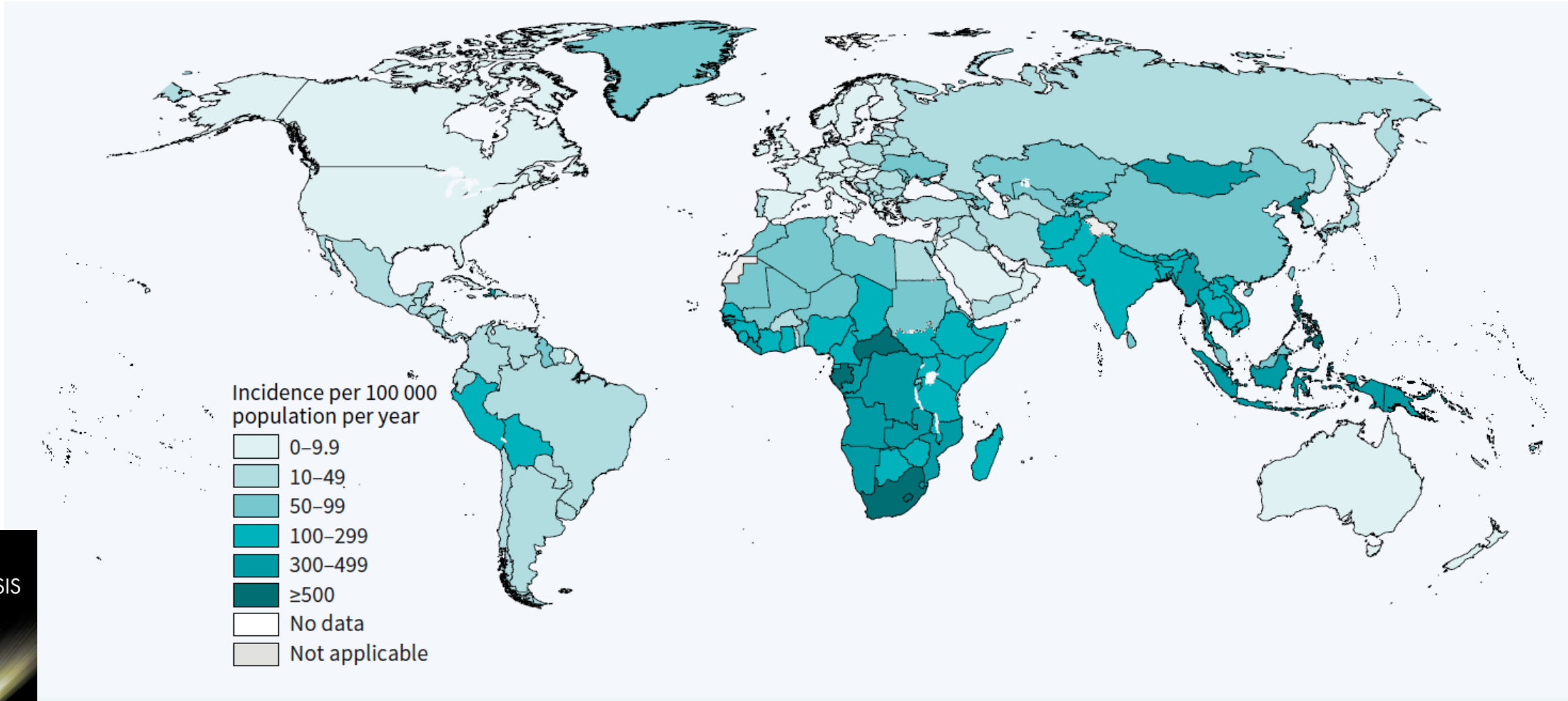
TUBERCULOSI MULTIRESISTENT

Assaigs clínics i reptes diagnòstics

Guies de maneig i tractament

fsanchezmartinez@psmar.cat

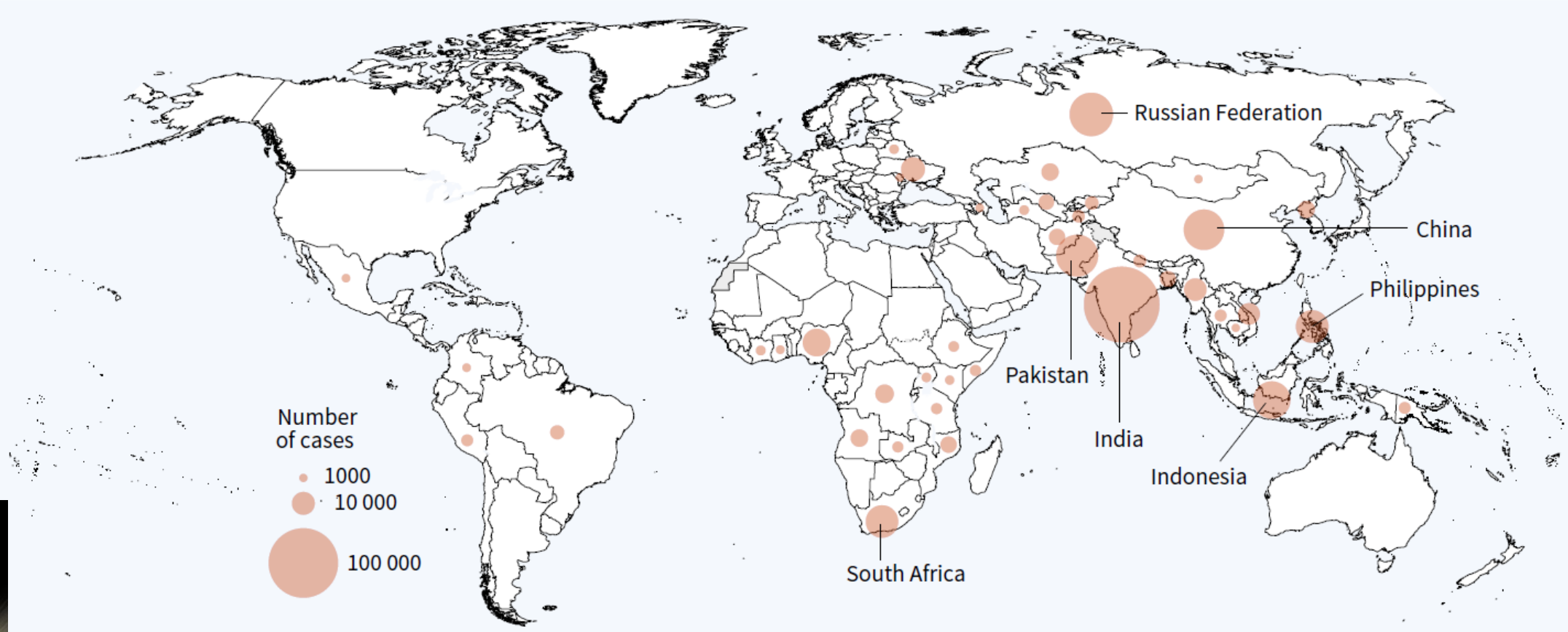
Estimated TB incidence rates, 2021



GLOBAL TUBERCULOSIS REPORT 2022

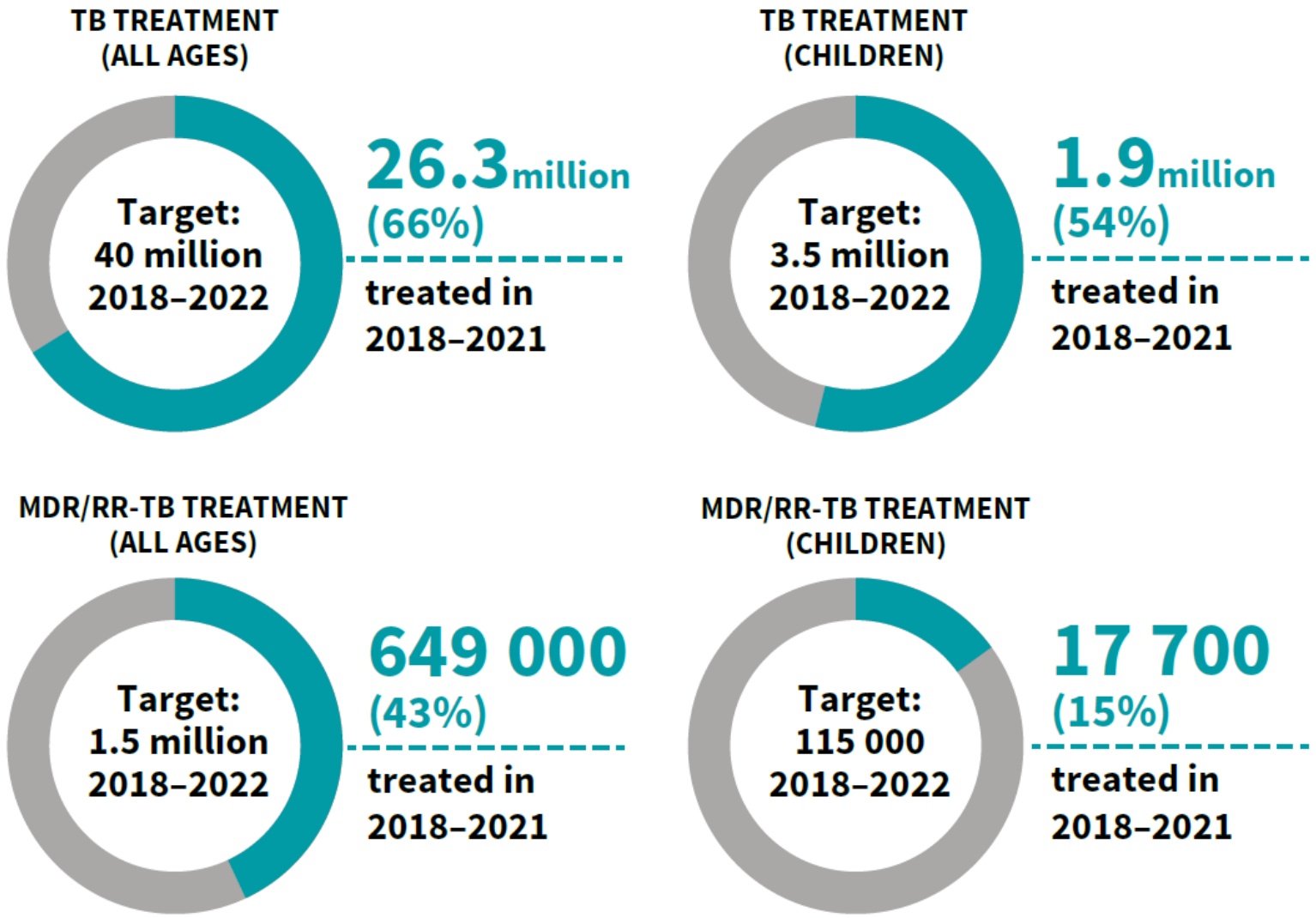
Estimated incidence of MDR/RR-TB in 2021, for countries with at least 1000 incident cases

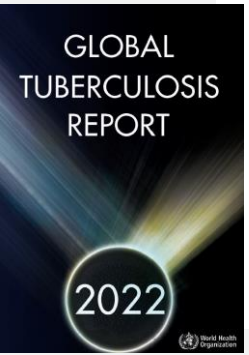
The seven countries with the highest burden in terms of numbers of MDR/RR-TB cases, and that accounted for two thirds of global MDR/RR-TB cases in 2021, are labelled.



