XXVII CURSO DE AVANCES EN ANTIBIOTERAPIA

NUEVOS FÁRMACOS EN EL TRATAMIENTO DE LA TUBERCULOSIS

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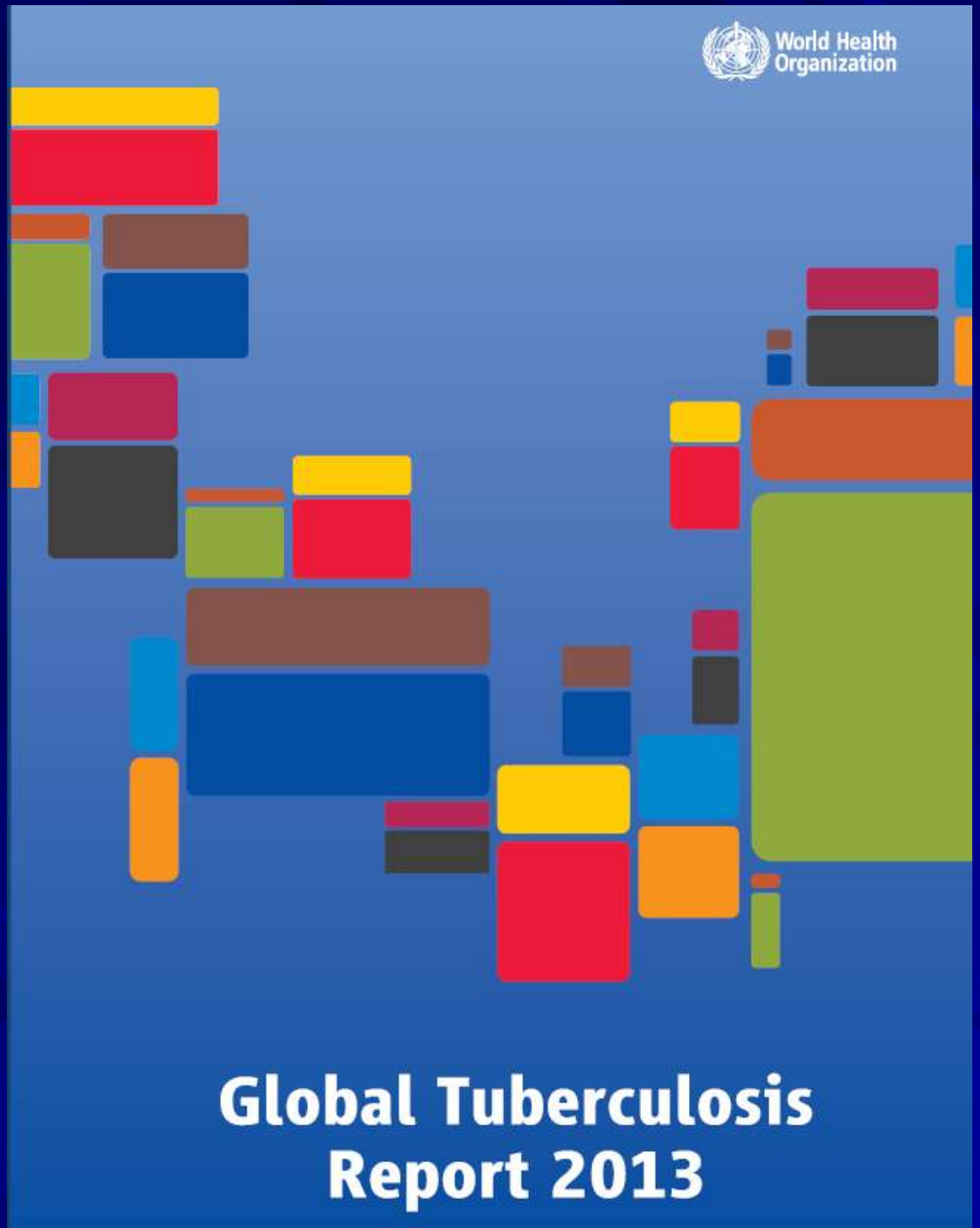


Prevalencia
Incidencia
Resistencia
Mortalidad
DOT
Tuberculosis/VIH
Cobertura

INFORME OMS 2013 TUBERCULOSIS

- En 2012, 8,6 millones de personas desarrollaron la tuberculosis.
- 1,3 millones murieron por esta enfermedad.
- La tasa de incidencia disminuye (2% al año).
- La tasa de mortalidad se ha reducido en un 45% desde 1995*.

*↑ América y Oeste Pacífico
↓ Africa y Europa

FIGURE 2.2

Estimated absolute numbers of TB cases and deaths (in millions), 1990–2012

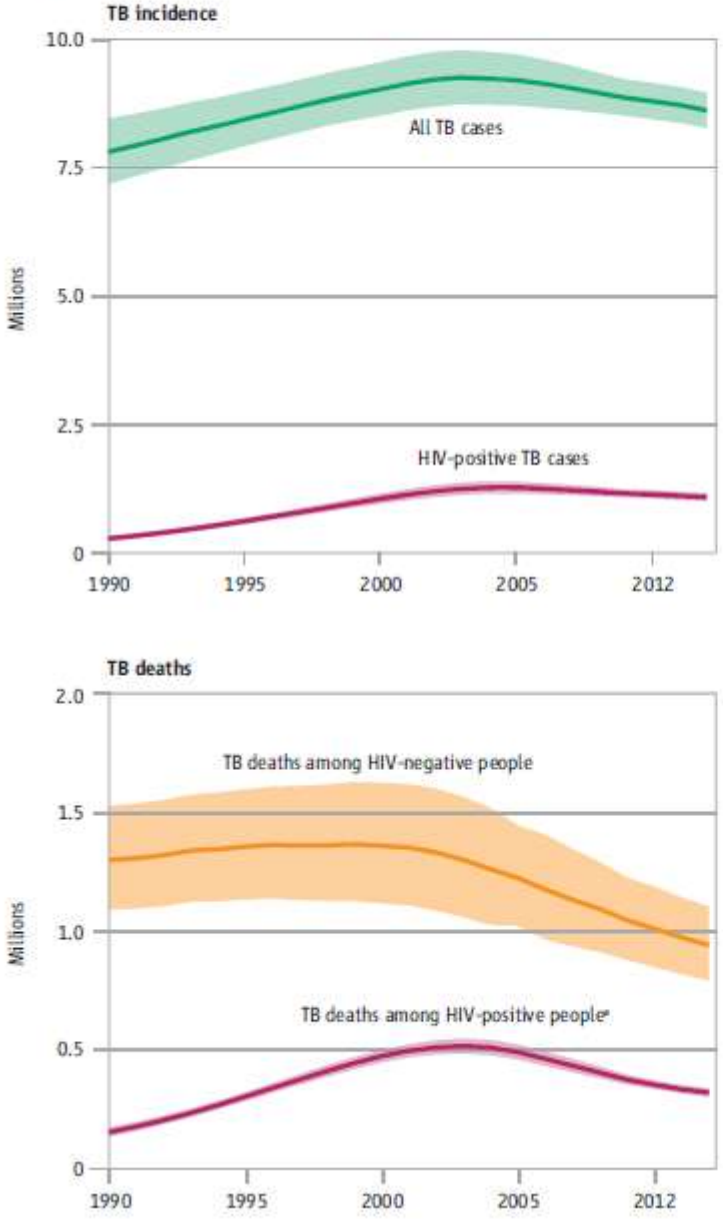
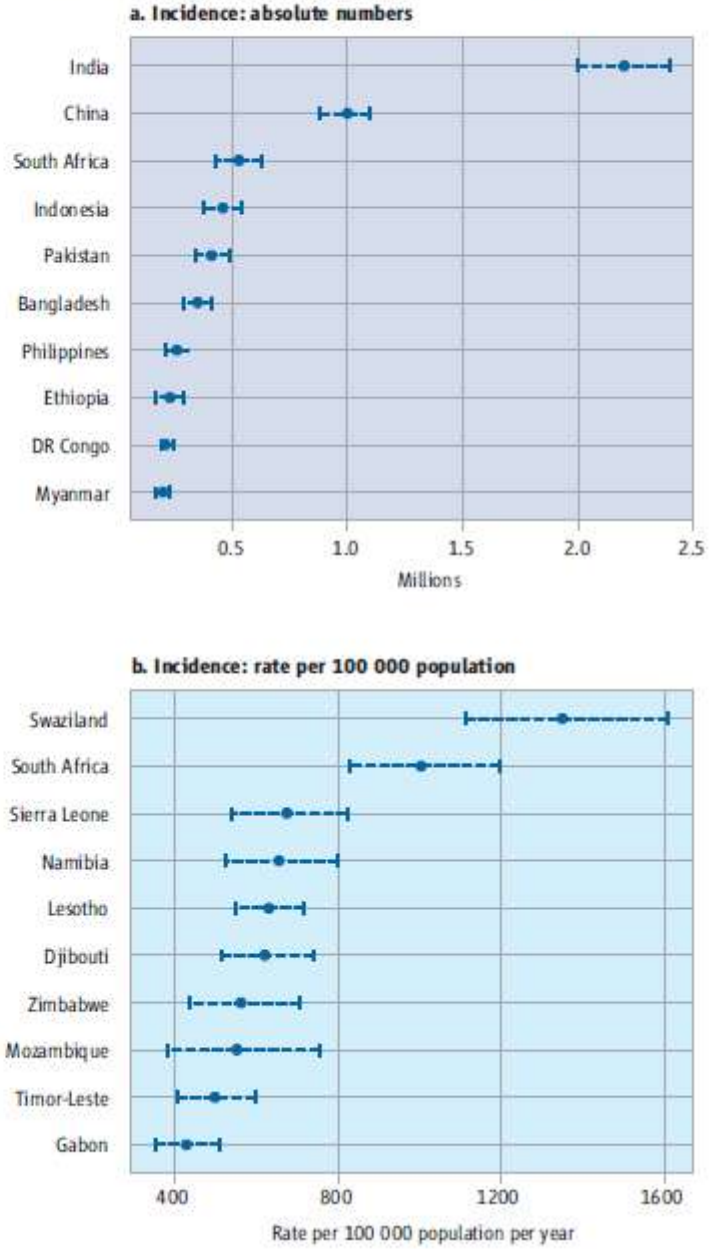
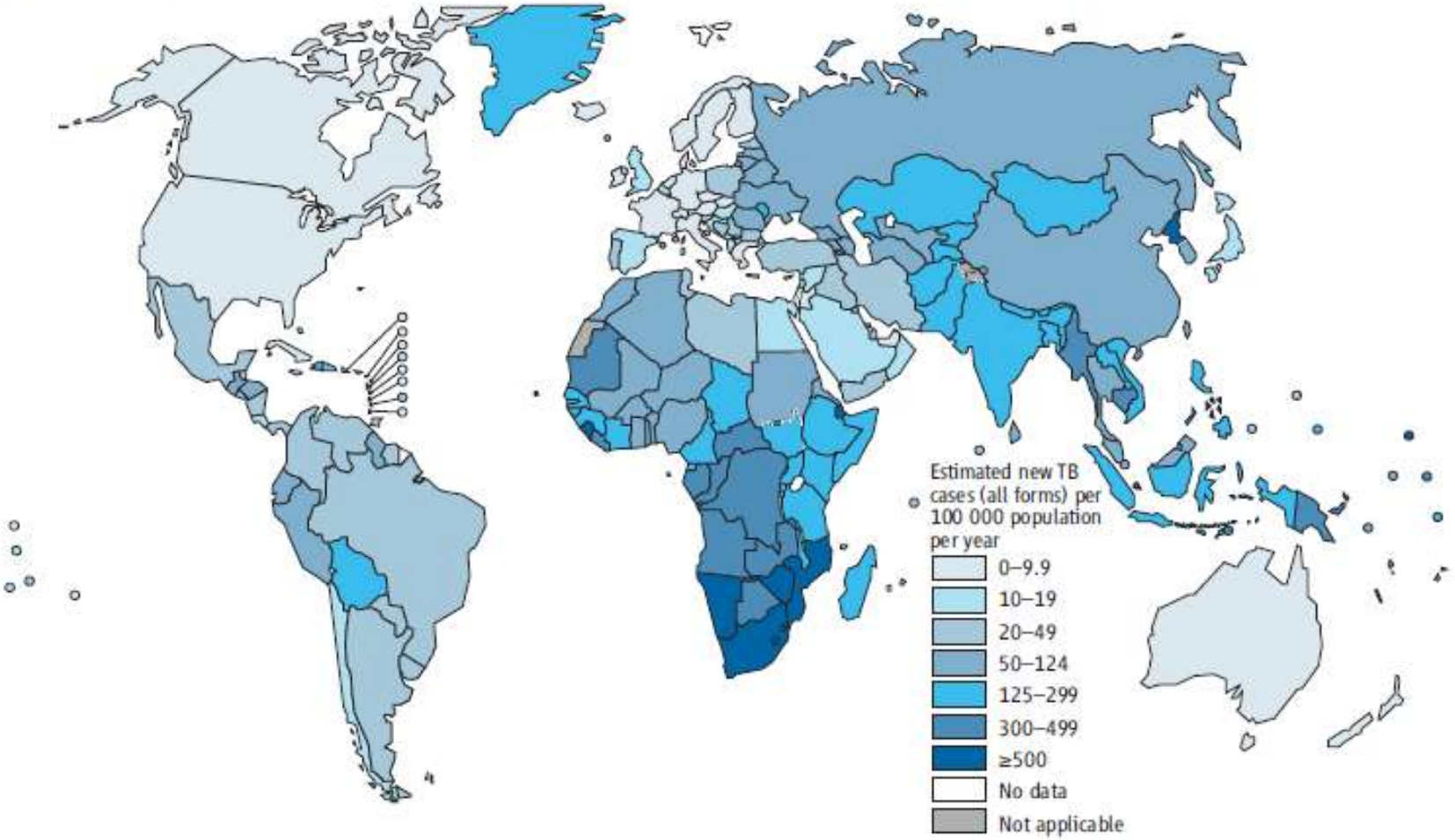


FIGURE 2.3

Estimated TB incidence: top-ten countries, 2012



Estimated TB incidence rates, 2012



	n por 1000	Incidencia/100.000 hab
1990	0.64 (0.560–0.720)	7.5 (6.6–8.5)
1995	0.65 (0.570–0.730)	7.3 (6.4–8.3)
2000	0.48 (0.420–0.540)	5.4 (4.7–6.1)
2005	0.62 (0.540–0.700)	6.9 (6.0–7.8)
2010	0.72 (0.630–0.810)	7.6 (6.7–8.6)
2011	0.63 (0.550–0.710)	6.6 (5.8–7.5)
2012	0.68 (0.600–0.770)	7.2 (6.3–8.1)

