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Viña del Mar

Agentes emergentes en IASS

TB con resistencia extendida

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Contenidos

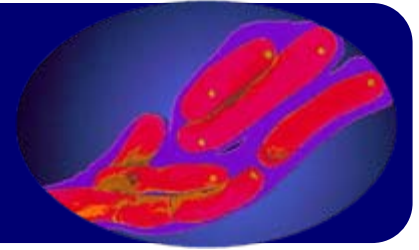
- **Generalidades**
- **Definiciones**
 - Multirresistencia (TB MDR)
 - Resistencia extendida (TB XDR)
- **Epidemiología**
 - Mundial
 - Nacional
- **Desafíos**
 - Manejo terapéutico
 - Medidas de prevención

Hitos en Tuberculosis

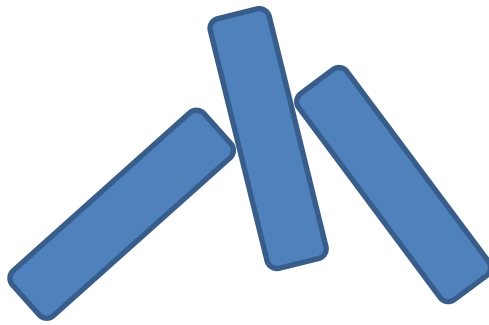
- Descripción del bacilo por el Dr. Robert Koch
- Incorporación de estreptomycin
- Introducción de terapia combinada
 - Sir John Crofton (1912-2009)
- Disponibilidad de vacuna
 - BCG (Bacillus Calmette-Guerin)



Generalidades



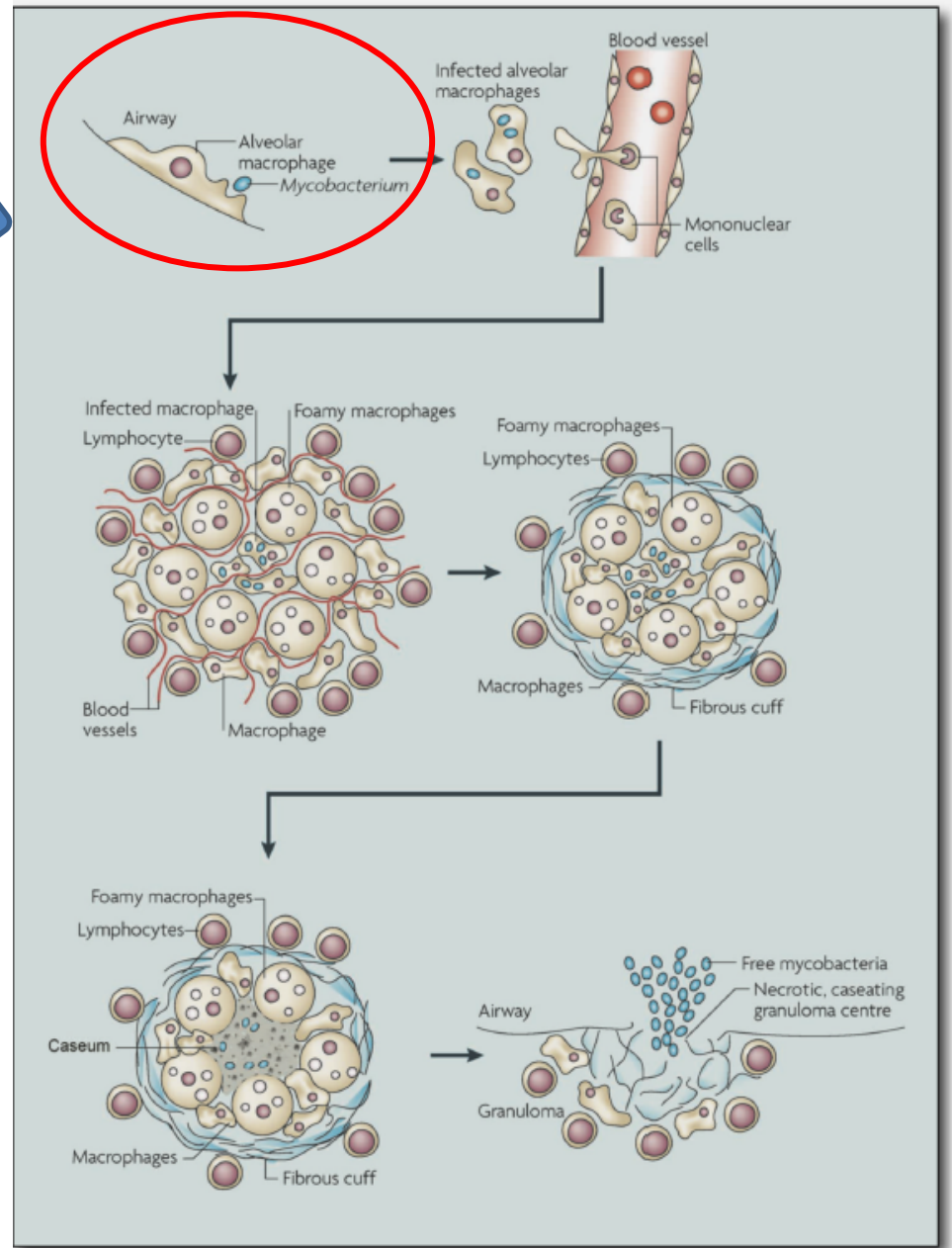
- Género *Mycobacterium*
 - Forma bacilar
 - Pared con alto contenido lipídico
 - Aerobio estricto
 - Lenta multiplicación
 - Requiere medios especiales para su crecimiento
- Baciloscopía (S: 45 - 80%)
- Cultivo: confirmación etiológica (gold estándar)
 - Medios sólidos: 30 – 60 días
 - Medios líquidos: 10 – 14 días
- Histología
- Biología molecular:
 - Múltiples test