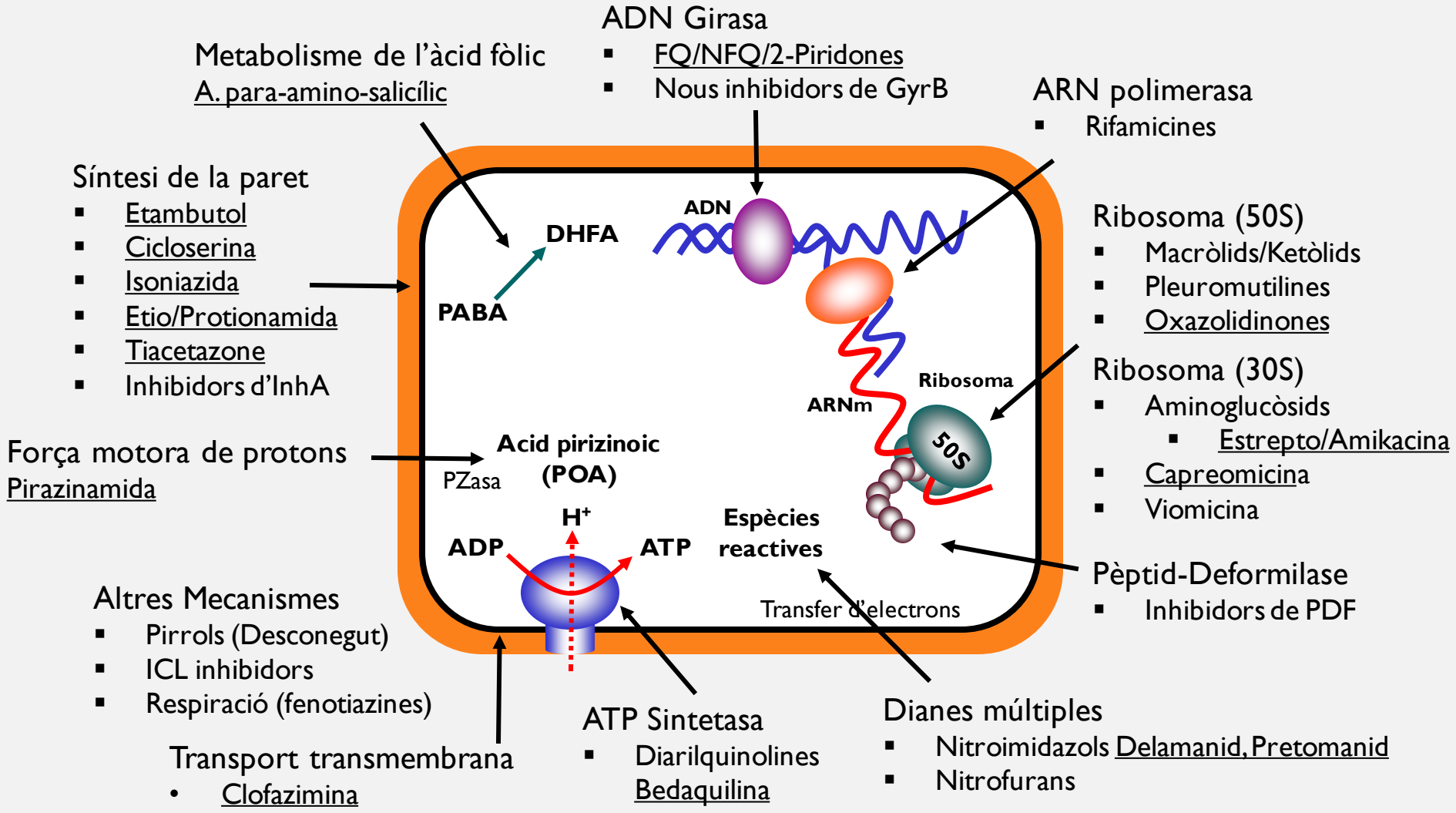
GLOBAL TUBERCULOSIS REPORT 2022

Global progress in the number of people treated for TB between 2018 and 2021, compared with cumulative targets set for 2018–2022 at the UN high-level meeting on TB





Fàrmacs antiTB MDR: dianes i mecanismes d'acció



MUTACIONS NATURALS I RESISTÈNCIA ADQUIRIDA

Fàrmac	Gen	Mecanisme de resistència	Tasa de mutació natural
Isoniazida	KatG	Inhibeix catalasa-peroxidasa (àc micòlic)	$1x10^{6}$
	inhA	Síntesi de enoil ACP reductasa (àc grasos)	
Rifampicina	rpoB	Subunitat β d'ARN polimerasa (replicació)	$1x10^{8}$
Pirazinamida	pncA	Pirazinaminidasa (pH)	$1x10^{3}$
Estreptomicina	rpsL	Subunitat ribosomal S12 (síntesi proteica)	$1x10^{6}$
	rrS	ARNr 16S (sínt. prot.)	
Etambutol	embB	Arabinosiltransferasa (paret celular)	$1x10^{6}$
Levofloxacino	GyrA	ADN Girasa (replicació)	$1x10^{6}$

- Mutacions cromosòmiques de la diana farmacològica induides durant el tractament, afavorides per
  - Durada
  - Mala adherència o situacions de desproveiment
  - Utilitzar tractaments ineficaços o dosis insuficients
- Les soques amb resistència adquirida són transmissibles.
- Les mutacions no són reversibles.

Mitchison DA. What is drug resistance? Tubercle 1969; 50: 44-47.
Mitchison DA. The action of antituberculosis drug in short-course chemotherapy. Tubercle 1985; 66: 219-225.
Mitchison DA, Nunn AJ. Influence of initial drug resistance on the response to short-course chemotherapy of pulmonary tuberculosis. Am Rev Respir Dis 1986; 133: 423-430.

J Antimicrob Chemother 2018; **73**: 1138–1151
doi:10.1093/jac/dkx506 Advance Access publication 19 January 2018

Journal of Antimicrobial Chemotherapy

Evolution of drug resistance in *Mycobacterium tuberculosis*: a review on the molecular determinants of resistance and implications for personalized care

Navisha Dookie[1]*, Santhuri Rambaran[1], Nesri Padayatchi[1,2], Sharana Mahomed[1] and Kogieleum Naidoo[1,2]

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy

Mutations in *pepQ* Confer Low-Level Resistance to Bedaquiline and Clofazimine in *Mycobacterium tuberculosis*

Antimicrob. Agents Chemother. August 2016 60:8 4590–4599; Accepted manuscript posted online 16 May 2016,

Published in final edited form as:

N Engl J Med. 2015 November 12; 373(20): 1986–1988. doi:10.1056/NEJMc1505196.

Acquired Resistance to Bedaquiline and Delamanid in Therapy for Tuberculosis

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Sebastien Gagneux, Ph.D., and
Swiss Tropical and Public Health Institute, Basel, Switzerland

Erik C. Böttger, M.D.
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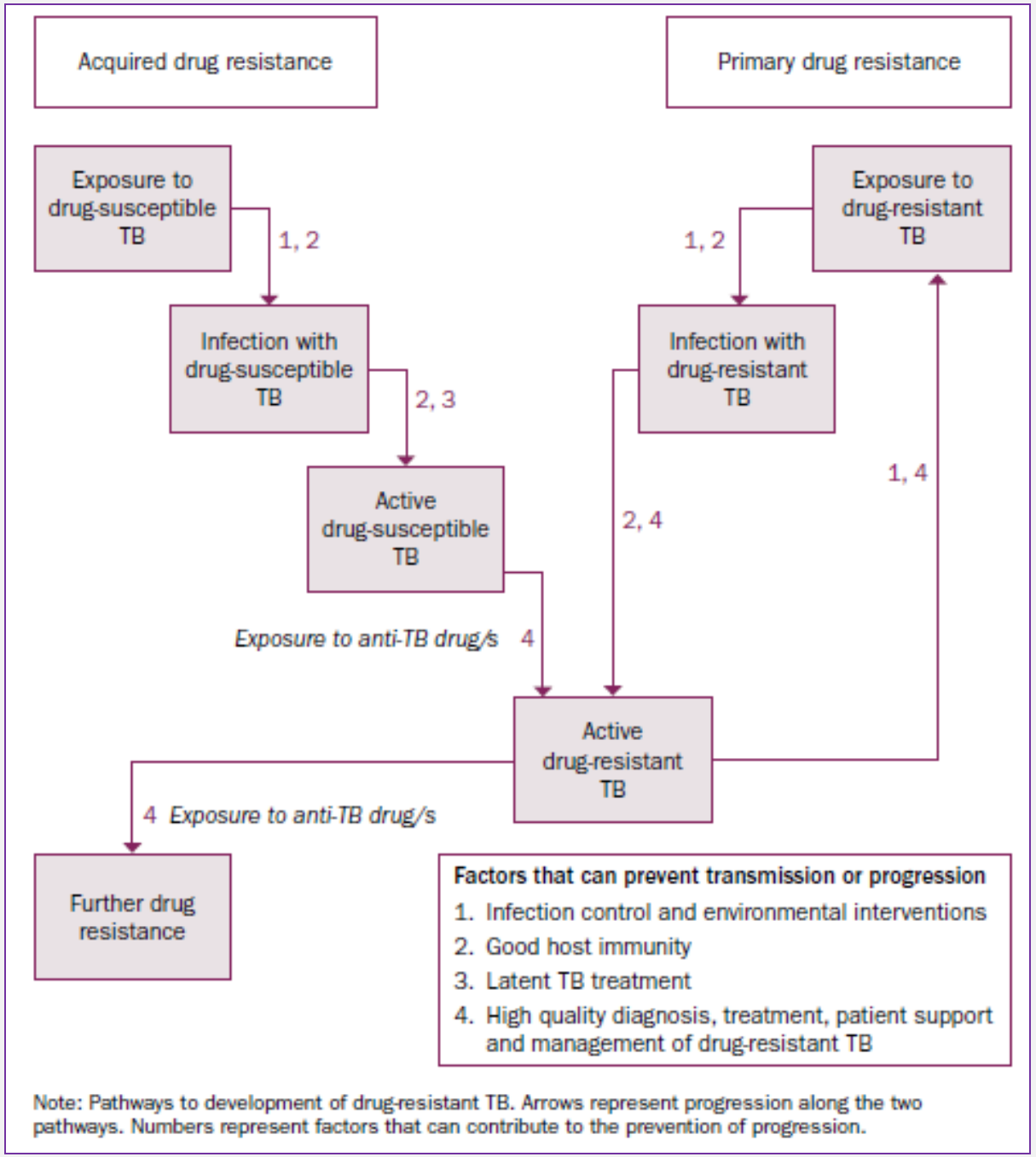


Note: Pathways to development of drug-resistant TB. Arrows represent progression along the two pathways. Numbers represent factors that can contribute to the prevention of progression.

