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HOSPITAL GENERAL de MÉXICO

CURSO

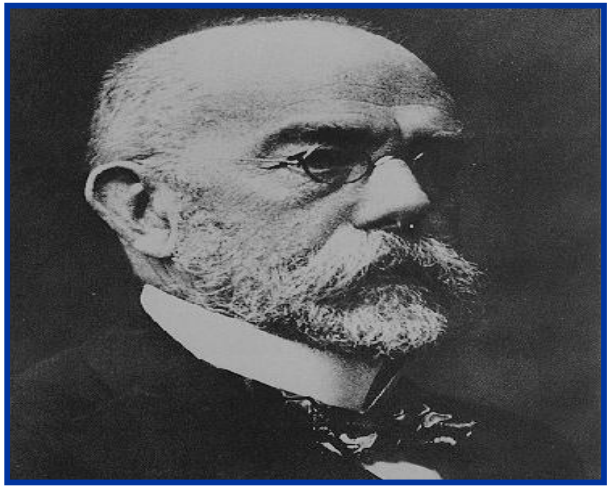
XIX

LABORATORIO
TUBERCULOSIS EN ADULTOS
PEDIATRÍA
SALUD PÚBLICA
FÁRMACORRESISTENCIA
TALLERES

DEL 8 AL 12 DE JUNIO DE 2015

ACTUALIZACIÓN EN EL DIAGNÓSTICO Y TRATAMIENTO DE LA TUBERCULOSIS EN EL NIÑO Y EL ADULTO

CENAPRECE
CENTRO NACIONAL DE PROGRAMAS PREVENTIVOS Y CONTROL DE ENFERMEDADES



12 DE JUNIO DE 2015
DR. MIGUEL A. SALAZAR L.

LA TBMDR / XDR-TB ha emergido y se ha diseminado debido a un tratamiento inadecuado. Hoy, el tratamiento de la tuberculosis fármaco resistente puede tomar hasta dos años, y es tan complejo, caro, desgastante y tóxico que un tercio de todos los pacientes MDR mueren.

Novel drugs against tuberculosis: a clinician's perspective

Ioana Diana Olaru[1], Florian von Groote-Bidlingmaier[2], Jan Heyckendorf[1], Wing Wai Yew[3], Christoph Lange[1,4,5,6] and Kwok Chiu Chang[7]

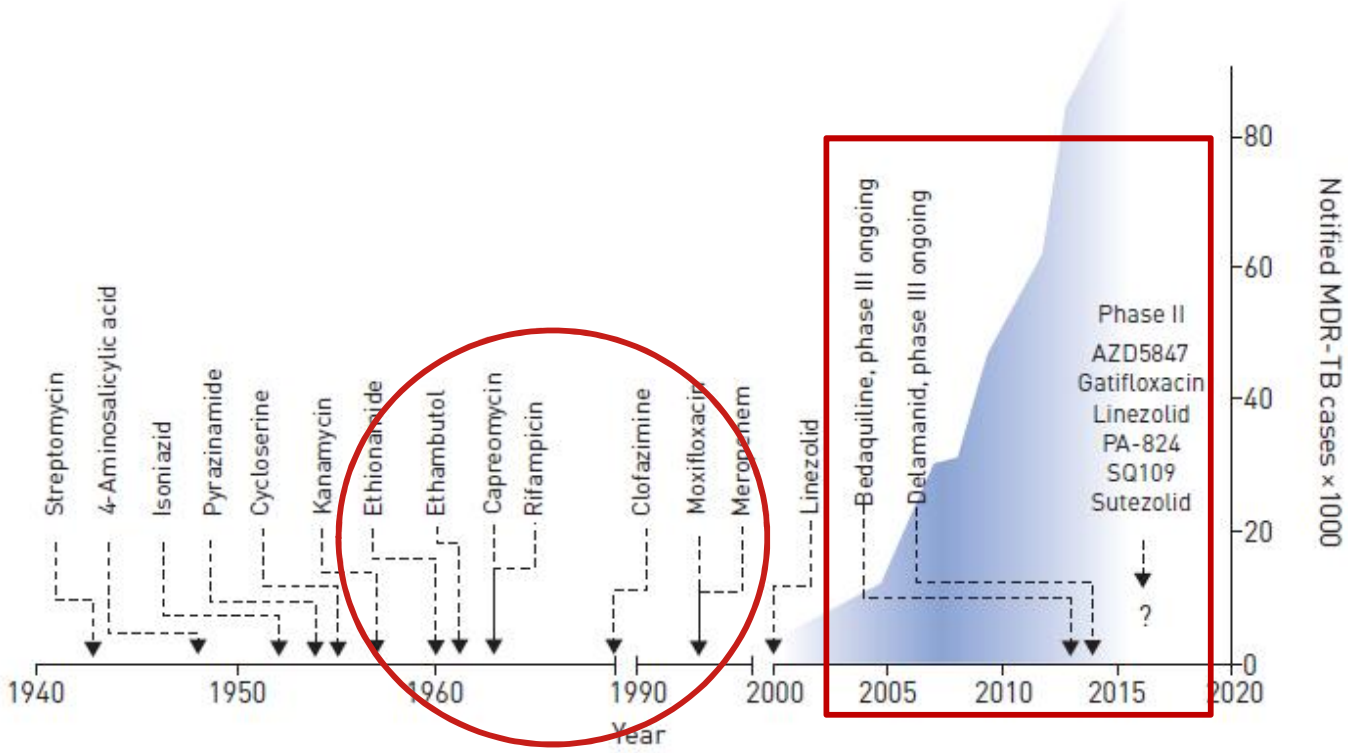


FIGURE 1 Anti-tuberculosis drug development and the increase in number of notified multidrug-resistant tuberculosis (MDR-TB) cases worldwide.

Eur Respir J 2014; in press | DOI: 10.1183/09031936.00162314

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MDR-TB RESPON POLICIES

WHO GUIDANCE FOR DIAGNOS 6

Surveillance data compiled since 1994 have been essential to inform and guide the response to MDR-TB. The first guidance on MDR-TB treatment and care was issued in 1996. Since then updated guidance has been issued, including guidelines on laboratories, diagnostics and infection control.

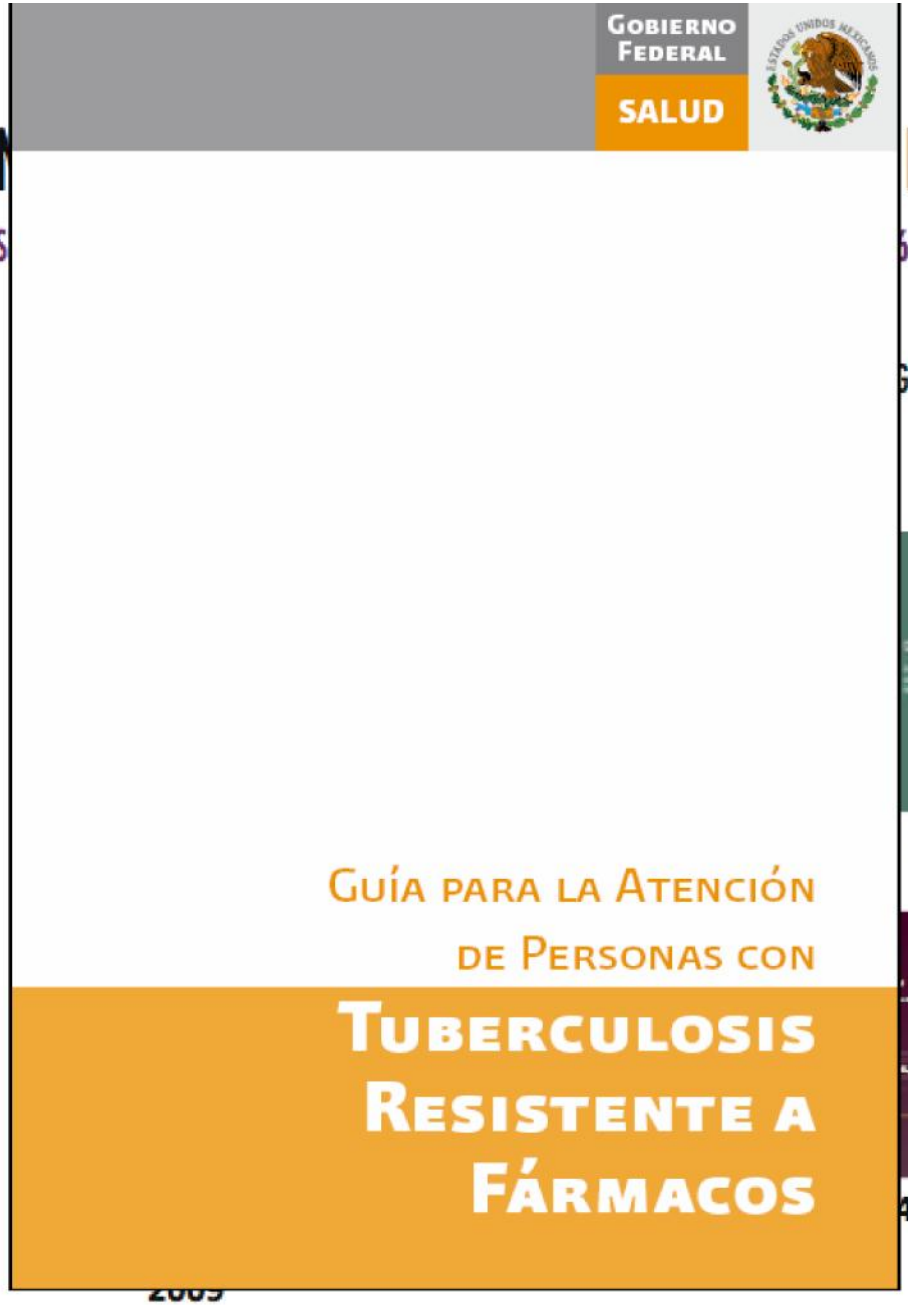
GUIDELINES ON TREATMENT AND CARE

2014

GUIDELINES ON TB AND MDR-TB DIAGNOSTICS AND INFECTION CONTROL

4

2009



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WHO GUIDELINES

WHO guidelines for the programmatic management of drug-resistant tuberculosis: 2011 update

D. Falzon, E. Jaramillo, H.J. Schünemann, M. Arentz, M. Bauer, J. Bayona, L. Blanc, J.A. Caminero, C.L. Daley, C. Duncombe, C. Fitzpatrick, A. Gebhard, H. Getahun, M. Henkens, T.H. Holtz, J. Keravec, S. Keshavjee, A.J. Khan, R. Kulier, V. Leimane, C. Lienhardt, C. Lu, A. Mariandyshev, G.B. Migliori, F. Mirzayev, C.D. Mitnick, P. Nunn, G. Nwagboniwe, O. Oxlade, D. Palmero, P. Pavlinac, M.I. Quelapio, M.C. Raviglione, M.L. Rich, S. Royce, S. Rüsch-Gerdes, A. Salakaia, R. Sarin, D. Sculier, F. Varaine, M. Vitoria, J.L. Walson, F. Wares, K. Weyer, R.A. White and M. Zignol

Eur Respir J 2011; 38: 516–528
DOI: 10.1183/09031936.00073611

TRATAMIENTO.

Recommendation 3. In the treatment of patients with MDR-TB, a fluoroquinolone should be used (strong recommendation, ⊕○○○/very low-quality evidence)

Recomendación 3. Una flouroquinolona siempre tiene que ser utilizada. (Última generación).
Recomendación 4. La Etio/protionamida siempre debe de ser utilizada.
Recomendación 6. Cuatro fármacos de segunda línea, (incluyendo un inyectable), deben de ser utilizados, así como Pirazinamida en la fase intensiva del Tx.

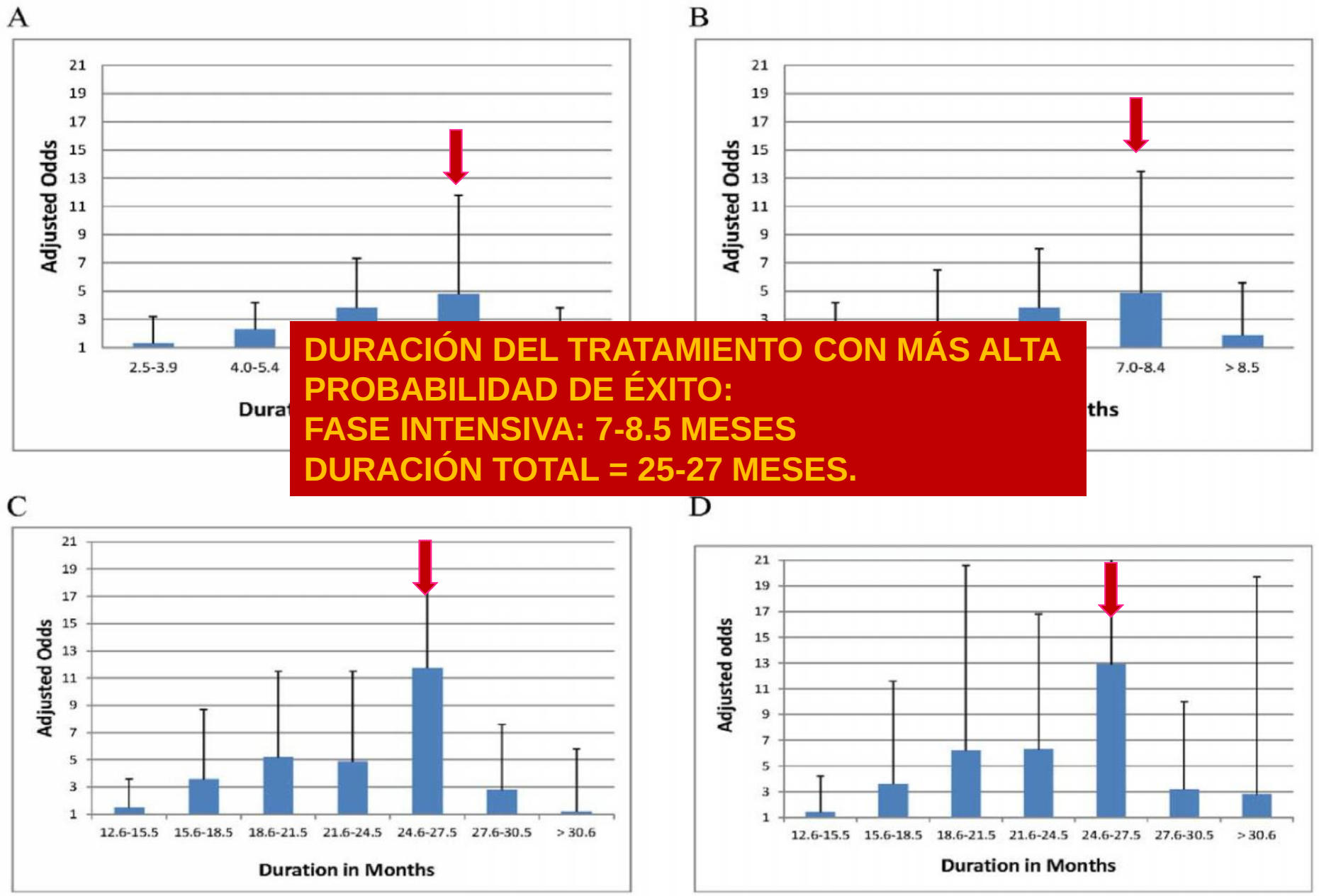
⊕○○○/very low-quality evidence)

Recommendation 7. In the treatment of patients with MDR-TB, regimens should include at least pyrazinamide, a fluoroquinolone, a parenteral agent (kanamycin, amikacin or capreomycin), ethionamide (or prothionamide), and either cycloserine or p-aminosalicylic acid (PAS) if cycloserine cannot be used (conditional recommendation, ⊕○○○/very low-quality evidence)

Recomendación 8. La fase intensiva de 8 meses está recomendada.
Recomendación 9. La duración del tratamiento debe de ser de al menos 20 meses.

patients without any previous MDR-TB treatment (conditional recommendation, ⊕◯◯◯/very low-quality evidence)

Figure 4. Association of treatment success with duration (adjusted odds and upper bound of CI shown).



