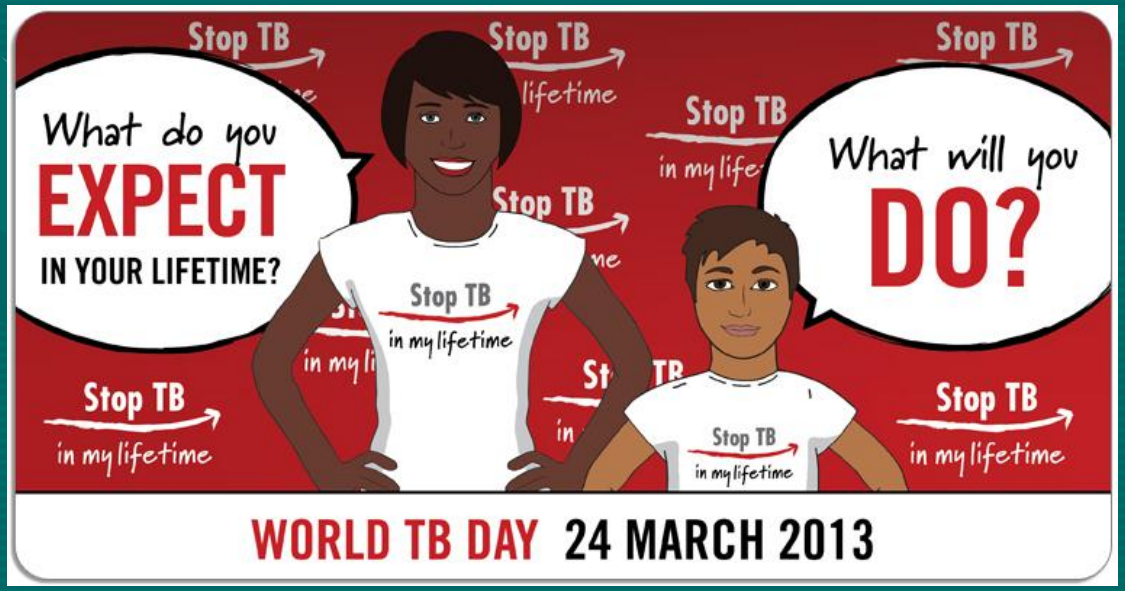
XXVI CURSO DE AVANCES EN ANTIBIOTERAPIA

NUEVAS ESTRATEGIAS EN TRATAMIENTO ANTITUBERCULOSO



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MADRID

THE INDEPENDENT ON SUNDAY

WIN

A LIMITED EDITION PRINT

Celebrating 40 years of Pink Floyd's 'The Dark Side of the Moon' I on Sunday P3

SPRING - AN APOLOGY

British Weather won't like to apologise for the late running of this season

P4-5

ASIAN ACHIEVERS

The nation's most inspiring women

P20-21

OFF THE SHOULDER

Bill Granger's unbeatable lamb recipes

The New Review

UK risks time bomb of untreatable TB

::: Doctors warn virulent strain of lung disease could get out of control

::: New government task force will meet next month to tackle crisis

THE INDEPENDENT ON SUNDAY
24 MARCH 2013

TB reasserts its deadly grip – and the drugs don't work

Experts warn of a potential health emergency as number of drug-resistant cases rises rapidly

By Sanchez Manning and Jonathan Owen

Medical experts warned last night that there could be a surge in cases of tuberculosis resistant to current drug treatments unless the Government takes urgent action.

Europe has seen a rapid increase in multi-drug-resistant – or MDR – tuberculosis, which cannot be treated with the two antibiotic treatments normally given to sufferers. In the past eight years scientists have seen an increase in another strain, known as XDR tuberculosis, which is resistant to even more TB drugs. A report published in *The Lancet* today warns that this more virulent variety could lead to the emergence of "untreatable tuberculosis".

In Britain the vast majority of TB cases are treatable. But cases of MDR jumped from 28 to 81 between 2000 and 2011, while some 24 cases of XDR tuberculosis have come to light in the past two years. Professor Alimuddin Zumla, from University College London and one of the authors of *The Lancet* report, warned that with growing immigration from eastern Europe these numbers could rise rapidly: "TB is a time bomb. If you don't curtail it now it will be out of control."

Professor Zumla cautioned that with the numbers of "home grown" resistant cases among the British-born population – particularly in London – also rising, the UK could find itself in the grip of a health emergency.

Tuberculosis was once one of the world's biggest killers and was known as the "white plague" when it ravaged Britain in Victorian times. By the 1970s it had almost been eradicated, but in the last 30 years there has been a major re-emergence of the disease, which is airborne and spread through close contact with others.

JUSTINE SUTCLIFFE

'It's been a long and hard eight months for me. It's a massive relief to finally have the all clear'

After six years travelling the world Simon Richardson, 28, from Burgh Castle, Norfolk returned to Britain last year and tried to join the Army, only to find he had drug-resistant TB. Now back to full health, he joined the Army last week.

"I started to get pains in the left side of my chest but didn't think anything of it until it wouldn't go away – and started to get worse ... It's been a long and hard eight months for me – the side-effects of the drugs were pretty bad – but it's a massive relief to finally have the all clear."

TB rates in Britain have increased rapidly and now stand at around 9,000 cases – the highest level since the 1970s. Between 2001 and 2010 more than 4,800 people died of TB in the UK. The Health Protection Agency has forecast that if the rise in TB continues at its current rate then by 2015 Britain will have more new cases each year than in the whole of the US.

Dr Paul Cosford, director for health protection at the newly formed Public Health England, said: "It's quite a striking figure that in the whole of the States there might be fewer cases of TB each year than in the whole of the UK, given the difference in population numbers. It's a bit of a wake-up call." He added: "The multi-drug resistance is a worry because this gets into an area where we're losing the ability to treat TB because of the lack of antibiotics."

A government task force is being set up to tackle the problem, and its first meeting will be next month. Dr Cosford said: "As a preventable and treatable condition which still causes much suffering, TB will be a major priority for Public Health England."

There is growing alarm at the rise of drug-resistant TB globally, with the World Health Organization estimating that there around 600,000 cases were diagnosed in 2011.

But experts say there are likely to be four times as many undiagnosed cases. It is now the world's second biggest infectious killer, and despite a recent decline in the number of TB-related mortalities, it was still blamed for an estimated 1.4 million deaths worldwide in 2011.

The highest levels of drug-resistant TB have emerged in the former Soviet Union. In countries such as Ukraine, Belarus and Kazakhstan more than 30 per cent of new TB patients have the MDR strain. Across the globe, it is estimated that there are around 40,000 people suffering from XDR TB.

The Lancet report, published to coincide with World TB Day, warns: "The widespread emergence of XDR tuberculosis could lead to virtually untreatable tuberculosis. With the ease of international travel and increased rates of MDR in eastern Europe, central Asia and elsewhere, the threat and range of untreatable tuberculosis is very real."

Professor Mario Raviglione, director of the World Health Organization's TB department, said with drug-resistant strains spreading to 84 countries there is a pressing need for better treatments. Current tests to diagnose and the cocktail of drugs used to treat the disease are increasingly ineffective in the face of MDR and XDR tuberculosis, he added. "They are also quite toxic, so some of them can cause problems with the liver."

"Some others can cause problems with the brain – you get convulsions and psychologically strange behaviour. That's why we badly need research and badly need new tuberculosis drugs."

THE INDEPENDENT (24-03-2013)

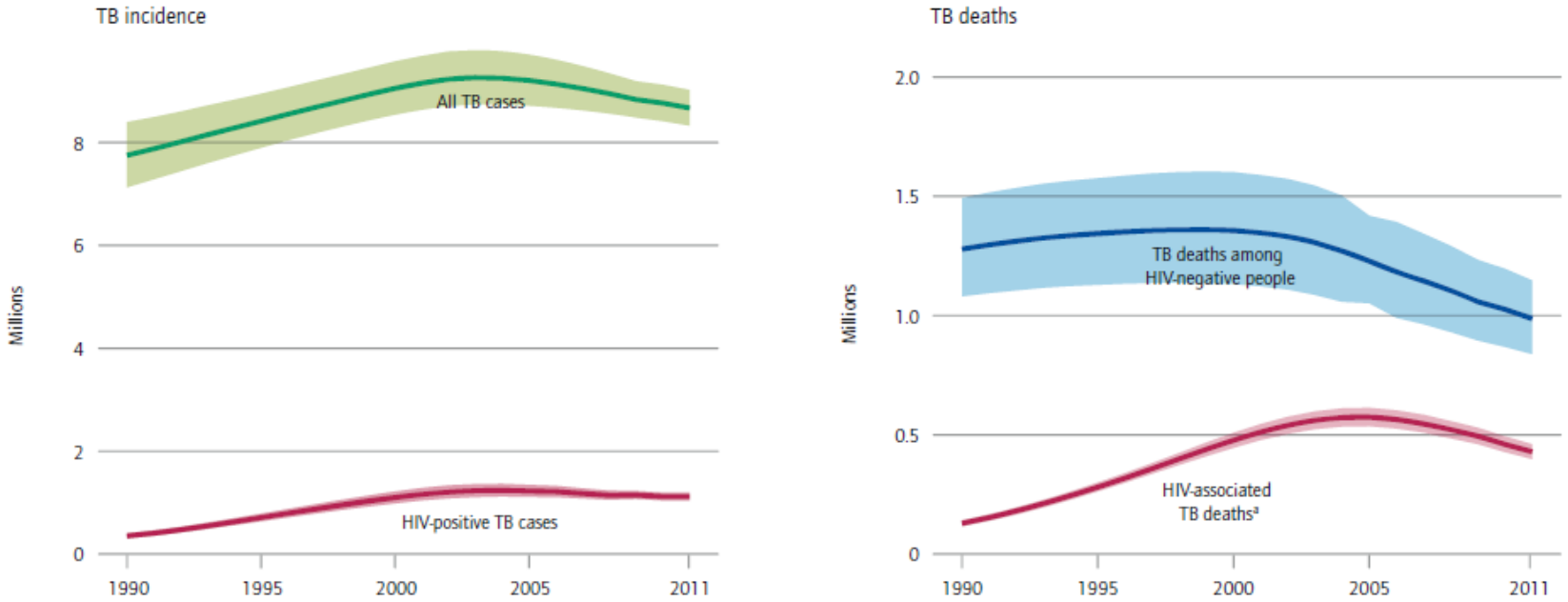
- 9000 casos en 2011 en UK
- 4800 muertes en los últimos 10 años
- MDR-TB: año 2000: 28 casos
  año 2011: 81 casos
- XDR-TB: 24 casos en los dos últimos años
- Aumento de casos con resistencias en autóctonos (Londres)
- Alertan de toxicidad en tratamientos de segunda línea
- "TB IS A TIME BOMB"
- "TB WILL BE A MAJOR PRIORITY FOR PUBLIC HEALTH ENGLAND"

Global Tuberculosis Report 2012

World Health Organization

FIGURE 2.5 **Estimated TB incidence rates, 2011**

FIGURE 2.4 **Estimated absolute numbers of TB cases and deaths (in millions), 1990–2011**



[a] HIV-associated TB deaths are classified as HIV deaths according to ICD-10.

- Incidencia 8,7 millones casos nuevos (125/10^5 habitantes)

- Distribución desigual: Asia (59%), África (26%), Mediterráneo oriental (7,7%), Europa (4,3%), América (3%)

- 13% infectados por VIH

- 1,4 millones de muertes (430.000 en infectados por VIH)

- 310.000 casos MDR-TB (casi el 60% del total en India, China y Rusia)

- 9% de MDR-TB son XDR-TB

- Europa: 380.000 casos (42/10^5 hab), 76.000 casos MDR-TB

- España: 7.200 casos declarados oficialmente (15/10^5 hab), aunque la SEPAR estima 25/10^5 hab. Altas tasas en población inmigrante

FIGURE 4.2 **Percentage of new TB cases with MDR-TB[a]**

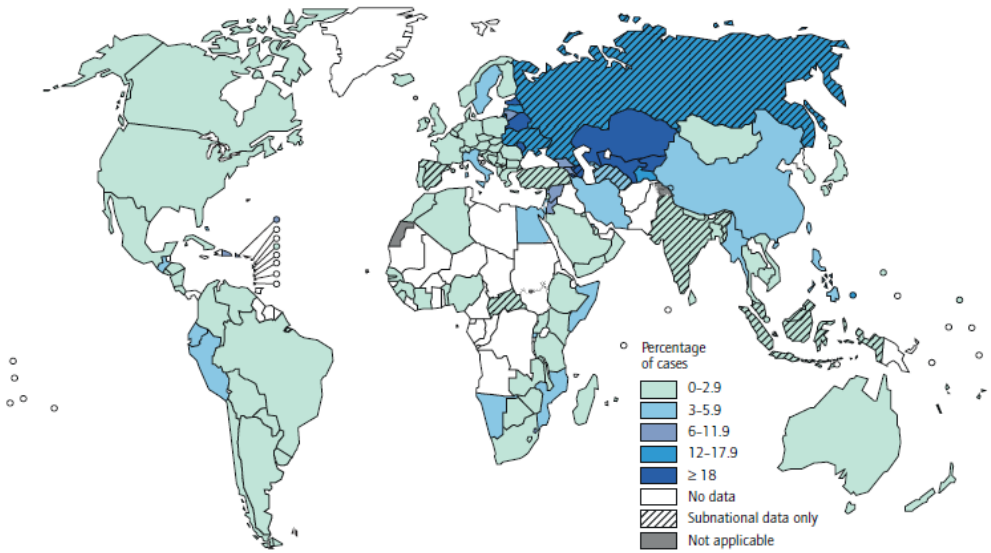


TABLE 2.3 **Estimated proportion of TB cases that have MDR-TB, 27 high MDR-TB burden countries and WHO regions**