SUECIA

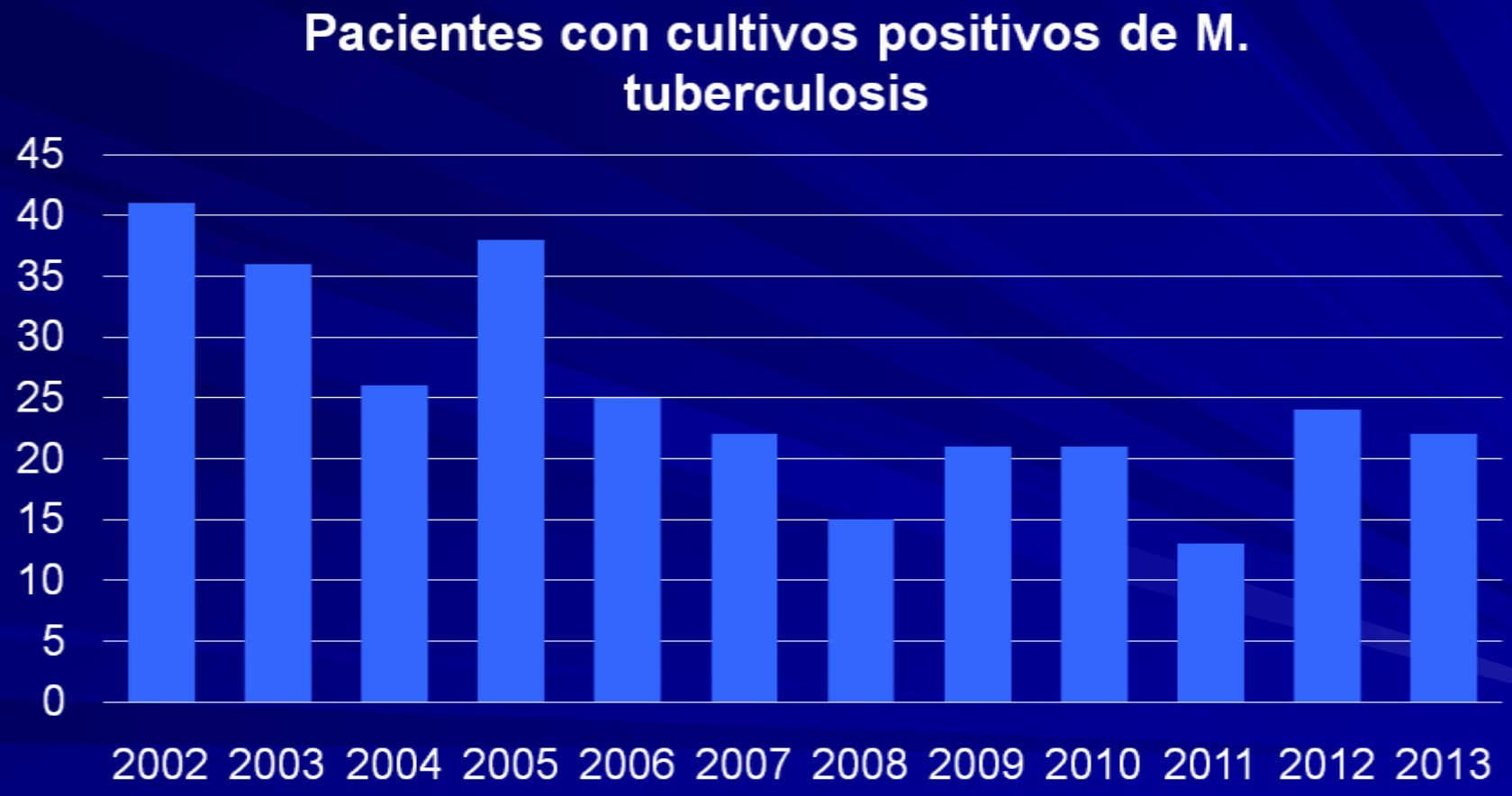
1990	8.7 (7.7–9.9)	22 (20–25)
1995	10 (8.8–11)	26 (22–29)
2000	9.2 (8.1–10)	23 (20–26)
2005	8.4 (7.3–9.5)	19 (17–22)
2010	7.8 (6.8–8.8)	17 (15–19)
2011	7.4 (6.4–8.3)	16 (14–18)
2012	6.5 (5.7–7.4)	14 (12–16)

ESPAÑA

1990	2.3 (1.4–3.4)	267 (165–394)
1995	3.2 (2.7–3.9)	337 (275–405)
2000	8.5 (7.0–10)	803 (657–964)
2005	13 (10–15)	1 150 (938–1 380)
2010	15 (13–18)	1 290 (1 060–1 530)
2011	16 (13–19)	1 320 (1 090–1 570)
2012	17 (14–20)	1 350 (1 110–1 610)

SWAZILANDIA

Hospital Universitario de La Princesa



TAXONOMIA DE LA TUBERCULOSIS

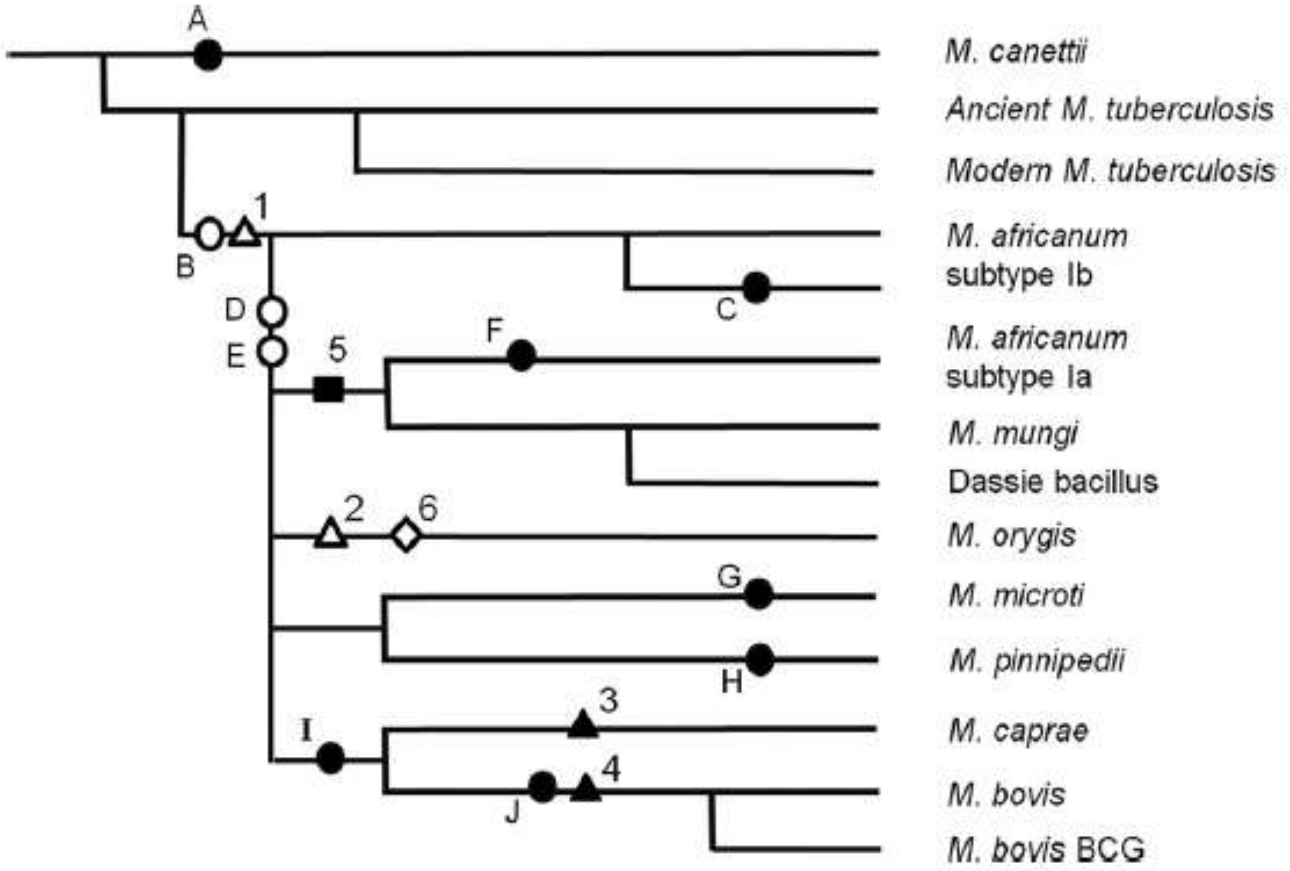
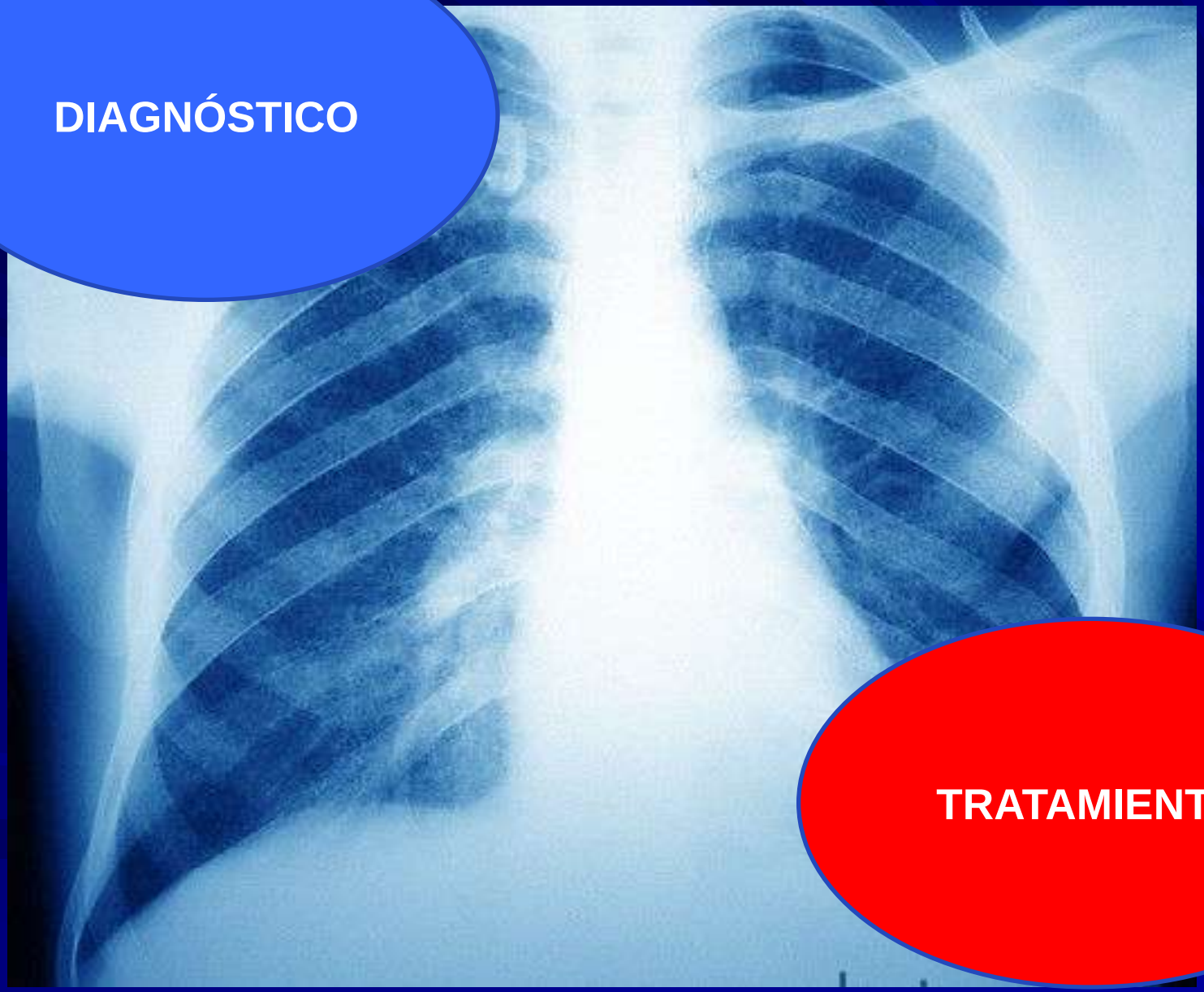


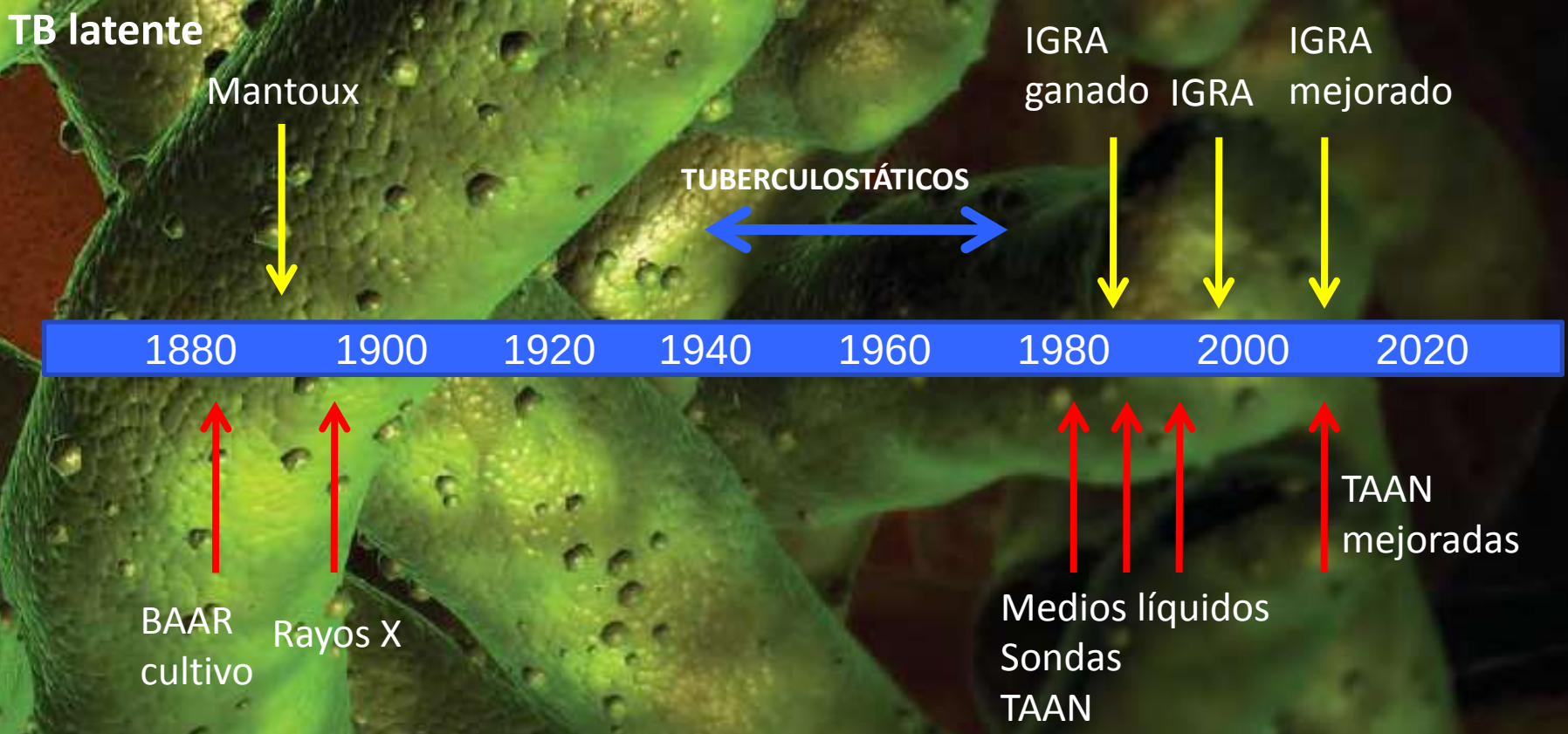
FIG 1 Summary diagram and phylogenetic positions of the genomic markers tested on the isolates from case A and case B as well as on one reference strain each of *M. tuberculosis*, *M. africanum*, *M. bovis*, *M. microti*, and *M. pinnipedii*. Ten RDs are represented by circles and denoted A to J; four different alleles of