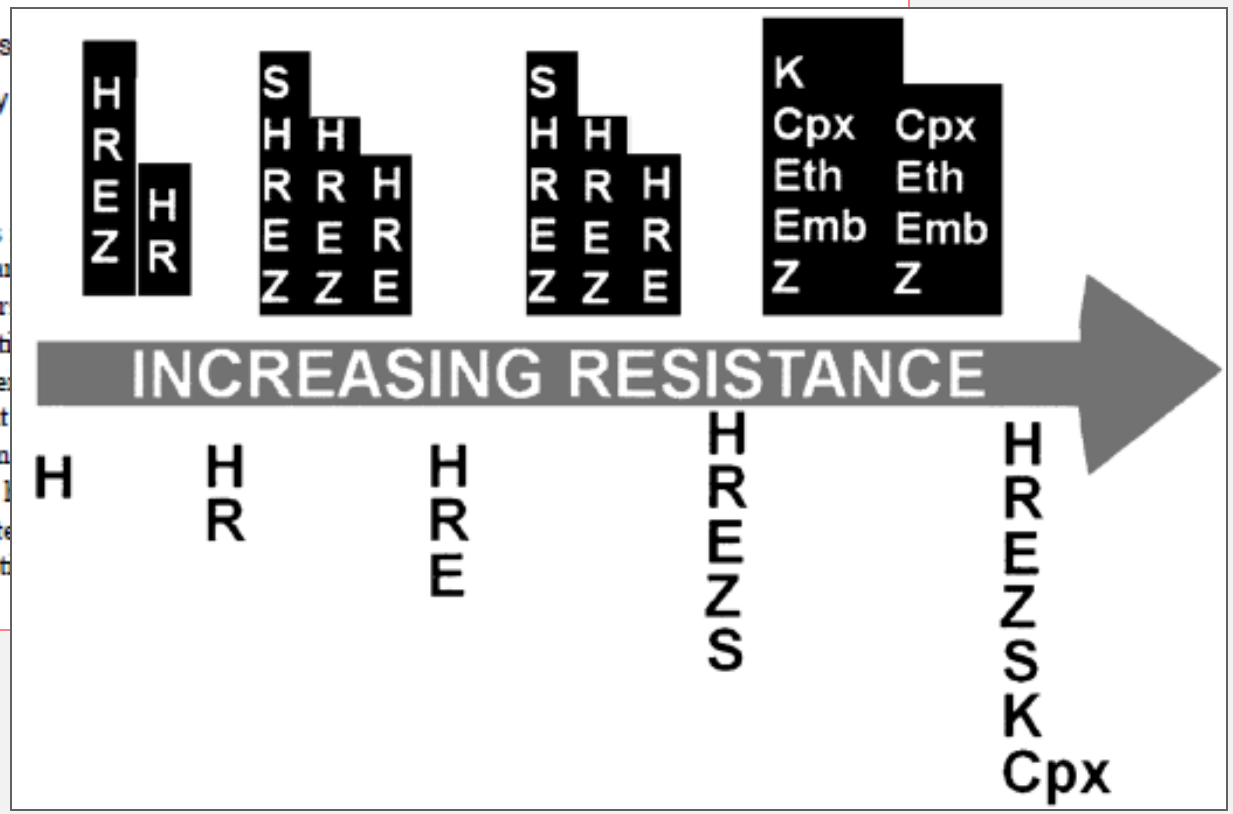
Published in final edited form as:
Semin Respir Crit Care Med. 2008 October ; 29(5): 499–524. doi:10.1055/s-0028-1085702.

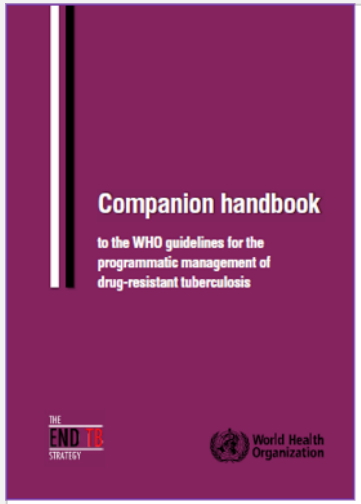
Epidemiology and Treatment of Multidrug Resistant Tuberculosis

Carole D. Mitnick, Sc.D.[1], **Sasha C. Appleton, Sc.M.**[2], and **Sonya S. Shin, M.D., M.P.H.**[3]
[1] Department of Global Health and Social Medicine, Harvard Medical School, Boston, Massachusetts;
[2] Partners In Health, Boston, Mas
[3] Division of Global Health Equity

Abstract

Multidrug resistant tuberculosis
Although significant regional va
data are limited by several factor
the estimated burden is substanti
possible, but all appropriate inte
regimens containing a sufficient
patients, and improved infection
transmission. Several obstacles
mostly attributable to inadequate
however, risk continued generat
morbidity and mortality.





GROUP	DESCRIPTION	DRUG	ABBREVIATION
1	First-line oral anti-TB drugs	Isoniazid	H
		Rifampicin	R
		Ethambutol	E
		Pyrazinamide	Z
		Rifabutin	Rfb
		Rifapentine	Rpt
2	Injectable anti-TB drugs (injectable agents or parenteral agents)	Streptomycin	S
		Kanamycin	Km
		Amikacin	Am
		Capreomycin	Cm
3	Fluoroquinolones (FQs)	Levofloxacin	Lfx
		Moxifloxacin	Mfx
		Gatifloxacin	Gfx
		Ofloxacin	Ofx
4	Oral bacteriostatic second-line anti-TB drugs	Ethionamide	Eto
		Prothionamide	Pto
		Cycloserine	Cs
		Terizidone	Trd
		p-aminosalicylic acid	PAS
		p-aminosalicylate sodium	PAS-Na
5	Anti-TB drugs with limited data on efficacy and/or long-term safety in the treatment of drug-resistant TB (This group includes new anti-TB agents).	Bedaquiline	Bdq
		Delamanid	Dlm
		Linezolid	Lzd
		Clofazimine	Cfz
		Amoxicillin/Clavulanate	Amx/Clv
		Imipenem/Cilastatin	Ipm/Cln
		Meropenem	Mpm
		High-dose isoniazid	High dose H
		Thioacetazone	T
		Clarithromycin	Clr

WHO treatment

A. Fluoroquinolones[2]		Levofloxacin Moxifloxacin Gatifloxacin	Lfx Mfx Gfx
B. Second-line injectable agents		Amikacin Capreomycin Kanamycin (Streptomycin)[3]	Am Cm Km (S)
C. Other core second-line agents[2]		Ethionamide / Prothionamide Cycloserine / Terizidone Linezolid Clofazimine	Eto / Pto Cs / Trd Lzd Cfz
D. Add-on agents (not part of the core MDR-TB regimen)	D1	Pyrazinamide Ethambutol High-dose isoniazid	Z E H^h
	D2	Bedaquiline Delamanid	Bdq Dlm
	D3	*p*-aminosalicylic acid Imipenem-cilastatin[4] Meropenem[4] Amoxicillin-clavulanate[4] (Thioacetazone)[5]	PAS Ipm Mpm Amx-Clv (T)

[1] This regrouping is intended to guide the design of conventional regimens; for shorter regimens lasting 9-12 months the composition is usually standardised (See Section A)

[2] Medicines in Groups A and C are shown by decreasing order of usual preference for use (subject to other considerations; see text)

[3] Refer to the text for the conditions under which streptomycin may substitute other injectable agents. Resistance to streptomycin alone does not qualify for the definition of extensively drug-resistant TB (XDR-TB)(26)

[4] Carbapenems and clavulanate are meant to be used together; clavulanate is only available in formulations combined with amoxicillin

[5] HIV-status must be tested and confirmed to be negative before thioacetazone is started

REGIMEN BANGLADESH

Short, Highly Effective, and Inexpensive Standardized Treatment of Multidrug-resistant Tuberculosis

Armand Van Deun[1,2], Aung Kya Jai Maug[3], Md Abdul Hamid Salim[3], Pankaj Kumar Das[3], Mihir Ranjan Sarker[3], Paul Daru[3], and Hans L. Rieder[1,4]

[1]International Union Against Tuberculosis and Lung Disease, Paris, France; [2]Mycobacteriology Unit, Institute of Tropical Medicine, Antwerp, Belgium; [3]Damien Foundation Bangladesh, Dhaka, Bangladesh; and [4]Institute of Social and Preventive Medicine, University of Zurich, Switzerland

COMENTARI A PRIMERA VISTA (AT GLANCE COMMENTARY)

En absència d'evidencia d'assaigs clínics en TB MDR (H+R), les guies actuals de maneig es basen en opinió d'experts i recomanen opcions de tractament llargues, mal tolerades i costoses. El resultat és que la seva implantació és difícil i els resultats "modestos".

Aquest estudi observacional mostra que un règim estandarditzat, curt, basat en fluoroquinolones combinades amb d'altres fàrmacs de segona línea i suplementat per medicaments de primera línia potencialment actius, va ser altamente efectiu en un entorn de pacients no infectats pel VIH i sense història d'exposición previa a fàrmacs de segona línia

Am J Respir Crit Care Med Vol 182. pp 684–692, 2010

INT J TUBERC LUNG DIS 18(10):1180–1187

http://dx.doi.org/10.5588/ijtld.14.0100

Successful '9-month Bangladesh regimen' for multidrug-resistant tuberculosis among over 500 consecutive patients

K. J. M. Aung,* A. Van Deun,†‡ E. Declercq,§ M. R. Sarker,* P. K. Das,* M. A. Hossain,* H. L. Rieder‡¶

*Damien Foundation, Dhaka, Bangladesh; †Mycobacteriology Unit, Institute of Tropical Medicine, Antwerp, Belgium; ‡International Union Against Tuberculosis and Lung Disease, Paris, France; §Damien Foundation, Brussels, Belgium; ¶University of Zürich, Zürich, Switzerland

Limitació: Investigació circumscrita a un sol lloc amb baixa prevalença d'infecció per VIH, per tant els resultat han d'ésser interpretats amb precaució.

SOCIETAT CATALANOBALEAR DE MEDICINA INTERNA

World Health Organization

THE SHORTER MDR-TB REGIMEN

BACKGROUND

- Multidrug-resistant tuberculosis (MDR-TB) is a public health crisis and a global health security risk carrying grave consequences for those affected.
- An estimated 480 000 people developed MDR-TB in 2014 and 190 000 people died as a result of it.
- MDR-TB cannot be treated with the standard 6-month course of first-line medication which is effective in most TB patients. Patients with rifampicin-resistant or MDR-TB are treated with a different combination of second-line drugs, usually for 18 months or more. Attempts to reduce the length of conventional MDR-TB regimens and to use a combination of drugs which is tolerable have been ongoing for several years through various studies.
- Recently, a standardized treatment regimen lasting less than 12 months has been used in a number of countries (see map). It has shown promising results in selected MDR-TB patients
- Based on data from these studies, WHO updated its treatment guidelines for drug-resistant TB in May 2016 and included a recommendation on the use of the shorter MDR-TB regimen under specific conditions.
- This new recommendation is expected to benefit the majority of MDR-TB patients worldwide; however, there are serious risks for worsening resistance if the regimen is used inappropriately (e.g. in XDR-TB patients).
- WHO encourages ongoing and future randomized controlled clinical trials to strengthen the evidence base for shorter and more effective regimens.

For more information please visit: www.who.int/tb

Countries using the shorter MDR-TB regimen
(in addition, Ethiopia, South Africa, Viet Nam and Mongolia are participating in the clinical trial)

FEATURES OF THE SHORTER MDR-TB REGIMEN

- Standardized shorter MDR-TB regimen with seven drugs and a treatment duration of 9-12 months
- Indicated conditionally in MDR-TB or rifampicin-resistant-TB, regardless of patient age or HIV status
- Monitoring
- be needed
- support to
- Programm
- worldwide
- Lowered c
- reduced p
- Exclusion
- extrapulm

REGIMEN

4-6 Km-Mfx-

Km=Kanamycin;
Cfz=Clofazimine
$H_{high-dose}$= high-d

REGIMEN COMPOSITION

4-6 Km-Mfx-Pto-Cfz-Z-$H_{high-dose}$-E / 5 Mfx-Cfz-Z-E

Km=Kanamycin; Mfx=Moxifloxacin; Pto=Prothionamide;
Cfz=Clofazimine; Z=Pyrazinamide;
$H_{high-dose}$= high-dose Isoniazid; E=Ethambutol

WHO RECOMMENDATIONS

ON THE USE OF THE SHO

In May 2016, WHO issued a conditional rec
MDR-TB regimen. A flow chart outlining sele
regimen is presented below.

CHOOSING THE MDR-TB TREATMEN
CONFIRMED RIFAMPICIN-R

CRITERIA: Do any of the following appl

- ✓ Confirmed resistance or suspected ineffectivene regimen (except isoniazid resistance)
- ✓ Exposure to ≥1 second-line medicines in the sho
- ✓ Intolerance to ≥1 medicines in the shorter MDR interactions)
- ✓ Pregnancy
- ✓ Extrapulmonary disease
- ✓ At least one medicine in the shorter MDR-TB re

NO

Shorter MDR-TB regimen

FAILING REGIMEN, DRUG
RETURN AFTER INTERRUPT
EMERGENCE OF ANY EXCL

Intensive phase
Duration: 4-6 months
Composition: 4 second-line drugs

Continuation phase
Duration: 5 months
Composition: 2 second-line drugs

Supported by selected first-line TB drugs

KEY TERMS

- TB bacteria resistant to the medicines used in its treat resistance is fuelled by inadequate treatment; once T from person to person in the same way as drug-susce
- **Rifampicin-resistant TB (RR-TB)** is caused by TB bacte most effective anti-TB medicines. These patients nee
- **Multidrug-resistant TB (MDR-TB)** is caused by TB ba rifampicin, the two most effective anti-TB drugs. These patients need second-line treatment
- **Extensively drug-resistant TB (XDR-TB)** is a form of MDR-TB that is also resistant to any fluoroquinolone and any of the second–line anti-TB injectable agents (i.e. amikacin, kanamycin or capreomycin).

