Tuberculosis – globalization and resistance

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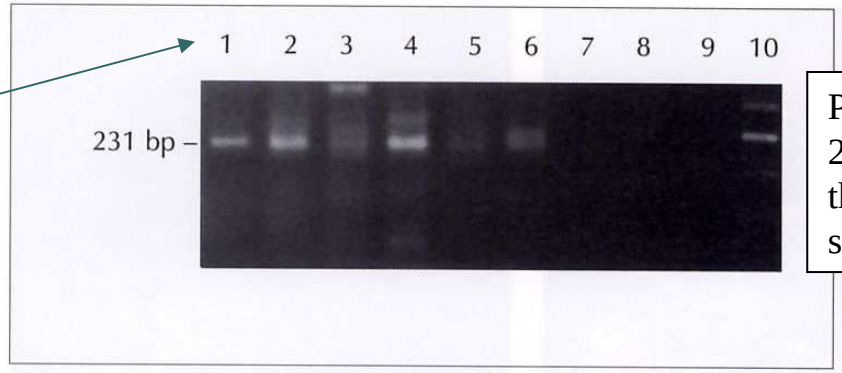
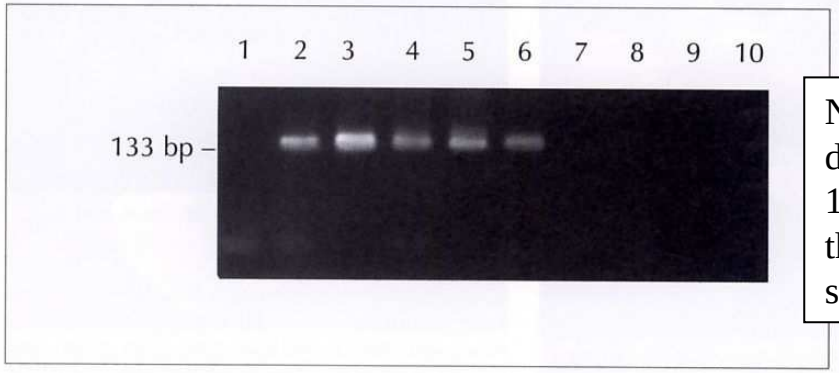
MWIA International Congress, Münster, 2010

The history of TB (7th to 8th century)

Tuberculous spondylitis (Pott's disease)
Avar Age female (died in her early 20's)
7th-8th century cemetery, Sükösd, Hungary



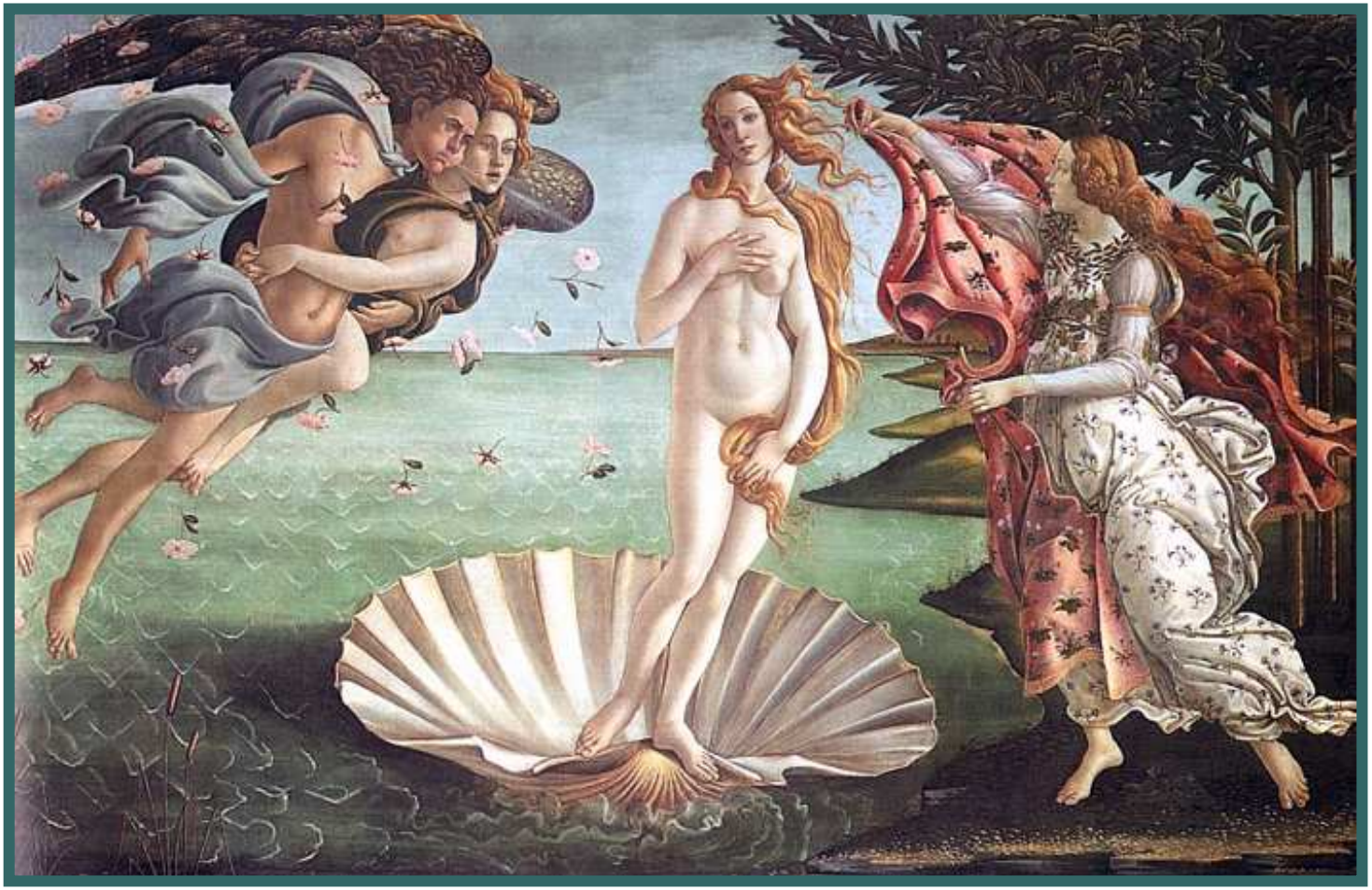
PCR detection of a 231bp segment of the *M. tuberculosis* specific gene



Nested PCR detection of a 133bp segment of the *M. tuberculosis* specific gene

Haas CJ, Pálfi Gy, et al.: Molecular evidence for tuberculosis in Hungarian skeletal samples. In: Tuberculosis Past and Present (1999)

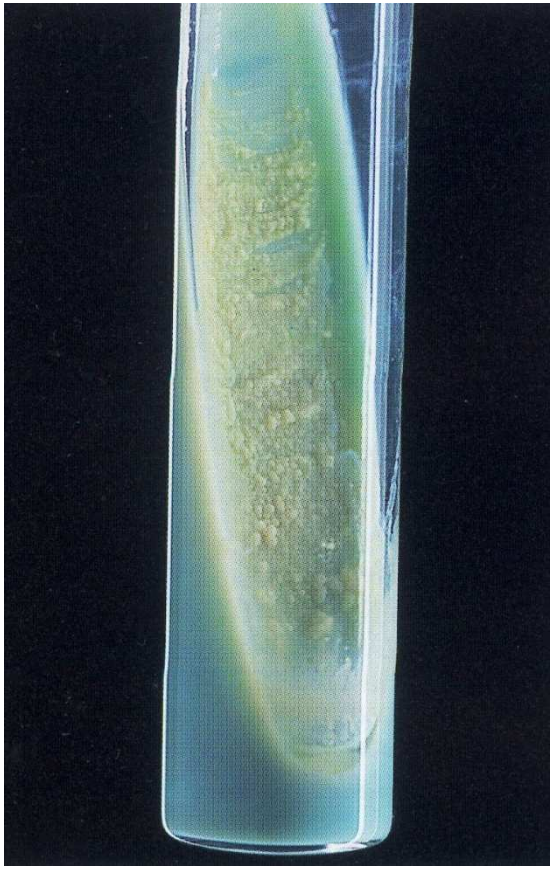
The history of TB (in the Renaissance)