DIAGNÓSTICO

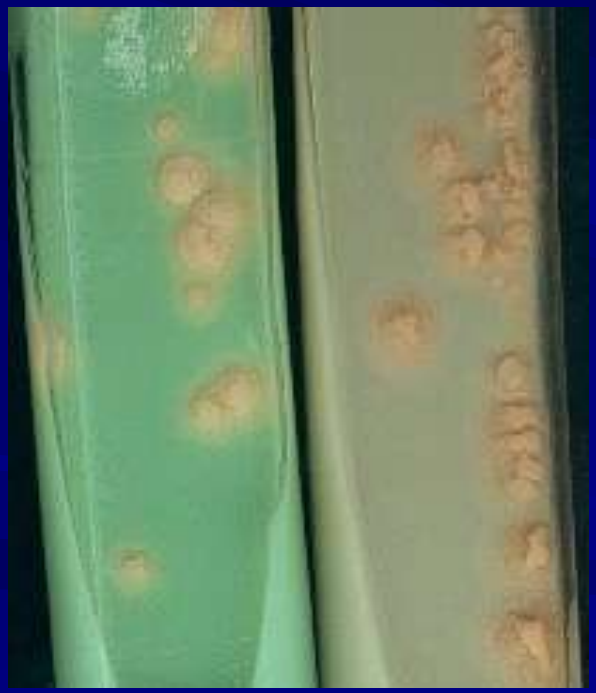


TRATAMIENTO

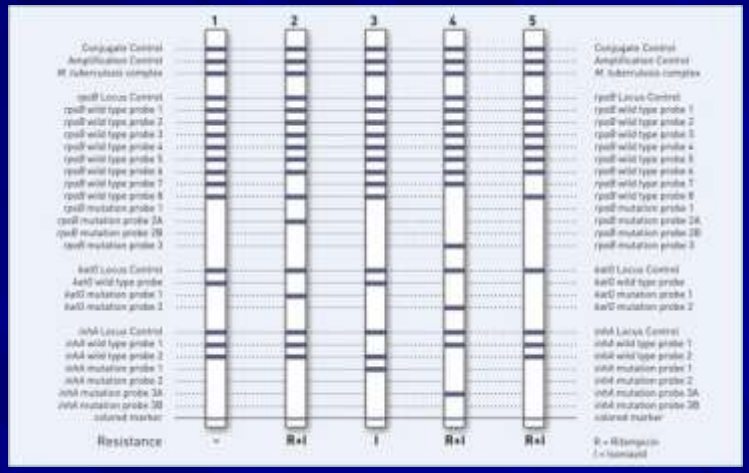
EVOLUCIÓN DEL DIAGNÓSTICO DE LA TUBERCULOSIS

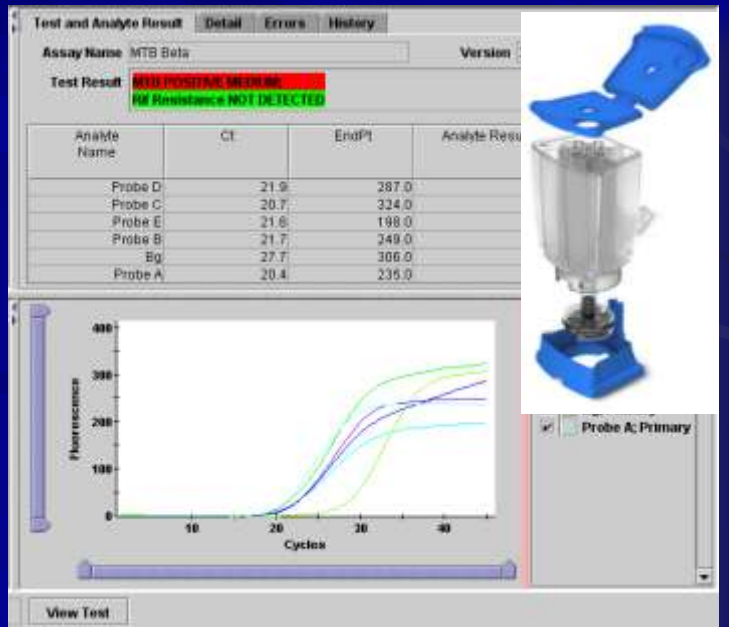


M. tuberculosis
CULTIVO

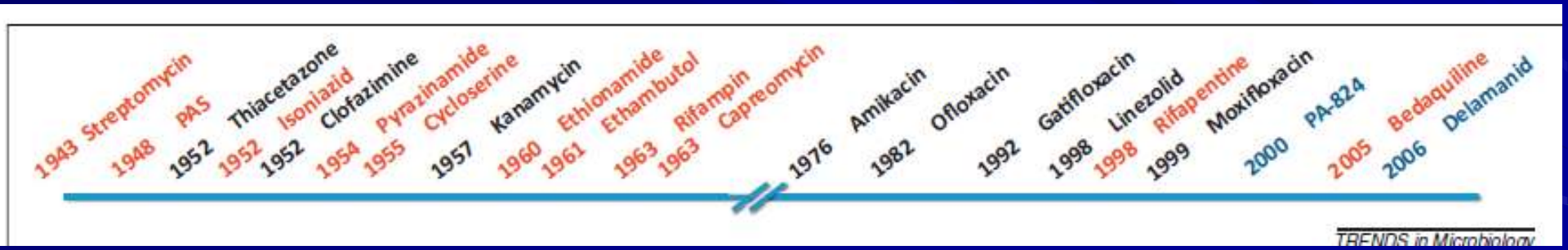


M. tuberculosis
Detección de resistencias





40 años no es nada…



	Daily dose
Group one: first-line oral antituberculosis drugs (use all possible drugs)	
Isoniazid	5 mg/kg
Rifampicin	10 mg/kg
Ethambutol	15–25 mg/kg
Pyrazinamide	30 mg/kg
Group two: fluoroquinolones (use only one, because they share genetic targets)	
Ofloxacin	15 mg/kg
Levofloxacin	15 mg/kg
Moxifloxacin	7·5–10 mg/kg
Group three: injectable antituberculosis drugs (use only one, because they share very similar genetic targets)	
Streptomycin	15 mg/kg
Kanamycin	15 mg/kg
Amikacin	15 mg/kg
Capreomycin	15 mg/kg
Group four: less-effective second-line antituberculosis drugs (use all possible drugs if necessary)	
Ethionamide/Prothionamide	15 mg/kg
Cycloserine/Terizidone	15 mg/kg
P-aminosalicylic acid (acid salt)	150 mg/kg
Group five: less-effective drugs or drugs on which clinical data are sparse (use all necessary drugs if there are less than four from the other groups)	
Clofazimine	100 mg
Amoxicillin with clavulanate	875/125 mg every 12 h
Linezolid	600 mg
Imipenem	500–1000 mg every 6 h
Clarithromycin	500 mg/12 h
High-dose isoniazid	10–15 mg/kg
Thioacetazone	150 mg

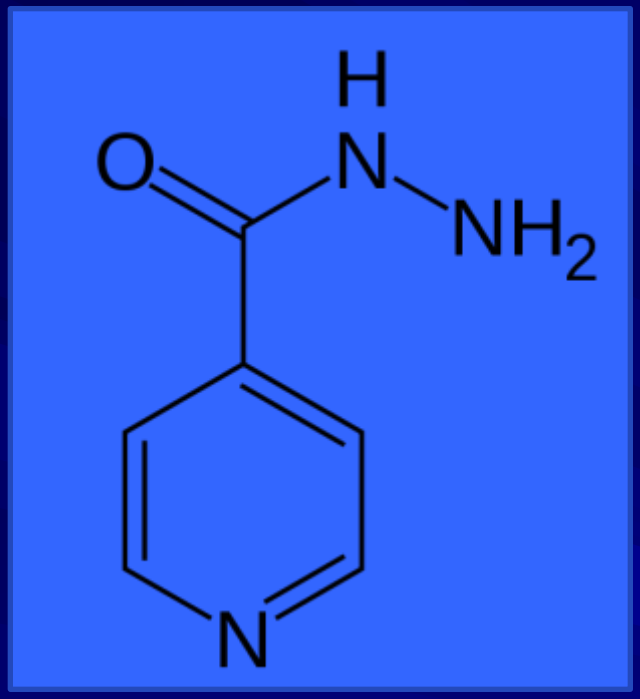
Table: Categories of antituberculosis drugs

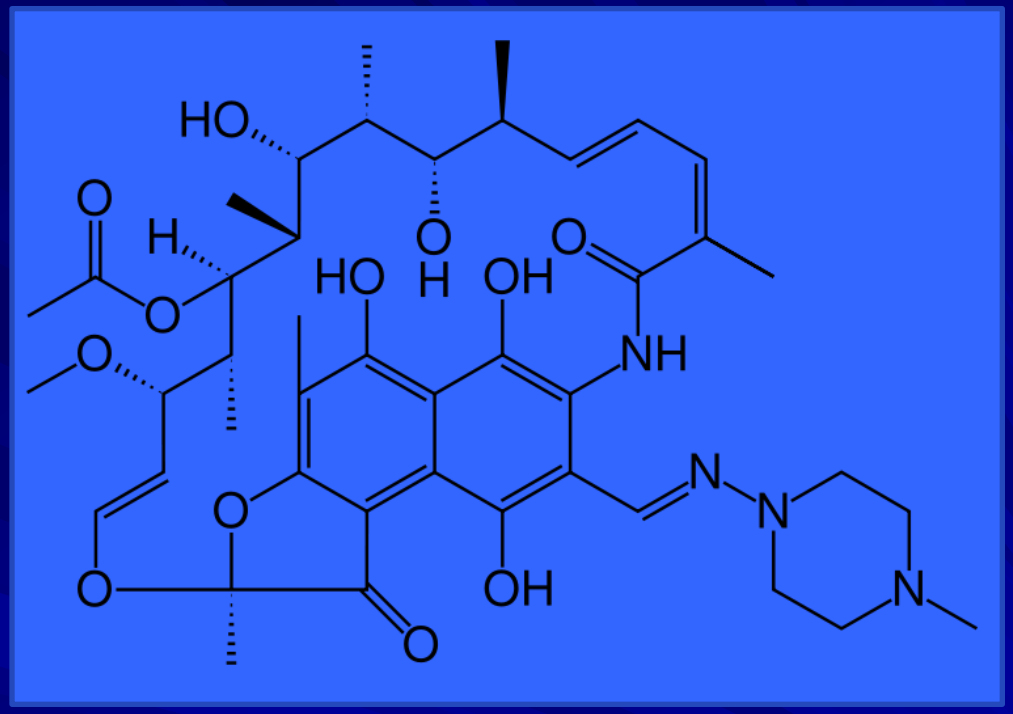
Drogas antituberculosas

Drogas de segunda línea tratamiento de la tuberculosis

Class	Agents
Aminoglycosides	Amikacin (Am) Kanamycin (Km)
Cyclic polypeptides	Capreomycin (Cm)
D-alanine analogues	Cycloserine (Cs) Terizidone (Trd)
Carbothionamides	Ethionamide (Eto) Protionamide (Pto)
Fluoroquinolones	Ciprofloxacin Gatifloxacin Levofloxacin (Lfx) Moxifloxacin (Mfx) Oxofloxacin (Ofx)
Antifolates	*p*-aminosalicylic acid (PAS)
Phenazine derivatives	Clofazimine (Cfz)

WHO guidelines for the programmatic management of drug-resistant tuberculosis: emergenc
update 2008. Available at:
http://www.who.int/tb/publications/2008/programmatic_guidelines_for_mdrtb/en/index.html





ISONIAZIDA

RIFAMPICINA

Tratamiento tuberculosis Normativa SEPAR

TABLA IV

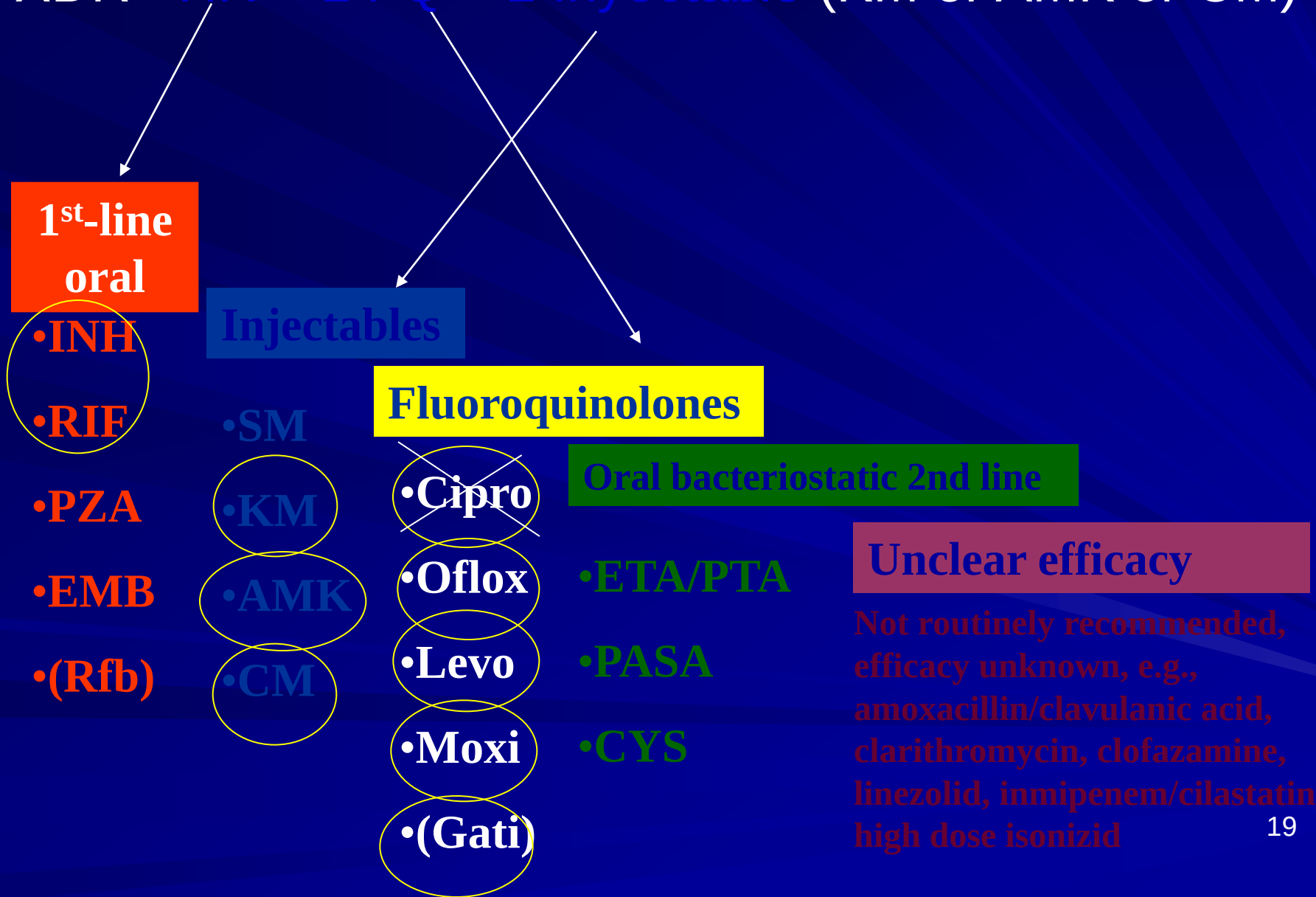
Tratamiento de la tuberculosis con preparados en combinación fija: número de pastillas, según el peso del paciente y el preparado

Peso (kg)	Rifater® (R 120 + H 50 + Z 300) Envase de 100 comprimidos	Peso (kg)	Rimcure® (R 150 + H 75 + Z 400) Envase de 100 comprimidos	Rimstar® (R 150 + H 75 + Z 400 + E 275) Envase de 60 comprimidos
< 40	3	38-54	3	3
40-49	4	55-70	4	4
50-64	5	> 70	5	5
> 64	6			
Fase de continuación: 4 meses				
Peso (kg)	**Rifinah® (R 300 + H 150) Envase de 60 comprimidos**		**Rimactazid® (R 300 + H 150) Envase de 60 comprimidos**	**Tisobrif® (R 600 + H 300) Envase de 30 sobres**
50-90	2		2	1

E: etambutol; H: isoniacida; R: rifampicina; Z: piracinamida.