CHOOSING THE MDR-TB TREATMENT REGIMEN IN PATIENTS WITH CONFIRMED RIFAMPICIN-RESISTANT OR MDR-TB

CRITERIA: Do any of the following apply ?

- ✓ Confirmed resistance or suspected ineffectiveness to a medicine in the shorter MDR-TB regimen (except isoniazid resistance)
- ✓ Exposure to ≥1 second-line medicines in the shorter MDR-TB regimen for >1 month
- ✓ Intolerance to ≥1 medicines in the shorter MDR-TB regimen or risk of toxicity (e.g. drug-drug interactions)
- ✓ Pregnancy
- ✓ Extrapulmonary disease
- ✓ At least one medicine in the shorter MDR-TB regimen not available in the programme

NO

Shorter MDR-TB regimen

Intensive phase
Duration: 4-6 months
Composition: 4 second-line drugs

Continuation phase
Duration: 5 months
Composition: 2 second-line drugs

Supported by selected first-line TB drugs

FAILING REGIMEN, DRUG INTOLERANCE, RETURN AFTER INTERRUPTION >2 MONTHS, EMERGENCE OF ANY EXCLUSION CRITERION

YES

Individualised ("conventional") MDR/RR-TB regimens

Intensive phase
Duration: Up to 8 months
Composition: 4 or more second-line drugs

Continuation phase
Duration: 12 months or more
Composition: 3 or more second-line drugs

Supported by selected first-line TB drugs

STREAM TRIALS

Standardised **T**reatment
REgimen of **A**nti-tuberculosis
Drugs for Patients with
Multidrug-resistant Tuberculosis

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 28, 2019 VOL. 380 NO. 13

A Trial of a Shorter Regimen for Rifampin-Resistant Tuberculosis

A.J. Nunn, P.P.J. Phillips, S.K. Meredith, C.-Y. Chiang, F. Conradie, D. Dalai, A. van Deun, P.-T. Dat, N. Lan, I. Master, T. Mebrahtu, D. Meressa, R. Moodliar, N. Ngubane, K. Sanders, S.B. Squire, G. Torrea, B. Tsogt, and I.D. Rusen, for the STREAM Study Collaborators*

CONCLUSIONS:

En persones amb TB resistent a rifampicina i sensible a fluoroquinolones i aminoglucòsids, el règim curt va ser no-inferior respecte al llarg en relació al desenllaç primari d'eficacia i va resultat similar quant a seguretat.

(Finançat per la US Agency for International Development i d'altres. ClinicalTrials.gov number NCT02409290)

Evaluation of two short standardised regimens for the treatment of rifampicin-resistant tuberculosis (STREAM stage 2): an open-label, multicentre, randomised, non-inferiority trial

*Ruth L Goodall, Sarah K Meredith, Andrew J Nunn, Adamu Bayissa, Anuj K Bhatnagar, Gay Bronson, Chen-Yuan Chiang, Francesca Conradie, Meera Gurumurthy, Bruce Kirenga, Nana Kiria, Daniel Meressa, Ronelle Moodliar, Gopalan Narendran, Nosipho Ngubane, Mohammed Rassool, Karen Sanders, Rajesh Solanki, S Bertel Squire, Gabriela Torrea, Bazarragchaa Tsogt, Elena Tudor, Armand Van Deun, I D Rusen, for the STREAM study collaborators**

Research in context

Evidence before this study

Few randomised phase 3 clinical trials in participants with rifampicin-resistant tuberculosis have been completed and published. We searched PubMed for randomised treatment trials with clinical outcomes in rifampicin-resistant or multidrug-resistant tuberculosis, published from Jan 1, 2000, to April 22, 2022. We used the following search terms: "trial" AND "tuberculosis" AND "rifampicin resistance" OR "MDR" OR "multi-drug" OR "multidrug" OR "rifampicin-resistance", with no language restrictions. This search yielded 243 results; studies that were not randomised control trials reporting

In 2019, a trial comparing delamanid or placebo added to an optimised background regimen was published. The primary endpoint showed no difference in sputum culture conversion, and neither was there any difference in the long-term outcome. In 2022, the NExT trial found that 51% of participants assigned to a 6-month all-oral regimen composed of WHO group A drugs plus two other group B or C drugs had a favourable outcome at 24 months compared with 23% assigned the injectable-based standard of care.

Added value of this study

The STREAM stage 2 study shows that both a 9-month oral bedaquiline-containing regimen and a 6-month bedaquiline-containing regimen including 8 weeks of a second-line injectable had superior favourable outcomes compared with a 9-month injectable-based regimen, with very little acquisition of phenotypic resistance to core drugs.

Implications of all the available evidence

The findings of the STREAM stage 2 trial, combined with results of previous trials, show that shorter bedaquiline-containing regimens are an effective treatment for patients with multidrug-resistant-tuberculosis.

Implicacions de l'evidència disponible:

Les troballes de l'assaig STREAM stage 2, combinades amb els resultats d'assaigs precedents, mostren que règims de curta durada basats en bedaquilina són eficaços per pacients amb TB-MDR

Short-course treatment for multidrug-resistant tuberculosis: the STREAM trials

Riya Moodley[1] and Thomas R. Godec[1] on behalf of the STREAM Trial Team[2]

Affiliations: [1]Medical Research Council Clinical Trials Unit at University College London, Institute of Clinical Trials and Methodology, London, UK. [2]A full list of the STREAM Trial Team members and their affiliations can be found in the Acknowledgements section.

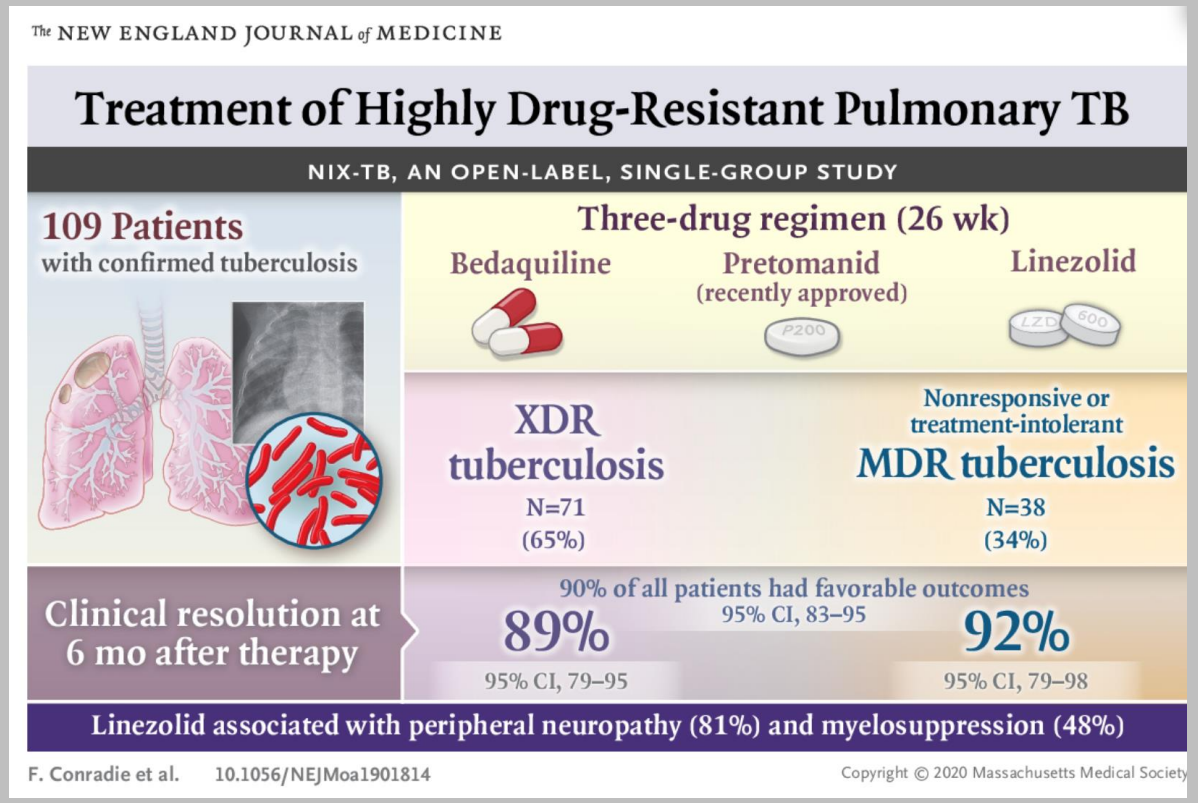
Correspondence: Riya Moodley, Medical Research Council Clinical Trials Unit at University College London, Institute of Clinical Trials and Methodology, Aviation House, 125 Kingsway, London, WC2B 6NH, UK. E-mail: riya.moodley@ucl.ac.uk

ABSTRACT Multidrug-resistant (MDR) tuberculosis (TB) is a threat to global TB control, as suboptimal and poorly tolerated treatment options have resulted in largely unfavourable outcomes for these patients. The last of six cohort studies conducted in Bangladesh which assessed a new shorter regimen using currently
more effe
of stage 1
for Patien
regimen,
bedaquilin
simplified
stage 1 st
regimen w
results fro
managem

STREAM: Evaluation of a Standardised Treatment Regimen of Anti-tuberculosis Drugs for Patients with Multidrug-resistant Tuberculosis. Compara la pauta recomanada per la OMS en front a combinacions sorgides a partir del "règim Bangladesh" (STREAM 1) i pautes basades en bedaquilina (STREAM 2)

NixTB TRIAL

Non-responsive or **I**ntolerant to conventional **X**DR-**TB** treatment



The NEW ENGLAND JOURNAL of MEDICINE

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

Treatment of Highly Drug-Resistant Pulmonary Tuberculosis

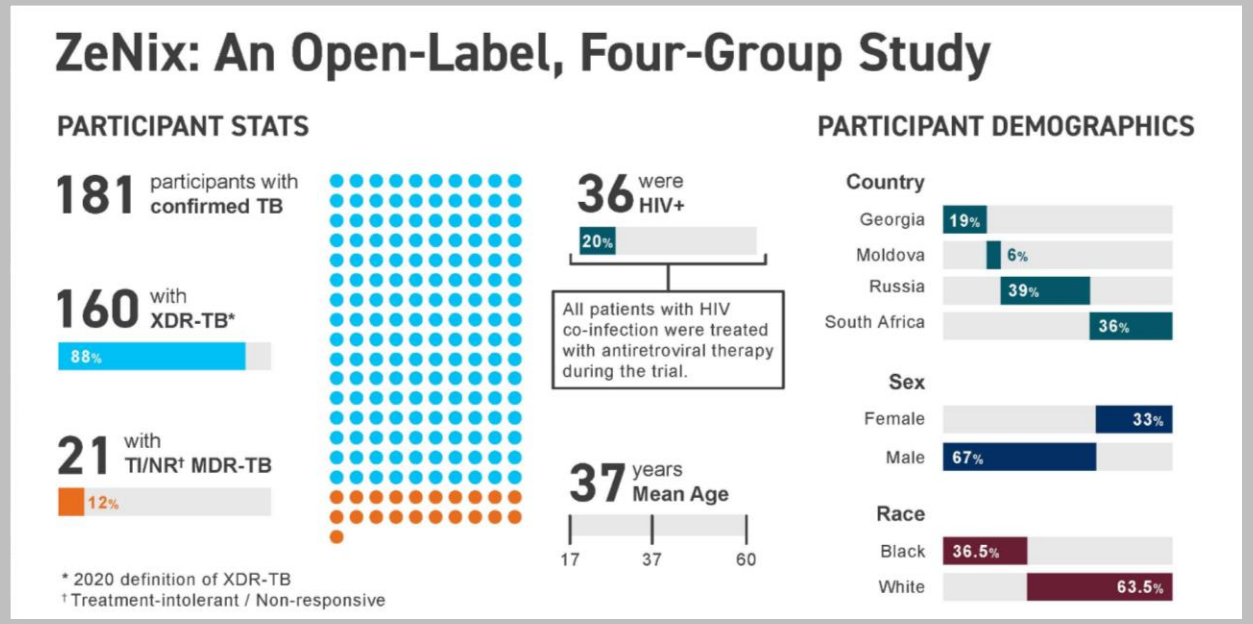
Francesca Conradie, M.B., B.Ch., Andreas H. Diacon, M.D., Nosipho Ngubane, M.B., B.Ch., Pauline Howell, M.B., B.Ch., Daniel Everitt, M.D., Angela M. Crook, Ph.D., Carl M. Mendel, M.D., Erica Egizi, M.P.H., Joanna Moreira, B.Sc., Juliano Timm, Ph.D., Timothy D. McHugh, Ph.D., Genevieve H. Wills, M.Sc., Anna Bateson, Ph.D., Robert Hunt, B.Sc., Christo Van Niekerk, M.D., Mengchun Li, M.D., Morounfolu Olugbosi, M.D., and Melvin Spigelman, M.D., for the Nix-TB Trial Team*