DURACIÓN DEL TRATAMIENTO CON MÁS ALTA PROBABILIDAD DE ÉXITO:
FASE INTENSIVA: 7-8.5 MESES
DURACIÓN TOTAL = 25-27 MESES.

PLoS Med. 2012;9(8):e1001300. Epub 2012 Aug 28.

Brecha en el Tratamiento de la TBMDR

Just over 77 000 people with MDR-TB were started on second-line treatment in 2012, equivalent to 82% of the 94 000 newly detected cases that were eligible for such treatment globally. Diagnostic:treatment gaps were much larger in some countries, especially in the African Region (51% of detected cases enrolled on treatment), and widened between 2011 and 2012 in China, Pakistan and South Africa.

77.000 de 94.000 (82%) iniciaron tratamiento para la TBMDR en 2012....pero hubieron 450.000 casos estimados!

WHO Global TB Report 2013

OPEN ACCESS Freely available online

PLOS | MEDICINE

Multidrug Resistant Pulmonary Tuberculosis Treatment Regimens and Patient Outcomes: An Individual Patient Data Meta-analysis of 9,153 Patients

Shama D. Ahuja[1], David Ashkin[2], Monika Avendano[3], Rita Banerjee[4], Melissa Bauer[5], Jamie N. Bayona[6], Mercedes C. Becerra[7,8], Andrea Benedetti[5], Marcos Burgos[9], Rosella Centis[10], Eward D. Chan[11], Chen-Yuan Chiang[12], Helen Cox[13], Lia D'Ambrosio[10], Kathy DeRiemer[14], Nguyen Huy Dung[15], Donald Enarson[16], Dennis Falzon[17], Katherine Flanagan[18], Jennifer Flood[19], Maria L. Garcia-Garcia[20], Neel Gandhi[21], Reuben M. Granich[17], Maria G. Hollm-Delgado[5], Timothy H. Holtz[22], Michael D. Iseman[23], Leah G. Jarlsberg[24], Salmaan Keshavjee[7], Hye-Ryoun Kim[25], Won-Jung Koh[26], Joey Lancaster[27], Christophe Lange[28], Wiel C. M. de Lange[29], Vaira Leimane[30], Chi Chiu Leung[31], Jiehui Li[32], Dick Menzies[5]*, Giovanni B. Migliori[10], Sergey P. Mishustin[33], Carole D. Mitnick[7], Masa Narita[34], Philly O'Riordan[35], Madhukar Pai[5], Domingo Palmero[36], Seung-kyu Park[37], Geoffrey Pasvol[38], Jose Peña[39], Carlos Pérez-Guzmán[40], Maria I. D. Quelapio[41], Alfredo Ponce-de-Leon[42], Vija Riekstina[30], Jerome Robert[43], Sarah Royce[24], H. Simon Schaaf[44], Kwonjune J. Seung[45], Lena Shah[5], Tae Sun Shim[46], Sonya S. Shin[45], Yuji Shiraishi[47], José Sifuentes-Osornio[48], Giovanni Sotgiu[49], Matthew J. Strand[23], Payam Tabarsi[50], Thelma E. Tupasi[41], Robert van Altena[29], Martie Van der Walt[27], Tjip S. Van der Werf[29], Mario H. Vargas[51], Pirett Viiklepp[52], Janice Westenhouse[53], Wing Wai Yew[54], Jae-Joon Yim[55], on behalf of the Collaborative Group for Meta-Analysis of Individual Patient Data in MDR-TB[¶]

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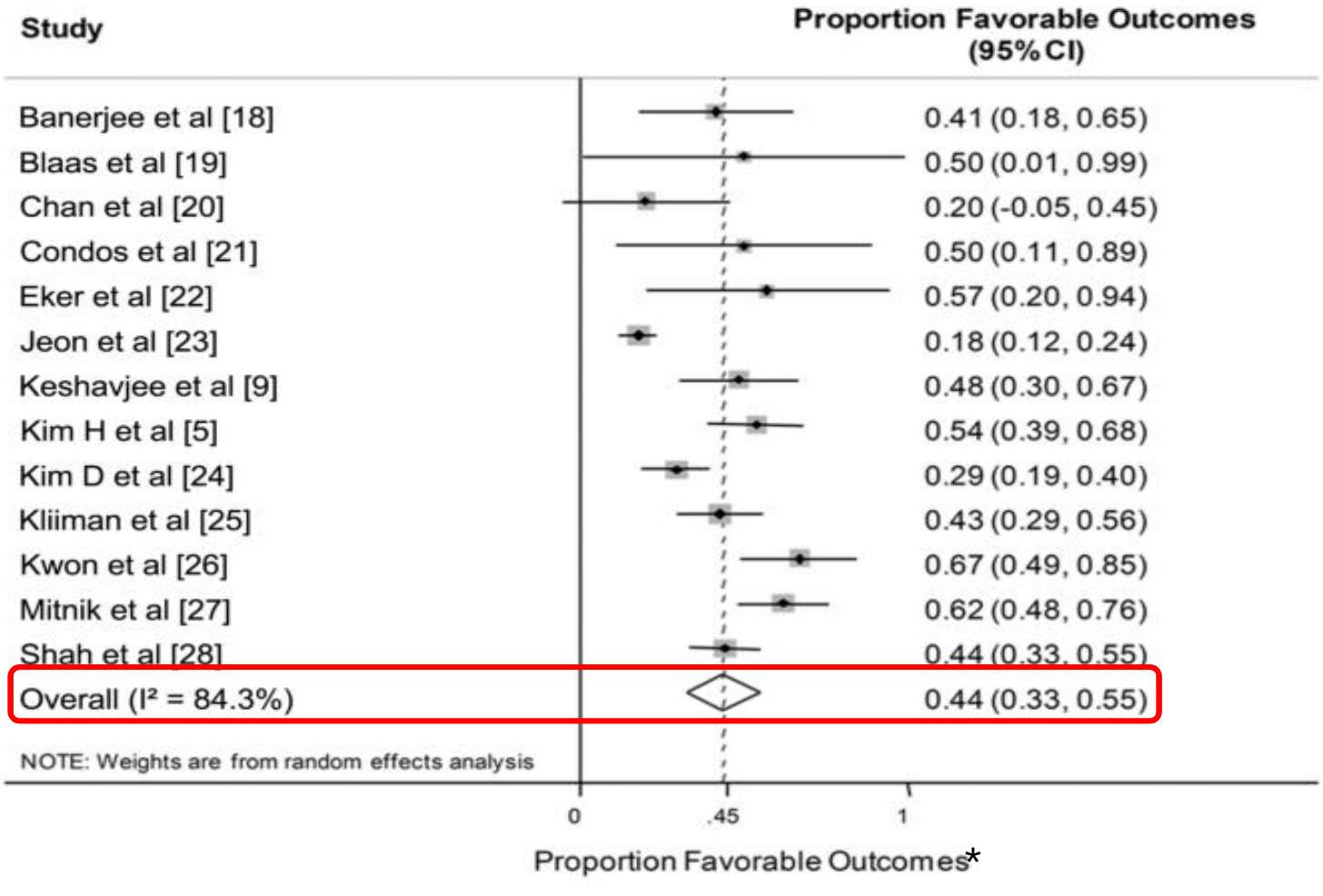
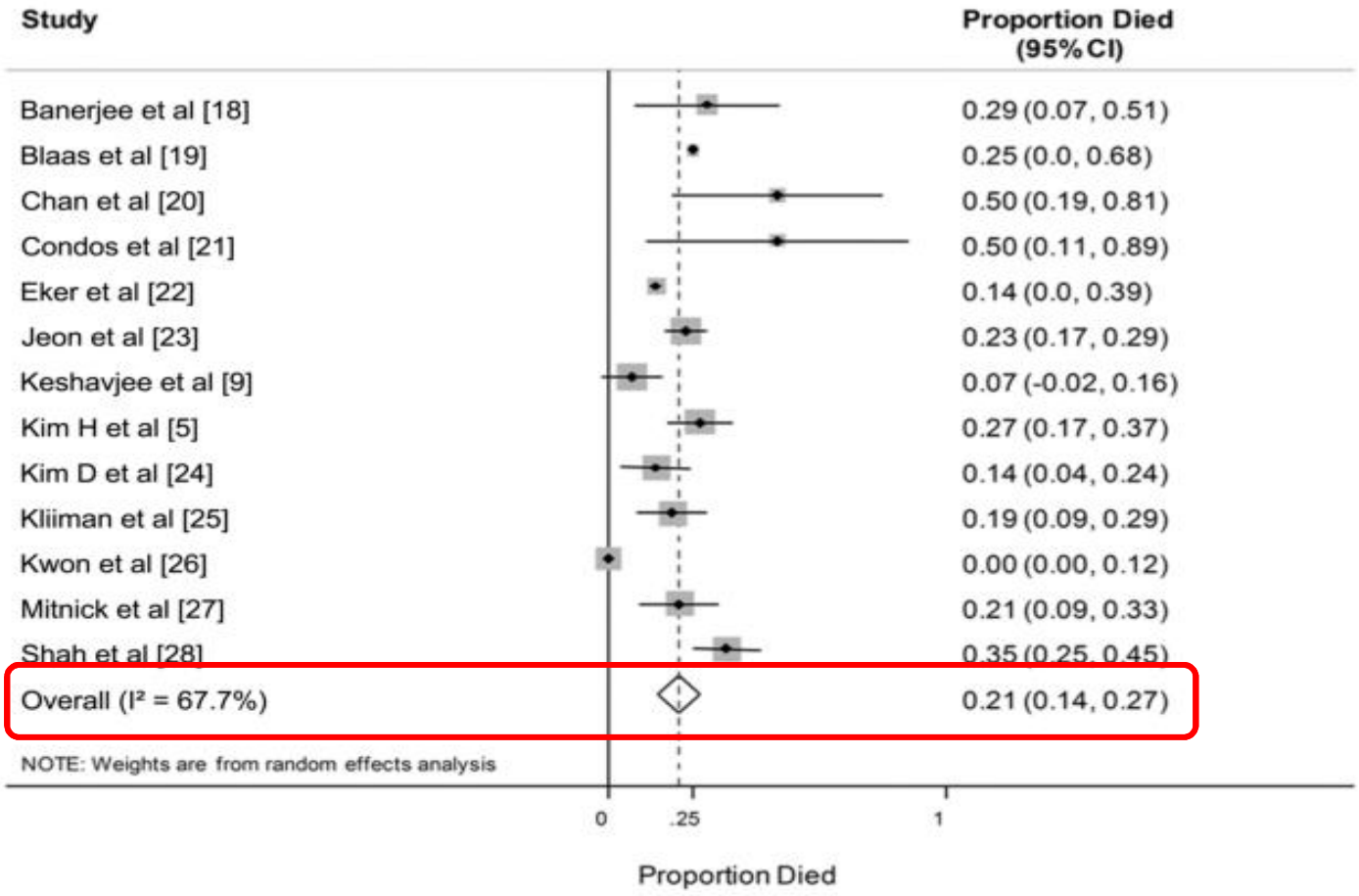
Treatment Outcomes among Patients with Extensively Drug-Resistant Tuberculosis: Systematic Review and Meta-Analysis



*curación o tratamiento completo

K. Jacobson et al. CID 2010; 51:6

Treatment Outcomes among Patients with Extensively Drug-Resistant Tuberculosis: Systematic Review and Meta-Analysis



K. Jacobson et al. CID 2010; 51:6

Treatment Outcomes among Patients with Extensively Drug-Resistant Tuberculosis: Systematic Review and Meta-Analysis

CID 2010:51 (1 July) • 000

Karen R. Jacobson,[1] Dylan B. Tierney,[1] Christie Y. Jeon,[2] Carole D. Mitnick,[3,4] and Megan B. Murray[1,2,4]

[1]Division of Infectious Disease, Massachusetts General Hospital, [2]Department of Epidemiology, Harvard School of Public Health, [3]Department of Global Health and Social Medicine, Harvard Medical School, and [4]Division of Global Health Equity, Brigham and Women's Hospital, Boston, Massachusetts

- 13 Estudios Observacionales → 560 patients:

- 43.7% (95% CI, 32.8%–54.5%) con Resultado Favorable

- 20.8% (95% CI, 14.2%–27.3%) Murieron.

- Estudios en los que una mayor proporción de pacientes recibían una nueva generación de Fq aportaban una más elevada tasa de Tratamientos Favorable

BRECHA DE TRATAMIENTO EN TBMDR

The 2015 treatment success target of ≥75% set in the *Global Plan to Stop TB 2011–2015* for MDR-TB was reached by 34 of 107 countries that reported outcome data for the 2010 patient cohort. However, overall only 48% of patients were successfully treated.

Únicamente 48% tasa de éxito globamente!

WHO Global TB Report 2013

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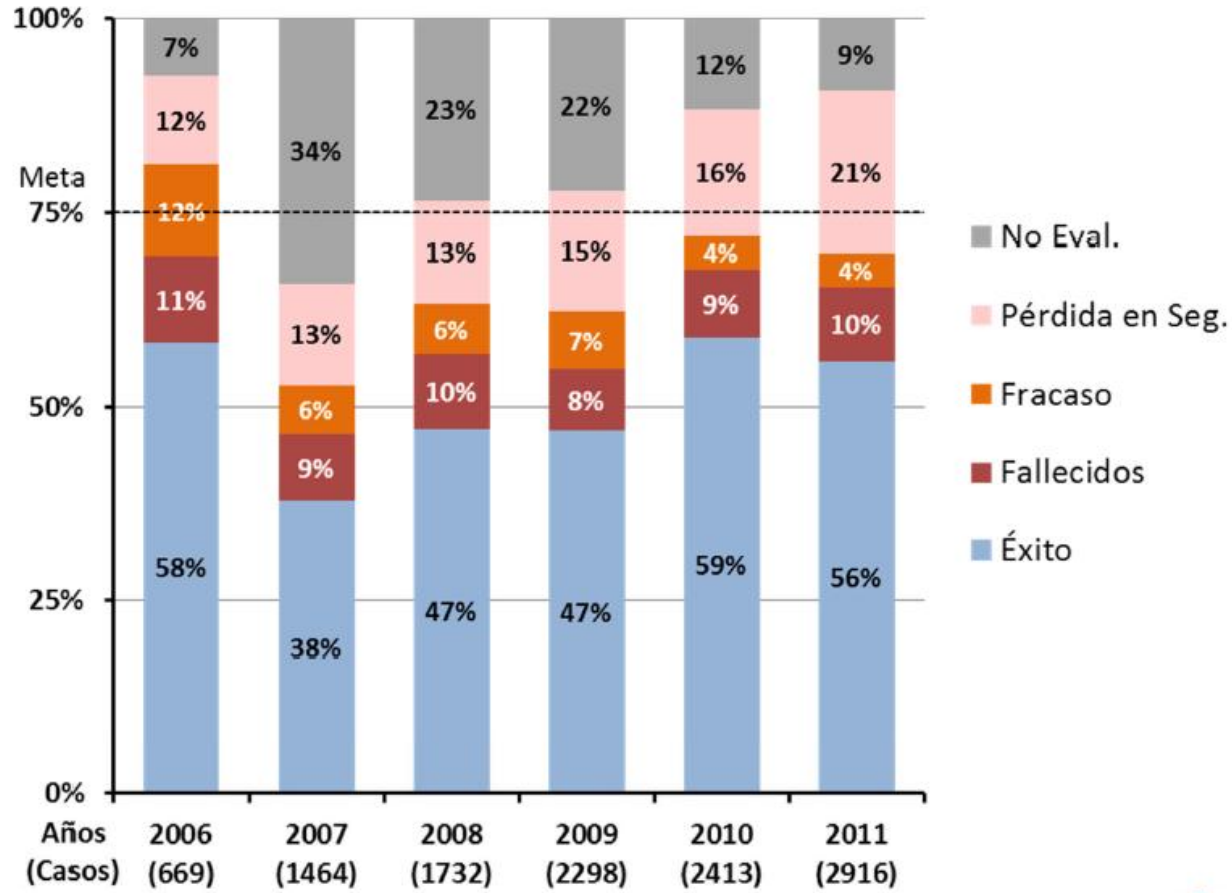
Manejo programático de la TB-MDR

75% de los casos de TB-MDR son tratados exitosamente



Organización Panamericana de la Salud

Organización Mundial de la Salud
Américas

Eur Respir J 2012; 40: 143–151
DOI: 10.1183/09031936.00204611

Tuberculosis: cost of illness in Germany

Roland Diel*, Stefan Rutz#, Stefanie Castell¶ and Tom Schaberg+

ABSTRAC**COSTO POR TRATAMIENTO MDR= 52,259 EUROS**09; of those, the proportion

On the l st Tuberculosis and the e mean direct outpatient and combined in- and outpatient costs of TB, together with other attributable costs of the disease on the basis of the most recent German official health statistics and scientific literature.