MR=H+R

XDR= HR + 1 FQ + 1 Inyectable (KM or AMK or CM)



Emergence and Spread of Extensively and Totally Drug-Resistant Tuberculosis, South Africa

Marisa Klopper, Robin Mark Warren, Cindy Hayes, Nicolaas Claudius Gey van Pittius, Elizabeth Maria Streicher, Borna Müller, Frederick Adriaan Sirgel, Mamisa Chabula-Nxiweni, Ebrahim Hoosain, Gerrit Coetzee, Paul David van Helden, Thomas Calldo Victor, and André Phillip Trollip

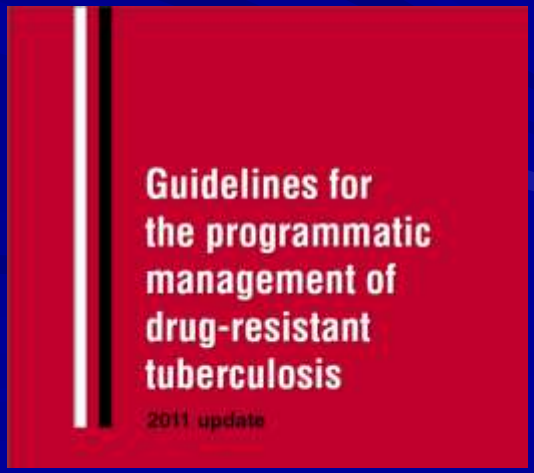
Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 19, No. 3, March 2013

1,7 drogas por paciente sensibles (10/11 ó 11/11, PAS incluído)
Tasa de muerte del 58%

- En el tratamiento de la tuberculosis multirresistente los regímenes deben incluir:
  - Pirazinamida
  - Fluorquinolona
  - Agente parenteral
  - Etionamida o protionamida
  - Cicloserina o PAS

DURACIÓN DEL TRATAMIENTO TB MULTIRRESISTENTE

- Fase intensiva de 8 meses y modificación según respuesta.
- En pacientes nuevamente diagnosticados con TB multi-R 20 meses de tratamiento, modificados según respuesta.



TRATAMIENTO TUBERCULOSIS XDR

NIH Public Access
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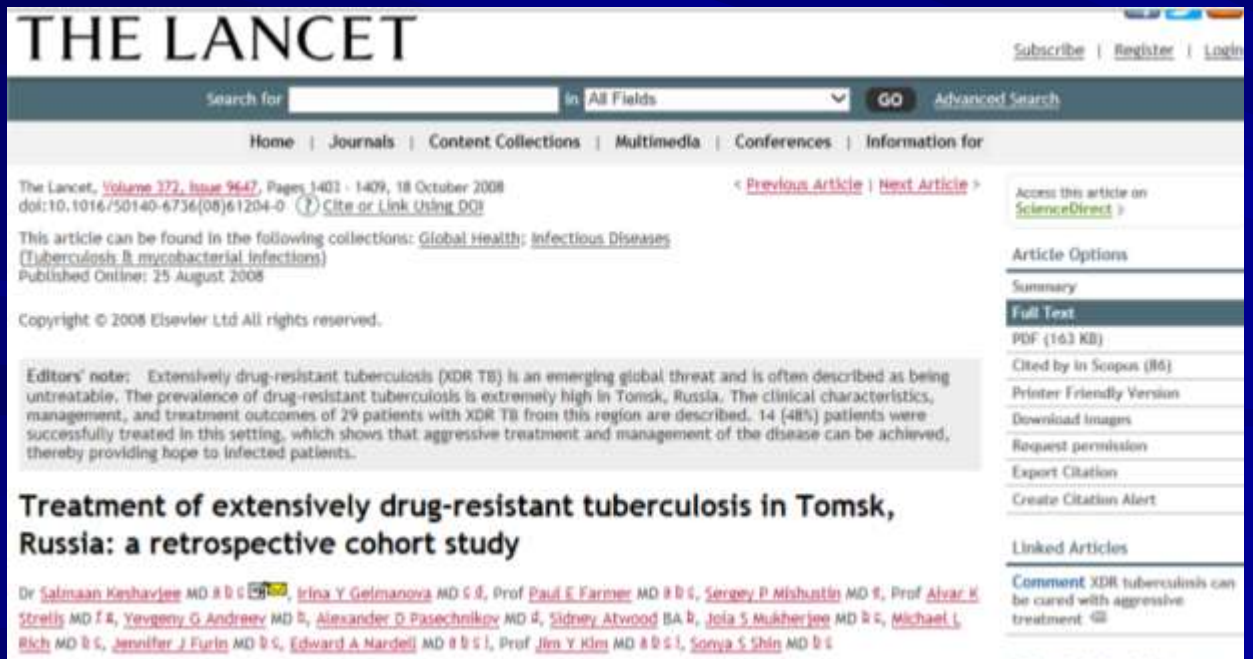
N Engl J Med. Author manuscript; available in PMC 2009 April 27.

Published in final edited form as:
N Engl J Med. 2008 August 7; 359(6): 563–574. doi:10.1056/NEJMoa0800106.

Comprehensive Treatment of Extensively Drug-Resistant Tuberculosis

Carole D. Mitnick, Sc.D., Sonya S. Shin, M.D., Kwonjune J. Seung, M.D., Michael L. Rich, M.D., Sidney S. Atwood, B.A., Jennifer J. Furin, M.D., Ph.D., Garrett M. Fitzmaurice, Sc.D., Felix A. Alcantara Viru, M.D., Sasha C. Appleton, Sc.M., Jaime N. Bayona, M.D., Cesar A. Bonilla, M.D., Katiuska Chalco, R.N., Sharon Choi, M.S., Molly F. Franke, B.A., Hamish S.F. Fraser, M.B., Ch.B., Dalia Guerra, Rocio M. Hurtado, M.D., Darius Jazayeri, M.S., Keith Joseph, M.D., Karim Llaro, R.N., Lorena Mestanza, R.N., Joia S. Mukherjee, M.D., Maribel Muñoz, R.N., Eda Palacios, R.N., Epifanio Sanchez, M.D., Alexander Sloutsky, Ph.D., and Mercedes C. Becerra, Sc.D.

60% vs. 66% curación o tto. completado en XDR vs. MDR



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The Lancet, Volume 372, Issue 9647, Pages 1403 - 1409, 18 October 2008
doi:10.1016/S0140-6736(08)61204-0 Cite or Link Using DOI

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This article can be found in the following collections: Global Health; Infectious Diseases (Tuberculosis & mycobacterial infections)
Published Online: 25 August 2008

Editors' note: Extensively drug-resistant tuberculosis (XDR TB) is an emerging global threat and is often described as being untreatable. The prevalence of drug-resistant tuberculosis is extremely high in Tomsk, Russia. The clinical characteristics, management, and treatment outcomes of 29 patients with XDR TB from this region are described. 14 (48%) patients were successfully treated in this setting, which shows that aggressive treatment and management of the disease can be achieved, thereby providing hope to infected patients.

Treatment of extensively drug-resistant tuberculosis in Tomsk, Russia: a retrospective cohort study

Dr Salmaan Keshavjee MD, Irina Y Gelmanova MD, Prof Paul E Farmer MD, Sergey P Mishustin MD, Prof Alvar K Strelis MD, Yevgeny G Andreev MD, Alexander D Pasechnikov MD, Sidney Atwood BA, Joia S Mukherjee MD, Michael L Rich MD, Jennifer J Furin MD, Edward A Nardell MD, Prof Jim Y Kim MD, Sonya S Shin MD

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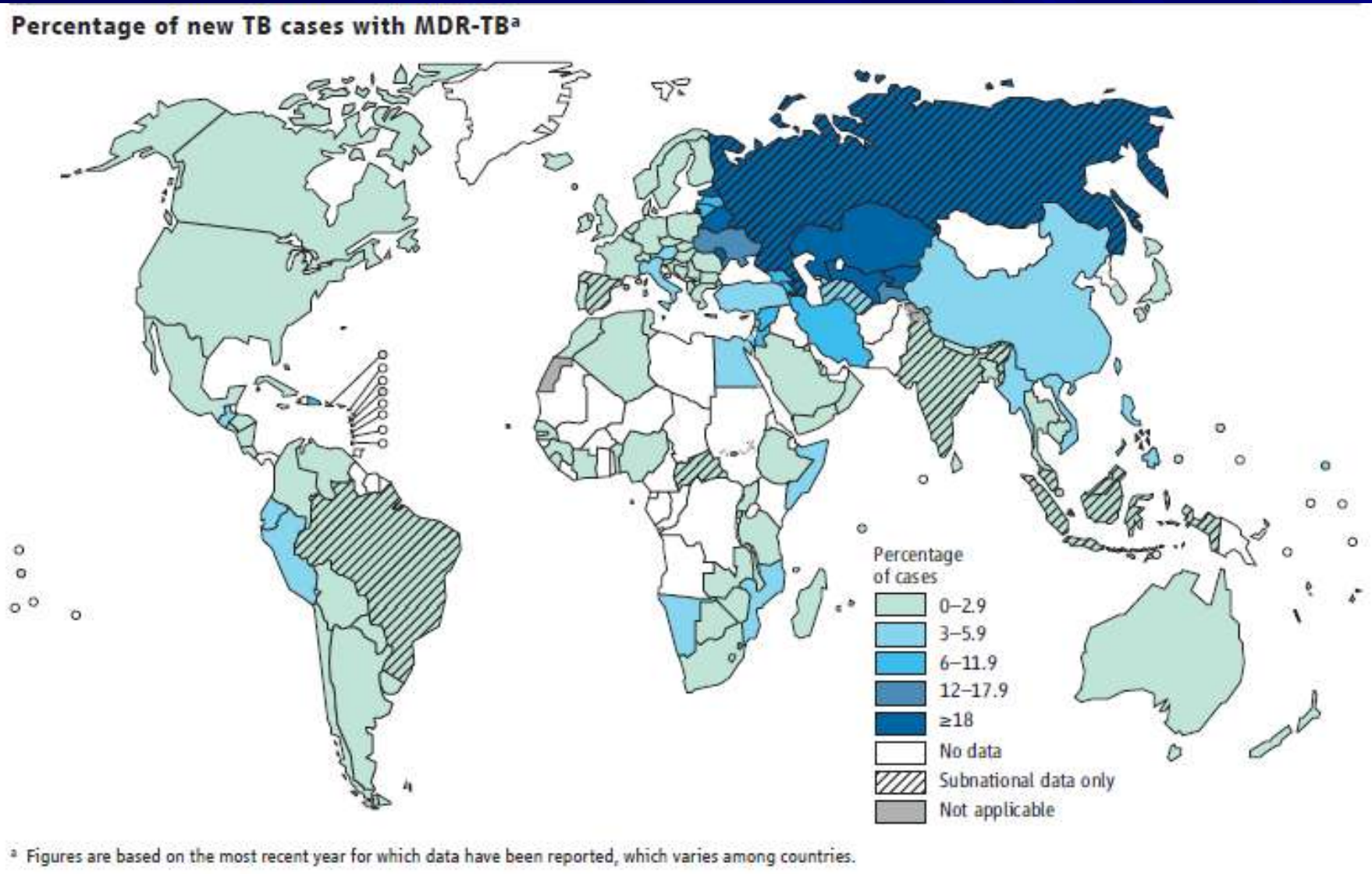
Comment XDR tuberculosis can be cured with aggressive treatment

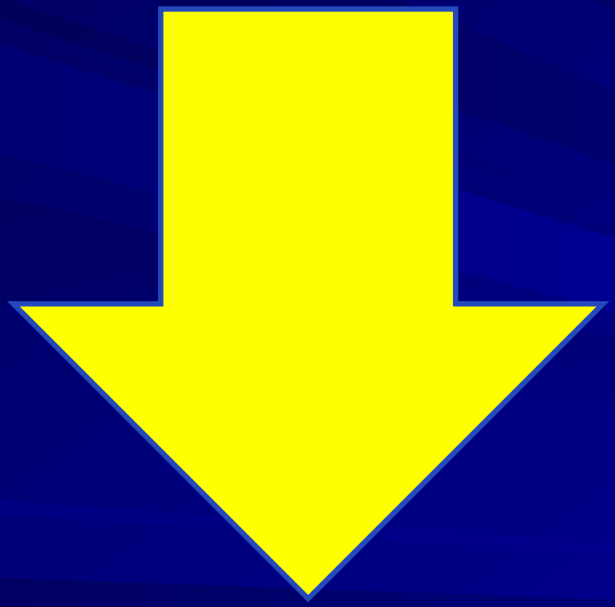
48% vs. 66% curación o tto. completado en XDR vs. MDR

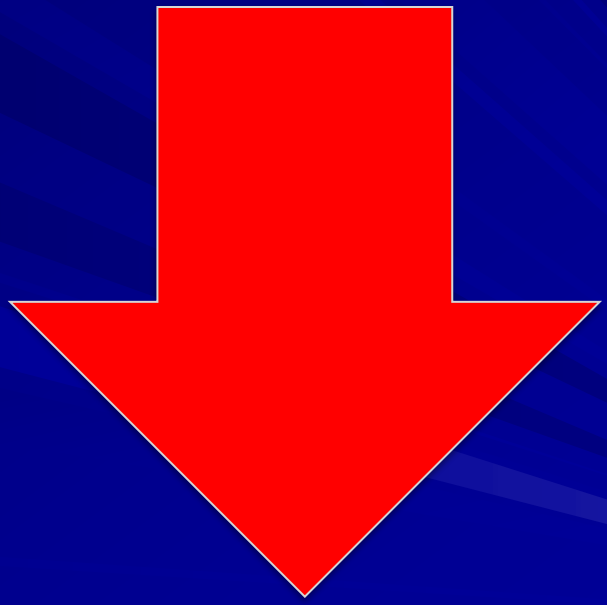
Porcentaje de casos nuevos MDR- TB



Hospital Universitario de La Princesa

Tratamiento de la tuberculosis
Nuevas estrategias

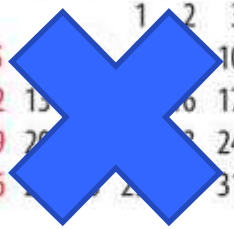




2014

January

Sun	Mon	Tue	Wed	Thu	Fri	Sat
			1	2	3	4
5					10	11
12	13				17	18
19	20				24	25
26					31	