CONCLUSIONS:

La combinació de bedaquilina, pretomanid i linezolid obté resultats favorables als 6 mesos d'haver finalitzat el tractament en un gran percetatge de pacients amb formes altamente resistents de tuberculosi. Es varen observar alguns efectes adversos associats. (Finançat per la TB Alliance i d'altres. ClinicalTrials.gov number NCT02333799)

ZeNixTB TRIAL

LineZolid lowered doses in Non-responsive or Intolerant to conventional XDR-TB treatment



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Bedaquiline–Pretomanid–Linezolid Regimens for Drug-Resistant Tuberculosis

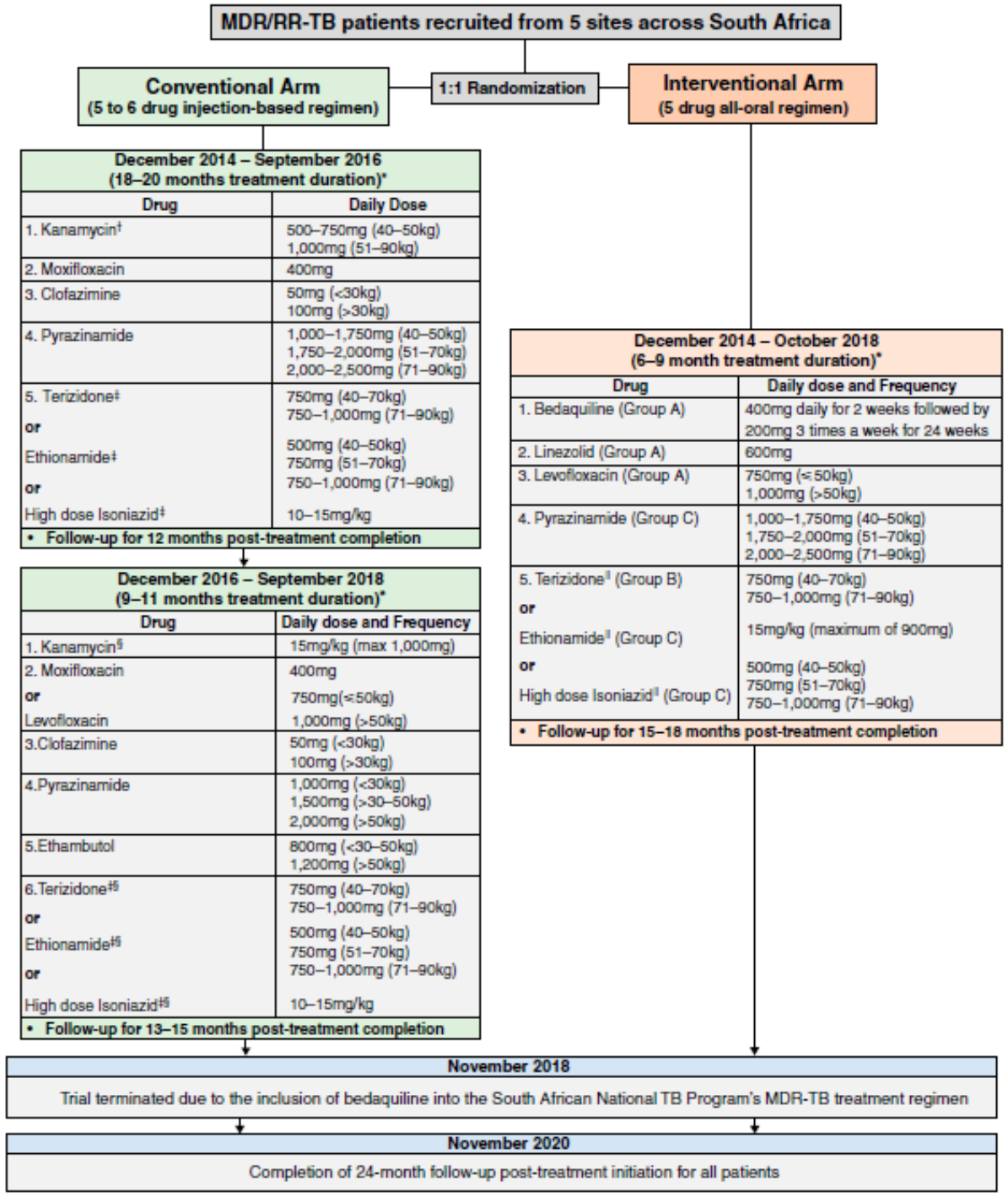
F. Conradie, T.R. Bagdasaryan, S. Borisov, P. Howell, L. Mikiashvili, N. Ngubane, A. Samoilova, S. Skornykova, E. Tudor, E. Variava, P. Yablonskiy, D. Everitt, G.H. Wills, E. Sun, M. Olugbosi, E. Egizi, M. Li, A. Holsta, J. Timm, A. Bateson, A.M. Crook, S.M. Fabiane, R. Hunt, T.D. McHugh, C.D. Tweed,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

CONCLUSIONS:

Del 84 a 93% dels participants en els 4 grups de tractament amb BPaL varen tenir un desenllaç favorable. La raó risc/benefici va afavorir, en general, al grup que va rebre l'esquema de 3 fàrmacs amb linezolid a dosis de 600 mg durant 6 setmanes, amb una menor incidencia d'efectes adversos registrats i amb menys modificacions de la dosi de linezoid (Finançat per la TB Alliance i d'altres. ZeNix ClinicalTrials.gov number NCT03086486)

NExT STUDY

NEw-injection free regimen to treat **X**DR-**T**B



Am J Respir Crit Care Med Vol 205, Iss 10, pp 1214–1227, May 15, 2022

ORIGINAL ARTICLE

An All-Oral 6-Month Regimen for Multidrug-Resistant Tuberculosis

A Multicenter, Randomized Controlled Clinical Trial (the NExT Study)

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CONCLUSIONS:

Comparat amb els règims tradicionals de la OMS de 24 mesos de durada, que inclouen injectables que s'han de suspendre/substituir per toxicitat, la combinación basada únicament en fàrmacs orals, levofloxacino, bedaquilina i linezolid pel tractament de la TB MDR i RR, es va associar amb una millora significativa en el desenllaç "èxit de tractament". La toxicitat associada als fàrmacs va ser freqüent en els dos braços del tractament.

TB PRACTECAL

PRAgmatic **C**linical **T**rial for a More **E**ffective **C**oncise **A**nd **L**ess Toxic MDR-TB Treatment Regimen(s)

Drug	Recommended dose by weight						
	30–35 kg	36–40 kg	41–45 kg	46–50 kg	51–55 kg	56–60 kg	61–70 kg
Isoniazid (high dose)	By weight, 15 mg/kg. Max 600 mg						
Ethambutol	800mg	800mg	800mg	800mg	1200mg	1200mg	1200mg
Pyrazinamide (20–30 mg/kg) Max 2000 mg	800 mg	800 mg	1200 mg	1200 mg	1600 mg	1600 mg	1600 mg
Amikacin	500 mg	500 mg	750 mg	750 mg	1000 mg	1000 mg	1000 mg
Levofloxacin	750 mg	750 mg	750 mg	750 mg	1000 mg	1000 mg	1000 mg
Moxifloxacin	400 mg	400 mg	400 mg	400 mg	400 mg	400 mg	400 mg
Ethionamide/prothionamide	500 mg	500 mg	500 mg	500 mg	750 mg	750 mg	750 mg
Terizidone/cycloserine	By weight (15–20 mg/kg)	750 mg	750 mg	750 mg	750 mg	750 mg	750 mg
Para-aminosalicylic acid	4 g	8 g	8 g	8 g	8 g	8 g	8 g
Clofazimine	100 mg						
Linezolid	300 mg	600 mg	600 mg	600 mg	600 mg	600 mg	600 mg
Bedaquiline	400mg once daily for 2 weeks then 200mg three times a week						
Delamanid	100 mg twice daily						
Imipenem/cilastatin	1000 mg imipenem/1000 mg cilastatin every 12 h						
Amoxicillin/clavulanate	500/125mg twice daily (*ONLY* for use in combination with Imipenem / cilastatin, give orally 30min before infusion)						

ORIGINAL ARTICLE

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

Bern-Thomas Nyang'wa, M.B., B.S., Catherine Berry, B.Med., Emil Kazounis, M.Med.Sci., Ilaria Motta, Ph.D., Nargiza Parpieva, Sc.D., Zinaida Tigay, M.D., Varvara Solodovnikova, M.D., Irina Liverko, Sc.D., Ronelle Moodliar, M.B., B.S., Matthew Dodd, M.Sc., Nosipho Ngubane, M.B., B.Ch., Mohammed Rassool, M.B., B.Ch., Timothy D. McHugh, Ph.D., Melvin Spigelman, M.D., David A.J. Moore, M.D., Koert Ritmeijer, Ph.D., Philipp du Cros, M.B., B.S., and Katherine Fielding, Ph.D., for the TB-PRACTECAL Study Collaborators*

CONCLUSIONS:

En pacients amb TB pulmonar resistent a rifampicina, un règim exclusivament oral de 24 setmanes va resultar no inferior al "standard of care" de la OMS i va mostrar un millor perfil de seguretat.