	ESTIMATED % OF NEW TB CASES WITH MDR-TB[a]	CONFIDENCE INTERVAL	ESTIMATED % OF PREVIOUSLY TREATED TB CASES WITH MDR-TB[a]	CONFIDENCE INTERVAL
Armenia	9.4	7.1–12	43	38–49
Azerbaijan	22	19–26	55	52–60
Bangladesh	1.4	0.7–2.5	29	24–34
Belarus	32	30–35	76	72–79
Bulgaria	2.0	1.1–3.2	26	19–33
China	5.7	4.6–7.1	26	22–30
DR Congo	*3.1*	*0.1–7.1*	*10*	*2.1–18*
Estonia	23	17–29	58	43–71
Ethiopia	1.6	0.9–2.7	12	5.6–21
Georgia	11	9.6–12	32	28–35
India	2.1	1.5–2.7	15	13–17
Indonesia	1.9	1.4–2.5	12	8.1–17
Kazakhstan	30	29–32	51	50–53
Kyrgyzstan	26	23–31	52	45–58
Latvia	13	10–16	29	20–40
Lithuania	11	9.2–13	49	44–54
Myanmar	4.2	3.1–5.6	10	6.9–14
Nigeria[b]	*3.1*	*0.1–7.1*	*10*	*2.1–18*
Pakistan	*3.4*	*0.1–11*	*29*	*2.6–56*
Philippines	4.0	2.9–5.5	21	14–29
Republic of Moldova	19	17–22	64	60–67
Russian Federation	20	18–22	46	41–52
South Africa	1.8	1.4–2.3	6.7	5.5–8.1
Tajikistan	13	9.8–16	54	48–59
Ukraine	16	14–18	44	40–49
Uzbekistan	23	18–30	62	53–71
Viet Nam	2.7	2–3.6	19	14–25

MDR-TB:

3,7% en nunca tratados

20% en previamente tratados

Europa: 15,1% MDR-TB primaria

44% MDR-TB secundaria

Debuta la TB-XDR
Marzo 2006

MMWR

Morbidity and Mortality Weekly Report

Weekly — March 24, 2006 / Vol. 55 / No. 11

World TB Day — March 24, 2006

World TB Day is March 24. This annual event commemorates the date in 1882 when Robert Koch announced his discovery of *Mycobacterium tuberculosis*, the bacterium that causes tuberculosis (TB). Worldwide, TB remains one of the leading causes of death from infectious disease. An estimated 2 billion persons (i.e., one third of the world's population) are infected with *M. tuberculosis*. Each year, approximately 9 million persons become ill from TB, and approximately 2 million die as a result. World TB Day provides an opportunity for TB programs, nongovernmental organizations, and other partners to describe TB-related problems and solutions and to support TB control worldwide.

During 1985–1992, after more than 30 years of decline, the number of TB cases reported in the United States increased by 20%. This resurgence generated a renewed emphasis on TB control and prevention during the 1990s, which reversed thereafter. Although the 2005 TB total was the lowest recorded in the United States since national reporting began in 1953, the average annual decline has slowed during the past 5 years, multidrug-resistant TB remains a threat, and disparate rates of TB persist among certain racial, ethnic, and foreign-born populations.

Many universities offering educational programs organized by local TB coalitions in recognition of World TB Day. For example, the Georgia Department of Human Resources, Division of Public Health, Tuberculosis Program is hosting an observance recognizing the activities of a coalition working to reduce disparities in TB among blacks in the Atlanta area. Additional information about World TB Day and CDC TB-elimination activities is available at http://www.cdc.gov/nchstp/tb/worldtbday/2006/activities.htm.

Emergence of *Mycobacterium tuberculosis* with Extensive Resistance to Second-Line Drugs — Worldwide, 2000–2004

During the 1990s, multidrug-resistant (MDR) tuberculosis (TB), defined as resistance to at least isoniazid and rifampin, emerged as a threat to TB control, both in the United States (1) and worldwide (2). MDR TB treatment requires the use of second-line drugs (SLDs) that are less effective, more toxic, and costlier than first-line isoniazid- and rifampin-based regimens (3). In 2000, the Stop TB Partnership's Green Light Committee was created to increase access to SLDs worldwide while ensuring their proper use to prevent increased drug resistance. While assisting MDR TB treatment programs worldwide, the committee encountered reports of multiple cases of TB with resistance to virtually all SLDs. To assess the frequency and distribution of extensively drug-resistant (XDR) TB cases,* CDC, and the World Health Organization (WHO) surveyed an international network of TB laboratories. This report summarizes the results of that survey, which determined that, during 2000–2004, of 17,690 TB isolates, 20% were MDR and 2% were XDR. In addition, population-based data

*Defined as cases in persons with TB whose isolates were resistant to isoniazid and rifampin and at least three of the six main classes of SLDs (aminoglycosides, polypeptides, fluoroquinolones, thioamides, cycloserine, and para-aminosalicylic acid).

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTERS FOR DISEASE CONTROL AND PREVENTION

XDR = Multidrogo-resistanciaTB (MDR-TB) más resistencia a (i) cualquier *fluoroquinolona*, y (ii) por lo menos a 1 de los 3 inyectables de segunda línea *capreomycina, kanamycina, amikacina*
(new definition agreed October 2006)

MDR-TB = resistencia a la *isoniazida* y *rifampicina*, combinada o no a resistencias a otros fármacos de 1ra línea

De 17,690 aislamientos procedentes de 49 países en el periodo 2000-2004, 20% fueron MDR-TB y 2% XDR-TB

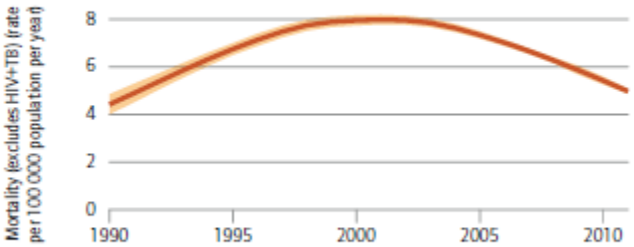
XDR-TB encontrada en:
Estados Unidos: 4% de MDR-TB
Letonia: 19% de MDR-TB
Corea del Sur: 15% de MDR-TB

WHO EUROPEAN REGION

Population 2011 **899 million**

WHO MEMBER STATES 53
OTHER COUNTRIES AND TERRITORIES 1

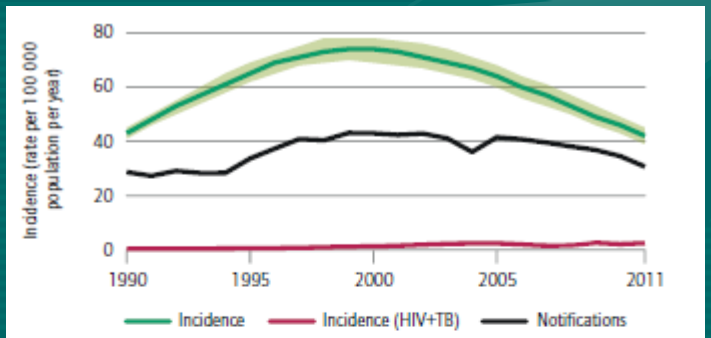
Estimates of TB burden[a] 2011	NUMBER (thousands)	RATE (per 100 000 population)
Mortality (excludes HIV+TB)	45 (44–46)	5 (4.9–5.1)
Prevalence (includes HIV+TB)	500 (370–650)	56 (41–73)
Incidence (includes HIV+TB)	380 (350–400)	42 (39–45)
Incidence (HIV+TB)	23 (20–25)	2.5 (2.2–2.8)
Case detection, all forms (%)	73 (69–78)	

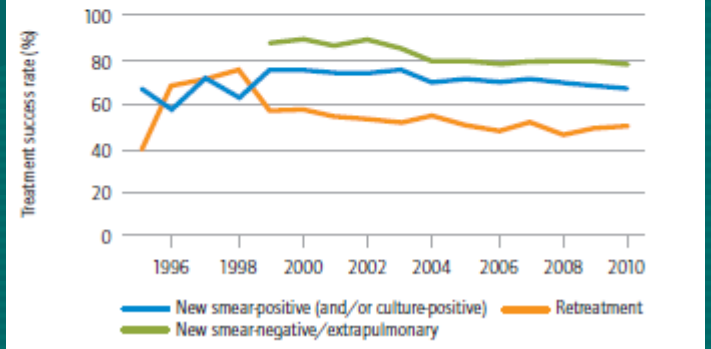


Estimates of MDR-TB burden 2011[a]	NEW	RETREATMENT
% of TB cases with MDR-TB	15 (10–20)	44 (40–49)
MDR-TB cases among notified pulmonary TB cases	32 000 (21 000–42 000)	42 000 (38 000–47 000)

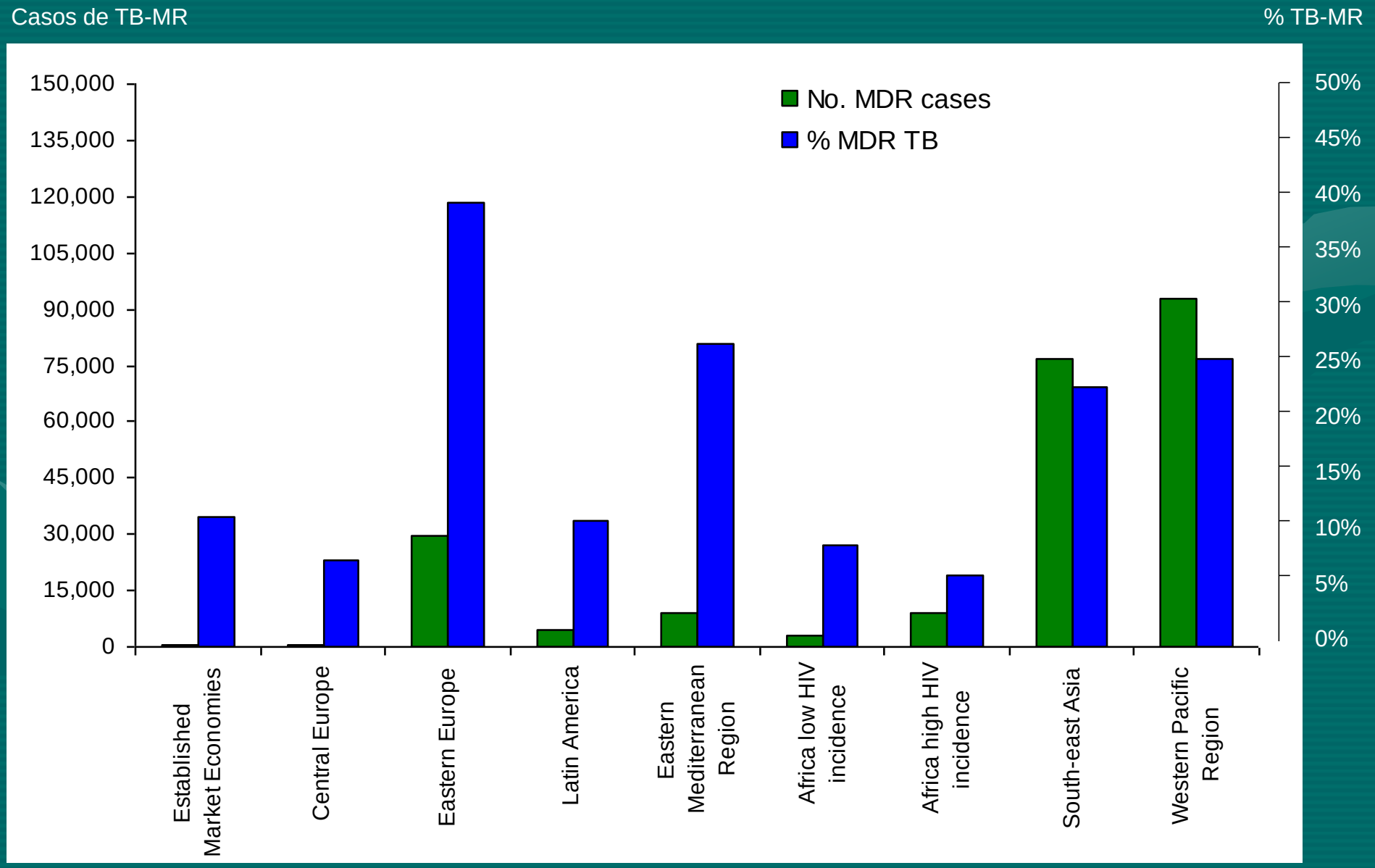
Reported cases of MDR-TB 2011	NEW	RETREATMENT	TOTAL
Cases tested for MDR-TB	69 467 (56%)	25 561 (27%)	99 470
Laboratory-confirmed MDR-TB cases	10 290	12 097	32 348
Patients started on MDR-TB treatment			34 769

Financing TB control (low- and middle-income countries)[d]	2012	2013
Total budget (US$ millions)	1 380	1 670
Available funding (US$ millions)	1 350	1 550
% of budget funded	98	92
% available funding from domestic sources	96	98
% available funding from Global Fund	3.7	1.9





Impacto por regiones de la TB-MR en pacientes previamente tratados



PAÍS	CASOS MDR-TB
AUSTRIA	19
BÉLGICA	15
FINLANDIA	5
ALEMANIA	56
FRANCIA	23 (2010)
ITALIA	87 (2010)
SUECIA	17
PORTUGAL	19 (2010)
REINO UNIDO	81
ESPAÑA	41

PAÍS	CASOS MDR-TB
TURQUÍA	262
UCRANIA	4305
GEORGIA	475
BULGARIA	55
BIELORRUSIA	1594
KAZAJISTAN	7408
UZBEKISTAN	1385
MOLDOVIA	1001
RUMANIA	485
RUSIA	13785

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EDITORIAL

Tuberculosis in prisons: anatomy of global neglect

J. O'Grady*,#, M. Maeurer¶, R. Atun+,§, I. Abubakar^f, P. Mwaba#,**,##, M. Bates*,#, N. Kapata^f, G. Ferrara¶, M. Hoelscher¶¶ and A. Zumla*,#

- Población carcelaria en Europa mayor de 2 millones
- Más de 10,5 millones pasan por las cárceles cada año
- Europa: ratio 15:1 en TB prisiones/TB población normal
- Prisiones son reservorio de TB resistente (Europa, África subs)
- EASAC: Europa está fallando en la respuesta adecuada a TB-MR y TB-XDR en los países del este → peligro para resto de Europa

Eur Respir J 2012; 39: 1290–1291
DOI: 10.1183/09031936.00214411

EDITORIAL

Multidrug-resistant tuberculosis in Eastern Europe: still on the increase?