February

Sun	Mon	Tue	Wed	Thu	Fri	Sat
						1
2	3				7	8
9	10				14	15
16	17				21	22
23	24				28	

March

Sun	Mon	Tue	Wed	Thu	Fri	Sat
						1
2					7	8
9					14	15
16	17				21	22
23					28	29
30	31					

April

Sun	Mon	Tue	Wed	Thu	Fri	Sat
		1	2	3	4	5
6					11	12
13	14				18	19
20	21				25	26
27						

May

Sun	Mon	Tue	Wed	Thu	Fri	Sat
					2	3
4	5					10
11	12	13			16	17
18	19					24
25	26		28		30	31

June

Sun	Mon	Tue	Wed	Thu	Fri	Sat
1	2		4		6	7
8	9				13	14
15	16				20	21
22	23				27	28
29	30					

July

Sun	Mon	Tue	Wed	Thu	Fri	Sat
		1	2	3	4	5
6	7	8	9	10	11	12
13	14	15	16	17	18	19
20	21	22	23	24	25	26
27	28	29	30	31		

August

Sun	Mon	Tue	Wed	Thu	Fri	Sat
					1	2
3	4	5	6	7	8	9
10	11	12	13	14	15	16
17	18	19	20	21	22	23
24	25	26	27	28	29	30
31						

September

Sun	Mon	Tue	Wed	Thu	Fri	Sat
	1	2	3	4	5	6
7	8	9	10	11	12	13
14	15	16	17	18	19	20
21	22	23	24	25	26	27
28	29	30				

October

Sun	Mon	Tue	Wed	Thu	Fri	Sat
			1	2	3	4
5	6	7	8	9	10	11
12	13	14	15	16	17	18
19	20	21	22	23	24	25
26	27	28	29	30	31	

November

Sun	Mon	Tue	Wed	Thu	Fri	Sat
						1
2	3	4	5	6	7	8
9	10	11	12	13	14	15
16	17	18	19	20	21	22
23	24	25	26	27	28	29
30						

December

Sun	Mon	Tue	Wed	Thu	Fri	Sat
	1	2	3	4	5	6
7	8	9	10	11	12	13
14	15	16	17	18	19	20
21	22	23	24	25	26	27
28	29	30	31			

TRATAMIENTO DE TUBERCULOSIS MDR Y XDR

Menos activos
Más tóxicos
Más caros
Más monitorización

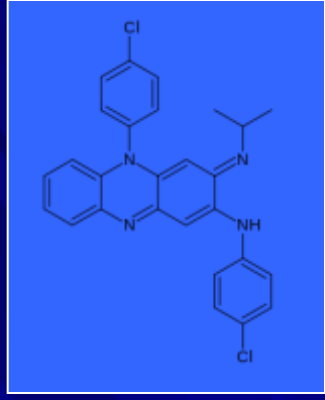
“Fármacos reemergentes”

“Fármacos actuales”

“Nuevos fármacos”

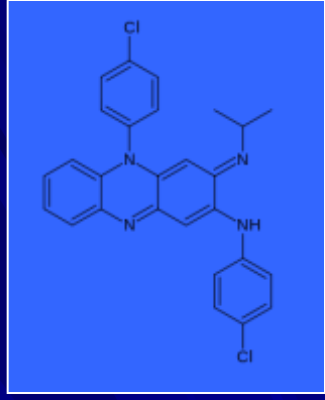
ESTRATEGIAS EN EL TRATAMIENTO DE LA TUBERCULOSIS

- CLOFAZIMINA
- RIFAPENTINA
- LINEZOLID
- BEDAQUILINA (TMC-207)
- DELAMANID (OPC-67683)
- PA-824
- SUTEZOLID
- POSIZOLID
- SQ-109



CLOFAZIMINA
TRATAMIENTO TUBERCULOSIS

- Derivado rimimofenazina.
- Actúa a nivel del ADN de la micobacteria.
- Diseñada en 1954 Trinity College (Dublín).
- Desde 1959 tratamiento de la lepra.
- Efectos secundarios: pigmentación piel, conjuntiva, intestinales.
- Problemas en la obtención del fármaco.



CLOFAZIMINA
TRATAMIENTO TUBERCULOSIS
EXPERIENCIA CLÍNICA

- Régimen de Bangladesh
  - GATI+CLOF+ETAM+PIRA 9 meses
  - PROT+KANA+INH 4 meses
  - 88% curación en MDR

    Van deun Am J Resp Car Dis 2010
- Dos ensayos clínicos en estudio
  - STREAM MOXI+CLOF+ETAM+PIR 9 meses
  - PROT+KANA+INH 4 meses.

    Hwang et al, BMJ Open 2014

Pharmaceuticals **2012**, *5*, 1021-1031; doi:10.3390/ph5091021

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pharmaceuticals

ISSN 1424-8247

www.mdpi.com/journal/pharmaceuticals

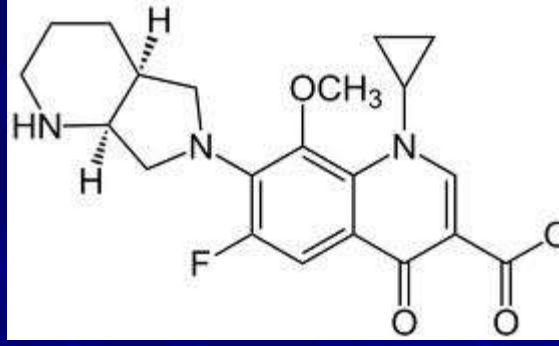
Review

Why and How the Old Neuroleptic Thioridazine Cures the XDR-TB Patient

Leonard Amaral [1,*] and Joseph Molnar [2]

FÁRMACOS ACTUALES

MOXIFLOXACINO



- Inhibidor de la DNA girasa

ELSEVIER

International Journal of Antimicrobial Agents 20 (2002) 464–467

www.isochem.org

In vitro activity of moxifloxacin, levofloxacin, gatifloxacin and linezolid against *Mycobacterium tuberculosis*

J.C. Rodríguez*, M. Ruiz, M. López, G. Royo

Section of Microbiology, Hospital General Universitario de Elche, Universidad Miguel Hernández, 03202 Elche, Alicante, Spain

Received 22 April 2002; accepted 10 May 2002

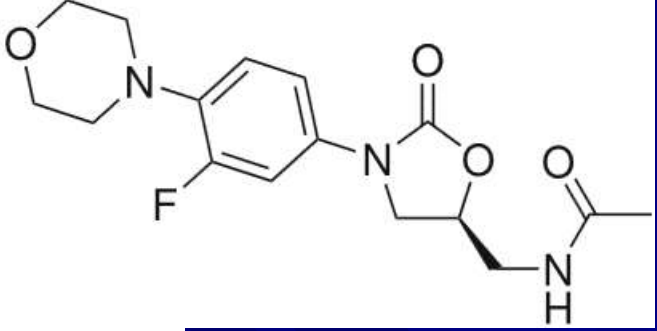
Table 1
Antibiotic activity against the studied strains

	0.06 mg/l	0.125 mg/l	0.25 mg/l	0.5 mg/l	1 mg/l	2 mg/l	4 mg/l	8 mg/l	16 mg/l	>16 mg/l
M[a]	7[e]	27	174	29	1	2	1	2	0	0
G[b]	13	106	100	18	0	3	0	2	0	1
L[c]	2	25	106	104	1	0	1	1	2	1
LI[d]	2	4	100	125	9	0	0	0	0	3

[a] Moxifloxacin.
[b] Gatifloxacin.
[c] Levofloxacin.
[d] Linezolid.
[e] Number of strains.

FÁRMACOS ACTUALES

LINEZOLID



Jpn. J. Infect. Dis., 65, 240-242, 2012

Short Communication

In Vitro Activity of Linezolid against Clinical Isolates of *Mycobacterium tuberculosis*, including Multidrug-Resistant and Extensively Drug-Resistant Strains from Beijing, China

Caie Yang[1†], Hong Lei[1†], Di Wang[2†] Xianghong Meng[1], Jufang He[1], Aihua Tong[1], Lei Zhu[1], Ying Jiang[1], and Mei Dong[1*]

[1]*Department of Cli*
[2]*309th*

Table 1. In vitro activity of linezolid against 84 clinical isolates of *M. tuberculosis*[1)]

Isolate	No. of isolates	Resistance phenotype	MIC (μg/ml)		
			Range	MIC_{50}	MIC_{90}
H37Rv	1	Susceptible			
(all susceptible INH-resistant)	15	Susceptible	0.125–0.5	0.25	0.25
	2	INH, SM			
	6	INH, EMB			
Total	8		0.125–0.25	0.25	0.25
MDR	8	RFP, INH			
	9	RFP, INH, SM			
	12	RFP, INH, EMB			
	2	RFP, INH, OFL			
	14	RFP, INH, EMB, SM			
Total	45		0.125–0.5	0.25	0.25
XDR	5	RFP, INH, EMB, SM, OFL, KN, PAS			
	11	RFP, INH, EMB, SM, OFL, AM, PAS			
Total	16		0.125–0.5	0.25	0.25

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A.A.C Sept. 2013

MINIREVIEW

WHO Group 5 Drugs and Difficult Multidrug-Resistant Tuberculosis: a Systematic Review with Cohort Analysis and Meta-Analysis

Kwok-Chiu Chang,[a] Wing-Wai Yew,[b] Cheuk-Ming Tam,[a] Chi-Chiu Leung[a]

Tuberculosis and Chest Service, Department of Heath, Hong Kong SAR, China[a]; Department of Microbiology, the Chinese University of Hong Kong, Hong Kong SAR, China[b]

TABLE 3 Robust Poisson regression models of favorable outcome and use of group 5 drugs[a]

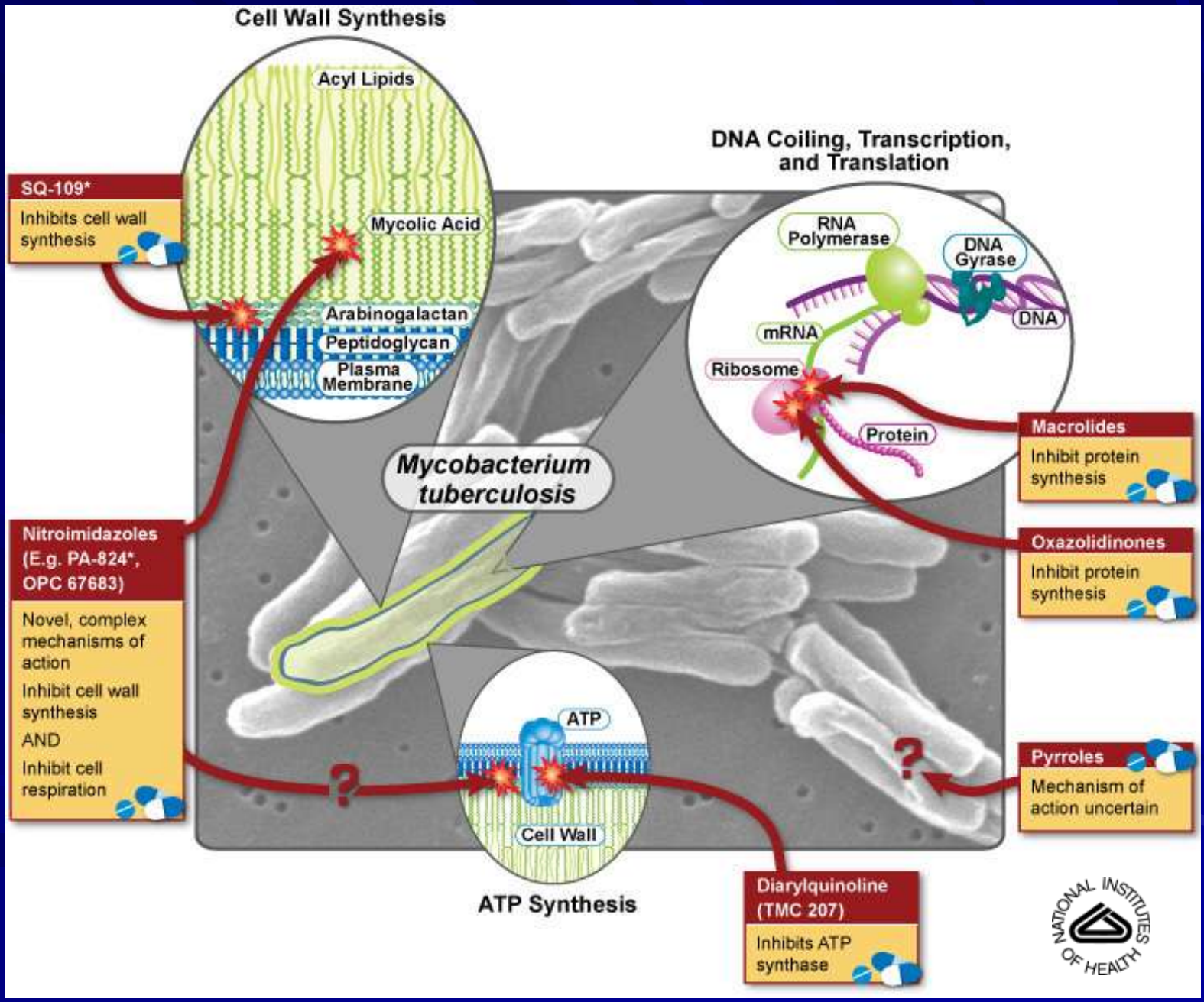
Model	Predictor variable	Risk ratio (95% confidence interval)
A	Linezolid	1.57 (1.10–2.24)
B	Linezolid	1.61 (1.10–2.35)
	High-dose isoniazid	1.12 (0.90–1.40)
	Clofazimine	1.01 (0.80–1.26)
	Amoxicillin with clavulanate	0.88 (0.71–1.09)
	Macrolides	1.13 (0.92–1.37)
	Carbapenem with or without clavulanate	1.09 (0.82–1.46)
	Thioridazine	0.86 (0.60–1.24)

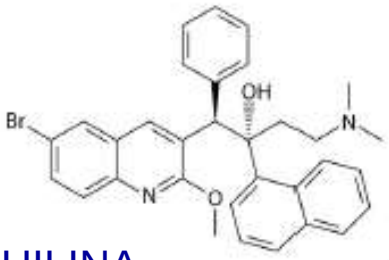
[a] The mention of a group 5 drug(s) refers to its use.