(Finançat per Médecins sans Frontières. TB-PRACTECAL ClinicalTrials.gov number NCT02589782)

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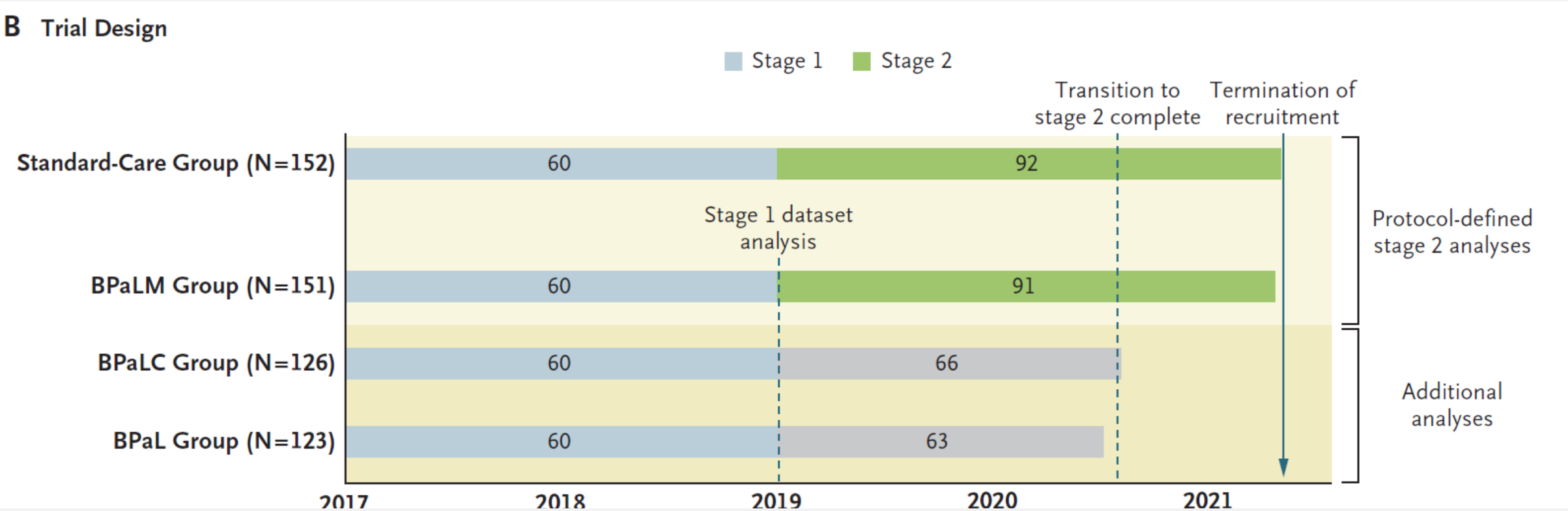
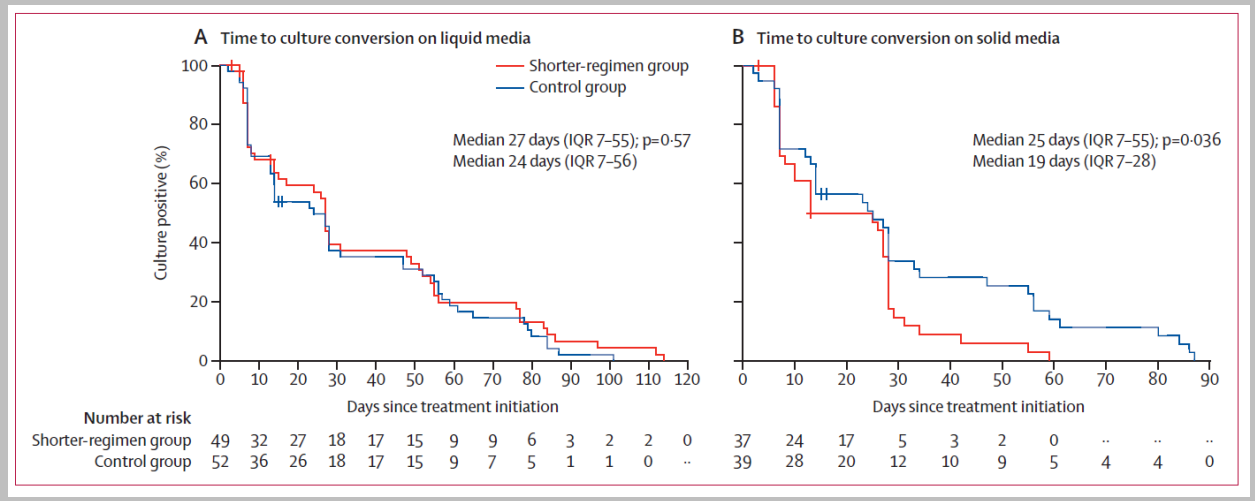
B Trial Design



MDR-END

Treatment Shortening of **MDR**-TB Using **E**xisting and **N**ew **D**rugs



9 months of delamanid, linezolid, levofloxacin, and pyrazinamide versus conventional therapy for treatment of fluoroquinolone-sensitive multidrug-resistant tuberculosis (MDR-END): a multicentre, randomised, open-label phase 2/3 non-inferiority trial in South Korea

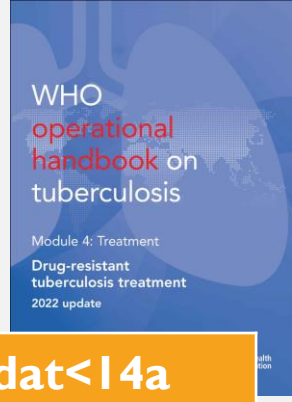
Jeongha Mok, Myungsun Lee*, Deog Kyeom Kim, Ju Sang Kim, Byung Woo Jhun, Kyung-Wook Jo, Doosoo Jeon, Taehoon Lee, Ji Yeon Lee, Jae Seuk Park, Seung Heon Lee, Young Ae Kang, Jung-Kyu Lee, Nakwon Kwak, Joong Hyun Ahn, Tae Sun Shim, Song Yee Kim, Seungmo Kim, Kyungjong Kim, Kwang-Hyuk Seok, Soyeong Yoon, Young Ran Kim, Jisu Kim, Dahae Yim, Seokyung Hahn, Sang Nae Cho, Jae-Joon Yim, on behalf of the MDR-END investigators*

Interpretation 9-month treatment with oral delamanid, linezolid, levofloxacin, and pyrazinamide could represent a new treatment option for participants with fluoroquinolone-sensitive multidrug-resistant tuberculosis.

Implicacions de l'evidència disponible:

Fins ara, aquest és el primer règim curt per la TB MDR únicamente oral, que conté delamanid, que mostra no-inferioritat respecte al tractament convencional, considerablement més llarg. Els resultats i l'evidència creixent de que els nous fàrmacs orals són efectius en pautes curtes, obren la possibilitat de múltiples pautes per la TB MDR en el futur.

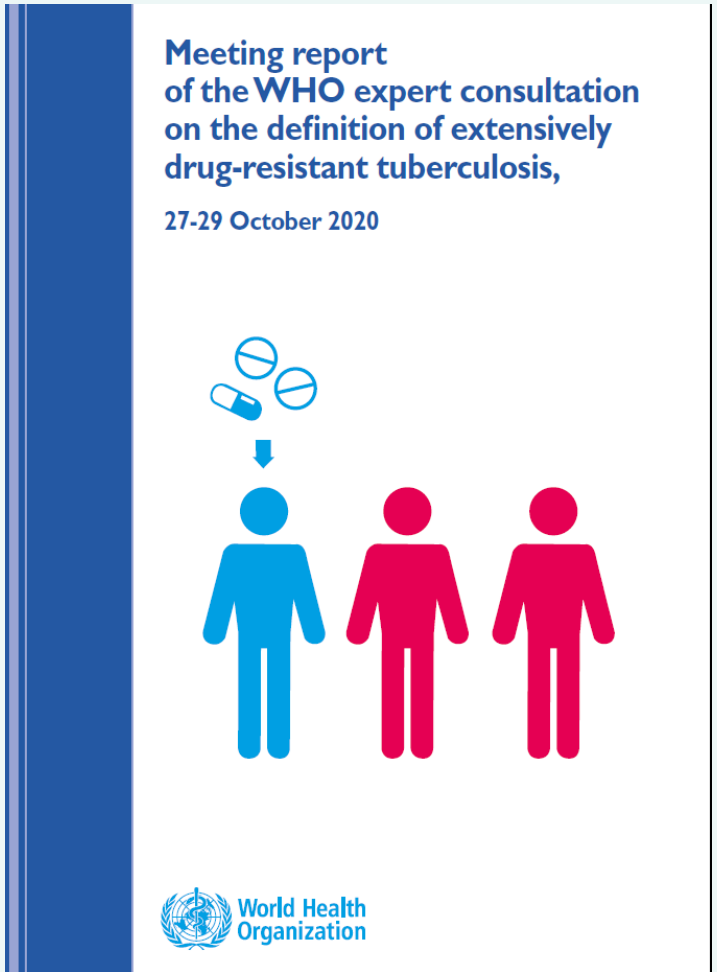
Règim	6 mesos BPaLM/BPaL	9 mesos "tot oral"	≥18 m individualitzat
TB MDR/RR Sensible a FQ	Sí (BPaLM)	Sí	Sí, quan no es poden utilitzar les pautes de 6-9 mesos
TB Pre-XDR (FQ-R)	Sí (només BPaL)	No	Sí, quan no es pot utilizar la pauta de 6 mesos
TB XDR	No	No	Sí
TB pulmonar extensa	No	No	Sí
TB extrapulmonar	Sí (excepte afectació del SNC, TB miliar i osteoarticular)	Sí (exepte meningitis, TB miliar, pericàrdica i osteoarticular)	Sí
Edat<14 anys	No	Sí	Sí
PVVIH	Sí	Sí	Sí
Embaràs/alletament	No	Sí, sense etionamida	Sí
Exposició als fàrmacs >30 d	No	No	Sí
Fàrmacs concomitants que allarguin QTc	Sí, però monitoritzar	Sí	Sí
IMC<17	Sí, però monitoritzar	Sí	Sí
Hb<8g/dL, plaquetes<75000/mm^3	Sí, però de preferència altres règimens	No utilitzar linezolid	No utilitzar linezolid
Neuropatia preexistent	Sí, però de preferència altres règimens	No utilitzar linezolid	No utilitzar linezolid



Règim	TB MDR/RR FQ-S	TB Pre-XDR	TB XDR	TB pulmonar extensa	TB extrapulmonar	Edat<14a
6BPaLM/BPaL	Sí (BPaLM)	Sí (BPaL)	No	Sí	Sí (excepte miliar, osteoarticular, SNC)	No
9 "tot oral"	Sí	No	No	No	Sí (excepte miliar, osteoarticular, meningitis, pericarditis)	Sí
Pautes individualitzades de 18 mesos	Sí / No	Sí / No	Sí	Sí	Sí	Sí

NOVA DEFINICIÓ TUBERCULOSI XDR

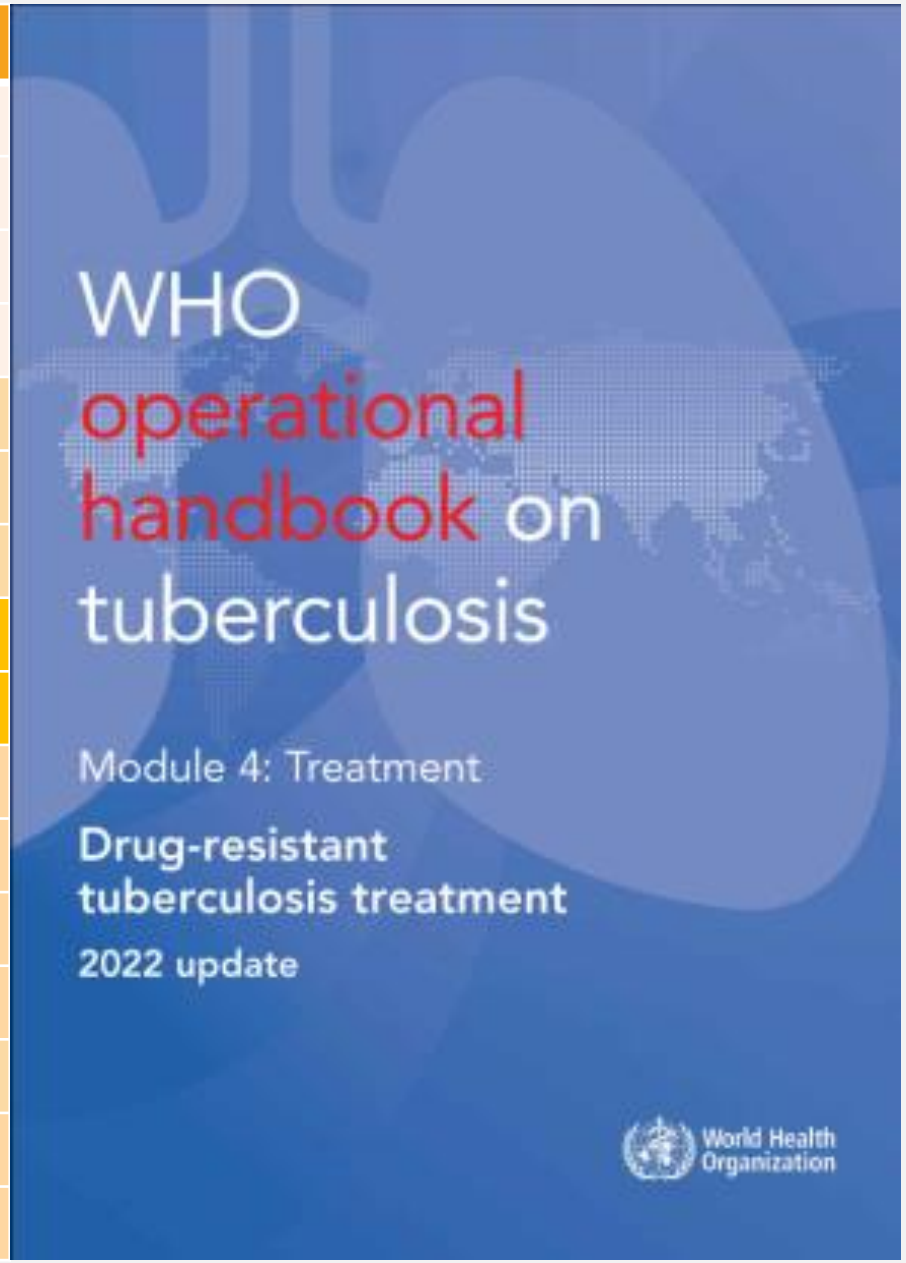
- Les soques de *M tuberculosis* poden ser resistents a un (monoresistents) o més fàrmacs (poliresistents). La màxima dificultat pel tractament és la combinació de resistències als fàrmacs essencials per a l'esterilització de les lesions.



