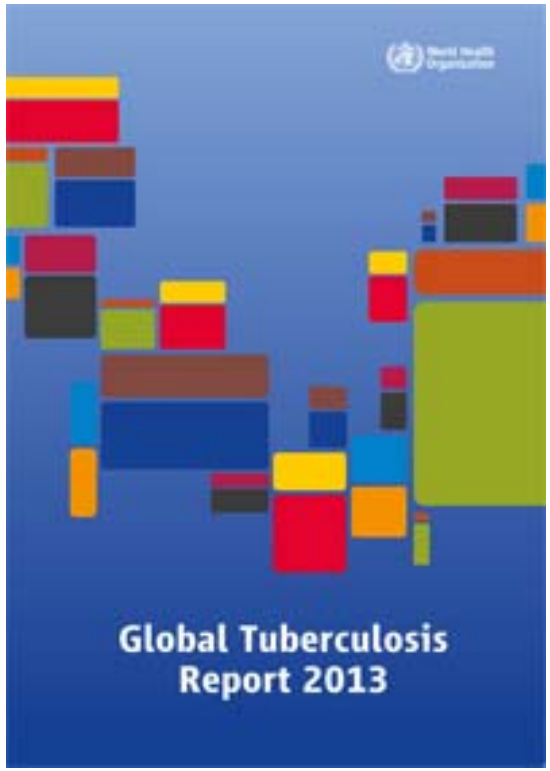
# Nuevas drogas y drogas ‘reutilizadas’ contra tuberculosis

Juan Carlos Palomino PhD

Ghent University - Belgium

December 2013

# Situacion Global TB




Año 2012

8.6 millones de casos de TB

1.3 millones de muertes por TB

320.000 muertes en HIV+

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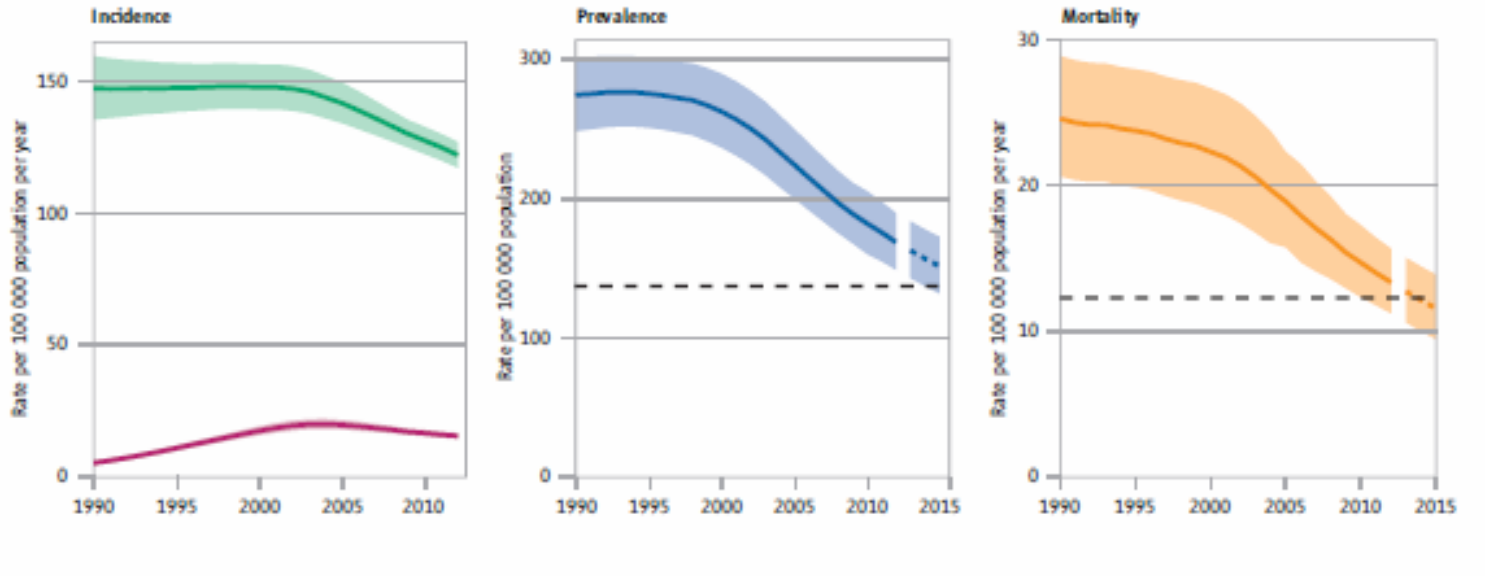
# Situacion Global TB

- Tasa de nuevos casos disminuyendo (2%)
- Mortalidad reducida en 45% desde 1990
- Regiones OMS: Americas y WPR
- 7/22 HBCs lograron objetivos 2015 MDGs

# Tendencias globales estimadas

FIGURE 2.6

**Global trends in estimated rates of TB incidence, prevalence and mortality.** Left: Global trends in estimated incidence rate including HIV-positive TB (green) and estimated incidence rate of HIV-positive TB (red). Centre and right: Trends in estimated TB prevalence and mortality rates 1990–2012 and forecast TB prevalence and mortality rates 2013–2015. The horizontal dashed lines represent the Stop TB Partnership targets of a 50% reduction in prevalence and mortality rates by 2015 compared with 1990. Shaded areas represent uncertainty bands. Mortality excludes TB deaths among HIV-positive people.



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# Situacion Global TB

- Disminucion prevalencia global 37%
- Europa y Africa: mortalidad y prevalencia
- 11/22 HBCs retrasados en objetivos MDG
- Objetivos MDR-TB lejos de conseguirse
- Menos de 25% MDR-TB detectado

# Multidrogo-resistencia

- MDR-TB: resistentes a INH y RIF
- 3.6% en nuevos casos y 20.2% en casos en tratamiento
- Europa del Este y Asia Central 20 y 50%
- 450.000 MDR-TB estimados en 2012 (India, China, Rusia)

# XDR-TB

- 9.6% de MDR-TB estimado XDR-TB
- MDR-TB + quinolona + inyectable 2° línea (CAP, KAN, AMK)
- Reportado en 92 paises

# XDR-TB

## Extensively drug-resistant tuberculosis as a cause of death in patients co-infected with tuberculosis and HIV in a rural area of South Africa

*Neel R Gandhi, Anthony Moll, A Willem Sturm, Robert Pawinski, Thiloshini Govender, Umesh Lalloo, Kimberly Zeller, Jason Andrews, Gerald Friedland*


### Summary

**Background** The epidemics of HIV-1 and tuberculosis in South Africa are closely related. High mortality rates in co-infected patients have improved with antiretroviral therapy, but drug-resistant tuberculosis has emerged as a major cause of death. We assessed the prevalence and consequences of multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis in a rural area in KwaZulu Natal, South Africa.

**Methods** We undertook enhanced surveillance for drug-resistant tuberculosis with sputum culture and drug susceptibility testing in patients with known or suspected tuberculosis. Genotyping was done for isolates resistant to first-line and second-line drugs.

**Results** From January, 2005, to March, 2006, sputum was obtained from 1539 patients. We detected MDR tuberculosis in 221 patients, of whom 53 had XDR tuberculosis. Prevalence among 475 patients with culture-confirmed tuberculosis was 39% (185 patients) for MDR and 6% (30) for XDR tuberculosis. Only 55% (26 of 47) of patients with XDR tuberculosis had never been previously treated for tuberculosis; 67% (28 of 42) had a recent hospital admission. All 44 patients with XDR tuberculosis who were tested for HIV were co-infected. 52 of 53 patients with XDR tuberculosis died, with median survival of 16 days from time of diagnosis (IQR 6–37) among the 42 patients with confirmed dates of death. Genotyping of isolates showed that 39 of 46 (85%, 95% CI 74–95) patients with XDR tuberculosis had similar strains.

**Conclusions** MDR tuberculosis is more prevalent than previously realised in this setting. XDR tuberculosis has been transmitted to HIV co-infected patients and is associated with high mortality. These observations warrant urgent intervention and threaten the success of treatment programmes for tuberculosis and HIV.


*Lancet* 2006; 368: 1575–80

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See Comment page 1554

AIDS Program, Section of Infectious Diseases, Department of Internal Medicine, Yale University School of Medicine, New Haven, CT, USA (N R Gandhi MD, J Andrews BA, K Zeller MD, G Friedland MD); Church of Scotland Hospital and Philanjalo, Tugela Ferry, South Africa (A Moll MBChB); Department of Medical Microbiology (A W Sturm MD) and Department of Medicine (R Pawinski MBChB, U Lalloo MD), Nelson R Mandela School of Medicine, Durban, South Africa; KwaZulu Natal Department of Health, KwaZulu Natal, South Africa

| | Group 1 | Group 2 | Group 3† | Total |
|---|---|---|---|---|
| Total tested | 86 | 25 | 1428 | 1539 |
| Culture-positive | 45 | 22 | 475 | 542 |
| MDR tuberculosis* | 26 | 10 | 185 | 221 |
| XDR tuberculosis | 17 | 6 | 30 | 53 |

Data are number of patients. * Includes cases

*Table 1:* Distribution of culture results a
group for all patients (n=1539) for who

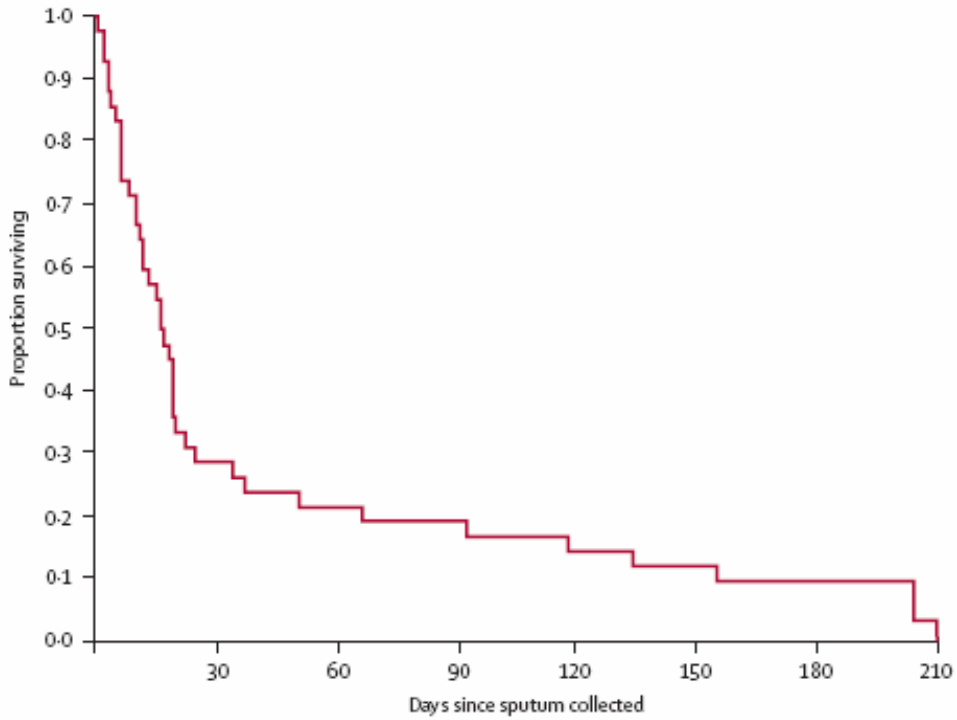


*Figure:* Survival after sputum collection in patients with XDR tuberculosis with confirmed dates of death (n=42)

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CHEST Original Research

TUBERCULOSIS

# Emergence of New Forms of Totally Drug-Resistant Tuberculosis Bacilli

## Super Extensively Drug-Resistant Tuberculosis or

Clinical Infectious Diseases Advance Access published December 21, 2011

# Correspondence

### Totally Drug-Resistant Tuberculosis in India

To THE EDITOR—Three years after ex-

individually and often in incorrect doses, from multiple private practitioners (mean, 4 physicians during a 18-month period)

**Note**

***Potential conflicts of interest.*** All author
No reported conflicts.

### Totally Drug-Resistant and Extremely Drug-Resistant Tuberculosis: The Same Disease?

To THE EDITOR—The emergence of totally drug-resistant (TDR) tuberculosis in India and Iran has been recently discussed in the literature [1, 2]. The 15

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SURVEILLANCE AND OUTBREAK REPORTS

# *Escherichia coli* and *Staphylococcus aureus*: bad news and good news from the European Antimicrobial Resistance Surveillance Network (EARS-Net, formerly EARSS), 2002 to 2009

C Gagliotti[1], A Balode[2], F Baquero[3], J Degener[4], H Grundmann[5], D Gür[6], V Jarlier[7], G Kahlmeter[8], J Monen[5], D L Monnet[1], G M Rossolini[9], C Suetens[1], K Weist[1], O Heuer (ole.heuer@ecdc.europa.eu)[1], the EARS-Net Participants (Disease Specific Contact Points for AMR)[10]

**FIGURE 1**

Annual number of bloodstream infections caused by *Escherichia coli* and *Staphylococcus aureus*, EARSS/EARS-Net, 2002-09 (22 countries/198 laboratories)

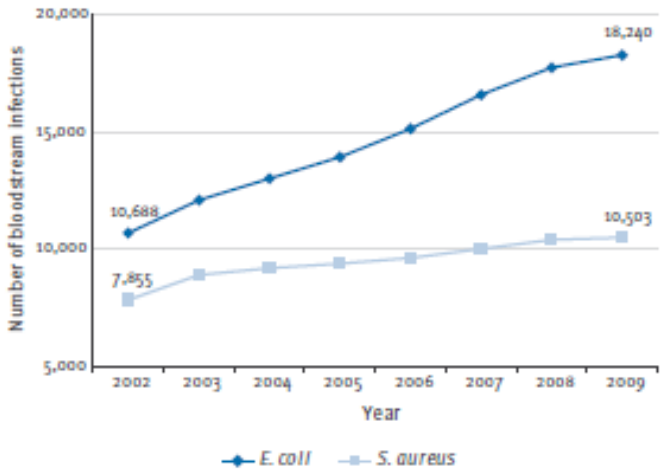
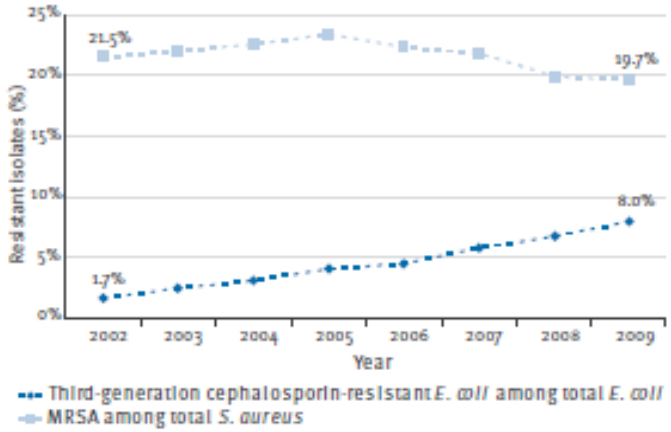



**FIGURE 2**

Proportion of third-generation cephalosporin-resistant *Escherichia coli* and of meticillin-resistant *Staphylococcus aureus*, EARSS/EARS-Net, 2002-09 (22 countries/198 laboratories)



International Journal of Antimicrobial Agents 39 (2012) 295–299

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journal homepage: http://www.elsevier.com/locate/ijantimicag

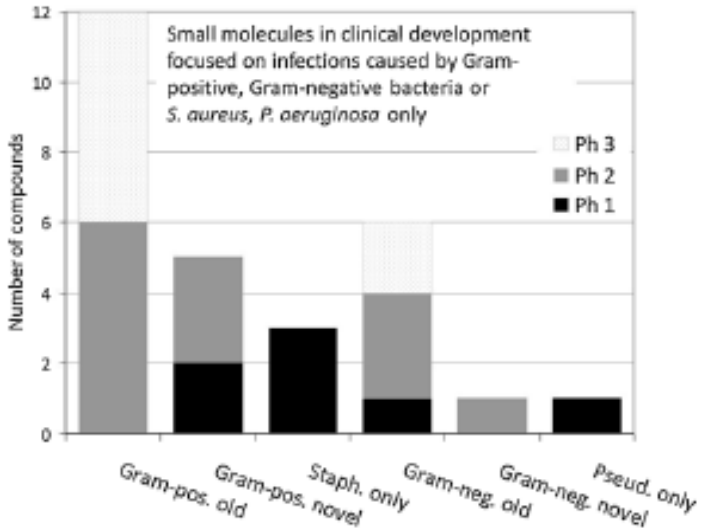
Review

# Accelerating resistance, inadequate antibacterial drug pipelines and international responses

Ursula Theuretzbacher*

*Center for Anti-Infective Agents, Eckpergasse 13, 1180 Vienna, Austria*





# Trends in Antimicrobial Drug Development: Implications for the Future

**Brad Spellberg,[1] John H. Powers,[3] Eric P. Brass,[1,2] Loren G. Miller,[1,2] and John E. Edwards, Jr.[1,2]**

[1]Research and Education Institute and Department of Medicine, Harbor–University of California, Los Angeles (UCLA), Medical Center, Torrance, and [2]David Geffen School of Medicine, UCLA, Los Angeles, California; and [3]Office of Drug Evaluation IV, Center for Drug Evaluation and Research, US Food and Drug Administration, Rockville, Maryland