TABLE 4 Results of random-effects meta-analysis of favorable outcome and use of group 5 drugs[a]

Group 5 drug(s)	*P* value of the Q-test for heterogeneity	*P* value of the Egger's regression test for funnel plot asymmetry	Pooled estimate of risk ratio (95% confidence interval)
Linezolid	1.00	0.41	1.55 (1.10–2.21)
High-dose isoniazid	0.998	0.23	0.95 (0.67–1.33)
Clofazimine	0.99	0.89	0.99 (0.76–1.31)
Amoxicillin with clavulanate	0.998	0.27	1.01 (0.78–1.30)
Macrolides	0.96	0.73	0.96 (0.76–1.22)
Carbapenem with or without clavulanate	1.00	0.24	0.76 (0.48–1.22)
Thioridazine	1.00	0.22	0.78 (0.54–1.13)

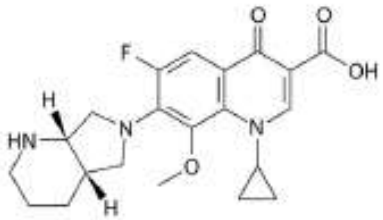
[a] Meta-analysis of linezolid involves the entire cohort of 194 patients, whereas that of each of the nonlinezolid group 5 drugs is restricted to the 162 patients given linezolid-containing regimens.


Cell Wall Synthesis
Acyl Lipids
Mycolic Acid
Arabinogalactan
Peptidoglycan
Plasma Membrane
SQ-109*
Inhibits cell wall synthesis
DNA Coiling, Transcription, and Translation
RNA Polymerase
DNA Gyrase
DNA
mRNA
Ribosome
Protein
Macrolides
Inhibit protein synthesis
Oxazolidinones
Inhibit protein synthesis
Mycobacterium tuberculosis
Nitroimidazoles (E.g. PA-824*, OPC 67683)
Novel, complex mechanisms of action
Inhibit cell wall synthesis
AND
Inhibit cell respiration
ATP
Cell Wall
?
?
Pyrroles
Mechanism of action uncertain
ATP Synthesis
Diarylquinoline (TMC 207)
Inhibits ATP synthase
NATIONAL INSTITUTES OF HEALTH



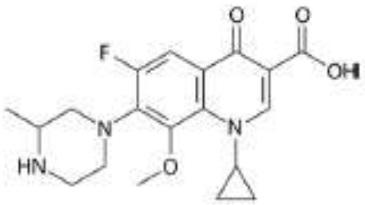
BEDAQUILINA
SIRTURO®

1



MOXIFLOXACINO

2



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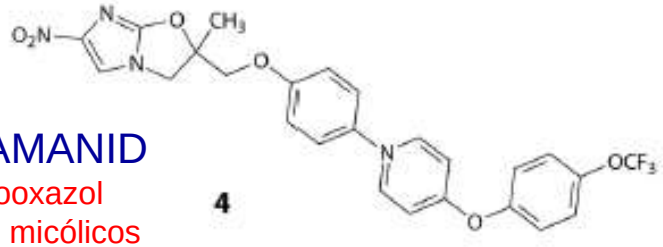
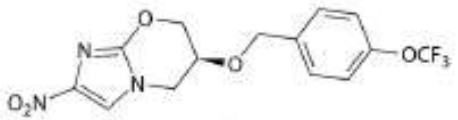
GATIFLOXACINO



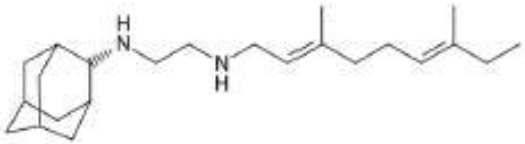
DELAMANID
Imidazooxazol
Sint. A. micólicos

4



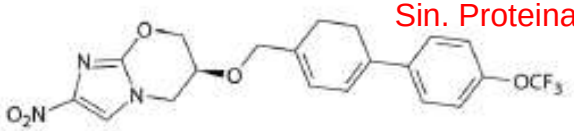
5

PA-824
Nitroimidazopirano
Sin. Proteinas, lip. pared



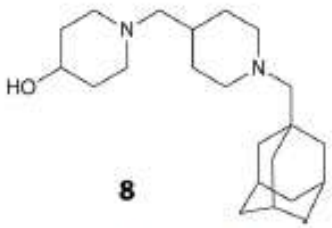
6

SQ-109
Etambutol-like
Pared celular



TBA-354

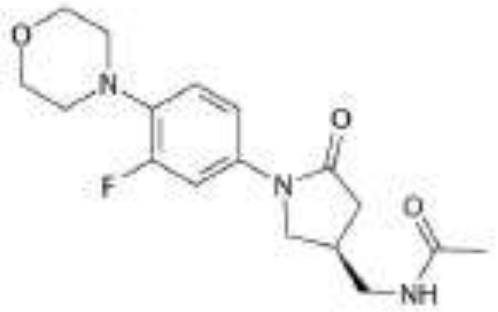
7



SQ-609

8

FIG 7 Structures of investigational agents with activity against *Mycobacterium tuberculosis*. 1, bedaquiline; 2, moxifloxacin; 3, gatifloxacin; 4, delamanid; 5, PA-824; 6, SQ-109; 7, TBA-354; 8, SQ-609.



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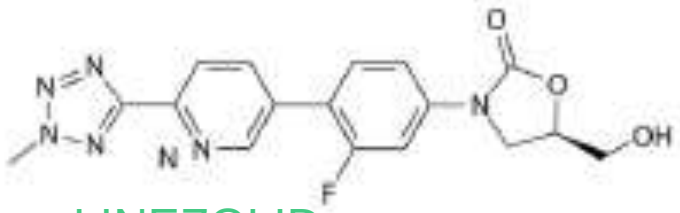
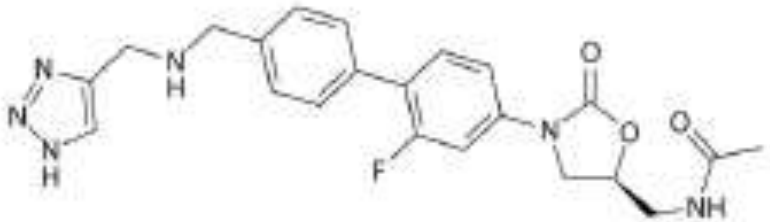


LINEZOLID

7



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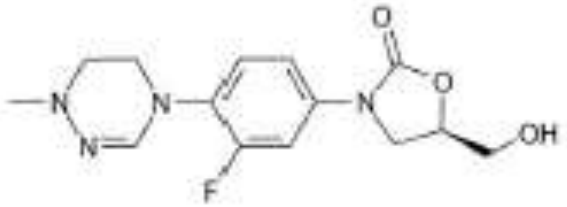

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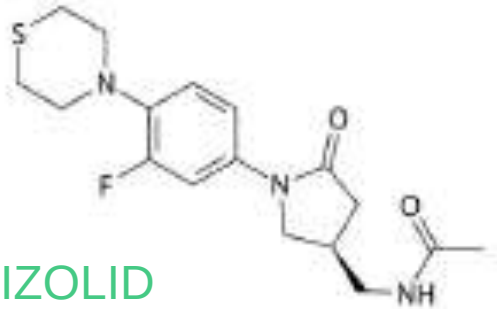
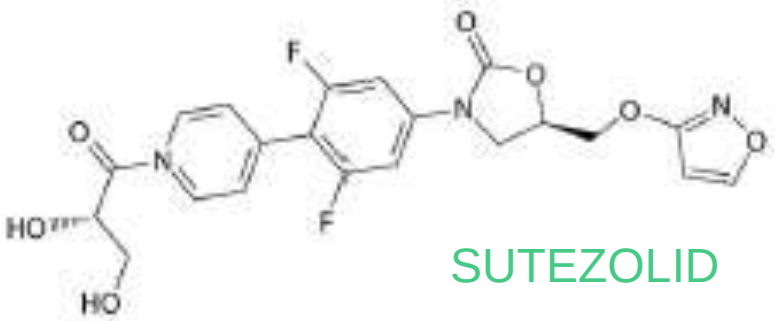


POSIZOLID

10

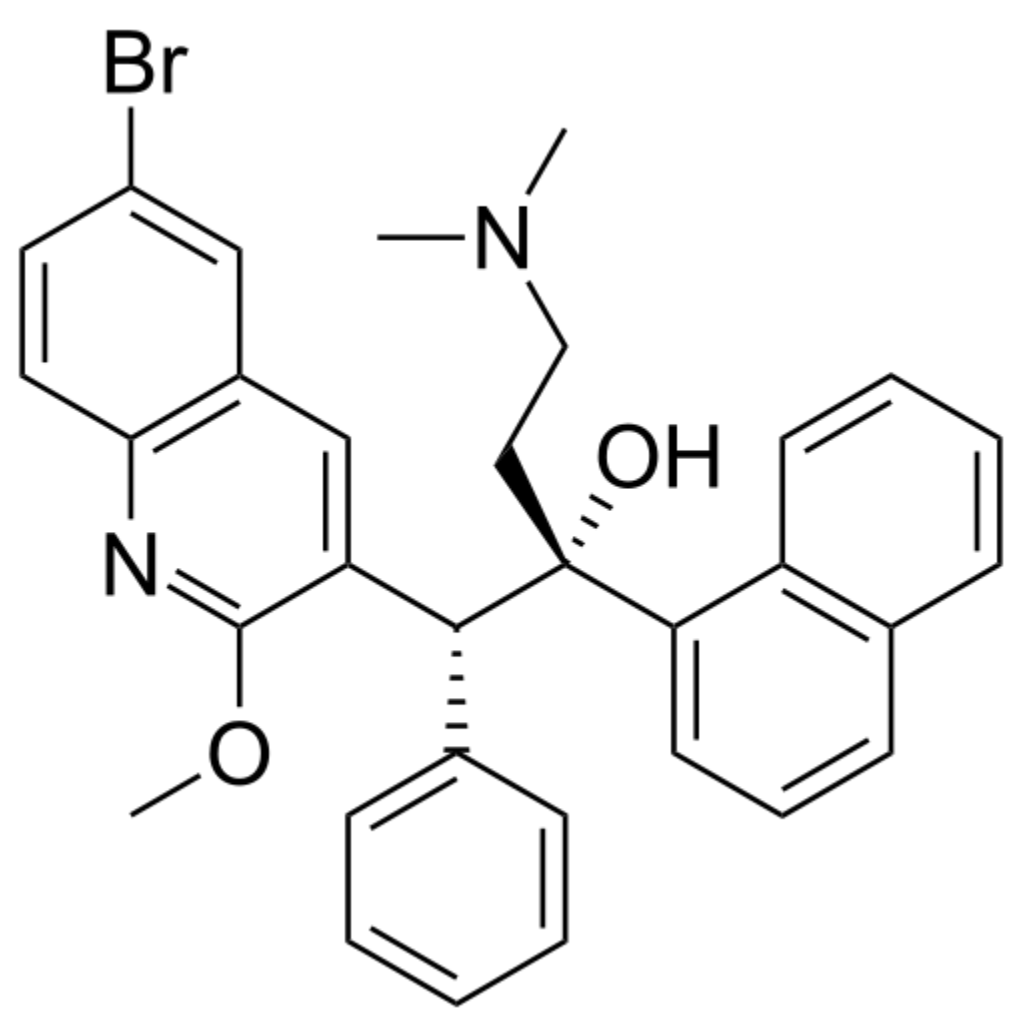


SUTEZOLID

11

NUEVOS FÁRMACOS

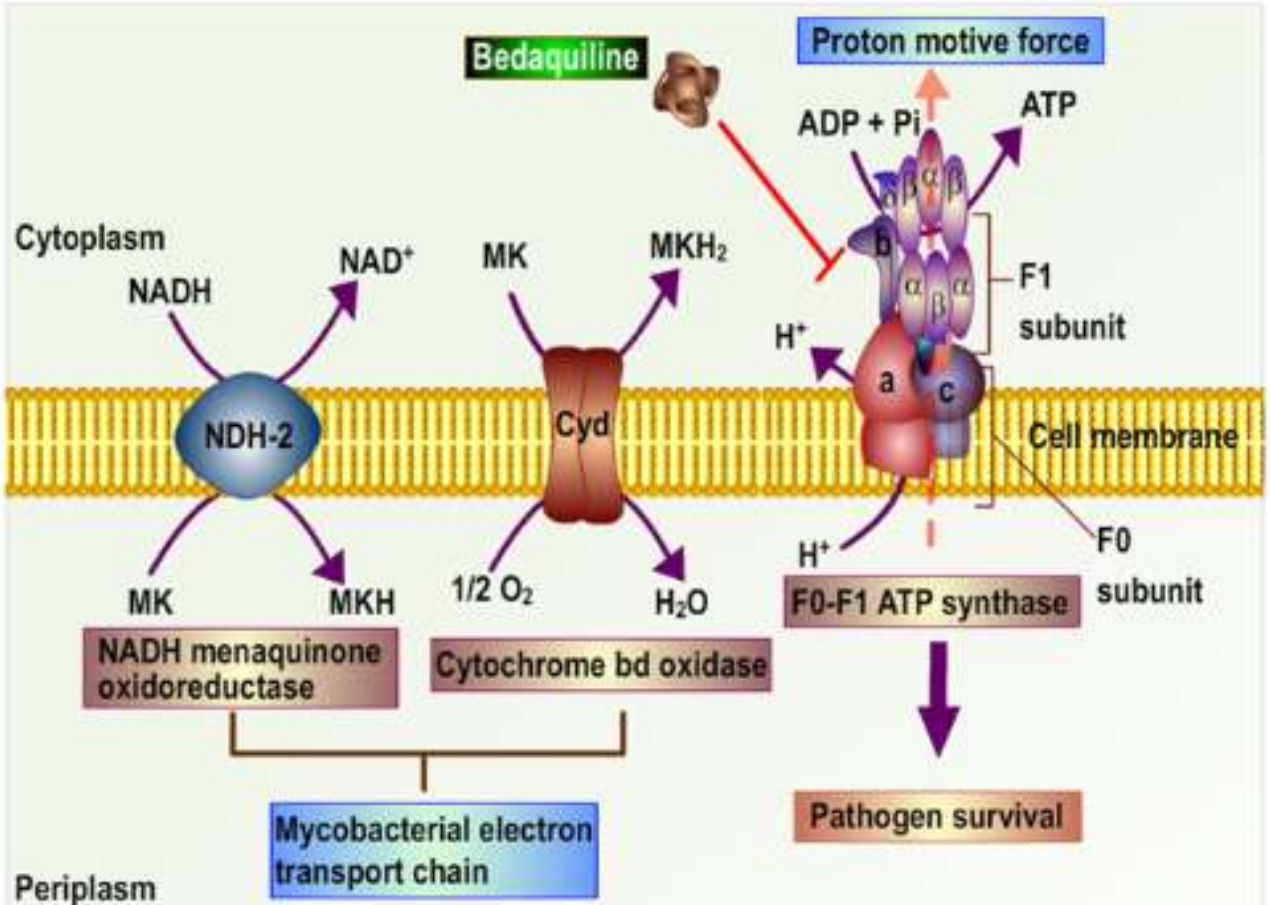
Bedaquilina / Estructura química
Diarilquinoleina



NUEVOS FÁRMACOS

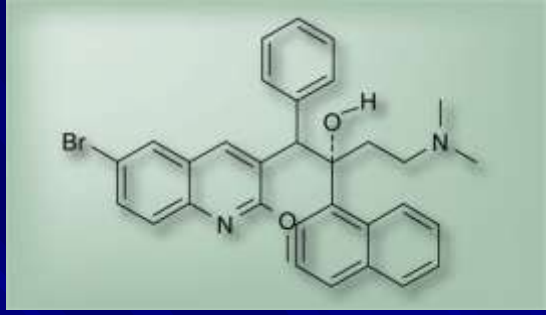
Bedaquilina
Mecanismo de acción

here.



NUEVOS FÁRMACOS

Bedaquilina
Actividad in vitro



TMC207-sensitive species	MIC range (μg/ml)	Median MIC_{99} (μg/ml)
Mycobacterium tuberculosis		
Drug-sensitive *M. tuberculosis*	0.030–0.120/0.002–0.06	0.060
Multidrug-resistant *M. tuberculosis*	0.030–0.030/0.004–0.13	0.030
Nontuberculous mycobacteria		
Mycobacterium avium	0.007–0.010/0.03–0.13	0.010
Mycobacterium intracellulare	0.007–0.010/0.03–0.25	0.010
Mycobacterium chelonae	0.06–0.5	–
Mycobacterium fortuitum	0.007–0.010/0.13–0.25	–
Mycobacterium kansasii	0.003/0.03	–
Mycobacterium malmoense	0.50	–
Mycobacterium gordonae	0.03	–
Mycobacterium scrofulaceum	0.03	–
Mycobacterium marinum	0.003	–
Mycobacterium xenopi	4.0–8.0	–
Mycobacterium shimoidei	8.0	–
Mycobacterium novocastrense	8.0	–

NUEVOS FÁRMACOS

Bedaquilina / Experiencia clínica

- Ensayo clínico en Tuberculosis multiR
  - Bedaquilina+ETI+KANA+PIRA+OFLOX+CICL
  - Placebo+ ETI+KANA+PIRA+OFLOX+CICL

  24 semanas y tto. habitual 18-24 meses

Periodo de conversión a cultivo negativo
83 días (bedaquilina)
125 (placebo)

Diacon et al, N Engl J Med 2009

Bedaquilina / Experiencia clínica

- Ensayo clínico similar
- 8 Semanas vs. 24

ALERTA
INDICES MAS ALTOS DE MUERTES NO EXPLICADAS EN EL GRUPO DE BEDAQUILINA
(11.4% VS. 2.5% P=0.03)

Bedaquilina

- Cuidado con inductores/inhibidores CYP3A4
- Vigilar intervalo QT
- Efectos secundarios: nausea,cefalea, artralgia
- Monitorizar parámetros bioquímicos

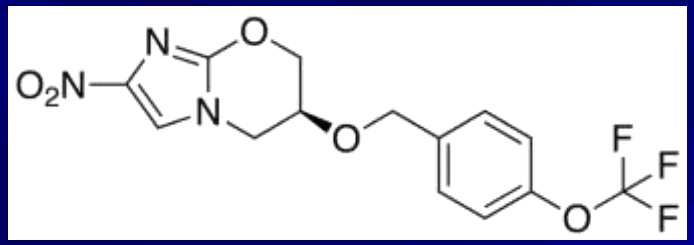
Centers for Disease Control and Prevention
MMWR
Morbidity and Mortality Weekly Report
Recommendations and Reports / Vol. 62 / No. 9
October 25, 2013

Expert opinion: The possible benefits of using bedaquiline outweigh the potential risk.

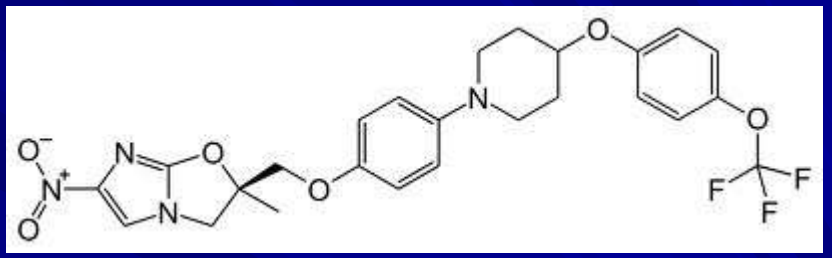
Provisional CDC Guidelines for the Use and Safety Monitoring of Bedaquiline Fumarate (Sirturo) for the Treatment of Multidrug-Resistant Tuberculosis

NUEVOS FÁRMACOS

NITROIMIDAZOPIRANOS



PA-824
nitroimidazoxazina

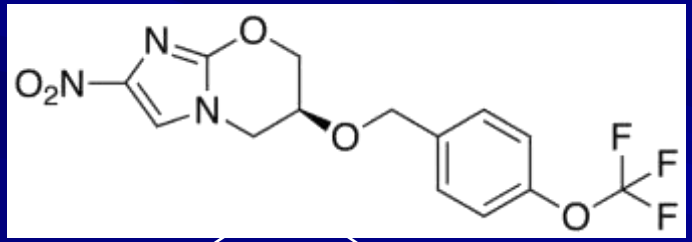


Delamanid OPC-67683
Nitro-dihidro-imidazoxazol

NUEVOS FÁRMACOS

Nitroimidazopiranos *Mycobacterium tuberculosis*

- Mecanismo de acción
  - Interferencia con la síntesis de ketomicolato
  - Actuando como donador de óxido nítrico, causando envenenamiento respiratorio



Actividad aerobia frente a bacterias en replicación

Actividad anaerobia frente a bacterias latentes

OPEN ACCESS Freely available online PLOS MEDICINE

OPC-67683, a Nitro-Dihydro-Imidazooxazole Derivative with Promising Action against Tuberculosis In Vitro and In Mice

Makoto Matsumoto[1*], Hiroyuki Hashizume[1], Tatsuo Tomishige[1], Masanori Kawasaki[1], Hidetsugu Tsubouchi[2], Hirofumi Sasaki[2], Yoshihiko Shimokawa[3], Makoto Komatsu[2]

1 Microbiological Research Institute, Otsuka Pharmaceutical, Tokushima, Japan, 2 Medicinal Chemistry Research Institute, Otsuka Pharmaceutical, Tokushima, Japan, 3 Tokushima Research Institute, Otsuka Pharmaceutical, Tokushima, Japan

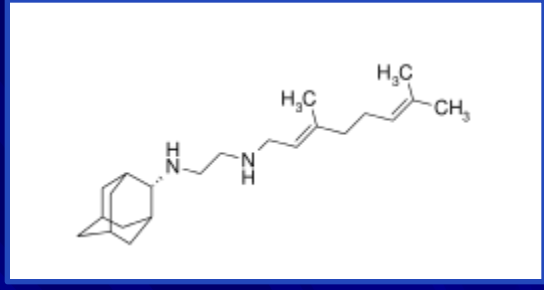
Table 3. MIC_{90} of OPC-67683 against Drug-Susceptible and Drug-Resistant *M. tuberculosis*

Organism Group (Number of Strains)	MIC (μg/ml)	
	MIC_{90}	95% Confidence Intervals
RFP-susceptible *M. tuberculosis* (31)	0.01248	0.01097–0.01535
RFP-resistant *M. tuberculosis* (36)	0.01221	0.01050–0.01583
INH-susceptible *M. tuberculosis* (31)	0.01194	0.01054–0.01452
INH-resistant *M. tuberculosis* (36)	0.01279	0.01094–0.01679
EB-susceptible *M. tuberculosis* (56)	0.01213	0.01081–0.01440
EB-resistant *M. tuberculosis* (11)	0.01341	0.01073–0.02450
SM-susceptible *M. tuberculosis* (49)	0.01203	0.01077–0.01416
SM-resistant *M. tuberculosis* (18)	0.0134	0.01068–0.02298

Susceptibility of OPC-67683 against 67 strains of clinically isolated *M. tuberculosis*: Resistant strains were selected based on the recommendations of the National Committee For Clinical Laboratory Standards [14] using the following criteria: 1.0 μg/ml for RFP, 1.0 μg/ml for INH, 7.5 μg/ml for EB, and 10 μg/ml for SM. We calculated the concentrations at which 90% (MIC_{90}) of the susceptible strains are inhibited. MIC_{90} and 95% confidence intervals were calculated using the actual data obtained by the probit method.

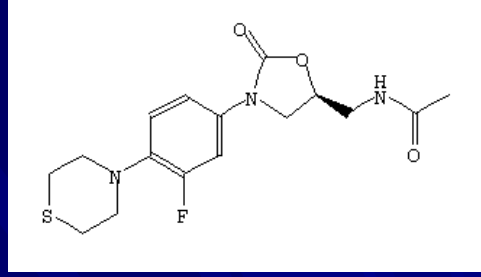
doi:10.1371/journal.pmed.0030466.t003

SQ-109



- Análogo de etambutol
- Diez veces más activo
- Bloqueo de la síntesis de la pared
- Sinergismo con isoniazida, rifampicina y bedaquilina
- Activo frente a cepas resistentes a etambutol

SUTEZOLID



- Oxazolidinona.
- Inhibición síntesis proteica.
- Menos tóxico que linezolid (neuropatía periférica y anemia).
- Menor penetración en mitocondria.
- Mejor CMIs frente a *M. tuberculosis*.
- Candidato en sensibles y resistentes

TABLE 1. MICs of linezolid and PNU-100480 and susceptibility to INH, rifampin, ethambutol, and streptomycin for 23 isolates of *Mycobacterium tuberculosis*

Isolate no.	Resistance/susceptibility profile[a] for:				MIC (mg/liter) of:	
	Isoniazid	Rifampin	Ethambutol	Streptomycin	Linezolid	PNU-100480
1	R	R	R	R	≤0.25	≤0.0625
2	R	R	S	R	≤0.25	0.125
3	R	R	R	R	≤0.25	≤0.0625
4	R	R	R	R	≤0.25	0.25
5	R	R	S	R	0.5	0.25
6	R	R	R	R	0.5	0.125
7	R	R	S	R	0.5	0.125
8	R	R	S	R	1	0.125
9	R	R	R	R	1	0.25
10	R	R	R	R	1	0.25
11	S	R	R	R	>1	0.5
12	S	S	S	R	1	0.125
13	R	R	R	S	≤0.25	0.125
14	R	R	R	S	≤0.25	0.125
15	R	R	S	S	0.5	0.25
16	R	R	R	S	0.5	0.125
17	R	R	S	S	0.5	≤0.0625
18	R	S	R	S	0.5	0.25
19	S	S	S	S	0.5	0.25
20	S	S	S	S	1	0.25
21	S	S	S	S	1	0.5
22	S	S	S	S	1	0.25
23	S	S	S	S	1	0.25

Actividad de sutezolid frente a tuberculosis
Alffenaar et al.
A.A.C. 2011

AAC
Journals.ASM.org

Sterilizing Activities of Novel Combinations Lacking First- and Second-Line Drugs in a Murine Model of Tuberculosis

Kathy Williams,[a] Austin Minkowski,[a] Opokua Amoabeng,[a] Charles A. Peloquin,[b] Dinesh Taylor,[a] Koen Andries,[c] Robert S. Wallis,[d] Khisimuzi E. Mdluli,[e] and Eric L. Nuermberger[a,f]

Center for Tuberculosis Research, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA[a]; College of Pharmacy, University of Florida, Gainesville, Florida, USA[b]; Tibotec BVBA, Johnson & Johnson, Beerse, Belgium[c]; Pfizer Inc., Groton, Connecticut, USA[d]; Global Alliance for TB Drug Development, New York, New York, USA[e]; and Department of International Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA[f]

TABLE 3 Lung CFU counts assessed during treatment and relapse, assessed 3 months after treatment completion in experiment 1

Group	Drug regimen	Mean (±SD) $\log_{10}$ CFU count at[a]:				Proportion (%) relapsing after treatment for:		
		D−13	D0	M1	M2	2 mos	3 mos	4 mos
Untreated		3.54 ± 0.52	7.27 ± 0.44	ND	ND	ND	ND	ND
A	RIF + PZA + INH[b]			4.73 ± 0.29	3.04 ± 0.27	ND	15/15 (100)	9/14 (64)
B	TMC + PNU + CFZ + PA-824			3.48 ± 0.57	0.37 ± 0.75	14/15 (93)	2/15 (13)	1/15 (7)
C	TMC + PNU + CFZ			3.37 ± 0.74	0	13/15 (87)	4/15 (27)	1/14 (7)
D	TMC + PNU + PA-824			3.99 ± 0.89	0.97 ± 1.18	15/15 (100)	6/14 (43)	0/15 (0)
E	TMC + CFZ + PA-824			4.39 ± 0.51	1.55 ± 1.14	15/15 (100)	9/15 (60)	5/15 (33)
F	PNU + CFZ + PA-824			4.47 ± 0.39	0.82 ± 1.64	15/15 (100)	15/15 (100)	15/15 (100)

[a] Time points are shown in days (e.g., D−13, day −13; D0, day 0) or months (e.g., M1, 1 month) of treatment. ND, not done.
[b] For the RIF + PZA + INH regimen, PZA was given for the first 2 months only.

TABLE 4 Relapse rates assessed 3 months after treatment completion in experiment 2

Drug regimen	Proportion (%) relapsing after treatment for:			
	4 wks	6 wks	8 wks	10 wks
RPT + PZA + MXF	ND[a]	ND	7/15 (47)	2/15 (13)
TMC + PZA	ND	14/15 (93)	10/15 (67)	8/15 (53)
TMC + PZA + RPT	ND	5/15 (33)	0/15 (0)	ND
TMC + PZA + CFZ	ND	1/15 (7)	0/15 (0)	ND
TMC + PZA + PNU	ND	8/15 (53)	6/15 (40)	ND
TMC + PZA + RPT + CFZ	4/15 (27	0/15 (0)	ND	ND

[a] ND, not done.

Clinical Development

TB Alliance manages the largest pipeline of new TB drugs in history. Projects with the potential to have the greatest impact on the disease, while being cost-effective and simple to administer, are prioritized.

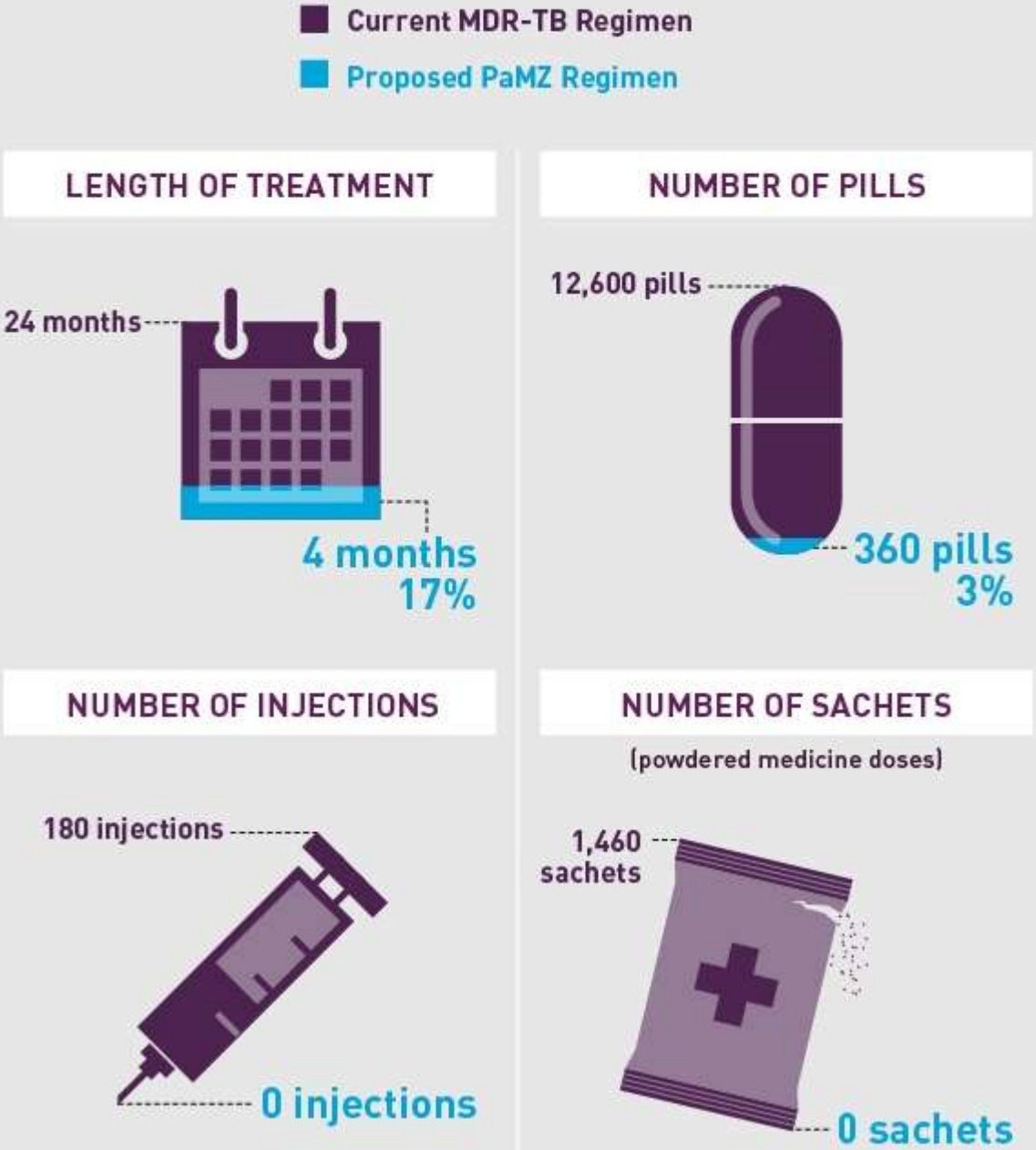
Phase 1	Phase 2 (Early)	Phase 2 (Advanced)	Phase 3	Phase 4
PK of First-Line Drugs in Children <5kg	NC-003	NC-002	REMox TB	Optimized First-Line Drugs in Children >5kg
Isoniazid / Rifampin / Pyrazinamide / Ethambutol (Pediatric HRZE)	Bedaquiline / Clofazimine / PA-824 (JCPa)	PA-824 / Moxifloxacin / Pyrazinamide (PaMZ)	Isoniazid / Rifampin / Pyrazinamide / Moxifloxacin (HRZM)	Ethambutol
	Bedaquiline / Pyrazinamide / PA-824 (JPaZ)		Ethambutol / Rifampin / Pyrazinamide / Moxifloxacin (ERZM)	Rifampin
	Bedaquiline / Clofazimine / Pyrazinamide / PA-824 (JCZPa)		Bayer Healthcare AG, Medical Research Council, University College London	Isoniazid
	Bedaquiline / Clofazimine / Pyrazinamide (JCZ)			Pyrazinamide

Ensayo Clínico fase II (avanzada)

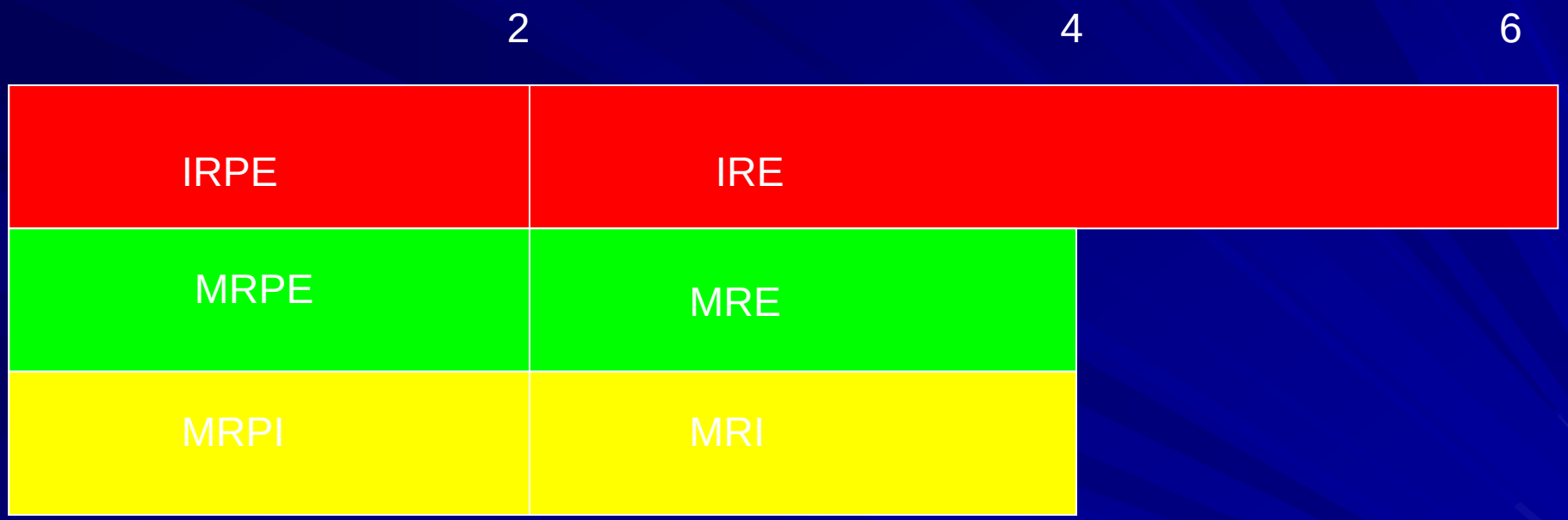
- PA-824+Moxifloxacino+Pirazinamida
- 4 meses de duración
- Cepas sensibles y multirresistentes
- 8 zonas de Suráfrica y Tanzania

Lancet 2012

The PaMZ (PA-824+moxifloxacin+pyrazinamide) regimen shows the potential to dramatically shorten, simplify, and improve the treatment of multidrug-resistant TB (MDR-TB). That's not all: the new regimen is expected to be **90% cheaper** than the existing treatment.



Ensayo clínico REMox TB



48 lugares de 9 países
Completado en 2013
1913 pacientes
Resultados: 2014

CONCLUSIONES

- La tasa global mundial de tuberculosis y la mortalidad relacionada disminuyen lentamente.
- Existen puntos calientes de tasas altas y resistencias importantes.
- Después de un tiempo importante de “estancamiento” se está invirtiendo en el desarrollo de nuevos fármacos.
- Dos líneas: disminución del tiempo de tratamiento y abordaje de las cepas resistentes.

who.int

China: improving home care for dementia patients

Xiong Bin

26 February 2014 -- Dementia affects more than 35 million people worldwide. This number is expected to almost double every 20 years as populations age. WHO Director-General Dr Margaret Chan emphasized recently that she could think of "no other condition that places such a heavy burden on society, families, communities, and economies." In some big cities in China, the lives of people with dementia and their caregivers have been improved through caregiver support groups that assist families who take care of dementia patients at home.

Read more on improving home care for dementia patients in China

China: improving home care for dementia patients

Physical activity saves lives

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WHO guidelines
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Health solutions for the poor

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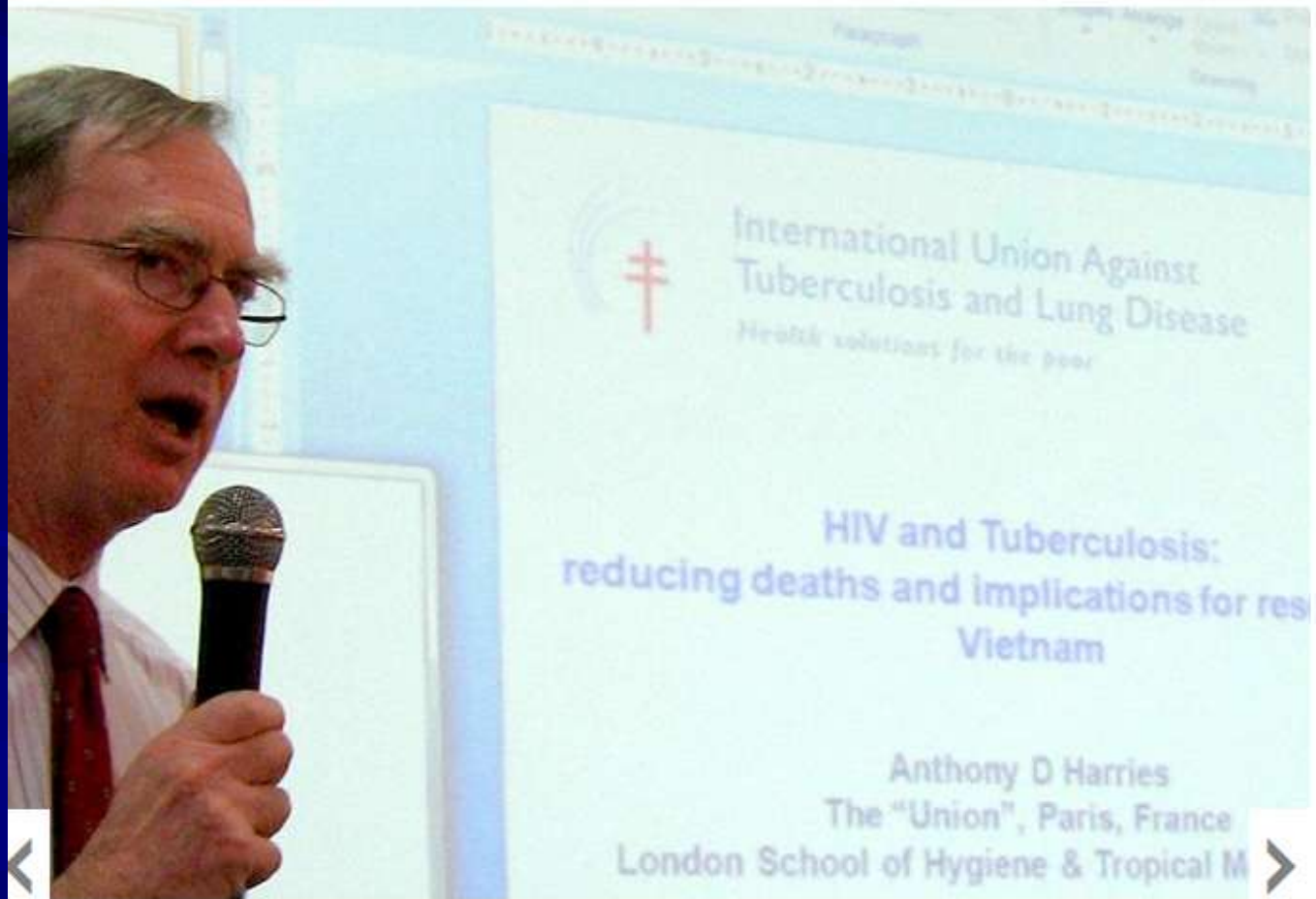

Clare Pierard: Carrying forward a 91-year tradition of publishing the latest research

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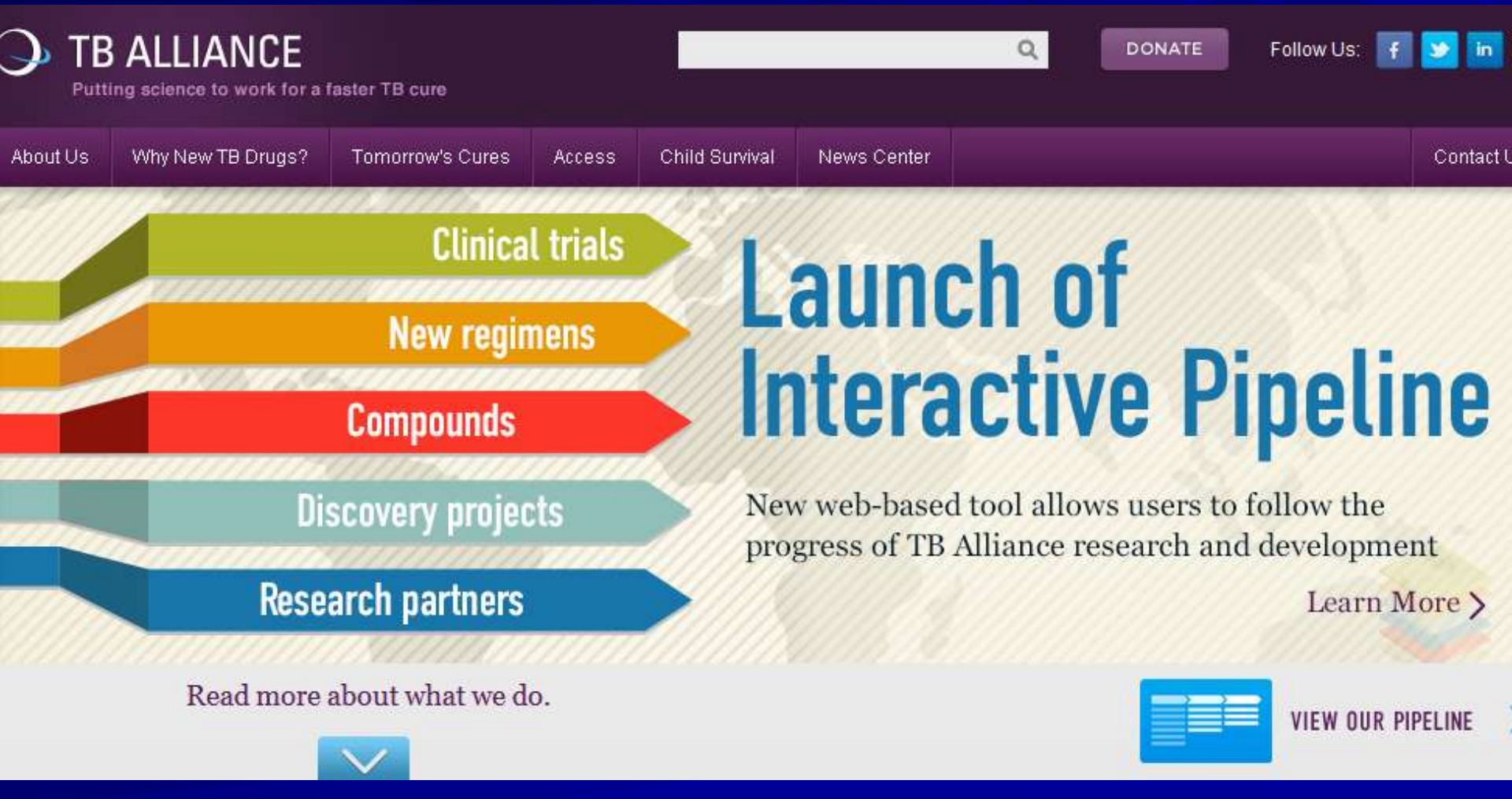

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Mining is Fueling a Global TB Epidemic

Tell the Southern African Development Community nations to prioritize TB R&D

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