- Tuberculosi multiresistent (TB-MDR): *M tuberculosis* resistent a isoniazida (H) i rifampicina (R).
  - TB-RR, considerar la TB-RR com TB-MDR quan el diagnòstic només es pot fer per proves moleculars (sense antibiograma ni estudi fenotípic)

- TB pre-XDR: *M tuberculosis* MDR o RR amb resistència a alguna fluorquinolona (FQ).
- TB XDR: *M tuberculosis* MDR o RR amb resistència a FQ i a algún dels fàrmacs del grup A de la OMS:
  - Fluorquinolones
  - Linezolid
  - Bedaquilina

Grup	Fàrmac
Primera línia	Rifampicina (R, RIF)
	Isoniazida (H, INH)
	Pirazinamida (Z, PZA)
	Etambutol (E, EMB)
Grup A	FQ Levo, Moxifloxacino(LFX, MXF)
	Bedaquilina (B, BDQ)
	Linezolid (L, LNZ)
Grup B	Clofazimina (C, CFZ)
	D-Cicloserina (Cs, DCS)
Grup C	Delamanid (Da, DLM)
	Imipenem-Cilastatina (IMP-CLN)
	Meropenem (MPM)
	Amikacina (Ak, AMK)
	Estreptomicina (S, STR)
	Etionamida/Protionamida (ETO/PTO)
	Acid Paraaminosalicílic (PAS)



WHAT IS ALREADY KNOWN ON THIS TOPIC

Previous molecular epidemiological studies have shown that drug resistant tuberculosis strains can be transmitted and that clusters of resistant strains can persist over long periods

Some studies have found that the risk of tuberculosis infection does not differ in household contacts exposed to drug resistant tuberculosis and drug sensitive disease

A recent study reported that household contacts exposed to multidrug resistant tuberculosis were half as likely to develop tuberculosis disease as those exposed to drug sensitive disease

WHAT THIS STUDY ADDS

Household contacts of patients with multidrug resistant tuberculosis were at higher risk of tuberculosis infection than contacts exposed to drug sensitive tuberculosis; the risk of developing tuberculosis disease did not differ among contacts in both groups

The evidence invites guideline producers to take action by targeting drug resistant and drug sensitive tuberculosis, such as early detection and effective treatment of infection and disease

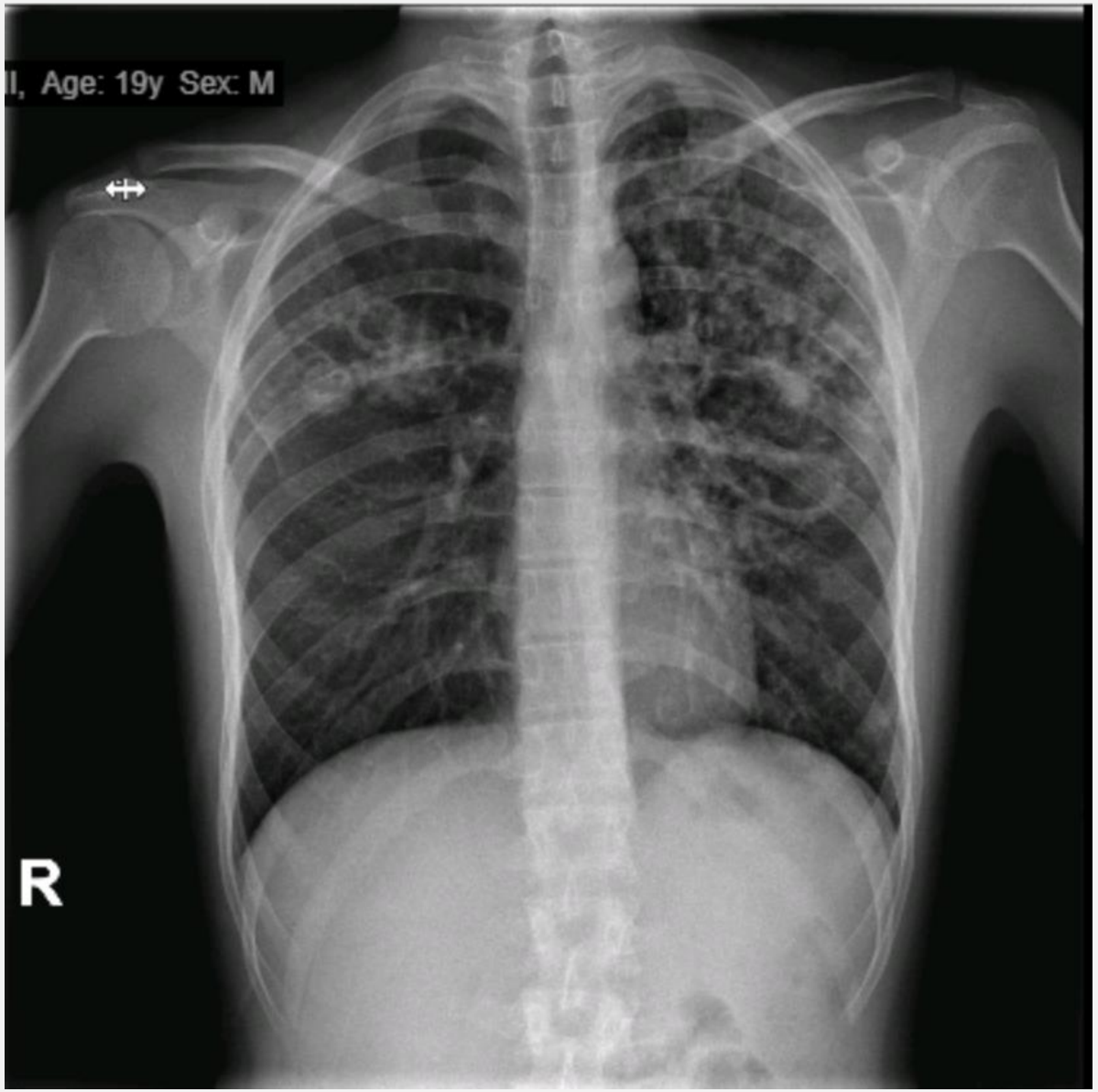
BMJ Open

Levofloxacin versus placebo for the treatment of latent tuberculosis among contacts of patients with multidrug-resistant tuberculosis (the VQUIN MDR trial): a protocol for a randomised controlled trial

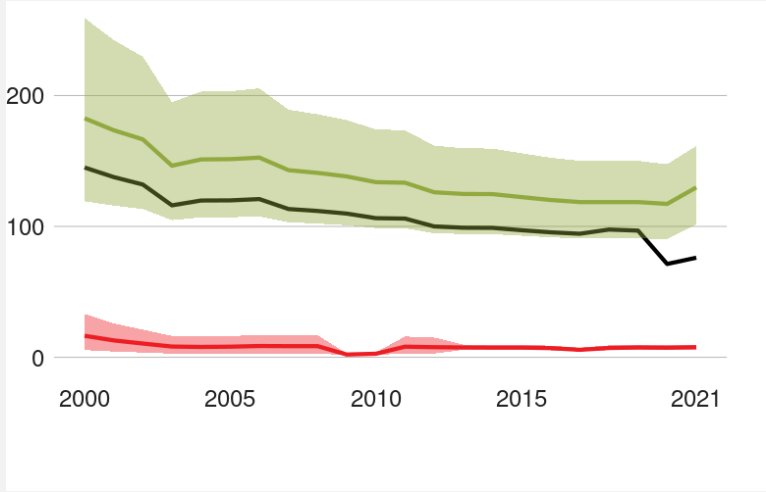
Greg J Fox ,[1,2] Cam Binh Nguyen,[2] Thu Anh Nguyen,[2] Phuong Thuy Tran,[2] Ben J Marais,[3,4] Steve M Graham,[5,6] Binh Hoa Nguyen,[7] Kavi Velen,[2,3] David W Dowdy,[8] Paul Mason,[9] Warwick J Britton,[3,10] Marcel A Behr,[11,12] Andrea Benedetti,[13] Dick Menzies,[12] Viet Nhung Nguyen,[7] Guy B Marks[2,14]

- Home de 19 anys natural de Perú.
- TDAH.
- Consulta reiteradament per sensació de reflux gastroesofàgic i epigastràlgia amb dolor abdominal que empitjora en decúbit.