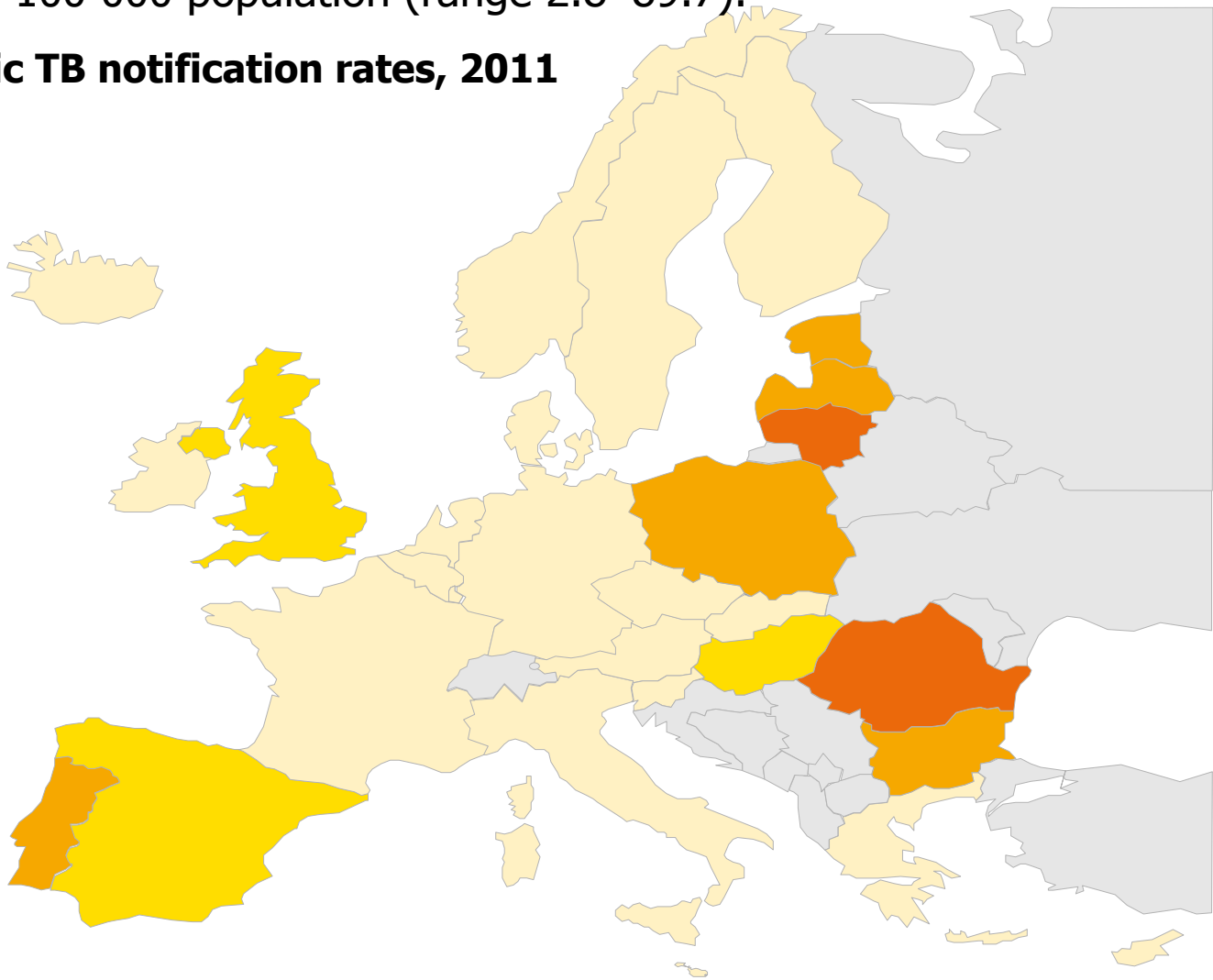
Giovanni Battista Migliori*, Masoud Dara#, Pierpaolo de Colombani#, Hans Kluge# and Mario C. Raviglione¶

- WHO prioriza MDR-TB desarrollando un plan de prevención y control
- Bielorrusia (Minsk):
  - 50% de casos dignosticados son cepas MDR
  - Transmisión reciente y acelerada
  - Causas: lentitud diagnóstica, ausencia seguimiento ambulatorio, hospitalización prolongada (diseminación nosocomial)
  - Actuación urgente y necesaria, con programas de control
  - Adecuada financiación

TB notification rates in EU/EEA, 2011

In the EU/EEA, 72 334 TB cases were reported in 2011.
Notification rate 14.2 per 100 000 population (range 2.8–89.7).

Figure 1: Country-specific TB notification rates, 2011



< 10 per 100 000

10 to 19 per 100 000

20 to 49 per 100 000

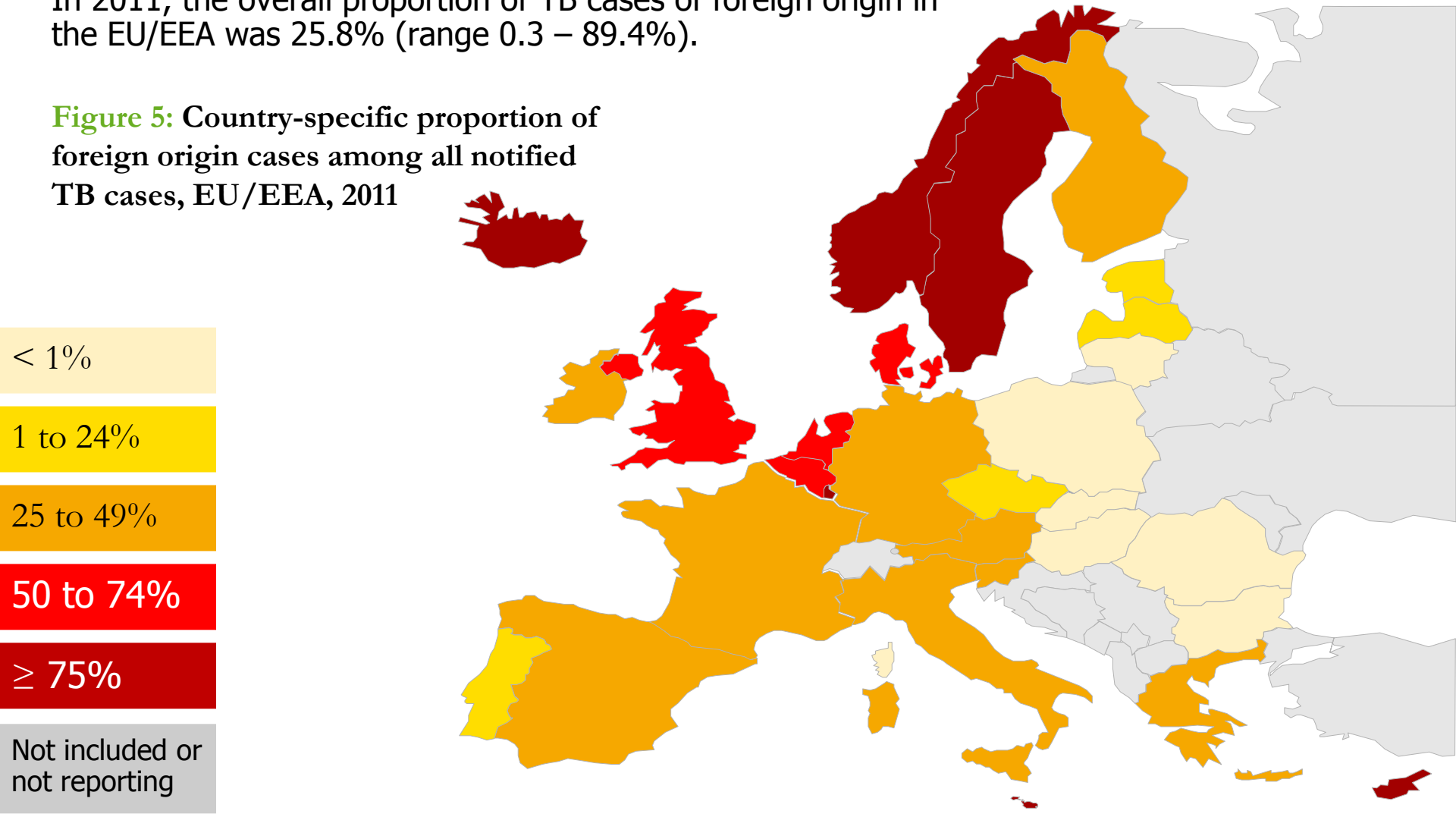
50 to 99 per 100 000

Not included or not reporting

Proportion of foreign origin among notified TB cases in EU/EEA, 2011

In 2011, the overall proportion of TB cases of foreign origin in the EU/EEA was 25.8% (range 0.3 – 89.4%).

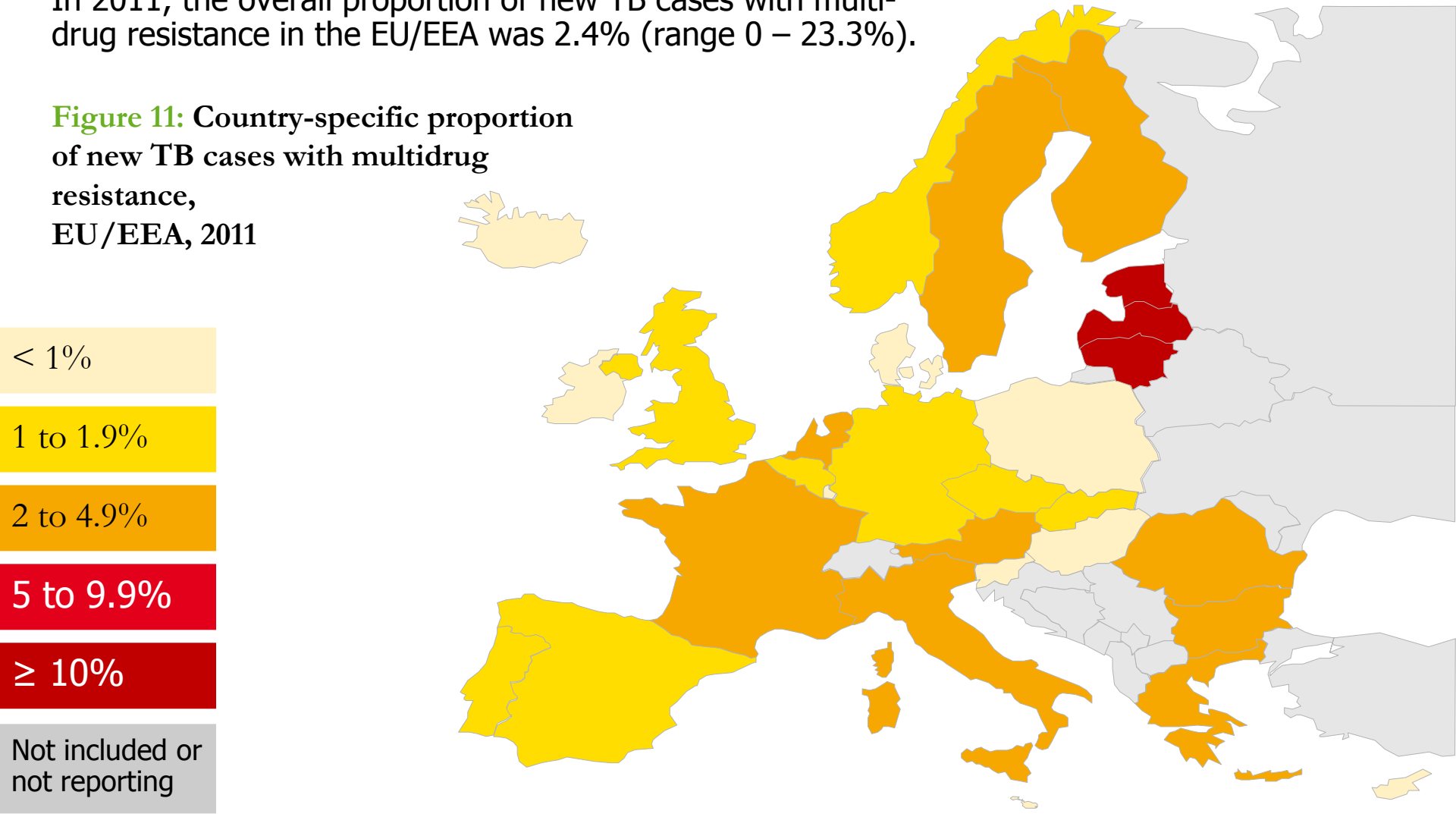
Figure 5: Country-specific proportion of foreign origin cases among all notified TB cases, EU/EEA, 2011



Proportion of notified new TB cases with multidrug resistance in EU/EEA, 2011

In 2011, the overall proportion of new TB cases with multi-drug resistance in the EU/EEA was 2.4% (range 0 – 23.3%).

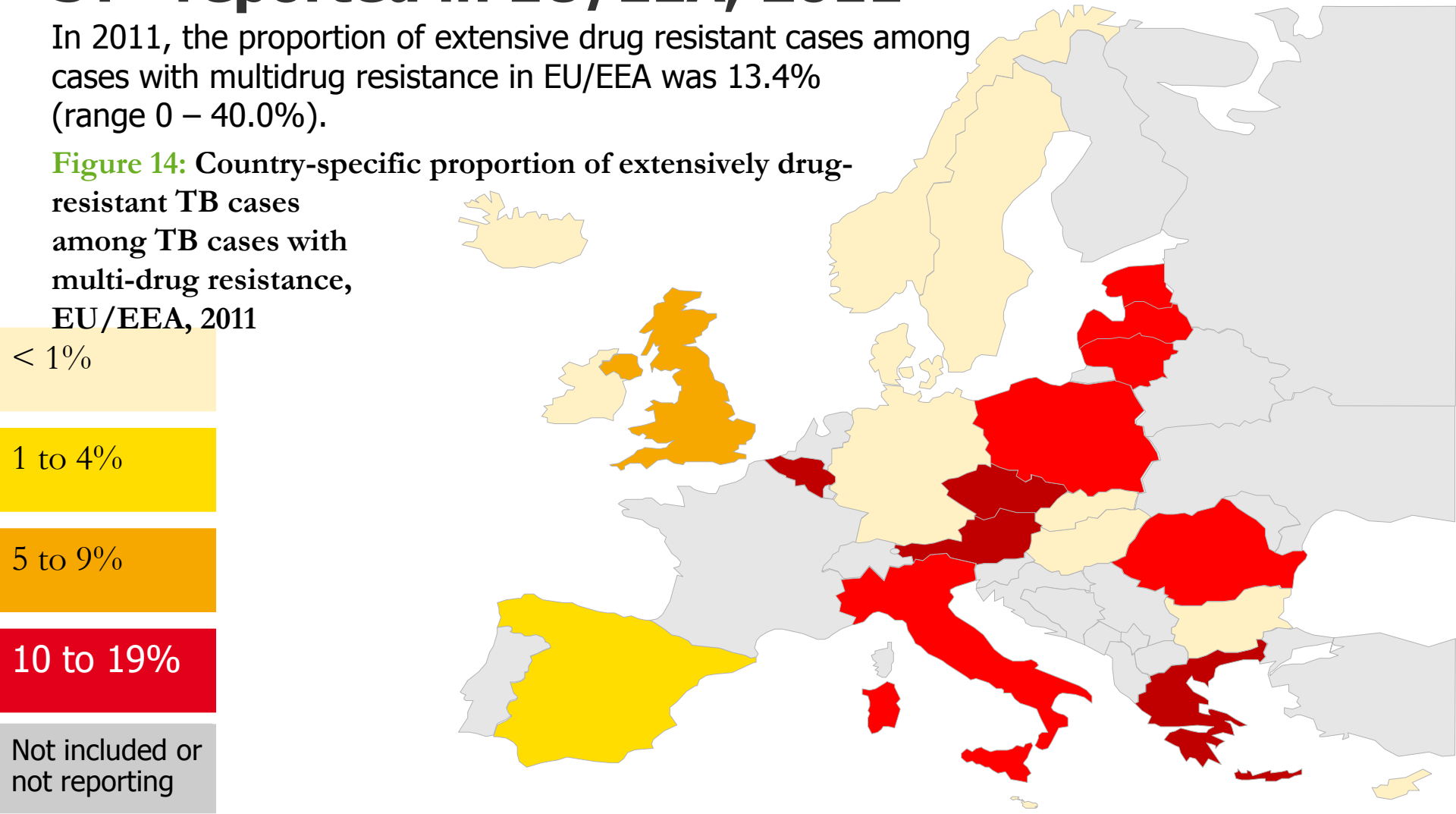
Figure 11: Country-specific proportion of new TB cases with multidrug resistance, EU/EEA, 2011



Proportion of TB cases with extensive drug resistance among MDR-TB cases with SLD ST* reported in EU/EEA, 2011

In 2011, the proportion of extensive drug resistant cases among cases with multidrug resistance in EU/EEA was 13.4% (range 0 – 40.0%).

Figure 14: Country-specific proportion of extensively drug-resistant TB cases among TB cases with multi-drug resistance, EU/EEA, 2011

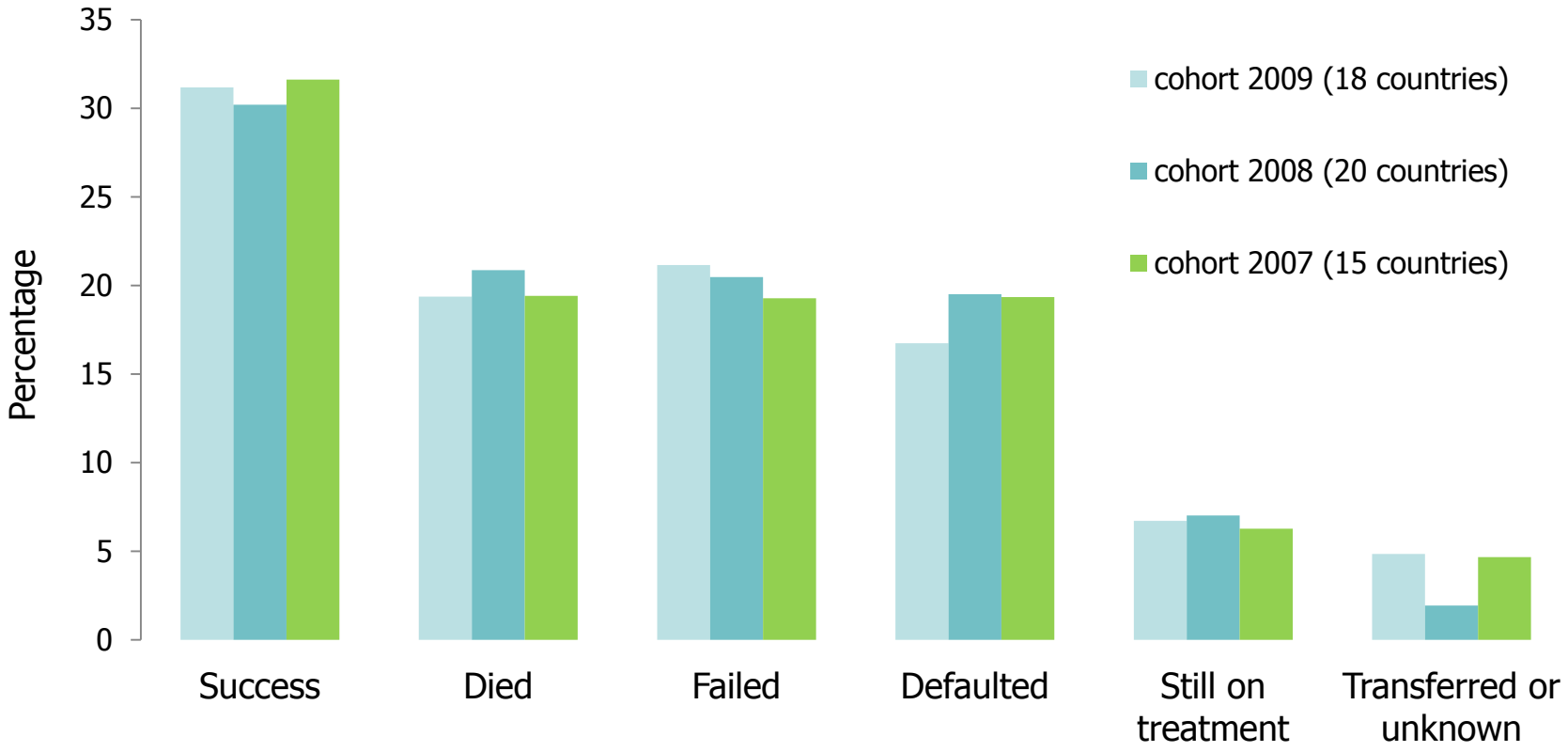


*SLD ST – second line drug susceptibility testing result

Treatment outcome for multidrug-resistant TB cases notified in 2007–2009

Treatment outcomes for multidrug-resistant TB cases did not improve between the 2007 and 2009 cohort, EU/EEA.

Figure 22: Treatment outcome at 24 months for multidrug-resistant TB cases diagnosed in 2009, compared with cases diagnosed in 2007 and 2008



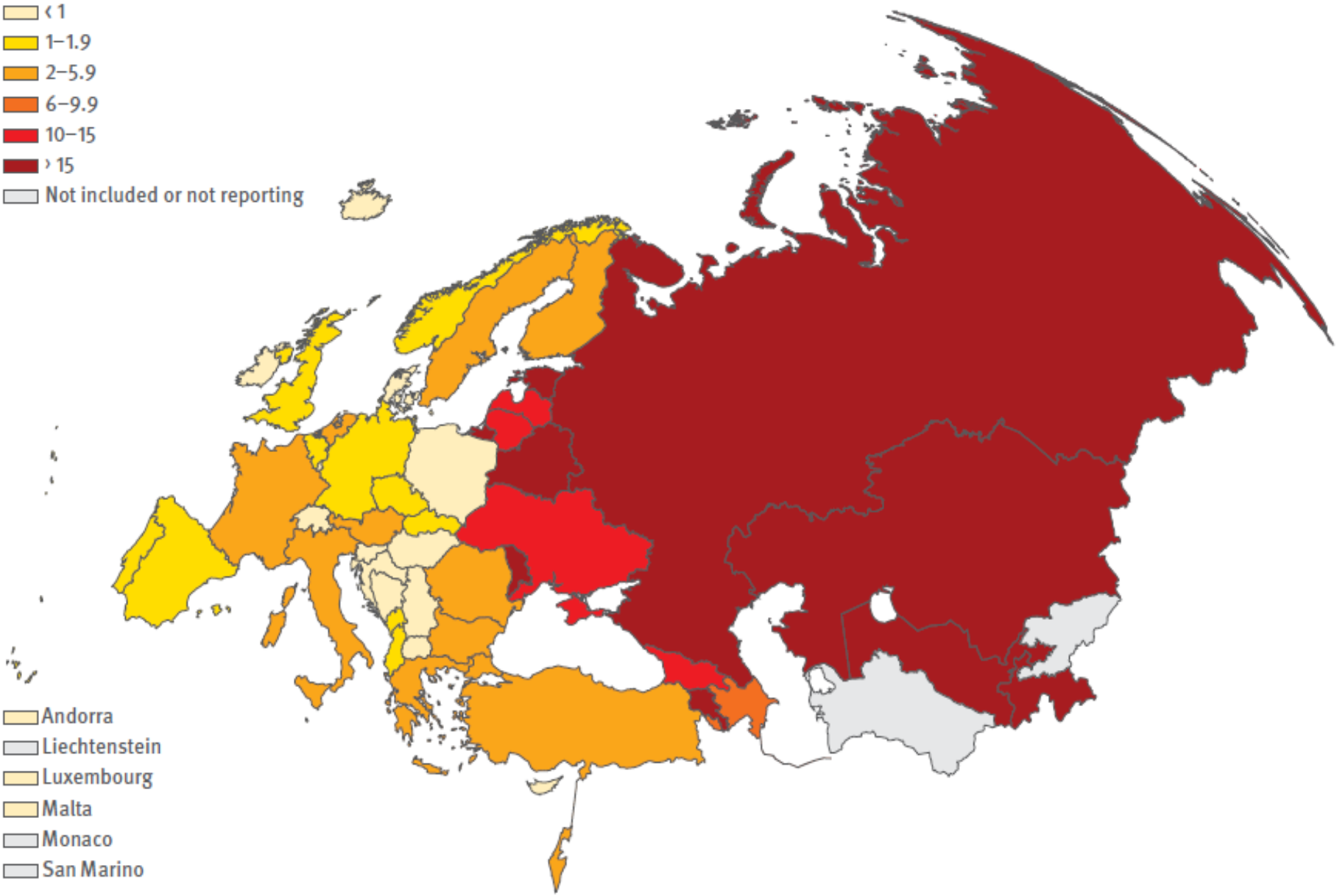
THE WHO EUROPEAN REGION

- 53 países
- 380.000 casos (incidencia 42/10^5 habitantes) (descenso anual del 5% desde 2000) (41% en grupo etario 25-44 años)
- 44.000 muertes (4,9/10^5 habitantes)
- 6% son VIH
- MDR-TB: 78.000 casos
  - 15,1% MDR-TB primaria
  - 44% MDR-TB secundaria
- XDR-TB: 381 casos (11% de MDR-TB)
- 18 países con alta prioridad:
  - Armenia, Azerbaijan, Bielorrusia, Bulgaria, Estonia, Georgia, Kazajistan, Kyrgyzstan, Letonia, Lituania, Moldovia, Rumania, Rusia, Tajikistan, Turquía, Turkmenistan, Ucrania y Uzbekistan

UNIÓN EUROPEA Y ÁREA ECONÓMICA EUROPEA

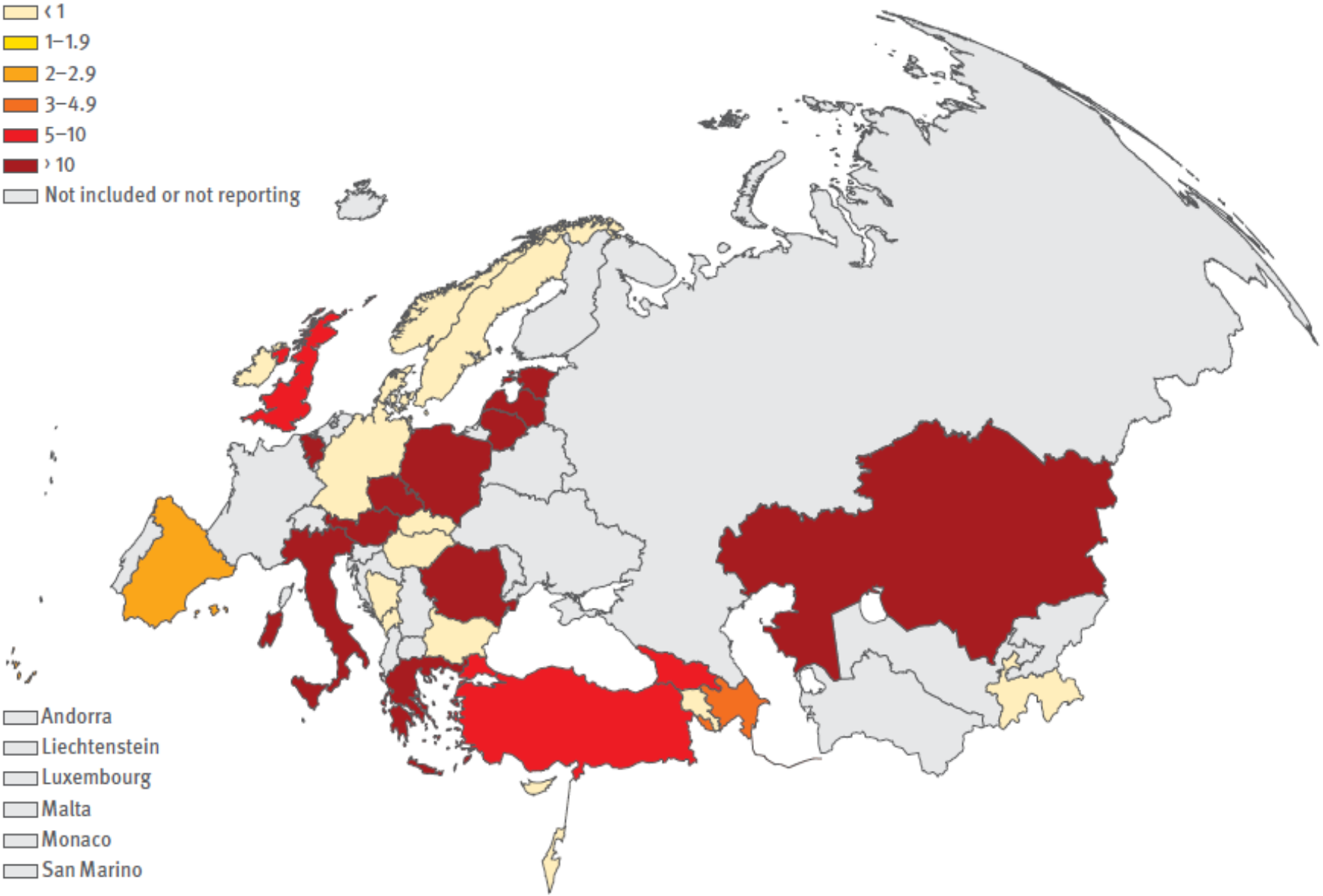
- 29 países
- 72.334 casos (incidencia 14,2/10^5 habitantes) (descenso del 4% sobre 2010) (sin predominio en grupos de edad)
- 26% con origen extranjero
- 5% son VIH
- MDR-TB: 2% en no tratados y 17% en tratados previamente
- XDR-TB: 13% de MDR-TB
- Vigilancia estricta en grandes ciudades de países occidentales

Map 8: Percentage of notified TB cases with multidrug resistance among new laboratory-confirmed pulmonary TB cases, European Region, 2011[a]



[a] Data from UN Administrated Province of Kosovo (in accordance with Security Council Resolution 1244 (1999)) is not included in the figures reported for Serbia

Map 11: Percentage of notified TB cases with extensive drug resistance among MDR-TB cases with second-line DST results, European Region, 2011[a]



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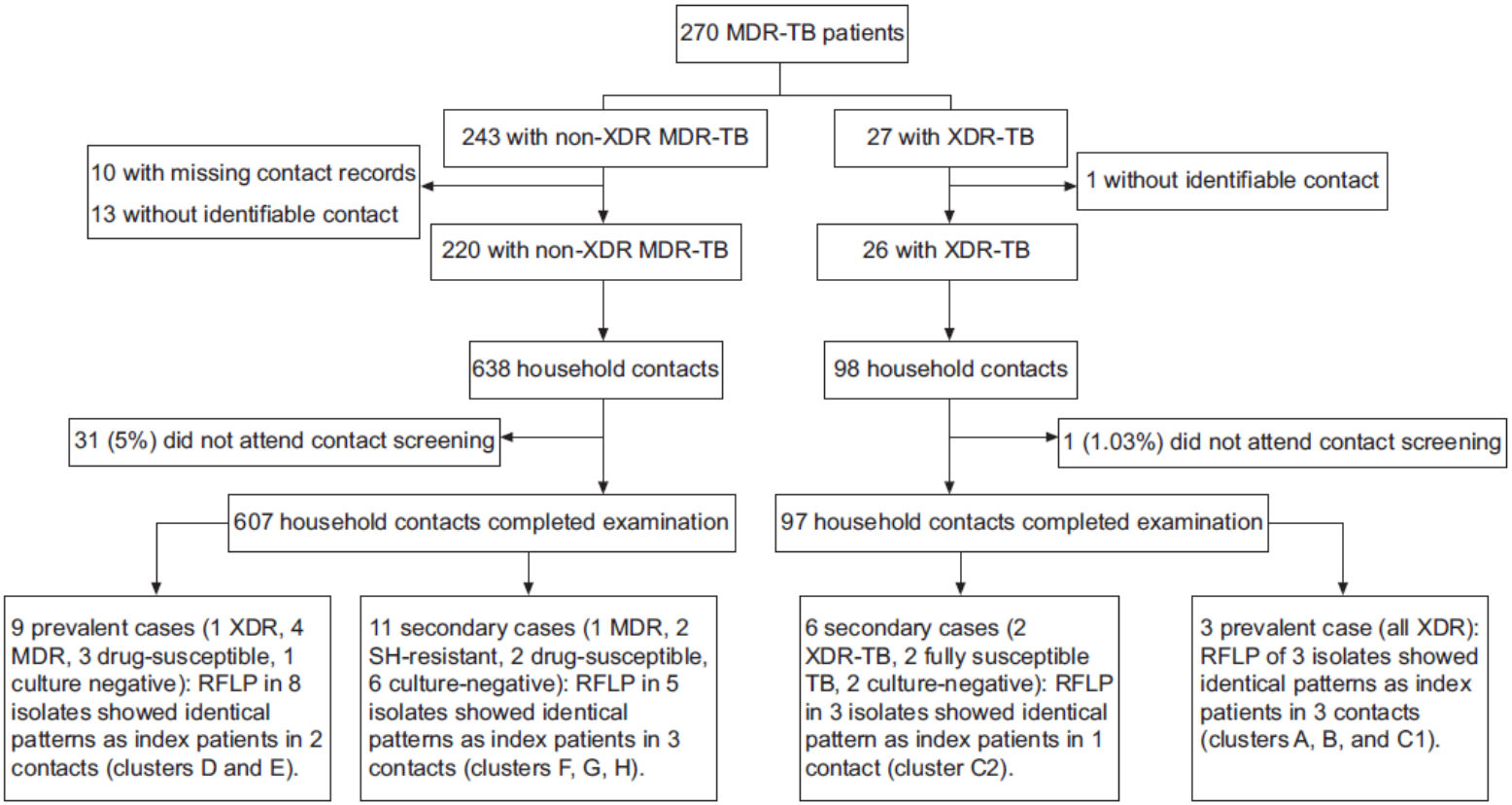
Transmission of multidrug-resistant and extensively drug-resistant tuberculosis in a metropolitan city

Eric Chung Ching Leung*, Chi Chiu Leung*, Kai Man Kam#, Wing Wai Yew¶, Kwok Chiu Chang*, Wai Man Leung* and Cheuk Ming Tam*



Comparado con 20-40 años atrás, el volumen de migraciones se ha multiplicado por 4

Spain

Total population at 1 January 2011 by EUROSTAT: 46 152 926

Tuberculosis case notifications, 2011

Total number of cases	6762	
Notification rate per 100 000	14.7	
New & relapses (lab+) number	6044	
New & relapses (lab+) notification rate per 100 000	13.1	
Pulmonary	4979	(73.6%)
of which smear-positive	2471	(49.6%)
Laboratory-confirmed pulmonary TB cases	3584	(72.0%)
Mean age of new TB cases, nationals	46.9 years	
Mean age of new TB cases, non-nationals	32.9 years	
Foreign origin of all TB cases	2138	(31.6%)
New (not previously treated)	6044	(89.4%)

Drug resistance surveillance & TB-HIV co-infection, 2011

Completeness of DRS data*	No	
Completeness of HIV data**	Yes	
Case-linked data reporting	No	
Cases with DST results	1273	(29.0%)
Cases resistant to isoniazid	108	(8.5%)
Cases resistant to rifampicin	45	(3.5%)
Estimated MDR N, (best-low-high)	36-15-58	
MDR cases	41	(3.2%)
of which XDR cases	1	(2.4%)
Cases resistant to ethambutol	-	-
Cases resistant to streptomycin	-	-
TB cases tested for HIV	4541	(67.2%)
HIV-positive TB cases	415	(9.1%)

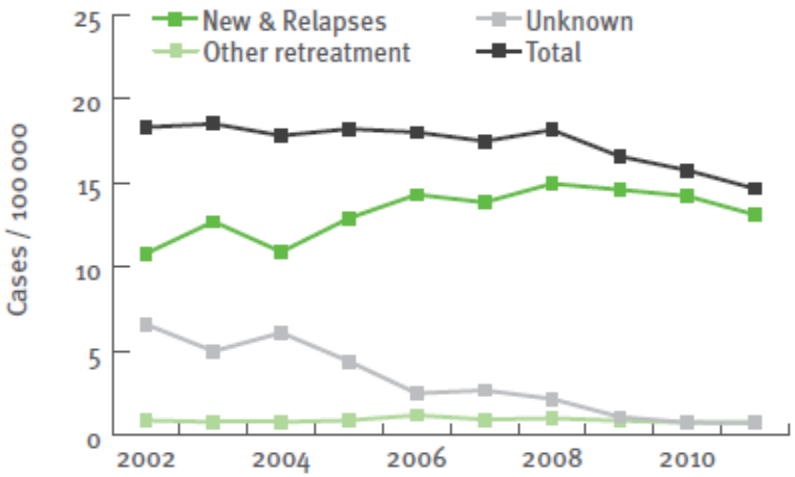
* National coverage 100% or culturing 90%, C+/All TB cases 50%, DST done for C+ 75%, EQA 95%

** More than 50% of TB cases tested for HIV.

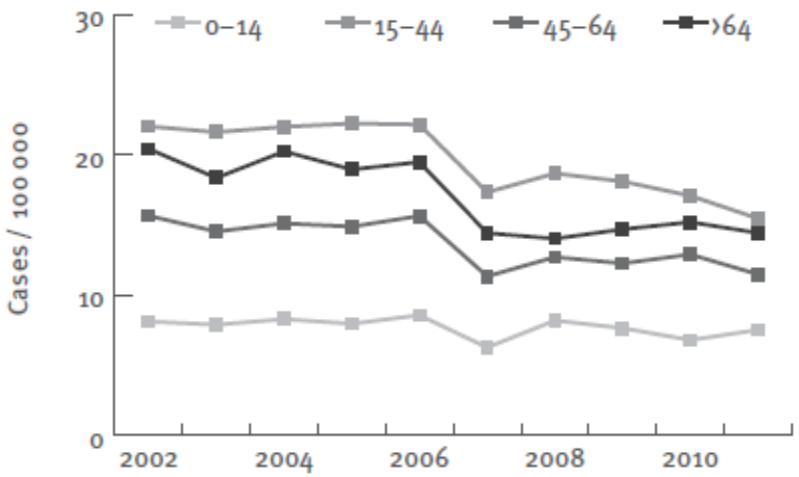
Treatment outcome monitoring, 2010

Geographical coverage	National	
Outcome cohort	New pulmonary culture positive	
Case-linked data reporting	Yes	
Notified in 2010	3574	
Success	2516	(70.4%)
Died	211	(5.9%)
Failed	5	(0.1%)
Defaulted	27	(0.8%)
Still on treatment	31	(0.9%)
Lost to follow up	784	(21.9%)

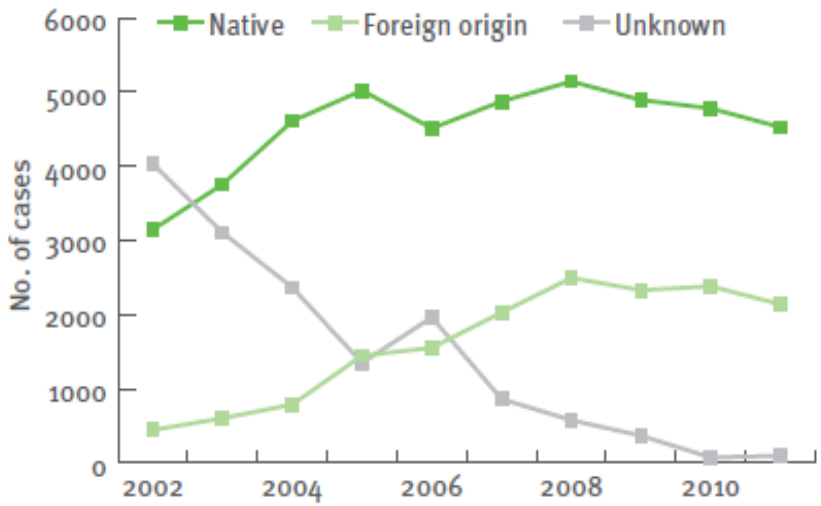
Tuberculosis notification rates by treatment history, 2002–2011



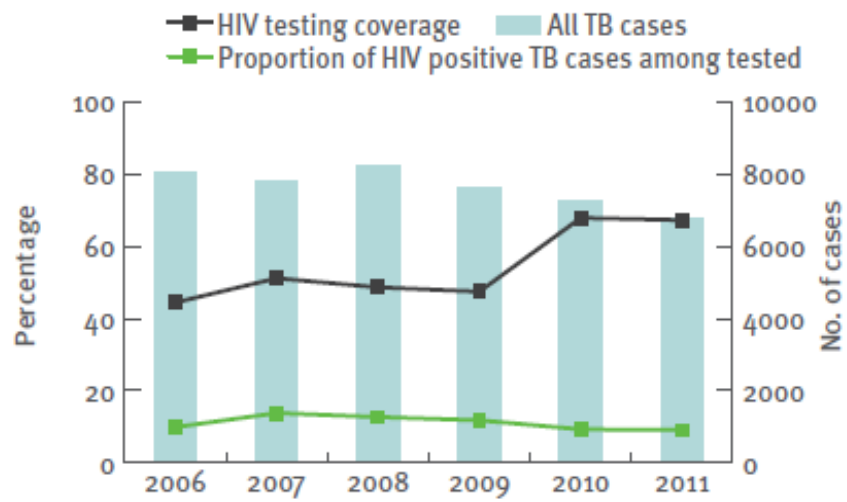
New TB cases - notification rates by age group, 2002–2011



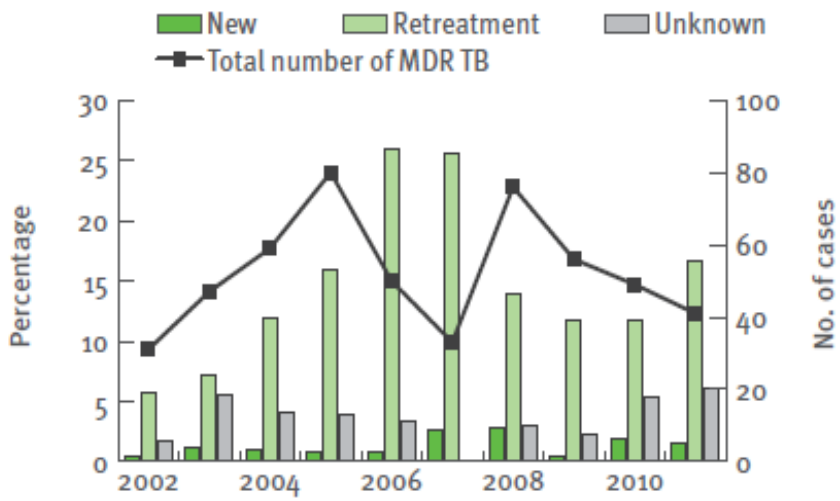
Tuberculosis cases by geographical origin, 2002–2011



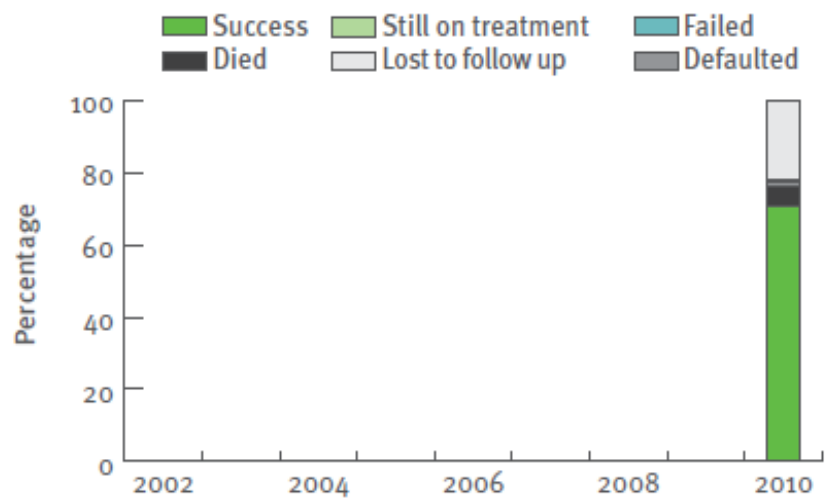
TB-HIV co-infection, 2006–2011



MDR-TB cases by previous treatment history, 2002–2011

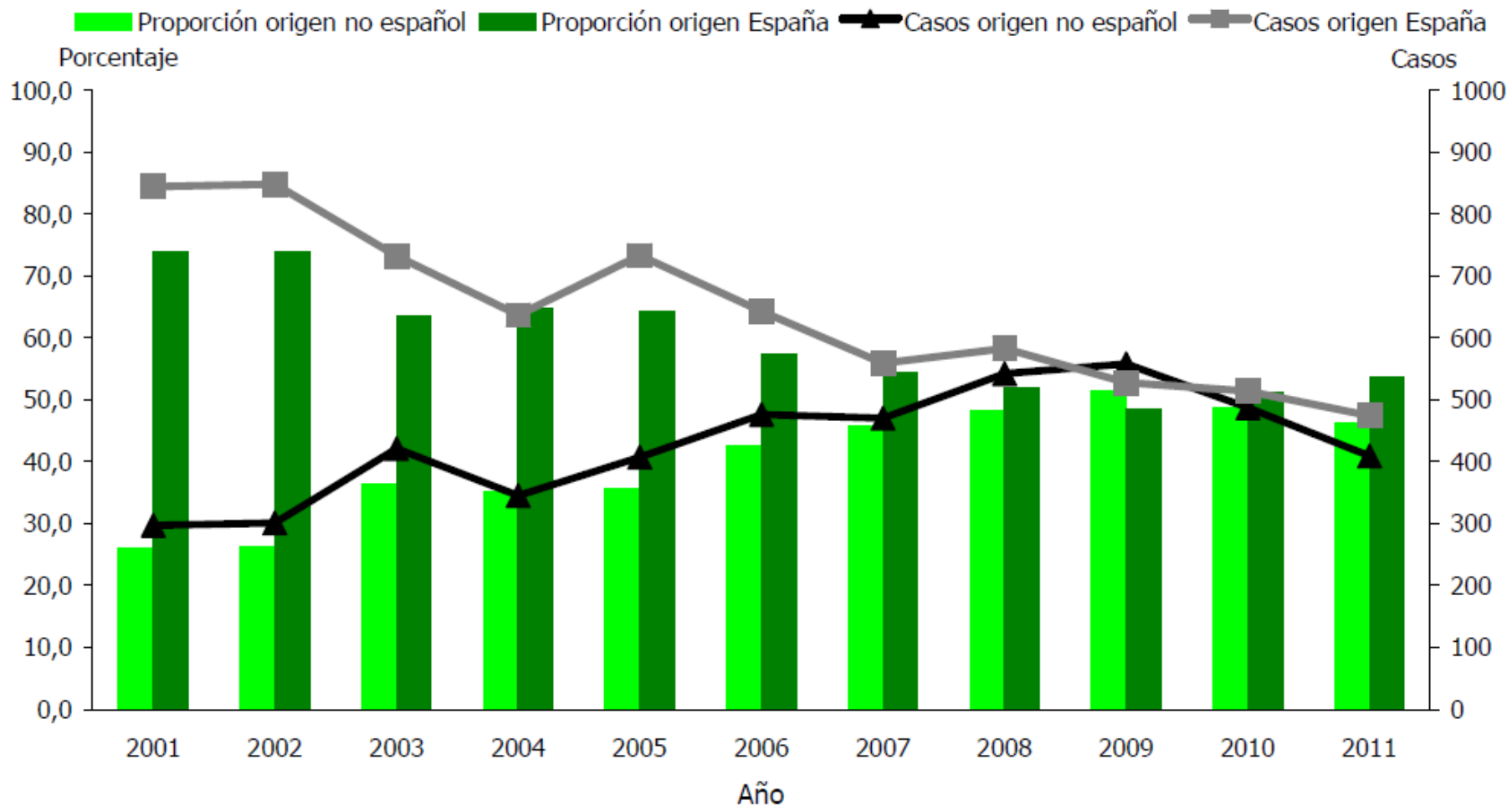


Treatment outcome, new pulmonary culture-positive cases, 2002–2010



REGISTRO REGIONAL DE CASOS DE TUBERCULOSIS EN LA COMUNIDAD DE MADRID (2011)

Evolución de la proporción y el número de casos de tuberculosis según el país de procedencia. Registro Regional de Casos de Tuberculosis de la Comunidad de Madrid. Período 2001-2011.



REGISTRO REGIONAL DE CASOS DE TUBERCULOSIS EN LA COMUNIDAD DE MADRID (2011)

Casos de tuberculosis resistentes a fármacos. Registro Regional de Casos de Tuberculosis de la Comunidad de Madrid, 2011.

	CASOS CON RESULTADO CULTIVO POSITIVO	CASOS CON RESULTADO CONOCIDO DEL ANTIBIOGRAMA	CASOS Y PORCENTAJE DE RESISTENCIAS A UNO O MÁS FÁRMACOS	CASOS Y PORCENTAJE DE RESISTENCIAS AL MENOS A ISONIACIDA Y RIFAMPICINA
Todos los casos (n=883)	654	603	82 (13,6%)	15 (2,5%)
VIH (+) (n=70)	57	51	4 (7,8%)	1 (2,0%)
Extranjeros (n=409)	316	294	49 (16,7%)	11 (3,7%)
Recaídas/abandonos/fracasos (n=24)	20	18	9 (50,0%)	3 (16,7%)

RESISTENCIA PRIMARIA A INH: 7,4% (8% INMIGRANTES; 6,9% AUTÓCTONOS)

ESTRATEGIAS BÁSICAS CONTROL TB

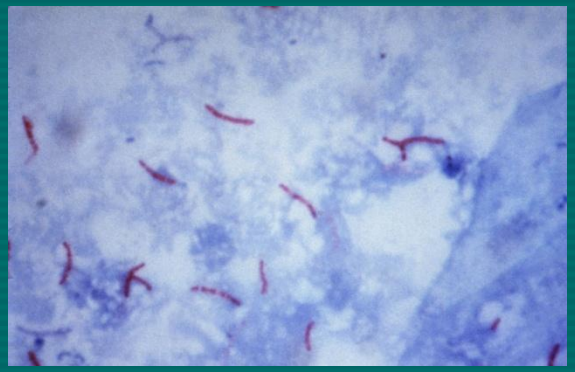
1. Detección y tratamiento precoz de enfermos

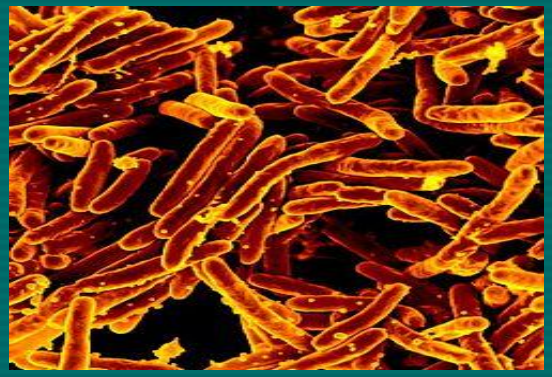
2. Identificación, protección y evaluación de los contactos de las formas contagiosas de TB

3. Prevención de la TB en la población con infección tuberculosa

4. Reducción de la carga creciente de TB, identificando y actuando en ambientes de alto riesgo de transmisión

ATS/CDC. Am J Respir Crit Care Med 2005; 172: 1169-1227





BACTEC
MGIT 960
BECTON DICKINSON

MÉTODOS MOLECULARES EN EL DIAGNÓSTICO DIRECTO

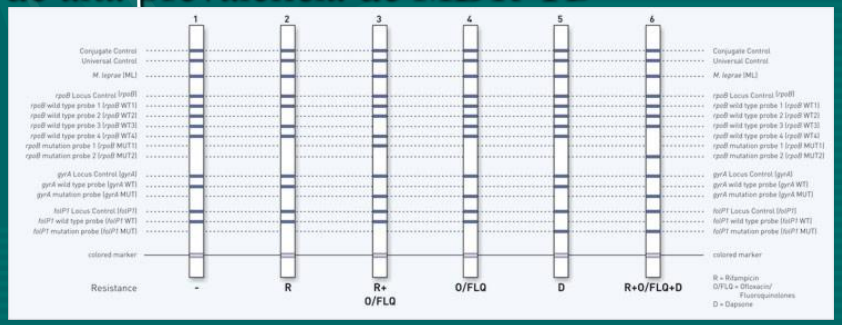
- Basados en amplificación de fragmentos genéticos específicos del bacilo directamente en muestras clínicas (dianas: IS6110, 165 rRNA…)
- La mayoría utilizan la técnica de reacción en cadena de la polimerasa (PCR); existen aplicaciones comercializadas y métodos caseros
- Pueden ser útiles en diagnóstico rápido (pocas horas) de TB en pacientes con datos sugerentes y baciloscopias negativas
- Mejor sensibilidad que la baciloscopia, aunque menor que el cultivo; dependerá de la carga bacteriana
- Problema: requieren mayor estandarización y sistematización de factores técnicos (dianas genéticas, extracción del ADN, técnicas de amplificación elegida…) y clínicos (grado de sospecha)
- Coadyuvantes en el diagnóstico de TB junto a otros datos clínicos y exploratorios
- Especificidad del 80% con grado de sospecha de TB moderado o alto; sospecha baja, especificidad máxima del 50%

GENEXPERT

- Prueba de PCR en tiempo real que permite detectar cepas del complejo M. tuberculosis y cepas resistentes a R (detecta mutación rpoB)
- Permite un análisis semicuantitativo in vitro de muestras de esputo y concentrado de LBA, con resultados en 90 minutos
- 99% de sensibilidad en baciloscopias positivas y 71% en baciloscopias negativas

GENOTYPE

- Técnica molecular que permite identificar en pocas horas MDR-TB, así como otras resistencias a fármacos de 1ª y 2ª línea
- Puede usar muestras clínicas o cultivos
- Fundamental en áreas de alta prevalencia de MDR-TB



TRATAMIENTO TB PULMONAR

- CASO INICIAL: PAUTA DIARIA
  - Resistencias primarias a H < 4%
    - 6 meses: 2 RHZ/ 4 RH
  - Resistencias primarias a H > 4%
    - 6 meses: 2 RHZE(S)/ 4 RH
  - VIH y SIDA : 6-9 meses: 2 RHZE(S)/ 4-7 RH

- INTOLERANCIA O RESISTENCIA
  - H: 2 REZ/ 7 RE ó 2 REZQ/ 7 REQ
  - R: 2 HEZ/ 16 HE (intolerancia) ó como MDR-TB (resistencia)
  - Z: 2 RHE/ 7 RH

TRATAMIENTO TB PULMONAR

- Niños: mismo esquema con ajuste de dosis; evitar etambutol
- Embarazo/lactancia: mismo esquema; evitar aminoglucósidos
- IRC: terapia estándar haciendo niveles de fármacos; si aclaramiento creatinina <30 ml/min o hemodiálisis, 3 dosis semanales despues de diálisis (excepto R y H)
- Hepatopatía crónica: régimen estándar con vigilancia estricta; si toxicidad moderada, intentar conservar R; ante daño severo, usar quinolona + aminoglucósido + etambutol o cicloserina

Fármaco	Dosis diaria	Ef. secundarios	Control	Acción
Isoniacida	5 mg/kg (máx 450)	Neuritis, hepatitis	Perfil hepático	Bactericida extra e intracel
Rifampicina	10 mg/kg (máx 600)	Hepatitis, fiebre, púrpura	Perfil hepático	Bactericida, esterilizante
Pirazinamida	25-30 mg/kg (máx 2500)	Hiperuricemia, hepatitis	Perfil hepático, ácido úrico	Bactericida intra, esteriliza
Etambutol	15-25 mg/kg (máx 2000)	Neuritis óptica	Agudeza visual	Bacteriostático extra e intracel
Estreptomicina	15 mg/kg (máx 1000)	Insuf. renal, sordera	Creatinina, audiograma	Bactericida extracelular

RETRATAMIENTO

- Instauración de una pauta terapeútica en un paciente ya tratado durante más de un mes; se plantea ante:
  - RECIDIVA:
    - reaparición de enfermedad clínica y de más de un cultivo positivo en paciente curado
    - 0-3% de pacientes curados
    - aunque, en teoría, se debe a bacilos latentes, las tasas de MDR-TB se incrementan 4-8 veces con respecto a enfermos iniciales, lo que indica que algunas recidivas son fracasos enmascarados, sobre todo las muy tempranas. Realizar siempre antibiograma
    - si la pauta era correcta y se realizó bien, se reinstaura pero durante 9-12 meses
    - si la quimioterapia fue incorrecta o mal cumplimentada, evaluar nueva pauta
  - FRACASO TERAPEÚTICO:
    - persistencia de dos cultivos positivos en el cuarto mes de tratamiento o reaparición de cultivos positivos tras negativización temporal
    - suele indicar resistencia a los fármacos empleados y exige una nueva pauta
    - hay algunas causas (negativización tardía por lesiones extensas, bacilos muertos, etc) que pueden justificar que un fracaso sea sensible. Realizar siempre antibiograma
  - ABANDONO:
    - el paciente deja de tomar la medicación durante más de 30 días
    - total (similar a recidiva) o parcial (se comporta como un fracaso). Realizar siempre antibiograma
- El retratamiento requiere pauta no estándar (PNE), basada en la historia de fármacos y un antibiograma ampliado; necesita 3-4 fármacos eficaces como mínimo y no hay posibilidad de pautas cortas; supervisión estricta

CAUSAS DE LA MDR-TB

- Tratamientos no estandarizados
- Mala adherencia de los pacientes al tratamiento

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SERIES "RATIONAL USE OF ANTI-TUBERCULOSIS DRUGS"
Edited by G.B. Migliori and D. Manissero
Number 3 in this Series

Multidrug resistance after inappropriate tuberculosis treatment: a meta-analysis

Marieke J. van der Werf*,#, Miranda W. Langendam¶, Emma Huitric+ and Davide Manissero+

ERJ Open

TUBERCULOSIS MULTIRRESISTENTE (MDR-TB)

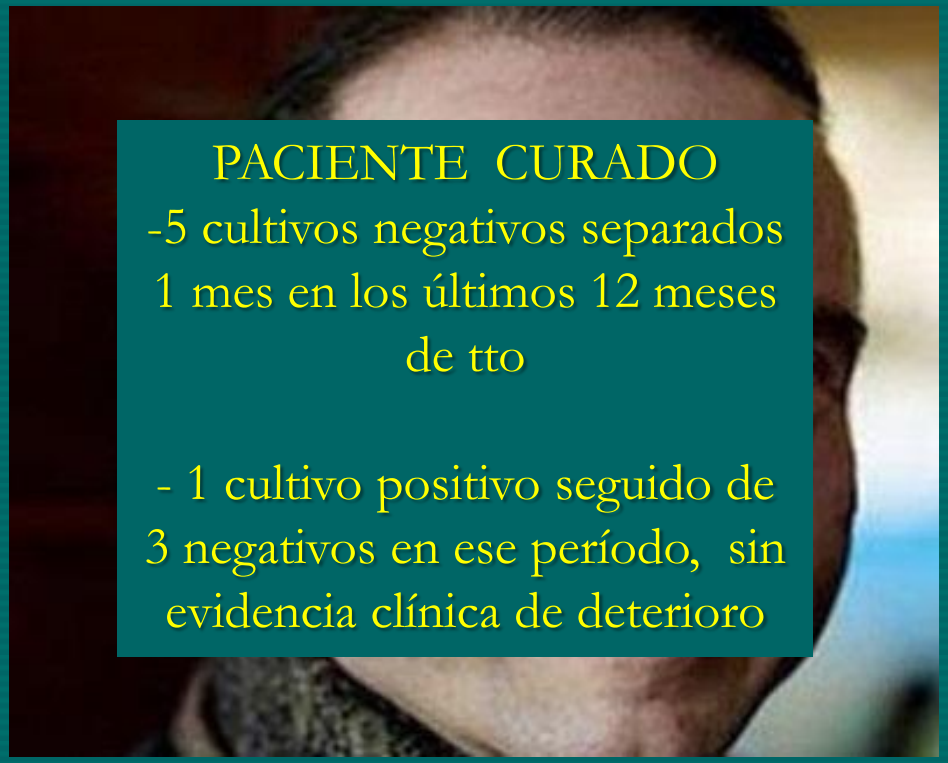
- TB resistente, al menos, a H y R
- Sospecha: Sobre todo en tratamientos previos y contactos con casos MDR-TB. También en colectivos de riesgo, mala respuesta terapeútica, viajes a países de alta prevalencia
- Anamnesis detallada; el diagnóstico y el antibiograma son fundamentales, con los medios de cultivo automatizados y las técnicas moleculares rápidas de detección de resistencias
- Recomendaciones en la pauta de tratamiento:
  - Individualizada
  - Integrada por 4 fármacos eficaces como mínimo, añadiendo además Z
  - Siempre una quinolona de nueva generación (moxifloxacino, levofloxacino), que son los mejores fármacos para tratar la MDR-TB
  - Un fármaco parenteral debe ser usado en la fase intensiva (6-8 meses) (no usar estreptomicina)
  - Se recomienda usar etionamida o protionamida
  - Se prolongará hasta cumplir 12-18 meses de cultivos negativos

MANEJO FARMACOLÓGICO DE MDR-TB Y XDR-TB

Grupos de fármacos	Fármacos	Número máximo a usar en MDR-TB o XDR-TB
Orales (1ª línea)	H,R,Z,E	2
Inyectables (bactericidas)	Capreomicina, Kanamicina, Amikacina	1
Quinolonas	Moxifloxacino, Levofloxacino	1
2ª línea (bacteriostáticos)	Protionamida/Etionamida, Cicloserina/Terizidona, PAS	3
Otros con dudosa eficacia o con toxicidad elevada	Linezolid, Amoxicilina-clavulánico, Clofazimina, Meropenem, H (altas dosis)	6

TUBERCULOSIS EXTREMADAMENTE RESISTENTE (XDR-TB)

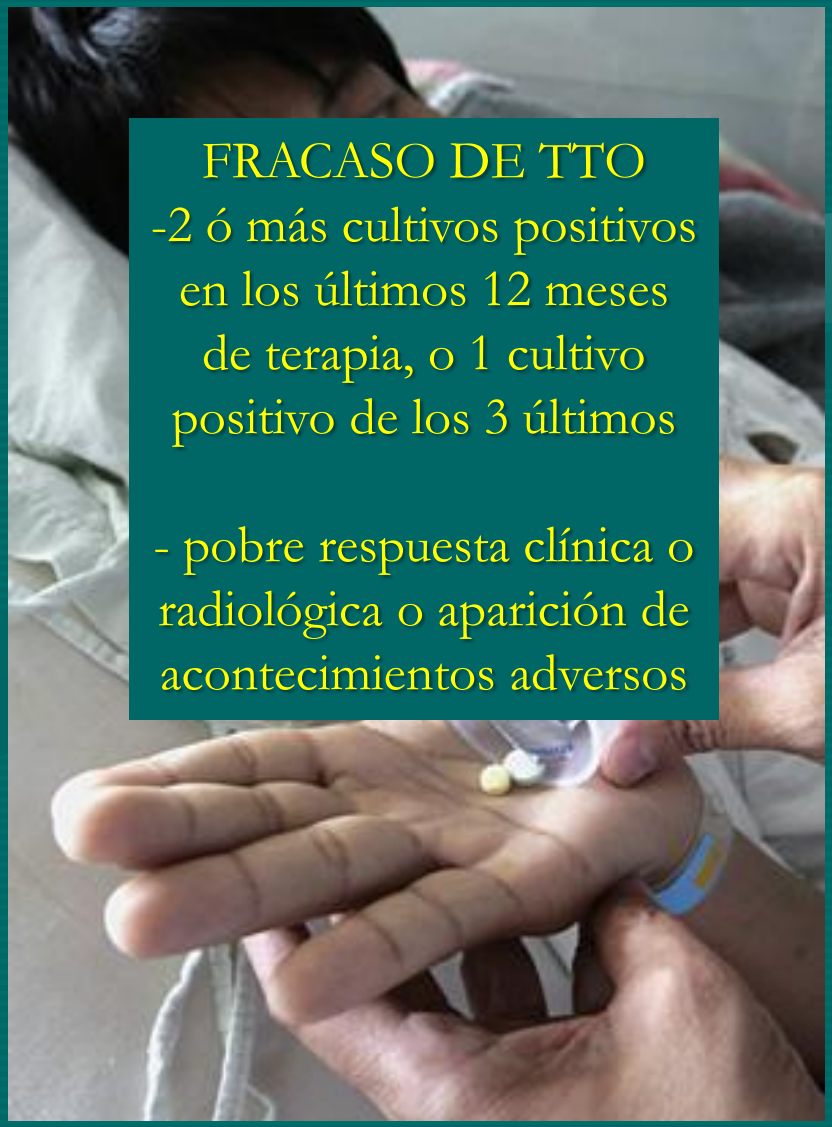
- Forma especial de MDR-TB que también es resistente a todas las quinolonas, y al menos a uno de los fármacos inyectables de 2ª línea (capreo, kana o amikacina)
- Pronóstico más sombrío, aunque puede curarse entre el 30 y el 50% de pacientes; dependerá del nivel de resistencia a drogas, de la gravedad del proceso y del sistema inmunitario del enfermo
- Según el último informe de la OMS, se ha descrito en 84 países y supone una media del 9% de todas las MDR-TB
- Su tratamiento se basará en las recomendaciones para la MDR-TB, teniendo en cuenta sus peculiaridades y los fármacos que no pueden usarse



PACIENTE CURADO

-5 cultivos negativos separados 1 mes en los últimos 12 meses de tto

- 1 cultivo positivo seguido de 3 negativos en ese período, sin evidencia clínica de deterioro



FRACASO DE TTO

-2 ó más cultivos positivos en los últimos 12 meses de terapia, o 1 cultivo positivo de los 3 últimos

- pobre respuesta clínica o radiológica o aparición de acontecimientos adversos

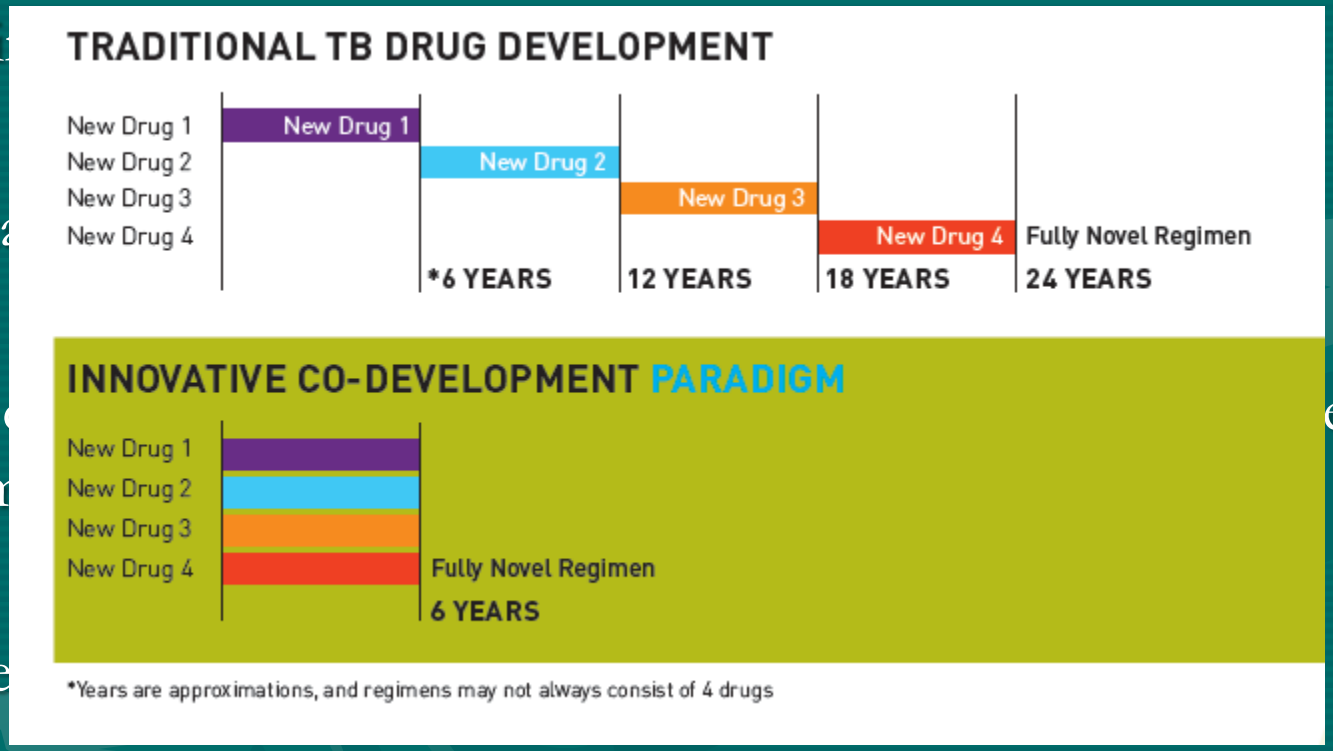
NECESIDAD DE NUEVOS FÁRMACOS

- Régi

- Trata

- 1/3 entre rifam

- Eme



- Con la relación entre TB y marginación-pobreza, una terapia más potente y más corta ayudaría rápidamente a conseguir objetivos

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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

ABSTRACT: **Linezolid is used off-label to treat multidrug-resistant tuberculosis (MDR-TB) in absence of systematic evidence. We performed a systematic review and meta-analysis on efficacy, safety and tolerability of linezolid-containing regimes based on individual data analysis.**

12 studies (11 countries from three continents) reporting complete information on safety, tolerability, efficacy of linezolid-containing regimes in treating MDR-TB cases were identified based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Meta-analysis was performed using the individual data of 121 patients with a definite treatment outcome (cure, completion, death or failure).

Most MDR-TB cases achieved sputum smear (86 (92.5%) out of 93) and culture (100 (93.5%) out of 107) conversion after treatment with individualised regimens containing linezolid (median (inter-quartile range) times for smear and culture conversions were 43.5 (21–90) and 61 (29–119) days, respectively) and 99 (81.8%) out of 121 patients were successfully treated. No significant differences were detected in the subgroup efficacy analysis (daily linezolid dosage $\leqslant$600 mg *versus* >600 mg). Adverse events were observed in 63 (58.9%) out of 107 patients, of which 54 (68.4%) out of 79 were major adverse events that included anaemia (38.1%), peripheral neuropathy (47.1%), gastro-intestinal disorders (16.7%), optic neuritis (13.2%) and thrombocytopenia (11.8%). The proportion of adverse events was significantly higher when the linezolid daily dosage exceeded 600 mg.

The study results suggest an excellent efficacy but also the necessity of caution in the prescription of linezolid.