According to this, the mean outpatient costs (rounded) per case were €1,197 (adults) and €1,006 (children) for standard therapy, but €36,543 for treatment of MDR-TB. The mean combined in-patient/outpatient costs were €7,364 (adults) and €7,300 (children), respectively; the combined costs for treatment of MDR-TB amounted to €52,259. Including MDR-TB cases the mean costs of treatment per TB case were €7,931. These are joined by the mean costs due to loss of productivity (€2,313), costs per case for rehabilitation (€74) and contact tracing (€922), adding up to €11,240.

When considering the probability of increasing numbers of MDR-TB cases in the near future, TB is still a disease of significant economic impact in Germany.

Treatment Practices, Outcomes, and Costs of Multidrug-Resistant and Extensively Drug-Resistant Tuberculosis, United States, 2005–07

Marks SM, Flood J, Seaworth B, Hirsch-Moverman Y, Armstrong L, Mase S, Salcedo K, Oh P, Graviss EA, Colson PW, Armitige L, Revuelta M, Sheeran K; TB Epidemiologic Studies Consortium.

Emerg Infect Dis. 2014 May;20(5):812-21.

- **Pacientes con TB reportados a los Centros de Control y Prevención de Enfermedades de from California, New York City, and Texas durinte 2005-2007.**

- **Los costos directos, mayormente cubiertos por el sector público, promediaron $134,000 para TBMDR y $430,000 para TBXDR por paciente; in comparación, para paciente no-TBMDR de $17,000.**

Novel drugs against tuberculosis: a clinician's perspective

Ioana Diana Olaru[1], Florian von Groote-Bidlingmaier[2], Jan Heyckendorf[1], Wing Wai Yew[3], Christoph Lange[1,4,5,6] and Kwok Chiu Chang[7]

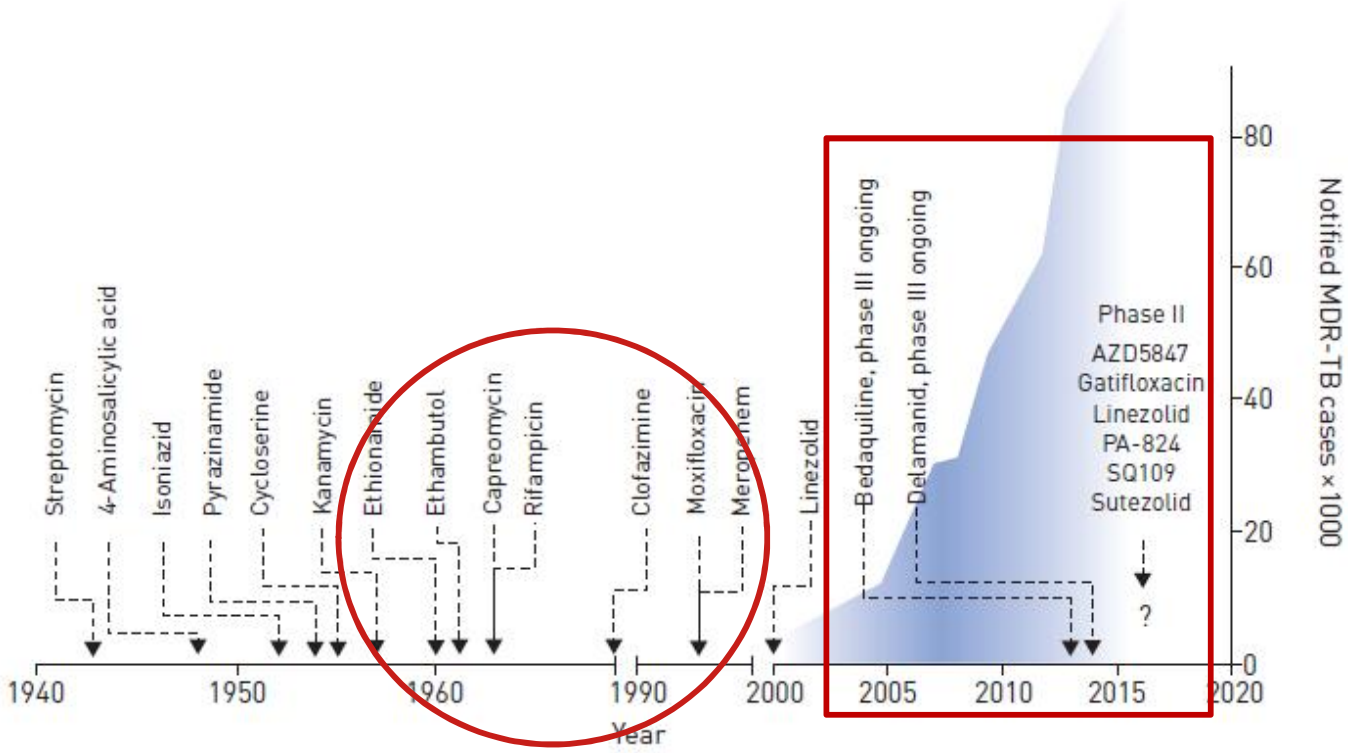


FIGURE 1 Anti-tuberculosis drug development and the increase in number of notified multidrug-resistant tuberculosis (MDR-TB) cases worldwide.

Eur Respir J 2014; in press | DOI: 10.1183/09031936.00162314

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ANTIMICROBIAL RESISTANCE INVITED ARTICLE

George M. Eliopoulos, Section Editor

Old Drugs, New Purpose: Retooling Existing Drugs for Optimized Treatment of Resistant Tuberculosis

Kelly E. Dooley,[1] Carole D. Mitnick,[2] Mary Ann DeGroote,[3] Ekwaro Obuku,[4,5] Vera Belitsky,[6] Carol D. Hamilton,[7] Mamodikoe Makhene,[8] Sarita Shah,[9] James C. M. Brust,[9] Nadza Durakovic,[6] Eric Nuermberger,[1] and on behalf of the Efficacy Subgroup, RESIST-TB

[1]Johns Hopkins University School of Medicine, Baltimore, Maryland, [2]Harvard Medical School, Boston, Massachusetts, [3]Mycobacterial Research Laboratories, Colorado State University, Fort Collins, [4]Institute of Human Virology, University of Maryland School of Medicine, Baltimore; [5]AIDS Relief Programme and Joint Clinical Research Centre, Kampala, Uganda; [6]Partners In Health, Boston, Massachusetts, [7]Health and Development Sciences, Family Health International, Durham, North Carolina, [8]National Institutes of Health, Bethesda, Maryland, and [9]Albert Einstein College of Medicine, Bronx, New York

Clinical Infectious Diseases 2012;55(4):572–81

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Table 3. Priority Ranking of Drugs for Additional Research on Optimization for Drug-Resistant Tuberculosis Treatment

Priority Ranking	Drug	Reasons for Continued Research on Use in Regimens for Drug-Resistant Tuberculosis	Barriers to Optimization for Drug-Resistant Tuberculosis Treatment
High	Pyrazinamide	Sterilizing activity in first-line regimens, so may shorten drug-resistant tuberculosis treatment duration Synergistic effects with new drugs in clinical development	Resistance may be common in multidrug-resistant tuberculosis strains Phenotypic resistance testing problematic Multiple different mutations can confer resistance, impeding development of rapid genotypic resistance test
	Isoniazid	Cheap, well tolerated, and widely available Low-level resistance may be overcome with higher doses Rapid genotypic resistance test may predict which patients with drug-resistant tuberculosis may benefit from higher doses	MIC distribution among resistant strains unknown Correlation between genotypic resistance test result and MIC not established Interpatient variability in PK and acetylation complicates dose selection
	Amikacin, kanamycin, capreomycin	Susceptibility to injectables confers better outcomes in drug-resistant tuberculosis Relative efficacy of injectable drugs is unknown Optimal treatment duration of injectable use is unknown Parenteral use requirement makes this group a target for replacement as new oral drugs are developed	Amikacin not widely available and expensive Poor early bactericidal activity prevents using this method to compare efficacy Large sample sizes needed to study comparative efficacy and treatment duration
Medium	Ethionamide and prothionamide	Only second-line oral drug with potential bactericidal activity Relationship between drug exposure and GI tolerability unknown	Use of isoniazid in initial tuberculosis treatment may select for isoniazid and ethionamide cross-resistance Ability of rapid genotypic tests to predict susceptibility requires further study
	Ethambutol	Better tolerated than many second-line drugs Relationship between drug exposure and ocular toxicity unknown Animal models suggest that neuroprotective agents may prevent optic neuritis, allowing for higher ethambutol dosing	Resistance may be common in drug-resistant tuberculosis strains given the use of ethambutol in first-line tuberculosis treatment Concerns over ocular toxicity may limit use doses that optimize efficacy
Low	Para-aminosalicylic acid	Minimum drug exposure necessary for bacteriostatic effect unknown Lower doses may have similar activity, better tolerability than currently recommended dose	Poor GI tolerability and risk of hypersensitivity
	Cycloserine and terizidone	Minimum drug exposure necessary for bacteriostatic effect unknown Lower doses may have similar activity, better tolerability than currently recommended dose	Not amenable to animal studies given marked interspecies PK differences Serious central nervous system side effects
	Rifabutin	Rifamycins are sterilizing drugs Some drug-resistant tuberculosis strains may retain susceptibility to rifabutin Rapid genotypic resistance tests may predict rifabutin efficacy	Most drug-resistant tuberculosis strains are rifabutin resistant Even drug-resistant tuberculosis strains considered rifabutin susceptible have reduced rifabutin susceptibility compared with wild-type strains Current genotypic resistance tests may not identify discordant susceptibility to rifampin and rifabutin

Abbreviations: GI, gastrointestinal; MIC, minimum inhibitory concentration; PK, pharmacokinetic.

Clinical Infectious Diseases 2012;55(4):572–81

J Antimicrob Chemother 2013; **68**: 275–283
doi:10.1093/jac/dks405 Advance Access publication 16 October 2012

Journal of Antimicrobial Chemotherapy

Is repositioning of drugs a viable alternative in the treatment of tuberculosis?

Juan Carlos Palomino* and Anandi Martin

Table 1. Main drugs proposed as repurposed antibiotics in TB

Drug	Main uses	Repositioned	References
Fluoroquinolones	broad-spectrum Gram-positives Gram-negatives	effective *in vitro*, *in vivo*, in TB patients	33–36, 41, 42
Linezolid	Gram-positives skin infections pneumonia	effective *in vitro*, *in vivo*, in TB patients	53, 59, 60
Trimethoprim/sulfamethoxazole	prophylactic HIV-infected patients, bacterial infections, non-tuberculous	effective *in vitro*; case report in one patient	71–73
Clofazimine	anti-leprosy anti-inflammatory	effective *in vitro*; limited studies in patients	83, 85, 86
Mefloquine	antimalarial	effective *in vitro*	99, 100
Thioridazine	anti-psychotic	effective *in vitro*, *in vivo*, *ex vivo*; limited studies in patients	108–111

Systematic review and meta-analysis of the efficacy and safety of therapy with linezolid containing regimens in the treatment of multidrug-resistant and extensively drug-resistant tuberculosis

Xin Zhang[1,2], Matthew E. Falagas[3], Konstantinos Z. Vardakas[3], Rui Wang[4], Rong Qin[4], Jin Wang[3], Youning Liu[1]

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Background: Linezolid containing regimens have been proposed as potentially valuable alternatives for the treatment of patients with multidrug-resistant tuberculosis (MDR-TB) or extensively drug-resistant TB (XDR-TB).

Methods: A systematic review and meta-analysis was conducted to assess the efficacy, safety and tolerability of linezolid for drug-resistant TB (DR-TB) treatment. We searched the Cochrane Controlled Trial Registry, PubMed, Embase, Science Citation Index Expanded (SCI) and China National Knowledge Infrastructure (CNKI), database up to May 2014 to identify studies providing data of the use of linezolid for the treatment of DR-TB.

Results: The search yielded 15 studies (367 patients) including one randomized controlled trial (RCT), covering 239 patients who could be evaluated for effectiveness; 83% [95% confidence interval (CI), 75-90%; I^2=62.8%] had a favorable outcome, defined as either cure or treatment completion. The pooled rate of culture conversion was 89% (95% CI, 83-95%; I^2=49.6%). Between the group receiving daily linezolid doses of ≤600 or >600 mg, the mortality was considerably lower in patients treated with less than 600 mg/day (P value <0.001). Of 367 patients for whom data on safety was available, peripheral neuropathy (31%, 95% CI, 19-42%; I^2=81.7%) and anemia (25%, 95% CI, 15-34%; I^2=76.6%) were the main adverse effects. Patients receiving less than 600 mg/day were more likely to experience nervous system adverse events (P value <0.01).

Conclusions: The available evidence suggests that linezolid could be considered as a promising option as treatment of MDR/XDR TB. Randomized trials are warranted to define the dose and frequency of administration.

Keywords: Multidrug-resistant tuberculosis (MDR-TB); extensively drug-resistant TB (XDR-TB); treatment; linezolid; meta-analysis

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doi: 10.3978/j.issn.2072-1439.2015.03.10
View this article at: http://dx.doi.org/10.3978/j.issn.2072-1439.2015.03.10

Introduction

Tuberculosis (TB) has attracted increasing public health attention due to the alarming rates of multidrug-resistant TB (MDR-TB, defined as resistance to at least isoniazid and rifampicin) and extensively drug-resistant TB (XDR-TB, defined as MDR-TB with additional bacillary resistance to any fluoroquinolone and at least one second-line injectable anti-TB drug) (1,2). MDR accounts for about 3.6% of new TB patients worldwide, accounting for an estimated 450,000 new cases in 2012. By September 2013, 92 countries had reported at least one case of XDR-TB. Among the developing countries, India and China has the two highest prevalence of TB in the world and troublingly high rates of MDR and XDR-TB (3,4). Furthermore, the treatment of

Eur Respir J 2012; 40: 1430–1442
DOI: 10.1183/09031936.00022912

Efficacy, safety and tolerability of linezolid containing regimens in treating MDR-TB and XDR-TB: systematic review and meta-analysis

Giovanni Sotgiu, Rosella Centis, Lia D'Ambrosio, Jan-William C. Alffenaar, Holly A. Anger, Jose A. Caminero, Paolo Castiglia, Saverio De Lorenzo, Giovanni Ferrara, Won-Jung Koh, Giesela F. Schecter, Tae S. Shim, Rupak Singla, Alena Skrahina, Antonio Spanevello, Zarir F. Udwadia, Miquel Villar, Elisabetta Zampogna, Jean-Pierre Zellweger, Alimuddin Zumla and Giovanni Battista Migliori

- **Doce estudios (11 países; tres continentes) → 121 pacientes**
- **La mayoría de los casosTBMDR tuvieron conversión del frotis (86/93, 92.5%) y cultivo (100/107, 93.5%) después del régimen individualizado con Linezolid.**
- **El tiempo promedio para conversión del frotis y cultivo fue de 43.5 (21-90) y 61 (29-119) días, respectivamente.**
- **99/121 (81.8%) exitosamente tratados.**
- **No hubo diferencias a dosis de ≤ 600 mg vs. > 600 mg**

Changes in treatment outcomes of multidrug-resistant tuberculosis

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Table 3 Clinical characteristics and treatment outcomes of MDR-TB patients diagnosed during different time periods

	MDR-TB patients (1996–2000) (n = 86)	MDR-TB patients (2001–2005) (n = 125)	MDR-TB patients (2006–2010) (n = 123)	P value
Parameter	Cohort 1	Cohort 2	Cohort 3	
Age, years, median [IQR]	41.0 [26.0–55.3]	35.0 [25.0–50.0]	37.0 [27.0–56.0]	0.099
Male sex	52 (60.5)	72 (57.6)	69 (56.1)	0.819
Comorbidities	31 (36.0)	44 (35.2)	36 (29.3)	0.498
Albumin, g/dl, median [IQR]	3.8 [3.5–4.1]	4.0 [3.7–4.3]	4.2 [3.9–4.5]	<0.001
XDR-TB	19 (22.1)	24 (19.2)	26 (21.1)	0.866
Number of drugs used, median [IQR]	6.0 [5.0–8.0]	6.0 [5.0–7.0]	5.0 [5.0–6.0]	0.002
Treatment duration, months, median [IQR]	41.5 [25.0–72.3]	31.5 [25.0–50.0]	24.4 [18.4–27.3]	<0.001
Surgical resection	37 (43.0)	26 (20.8)	18 (14.6)	<0.001
Adverse drug reactions	31 (36.5)	44 (35.2)	31 (25.2)	0.275
Treatment success				
Total	46 (53.5)	86 (68.8)	103 (83.7)	<0.001
Cure	43 (50.0)	64 (51.2)	92 (74.8)	
Completed	3 (3.5)	22 (17.6)	11 (8.9)	
Unfavourable outcomes				
Total	40 (46.5)	39 (31.2)	20 (16.3)	<0.001
Failure	24 (27.9)	16 (12.8)	7 (5.8)	
Relapse	3 (3.5)	3 (2.4)	2 (1.6)	
Death	9 (10.5)	10 (8.0)	5 (4.1)	
Default	4 (4.6)	10 (8.0)	6 (4.8)	
Relapse rate (cases per 1000 person-years)	10.9	6.9	8.2	0.174

MDR-TB = multidrug-resistant TB; IQR = interquartile range; XDR-TB = extensively drug-resistant tuberculosis.