27-11-22 09:19	27-11-22 09:18	27-11-22 09:18
Z3	Z3	Z3
ACMB	ACMB	ACMB
SOBAAR	SOBAAR	SOBAAR
MOID	MOID	MOID
Z3	Z3	Z3



Tuberculosis (perfil): Perú
Població 2021: 34 milions



Estimacions de la càrrega de TB 2021

	Nombre	(Tasa per 100 000 habitants)
TB casos incidents	44 000 (34 000-54 000)	130 (102-161)
VIH-positius en casos de TB	2 600 (2 000-3 200)	7.7 (6-9.6)
MDR/RR-TB	2 400 (1 800-3 000)	7.1 (5.4-8.8)
Mortalitat per TB en VIH neg	4 000 (3 200-4 900)	12 (9.5-14)
Mortalitat per TB en VIH pos	670 (530-820)	2 (1.6-2.4)

	28-11-22 09:02	27-11-22 17:41	27-11-22 13:07	27-11-22 09:19
rpoB_510-517				NSD
rpoB_513-519				SD
rpoB_516-522				NSD
rpoB_518-525				NSD
rpoB_526-529				NSD
rpoB_530-533				NSD
katG MUT1 (315)				SD
inhA MUT1				NSD
inhA MUT2				NSD

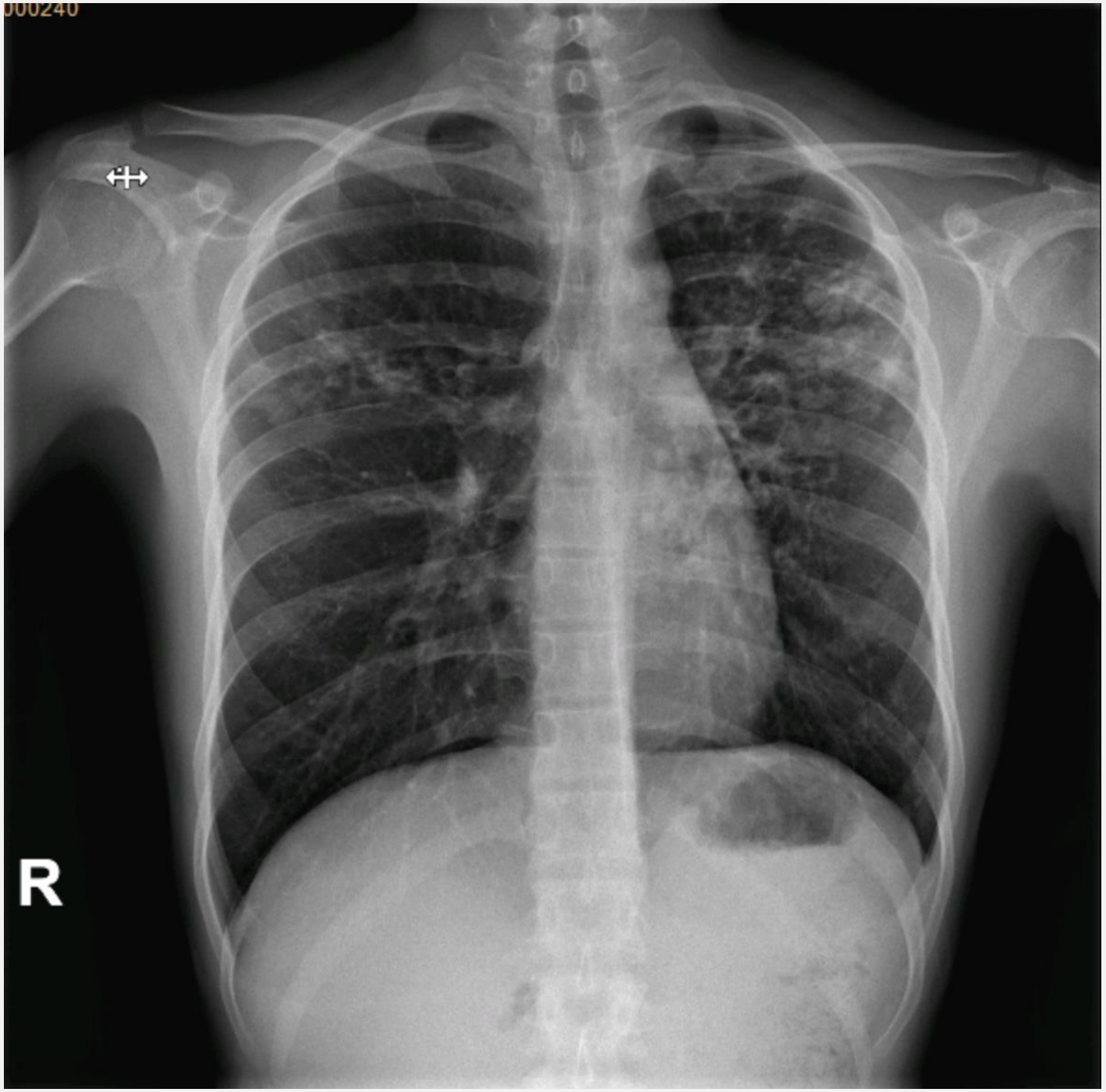
	Mycobacterium tuberculosis complex	
Etambutol	Resistent	
Isoniacida	Resistent	
Pirazinamida	Resistent	
Rifampicina	Resistent	
Estreptomicina	Resistent	

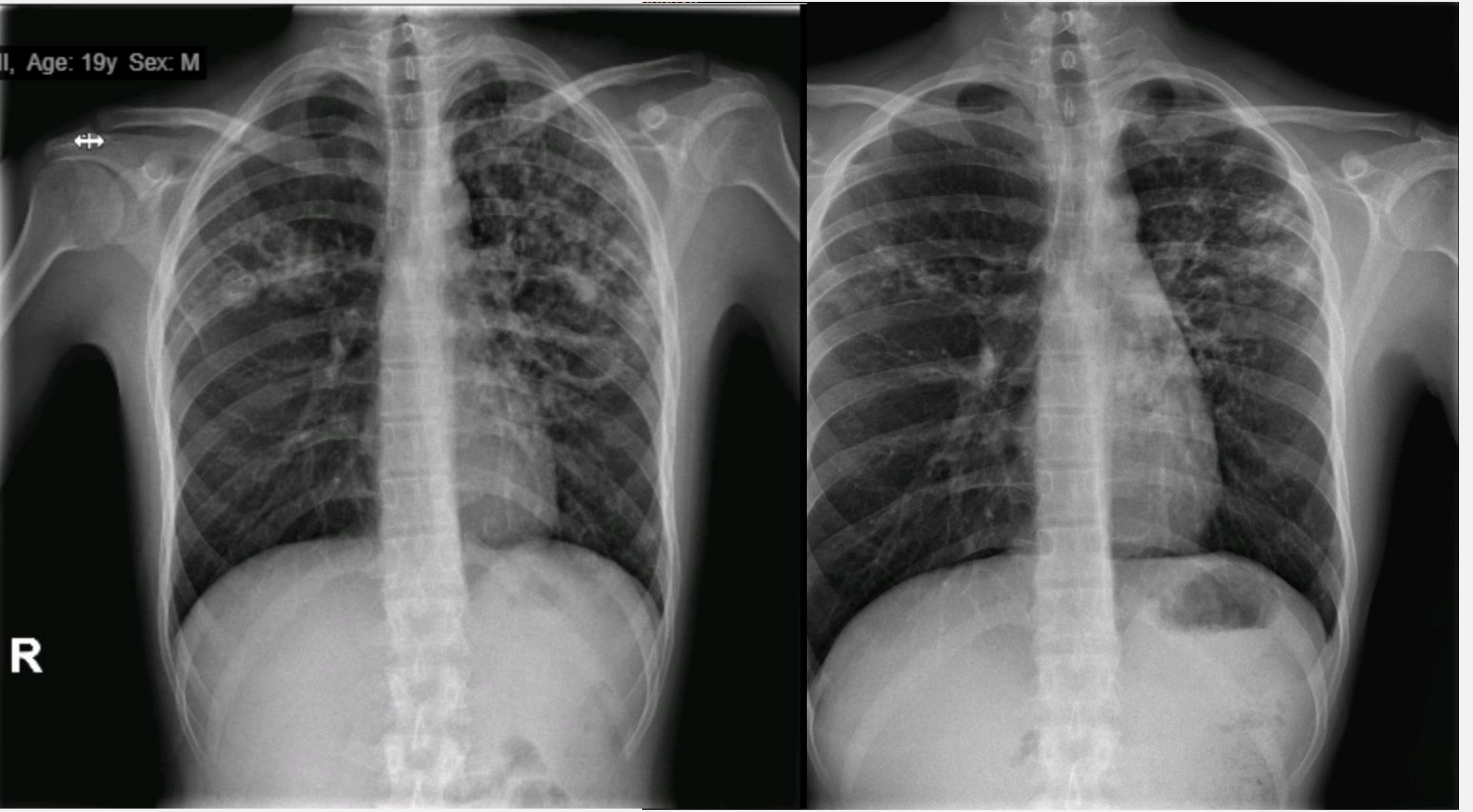
SOCIETAT CATALANOBALEAR DE MEDICINA INTERNA

ATBMICOBACTERIS P Antibiograma

	Mycobacterium tuberculosis complex	
Amikacina	Resistent	1
Bedaquilina	Sensible	
Capreomicina	Resistent	1.25
Cicloserina	Sensible	
Etionamida	Sensible	2.5
Kanamicina	Resistent	5
Levofloxacina	Resistent	1.5
Linezolid	Sensible	1
Moxifloxacin	Resistent	0.25
Rifabutina	Sensible	0.5

1. HRZE
2. ZEMfxLC
3. BDaLC

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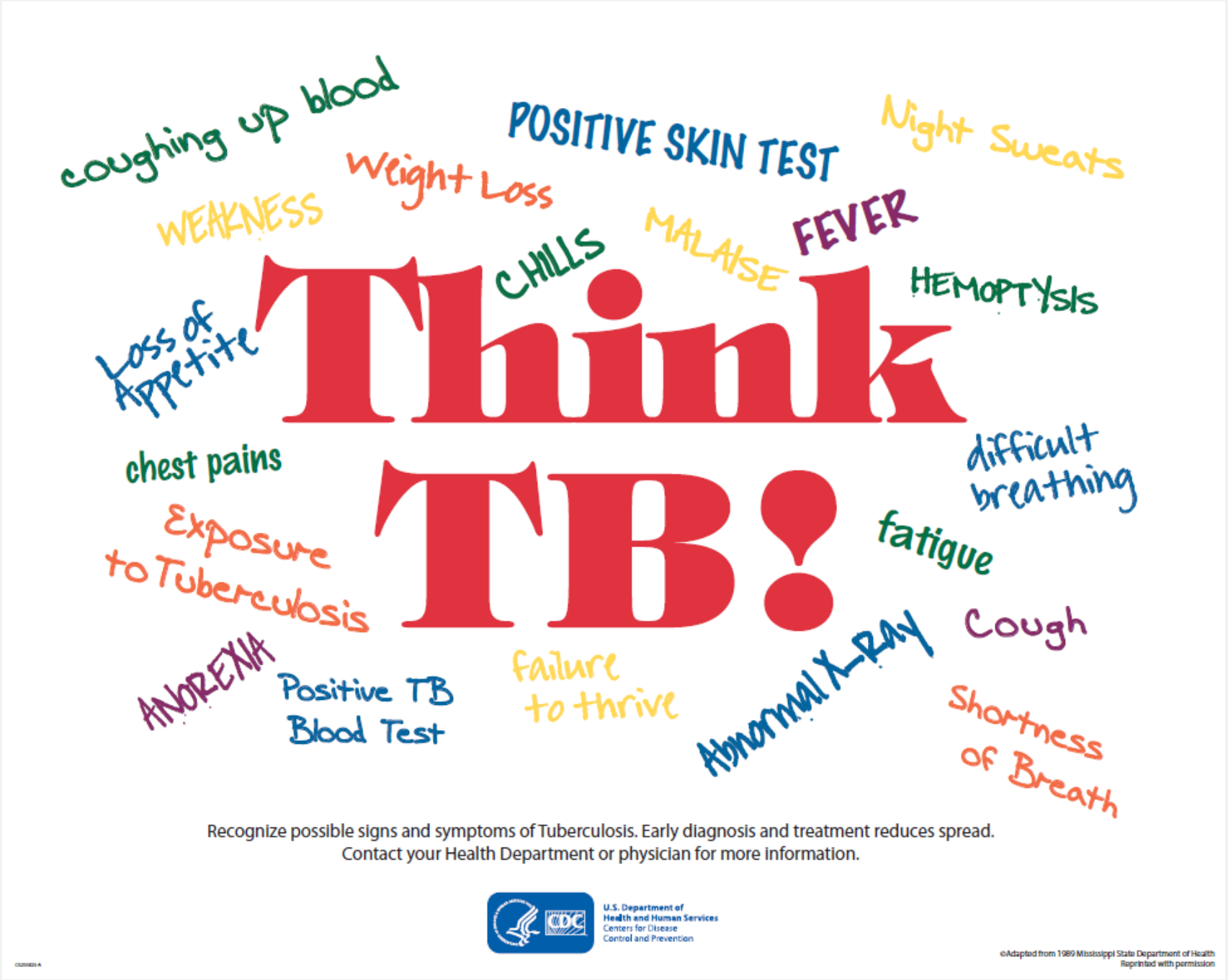

Recognize possible signs and symptoms of Tuberculosis. Early diagnosis and treatment reduces spread.
Contact your Health Department or physician for more information.

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention