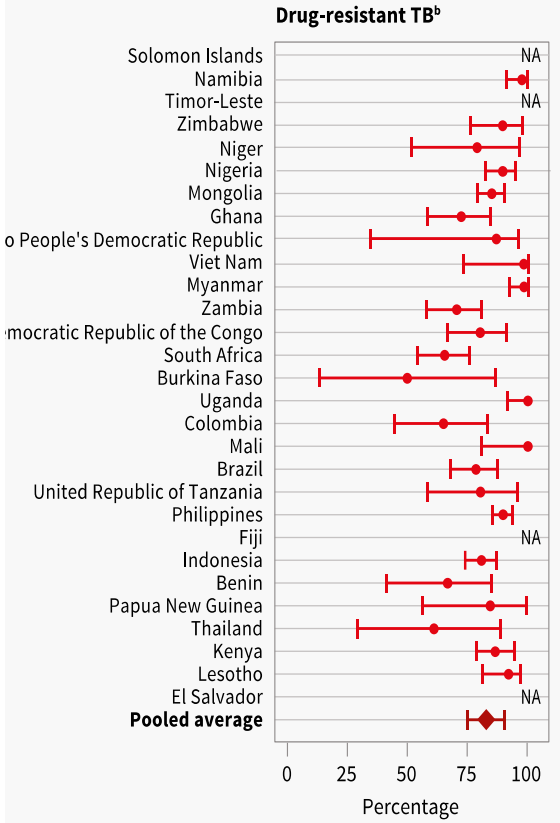
Global number of people diagnosed with MDR/RR-TB (blue) and number enrolled on an MDR-TB treatment regimen (red), compared with estimates of the global number of incident cases of MDR/RR-TB (95% uncertainty interval shown in green), 2015–2022[a]



Map 2. Percentage of notified TB cases with RR/MDR among new pulmonary laboratory-confirmed TB cases, European Region, 2021



Sources: 2021 data from the European Surveillance Systems (TESSy) and 2021 data from the WHO global TB data-collection system. Map production: ©ECDC.



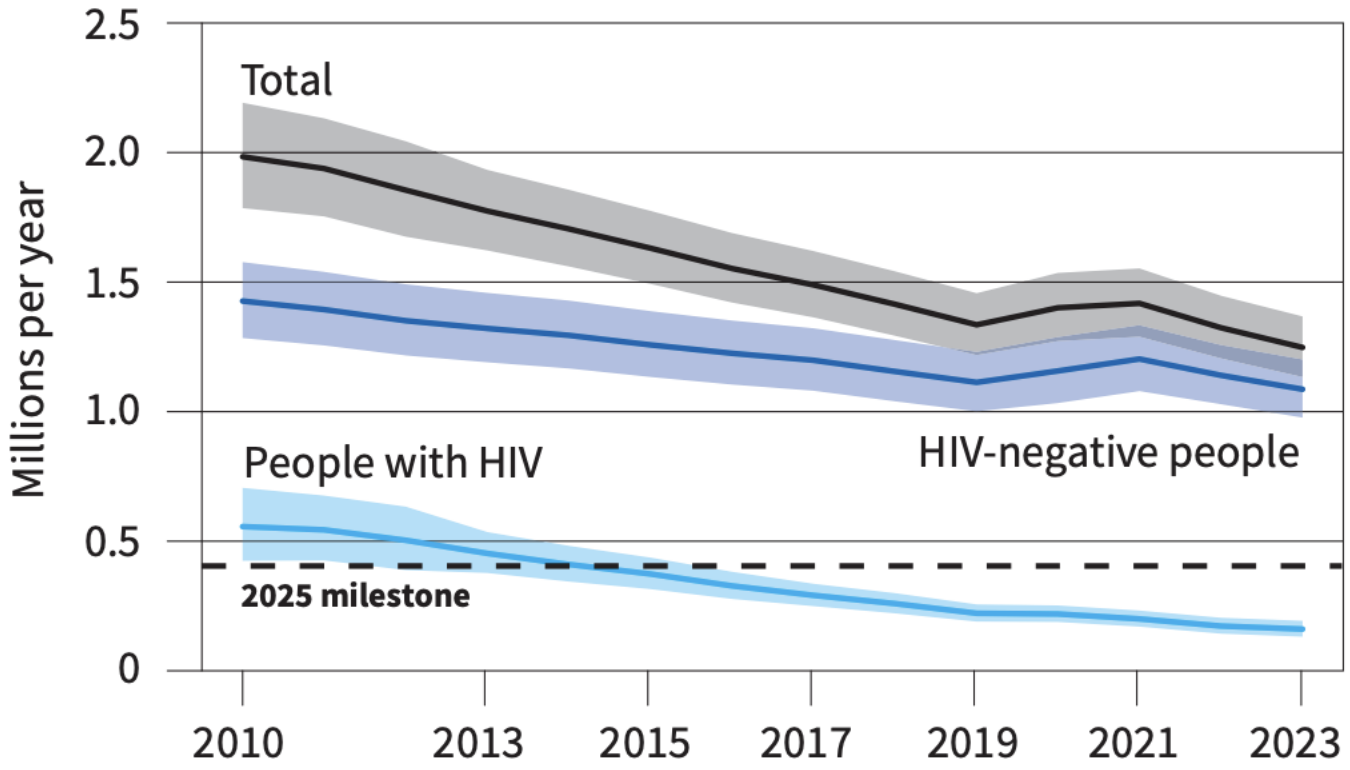
Estimates of the percentage of TB patients and their households facing catastrophic total costs,a national surveys completed 2015–2022


SANTUARIO MARIANO DI MONTE GRISA - TRIESTE
TV2000
DIRETTA

Critical group

- Enterobacterales, carbapenem-resistant
- Enterobacterales, third-generation cephalosporin-resistant
- *Acinetobacter baumannii*, carbapenem-resistant
- *Mycobacterium tuberculosis*, rifampicin-resistant[a]

[a]RR-TB was included after an independent analysis with parallel criteria and subsequent application of an adapted MCDA matrix.