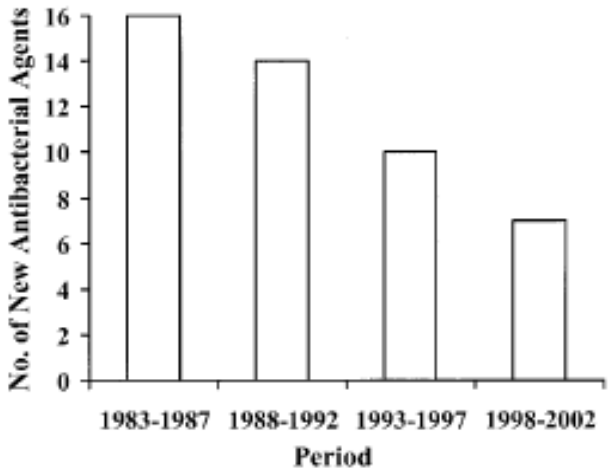


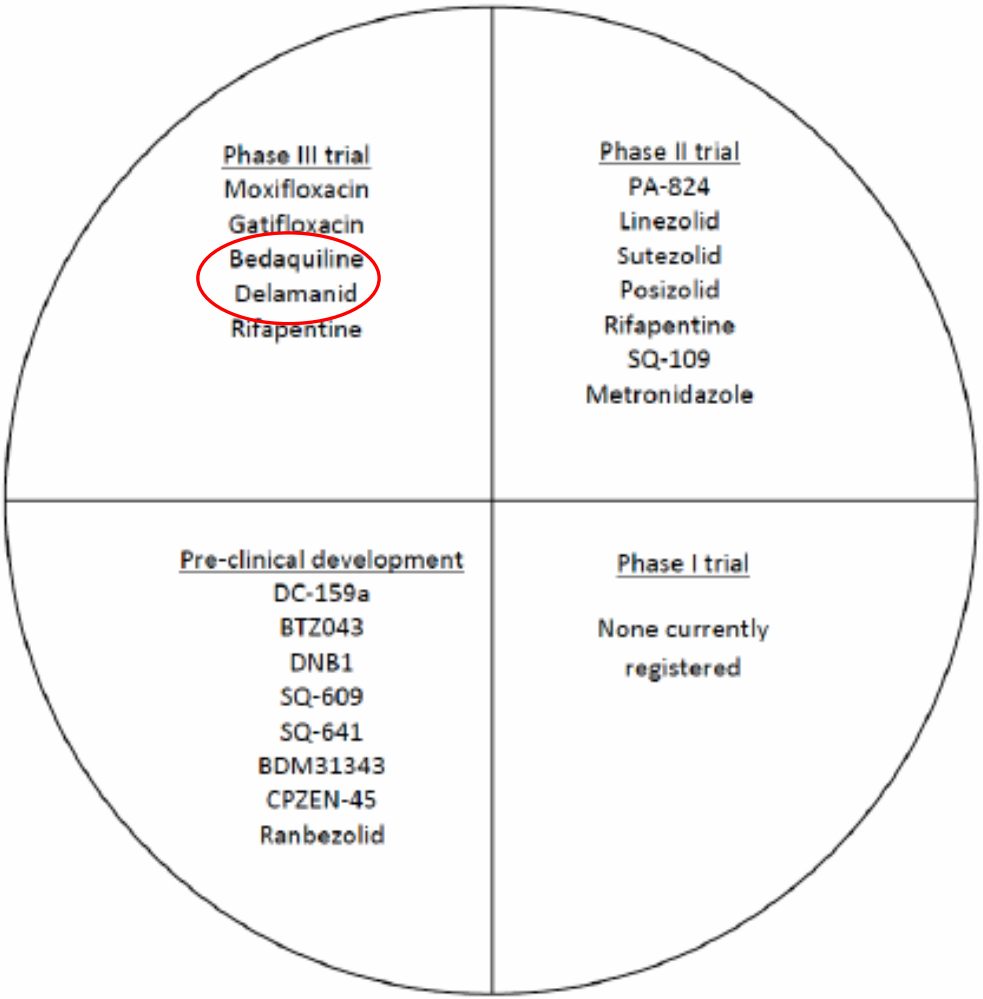

**Figure 1.** New antibacterial agents approved in the United States, 1983–2002, per 5-year period.

**Table 1. New antibacterial agents approved since 1998.**

| Drug | Year approved | Novel mechanism |
|---|---|---|
| Rifapentine | 1998 | No |
| Quinupristin/dalfopristin | 1999 | No[a] |
| Moxifloxacin | 1999 | No |
| Gatifloxacin | 1999 | No |
| Linezolid | 2000 | Yes |
| Cefditoren pivoxil | 2001 | No |
| Ertapenem | 2001 | No |
| Gemifloxacin | 2003 | No |
| Daptomycin | 2003 | Yes |

[a] The mechanism of the streptogramins (quinupristin and dalfopristin) is closely related to that of the macrolide/lincosamide families [63].

# Drogas anti-tuberculosis



# Bedaquiline

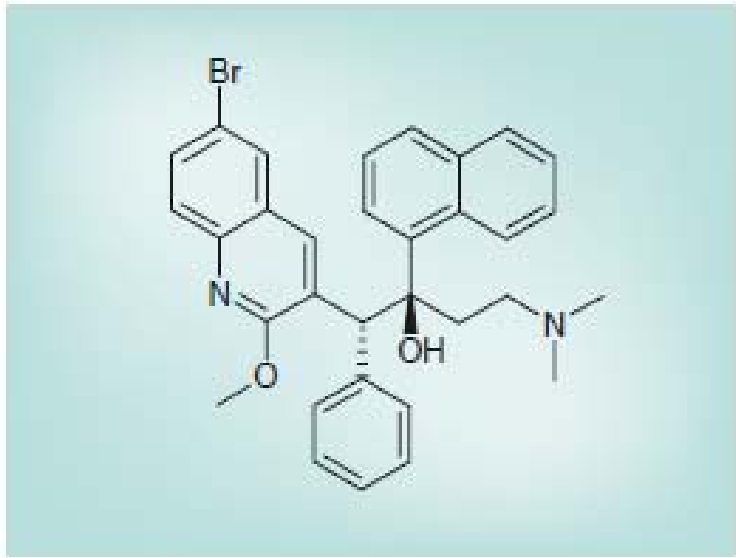
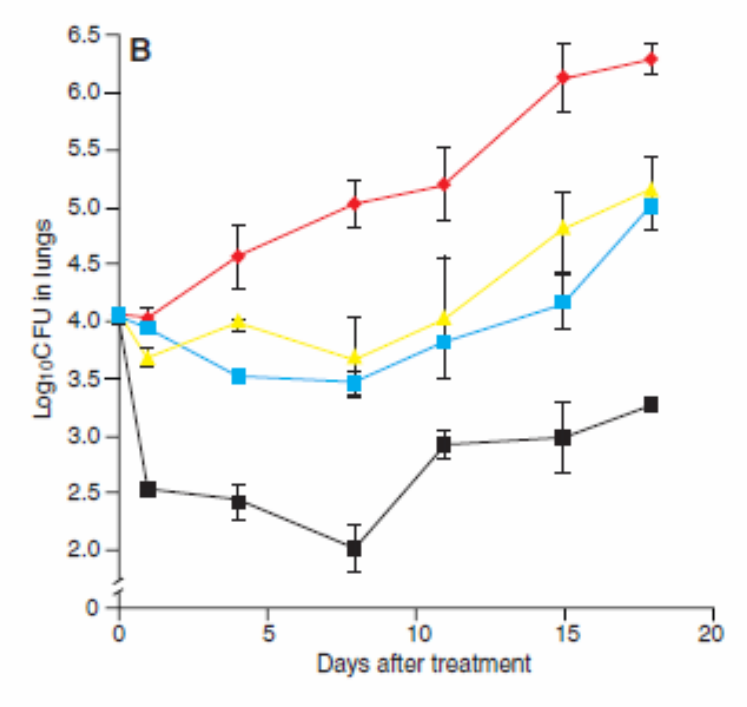
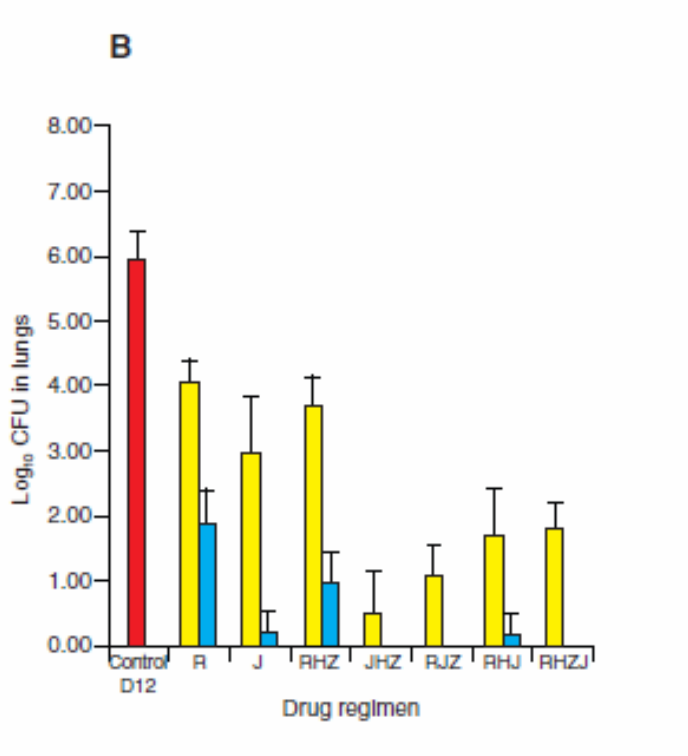



Figure 1. Bedaquiline.

R207910 => TMC207 => Bedaquiline => Sirturo

# Bedaquiline actividad in vivo



# Bedaquiline: modo de acción

nature chemical biology

## Diarylquinolines target subunit c of mycobacterial ATP synthase

Anil Koul[1,4], Najoua Dendouga[1,4], Karen Vergauwen[1], Brenda Molenberghs[1], Luc Vranckx[1], Rudy Willebrords[1], Zorica Ristic[2], Holger Lill[2], Ismet Dorange[3], Jerome Guillemont[3], Dirk Bald[2] & Koen Andries[1]

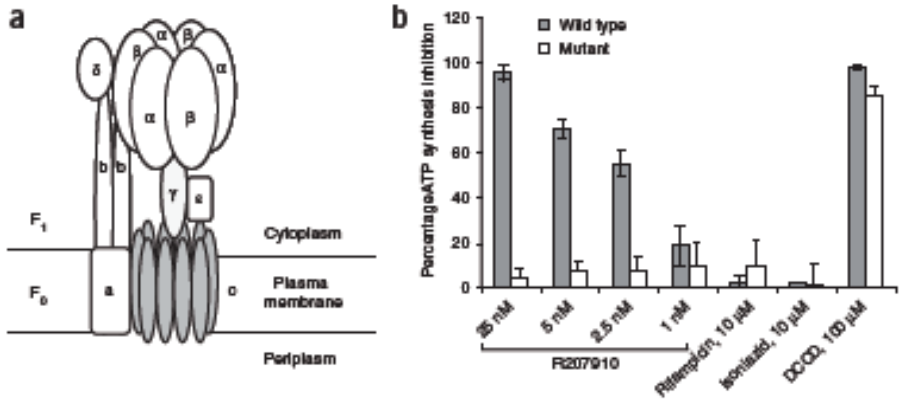



**Figure 1** ATP synthase subunit composition and inhibition by R207910. (a) ATP synthase has a transmembrane $F_O$ part (subunits a, b and c) and a cytoplasmic $F_1$ part (subunits α, β, γ, δ and ε). The oligomeric subunit c (AtpE), forming a ring-like structure, is highlighted in *gray*. (b) Effect of R207910 on ATP synthase from wild-type or mutant ($atpE^{D32V}$) *M. smegmatis*; shown are mean values of three independent experiments with s.d.

# Bedaquiline: ensayos clínicos

**Table 1. Overview of clinical studies performed with bedaquiline.**

| Study (year) | Phase | Test arm | Control arm | Subjects |
|---|---|---|---|---|
| 11 studies (single dose and multiple dose) | I | Bedaquiline | Placebo | 265 |
| C202 (EBA study) in DS-TB | IIa | Bedaquiline (up to 400 mg daily) | INH + RIF | 75 |
| C208, stage 1 MDR-TB and pre-XDR-TB | IIb | Bedaquiline + BR over 8 weeks | Placebo + BR | 47 |
| C208, stage 2 MDR-TB and pre-XDR-TB | IIb | Bedaquiline + BR over 24 weeks | Placebo + BR | 160 |
| C209, MDR-TB, pre-XDR-TB and XDR-TB | IIb | Bedaquiline + individualized MDR-TB treatment over 24 weeks | No placebo (single-arm trial) | 233 |
| C210, MDR-TB and pre-XDR-TB | III | Bedaquiline + BR over 9 months | Placebo + BR over 9 months | Expected 600 |

*BR: Background regimen; DS: Drug-susceptible; EBA: Early bactericidal activity; INH: Isoniazid; MDR: Multidrug-resistant; RIF: Rifampicin; XDR: Extensively drug-resistant.*
*Data taken from* [103].

*Palomino & Martin Future Microbiology 8(9), 2013*

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The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 4, 2009 VOL. 360 NO. 23

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# The Diarylquinoline TMC207 for Multidrug-Resistant Tuberculosis

Andreas H. Diacon, M.D., Ph.D., Alexander Pym, M.D., Ph.D., Martin Grobusch, M.D., D.T.M.&H., Ramonde Patientia, M.D., Roxana Rustomjee, M.D., Ph.D., Liesl Page-Shipp, M.D., Christoffel Pistorius, M.D., Rene Krause, M.D., Mampedi Bogoshi, M.D., Gavin Churchyard, M.B., Ch.B., Amour Venter, Nat.Dip.Med.Tech.(Micro), Jenny Allen, B.Sc., Juan Carlos Palomino, Ph.D., Tine De Marez, Ph.D., Rolf P.G. van Heeswijk, Pharm.D., Ph.D., Nacer Lounis, Ph.D., Paul Meyvisch, M.Sc., Johan Verbeeck, D.V.M., Ph.D., Wim Parys, M.D., Karel de Beule, Pharm.D., Koen Andries, D.V.M., Ph.D., and David F. Mc Neeley, M.D., M.P.H.T.M.

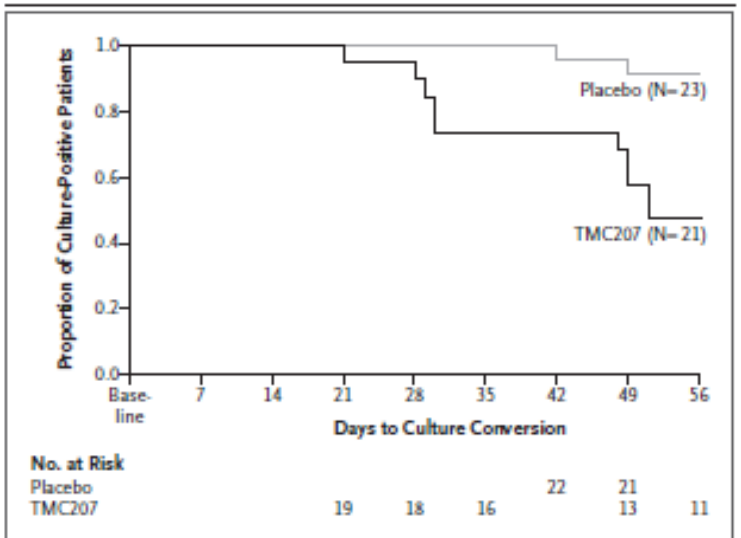


**Figure 2. The Proportion of Patients with Positive Sputum Cultures and Time to Conversion.**

Proportions of positive cultures were determined according to the mycobacteria growth indicator tube (MGIT) system.

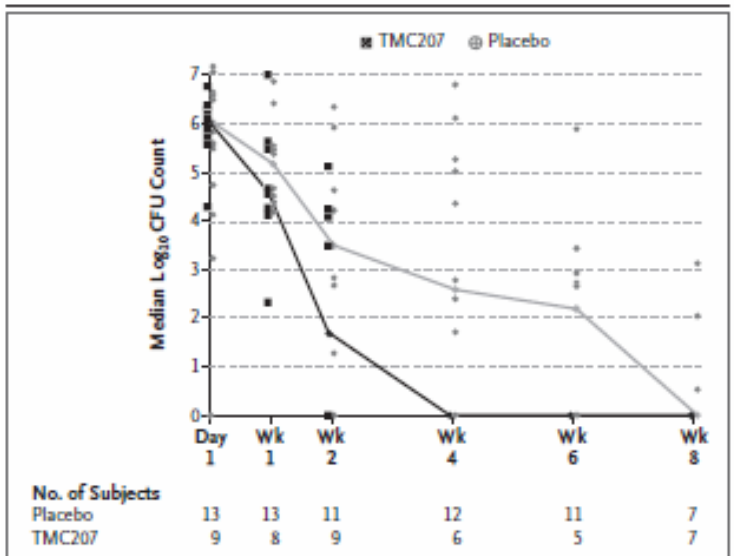


**Figure 3. Median (±SD) $Log_{10}$ Count of Colony-Forming Units (CFUs).**

Median (±SD) $log_{10}$ CFU counts over time are shown in the subgroup of 22 patients who provided pooled-sputum samples.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204384

**ACCELERATED APPROVAL**

Janssen Research and Development, LLC
Attention: Gary Lewis
Associate Director, Global Regulatory Affairs
920 Route 202 South
Raritan, NJ 08869

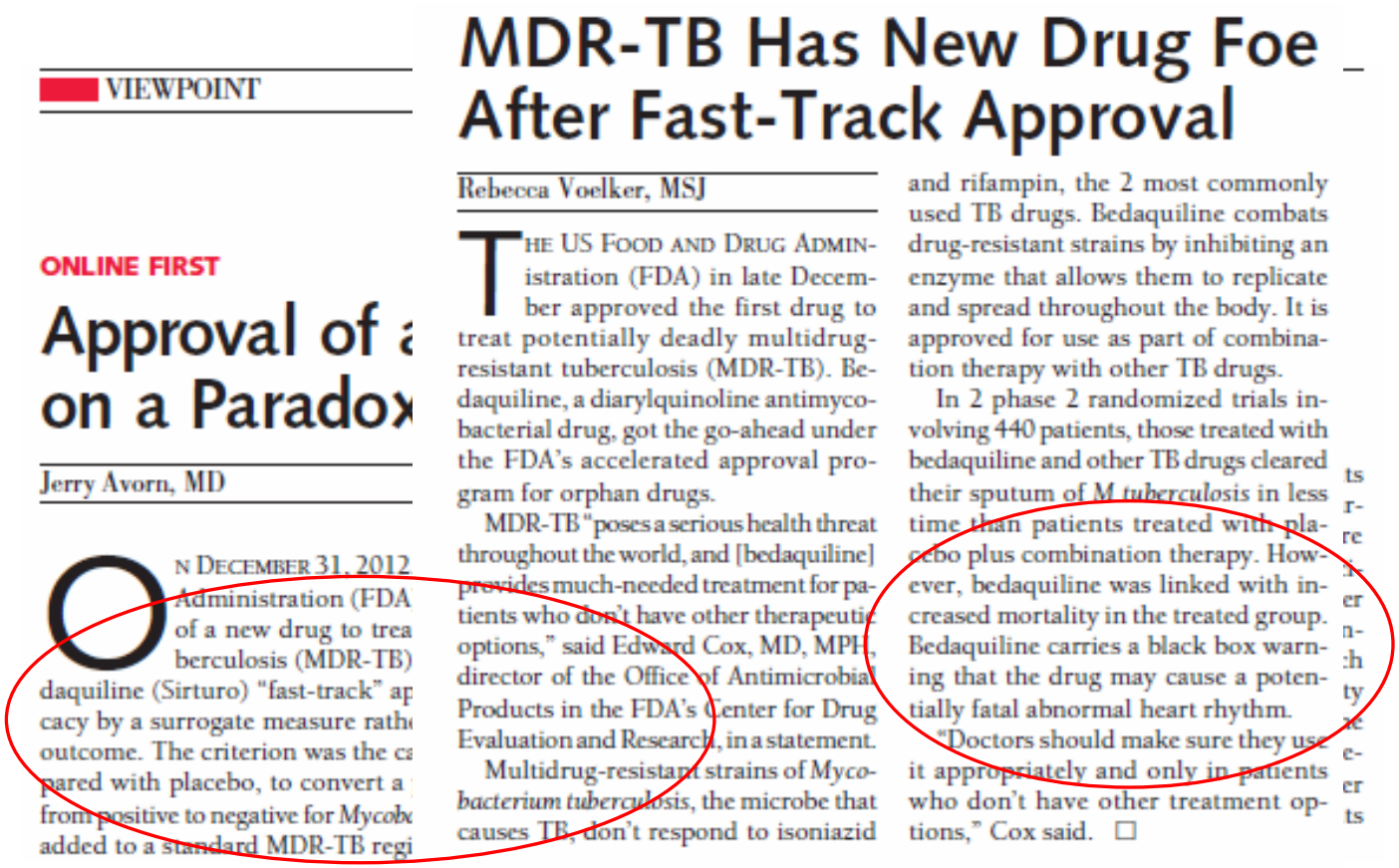
Dear Mr. Lewis:

Please refer to your New Drug Application (NDA) dated June 28, 2012, received June 29, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for SIRTURO (bedaquiline) 100 mg tablets.

We have completed our review of this application, as amended. It is approved under the provisions of the accelerated approval regulations (21 CFR 314.500), effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text. Marketing of this drug product and related activities must adhere to the substance and procedures of the referenced accelerated approval regulations.

EDWARD M COX
12/28/2012

# Bedaquiline: críticas



VIEWPOINT

ONLINE FIRST

## Approval of a … on a Paradox

Jerry Avorn, MD

On December 31, 2012 … Administration (FDA … of a new drug to trea… berculosis (MDR-TB) … daquiline (Sirturo) "fast-track" ap… cacy by a surrogate measure rath… outcome. The criterion was the ca… pared with placebo, to convert a … from positive to negative for *Mycob…* added to a standard MDR-TB regi…

## MDR-TB Has New Drug Foe After Fast-Track Approval

Rebecca Voelker, MSJ

The US Food and Drug Administration (FDA) in late December approved the first drug to treat potentially deadly multidrug-resistant tuberculosis (MDR-TB). Bedaquiline, a diarylquinoline antimycobacterial drug, got the go-ahead under the FDA's accelerated approval program for orphan drugs.

MDR-TB "poses a serious health threat throughout the world, and [bedaquiline] provides much-needed treatment for patients who don't have other therapeutic options," said Edward Cox, MD, MPH, director of the Office of Antimicrobial Products in the FDA's Center for Drug Evaluation and Research, in a statement.

Multidrug-resistant strains of *Mycobacterium tuberculosis*, the microbe that causes TB, don't respond to isoniazid and rifampin, the 2 most commonly used TB drugs. Bedaquiline combats drug-resistant strains by inhibiting an enzyme that allows them to replicate and spread throughout the body. It is approved for use as part of combination therapy with other TB drugs.

In 2 phase 2 randomized trials involving 440 patients, those treated with bedaquiline and other TB drugs cleared their sputum of *M tuberculosis* in less time than patients treated with placebo plus combination therapy. However, bedaquiline was linked with increased mortality in the treated group. Bedaquiline carries a black box warning that the drug may cause a potentially fatal abnormal heart rhythm.

"Doctors should make sure they use it appropriately and only in patients who don't have other treatment options," Cox said. □

# Delamanid

OPEN ACCESS Freely avail

PLOS MEDICINE

OPC-6768 zole

Derivative

against Tu e

Makoto Matsumoto[1*], Hir bouchi[2],

Hirofumi Sasaki[2], Yoshihil

1 Microbiological Research Institute ceutical, Tokushima, Japan,

3 Tokushima Research Institute, Otsu

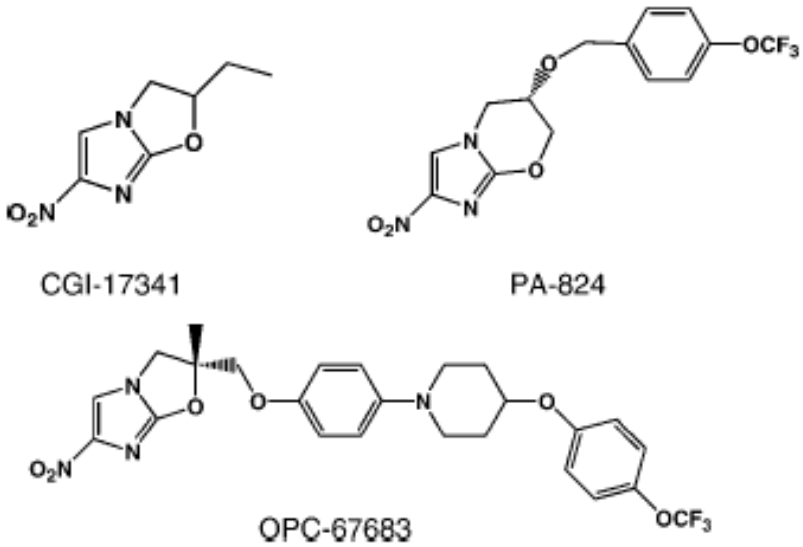



**Figure 1.** Structure of CGI-17341, PA-824, and OPC-67683

OPC-67683: (*R*)-2-methyl-6-nitro-2-{4-[4-(4-trifluoromethoxyphenoxy)piperidin-1-yl]phenoxymethyl}-2,3-dihydroimidazo[2,1-*b*]oxazole.

doi:10.1371/journal.pmed.0030466.g001

# Delamanid

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 2.** In Vitro Anti-Mycobacterial Activity of OPC-67683 Compared with RFP, INH, EB, SM, CGI-17341, and PA-824

| Type Strain | MIC (μg/ml) | | | | | | |
|---|---|---|---|---|---|---|---|
| | OPC-67683 | RFP | INH | EB | SM | CGI-17341 | PA-824 |
| *M. tuberculosis* ATCC 25618 (H37Rv) | 0.012 | 0.78 | 0.1 | 1.56 | 1.56 | 0.2 | 0.2 |
| *M. tuberculosis* ATCC 35838 (H37Rv-R-R) | 0.006 | >100 | 0.1 | 1.56 | 0.78 | 0.05 | 0.1 |
| *M. tuberculosis* ATCC 35822 (H37Rv-H-R) | 0.012 | 0.39 | >100 | 3.13 | 0.78 | 0.2 | 0.05 |
| *M. tuberculosis* ATCC 35837 (H37Rv-E-R) | 0.012 | 0.2 | 0.2 | 50 | 0.78 | 0.2 | 0.2 |
| *M. tuberculosis* ATCC 35820 (H37Rv-S-R) | 0.012 | 0.78 | 0.1 | 3.13 | >100 | 0.2 | 0.2 |
| *M. tuberculosis* ATCC 35812 (Kurono) | 0.012 | 0.39 | 0.1 | 3.13 | 0.78 | 0.2 | 0.2 |

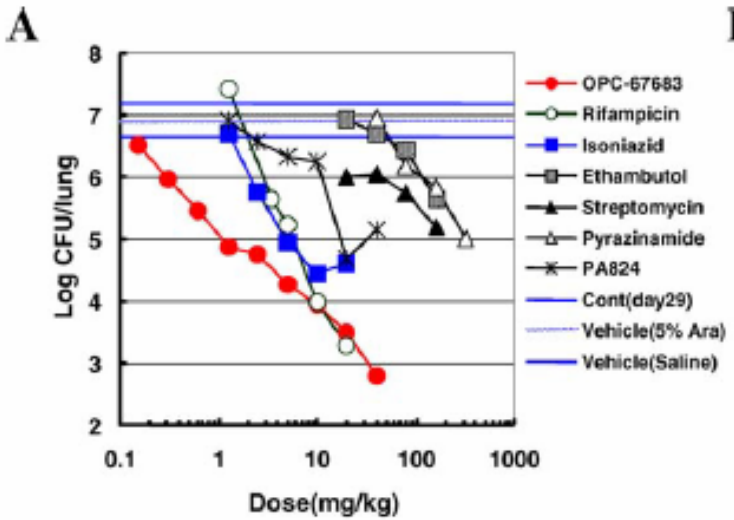
# Delamanid

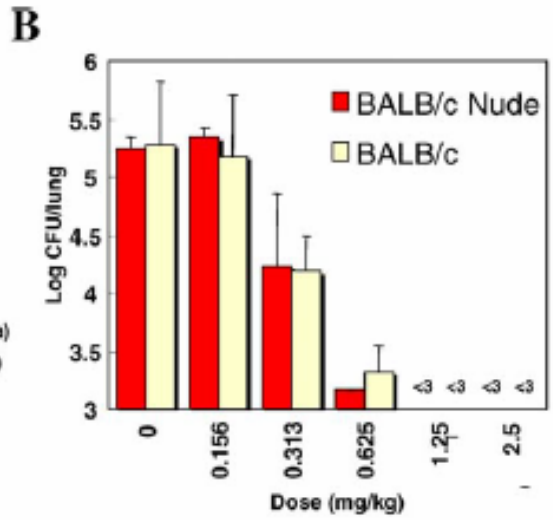
**Table 5.** $IC_{50}$ of OPC-67683 and INH against Mycolic Acid Synthesis

| Compound | Subclass Mycolic Acid and Fatty Acid | IC50 (μg/ml) | 95% Confidence Interval (μg/ml) |
|---|---|---|---|
| OPC-67683 | Fatty acid | >0.25 | — |
| | α-Mycolic acid | >0.25 | — |
| | Methoxy-mycolic acid | 0.036 | 0.020–0.068 |
| | Keto-mycolic acid | 0.021 | 0.009–0.059 |
| INH | Fatty acid | >4 | — |
| | α-Mycolic acid | 1.851 | 1.109–3.090 |
| | Methoxy-mycolic acid | 0.63 | 0.537–0.738 |
| | Keto-mycolic acid | 0.69 | 0.422–1.129 |

The $IC_{50}$ (concentration required to inhibit activity by 50%) of OPC-67683 against mycolic acid synthesis in *M. bovis* BCG was determined and compared with that of INH, a well-known inhibitor of mycolic acid synthesis. $^{14}$C-labeled acetic acid was incorporated to mycolic acid by incubation with *M. bovis* BCG cell cultures in the presence of OPC-67683 or INH as a reference. $^{14}$C-labeled fatty acid and mycolic acid subclasses were detected using thin-layer chromatography (TLC, $n = 3$), and analyzed by BAS-2500 (Fujifilm). The radioactivity of each fatty acid and mycolic acid subclasses was calculated using photo-stimulated luminescence, expressed as the percentage of incorporation in untreated controls, and statistical analysis was conducted by linear regression analysis to calculate $IC_{50}$ values and 95% confidence intervals (significance level: 5%).

doi:10.1371/journal.pmed.0030466.t005




C

| Compound | mouse | | | human | | |
|---|---|---|---|---|---|---|
| | Dose (mg/kg) | Cmax (μg/mL) | AUCt (μg.h/mL) | Dose | Cmax (μg/mL) | AUCt (μg.h/mL) |
| OPG67683 | 2.5 | 0.297 | 4.13 | | | |
| RFP | 5 | 5.10 | 48.2 | 450mg | 5.5 | 29.7 |
| INH | 10 | 3.06 | 4.55 | 300mg | 4.5 | 22.9 |
| EB | 100 | 3.51 | 12.1 | 850mg | 3.7 | 13.0 |
| PZA | 100 | 63.2 | 198 | 1-2g | 59.33 | |

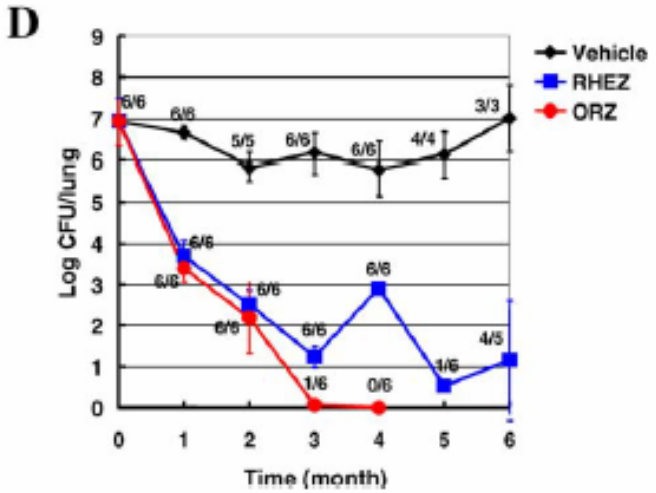



**Figure 4.** Effects of OPC-67683 in an Experimental Mouse Model of TB

Matsumoto et al. PLoS Med. 2006

INT J TUBERC LUNG DIS 15(7):949–954

doi:10.5588/ijtld.10.0616

# Early bactericidal activity of delamanid (OPC-67683) in smear-positive pulmonary tuberculosis patients

A. H. Diacon,* R. Dawson,† M. Hanekom,* K. Narunsky,† A. Venter,* N. Hittel,‡ L. J. Geiter,§ C. D. Wells,§ A. J. Paccaly,§ P. R. Donald¶

*Department of Biomedical Sciences, Stellenbosch University, Cape Town, †Centre for TB Research Innovation, University of Cape Town Lung Institute, Cape Town, South Africa; ‡Otsuka Frankfurt Research Institute GmbH, Frankfurt am Main, Germany; §Otsuka Pharmaceutical Development and Commercialization, Rockville, Maryland, USA; ¶Department of Paediatrics and Child Health, Stellenbosch University, Cape Town, South Africa

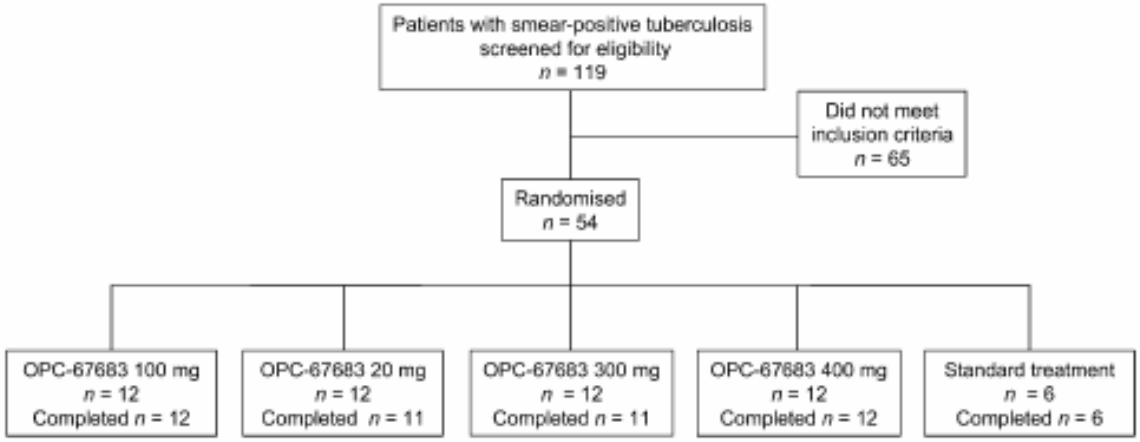



**Figure 1** Flow of participants. The two patients who did not complete the study were withdrawn on day 1 of drug intake due to protocol violation and insufficient sputum production, respectively. OPC-67683 = delamanid.

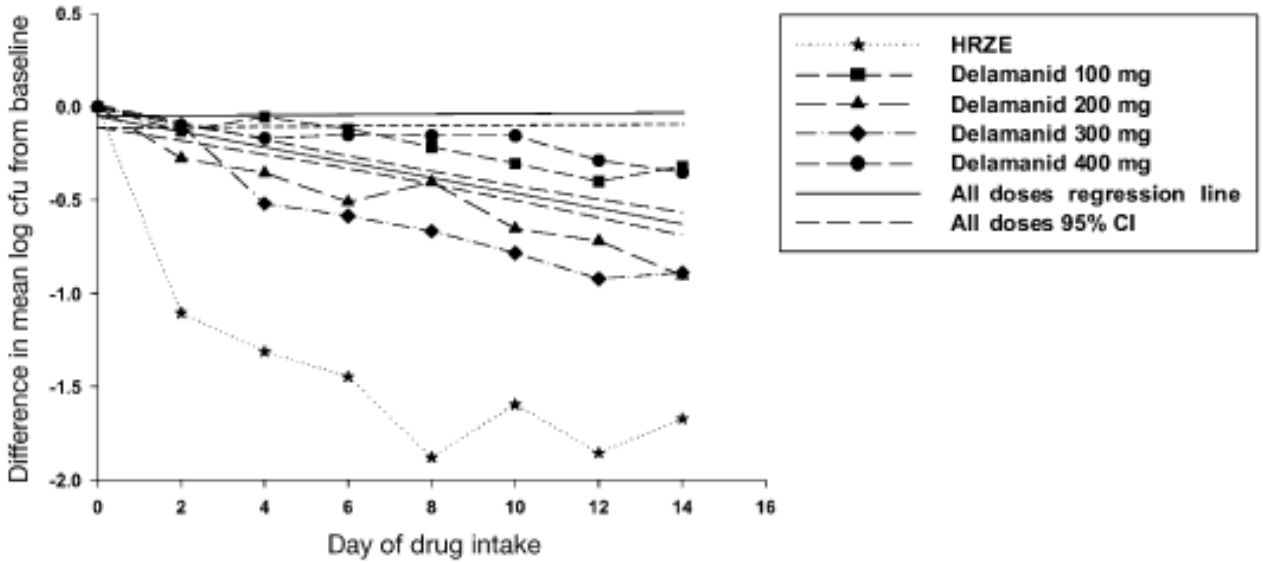



**Figure 2** Fall of mean sputum counts over time. Single data points represent mean values of individual treatment groups. All delamanid dosages follow a monophasic decline. The fall of $\log_{10}$ cfu in sputum over time increases from the 100 mg to the 200 mg dosage and plateaus at the 300 mg dosage. The activity of delamanid 400 mg is lower again indicating reduced drug exposure in this group. Shown is a fitted linear regression line for all delamanid treatment groups, with 95%CIs represented by dotted lines. The horizontal lines are the mean baseline count (top) with lower 95%CI (bottom). A significant decrease is found from day 3 onwards, indicated by CIs no longer including baseline. Standard anti-tuberculosis treatment (HRZE) as the positive control shows the expected biphasic pattern with a steep initial decline. cfu = colony forming units; H = isoniazid; R = rifampicin; Z = pyrazinamide; E = ethambutol; CI = confidence interval.

Diacon et al. IJTLD 2011

# Delamanid

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.

ABSTRACT

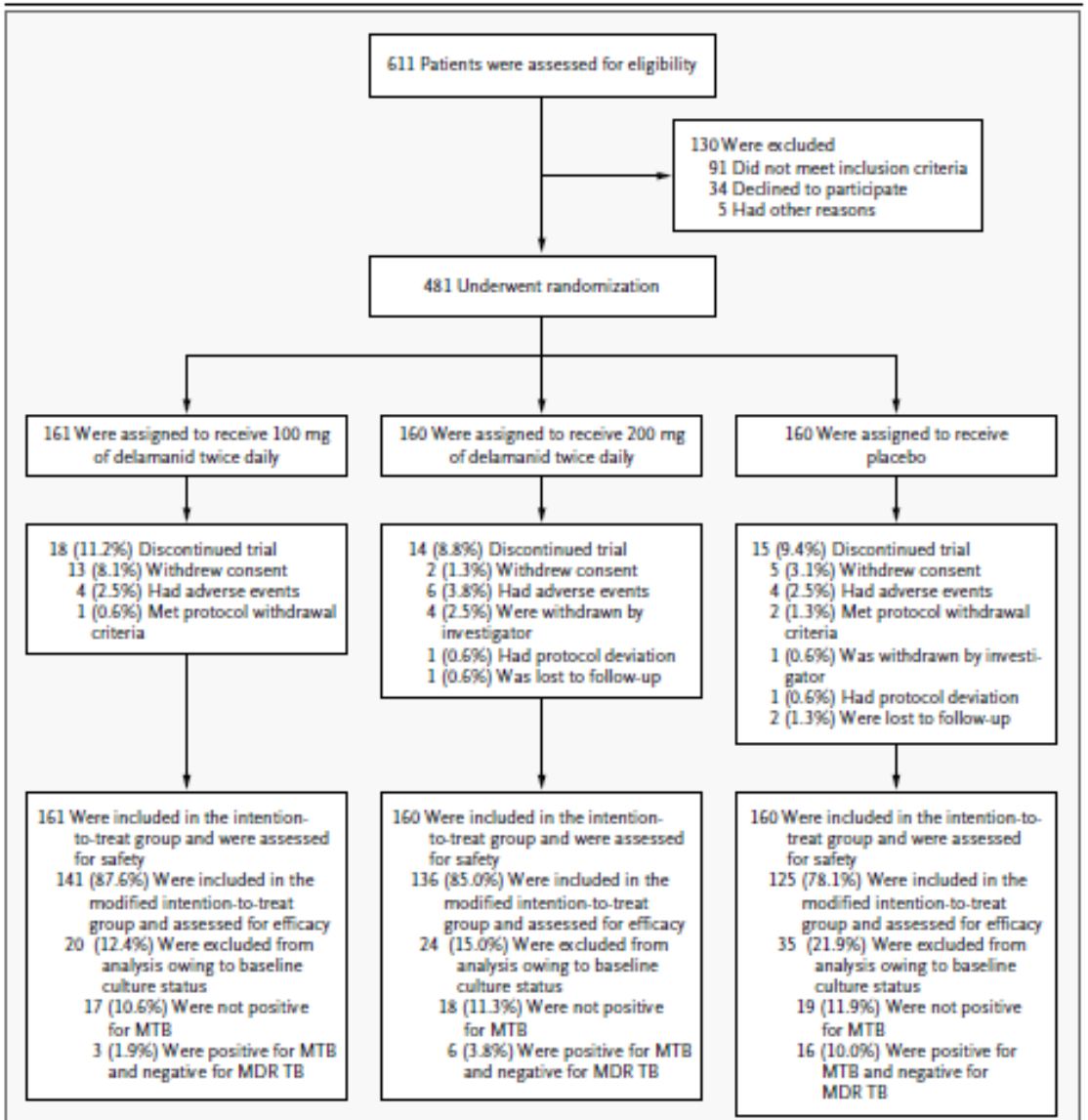



**Figure 1. Enrollment, Study-Drug Assignments, Follow-up, and Assessment of Patients.**

MDR TB denotes multidrug-resistant tuberculosis, and MTB *Mycobacterium tuberculosis*.

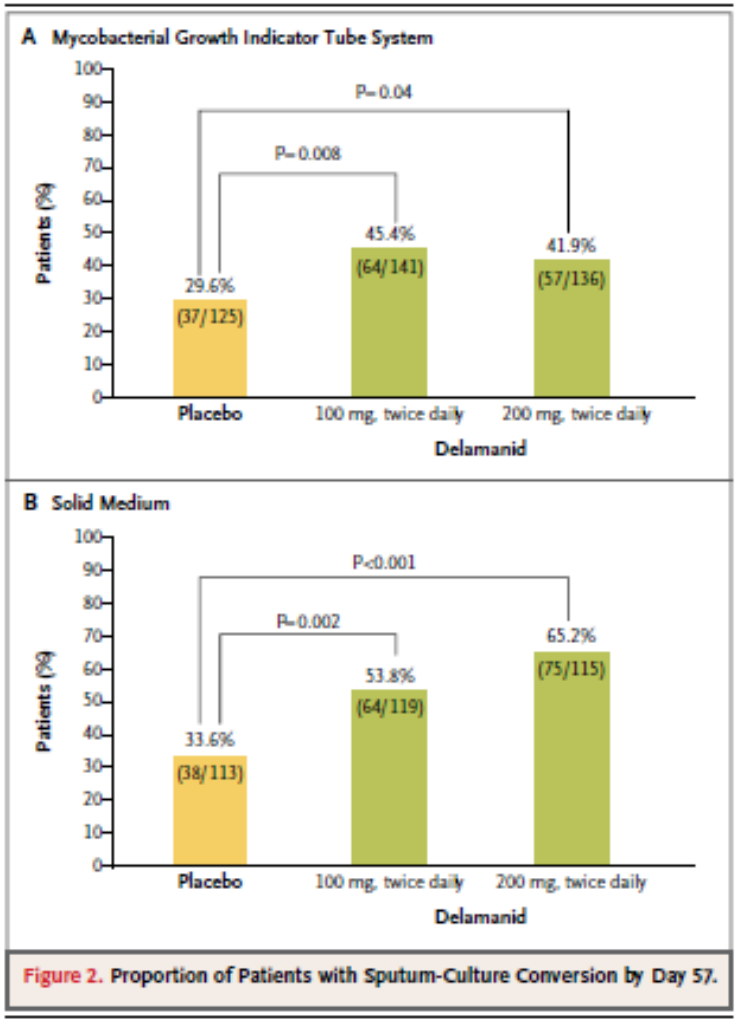



Figure 2. Proportion of Patients with Sputum-Culture Conversion by Day 57.

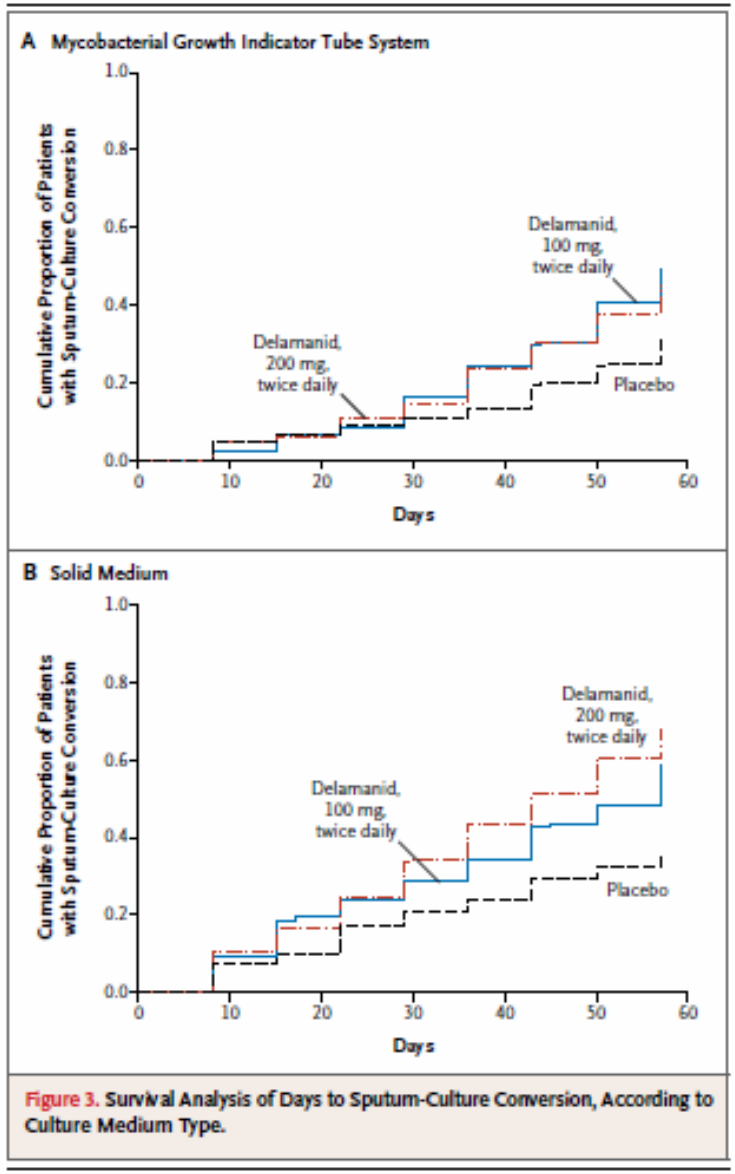



Figure 3. Survival Analysis of Days to Sputum-Culture Conversion, According to Culture Medium Type.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

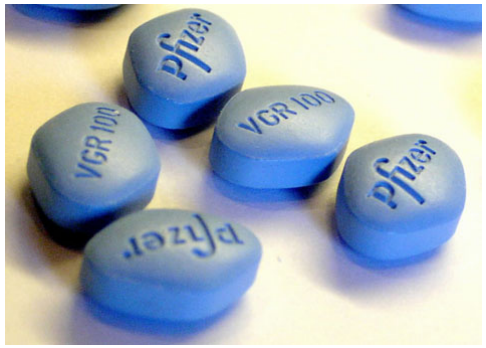
26 July 2013
EMA/446276/2013
EMEA/H/C/002552

# Refusal of the marketing authorisation for Delamanid (delamanid)

On 25 July 2013, the Committee for Medicinal Products for Human Use (CHMP) adopted a negative opinion, recommending the refusal of the marketing authorisation for the medicinal product Delamanid, intended for the treatment of multi-drug resistant tuberculosis.

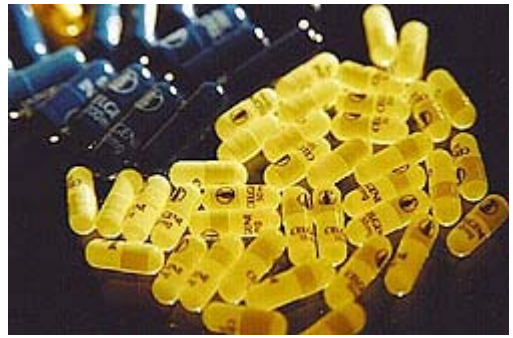
## What were the CHMP's main concerns that led to the refusal?

The CHMP's main concern was that the benefits of Delamanid in the treatment of multi-drug resistant tuberculosis had not been sufficiently shown. The CHMP considered that the duration of treatment in the main study (two months) was too short to establish the effectiveness of delamanid in treating tuberculosis when added to other anti-tuberculosis medicines. As Delamanid was to be used for at least six months the data from two months' treatment could not be used to predict the effectiveness of delamanid when given for six months. In addition, the results of the extension and follow-up studies could not be used to support the longer term use of Delamanid as the studies included only those patients who had agreed to take part and who might therefore not be representative of the patients as a whole. Finally, the CHMP was of the view that it was not possible from the data submitted to determine the most appropriate dosing for Delamanid.




Sildenafil

Minoxidil



Thalidomide

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, July 1984, p. 94–96
0066-4804/84/070094-03$02.00/0

Vol. 26, No. 1

# NOTES

## In Vitro Activities of Norfloxacin and Ciprofloxacin Against *Mycobacterium tuberculosis*, *M. avium* Complex, *M. chelonei*, *M. fortuitum*, and *M. kansasii*

J. DOUGLAS GAY, DONALD R. DEYOUNG, AND GLENN D. ROBERTS*

*Section of Clinical Microbiology, Department of Laboratory Medicine, Mayo Clinic and Mayo Foundation, Rochester, Minnesota 55905*

**Therapeutic effect of a new antibacterial substance ofloxacin (DL8280) on pulmonary tuberculosis.**

Tsukamura M, Nakamura E, Yoshii S, Amano H.

Am Rev Respir Dis. 1985 Mar;131(3):352-6.

# Definición

- Reutilización (repurposing/repositioning)
  - Investigar nuevos usos de drogas existentes ya **'aprobadas'**

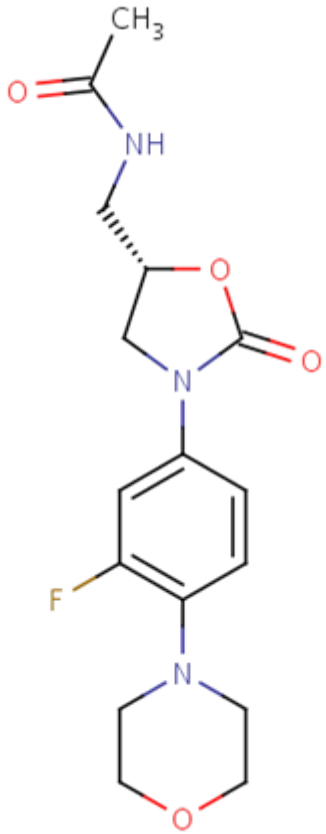

**Duración: 10-17 años. Costo: 800-1000 millones USD**

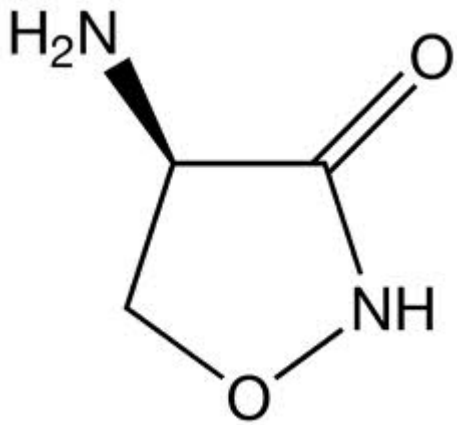
| Stage of Development | Phase 1 | Phase 2 | Phase 3 | Phase 4 |
|---|---|---|---|---|
| End Point | Safety | Efficacy | Efficacy | Efficacy |
| Specific End Point | Safety Profile | Cardiac Output | Reduction in Mortality Rate | Reduction in Mortality Rate |
| Types of Studies | Different Indications; Single or Multiple Dose | Placebo Controlled; Dose Escalation | Placebo Controlled; Long Term Follow Up | Comparative; New Indications |

# (Fluoro)quinolonas

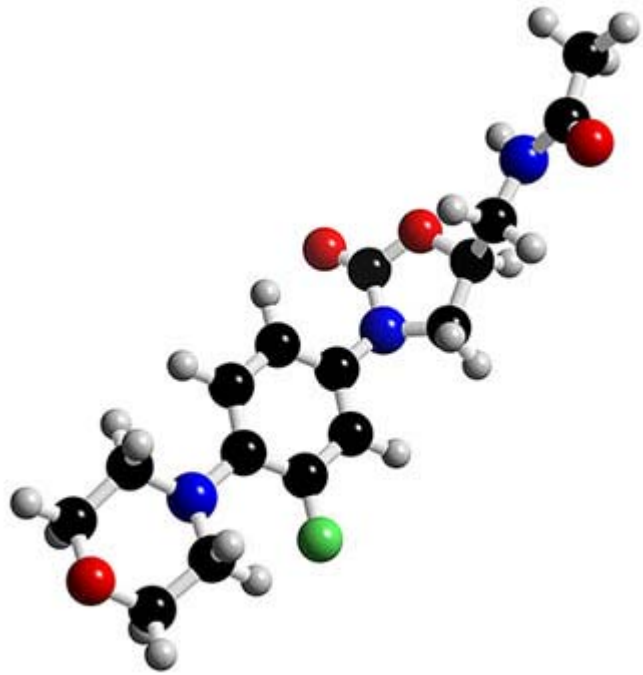
- Acido nalidíxico (1962), acido oxolínico
- Norfloxacin 1980s
- Ciprofloxacin, Ofloxacin, Levofloxacin
- Gatifloxacin, Moxifloxacin
- Tratamiento de MDR-TB
- Ensayos clínicos fase III en marcha (Tx de DS-TB)

# Linezolid

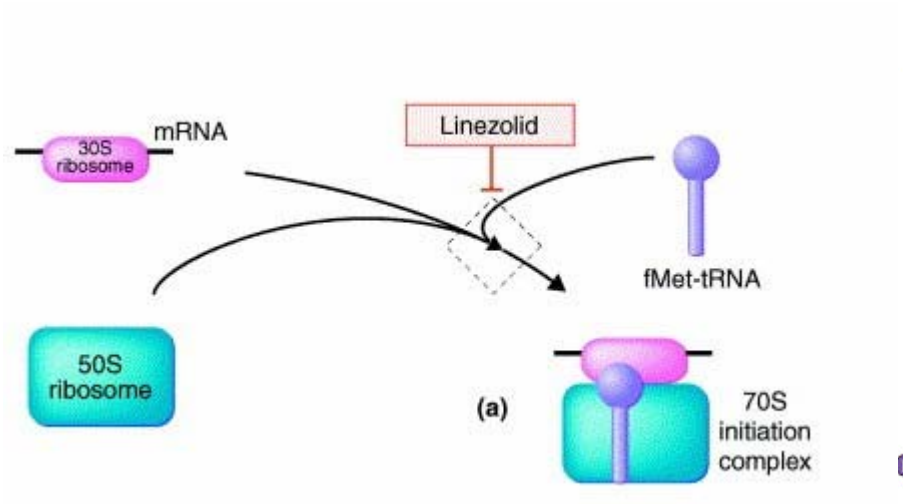


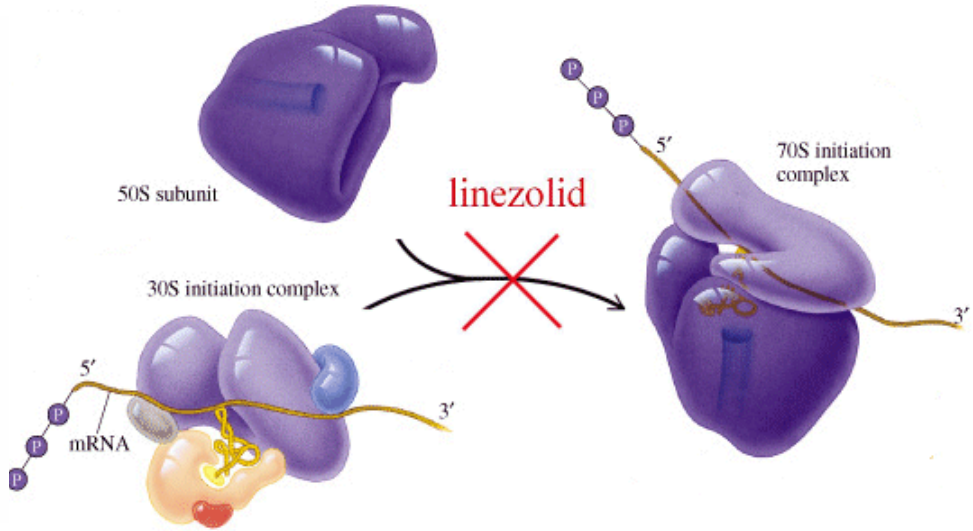




**Cicloserina**



# Mecanismo de acción



# Linezolid (Zyvox™)

- Oxazolidinona aprobada por FDA (2000)
- Bacteria Gram positivas
- Neumonía nosocomial, infecciones de tejido blando
- MRSA, VRE
- 'Off-label' contra MDR-TB
- Effectos secundarios: anemia, polineuritis

**Oxazolidinones, a new class of synthetic antituberculosis agent. In vitro and in vivo activities of DuP-721 against *Mycobacterium tuberculosis***

Ashtekar DR, Costa-Periera R, Shrinivasan T, Iyyer R, Vishvanathan N, Rittel W

Diagn Microbiol Infect Dis. 1991 Nov-Dec;14(6):465-71

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, May 1999, p. 1189–1191 Vol. 43, No. 5
0066-4804/99/$04.00+0


## Activities of Several Novel Oxazolidinones against *Mycobacterium tuberculosis* in a Murine Model

M. H. CYNAMON,* S. P. KLEMENS, C. A. SHARPE, AND S. CHASE

*Veteran Affairs Medical Center and State University of New York Health Science Center, Syracuse, New York 13210*

*Journal of Antimicrobial Chemotherapy* (2006) **58**, 701–704
doi:10.1093/jac/dkl298
Advance Access publication 19 July 2006

JAC

## Efficacy and tolerability of daily-half dose linezolid in patients with intractable multidrug-resistant tuberculosis

**I-Nae Park[1], Sang-Bum Hong[1], Yeon-Mok Oh[1], Mi-Na Kim[2], Chae-Man Lim[1], Sang Do Lee[1], Younsuck Koh[1], Woo Sung Kim[1], Dong Soon Kim[1], Won Dong Kim[1] and Tae Sun Shim[1]***

*[1]Division of Pulmonary & Critical Care Medicine, University of Ulsan College of Medicine, Asan Medical Center, 388-1 Pungnap-dong, Songpa-gu, Seoul, Korea; [2]Department of Diagnostic Laboratory Medicine, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Korea*

EurolacTB
European-Latin American-Caribbean-Tuberculosis Consortium

N Engl J Med 2012;367:1508-18.
DOI: 10.1056/NEJMoa1201964


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Linezolid for Treatment of Chronic Extensively Drug-Resistant Tuberculosis

Myungsun Lee, M.D., Jongseok Lee, Ph.D., Matthew W. Carroll, M.D., Hongjo Choi, M.D., Seonyeong Min, R.N., Taeksun Song, Ph.D., Laura E. Via, Ph.D., Lisa C. Goldfeder, C.C.R.P., Eunhwa Kang, M.Sc., Boyoung Jin, R.N., Hyeeun Park, R.N., Hyunkyung Kwak, B.S., Hyunchul Kim, Ph.D., Han-Seung Jeon, M.S., Ina Jeong, M.D., Joon Sung Joh, M.D., Ray Y. Chen, M.D., Kenneth N. Olivier, M.D., Pamela A. Shaw, Ph.D., Dean Follmann, Ph.D., Sun Dae Song, M.D., Ph.D., Jong-Koo Lee, M.D., Dukhyoung Lee, M.D., Cheon Tae Kim, M.D., Veronique Dartois, Ph.D., Seung-Kyu Park, M.D., Sang-Nae Cho, D.V.M., Ph.D., and Clifton E. Barry III, Ph.D.

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Apr. 2007, p. 1534–1536 Vol. 51, No. 4
0066-4804/07/$08.00+0 doi:10.1128/AAC.01113-06

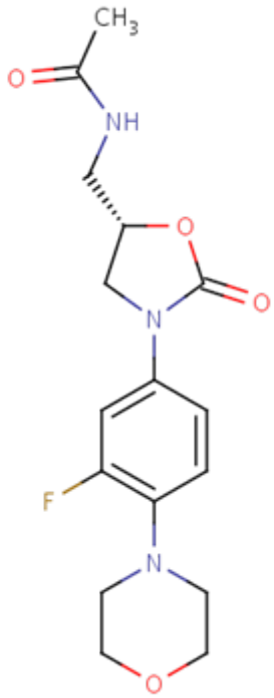

# First Linezolid-Resistant Clinical Isolates of *Mycobacterium tuberculosis*▽

Elvira Richter, Sabine Rüsch-Gerdes, and Doris Hillemann*

*Forschungszentrum Borstel, National Reference Center for Mycobacteria, D-23845 Borstel, Germany*

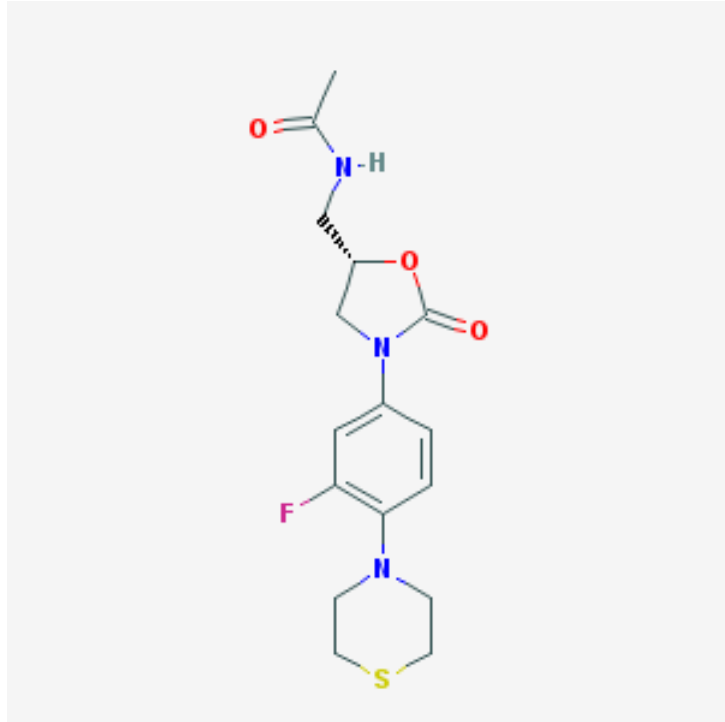
Received 4 September 2006/Returned for modification 10 October 2006/Accepted 10 January 2007

## Linezolid




Zyvox™

## Sutezolid




PNU-100480

EurolacTB
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# Addition of PNU-100480 to First-Line Drugs Shortens the Time Needed to Cure Murine Tuberculosis

Kathy N. Williams[1], Steven J. Brickner[2*], Charles K. Stover[3†], Tong Zhu[2], Adam Ogden[2], Rokeya Tasneen[1], Sandeep Tyagi[1], Jacques H. Grosset[1], and Eric L. Nuermberger[1]

[1]Center for Tuberculosis Research, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland; [2]Pfizer Inc., Groton, Connecticut; and [3]Pfizer Inc., Kalamazoo, Michigan

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Feb. 2011, p. 567–574 Vol. 55, No. 2
0066-4804/11/$12.00 doi:10.1128/AAC.01179-10

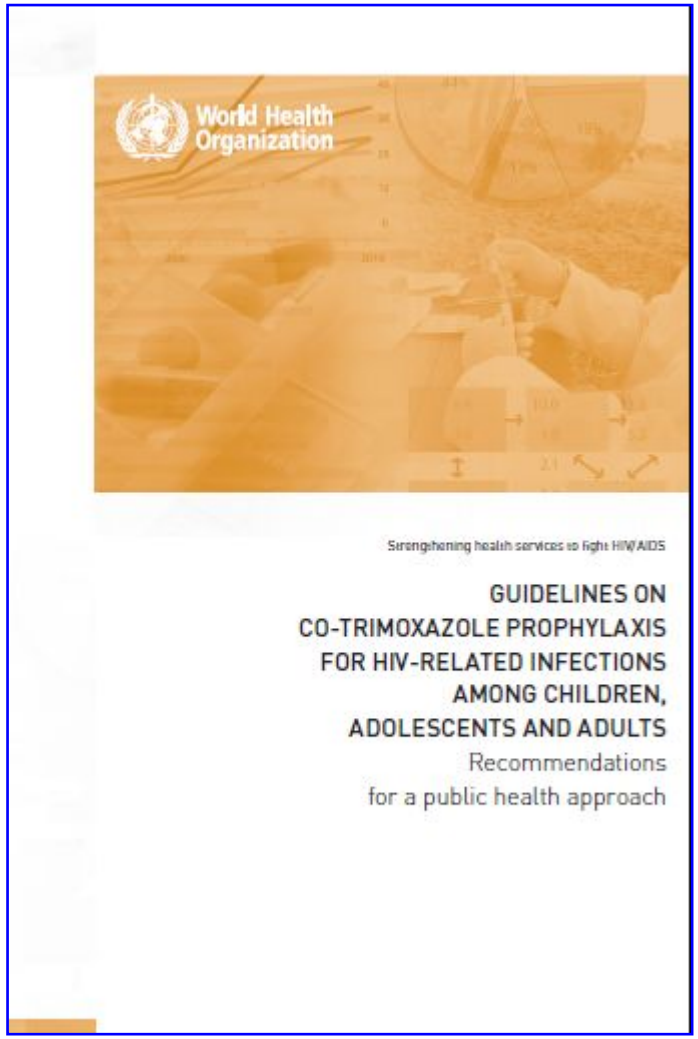

# Biomarker-Assisted Dose Selection for Safety and Efficacy in Early Development of PNU-100480 for Tuberculosis[▽]

Robert S. Wallis,[1*] Wesley Jakubiec,[2] Vikas Kumar,[1] Gabriella Bedarida,[1] Annette Silvia,[1] Darcy Paige,[1] Tong Zhu,[1] Mark Mitton-Fry,[1] Lynn Ladutko,[2] Sheldon Campbell,[2,3] and Paul F. Miller[1]

*Pfizer, Groton-New London, Connecticut[1]; VA CT Healthcare, West Haven, Connecticut[2]; and Yale University, New Haven, Connecticut[3]*

Received 26 August 2010/Returned for modification 4 October 2010/Accepted 4 November 2010

# Co-trimoxazole



ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Nov. 2009, p. 4789–4793 Vol. 53, No. 11
0066-4804/09/$12.00 doi:10.1128/AAC.01658-08


# Tuberculosis and Trimethoprim-Sulfamethoxazole[▽]

Pierre Forgacs,[1]* Nancy L. Wengenack,[2] Leslie Hall,[2] Sarah K. Zimmerman,[3] Mark L. Silverman,[4] and Glenn D. Roberts[2]

*Departments of Infectious Diseases and Research,[1] Clinical Microbiology,[3] and Anatomic Pathology,[4] Lahey Clinic Medical Center, Burlington, Massachusetts, and Department of Clinical Microbiology, Mayo Clinic, Rochester, Minnesota[2]*

Received 17 December 2008/Returned for modification 26 February 2009/Accepted 24 June 2009

- Paciente inmunodeficiente de 81años
- Sospecha de nocardiosis
- TMP-SMX por 2 ½ semanas => no síntomas clinicos
- Dx de TB pero no *Nocardia*
- DST del aislado *M. tuberculosis* => susceptible a TMP-SMX
- 43/44 aislados susceptibles a ≤ 1/19 µg/ml TMP-SMX

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ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, June 2010, p. 2748–2749
0066-4804/10/$12.00 doi:10.1128/AAC.00029-10


**Wendy Ong**
**Aina Sievers**
**David E. Leslie***
*Mycobacterium Reference Laboratory*
*Victorian Infectious Diseases Reference Laboratory*
*10 Wreckyn St.*
*North Melbourne, Victoria 3051, Australia*

# *Mycobacterium tuberculosis* and Sulfamethoxazole Susceptibility

*J Antimicrob Chemother* 2012; **67**: 633–637
doi:10.1093/jac/dkr501 Advance Access publication 29 November 2011

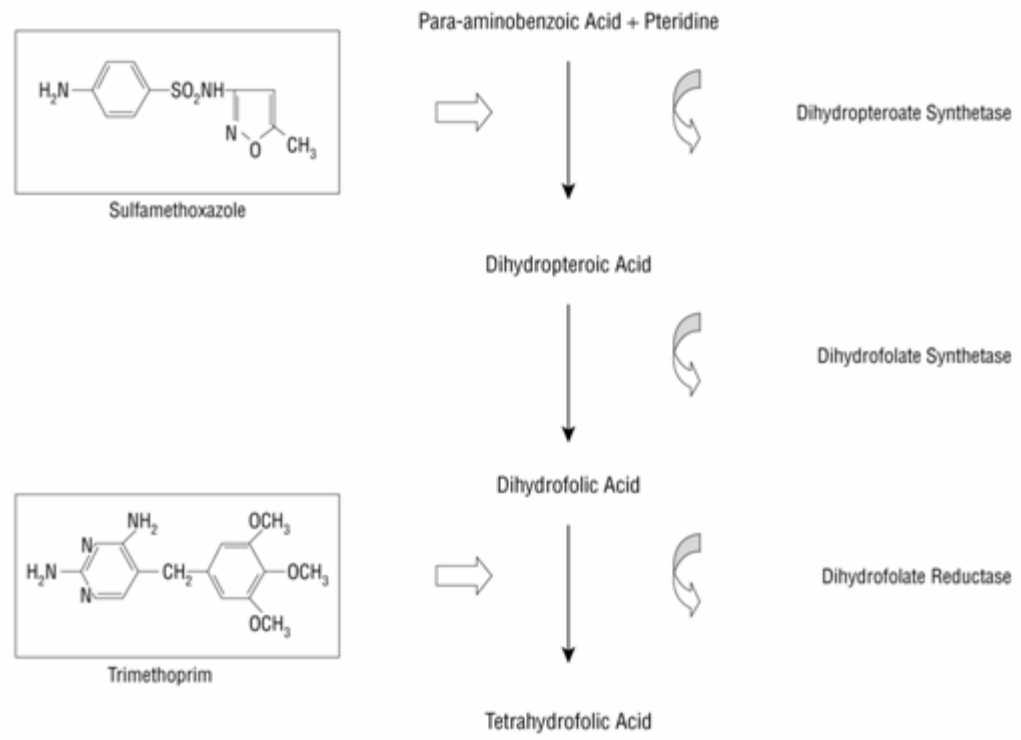
Journal of Antimicrobial Chemotherapy

# Susceptibility of *Mycobacterium tuberculosis* to sulfamethoxazole, trimethoprim and their combination over a 12 year period in Taiwan

**Tsi-Shu Huang[1–3], Calvin M. Kunin[4,5], Bo-Shiun Yan[6], Yao-Shen Chen[7,8], Susan Shin-Jung Lee[7] and Wan-Jr Syu[9]***

*[1]Institute of Clinical Medicine, National Yang-Ming University, Taipei, Taiwan; [2]Section of Microbiology, Department of Pathology and Laboratory Medicine, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan; [3]Department of Medical Technology, Fooyin University, Kaohsiung, Taiwan; [4]Department of Internal Medicine, Ohio State University, Columbus, OH, USA; [5]Department of Internal Medicine, University of Arizona, Tucson, AZ, USA; [6]Institute of Biochemistry and Molecular Biology, National Taiwan University, Taipei, Taiwan; [7]Department of Infectious Diseases, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan; [8]Graduate Institute of Environmental Education, National Kaohsiung Normal University, Kaohsiung, Taiwan; [9]Institute of Microbiology and Immunology, National Yang-Ming University, Taipei, Taiwan*

# Vía metabólica síntesis de folato y sitio de acción de TMP y SMX.




**DfrA**

*Arch Intern Med. 2003;163(4):402-410. doi:10.1001/archinte.163.4.402*

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nature structural & molecular biology

VOLUME 13 NUMBER 5 MAY 2006 NATURE STRUCTURAL & MOLECULAR BIOLOGY

# *Mycobacterium tuberculosis* dihydrofolate reductase is a target for isoniazid

Argyrides Argyrou[1], Matthew W Vetting[1], Bola Aladegbami[1,2] & John S Blanchard[1]

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Sept. 2010, p. 3776–3782 Vol. 54, No. 9
0066-4804/10/$12.00 doi:10.1128/AAC.00453-10


# *Mycobacterium tuberculosis* Dihydrofolate Reductase Is Not a Target Relevant to the Antitubercular Activity of Isoniazid[▽]

Feng Wang,[1] Paras Jain,[2] Gulcin Gulten,[1] Zhen Liu,[1] Yicheng Feng,[1] Krishna Ganesula,[3] Alifiya S. Motiwala,[4] Thomas R. Ioerger,[3]* David Alland,[4] Catherine Vilchèze,[2] William R. Jacobs, Jr.,[2] and James C. Sacchettini[1]

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Oct. 2010, p. 4522–4525 Vol. 54, No. 10
0066-4804/10/$12.00 doi:10.1128/AAC.00422-10


# Role of Mutations in Dihydrofolate Reductase DfrA (Rv2763c) and Thymidylate Synthase ThyA (Rv2764c) in *Mycobacterium tuberculosis* Drug Resistance

# Estudios adicionales

- TMP-SMX: mayores estudios con aislados clínical (different regiones)
- TMP, SMX, la combinación
- Resistencia cruzada con PAS, INH, Eth
- Investigar mutaciones en *dfrA*, *thyA*

EurolacTB
European-Latin American-Caribbean-Tuberculosis Consortium

Antimicrobial Agents and Chemotherapy p. 5142–5148 October 2012 Volume 56 Number 10

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AAC
JournalsASM.org

# The Combination of Sulfamethoxazole, Trimethoprim, and Isoniazid or Rifampin Is Bactericidal and Prevents the Emergence of Drug Resistance in *Mycobacterium tuberculosis*

**Catherine Vilchèze and William R. Jacobs, Jr.**
Howard Hughes Medical Institute, Department of Microbiology and Immunology, Albert Einstein College of Medicine, Bronx, New York, USA

*J Antimicrob Chemother* 2012; **67**: 2908–2911
doi:10.1093/jac/dks306 Advance Access publication 8 August 2012

Journal of Antimicrobial Chemotherapy

# Sulfamethoxazole enhances the antimycobacterial activity of rifampicin

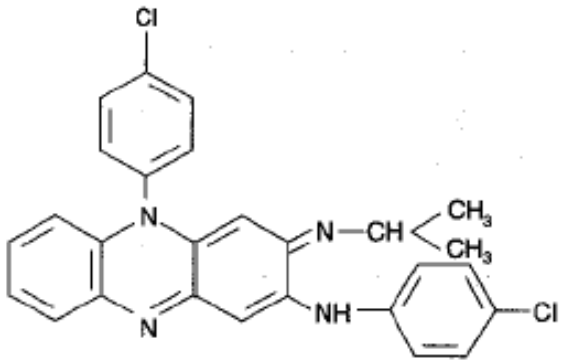
**Lubabalo Macingwana[1], Bienyameen Baker[1], Andile H. Ngwane[1], Catriona Harper[1], Mark F. Cotton[2], Anneke Hesseling[2], Andreas H. Diacon[1], Paul van Helden[1] and Ian Wiid[1]***

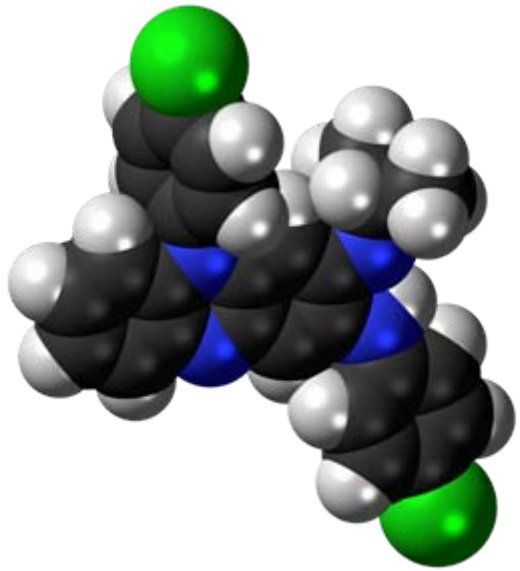
*ERJ Express*. Published on October 25, 2012 as doi: 10.1183/09031936.00114812

# Evaluation of Co-trimoxazole in treatment of multidrug-resistant tuberculosis

N. Alsaad [1], R. van Altena[2], A.D. Pranger[1], D. van Soolingen[3,4], W.C.M de Lange[2], T.S. van der Werf [5], J.G.W.Kosterink[1], J.W.C Alffenaar[1]

# Clofazimine (1957)



- OMS Tratamiento multidroga para lepra
- OMS lista drogas de segunda-línea grupo 5 para MDR-TB

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UNIVERSITEIT GENT

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

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

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

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

*J Antimicrob Chemother* 2012; **67**: 290–298
doi:10.1093/jac/dkr444 Advance Access publication 20 October 2011

Journal of Antimicrobial Chemotherapy

# Clofazimine: current status and future prospects

**Moloko C. Cholo[1]*, Helen C. Steel[1], P. B. Fourie[2], Willem A. Germishuizen[1] and Ronald Anderson[1]**

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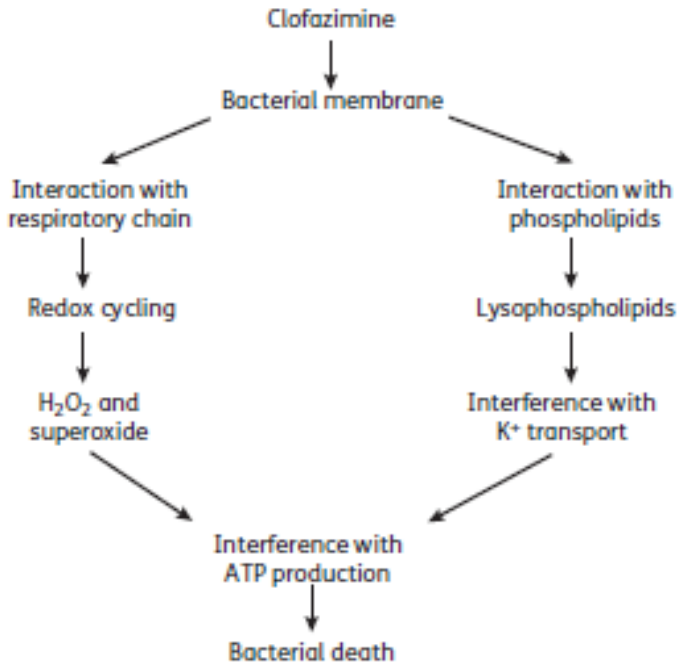
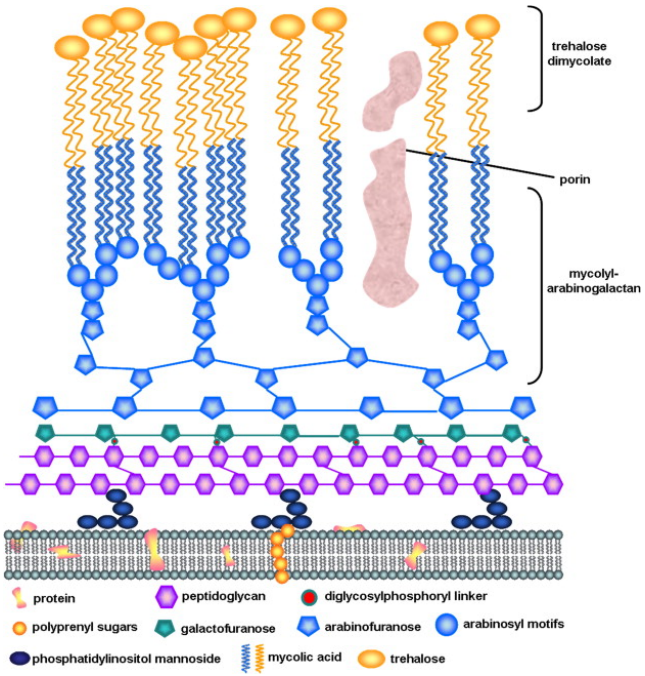
# Modo de acción



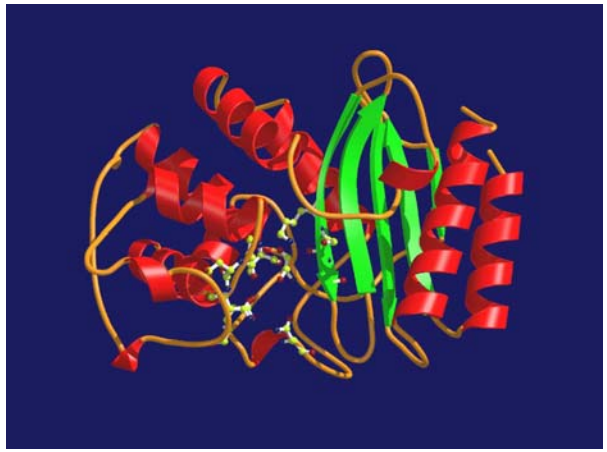

Cholo *et al.* J Antimicrob Chemother 2012

# β-lactámicos y TB

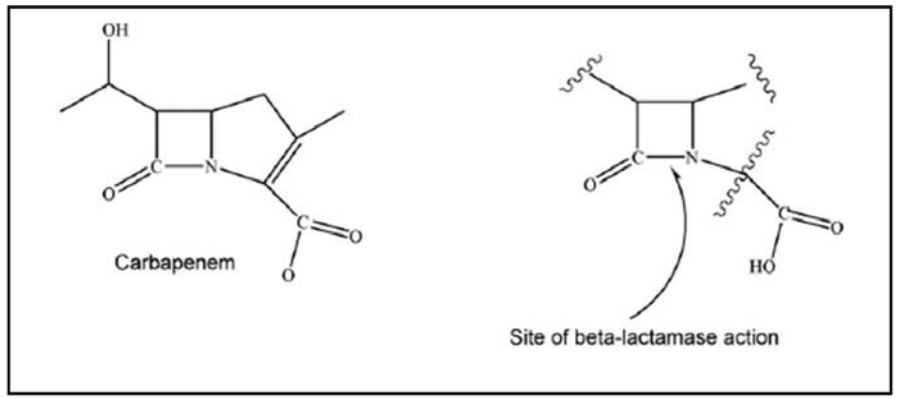
- Dogma: ineficaz contra *M. tuberculosis*




*McLean et al. Arch Biochem Biophys 2007*



*Fonzé et al. Acta Cryst. 1995*



ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Dec. 1995, p. 2620–2624
0066-4804/95/$04.00+0

Vol. 39, No. 12



# Can Penicillins and Other β-Lactam Antibiotics Be Used To Treat Tuberculosis?

HENRY F. CHAMBERS,[1]* DELPHINE MOREAU,[1] DAVID YAJKO,[2] CATHLEEN MIICK,[1] CINDY WAGNER,[1] CORINNE HACKBARTH,[1] SESIN KOCAGÖZ,[1] EMIKO ROSENBERG,[3] W. K. HADLEY,[2] AND HIROSHI NIKAIDO[3]

TABLE 2. Permeability coefficients of mycobacterial cell wall by beta-lactam antibiotics

| Antibiotic | Hydrophobicity [$\log_{10} P_w$ (octanol)][a] | Permeability coefficient (nm/s) | |
|---|---|---|---|
| | | *M. chelonei* PS4770[b] | *M. tuberculosis* H37Ra |
| Cephaloridine | 2.0 | 1.0 | 9.4 |
| Cephalothin | 1.1 | 0.3 | 2.2 |
| Cefazolin | −0.25 | 0.2 | 1.6 |
| Cephacetrile | −0.45 | 0.2 | 2.4 |
| Amoxicillin | | | 2.3 |
| Ampicillin | | | 3.1 |
| Benzylpenicillin | | | 4.9 |
| Carbenicillin | | | 2.1 |

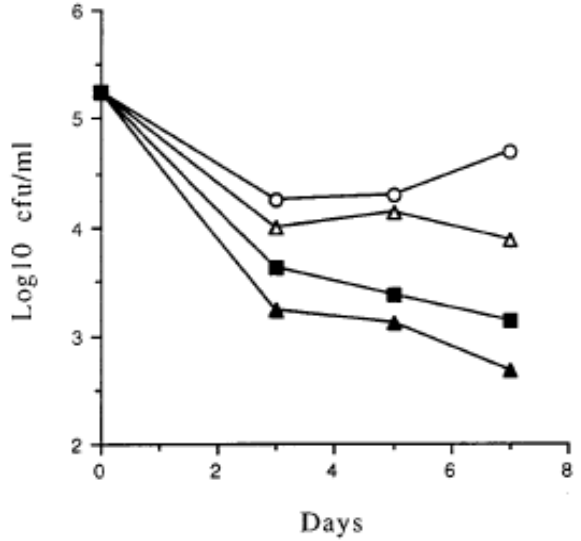



FIG. 2. Reduction of mycobacterial cell counts for J774 cells infected with *M. tuberculosis* H37Ra. Data are means of two separate experiments. ○, control (cells were incubated in drug free medium); △, 8 μg of amoxicillin per ml was added; ▲, amoxicillin plus 4 μg of clavulanic acid per ml; ■, amoxicillin plus 4 μg of sulbactam per ml. $P < 0.005$ for control versus amoxicillin plus clavulanic acid; $P < 0.005$ for control versus amoxicillin plus sulbactam; $P < 0.005$ for amoxicillin versus amoxicillin plus clavulanic acid; $P < 0.05$ for amoxicillin versus amoxicillin plus sulbactam; $P > 0.05$ for amoxicillin versus control ($P$ values were determined by analysis of variance with Bonferoni correction). In separate experiments, neither clavulanic acid nor sulbactam alone had antibacterial activity (data not shown).

(2005), 151, 521–532 DOI 10.1099/mic.0.27629-0



# Genetic analysis of the β-lactamases of *Mycobacterium tuberculosis* and *Mycobacterium smegmatis* and susceptibility to β-lactam antibiotics

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**Table 3.** Susceptibility determined by disc diffusion for *M. smegmatis* strains

Zone diameters reported are the mean of triplicate determinations with variation <2 mm. The genotypes of the respective strains are as follows: PM274, *blaS*$^+$; PM759, Δ*blaS1*; PM791, PM759 *attB*::pMP283; PM876, PM759 *attB*::pMV361.*hyg*.

| Antibiotic (amount per disc) | Zone diameter (mm) for strain: | | | |
|---|---|---|---|---|
| | PM274 | PM759 | PM791 | PM876 |
| Oxacillin (10 μg)* | 0 | 0 | 0 | 0 |
| Ampicillin (10 μg) | 0 | 17 | 0 | 17 |
| Ampicillin (100 μg)* | 0 | 43 | 0 | 43 |
| Piperacillin (100 μg) | 0 | 14 | 0 | 11 |
| Mezlocillin (75 μg) | 0 | 12 | 0 | 10 |
| Carbenicillin (100 μg) | 0 | 13 | 0 | 14 |
| Amoxicillin (20 μg) | 0 | 24 | 0 | 22 |
| Amox/clav (20 μg/10 μg) | 22 | 27 | 21 | 23 |
| Cefoxitin (30 μg) | 0 | 11 | 0 | 11 |
| Cefoxitin (100 μg)* | 22 | 20 | 22 | 23 |
| Ceftriaxone (30 μg) | 0 | 0 | 0 | 0 |
| Cefixime (5 μg) | 0 | 0 | 0 | 0 |
| Imipenem (10 μg) | 23 | 25 | 27 | 26 |

*Antibiotic spotted on blank disc from stock solution, as described in Methods.

**Table 4.** Susceptibility determined by disc diffusion for *M. tuberculosis* strains

Zone diameters reported are the mean of triplicate determinations with variation <10 mm. The genotypes of the respective strains are as follows: H37Rv, *blaC*$^+$; PM638, Δ*blaC1*; PM669, PM638 *attB*::pMP199; PM670, PM638 *attB*::pMV361.*hyg*.

| Antibiotic (amount per disc) | Zone diameter (mm) for strain: | | | |
|---|---|---|---|---|
| | H37Rv | PM638 | PM669 | PM670 |
| Oxacillin (10 μg)* | 0 | 0 | 0 | 0 |
| Ampicillin (10 μg) | 0 | 25 | 0 | 25 |
| Piperacillin (100 μg) | 0 | 40 | 0 | 15 |
| Mezlocillin (75 μg) | 0 | 55 | 0 | 30 |
| Carbenicillin (100 μg) | 0 | 60 | 0 | 50 |
| Amoxicillin (20 μg) | 0 | 45 | 0 | 45 |
| Amox/clav (20 μg/10 μg) | 15 | 60 | 20 | 40 |
| Cefoxitin (30 μg) | 0 | 20 | 0 | 0 |
| Ceftriaxone (30 μg) | 15 | 20 | 20 | 10 |
| Cefixime (5 μg) | 0 | 0 | 0 | 0 |
| Imipenem (10 μg) | 25 | 45 | 25 | 25 |

*Antibiotic spotted on blank disc from stock solution, as described in Methods.

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*Biochemistry*. 2007 October 30; 46(43): 11998–12004. doi:10.1021/bi701506h.

# Irreversible Inhibition of the *Mycobacterium tuberculosis* β-lactamase by Clavulanate

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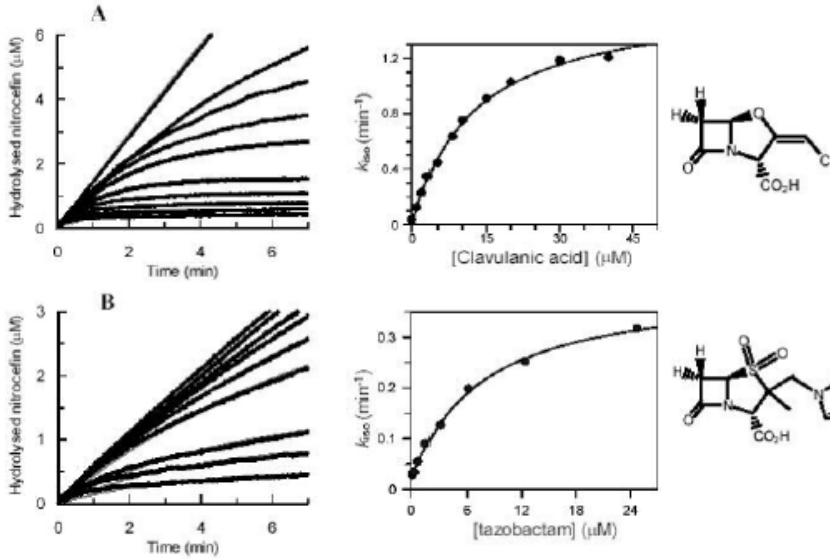
## Abstract







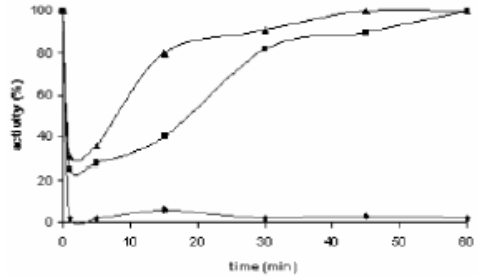




**Figure 4. Recovery of BlaC activity after incubation with β-lactamase inhibitors**
Enzyme (20 μM) was incubated with 100 μM sulbactam (▲), 100 μM tazobactam (■) or 100 μM clavulanate (●), and activity was determined at the indicated times.

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# Meropenem-Clavulanate Is Effective Against Extensively Drug-Resistant *Mycobacterium tuberculosis*

Jean-Emmanuel Hugonnet,[1] Lee W. Tremblay,[1] Helena I. Boshoff,[2] Clifton E. Barry 3rd.[2] John S. Blanchard[1]*

www.sciencemag.org SCIENCE VOL 323 27 FEBRUARY 2009

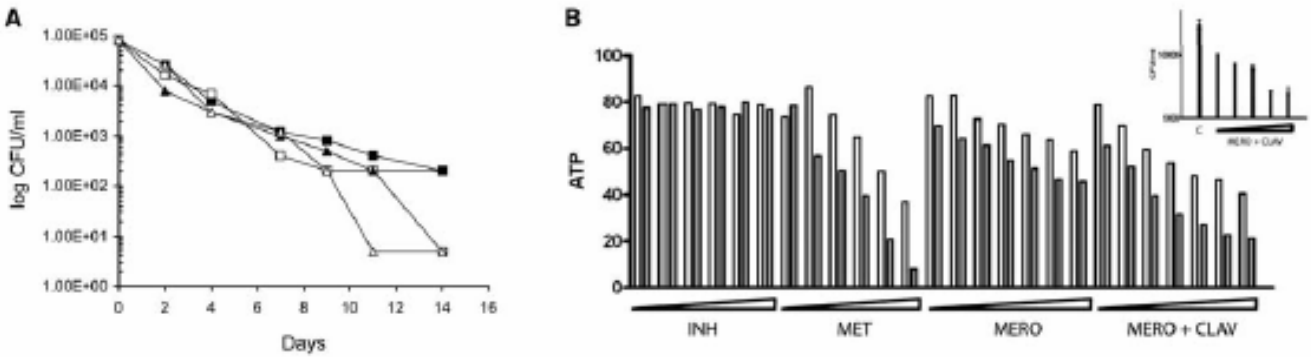


**Fig. 3.** Killing curves of *M. tuberculosis* after exposure to β-lactams and clavulanate. (**A**) Aerobic growth using the microdilution method. Meropenem and clavulanate were added at 2 μg ml$^{-1}$ + 1 μg ml$^{-1}$ (■), 2 μg ml$^{-1}$ + 2 μg ml$^{-1}$ (□), 4 μg ml$^{-1}$ + 1 μg ml$^{-1}$ (▲), and 4 μg ml$^{-1}$ + 2 μg ml$^{-1}$ (Δ), respectively, for 5 consecutive days. (**B**) Meropenem is cidal for nonreplicating anaerobic *M. tuberculosis*. Hypoxically adapted *M. tuberculosis* H37Rv was treated under anaerobic conditions with twofold dilutions of meropenem (0.19 to 12.5 μg ml$^{-1}$) in the presence or absence of 2.5 μg ml$^{-1}$ clavulanate. Isoniazid (0.16 to 1.0 μg ml$^{-1}$) and metronidazole (4.6 to 73 mM) served as negative and positive controls, respectively. Survival was determined by measurement of ATP amounts in surviving bacteria during aerobic outgrowth of 100-fold diluted cells at either 1 week (white bars) or 2 weeks (shaded bars) of treatment or by enumeration of CFUs (inset) after 2 weeks of compound exposure.

# Meropenem + clavulanate

- Inhibición de XDR *M. tuberculosis* (n=13)

**Table 1.** MIC values for β-lactams in the presence of 2.5 μg $ml^{-1}$ clavulanic acid. The XDR strains were a subset of those previously reported (*18*).

| Strain | β-lactam | MIC value (μg $ml^{-1}$) |
|---|---|---|
| Erdman | Meropenem | 0.5 |
| H37Rv | Amoxicillin | >10 |
| H37Rv | Ampicillin | 5.0 |
| H37Rv | Cefotaxime | 1.25 |
| H37Rv | Cephalothin | 0.94 |
| H37Rv | Imipenem | 0.16 |
| H37Rv | Meropenem | 0.32 |
| XDR-1 | Meropenem | 0.94 |
| XDR-2 | Meropenem | 0.625 |
| XDR-3 | Meropenem | 0.625 |
| XDR-4 | Meropenem | 0.625 |
| XDR-5 | Meropenem | 0.625 |
| XDR-6 | Meropenem | 0.625 |
| XDR-7 | Meropenem | 0.625 |
| XDR-8 | Meropenem | 0.94 |
| XDR-9 | Meropenem | 1.25 |
| XDR-10 | Meropenem | 0.47 |
| XDR-11 | Meropenem | 0.23 |
| XDR-12 | Meropenem | 0.625 |
| XDR-13 | Meropenem | 0.32 |

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04/05/$08.00+0 doi:10.1128/AAC.49.7.2816–2821.2005




# Imipenem for Treatment of Tuberculosis in Mice and Humans

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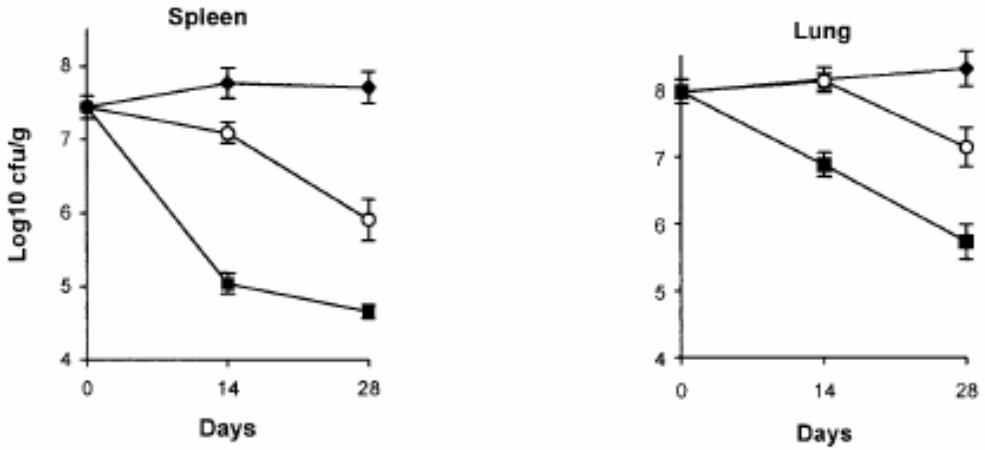


FIG. 1. Mean burdens of *M. tuberculosis* strain H37Rv as $\log_{10}$ CFU/g in spleen and lung tissues. The numbers of mice are as follows: for untreated mice (black diamonds), 14, 19, and 14 on days 0, 14, and 28, respectively; for imipenem-treated mice (open circles), 22 and 15 for days 14 and 28, respectively; and for isoniazid-treated (black squares), 14 and 15 for days 14 and 28, respectively. The standard errors of the means are indicated by the bars.

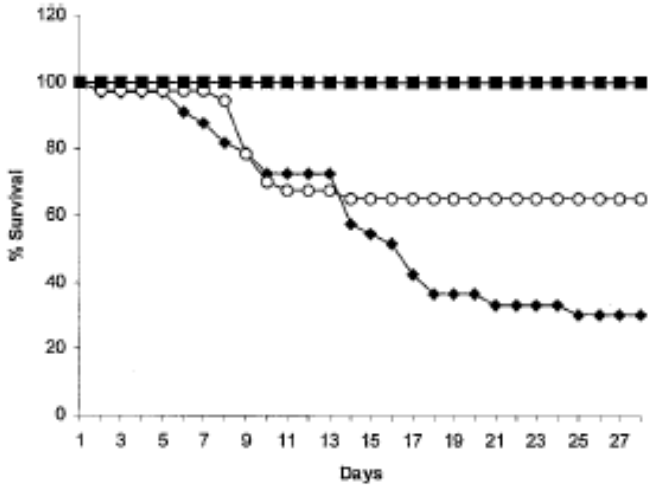


FIG. 2. Survival curves for untreated mice (black diamonds), imipenem-treated mice (open circles), and isoniazid-treated mice (black squares).

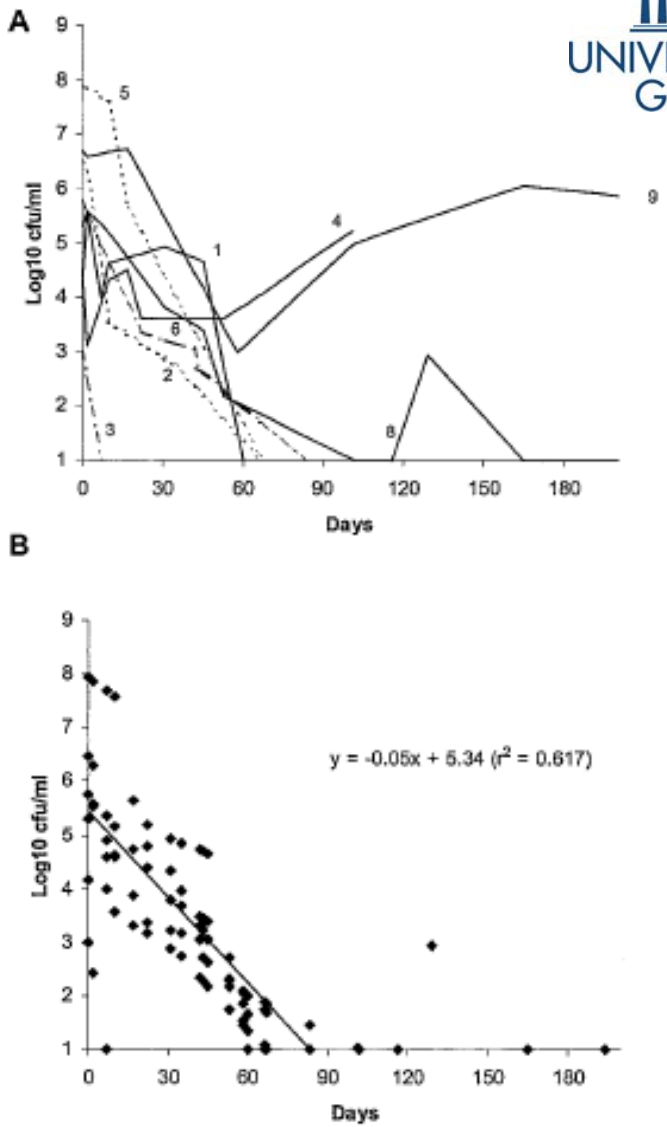


FIG. 3. Results of quantitative sputum cultures indicating *M. tuberculosis* burdens, expressed as $\log_{10}$ CFU/ml, over time in sputa of individual patients (numbers correspond to patient numbers in Table 1) (A) and as a calculation of the overall elimination rate by linear regression for those patients who responded to treatment (B). The linear regression equation is shown.

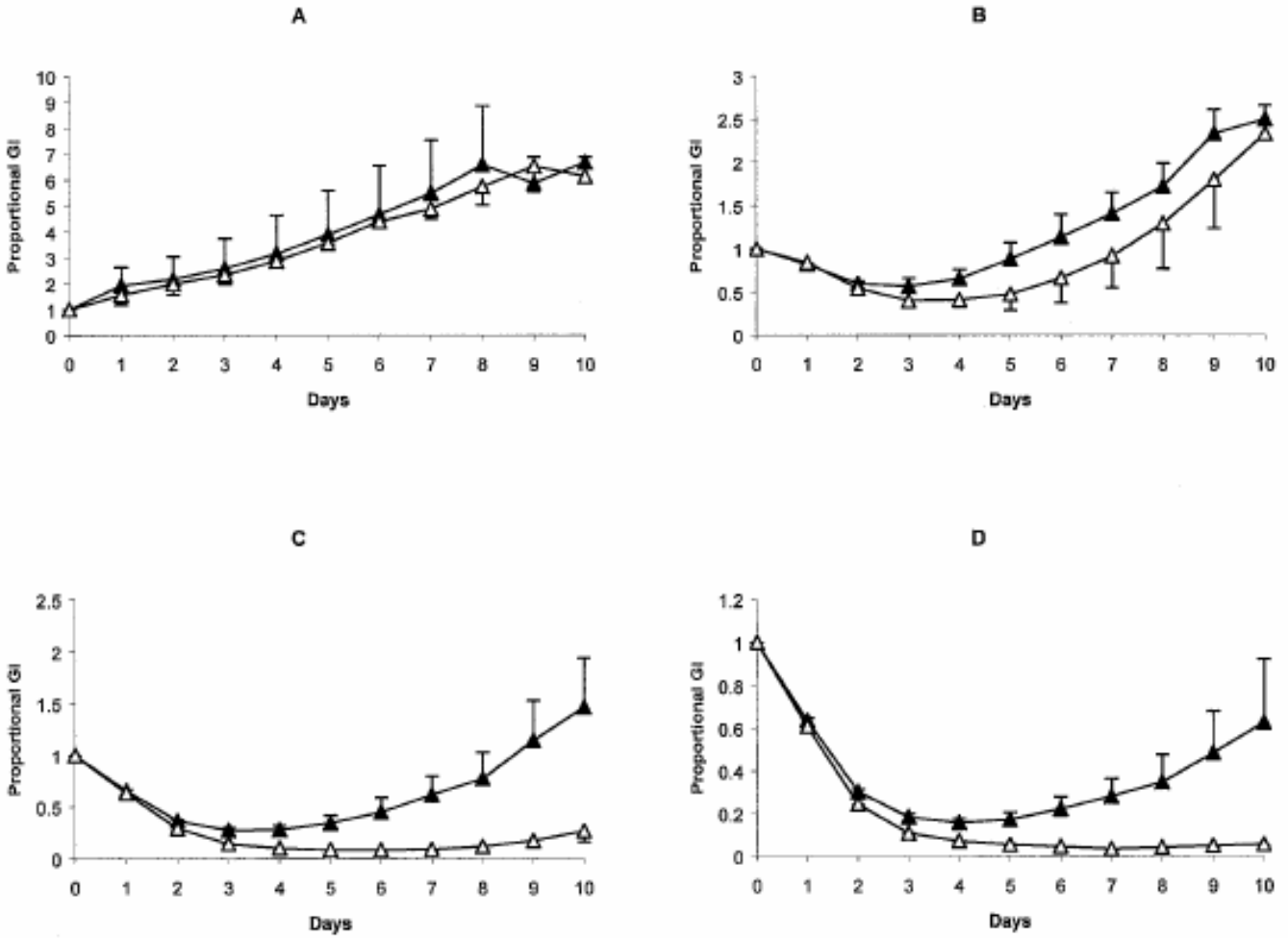


FIG. 4. Means and standard errors for proportional growth indices (GI) (the ratio of counts per minute on each day to counts per minute for the strain at day 0) for three separate experiments performed with starting growth indices ranging between 100 and 300. The open triangles indicate the prestudy isolate, and the closed triangles indicate the 18-week isolate for untreated cultures (A) or cultures to which imipenem at concentrations of 4 μg/ml (B), 8 μg/ml (C), or 16 μg/ml (D) had been added on day 0.

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, June 2011, p. 2597–2600 Vol. 55, No. 6
0066-4804/11/$12.00 doi:10.1128/AAC.01824-10




# Activity of Carbapenems Combined with Clavulanate against Murine Tuberculosis[▽]

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TABLE 1. MICs of imipenem, meropenem, and ertapenem alone and in the presence of 2.5 mg of clavulanate/liter

| Treatment | MIC (mg/liter) | | |
|---|---|---|---|
| | Without clavulanate | With clavulanate | EUCAST susceptibility breakpoints[a] |
| Imipenem | 16 | 1 | 2–8 |
| Meropenem | 8 | 1 | 2–8 |
| Ertapenem | 16 | 4 | 0.5–1 |

[a] EUCAST (9).

TABLE 2. Mean CFU counts in mouse lungs after 28 days of carbapenem treatment (with or without clavulanate)

| Treatment | Mean $\log_{10}$ CFU lung count ± SEM | |
|---|---|---|
| | CFU on day 1 | CFU on day 28[a] |
| None | 5.49 ± 0.53 | 7.07 ± 0.3* |
| Isoniazid | | 4.34 ± 0.82† |
| Imipenem | | 6.66 ± 0.18 |
| Imipenem + clavulanate | | 6.36 ± 0.3† |
| Meropenem | | 7.28 ± 0.21 |
| Meropenem + clavulanate | | 6.88 ± 0.31 |
| Ertapenm | | 7.23 ± 0.13 |
| Ertapenem + clavulanate | | 7.08 ± 0.3 |
| Clavulanate | | 7.30 ± 0.52 |

[a] Values indicated by "†" were significantly different from the value indicated by "*".

AAC Journals.ASM.org
Antimicrobial Agents and Chemotherapy p. 3384–3387 June 2012 Volume 56 Number 6



# Meropenem-Clavulanic Acid Shows Activity against *Mycobacterium tuberculosis In Vivo*

Kathleen England, Helena I. M. Boshoff, Kriti Arora, Danielle Weiner, Emmanuel Dayao, Daniel Schimel, Laura E. Via, and Clifton E. Barry III

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**The carbapenems imipenem and meropenem in combination with clavulanic acid reduced the bacterial burden in *Mycobacterium tuberculosis*-infected macrophages by 2 logs over 6 days. Despite poor stability in solution and a short half-life in rodents, treatment of chronically infected mice revealed significant reductions of bacterial burden in the lungs and spleens. Our results show that meropenem has activity in two *in vivo* systems, but stability and pharmacokinetics of long-term administration will offer significant challenges to clinical evaluation.**

INT J TUBERC LUNG DIS 16(4):558–560

http://dx.doi.org/10.5588/ijtld.11.0414
Published online 8 February 2012

**CASE STUDY**

# Clinical use of the meropenem-clavulanate combination for extensively drug-resistant tuberculosis

M. C. Payen,* S. De Wit,* C. Martin,* R. Sergysels,† I. Muylle,† Y. Van Laethem,* N. Clumeck*

Departments of *Infectious Diseases and †Pneumology, Centre Hospitalier Universitaire Saint-Pierre, Brussels, Belgium

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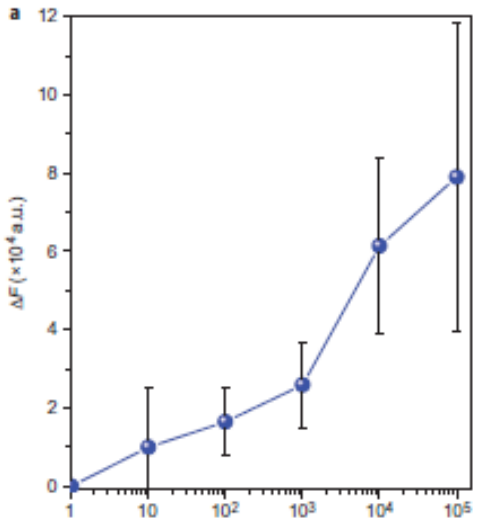
nature chemistry

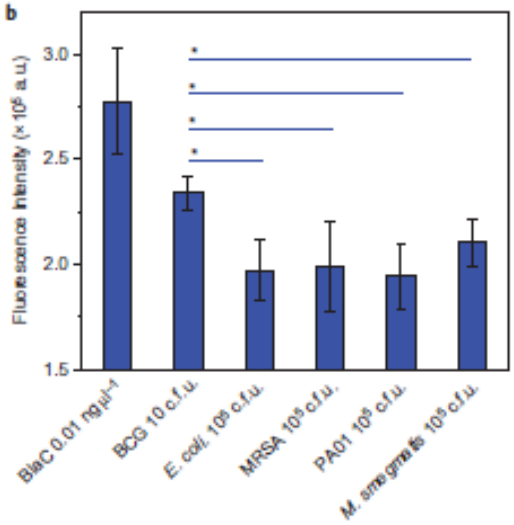
ARTICLES

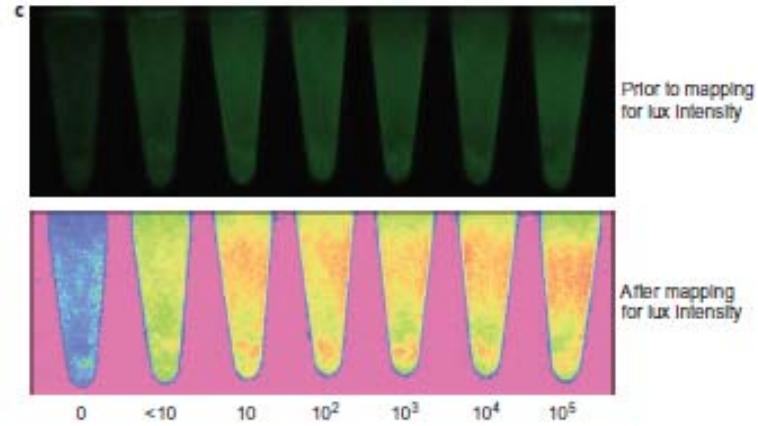
PUBLISHED ONLINE: 2 SEPTEMBER 2012 | DOI: 10.1038/NCHEM.1435

# Rapid point-of-care detection of the tuberculosis pathogen using a BlaC-specific fluorogenic probe

Hexin Xie[1†], Joseph Mire[2†], Ying Kong[3†], MiHee Chang[3], Hany A. Hassounah[3], Chris N. Thornton[4], James C. Sacchettini[2], Jeffrey D. Cirillo[3] and Jianghong Rao[1*]



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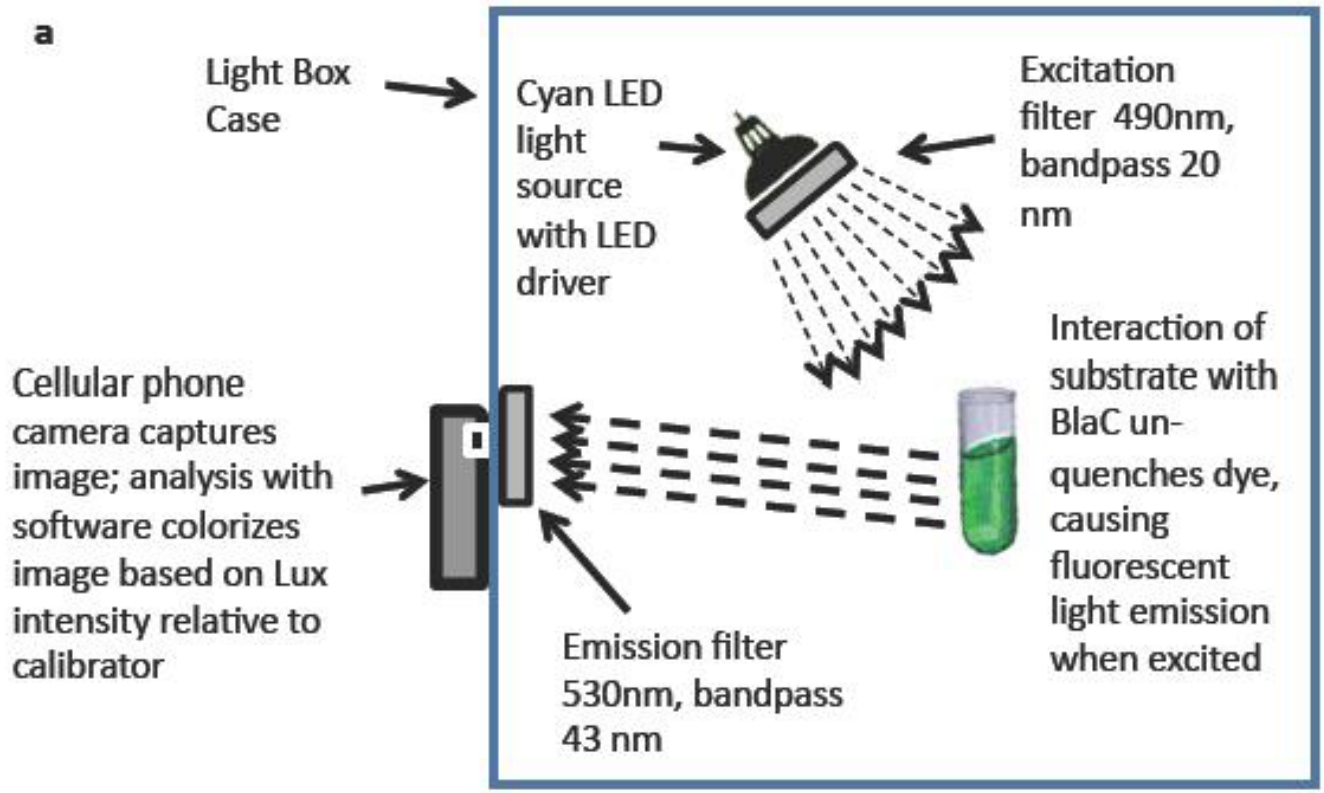

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# (Un)usual suspects

- Mefloquina (Lariam)
  - Malaria cloroquine-resistente
- Phenothiazinas
  - Thioridazina: anti-psicótico

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Aug. 1999, p. 1870–1874
0066-4804/99/$04.00+0

Vol. 43, No. 8



# Mefloquine Is Active In Vitro and In Vivo against *Mycobacterium avium* Complex

LUIZ E. BERMUDEZ,[1]* PETER KOLONOSKI,[1] MARTIN WU,[1] PRISCILLA A. ARALAR,[2] CLARK B. INDERLIED,[2] AND LOWELL S. YOUNG[1]

*Kuzell Institute for Arthritis and Infectious Diseases, San Francisco,[1] and Department of Pathology and Laboratory Medicine, Children's Hospital of Los Angeles, University of Southern California, Los Angeles,[2] California*



TABLE 1. Effect of treatment with mefloquine on the number of MAC organisms in liver

| Dose (mg/kg) or regimen | No. of MAC organisms (mean ± SE) with frequency of administration[a] | | | |
|---|---|---|---|---|
| | QW | BIW | TIW | QD |
| 5 | $(7.0 \pm 1.0) \times 10^8$ | $(9.2 \pm 1.2) \times 10^8$ | $(1.5 \pm 0.9) \times 10^9$ | $(8.1 \pm 1.7) \times 10^8$ |
| 10 | $(6.4 \pm 1.4) \times 10^8$ | $(7.5 \pm 1.0) \times 10^8$ | $(6.0 \pm 0.8) \times 10^8$ | $(6.8 \pm 1.4) \times 10^8$ |
| 20 | $(6.5 \pm 1.1) \times 10^8$ | $(6.3 \pm 1.2) \times 10^8$ | $(6.5 \pm 0.8) \times 10^8$ | $(3.9 \pm 1.2) \times 10^{8**,***}$ |
| 40 | $(6.6 \pm 1.1) \times 10^8$ | $(5.3 \pm 0.9) \times 10^8$ | $(3.6 \pm 0.5) \times 10^{8**,***}$ | $(1.1 \pm 0.3) \times 10^{8**,***}$ |
| Control at 4 wk | $(1.1 \pm 0.2) \times 10^9$ | | | |
| Control at 1 wk | $(1.1 \pm 0.2) \times 10^8$ | | | |

[a] Mice infected with MAC strain 101 were treated for 4 weeks, and then the bacterial load was determined as described in Materials and Methods. Values are CFU per gram of tissue. QW, once a week; BIW, twice a week; TIW, three times a week; QD, daily. **, $P < 0.05$ compared with control at 4 weeks; ***, $P > 0.05$ compared with control at 1 week.

layers were treated with different concentrations of mefloquine for 4 days. The cells were subsequently lysed, and the mycobacteria were plated for quantitation, as described in Materials and Methods.

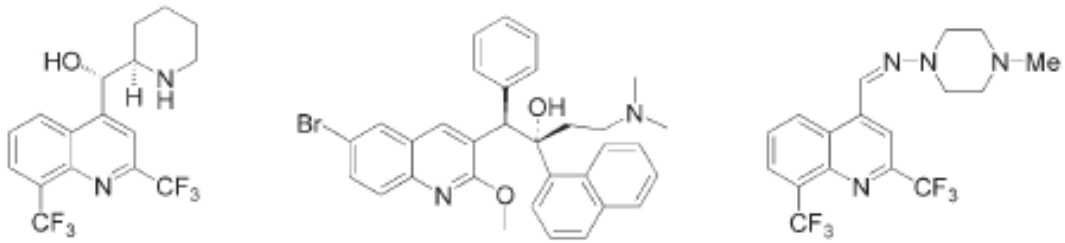
CHEMMEDCHEM

DOI: 10.1002/cmdc.200700112

# Design, Synthesis, and Pharmacological Evaluation of Mefloquine-Based Ligands as Novel Antituberculosis Agents

Jialin Mao,[a, b] Yuehong Wang,[b] Baojie Wan,[b] Alan P. Kozikowski,*[a] and Scott G. Franzblau*[b]

TMC207 Bedaquiline

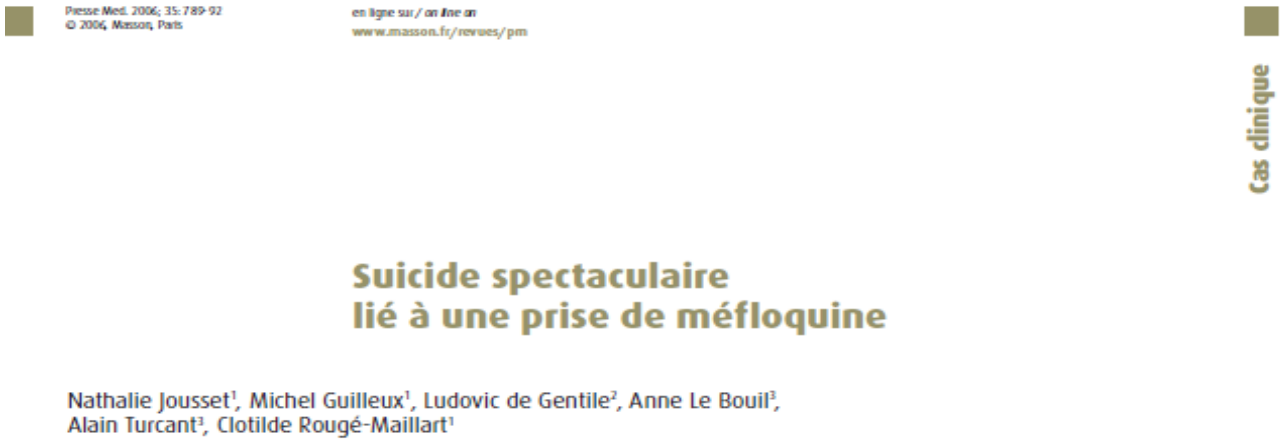



(+)-(11*S*,12*R*) Mefloquine R207910 **10a**

**Figure 1.** Structures of mefloquine, R207910, and **10a**.

# Desventajas

- Efectos neurosiquiátricos reportados
- Riesgo de aborto



Presse Med. 2006; 35: 789-92
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en ligne sur / on line on
www.masson.fr/revues/pm

Cas clinique

## Suicide spectaculaire lié à une prise de méfloquine

Nathalie Jousset[1], Michel Guilleux[1], Ludovic de Gentile[2], Anne Le Bouil[3], Alain Turcant[3], Clotilde Rougé-Maillart[1]

# Phenothiazinas

- Thioridazina: acción en membrana celular

*Journal of Antimicrobial Chemotherapy* (1997) **40**, 319–327

JAC

Review

## The potential management of resistant infections with non-antibiotics

**Jette Elisabeth Kristiansen and Leonard Amaral†**

*Department of Clinical Microbiology, Sønderborg Sygehus, County of Sønderjylland, 6400-DK, Denmark*

*Current Drug Targets*, 2006, *7*, 887-891



# "Non-Antibiotics": Alternative Therapy for the Management of MDRTB and MRSA in Economically Disadvantaged Countries

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0066-4804/03/$08.00+0 DOI: 10.1128/AAC.47.3.917–922.2003


# Clinical Concentrations of Thioridazine Kill Intracellular Multidrug-Resistant *Mycobacterium tuberculosis*

Diane Ordway,[1] Miguel Viveiros,[1] Clara Leandro,[1] Rosário Bettencourt,[1] Josefina Almeida,[1] Marta Martins,[1] Jette E. Kristiansen,[2] Joseph Molnar,[3] and Leonard Amaral[1]*

*Unit of Mycobacteriology, Instituto de Higiene e Medicina Tropical, Universidade Nova de Lisboa, 1349-008 Lisbon, Portugal*[1]*; Department of Clinical Microbiology, Sonderborg Sygehus, 6400 Sonderborg, Denmark*[2]*; and Institute of Medical Microbiology, Albert-Szent Gyorgyi School of Medicine, 6720 Szeged, Hungary*[3]

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PLoS one



# The Antipsychotic Thioridazine Shows Promising Therapeutic Activity in a Mouse Model of Multidrug-Resistant Tuberculosis

**Dick van Soolingen[1,2]*, Rogelio Hernandez-Pando[3], Hector Orozco[3], Diana Aguilar[3], Cecile Magis-Escurra[4], Leonard Amaral[5], Jakko van Ingen[1,4], Martin J. Boeree[4]**

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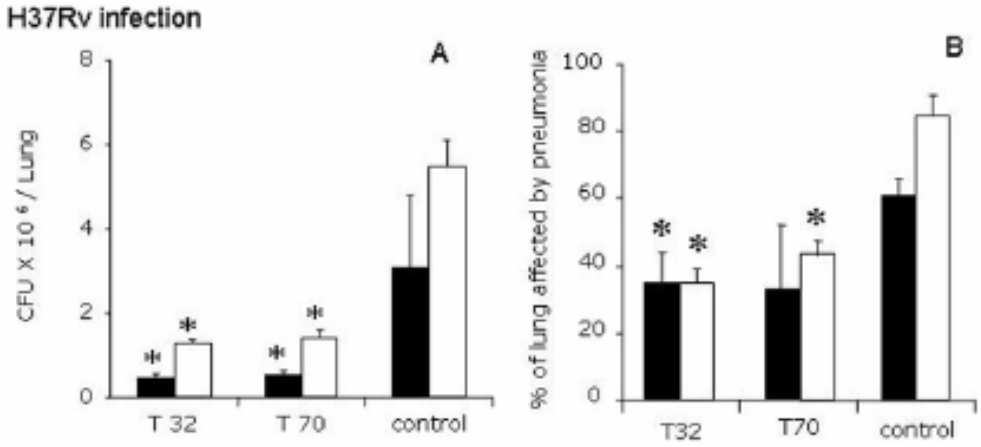


**Figure 1. Effect of Thioridazine administration on the bacillary loads (CFU) and histological damage of mice infected with drug susceptible strain H37Rv strain.** (A) Both doses of 32 (T32) and 70 (T70) mg/kg of thioridazine administered daily from day 60 after infection significantly reduced CFU by day 30 (black bars) and 60 (white bars) after initiation of treatment. CFU rose progressively in the untreated control animals. (B) In the thioridazine treated animals, the percentage of the lung surface affected by pneumonia was significantly smaller in thioridazine treated- than in control animals after one (black bars) and two months (white bars) of treatment. Data is expressed as means ± SD, 8 mice per time point, asterisks represent statistical significance ($p<0.05$).
doi:10.1371/journal.pone.0012640.g001

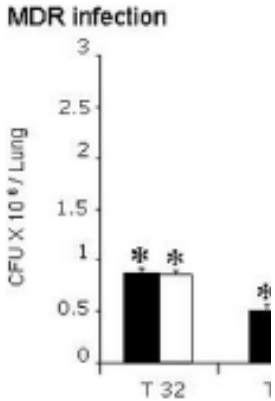


**Figure 2. Effect of Thioridi**
**MDR-TB strain.** (A) In comp
bars) and 60 (white bars) day
animals, the percentage of th
two months (white bars) of tr
doi:10.1371/journal.pone.0012

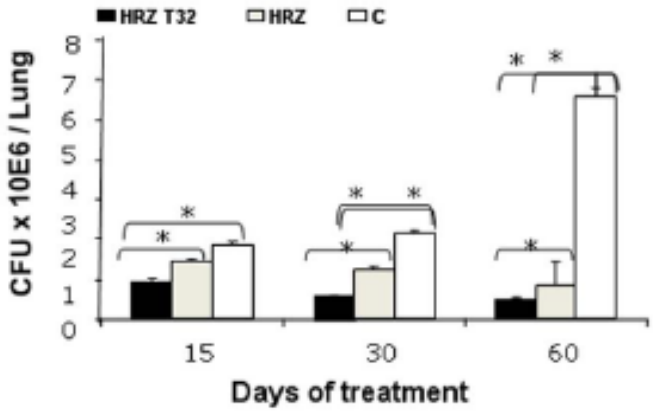


**Figure 3. Effect of combined treatment with standard anti-tuberculosis treatment and thioridazine on lung bacillary load in mice infected with *M. tuberculosis* H37Rv.** Animals were treated from day 60 with conventional chemotherapy alone (isoniazid [H], rifampicin [R] and pyrazinamide [Z], gray bars), or in combination with thioridazine 32 mg daily (black bars). In comparison with untreated control mice (white bars), both treatments produced significant reduction of bacilli loads after 30 and 60 days of treatment, being higher and faster in the combined treatment group. Data are expressed as means ± SD, 8 mice per time point, asterisks represent statistical significance ($p<0.05$). T32 HRZ, first line anti-tuberculosis treatment with adjunctive thioridazine 32 mg/kg; HRZ, first line treatment only; C, controls.
doi:10.1371/journal.pone.0012640.g003

**damage of mice infected with the**
gnificantly reduced the CFU, 30 (black
nimals. (B) In the thioridazine treated
rol animals after one (black bars) and
esent statistical significance ($p<0.05$).

Journal of Antimicrobial Chemotherapy Advance Access published December 1, 2011

J Antimicrob Chemother
doi:10.1093/jac/dkr500

Journal of Antimicrobial Chemotherapy

# Successful alternative treatment of extensively drug-resistant tuberculosis in Argentina with a combination of linezolid, moxifloxacin and thioridazine

**Eduardo Abbate[1], Marisa Vescovo[1], Marcela Natiello[1], Mónica Cufré[1], Ana García[1], Pablo Gonzalez Montaner[1], Marta Ambroggi[1], Viviana Ritacco[2,3]* and Dick van Soolingen[4,5,6]**

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# Desventajas

- Posible prolongación de intervalo QT
- Estigma?
- Disponibilidad

# Perspectivas

- Poca inversión en R & D de antibióticos (aprobados *vs* inversión)
- Estrategia de desarrollo de nuevas drogas (orientado a un blanco)
- No investigar efectos adicionales
- Reutilización puede ser buena alternativa

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- Gent Universiteit – Belgium
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- European Commission