EL AUMENTO DEL ÉXITO EN EL TRATAMIENTO SE EXPLICA POR EL USO DE QUINOLONAS DE ÚLTIMA GENERACIÓN Y LINEZOLID

INT J TUBERC LUNG DIS 17(8):1001–1007

http://dx.doi.org/10.5588/ijtld.12.0144
E-published ahead of print 25 March 2013

REVIEW ARTICLE

Systematic review of clofazimine for the treatment of drug-resistant tuberculosis

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- **Nueve estudios observacionales (seis sobre TB-MDR y tres sobre TBXDR).**
- **En general, el 65% de los pacientes alcanzó un desenlace favorable (IC95% 54–76)**
- **Mediante un meta-análisis de efectos aleatorios, se encontró que 65% de los pacientes con TB-MDR (IC95% 52–79) y 66% de los pacientes con TB-XDR (IC95% 42–89) lograron un desenlace terapéutico favorable.**

International Journal of Antimicrobial Agents 45 (2015) 71–75

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Short Communication

In vitro synergistic activity of clofazimine and other antituberculous drugs against multidrug-resistant *Mycobacterium tuberculosis* isolates

Zhijian Zhang[a,b,1], Tianzhi Li[a,1], Geping Qu[a], Yu Pang[a,b,*], Yanlin Zhao[b]

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Table 2
Minimum inhibitory concentrations (MICs) and fractional inhibitory concentration indexes (FICIs) of clofazimine (CLO) and fluoroquinolones against 24 multidrug-resistant *Mycobacterium tuberculosis* isolates.

Strain no.	MIC (μg/mL)				FICI	Relationship	MIC (μg/mL)				FICI	Relationship
	CLO alone	LEV alone	CLO combination	LEV combination			CLO alone	MOX alone	CLO combination	MOX combination		
MDR6	0.25	0.0625	0.125	0.03125	1	I	0.25	2	0.0625	1	0.75	I
MDR21	1	2	0.5	1	1	I	1	1	0.25	1	1.25	I
MDR11	1	0.125	0.25	0.125	1.25	I	1	1	0.25	0.125	0.375	S
MDR3	32	0.5	32	0.125	1.25	I	32	0.125	32	0.0625	1.5	I
MDR19	0.5	0.125	0.125	0.125	1.25	I	0.5	0.0625	0.25	0.03125	1	I
MDR20	1	0.0625	0.25	0.0625	1.25	I	1	2	0.25	1	0.75	I
MDR1	1	0.125	0.5	0.125	1.5	I	1	0.03125	0.5	0.03125	1.5	I
MDR18	2	0.125	0.5	0.125	2	I	2	0.125	0.25	0.03125	0.325	S
MDR2	8	64	8	64	2	I	8	32	8	32	2	I
MDR4	0.5	0.125	0.5	0.125	2	I	0.5	0.0625	0.125	0.03125	0.75	I
MDR5	0.25	0.125	0.125	0.125	2	I	0.25	0.0625	0.125	0.03125	1	I
MDR10	0.25	0.125	0.25	0.125	2	I	0.25	0.0625	0.25	0.03125	1.5	I
MDR14	0.5	32	0.5	32	2	I	0.5	2	0.25	1	1	I
MDR8	4	16	4	32	2.5	A	4	0.25	2	0.5	2.5	A
MDR9	0.25	1	0.5	1	3	A	0.25	0.0625	0.25	0.03125	1.5	I
MDR22	0.25	2	0.5	2	3	A	0.25	0.0625	0.5	0.0625	3	A

LEV, levofloxacin; MOX, moxifloxacin; S, synergy; I, indifference; A, antagonism.

LA COMBINACIÓN DE CLOFAZIMINA CON ETAMBUTOL O MOXIFLOXACINO PUEDEN GENERAR UN PROMISORIO RÉGIMEN PARA EL TRATAMIENTO DE LA TBMDR.

REVIEW ARTICLE The Journal of Infectious Diseases 2013;207:1352–8

World Health Organization Group 5 Drugs for the Treatment of Drug-Resistant Tuberculosis: Unclear Efficacy or Untapped Potential?

Kelly E. Dooley,[1] Ekwaro A. Obuku,[2] Nadza Durakovic,[3] Vera Belitsky,[3] Carole Mitnick,[4] and Eric L. Nuermberger[1] on behalf of the Efficacy Subgroup, RESIST-TB

[1]Johns Hopkins University School of Medicine, Baltimore, Maryland; [2]Institute of Human Virology, University of Maryland School of Medicine, AIDS Relief Programme and Joint Clinical Research Centre, Kampala, Uganda; [3]Partners In Health, Boston, Massachusetts; and [4]Harvard Medical School, Boston, Massachusetts

- **Clofazimina puede contribuir a nuevos regímenes cortos.**
- **Los Beta-lactámicos ameritan posterior evaluación—específicamente optimización de dosis y tiempo..**
- **Linezolid parece ser efectivo pero es frecuentemente descontinuado debido a su toxicidad.**
- **Mycobacterium tuberculosis tiene una resistencia intrínseca a clarithromycin.**

Potential antimicrobial agents for the treatment of multidrug-resistant tuberculosis

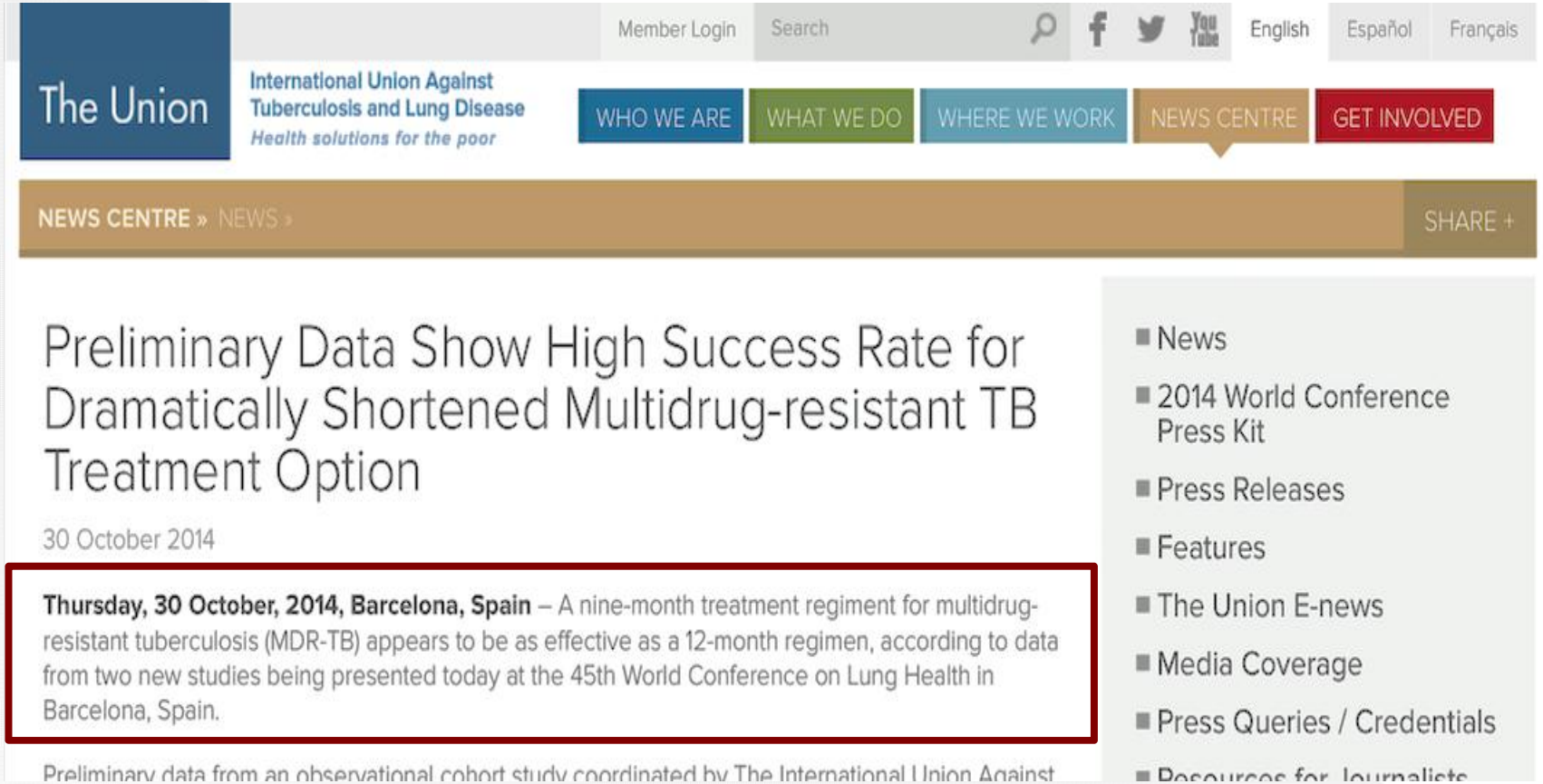
Noor Alsaad[1], Bob Wilffert[1,2], Richard van Altena[3], Wiel C.M. de Lange[3], Tjip S. van der Werf[4], Jos G.W. Kosterink[1,2] and Jan-Willem C. Alffenaar[1]

TABLE 3 Clinical studies showing response of tuberculosis (TB) patients to the selected drugs

Drug	Treatment regimen	Patient population	Dose regimen	Response	Ref.
Thioridazine	Combination with linezolid and/or moxifloxacin	XDR-TB patients	25 mg per day for 2 weeks; followed by a dose increase of 25 mg weekly until the maximum dose of 200 mg per day was reached	Earlier bacteriological sputum conversion Relapse-free cure	[58]
Metronidazole	Antituberculous regimen (streptomycin, isoniazid and rifampicin)	Advanced pulmonary TB patients	400 mg three times per day for 8 weeks	Significant improvement in clinical response Reduction of sputum quantity Enhanced radiographic improvement Improvement in susceptibility to anti-TB drugs	[50]
Doxycycline		TB patients	20 mg three times per day	Suppress immunopathologic MMPs to reduce tissue damage	[31]
Tigecycline				No clinical data available	
Disulfiram					
Co-trimoxazole	With antituberculous regimen	MDR-TB patients	480 mg, 960 mg per day	No treatment discontinuation No serious side-effects	[55]

XDR: extensively drug-resistant; MMPs: matrix metalloproteinases; MDR: multidrug-resistant.

Eur Respir J 2014; 43: 884–897



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Preliminary Data Show High Success Rate for Dramatically Shortened Multidrug-resistant TB Treatment Option

30 October 2014

Thursday, 30 October, 2014, Barcelona, Spain – A nine-month treatment regiment for multidrug-resistant tuberculosis (MDR-TB) appears to be as effective as a 12-month regimen, according to data from two new studies being presented today at the 45th World Conference on Lung Health in Barcelona, Spain.

Preliminary data from an observational cohort study coordinated by The International Union Against

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- Press Queries / Credentials
- Resources for Journalists

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]

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

[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

- Bangladesh: 427 MDR-TB (1997-2007) no habían recibido previamente DSL

- 206 (4 Kn-Gx-Cfz-E-Z-H-Pth / 5 Gx-Cfz-E-Z) → CURADOS 87.9% (libre de recaídas) (95% CI, 82.7–91.6)

- Reacciones adversas severas fueron infrecuentes y manejables.

- Comparados con 221 enfermos tratados con regímenes basados en Ofloxaxina y comúnmente protionamida durante todo el tratamiento, la probabilidad de efectos adversos (hazard ratio) fue 0.39 (95% intervalo de confianza, 0.26–0.59).

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

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*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

- **RESULTADOS : De los 515 pacientes que llenaron los criterios de inclusión en el estudio de 2005 to 2011, 84.4% tuvieron un favorable término de tratamiento bacteriológico. Debido a la extensión de la enfermedad, y a la conversión tardía, únicamente la mitad de los pacientes completó el tratamiento dentro de los 9 meses; sin embargo, 95% completaron tratamiento a los 12 meses.**

INT J TUBERC LUNG DIS 18(10):1188–1194

http://dx.doi.org/10.5588/ijtld.13.0075

High cure rate with standardised short-course multidrug-resistant tuberculosis treatment in Niger: no relapses

A. Piubello,* S. Hassane Harouna,* M. B. Souleymane,* I. Boukary,* S. Morou,* M. Daouda,* Y. Hanki,† A. Van Deun‡§

*Damien Foundation, Niamey, †National Hospital of Niamey, Niger; ‡International Union Against Tuberculosis and Lung Disease, Paris, France; §Institute of Tropical Medicine, Antwerp, Belgium

- La curación fue obtenida en 58 patients (89.2%, 95%CI 81.7–96.7), 6 murieron y 1 abandonó. 49 pacientes valorados en 24 meses de seguimiento, permanecieron BAAR y cultivo negativos. Los principales eventos adversos fueron vómito (26.2%) y disminución de la agudeza auditiva (20%), pero ningún tratamiento fué suspendido.

High effectiveness of a 12-month regimen for MDR-TB patients in Cameroon

C. Kuaban,*† J. Noeske,‡ H. L. Rieder,§¶ N. Aït-Khaled,§ J. L. Abena Foe,# A. Trébucq§

Table 2 Binary treatment outcome and patient characteristics at intake, univariate and multivariate analysis (the latter for age, sex and HIV infection only), Cameroon, treatment of patients with MDR. Odds ratios refer to non-success

	Outcome					Crude OR		Adjusted OR			
		Success		Total				95%CI			
Patient characteristic	Non-success	*n*	Row %	*n*	Column %	Point	*P* value	Point	Low	High	*P* value
Total	16	134	89.3	150	100.0	—	—	—	—	—	—
Age quartiles, years											
17–24	1	31	96.9	32	21.3	1		1			
25–29	2	36	94.7	38	25.3	1.7	0.660	1.6	0.14	35.3	0.713
30–40	6	34	85.0	40	26.7	5.5	0.091	2.2	0.23	48.6	0.520
41–68	7	33	82.5	40	26.7	6.6	0.054	2.2	0.25	47.4	0.515

CONCLUSIONES: Estos resultados añaden evidencia sobre la utilidad de regímenes estandarizados más cortos en pacientes SIN RESISTENCIA A FÁRMACOS DE SEGUNDA LÍNEA.