TB caused an estimated 1.25 million deaths in 2023 (95% UI: 1.13–1.37 million) with 160000 deaths due to DR-TB

WHO Bacterial Priority Pathogens List, 2024; Global tuberculosis report 2024. Geneva: World Health Organization 2024

In Italia

Non ci sono dati certi

Le stime ci dicono che i nuovi casi DR ogni anno si aggirano sui 70/80 casi

Apparentemente in linea con i dati internazionali del 3%

Stop TB sta producendo, se riuscirà a superare gli ostacoli dei comitati etici, un registro che ci consentirà di valutare meglio epidemiologia e outcome

Di fatto è una malattia rara, e come tale andrebbe trattata...

Articles

Open Access

First tuberculosis cases in Italy resistant to all tested drugs

G B Migliori , G De Iaco , G Besozzi , R Centis , D M Cirillo

Hide Citation

Citation style for this article: Migliori G B, De Iaco G, Besozzi G, Centis R, Cirillo D M. First tuberculosis cases in Italy resistant to all tested drugs. Euro Surveill. 2007;12(20):pii=3194. https://doi.org/10.2807/esw.12.20.03194-en

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Extensively Drug Resistant Tuberculosis (XDR-TB) is a very serious form of TB against which our treatment weapons have lost the majority of, if not all, their power

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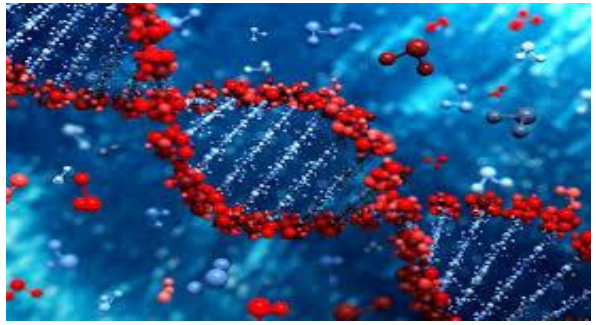
Anni '60

Terreno L J

Anni '80

Bactec

Anno 1991



PCR

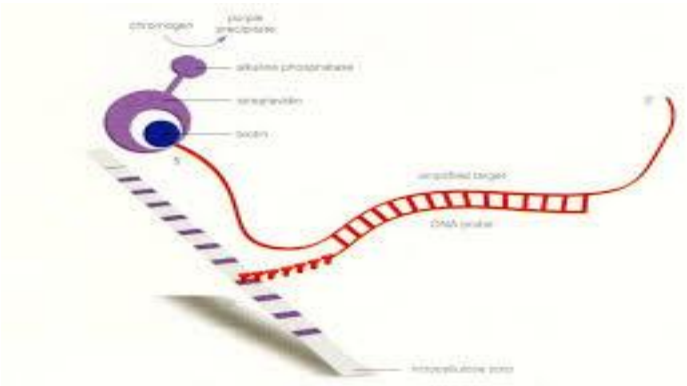
Anni '90

Migit

Anni 2000

Xpert

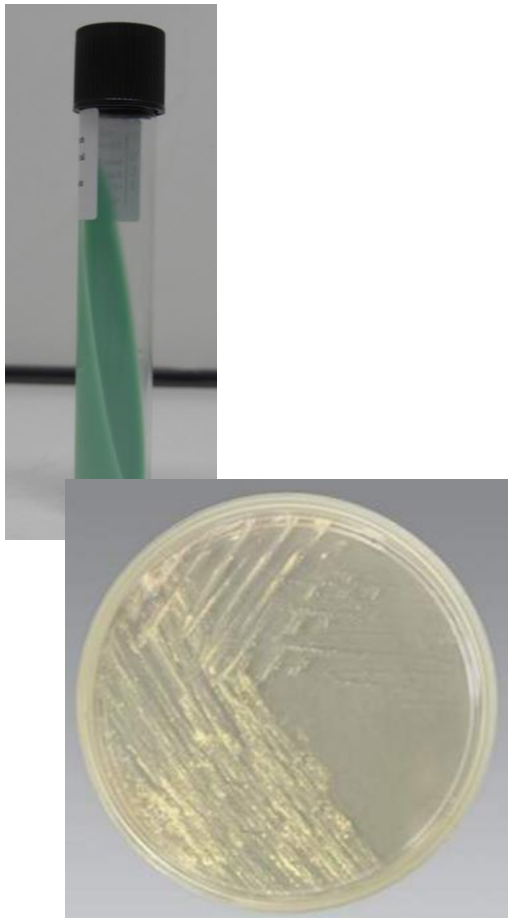
Oggi



Sequenziamento

Culture-based technologies

Solid Media



- Types most commonly used are:
  - Lowenstein-Jensen: egg-based
  - Middlebrook 7H10 or 7H11: agar based
  - Ogawa

- Low cost for reagents, not automated
- Culture level infrastructure
- Low contamination rate
- Long time to positivity
- Colony morphology
- ID required
- DST only for selected drugs

Culture-based technologies

Liquid Media

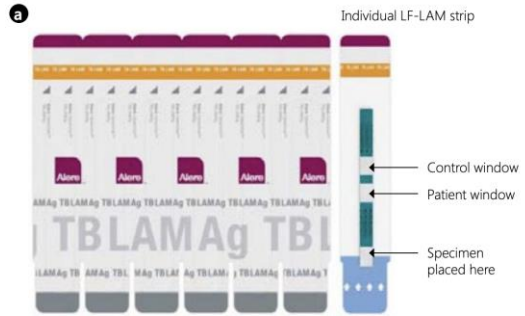
MGIT 960

- Complex and expensive can be automated (MGIT)
- Highest infrastructure and biosafety levels
- Case finding increased 10% over solid
- Diagnostic delay reduced to days (primary culture: mean of 14 days)
- ID required
- DST only for selected drugs

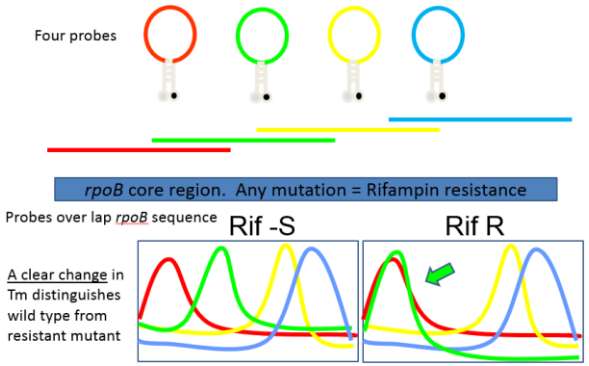
TB diagnostic test

Point-of-care biomarker-based tests that do not require sputum

ALERE TB LAM/SILVAMP



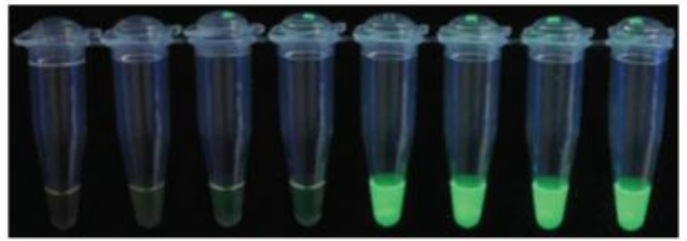
Xpert MTB/RIF Ultra
Xpert XDR-TB



Molbio

Tests to replace smear microscopy as the initial TB diagnostic test

TB LAMP



TB diagnostic test

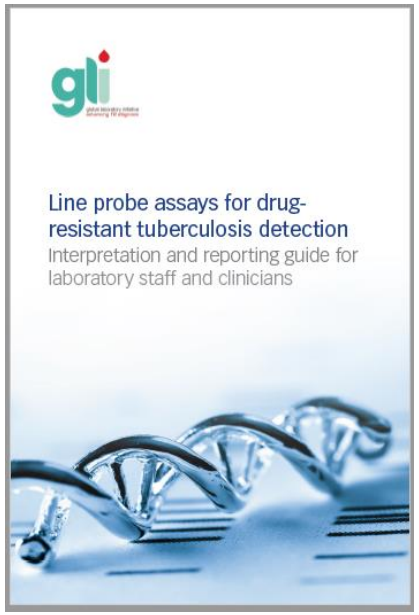
Next-generation DST to inform TB treatment

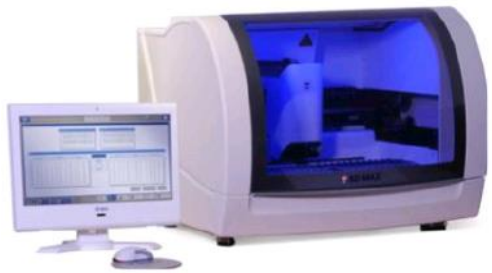
FluoroType® MTB and MTBDR assays; Hain Lifescience

Abbott Molecular RealTi*me MTB; (WHO approved)*

COBAS TaqMan RT-PCR (WHO Approved)

LPA





BD MAX™ platform; Becton Dickinson (WHO approved)

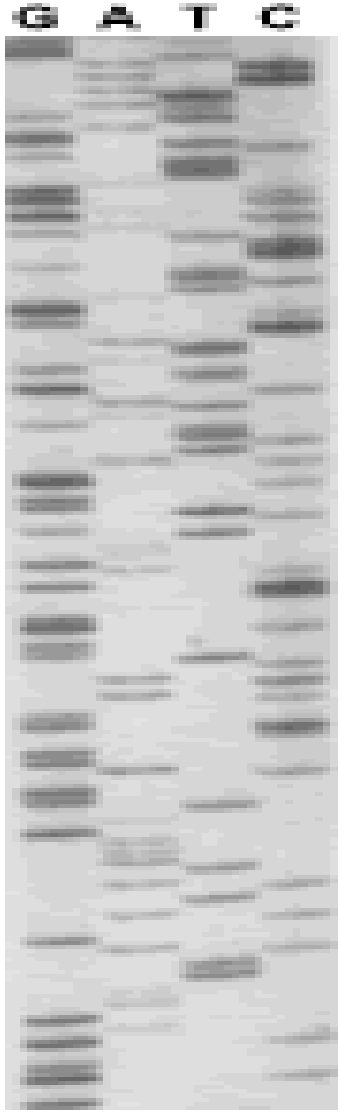
Ultimate TB diagnostic tool: whole genome sequencing

WGS Applications

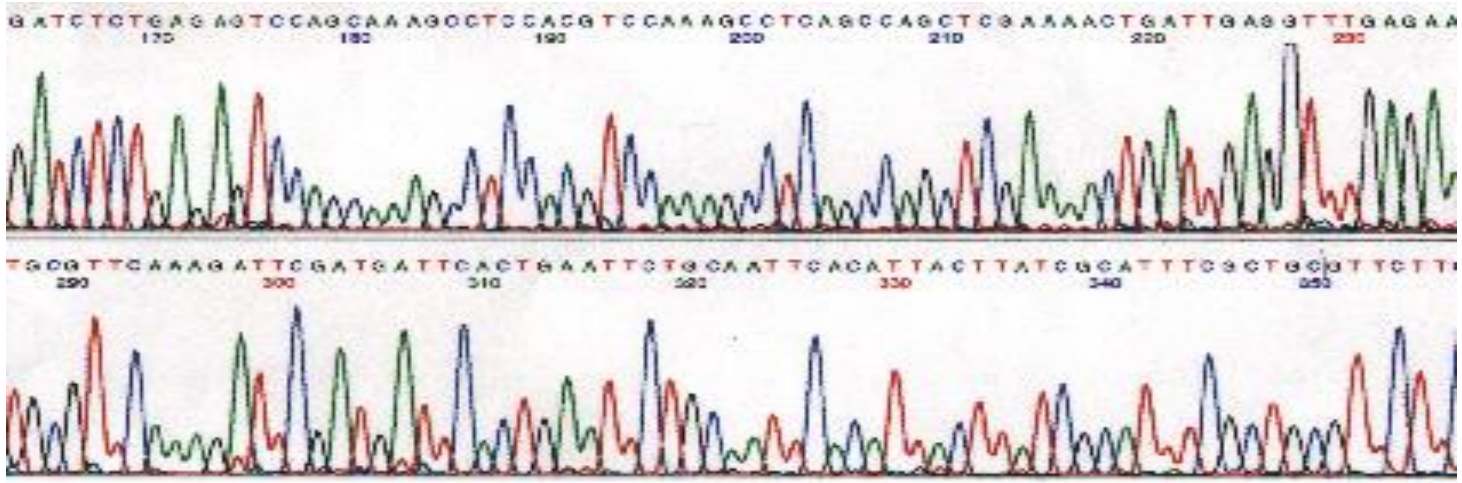
- **Multi-purpose assay**
- Genetic diversity: phylogenesis/epidemiology
  (Higher resolution, Directionality, Discriminatory capability (relapse *vs* re-infection...))
- Fast detection of phenotypic drug resistance
  (heterorestance, new DR-associated mutations, cross-resistance)
- Public health applications (DR/epidemiology surveillance)
- Cons:
  - Capital investment (infrastructure, personnel)
  - Biosafety
  - Cost-effectiveness only on multiplexing approach
  - No “one-fits-all” NGS technology available
  - Data analysis
  - Portability of data

Illumina Platform

Sequenziamento: “gold standard”



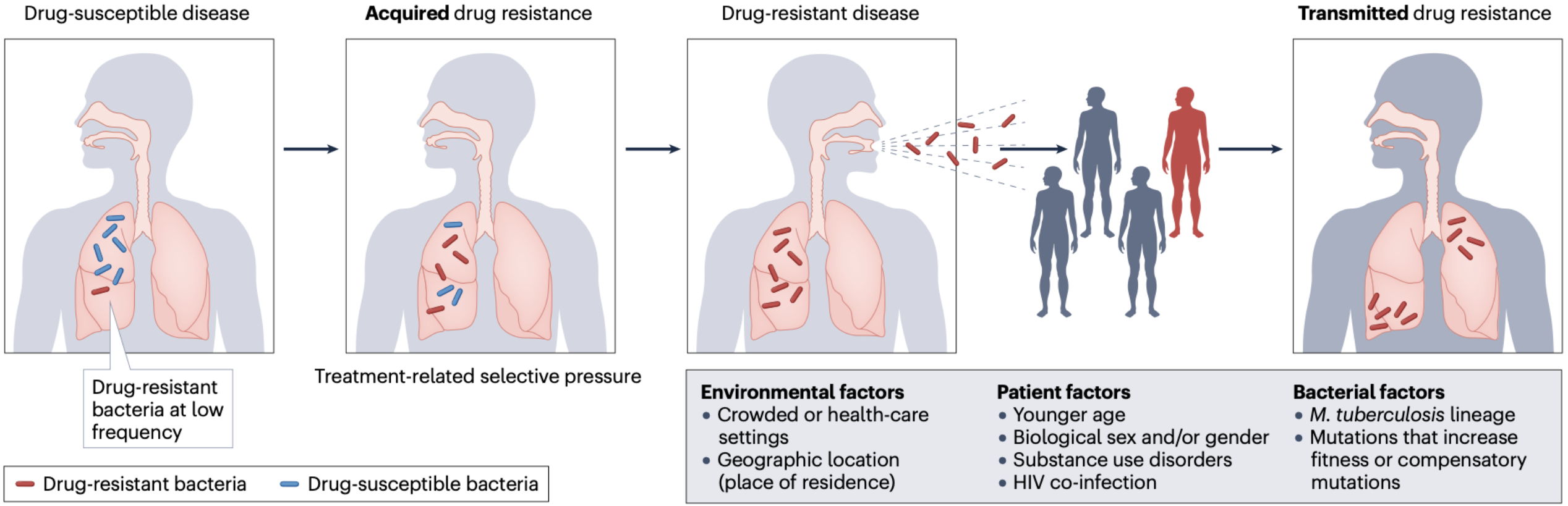
Permette di ottenere informazioni più precise e dettagliate sui geni in esame. Si basa sul principio della metodica di Sanger
(sintesi di una copia del filamento in esame con una reazione di polimerizzazione che si arresta in modo specifico per incorporazione di ddNTPs): gold standard per la determinazione e lo studio di mutazioni geniche



Oggi, in poche ore, sappiamo se il
BAAR che abbiamo visto al microscopio
è un micobatterio umano,
se è vivo,
se è resistente alla Rifampicina
e, a breve, a tutti
i farmaci di cui disponiamo

- Always test for RIFAMPICIN RESISTANCE.
- Always perform CULTURE with complete DST (genotypic and phenotypic) to YOUR reference laboratory.
- Send the culture for WGS in REGIONAL/NATIONAL reference laboratory.

RIGHT DIAGNOSIS FOR THE RIGHT TREATMENT



Farhat M, Nat Rev Microbiol. 2024 Oct;22(10):617-635.

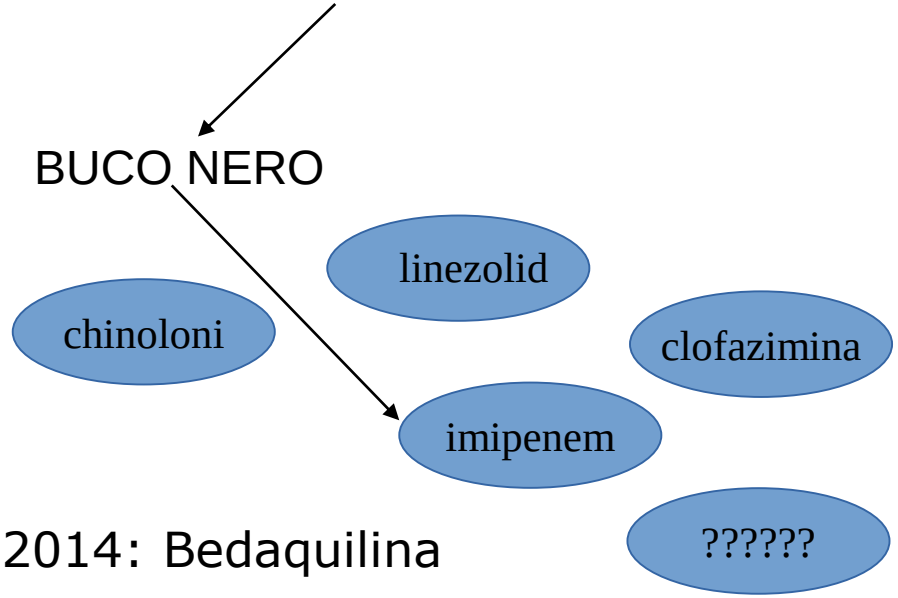
OUTLINE

- ✓ DEFINITION and GOALS
- ✓ EPIDEMIOLOGY (WHO REPORT 2024)
- ✓ DIAGNOSIS
- ➢ **TRATTAMENTO**
- **RUOLO DEI CENTRI DI RIFERIMENTO**

I farmaci

1944 streptomicina

1968 rifampicina



2014: Bedaquilina

2015: Delamanid

2020: Pretomanid

I nuovi farmaci

Bedaquilina, Delamanid, Pretomanid hanno cambiato la prognosi dei pazienti MDR

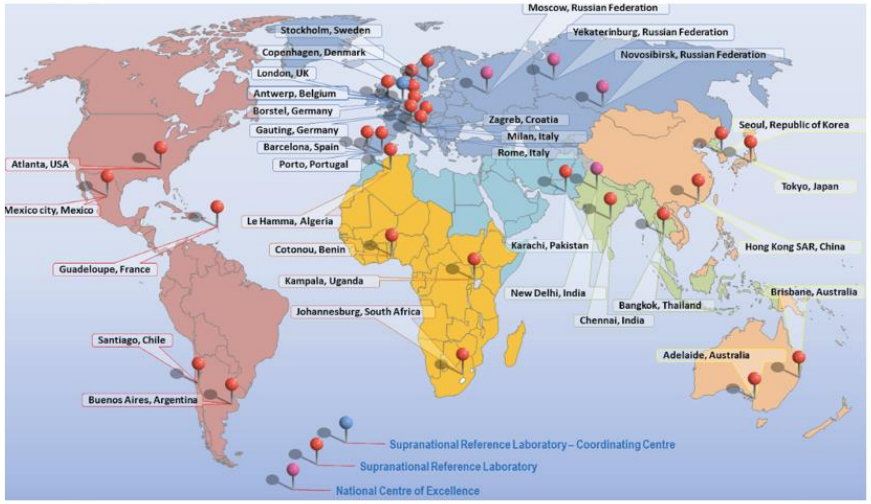
Hanno modificato l’approccio terapeutico ospedale- territorio

Hanno ridotto in modo drammatico i tempi di trattamento

Non devono sostituire gli aspetti “preventivi”

REFERENCE CENTRES FOR DIAGNOSIS and TREATMENT

"Laboratories are not just technologies, equipment and buildings; they are people and systems that manage the processes and standards required to produce accurate and timely results".