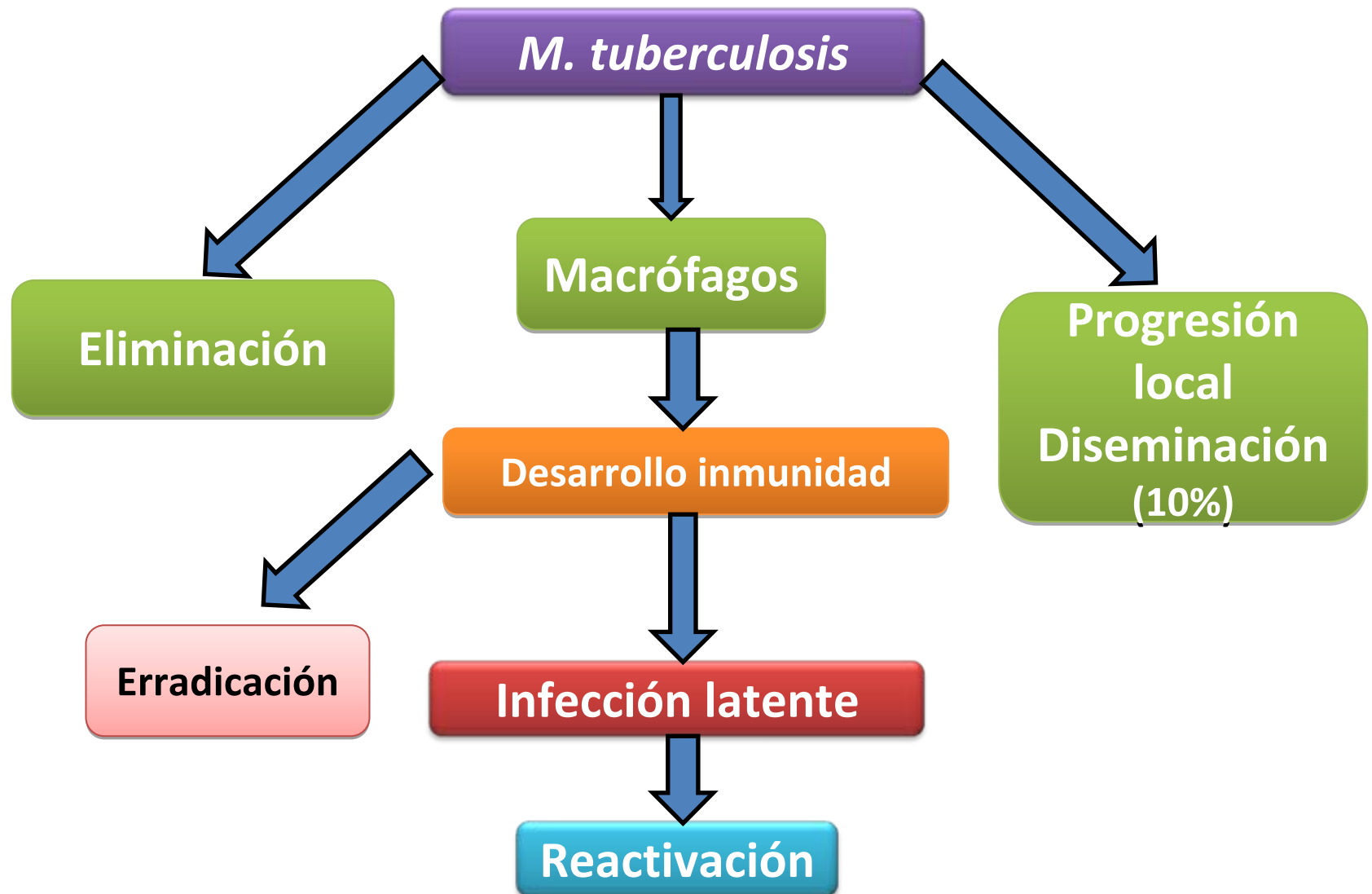
Ciclo biológico

Importantes en el control de la infección:

- Activación de macrófagos
- LTCD4
- Factor de necrosis tumoral



Historia natural de la infección



Limitaciones en el control de la TB

- **Mayor incidencia en:**
 - Países de bajos recursos
 - Usuarios de drogas ilícitas
 - Inmunosuprimidos (VIH)
- Técnicas para el diagnóstico microbiológico con baja sensibilidad y tardías
- Problemas de adherencia a terapia
 - Múltiples drogas y por tiempo prolongado
- Baja sospecha diagnóstica, uso de esquemas sub óptimos

Definiciones

- **Resistencia Primaria:** presente antes de iniciar terapia
- **Resistencia Secundaria:** adquirida durante o luego de haber recibido terapia
- **Multirresistencia** (MDR): resistencia a isoniazida y rifampicina
- **Resistencia extendida** (XDR TB): resistencia a isoniazida y rifampicina, todas las fluoroquinolonas y al menos a un aminoglicósido.