INT J TUBERC LUNG DIS 19(5):517–524

http://dx.doi.org/10.5588/ijtld.14.0535

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

High-Dose Rifapentine with Moxifloxacin for Pulmonary Tuberculosis

Amina Jindani, F.R.C.P., Thomas S. Harrison, F.R.C.P., Andrew J. Nunn, M.Sc., Patrick P.J. Phillips, Ph.D., Gavin J. Churchyard, Ph.D., Salome Charalambous, Ph.D., Mark Hatherill, M.D., Hennie Geldenhuys, M.B., Ch.B., Helen M. McIlleron, Ph.D., Simbarashe P. Zvada, M.Phil., Stanley Mungofa, M.P.H., Nasir A. Shah, M.B., B.S., Simukai Zizhou, M.B., Ch.B., Lloyd Magweta, M.B., Ch.B., James Shepherd, Ph.D., Sambayawo Nyirenda, M.D., Janneke H. van Dijk, Ph.D., Heather E. Clouting, M.Sc., David Coleman, M.Sc., Anna L.E. Bateson, Ph.D., Timothy D. McHugh, Ph.D., Philip D. Butcher, Ph.D., and Denny A. Mitchison, F.R.C.P., for the RIFAQUIN Trial Team*

Table 1. Baseline Characteristics of the Patients Included in the Modified Intention-to-Treat Analysis.

Characteristic	Control Regimen (N=188)	4-Month Regimen (N=193)	6-Month Regimen (N=212)	Total (N=593)
Male sex — no. (%)	121 (64)	121 (63)	137 (65)	379 (64)
HIV-positive — no. (%)	54 (29)	55 (28)	49 (23)	158 (27)
Age — no. (%)				
18–34 yr	115 (61)	132 (68)	127 (60)	374 (63)
35–54 yr	66 (35)	55 (28)	78 (37)	199 (34)
>55	7 (4)	6 (3)	7 (3)	20 (3)
Weight — no. (%)				
<40 kg	9 (5)	8 (4)	8 (4)	25 (4)
40–54 kg	103 (55)	100 (52)	120 (57)	323 (54)
55–69 kg	71 (38)	77 (40)	82 (39)	230 (39)
≥70 kg	5 (3)	8 (4)	2 (1)	15 (3)
Smoking status — no. (%)				
Former smoker	47 (25)	46 (24)	47 (22)	140 (24)
Current smoker	46 (24)	51 (26)	64 (30)	161 (27)
Never smoked	95 (51)	96 (50)	101 (48)	292 (49)
Cavitation — no. (%)*				
None	57 (33)	64 (35)	73 (37)	194 (35)
1–5 cm	86 (50)	85 (47)	91 (46)	262 (48)
>5 cm	30 (17)	32 (18)	33 (17)	95 (17)
CD4 cell count†				
Median	355	317	298	314
Interquartile range	247–455	256–427	247–383	253–441
Days of previous tuberculosis treatment at randomization — no.				
Median	5	4	4	4
Interquartile range	1–8	1–8	1–7	1–8

* Radiographs obtained at baseline were not available for 42 patients. Between-group baseline characteristics were compared by means of a chi-square test for independence for categorical variables and a nonparametric K-sample test of the equality of the medians for continuous variables. There were no statistically significant between-group differences in any of these baseline characteristics among the three treatment groups (P>0.1).
† CD4 cell counts are based on counts from 158 patients coinfected with the human immunodeficiency virus (HIV).

RÉGIMEN 1: 2HRZE/4HR

RÉGIMEN 2. 2EMxRZ/2RPMx

RÉGIMEN 3. 2EMxRZ/4MxRP

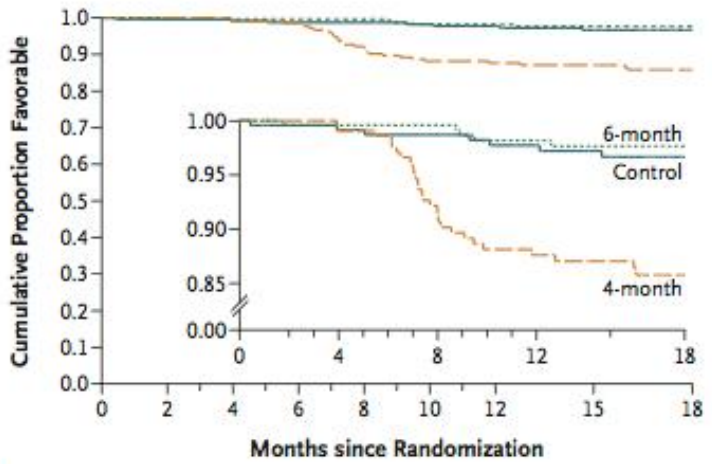
N Engl J Med 2014;371:1599-608.
DOI: 10.1056/NEJMoa1314210

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

High-Dose Rifapentine with Moxifloxacin for Pulmonary Tuberculosis

Amina Jindani, F.R.C.P., Thomas S. Harrison, F.R.C.P., Andrew J. Nunn, M.Sc., Patrick P.J. Phillips, Ph.D., Gavin J. Churchyard, Ph.D., Salome Charalambous, Ph.D., Mark Hatherill, M.D., Hennie Geldenhuys, M.B., Ch.B., Helen M. McIlleron, Ph.D., Simbarashe P. Zvada, M.Phil., Stanley Mungofa, M.P.H., Nasir A. Shah, M.B., B.S., Simnukai Zizhou, M.B., Ch.B., Lloyd Magweta, M.B., Ch.B., James Shepherd, Ph.D., Sambayawo Nyirenda, M.D., Janneke H. van Dijk, Ph.D., Heather E. Clouting, M.Sc., David Coleman, M.Sc., Anna L.E. Bateson, Ph.D., Timothy D. McHugh, Ph.D., Philip D. Butcher, Ph.D., and Denny A. Mitchison, F.R.C.P., for the RIFAQUIN Trial Team*



No. at Risk									
Control	240	232	227	213	210	203	195	175	142
4-month	239	223	211	202	185	172	169	147	127
6-month	251	234	224	217	212	207	205	180	153

Figure 3. Kaplan–Meier Failure Estimates of the Time to a Favorable Outcome in the Per-Protocol Population.
The inset shows the same data on an enlarged y axis.

CONCLUSIONES

El régimen de 6 meses que incluyó la administración de altas dosis de rifapentina y moxifloxacino fue tan efectivo como el régimen control . El de 4 meses no fue no-inferior al régimen control.

N Engl J Med 2014;371:1599-608.
DOI: 10.1056/NEJMoa1314210

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 OCTOBER 23, 2014 VOL. 371 NO. 17

Four-Month Moxifloxacin-Based Regimens for Drug-Sensitive Tuberculosis

Stephen H. Gillespie, M.D., D.Sc., Angela M. Crook, Ph.D., Timothy D. McHugh, Ph.D., Carl M. Mendel, M.D., Sarah K. Meredith, M.B., B.S., Stephen R. Murray, M.D., Ph.D., Frances Pappas, M.A., Patrick P.J. Phillips, Ph.D., and Andrew J. Nunn, M.Sc., for the REMoxTB Consortium*

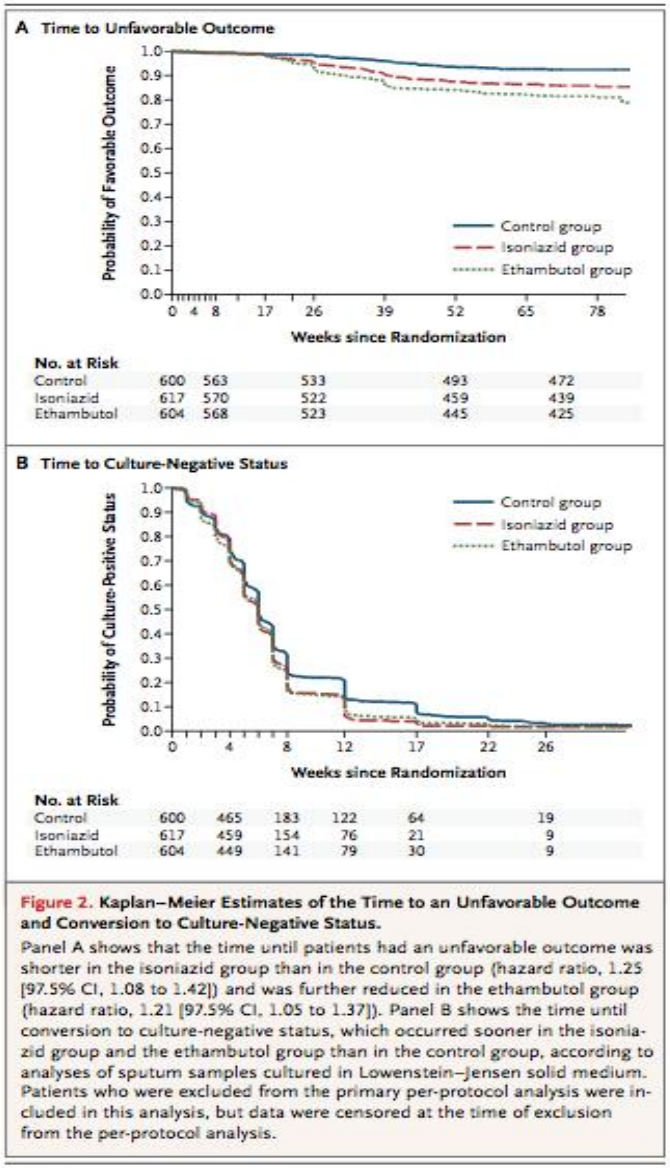


Figure 2. Kaplan–Meier Estimates of the Time to an Unfavorable Outcome and Conversion to Culture-Negative Status.

Panel A shows that the time until patients had an unfavorable outcome was shorter in the isoniazid group than in the control group (hazard ratio, 1.25 [97.5% CI, 1.08 to 1.42]) and was further reduced in the ethambutol group (hazard ratio, 1.21 [97.5% CI, 1.05 to 1.37]). Panel B shows the time until conversion to culture-negative status, which occurred sooner in the isoniazid group and the ethambutol group than in the control group, according to analyses of sputum samples cultured in Lowenstein–Jensen solid medium. Patients who were excluded from the primary per-protocol analysis were included in this analysis, but data were censored at the time of exclusion from the per-protocol analysis.

Conclusiones

Los regímenes conteniendo moxifloxacino produjeron una caída más rápida inicial de la carga bacteriana comparada al grupo control. Sin embargo, no fue demostrada la, no-inferioridad para estos regímenes, lo cual indica que acortar el tratamiento a 4 meses no es efectivo en este lugar.

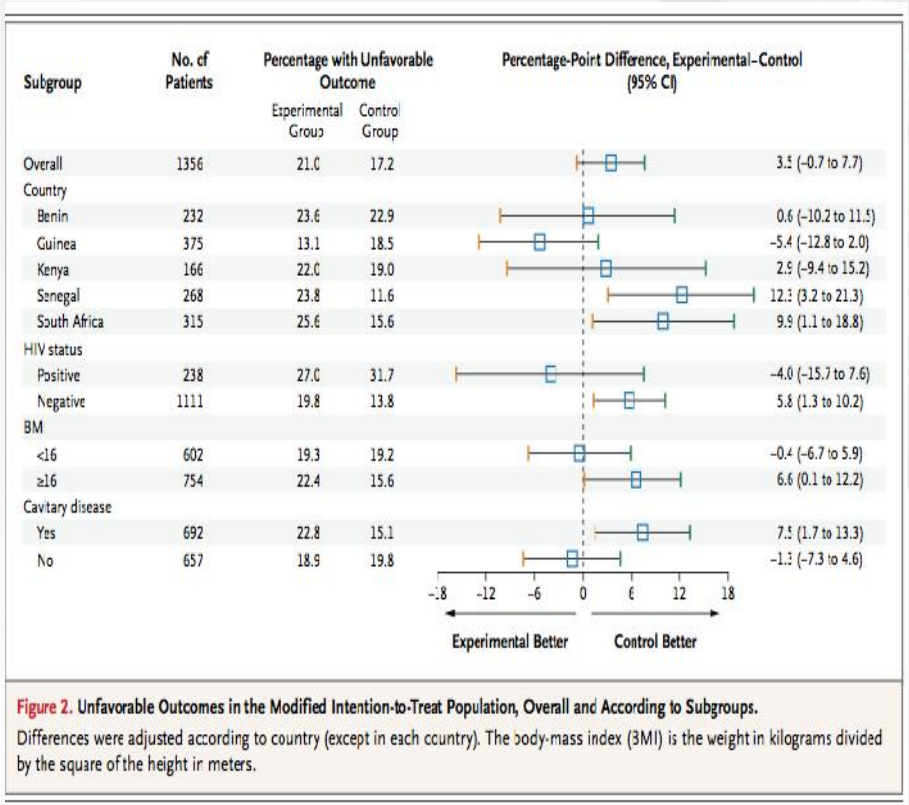
N Engl J Med 2014;371:1577-87.
DOI: 10.1056/NEJMoa1407426

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Four-Month Gatifloxacin-Containing Regimen for Treating Tuberculosis

Corinne S. Merle, M.D., Katherine Fielding, Ph.D., Omou Bah Sow, M.D., Martin Gninafon, M.D., Mame B. Lo, M.D., Thuli Mthiyane, M.Sc., Joseph Odhiambo, M.D., Evans Amukoye, M.D., Boubacar Bah, M.D., Ferdinand Kassa, M.D., Alimatou N'Diaye, M.D., Roxana Rustomjee, M.D., Bouke C. de Jong, M.D., Ph.D., John Horton, M.D., Christian Perronne, M.D., Charalambos Sismanidis, Ph.D., Olivier Lapujade, B.Sc., Piero L. Olliaro, M.D., Ph.D., and Christian Lienhardt, M.D., Ph.D., for the OFLOTUB/Gatifloxacin for Tuberculosis Project*



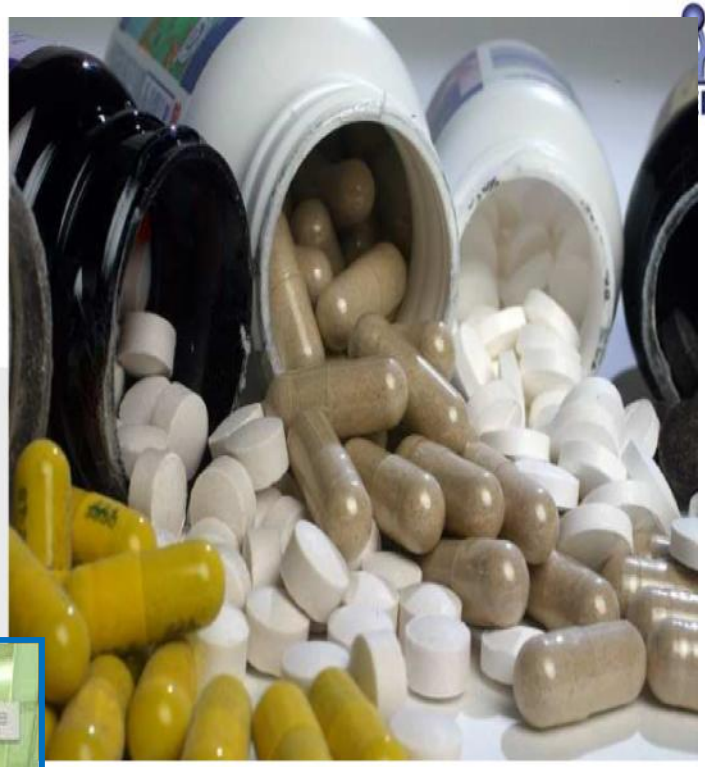
Subgroup	No. of Patients	Percentage with Unfavorable Outcome		Percentage-Point Difference, Experimental–Control (95% CI)
		Experimental Group	Control Group	
Overall	1356	21.0	17.2	3.5 (−0.7 to 7.7)
Country				
Benin	232	23.6	22.9	0.6 (−10.2 to 11.5)
Guinea	375	13.1	18.5	−5.4 (−12.8 to 2.0)
Kenya	166	22.0	19.0	2.9 (−9.4 to 15.2)
Senegal	268	23.8	11.6	12.3 (3.2 to 21.3)
South Africa	315	25.6	15.6	9.9 (1.1 to 18.8)
HIV status				
Positive	238	27.0	31.7	−4.0 (−15.7 to 7.6)
Negative	1111	19.8	13.8	5.8 (1.3 to 10.2)
BMI				
<16	602	19.3	19.2	−0.4 (−6.7 to 5.9)
≥16	754	22.4	15.6	6.6 (0.1 to 12.2)
Cavitary disease				
Yes	692	22.8	15.1	7.5 (1.7 to 13.3)
No	657	18.9	19.8	−1.3 (−7.3 to 4.6)

Figure 2. Unfavorable Outcomes in the Modified Intention-to-Treat Population, Overall and According to Subgroups.
Differences were adjusted according to country (except in each country). The body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters.

Conclusiones.

No se pudo demostrar Noninferioridad en el régimen de 4 meses al estándar con respecto a la eficacia primaria y al punto final.

N Engl J Med 2014;371:1588-98.
DOI: 10.1056/NEJMoa1315817



A review of tuberculosis: Focus on bedaquiline

BONNIE CHAN, TINA M. KHADEM, AND JACK BROWN

"CONCLUSIÓN: La aprobación del Bedaquiline representa un hito mayor en el tratamiento de la TBMDR. El Bedaquiline debe de ser considerado en pacientes que no han respondido a un régimen conteniendo 4 fármacos y pirazinamida con evidencia documentada a fluoroquinolonas.
Sin embargo, el papel exacto de Bedaquiline no puede ser determinado hasta que la eficacia y seguridad pueda ser estudiada en estudios Fase III."

Conclusion. The approval of bedaquiline represents a major milestone in MDR tuberculosis therapy. Bedaquiline should be considered in patients who have not responded to a regimen containing four second-line drugs and pyrazinamide and patients with documented evidence of MDR tuberculosis resistant to fluoroquinolones. The exact role of bedaquiline cannot be determined until further efficacy and safety data are obtained through ongoing Phase III trials.

Am J Health-Syst Pharm. 2013; 70:1984-94

INT J TUBERC LUNG DIS 18(11):1315–1318

http://dx.doi.org/10.5588/ijtld.14.0284

Initial experience of bedaquiline use in a series of drug-resistant tuberculosis patients from India

Z. F. Udwadia, R. A. Amale, J. B. Mullerpattan

Department of Respiratory Medicine, Medical Research Centre, P D Hinduja National Hospital, Mumbai, India

SUMMARY

Drug-resistant tuberculosis (DR-TB) is a major problem both in India and worldwide. Newer drugs such as TMC-207 (bedaquiline) may have an important role to play in making up an effective drug regimen in such cases. There have been a few reports of bedaquiline use in a non-trial setting from Europe. Our series of five patients is the first series of DR-TB patients from India to receive bedaquiline. All five patients showed striking improvement, with microbiological conversion and an absence of notable adverse effects (e.g., prolonged QTcF), indicating the potential impact of this drug in such a population.

KEY WORDS: XDR-TB; TMC-207; outcomes

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Multidrug-Resistant Tuberculosis and Culture Conversion with Bedaquiline

Andreas H. Diacon, M.D., Ph.D., Alexander Pym, M.D., Ph.D., Martin P. Grobusch, M.D., Ph.D., Jorge M. de los Rios, M.D., Eduardo Gotuzzo, M.D., Irina Vasilyeva, M.D., Ph.D., Vaira Leimane, M.D., Koen Andries, D.V.M., Ph.D., Nyasha Bakare, M.D., M.P.H., Tine De Marez, Ph.D., Myriam Haxaire-Theeuwes, D.D.S., Nacer Lounis, Ph.D., Paul Meyvisch, M.Sc., Els De Paepe, M.Sc., Rolf P.G. van Heeswijk, Pharm.D., Ph.D., and Brian Dannemann, M.D., for the TMC207-C208 Study Group*

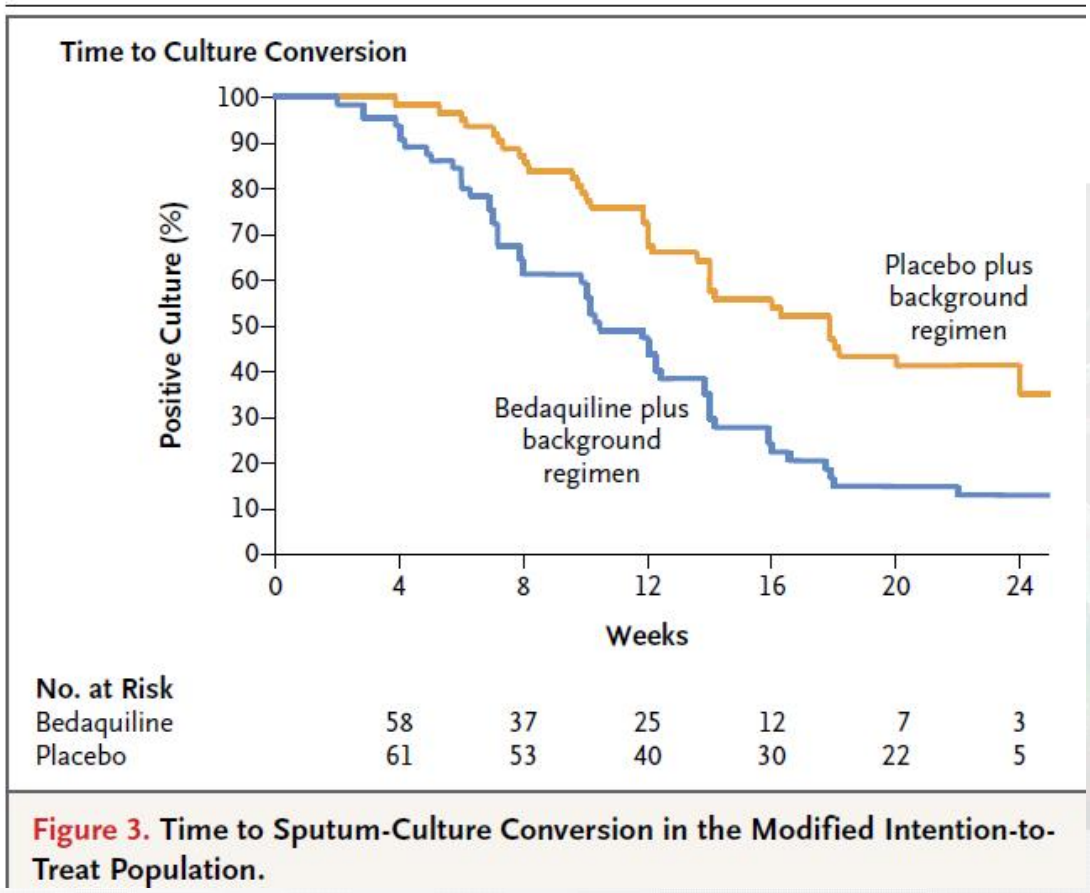


Figure 3. Time to Sputum-Culture Conversion in the Modified Intention-to-Treat Population.

CONVERSIÓN DEL CULTIVO: 125 vs 83 DÍAS. (I.C. 95% 1.57 a 3.80; P <0.001

CURACIÓN A LAS 120 SEMANAS 58% vs 32% (P=0.003)

10 MUERTES EN EL GRUPO DE BEDAQUILINE vs 2 EN EL GRUPO PLACEBO.

SALUD
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INER

Novel drugs against tuberculosis: a clinician's perspective

Ioana Diana Olaru[1], Florian von Groote-Bidlingmaier[2], Jan Heyckendorf[1], Wing Wai Yew[3], Christoph Lange[1,4,5,6] and Kwok Chiu Chang[7]

TABLE 2 Evidence from *in vitro* data or animal models that may affect the choice of combining novel drugs in clinical trials

Novel drugs in combination	Evidence
Bedaquiline and PA-824	Murine TB model: sterilising activity [45]
Bedaquiline, PA-824 and pyrazinamide	Murine TB model: treatment over 4 months prevented relapse [45]
Bedaquiline, PA-824 and pyrazinamide	*In vitro*: antagonistic effect due to PA-824
Bedaquiline and SQ109	*In vitro*: synergy [96]
Bedaquiline, SQ109 and pyrazinamide	Murine TB model: sterilising activity [89]
Bedaquiline and sutezolid	Murine TB model: sterilising activity [46]
Bedaquiline, sutezolid and SQ109	*In vitro*: additive activity [97]
Bedaquiline, sutezolid and/or PA-824, and clofazimine	Murine TB model: treatment over 4 months resulted in low relapse rates [46]
Sutezolid and SQ109	*In vitro*: additive activity [98]

Eur Respir J 2014; in press | DOI: 10.1183/09031936.00162314

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 7, 2012 VOL. 366 NO. 23

Delamanid for Multidrug-Resistant Pulmonary Tuberculosis

Maria Tarcela Gler, M.D., Vija Skripconoka, M.D., Epifanio Sanchez-Garavito, M.D., Heping Xiao, M.D., Jose L. Cabrera-Rivero, M.D., Dante E. Vargas-Vasquez, M.D., Mengqiu Gao, M.D., Ph.D., Mohamed Awad, M.B., B.Ch., M.D., Seung-Kyu Park, M.D., Ph.D., Tae Sun Shim, M.D., Ph.D., Gee Young Suh, M.D., Manfred Danilovits, M.D., Hideo Ogata, M.D., Anu Kurve, M.D., Joon Chang, M.D., Ph.D., Katsuhiro Suzuki, M.D., Thelma Tupasi, M.D., Won-Jung Koh, M.D., Barbara Seaworth, M.D., Lawrence J. Geiter, Ph.D., and Charles D. Wells, M.D.

CONCLUSIONS

Delamanid was associated with an increase in sputum-culture conversion at 2 months among patients with multidrug-resistant tuberculosis. This finding suggests that delamanid could enhance treatment options for multidrug-resistant tuberculosis. (Funded by Otsuka Pharmaceutical Development and Commercialization; ClinicalTrials.gov number, NCT00685360.)

N Engl J Med 2012;366:2151-60.

Eur Respir J 2013; 41: 1393–1400
DOI: 10.1183/09031936.00125812

Delamanid improves outcomes and reduces mortality in multidrug-resistant tuberculosis

143/192: 74.5%
ÉXITO

Vija Skripconoka*, Manfred Danilovits#, Lea Pehme#, Tarmo Tomson¶, Girts Skenders*, Tiina Kummik#, Andra Cirule*, Vaira Leimane*, Anu Kurve¶, Klavdia Levina¶, Lawrence J. Geiter+, Davide Manissero§ and Charles D. Wells+

TABLE 2 Long-term (24 month) treatment outcomes after treatment with delamanid in combination with an optimised background treatment regimen: MDR- and XDR-TB patients

Treatment outcome	Long-term treatment#	Short-term treatment¶	All patients+
Favourable	143 (74.5; 67.7–80.5)§	126 (55.0; 48.3–61.6)§	269 (63.9; 59.1–68.5)
Cured	110 (57.3; 50.0–64.4)	111 (48.5; 41.8–55.1)	221 (52.5; 47.6–57.4)
Completed	33 (17.2; 12.1–23.3)§	15 (6.6; 3.7–10.6)§	48 (11.4; 8.5–14.8)
Unfavourable	49 (25.5; 19.5–32.3)§	103 (45.0; 38.4–51.7)§	152 (36.1; 31.5–40.9)
Died	2 (1.0; 0.1–3.7)§	19 (8.3; 5.1–12.7)§	21 (5.0; 3.1–7.5)
Failed	32 (16.7; 11.7–22.7)	26 (11.4; 7.6–16.2)	58 (13.8; 10.6–17.4)
Defaulted	15 (7.8; 4.4–12.6)§	58 (25.3; 19.8–31.5)§	73 (17.3; 13.8–21.3)

Data are presented as n (%; 95% CI). MDR: multidrug-resistant; TB: tuberculosis; XDR: extensively drug-resistant. #: 192 patients received delamanid (100 mg and/or 200 mg twice a day) for at least 6 months; ¶: 229 patients received delamanid (100 mg or 200 mg twice a day) or placebo for 2 months; +: n=421; §: differences between the long-term and the short-term treatment groups for the corresponding treatment outcome were statistically significant ($p<0.001$), all other differences did not reach statistical significance ($p \geq 0.05$).

A Novel Inhibitor of Gyrase B Is a Potent Drug Candidate for Treatment of Tuberculosis and Nontuberculosis Mycobacterial Infections

Christopher P. Locher,[a] Steven M. Jones,[a] Brian L. Hanzelka,[a] Emanuele Perola,[a] Carolyn M. Shoen,[b] Michael H. Cynamon,[b] Andile H. Ngwane,[c] Ian J. Wiid,[c] Paul D. van Helden,[c] Fabrice Betoudji,[d] Eric L. Nuermberger,[d] John A. Thomson[a]

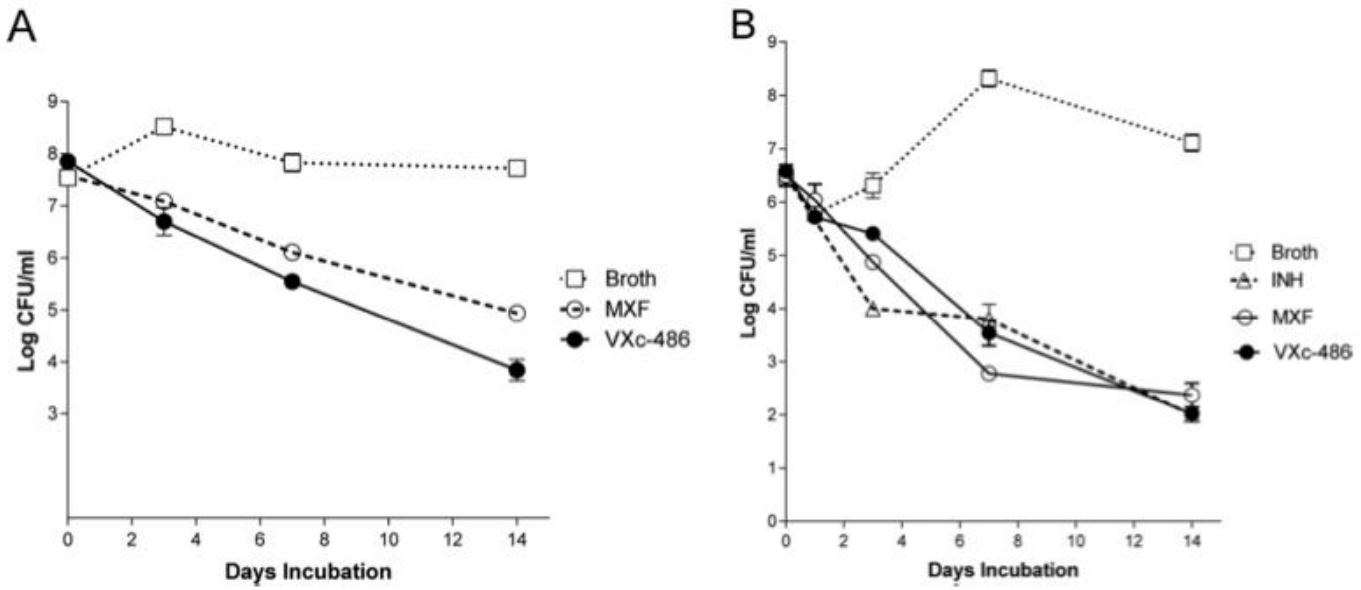

FIG 1 (A) Bactericidal activities of VXc-486 and moxifloxacin (MXF) against *Mycobacterium tuberculosis* (Erdman strain). Representative results from two independent experiments cultured in triplicate are shown. Both VXc-486 and MXF were used at 4-fold MICs; VXc-486 was used at a concentration of 0.24 μg/ml and MXF was used at a concentration of 0.12 μg/ml. (B) Bactericidal activities of VXc-486, isoniazid (INH), and moxifloxacin (MXF) against *Mycobacterium kansasii* (strain 0008)

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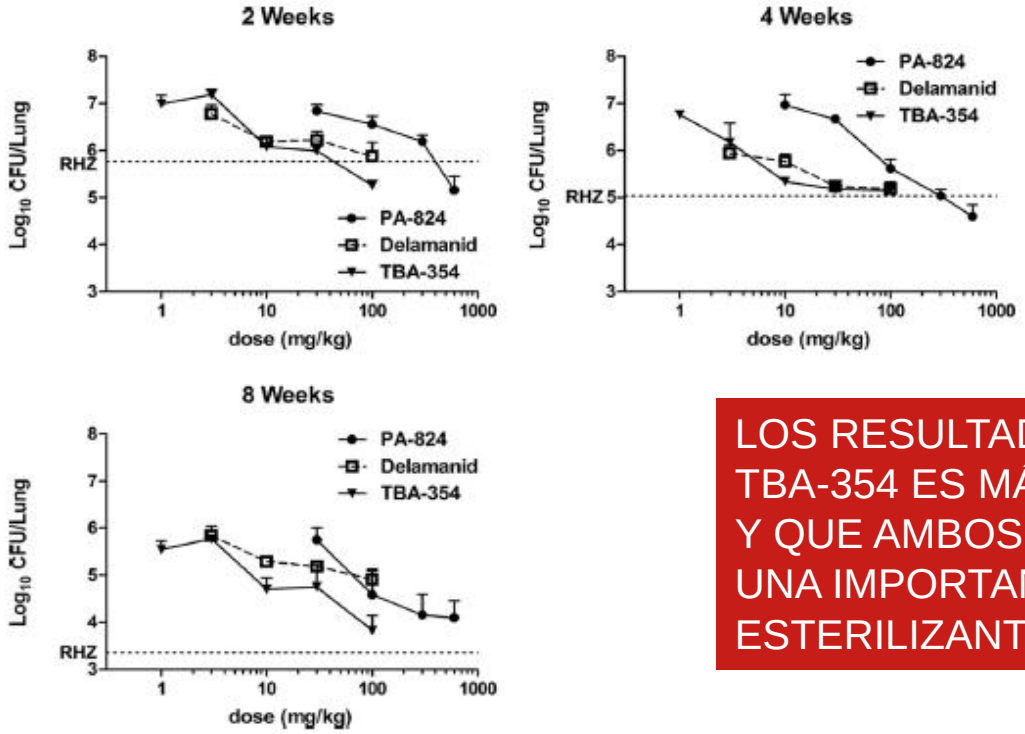
Contribution of the Nitroimidazoles PA-824 and TBA-354 to the Activity of Novel Regimens in Murine Models of Tuberculosis

Rokeya Tasneen,[a] Kathy Williams,[a] Opokua Amoabeng,[a] Austin Minkowski,[a] Khisimuzi E. Mdluli,[b] Anna M. Upton,[b] Eric L. Nuermberger[a,c]

Center for Tuberculosis Research, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA[a]; Global Alliance for TB Drug Development, New York, New York, USA[b]; Department of International Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA[c]



LOS RESULTADOS DEMUESTRAN QUE TBA-354 ES MÁS POTENTE QUE PA-824 Y QUE AMBOS, COMBINADOS, TIENEN UNA IMPORTANTE ACTIVIDAD ESTERILIZANTE.

Antimicrobial Agents and Chemotherapy January 2015 Volume 59 Number 1

In Vitro Activity of AZD5847 against Geographically Diverse Clinical Isolates of *Mycobacterium tuberculosis*

Jim Werngren,[a] Maria Wijkander,[a] Nasrin Perskvist,[b] V. Balasubramanian,[c]* Vasan K. Sambandamurthy,[c] Camilla Rodrigues,[d] Sven Hoffner[a]

The Public Health Agency of Sweden, Department of Microbiology, Unit of Highly Pathogenic Bacteria, Solna, Sweden[a]; Karolinska University Hospital, Laboratory Medicine, Department of Pathology, Huddinge, Sweden[b]; Infection Innovative Medicines Unit, AstraZeneca R&D, Bangalore, India[c]; P.D. Hinduja National Hospital and Medical Research Centre, Mumbai, India[d]

TABLE 1 MIC distribution for the 146 *M. tuberculosis* strains categorized as drug susceptible or drug resistant

M. tuberculosis strain category[a]	No. of strains	MIC range (mg/liter)	MIC_{50} (mg/liter)	MIC_{90} (mg/liter)
Drug sensitive	73	0.125–4	1.0	1.0
SDR	11	0.125–4	1.0	1.0
MDR	48	0.5–2.0	1.0	1.0
XDR	14	0.5–4.0	1.0	1.0

[a] SDR, singly drug resistant (singly resistant to isoniazid, rifampin, ethambutol, streptomycin, or ofloxacin); MDR, multidrug resistant (resistant to isoniazid and rifampin); XDR, extensively drug resistant (MDR strain resistant to fluoroquinolone and an injectable drug such as amikacin, kanamycin, or capreomycin).

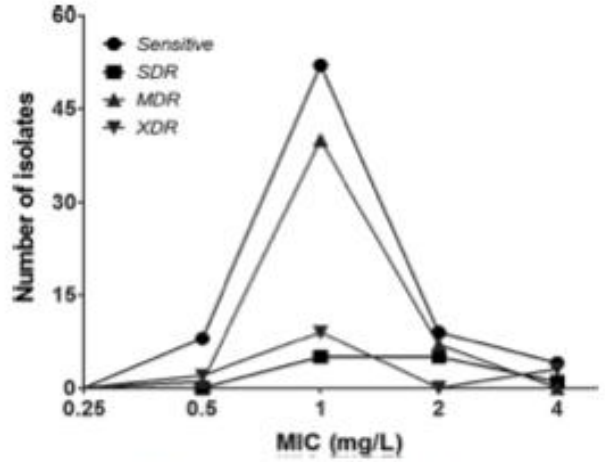


FIG 1 Activity of AZD5847 across a panel of 146 *M. tuberculosis* strains categorized as drug susceptible or drug resistant.

AZD5847 tuvo buena actividad contra *M. tuberculosis* y no hay resistencia cruzada contra otros antituberculosis. Tiene una alta actividad en las fases bactericida y esterilizante.

Antimicrobial Agents and Chemotherapy p. 4222–4223 July 2014 Volume 58 Number 7

SALUD
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14-day bactericidal activity of PA-824, bedaquiline, pyrazinamide, and moxifloxacin combinations: a randomised trial

Lancet 2012;380:986-93

Andreas H Diacon, Rodney Dawson, Florian von Groote-Bidlingmaier, Gregory Symons, Amour Venter, Peter R Donald, Christo van Niekerk, Daniel Everitt, Helen Winter, Piet Becker, Carl M Mendel, Melvin K Spigelman

Panel 1: Treatment groups

Bedaquiline
Bedaquiline 400 mg a day, but preceded by a dose of 700 mg on treatment day 1, 500 mg on treatment day 2, and 400 mg a day thereafter and accompanied by a pyrazinamide placebo

Bedaquiline-PA-824
Bedaquiline given in doses as in the bedaquiline alone group, but accompanied by PA-824 200 mg a day

Bedaquiline-pyrazinamide
Bedaquiline given in doses as in the bedaquiline alone group but accompanied by pyrazinamide 25 mg/kg bodyweight (range 20–30 mg/kg) a day

PA-824-pyrazinamide
PA-824 200 mg a day accompanied by pyrazinamide 25 mg/kg (range 20–30 mg/kg) bodyweight a day

PA-824- moxifloxacin-pyrazinamide
PA-824 200 mg a day, pyrazinamide 25 mg/kg (range 20–30 mg/kg) a day, and moxifloxacin 400 mg a day

Isoniazid-rifampicin-pyrazinamide-ethambutol
Rifafour e-275 dosed according to bodyweight: 30–37 kg two tablets; 38–54 kg three tablets; and 55–70 kg four tablets. Each tablet of Rifafour e-275 contains isoniazid 75 mg, rifampicin 150 mg, pyrazinamide 400 mg, and ethambutol 275 mg

- La actividad bactericida temprana de PA-824-moxifloxacino-pirazinamida, fue significativamente más alta que bedaquiline; bedaquiline-pirazinamida; PA-824, pero no PA-824-pirazinamida, y comparable con el tratamiento estándar.

- Interpretación: PA-824-moxifloxacino-pirazinamida es potencialmente adecuado para tratar casos drogo sensibles y multidrogo resistentes.

Six- vs. eight-month anti-tuberculosis regimen for pulmonary tuberculosis under programme conditions

K. N. Ukwaja,* S. N. Oshi,† I. Alobu,‡ D. C. Oshi†

*Department of Internal Medicine, Federal Teaching Hospital, Abakaliki, Ebonyi State, †Centre for Development and Reproductive Health, Enugu, Enugu State, ‡National Tuberculosis and Leprosy Control Programme, Ministry of Health, Abakaliki, Ebonyi State, Nigeria

Table 2 Treatment outcomes of smear-positive TB patients by anti-tuberculosis regimen received

Variables	Regimen 1* *n* (%)	Regimen 2† *n* (%)	χ^2 (*P* value)
Treatment outcome (*n* = 928)			8.32 (0.004)
Successful	381 (77.8)	373 (85.2)	
Unsuccessful	109 (22.2)	65 (14.8)	
Failure	14 (2.9)	7 (1.6)	2.13 (0.15)
Death	24 (4.9)	28 (6.4)	0.37 (0.54)
Loss to follow-up	70 (14.3)	24 (5.5)	19.2 (<0.001)
Transferred out	1 (0.2)	6 (1.4)	3.64 (0.06)
Total	490	438	
Smear microscopy after 2 months (*n* = 879)			0.63 (0.43)
Negative	364 (78.6)	336 (80.8)	
Positive	99 (21.4)	80 (19.2)	
Total	463	416	
Smear microscopy after 5 months (*n* = 812)			1.7 (0.2)
Negative	417 (96.8)	374 (98.2)	
Positive	14 (3.2)	7 (1.8)	
Total	431	381	

* 2RHZE/6EH.
† 2RHZE/4RH.
TB = tuberculosis, R = rifampicin; H = isoniazid; Z = pyrazinamide; E = ethambutol.

CONCLUSIONES : Los pacientes nuevos diagnosticados con TB en 2RHZE/4RH tuvieron una mayor tasa de éxito de tratamiento que aquellos tratados con 2RHZE/6EH bajo condiciones de programa en un país de bajos recursos y alta carga de la enfermedad.

Las recomendaciones de la OMS deben de ser mantenidas..

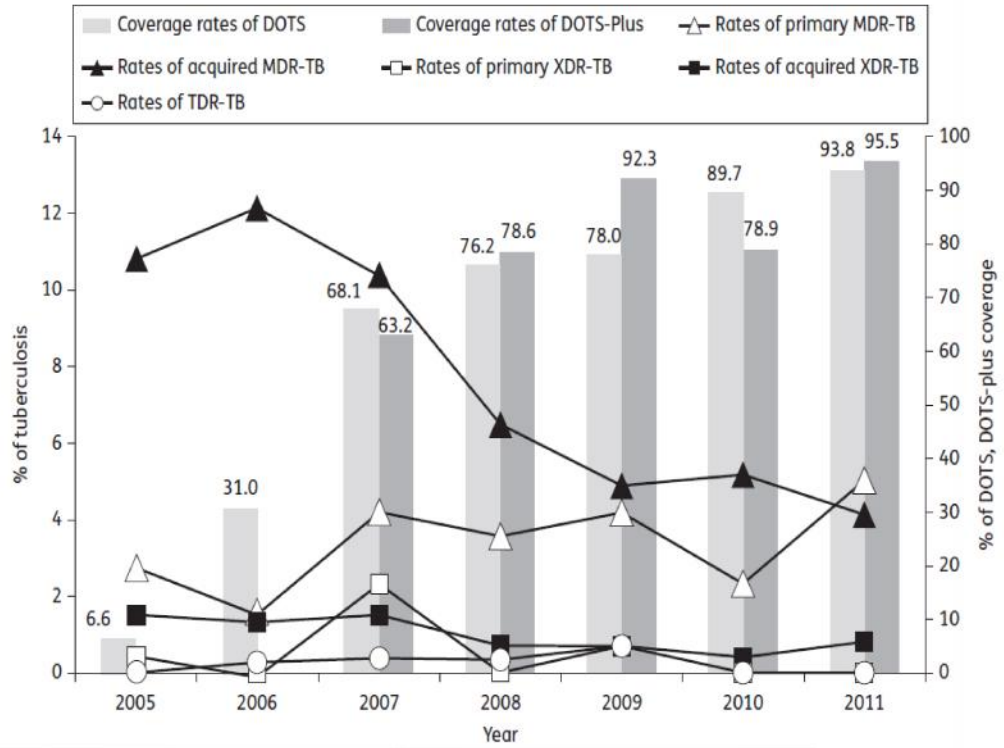
INT J TUBERC LUNG DIS 19(3):295–301

http://dx.doi.org/10.5588/ijtld.14.0494

Decline in rates of acquired multidrug-resistant tuberculosis after implementation of the directly observed therapy, short course (DOTS) and DOTS-Plus programmes in Taiwan

Jung-Yien Chien[1,2], Chih-Cheng Lai[3], Che-Kim Tan[4], Shun-Tien Chien[1], Chong-Jen Yu[2] and Po-Ren Hsueh[2,5]*

DOTS and DOTS-Plus and acquired MDR-TB



J Antimicrob Chemother 2013; **68**: 1910–1916
doi:10.1093/jac/dkt103 Advance Access publication 10 April 2013

PREVENT THE DEVELOPMENT OF DRUG RESISTANCE THROUGH HIGH QUALITY TREATMENT OF DRUG-SUSCEPTIBLE TB

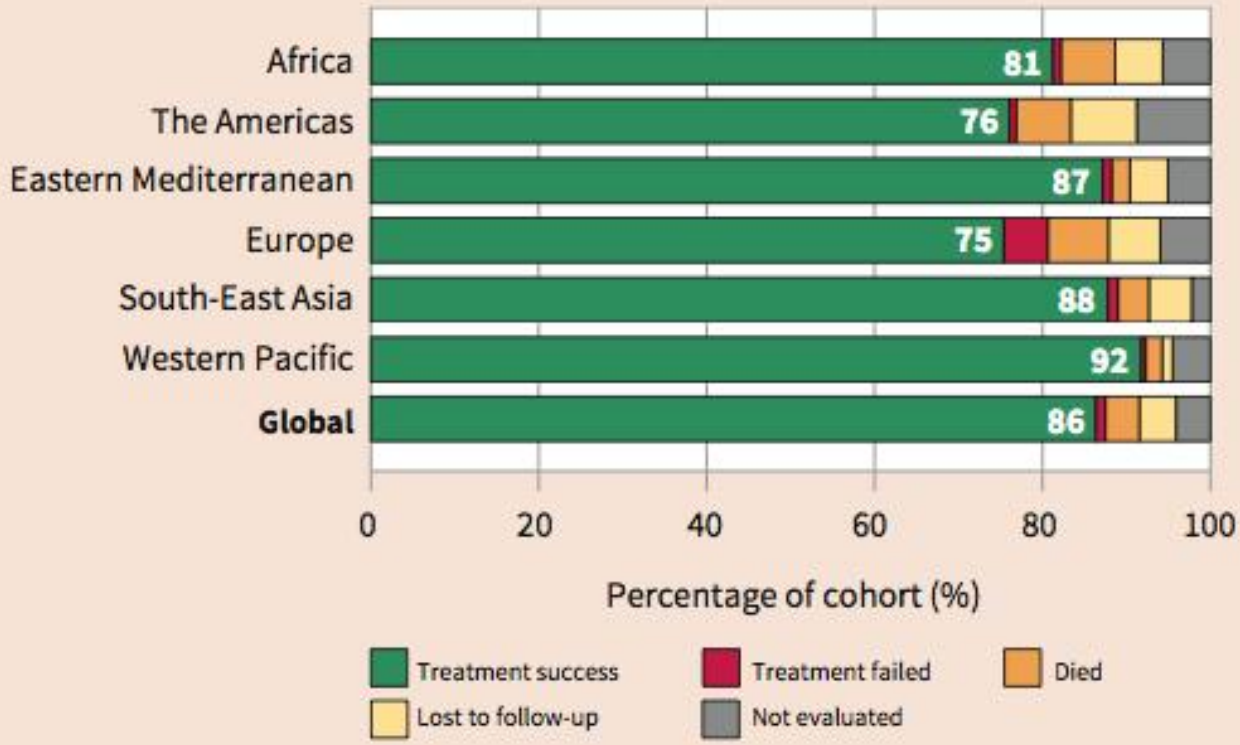
THE BEST PREVENTION AGAINST MDR-TB IS QUALITY TREATMENT OF DRUG-SUSCEPTIBLE TB

Adequate treatment of drug-susceptible TB remains the cornerstone of efforts to prevent the emergence and spread of drug-resistant TB.

Globally, more than 95% of people who develop TB for the first time do not have rifampicin resistance or MDR-TB and can thus be treated successfully using a standard, inexpensive, 6-month course of treatment.

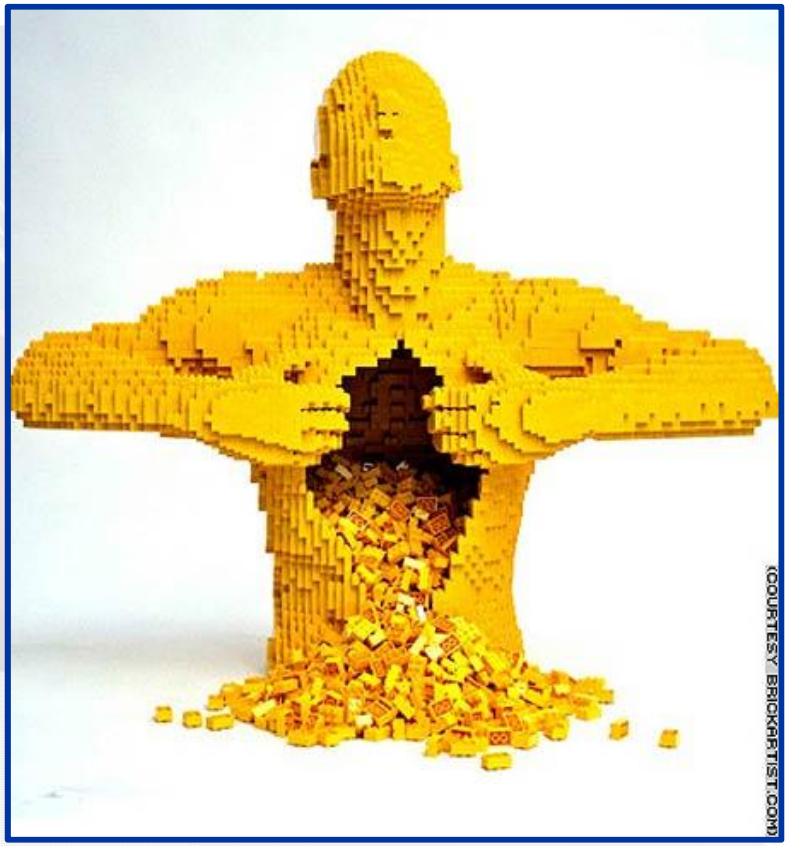
Globally in 2012, the treatment success rate for drug-susceptible TB was 86%, a level that has been maintained for several years.

TREATMENT OUTCOMES FOR NEW AND RELAPSE CASES, 2012, GLOBALLY AND FOR THE SIX WHO REGIONS



CONCLUSIÓN

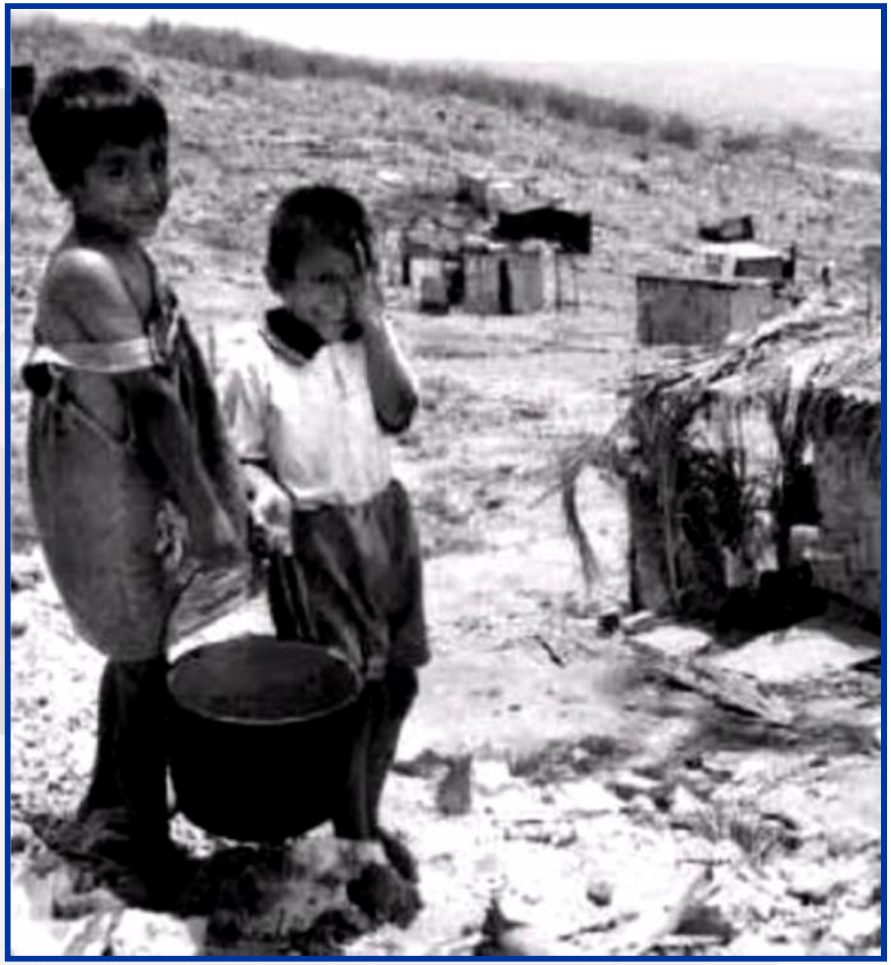
- Por lo menos en 10 años vamos a tener un régimen standard acortado con solo nuevas drogas o una combinación de nuevos y viejos fármacos
- Un reto sera el prevenir el desarrollo de tuberculosis resistente a estos nuevos fármacos



“LA TORMENTA PERFECTA”

MÉXICO, DM Y POBREZA

- 11% de la población entre 20 y 69 años padece DM
- La DM multiplica el riesgo de desarrollar TBP x 2-4
- 53% de los mexicanos vive en situación de pobreza
- 17.8% en pobreza extrema
- La malnutrición duplica el riesgo de padecer TB

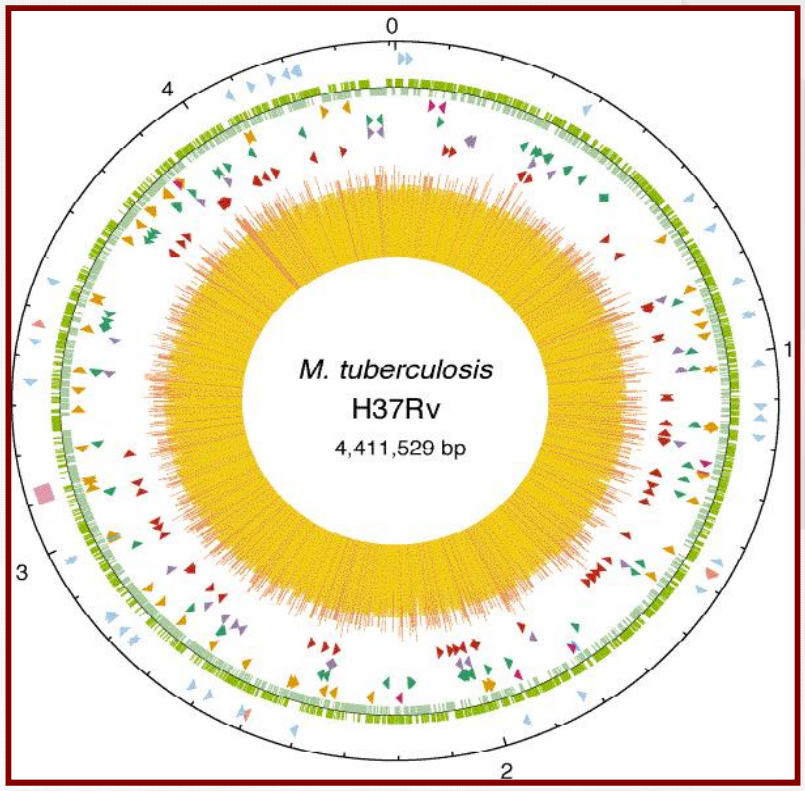


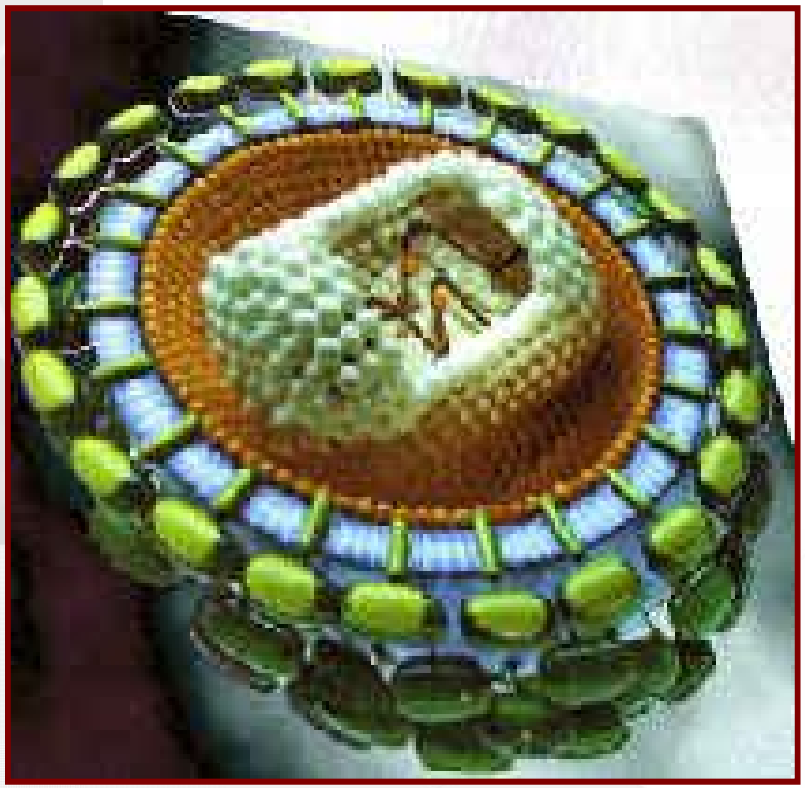
TUBERCULOSIS Y DIABETES

La asociación entre DM y TB fue documentada por Avicena, (980-1027)

A principios del siglo XX se decía que “el paciente que no moría de un coma diabético, probablemente moriría de tuberculosis”

VIH → El Mejor Socio de M. tuberculosis





V.I.H.

"La bestia" Guatemala-México……..¿USA?

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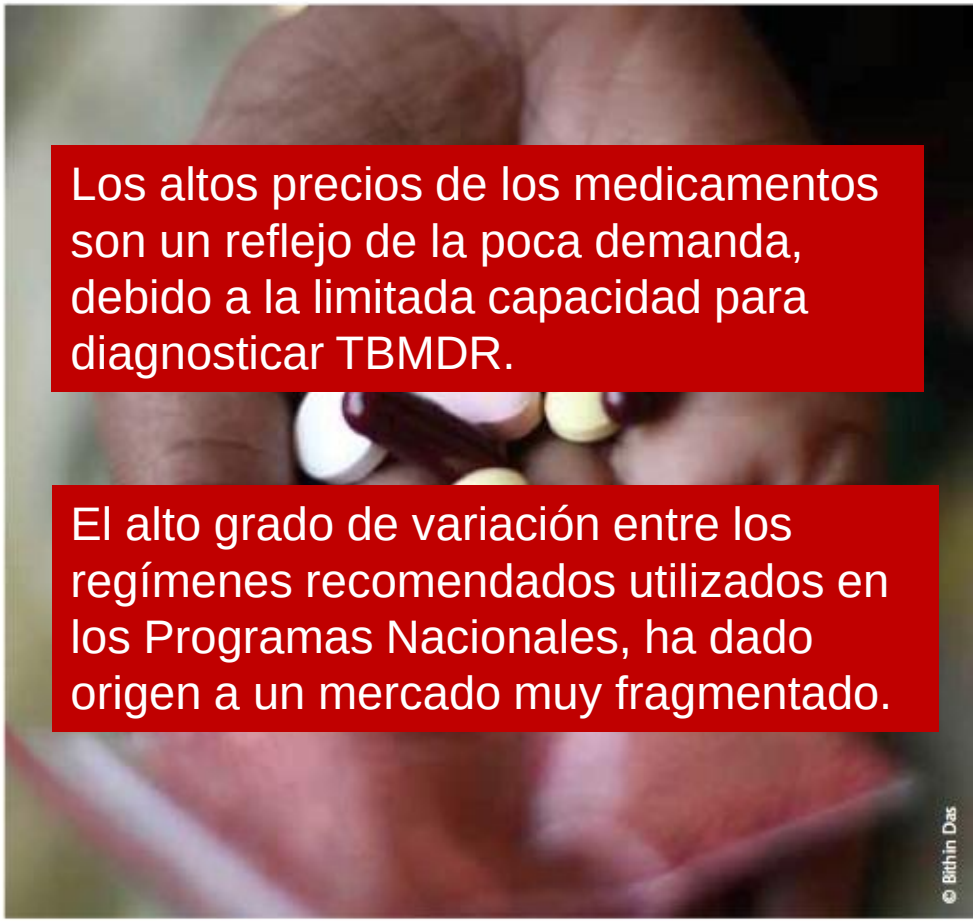
THE MARKET IS SMALL AND FRAGMENTED

For most DR-TB drugs, with the notable exceptions of linezolid and moxifloxacin, the medicines were developed so long ago that patents, which typically act to prevent competition and thereby keep prices higher for longer, have long run out, and do not act as a barrier.

These high prices are rather a reflection of the fact that current market demand is low, due to limited capacity to diagnose and treat DR-TB, which does not provide a sufficient incentive to manufacturers. The global DR-TB market was estimated to be worth $300 million in 2010, with only $125 million procured through the public sector.[3]

Considering the current capacity to diagnose and treat DR-TB is limited, the small international market size is not appealing for manufacturers. Furthermore, there is still a high degree of variation between regimens used by country programs, which leads to a very fragmented market. For example, there is no general consensus between the use of ethionamide or prothionamide, between cycloserine or terizidone, nor between capreomycin or other injectable drugs. Even packaging requirements for DR-TB drugs differ between India and the rest of the world.



Los altos precios de los medicamentos son un reflejo de la poca demanda, debido a la limitada capacidad para diagnosticar TBMDR.

El alto grado de variación entre los regímenes recomendados utilizados en los Programas Nacionales, ha dado origen a un mercado muy fragmentado.

UNCOVERING THE EPIDEMIC OF DR-TB

While timely and accurate diagnosis of DR-TB remains a significant challenge for most high-burden countries, recent diagnostic advances provide a key opportunity to significantly

culture, phenotypic drug sensitivity testing and line probe assay – are key to uncovering the epidemic of DR-TB. Moving forward, developing more robust and less sophisticated next-generation

En el rescate de las instituciones financieras se gastaron $17 trillones de dólares en el fraude que llevó al mundo al desastre económico. Esto significa 22 veces más que los 750 mil millones de dólares que se requieren para obtener las metas del desarrollo del milenio y que no han podido ser alcanzadas.

INT J TUBERC LUNG DIS 14(10):1215–1221