Bulletin of the World Health Organization

DR-TB

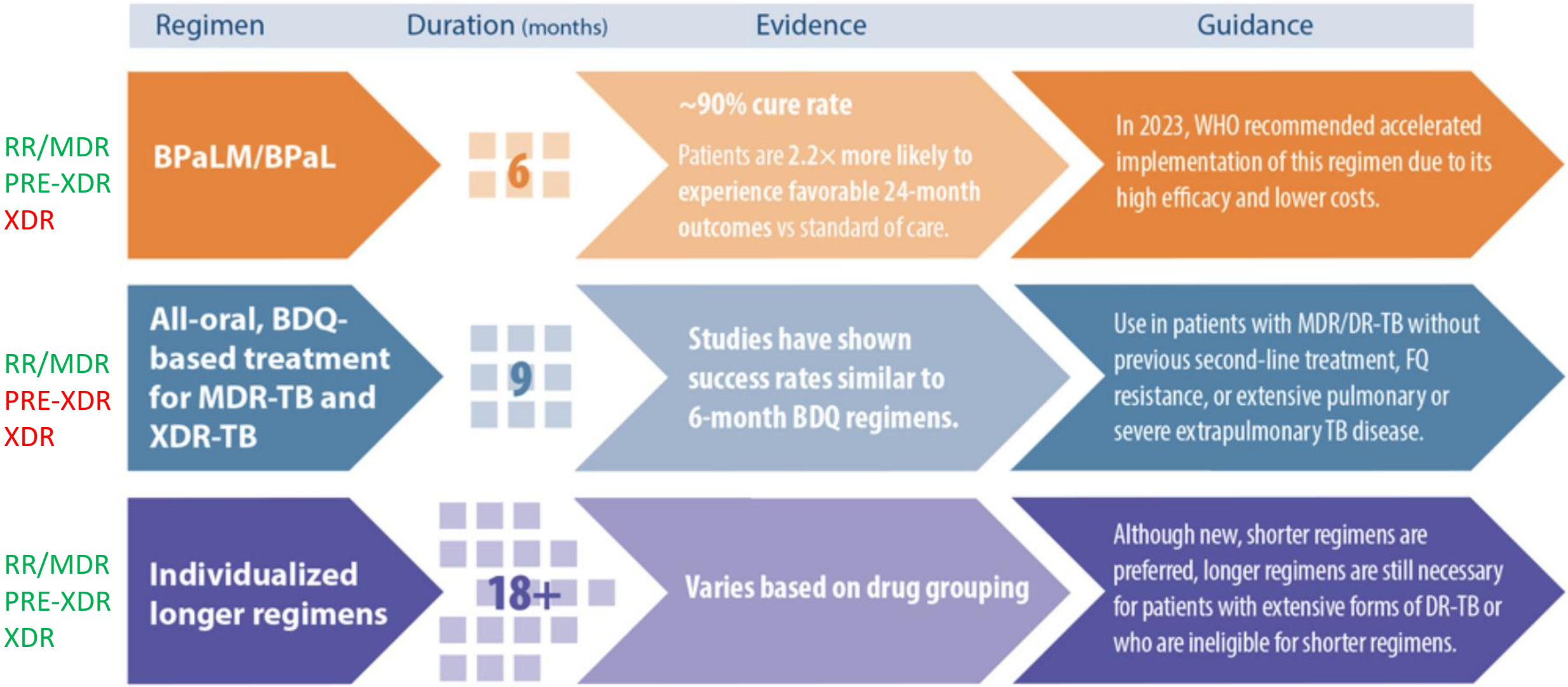
1. Consultation should be requested with a TB expert when there is suspicion of or confirmation of DR-TB. In the United States, TB experts can be found through CDC-supported TB Centers of Excellence for Training, Education, and Medical Consultation (http://www.cdc.gov/tb/education/rtmc/default.htm), through local health department TB control programs (https://www.cdc.gov/tb/links/tboffices.htm), and through international MDR-TB expert groups such as the Global TB Network (6).

AMERICAN THORACIC SOCIETY DOCUMENTS

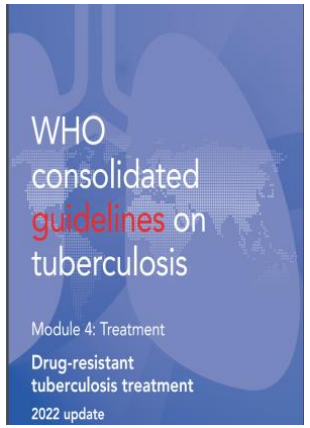
Treatment of Drug-Resistant Tuberculosis
An Official ATS/CDC/ERS/IDSA Clinical Practice Guideline

Payam Nahid, Sundari R. Mase, Giovanni Battista Migliori, Giovanni Sotgiu, Graham H. Bothamley, Jan L. Brozek, Adithya Cattamanchi, J. Peter Cegielski, Lisa Chen, Charles L. Daley, Tracy L. Dalton, Raquel Duarte, Federica Fregonese, C. Robert Horsburgh, Jr., Faiz Ahmad Khan, Fayez Kheir, Zhiyi Lan, Alfred Lardizabal, Michael Lauzardo, Joan M. Mangan, Suzanne M. Marks, Lindsay McKenna, Dick Menzies, Carole D. Mitnick, Diana M. Nilsen, Farah Parvez, Charles A. Peloquin, Ann Raftery, H. Simon Schaaf, Neha S. Shah, Jeffrey R. Starke, John W. Wilson, Jonathan M. Wortham, Terence Chorba, and Barbara Seaworth; on behalf of the American Thoracic Society, U.S. Centers for Disease Control and Prevention, European Respiratory Society, and Infectious Diseases Society of America

This official clinical practice guideline was approved by the American Thoracic Society, the European Respiratory Society, and the Infectious Diseases Society of America September 2019, and was cleared by the U.S. Centers for Disease Control and Prevention September 2019


Regimen
Duration (months)
Evidence
Guidance
RR/MDR
PRE-XDR
XDR
BPaLM/BPaL
6
~90% cure rate
Patients are 2.2× more likely to experience favorable 24-month outcomes vs standard of care.
In 2023, WHO recommended accelerated implementation of this regimen due to its high efficacy and lower costs.
RR/MDR
PRE-XDR
XDR
All-oral, BDQ-based treatment for MDR-TB and XDR-TB
9
Studies have shown success rates similar to 6-month BDQ regimens.
Use in patients with MDR/DR-TB without previous second-line treatment, FQ resistance, or extensive pulmonary or severe extrapulmonary TB disease.
RR/MDR
PRE-XDR
XDR
Individualized longer regimens
18+
Varies based on drug grouping
Although new, shorter regimens are preferred, longer regimens are still necessary for patients with extensive forms of DR-TB or who are ineligible for shorter regimens.

BPaLM / BPaL



Drug susceptibility testing (DST) for fluoroquinolones is strongly encouraged in people with MDR/RR-TB, and although it should not delay initiation of the BPaLM, results of the test should guide the decision on whether moxifloxacin can be retained or should be dropped from the regimen – in cases of documented resistance to fluoroquinolones, BPaL without moxifloxacin would be initiated or continued.

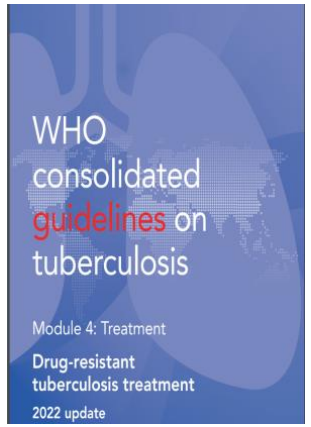
Regimen	MDR/RR-TB fluoroquinolone susceptible	Pre-XDR-TB	XDR-TB	Extensive pulmonary TB	Extrapulmonary TB	Age <14 years
6-month BPaLM/BPaL	Yes (BPaLM)	Yes (BPaL)	No	Yes	Yes – except TB involving CNS, miliary TB and osteoarticular TB	No

- ❑ Bedaquiline (4 tablets 100 mg die for the first 14 days, 2 tablets 100 mg 3 times per week from the day 15)

- ❑ Pretomanid (1 tablet 200 mg die) full stomach
- ❑ Linezolid (1 tablet 600 mg die)

- ❑ Moxifloxacin (1 tablet 400 mg die)

- **All patients with MDR/RR-TB**, including those with additional resistance to fluoroquinolones, stand to benefit from effective all-oral treatment regimens.



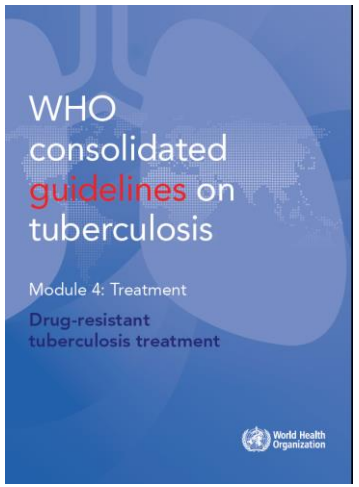
- treatment duration of BPaLM to 6 months (26 weeks) during programmatic implementation;
- for BPaL possibility of extension to a total of 9 months (39 weeks) if sputum cultures are positive between months 4 and 6. All medicines in the regimen are to be used throughout treatment duration, including a potential extension from 26 to 39 weeks (when BPaL is used).
- Ideally, missing doses of all three or four drugs in the regimen should be avoided; however, if doses are missed, any interruption of longer than 7 days should be made up by extending the treatment duration (for the number of missed doses);
- therefore, 26 or 39 weeks of prescribed doses should be completed within an overall period of 7 or 10 months, respectively

SHORT REGIMEN 9-12 MONTHS

The regimen can be summarized as: **4–6 $Bdq_{(6\ m)}$ -Lfx-Cfz-Z-E-Hh-Eto / 5 Lfx-Cfz-Z-E**

Initial phase: **4–6 $Bdq_{(6\ m)}$-Lfx-Cfz-Z-E-Hh-Eto**

Continuation phase: **5 Lfx-Cfz-Z-E**



Main recommendation 2019 vs 2022

4–6 (**Km**)–Mfx–Cfz–(**Eto**)–Z–E–Hh/5Mfx–Cfz–Z–E

BQ **LZD**

Remarks

1. The 9-month all-oral regimen consists of bedaquiline (used for 6 months), in combination with levofloxacin/moxifloxacin, ethionamide, ethambutol, isoniazid (high-dose), pyrazinamide and clofazimine (for 4 months, with the possibility of extending to 6 months if the patient remains sputum smear positive at the end of 4 months), followed by treatment with levofloxacin/ moxifloxacin, clofazimine, ethambutol and pyrazinamide (for 5 months). Ethionamide can be replaced by 2 months of linezolid (600 mg daily).
2. A 9-month regimen with linezolid instead of ethionamide may be used in pregnant women, unlike the regimen with ethionamide.
3. This recommendation applies to:
   a. people with MDR/RR-TB and without resistance to fluoroquinolones;
   b. patients without extensive TB disease[22] and without severe extrapulmonary TB;[23]
   c. patients with less than 1 month exposure to bedaquiline, fluoroquinolones, ethionamide, linezolid and clofazimine; when exposure is greater than 1 month, these patients may still receive this regimen if resistance to the specific medicines with such exposure has been ruled out;
   d. all people regardless of HIV status;
   e. children (and patients in other age groups) who do not have bacteriological confirmation of TB or resistance patterns but who do have a high likelihood of MDR/RR-TB (based on clinical signs and symptoms of TB, in combination with a history of contact with a patient with confirmed MDR/RR-TB).

SHORT REGIMEN 9-12 MONTHS

- Bedaquiline (4 tablets 100 mg die for the first 14 days, 2 tablets 100 mg 3 times per week from the day 15)
- Moxifloxacin (1 tablet 400 mg die)
- Clofazimine (1 tablet 100 mg die)
- Linezolid (1 tablet 600 mg die)
- Pyrazinamide (20-30 mg/Kg die)
- Ethambutol (20 mg/Kg die)
- HD-Isoniazid (10-15 mg/Kg die)

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I centri di riferimento

La rarità delle forme DR/TB impone la concentrazione dei casi in pochi centri identificati e riconosciuti

La possibilità di terapie solo orali ha superato l'ipotesi di creare strutture simil-sanatoriali per la cura e l'isolamento di questi pazienti

I centri di riferimento

Devono avere un laboratorio di terzo livello, con personale qualificato e strumentazione d'avanguardia

Devono disporre di tutti i farmaci e avere possibilità di rapido approvvigionamento

Devono avere riconoscimento formale ministeriale e riconoscimento economico regionale

Devono fare diagnosi e terapia

Devono insegnare

Devono fare consulenza di laboratorio, clinica ed epidemiologica agli altri centri antitubercolari

INT J TUBERC LUNG DIS 27(5):381–386

http://dx.doi.org/10.5588/ijtld.22.0536

Primary bedaquiline resistance in Karakalpakstan, Uzbekistan

S. Moe,[1] M. L. Rekart,[1] D. Hernandez,[1] A. Sholpan,[1] A. Ismailov,[1] M. Oluya,[1] A. Bayniyazova,[1] T. Zinaida,[2] P. Nargiza,[3] C. Gomez-Restrepo,[4] N. Sitali,[5] A. Sinha[6]

[1]Medecins Sans Frontières, Karakalpakstan, [2]Republican Center of Tuberculosis and Pulmonology, Nukus, [3]Republican Specialized Scientific and Practical Medical Center of Tuberculosis and Pulmonology, Tashkent, [4]Medecins Sans Frontières (MSF), Tashkent, Uzbekistan; [5]MSF, Berlin, Germany; [6]MSF, London, UK

SUMMARY

BACKGROUND: Bedaquiline (BDQ) is widely used in the treatment of rifampicin-resistant TB (RR-TB). However, resistance to BDQ is now emerging. There are no standardised regimens for BDQ-resistant TB. This study aims to share experience in managing primary BDQ-resistant TB.

METHODS: We performed a retrospective study of patients treated for RR-TB in Karakalpakstan, Uzbekistan, from January 2017 to March 2022. We identified patients with resistance to BDQ with no history of BDQ exposure. We describe baseline characteristics, treatment and follow-up of these patients.

RESULTS: Twelve of the 1,930 patients (0.6%) had baseline samples resistant to BDQ with no history of BDQ exposure, 75% (9/12) of whom had been previously treated for TB. Ten (83.3%) were resistant to fluoroquinolones; respectively 66% and 50% had culture conversion by Month 3 and Month 6. The interim treatment outcomes were as follows: unfavourable treatment outcomes (3/12, 25%), favourable outcomes (2/12, 17%); the remaining seven (58%) were continuing treatment.

CONCLUSIONS: A large proportion of the cases had previously been treated for TB and had TB resistant to quinolone. Both patients who had not experienced culture conversion by Month 3 had an unfavourable treatment outcome. Therefore, we recommend monthly monitoring of culture status for patients on treatment regimens for BDQ resistance.

KEY WORDS: XDR-TB; DR-TB treatment; Class A TB drugs; BDQ-resistant TB; Central Asia

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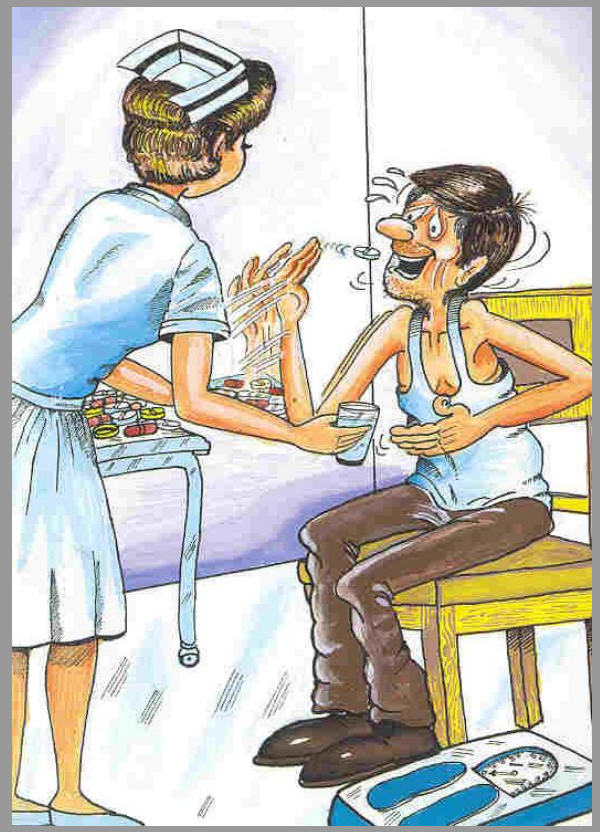


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