Epidemiología mundial

OMS 2010

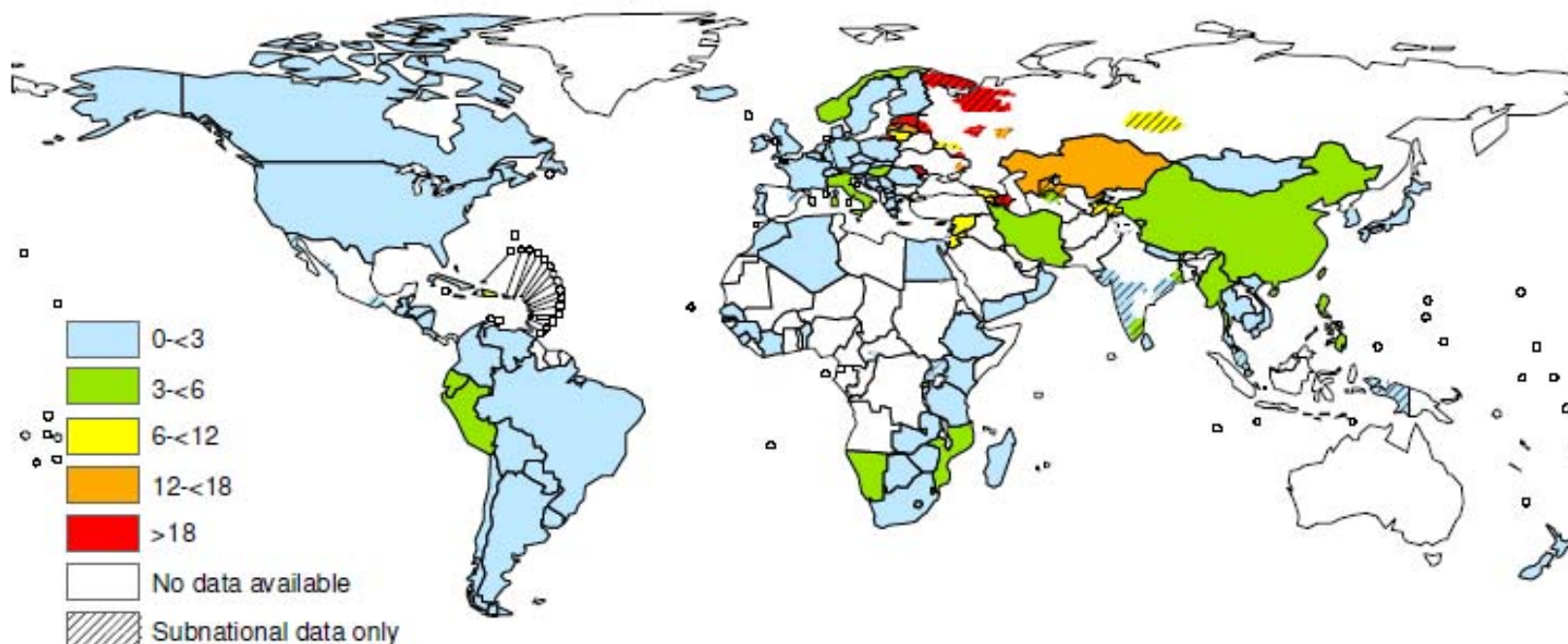
- 1/3 de la población mundial infectada por *M. tuberculosis*
 - 9,4 millones de casos nuevos
- **Emergencia de multi-resistencia como amenaza mundial**
 - Dificultades en el reconocimiento, solo 11% de los casos son identificados
 - Últimos 10 años
 - 5 millones de casos, solo 1 millón con acceso a terapia
 - 440.000 casos el año 2008

Países con mayores incidencias de TB

TABLE 1. The 22 high-burden countries with 80% of the tuberculosis cases worldwide^a

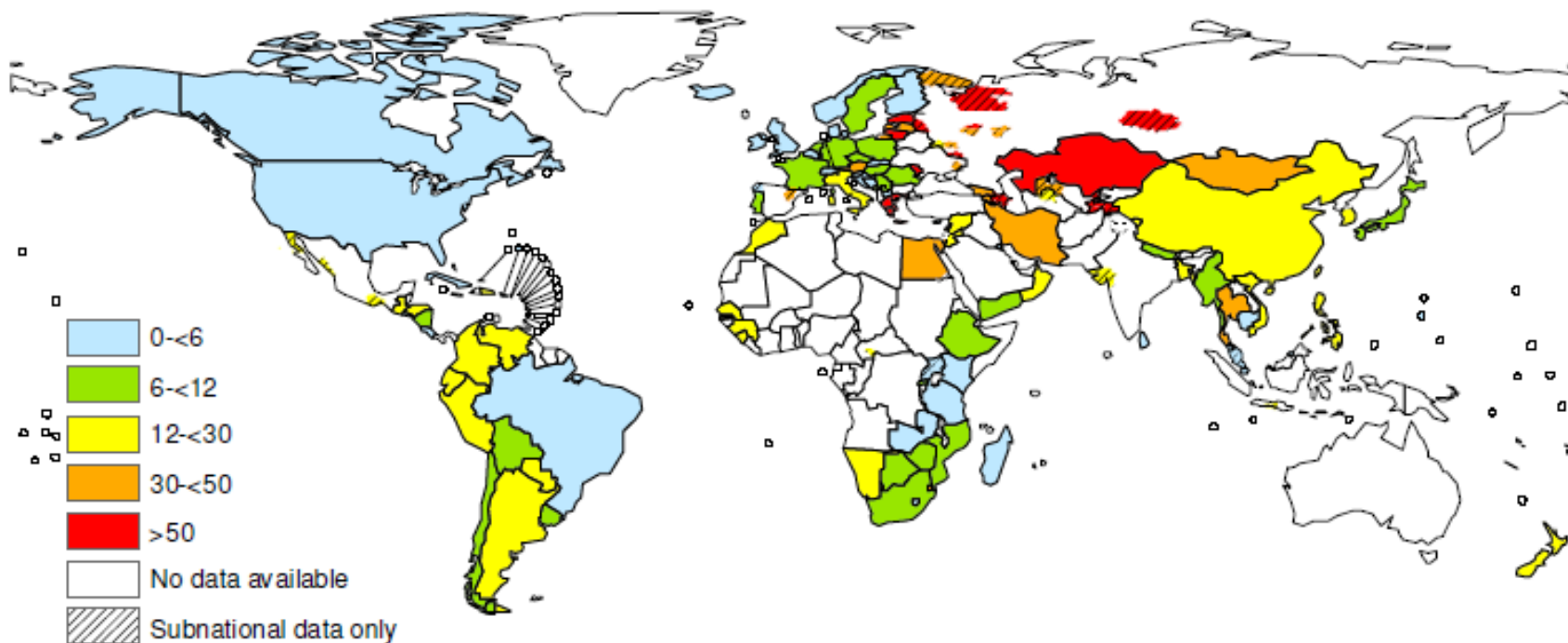
Country	Burden of TB incidence (no. of cases/100,000 individuals/yr)	Global rank (by estimated cases)
Afghanistan	333	21
Bangladesh	246	5
Brazil	62	15
Cambodia	508	23
China	102	2
Democratic Republic of Congo	369	11
Ethiopia	356	7
India	168	1
Indonesia	285	3
Kenya	610	10
Mozambique	431	19
Myanmar	171	20
Nigeria	293	4
Pakistan	181	6
Philippines	296	9
Russian Federation	110	11
South Africa	948	5
Thailand	142	17
Uganda	411	16
United Republic of Tanzania	371	14
Vietnam	178	13
Zimbabwe	569	19

Proportions of MDR among new TB cases, 1994-2010



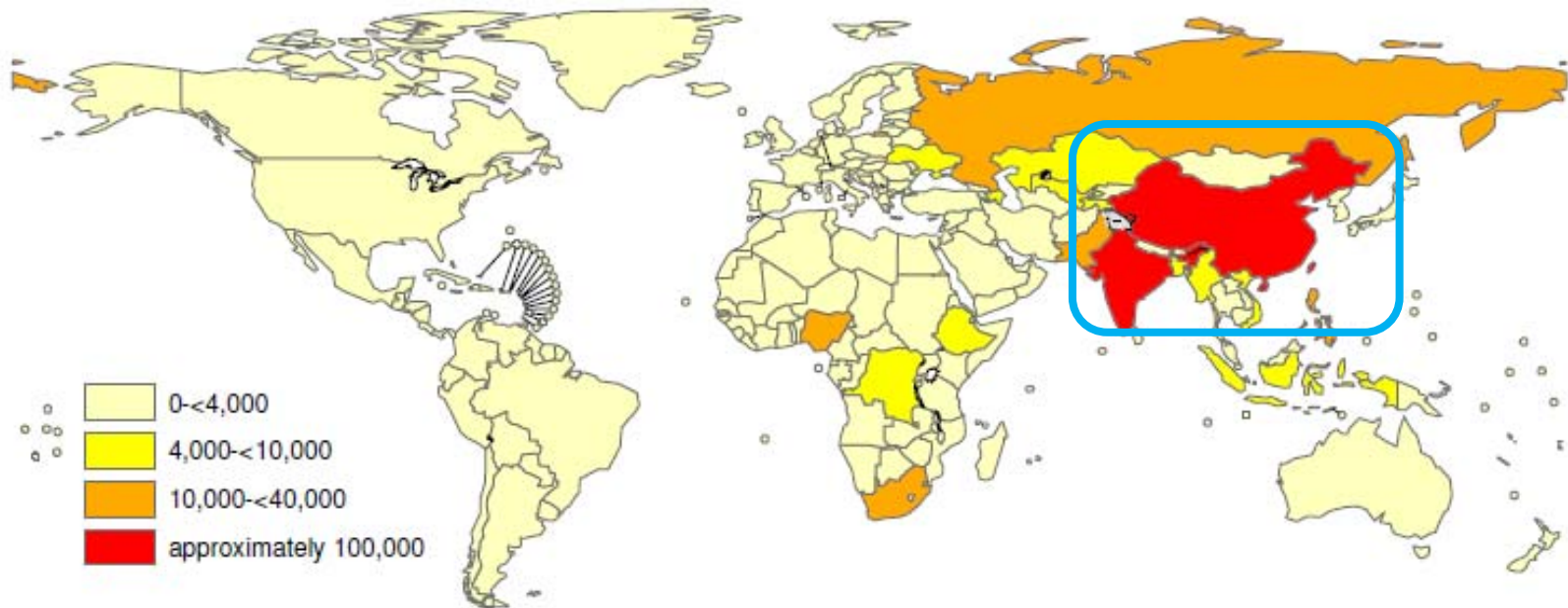
The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement. ©WHO 2011. All rights reserved

Proportions of MDR among previously treated TB cases, 1994-2010



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Estimated absolute number of MDR-TB cases, 2009



Año 2008 440.000 casos

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Countries that had reported at least one XDR-TB case by end 2010



38 países

Argentina	Bhutan	France	Kazakhstan	Nepal	Republic of Moldova	Togo
Armenia	Cambodia	Georgia	Kenya	Netherlands	Romania	Tunisia
Australia	Canada	Germany	Kyrgyzstan	Norway	Russian Federation	Ukraine
Austria	Chile	Greece	Latvia	Pakistan	Slovenia	United Arab Emirates
Azerbaijan	China	India	Lesotho	Peru	South Africa	United Kingdom
Bangladesh	Colombia	Iran (Islamic Rep. of)	Lithuania	Philippines	Spain	United States of America
Belgium	Czech Republic	Ireland	Mexico	Poland	Swaziland	Uzbekistan
Botswana	Ecuador	Israel	Mozambique	Portugal	Sweden	Viet Nam
Brazil	Egypt	Italy	Myanmar	Qatar	Tajikistan	
Burkina Faso	Estonia	Japan	Namibia	Republic of Korea	Thailand	

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Incidencia TB en Chile 2000 - 2009

Tasa de Incidencia de Tuberculosis en todas sus formas, por regiones. Chile 2000-2009 >> >>
2009

13,1/100.000 hab.

Datos

TBC en todas sus formas, CIE 10: A15..A19

Mapa de Chile

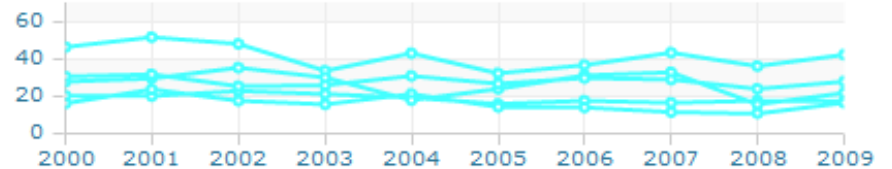
- 8,5 - 10,5
- 10,6 - 15,8
- 15,9 - 41,9

Gráfico circular



Fuente: Programa Nacional TBC.

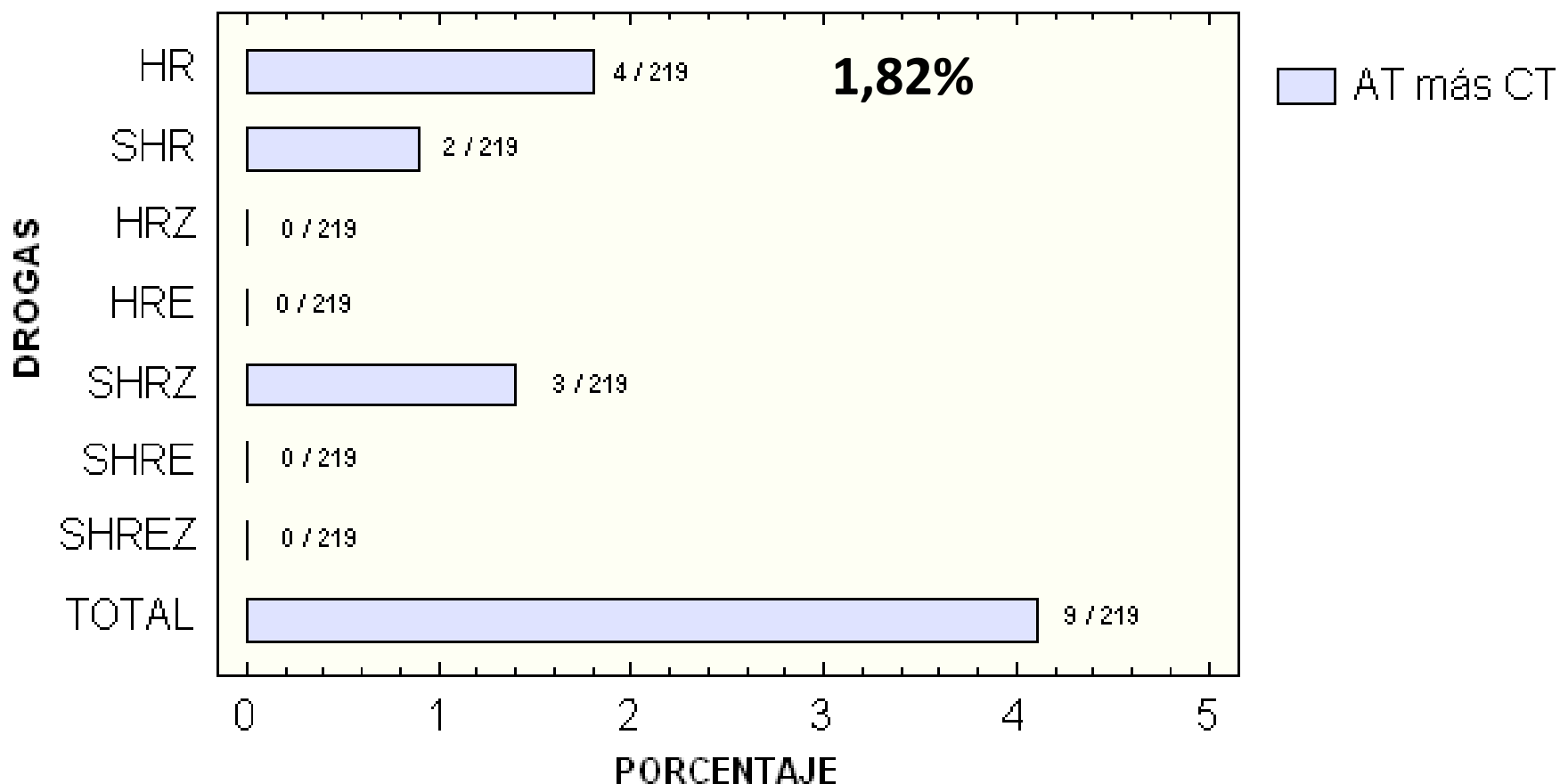
	Nombre ▲	Indicador
	Aisén	9,6
	Antofagasta	10,0
	Araucanía	10,8
	Arica y Parinacota	41,9
	Atacama	15,4
	Biobío	16,9
	Coquimbo	10,7
	L.B. O'Higgins	8,5
	Los Lagos	13,7
	Los Ríos	16,1
	Magallanes	21,5
	Maule	8,9
	Metropolitana	13,0
	Tarapacá	27,6
	Valparaíso	10,2



TB multirresistente, Chile 2008

Evaluación de Multidrogoresistencia
CHILE. 2008

AT: antes tratado
CT fracaso bacteriológico



Estudio de susceptibilidad en Chile

- **No de rutina, se realiza en:**
 - Todo paciente antes tratado (AT): recaídas y abandonos.
 - Todo paciente con sospecha de fracaso bacteriológico (CT 4 meses)
 - Paciente proveniente de países con alta prevalencia de TBC.
 - PS con TBC confirmada bacteriológicamente con contacto con pacientes TB MDR demostrada.
 - Todo paciente con infección por VIH como vigilancia continua
- En paciente virgen a tratamiento **sólo cuando se programa estudio epidemiológico.**

Evolución de pacientes TB MDR y TB XDR

- **Mortalidad elevada**
 - 98% cuando co-existe TB XDR y VIH
- **En programas de TO (Perú)**
 - 60% de curación
 - 15% cirugía
 - 29% mortalidad
 - 23% mortalidad

NEJM 2007, 356
NEJM 2008, 359


Table 3. Hospitalization and Resective Thoracic Surgery among Patients with XDR Tuberculosis.*

Characteristic	Value
Patients hospitalized during individualized treatment regimen — no./total no. (%)	11/48 (22.9)
No. of days of hospitalization during individualized treatment regimen — median (interquartile range)	14 (5–54)
Patients undergoing surgical resection during individualized treatment regimen — no./total no. (%)	7/48 (14.6)
Type of surgery — no. (%)	
Lobectomy	5 (10.4)
Pneumonectomy	1 (2.1)
Cavitary resection	1 (2.1)
No. of months from treatment initiation to surgery — median (interquartile range)	11.6 (7.1–24.1)
Patients with positive sputum culture at surgery — no. (%)	3 (42.9)
No. of months of treatment for patients undergoing surgery — median (interquartile range)	31.2 (25.1–57.9)
Patients undergoing surgery who subsequently died or whose treatment failed — no. (%)	2 (28.6)

Cuando sospechar TB MDR y TB XDR

- Individuo expuesto a paciente TB MDR XDR confirmada
- Individuo expuesto a paciente con BK persistentemente (+) después de 2 meses de tratamiento (fracaso)
- Individuo expuesto a paciente con abandono a tratamiento.
- Exposición en áreas geográficas con alta prevalencia de TB MDR XDR

Medidas de prevención

 Prevention of nosocomial transmission of extensively drug-resistant tuberculosis in rural South African district hospitals: an epidemiological modelling study

Sanjay Basu, Jason R Andrews, Eric M Poolman, Neel R Gandhi, N Sarita Shah, Anthony Moll, Prashini Moodley, Alison P Galvani, Gerald H Friedland

- Reducción de tiempos de hospitalización
- Precauciones de aerosoles
- Uso de mascarilla facial
- Optimización de la ventilación
- Estudios rápidos de susceptibilidad
- Diagnóstico de VIH

The Lancet, 2007, vol 370

Desafíos en TB MDR y TB XDR

- Facilitar acceso a sistemas de salud
- **Sospecha y diagnóstico precoz**
- **Personal de salud capacitado**
 - Precauciones por aerosoles
- Disponibilidad de técnicas microbiológicas sensibles y rápidas (Dg y resistencia)
 - Amplificación de ácidos nucleicos
- Disponibilidad de nuevas drogas
- Disponibilidad de vacuna efectiva

Técnicas diagnósticas..

Técnicas diagnósticas para infección latente

- Quantiferon Gold
- ELISPOT
 - Basados en la detección y medición de interferón gama liberado por linfocitos incubados con Ag de MTB
 - Antígenos no presentes en la BCG por lo tanto no interfiere en la interpretación
- Baja sensibilidad para detectar infección aguda
 - 242 sujetos, 37 cultivos (+), 23 (+) por QTF, sensibilidad 64%

Nuevas técnicas diagnósticas TB

- **Complementarios a los métodos tradicionales**
 - Métodos no moleculares
 - Métodos moleculares

Métodos no moleculares

Sputum smear microscopy

Processing of sputum sample prior to smear examination (eg, use of bleach then centrifugation or use of bleach or sodium hydroxide then overnight sedimentation)

This is 18%–23% more sensitive than direct microscopy

Fluorescence microscopy

This is 10% more sensitive than conventional microscopy; use to determine viability of *Mycobacterium tuberculosis* in follow-up sputum specimens to detect treatment failure

Fluorescence microscopy using light-emitting diode light source

These light sources are cheaper, last longer, and have less potential for environmental contamination than do traditional lamps used in this method

Culture-based methods

Liquid culture (eg, automated mycobacteria growth indicator tube)

Faster and more sensitive than solid media; recommended standard practice

Microscopic observation drug susceptibility assay

Yields faster culture and DST results than do liquid or solid media and is inexpensive, but requires inverted microscope and skilled technician to interpret culture appearance of *M. tuberculosis*

Thin-layer agar methodology

Yields faster culture and DST results than do liquid or solid media and is inexpensive, but requires skilled technician to recognize *M. tuberculosis* colony formation.

Colorimetric DST methods using redox indicators, tetrazolium salts, or a nitrate reductase assay

These are low-cost, low-tech, and able to yield DST results within 2 weeks; potential for biosafety hazard

Métodos moleculares

Molecular methods

Line probe assays (eg, Genotype MTBDR_{plus} assay [Hain] and INNO-LiPA Rif.TB assay [Immunogenetics])

High sensitivity and specificity for detection of rifampicin (with or without isoniazid) resistance, with a 1–2 day turnaround time directly for smear-positive sputum; requires DNA extraction and amplification facilities

Nucleic acid amplification tests

High specificity; important role in confirming mycobacterial identity; poor negative predictive value for pulmonary and extrapulmonary TB; updated US CDC guidelines recommend sputum *M. tuberculosis* nucleic acid amplification tests for cases of suspected, unconfirmed TB if results would alter management [111]

Detectan *Mycobacterium* y resistencia

Rápidos

Caros

Gen Xpert MTB/RIF

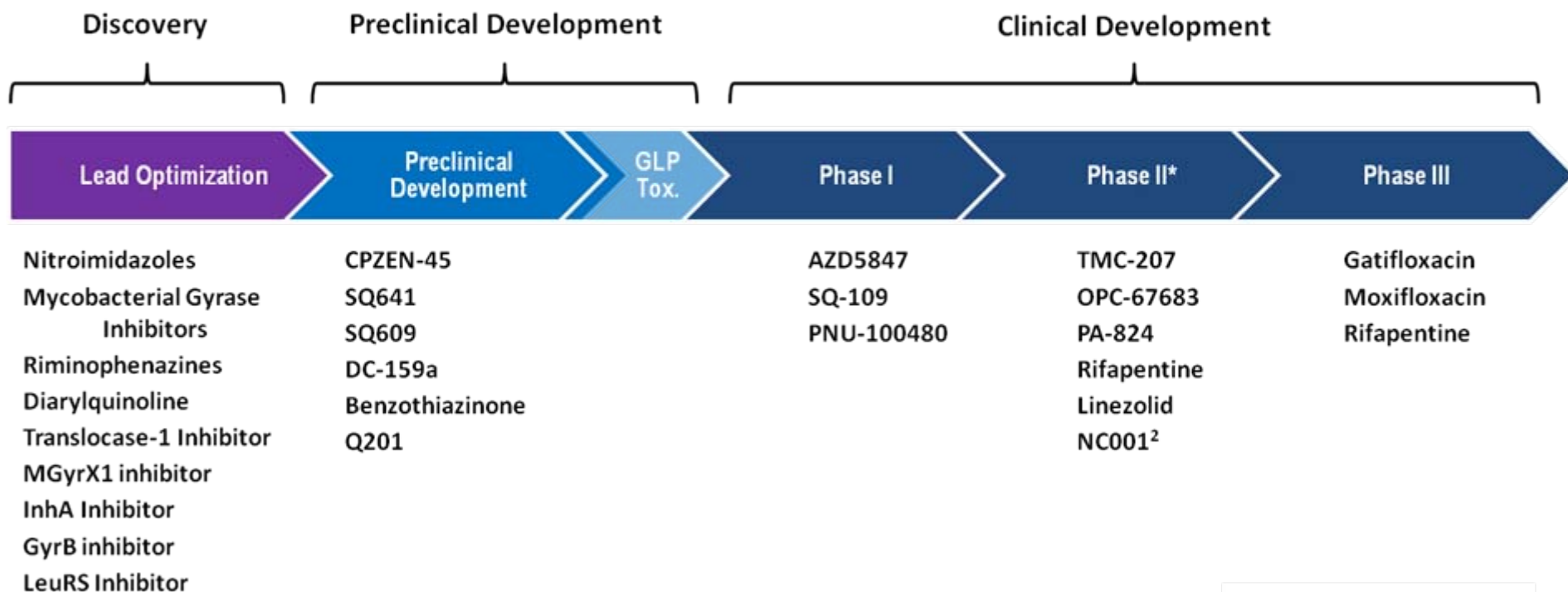
- **PCR en tiempo real**
 - Detección de *Mycobacterium tuberculosis complex*
 - Detección de resistencia a rifampicina
 - **S** 98% en cultivo (+)
 - **S** 71% en cultivos (-)
 - **E** 99,2%
- Directo de la muestra
- Rápido: resultados en 1 día
- No requiere gran infraestructura



Diciembre 2010 la OMS recomienda su uso para el diagnóstico de tuberculosis

Terapia en desarrollo..

Global TB Drug Pipeline[†]



[†] Projects that have not identified a lead compound series are considered to be in the screening phase of development and are not included. As of publication, there are 11 screening projects in progress as described on <http://www.newtbdrugs.org/pipeline.php>.

² First clinical trial of a novel TB drug regimen testing the three drug combination of PA-824, moxifloxacin, and pyrazinamide; more information is located at <http://www.newtbdrugs.org/pipeline.php>.

*Initiation of drug combination studies

Drogas en estudio y desarrollo

Antituberculosis agents	Agent	Agents
Current antituberculosis agents, WHO classification [26]		
Group 1	First-line oral antituberculosis agents	Isoniazid, rifampicin, ethambutol, pyrazinamide, rifabutin
Group 2	Injectible antituberculosis agents	Streptomycin, kanamycin, amikacin, capreomycin
Group 3	Fluoroquinolones	Moxifloxacin, levofloxacin, ofloxacin
Group 4	Second-line oral bacteriostatic anti-tuberculosis agents	Ethionamide or protionamide, cycloserine or terizidone, para-aminosalicylic acid
Group 5	Antituberculosis agents with unclear efficacy	Clofazimine, amoxicillin-clavulanate, linezolid, thioacetazone (contraindicated for HIV-infected patients), imipenem-cilastin, high-dose isoniazid, clarithromycin
New drugs		
Group 6	New drugs undergoing clinical evaluation	Diarylquinolone (TMC-207, also known as R207910), nitroimidazopyrans (PA-824 and OPC-67683), diamine (SQ-109)
Group 7	New drugs at discovery stage	Benzothiazinones (eg, BTZ043), LL-3858, cell-wall inhibitors, multifunctional molecules, diaryl oxides, dihydro-lipoamide acyltransferase inhibitors, dipiperidine SQ-609, econazole, fatty acid synthase inhibitors, hydrazones, InhA inhibitors, isocitrate lyase inhibitors, malate synthase inhibitors, mefloquine analogues, oxazolidinones, peptide diformylase inhibitors, plueromutilins, riminophenazines, thiolactomycin inhibitors, topoisomerase inhibitors, translocase inhibitors

Aspectos éticos

- Aislamiento social prolongado
- **¿Cómo manejar aquellos pacientes sin opción terapéutica?**
 - Aislamiento social definitivo
 - Riesgo para la familia?
 - Riesgo del PS?

Para finalizar

- El mayor desastre para un paciente con tuberculosis es que sus bacilos desarrollen resistencia a dos o más drogas pilares del tratamiento.
- El desarrollo de resistencia a los medicamentos puede ser una tragedia no sólo para el propio paciente sino para los demás.
- Puede hacer la diferencia entre la supervivencia y la muerte.