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Table 2. Status of Selected Trials of Tuberculosis Treatments.*

Trial or Investigational Drug	Description	Comments
Treatment of drug-sensitive active disease		
REMox	Standard 6-mo regimen vs. two 4-mo regimens including moxifloxacin	Results in 2014 have potential to shorten standard therapy to 4 mo
OFLOTUB III	Standard 6-mo regimen vs. 4-mo regimen including gatifloxacin	Results by mid-2013 have potential to shorten standard therapy to 4 mo
RIFAQUIN	Two experimental groups in which moxifloxacin is substituted for ethambutol for 2 mo, followed by moxifloxacin plus rifapentine twice weekly for 2 mo or moxifloxacin plus rifapentine weekly for 4 mo	Results expected by mid-2013
Multiple trials	Increased doses of rifampin and rifapentine	Higher doses of rifamycins may permit shorter regimens with standard drugs
Treatment of drug-resistant active disease		
Bedaquiline (TMC207)	Background therapy for multidrug-resistant disease plus bedaquiline	Mycobacterial ATP synthase inhibitor shown to improve sputum conversion at 8 wk; also to be studied in new regimens for drug-sensitive tuberculosis
Delamanid (OPC-67683)	Background therapy for multidrug-resistant disease plus delamanid	A nitroimidazole with activity against replicating bacilli through inhibition of mycolic acid synthesis; active against nonreplicating bacilli through generation of reactive nitrogen intermediates; shown to improve sputum-culture conversion at 8 wk
PA-824	PA-824 combined with moxifloxacin and pyrazinamide is being studied in a phase 2b trial (8 wk) for treatment of drug-sensitive and drug-resistant disease	A nitroimidazole with the same mechanism of action as delamanid; when combined with moxifloxacin and pyrazinamide, has high bactericidal activity at 14 days, suggesting promise for treatment of sensitive and resistant disease
Linezolid	Background therapy plus linezolid added immediately or 2 mo later in patients with extensively drug-resistant disease	A marketed oxazolidinone that improved sputum-culture conversion at 4 mo in a group receiving immediate versus delayed linezolid; for both linezolid regimens, 89% of patients had sputum-culture conversion on solid medium by 6 mo; high rate of peripheral neuropathy, including some cases of optic neuropathy
Sutezolid	Dose-ranging phase 2a trial completed	Analogue of linezolid that may have improved activity
AZD 5847	Phase 2a trial under way	More highly modified oxazolidinone
SQ109	Phase 2a trial completed; phase 2b combination trials to begin early in 2013	An ethylenediamine-based compound that is structurally related to ethambutol but has an entirely different mechanism of action
Empirical treatment of active disease		
PROMPT	Empirical therapy provided within 2 wk after start of antiretroviral therapy in patients with CD4+ cell count of $<50/mm^3$ and body-mass index of <18.5	Designed to reduce mortality from undiagnosed tuberculosis in HIV-infected patients
REMEMBER	Empirical therapy provided within 7 days after start of antiretroviral therapy in patients with CD4+ cell count of $<50/mm^3$	Designed to reduce mortality from undiagnosed tuberculosis in HIV-infected patients
Prevention of active disease in patients with latent infection		
ACTG 5279	Daily rifapentine plus isoniazid for 4 wk vs. daily isoniazid for 9 mo	Designed to determine whether shorter treatment is effective in HIV-positive patients

TB ALLIANCE

GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT

March 2013

Discovery

LEAD IDENTIFICATION

- ATP Synthesis Inhibitors *Calibr*
- Energy Metabolism Inhibitors *AZ/University of Penn*
- Whole-Cell Hit-to-Lead Program *AZ*
- Whole-Cell Hit-to-Lead Program *Sanofi*
- Whole-Cell Hit-to-Lead Program *NITD*
- Whole-Cell Hit-to-Lead Program *GSK*
- RNA Polymerase Inhibitors *Rutgers University*

LEAD OPTIMIZATION

- Mycobacterial Gyrase Inhibitors *GSK*
- THPP Series *GSK*
- Spiro Series *GSK*
- Pyrazinamide Analogs *Yonsei University*
- Diarylquinolines *Janssen/University of Auckland/UIC*
- Riminophenazines *IMM/BTTTRI*
- DprE Inhibitors *Calibr*
- Cyclopeptides *Sanofi*
- Macrolides *Sanofi*
- Novel Structural Series *NITD*

Early Development

PRECLINICAL DEVELOPMENT

- TBA-354
- Preclinicall Regimen Development *JHU, UIC*

PHASE 1

PHASE 2A

NC-003

- Bedaquiline/ Clofazimine/ Pyrazinamide
- PA-824/ Bedaquiline/ Clofazimine/ Pyrazinamide
- PA-824/ Bedaquiline/ Clofazimine
- PA-824/ Bedaquiline/ Pyrazinamide

Late Development

PHASE 2B

NC-002

- PA-824/ Moxifloxacin/ Pyrazinamide (PaMZ)

PHASE 3

REMox-TB

- Moxifloxacin/ Isoniazid/ Rifampin/ Pyrazinamide *Bayer, MRC, UCL*
- Moxifloxacin/ Rifampin/ Isoniazid/ Ethambutol *Bayer, MRC, UCL*

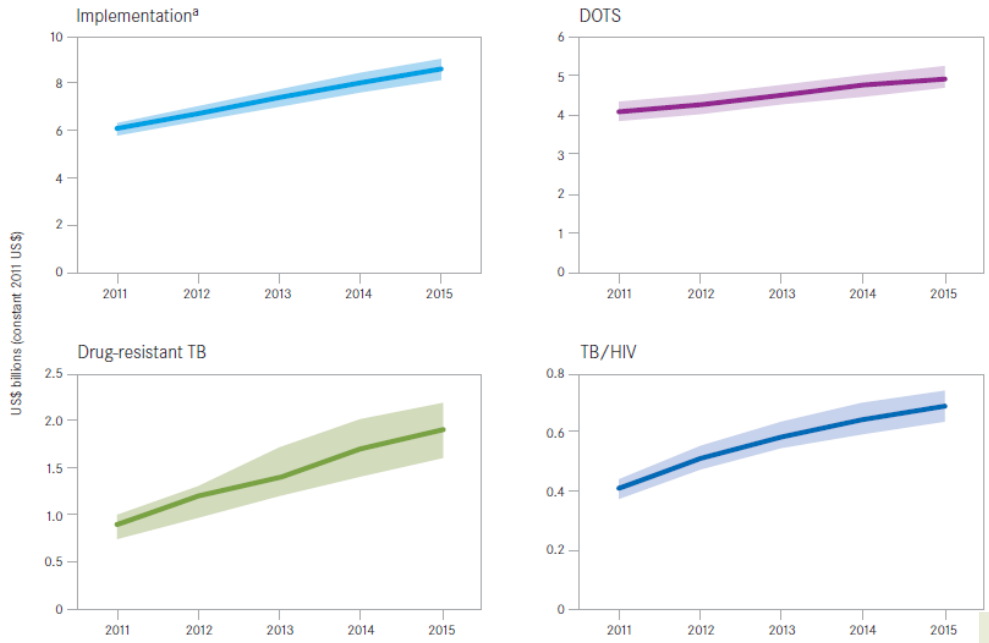
TB Alliance R&D Partners:

AstraZeneca (AZ)
Bayer Healthcare AG (Bayer)
Beijing Tuberculosis and Thoracic Tumor Research Institute
Calibr
GlaxoSmithKline (GSK)
Institute of Materia Medica (IMM)
Janssen (Johnson & Johnson)
Johns Hopkins University (JHU)
Medical Research Council (MRC)
Novartis Institute for Tropical Diseases (NITD)
New York Medical College
Rutgers University
Sanofi
Stellenbosch University
University College London (UCL)
University of Auckland
University of Illinois at Chicago (UIC)
University of Pennsylvania School of Medicine
Yonsei University

MOXIFLOXACINO
PIRAZINAMIDA
PA-824 (nitroimidazooxacina)

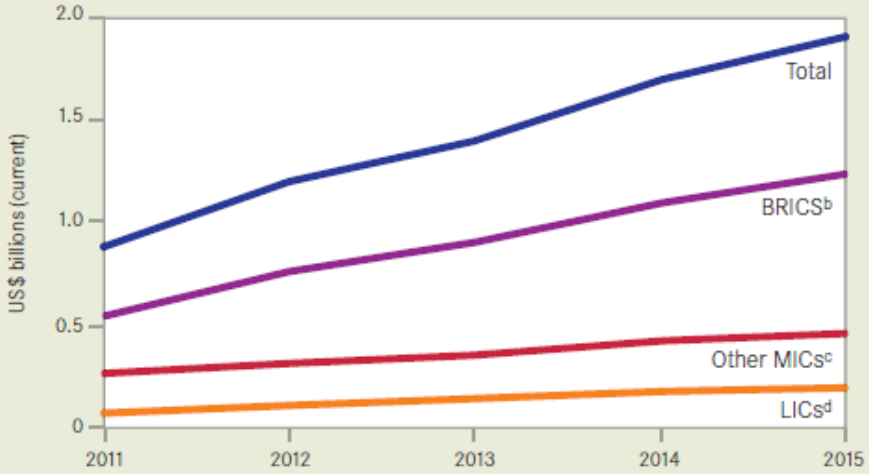
CLOFAZIMINA
PIRAZINAMIDA
PA-824
TMC-207 (BEDAQUILINA)

Funding required to implement the Global Plan to Stop TB, 2011–2015



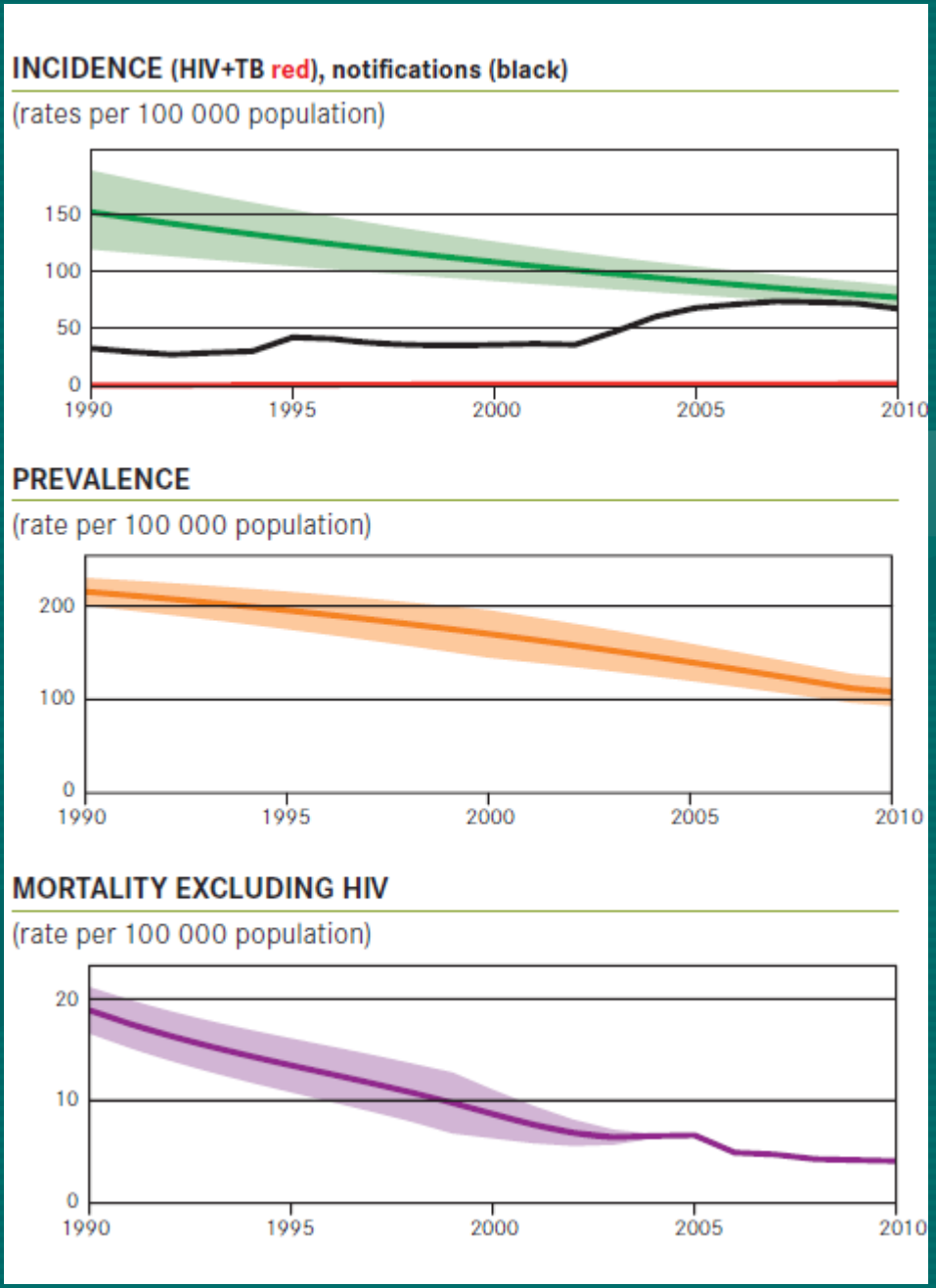
[a] Implementation includes DOTS, Drug-resistant TB, TB/HIV, Laboratory strengthening and Technical assistance.

Funding required for MDR-TB, Global Plan to Stop TB, 2011–2015[a]



[a] Total funding required is the best estimate from the range of plausible values reported in the Global Plan to Stop TB, 2011–2015.
[b] Brazil, the Russian Federation, India, China and South Africa.
[c] Other middle-income countries (not including BRICS).
[d] Low-income countries.

CHINA


INCIDENCE (HIV+TB red), notifications (black)
(rates per 100 000 population)
150
100
50
0
1990
1995
2000
2005
2010
PREVALENCE
(rate per 100 000 population)
200
100
0
1990
1995
2000
2005
2010
MORTALITY EXCLUDING HIV
(rate per 100 000 population)
20
10
0
1990
1995
2000
2005
2010

REVISTA TIME
March 4, 2013

The Drugs Don't Work

I AM Stopping TB

我来控制结核病

Je m'engage. HALTE À LA TUBERCULOSE

أنا ملتزم بدحر السل

Yo puedo frenar la TB

Я МОГУ ОСТАНОВИТЬ ТБ