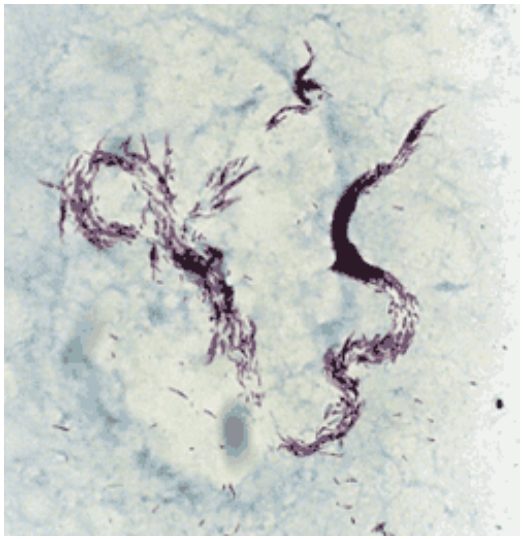
The Birth of Venus by Sandro Botticelli (Museo de Uffici, Firenze)

The model Simonetta Catanea died of TB at the age of 23.

The history of TB

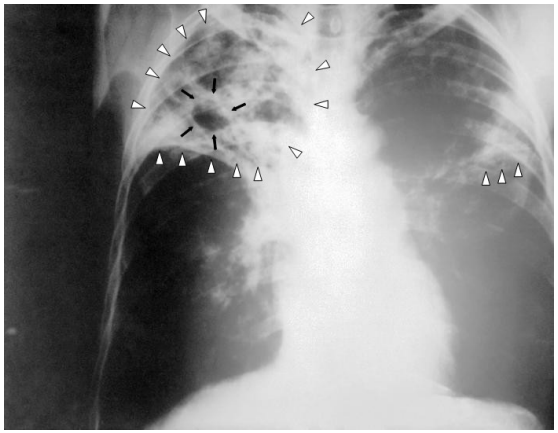


Typical colonies of *M. tuberculosis* after incubation for 5 weeks on Löwenstein-Jensen medium



Acid-fast bacilli (cord formation) in the sputum sample

Robert Koch (1843-1910)



Typical X-ray picture of pulmonary tuberculosis

Outline of my talk

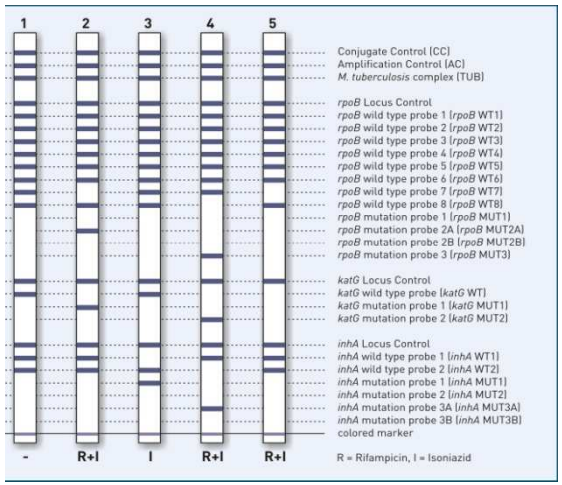
- Diagnostic methods for TB
- Emerging resistance to anti-tuberculosis drugs
- TB and HIV
- Global burden of TB and MDR-TB
- TB surveillance data in Europe
- The global plan to stop TB (2006-2015)

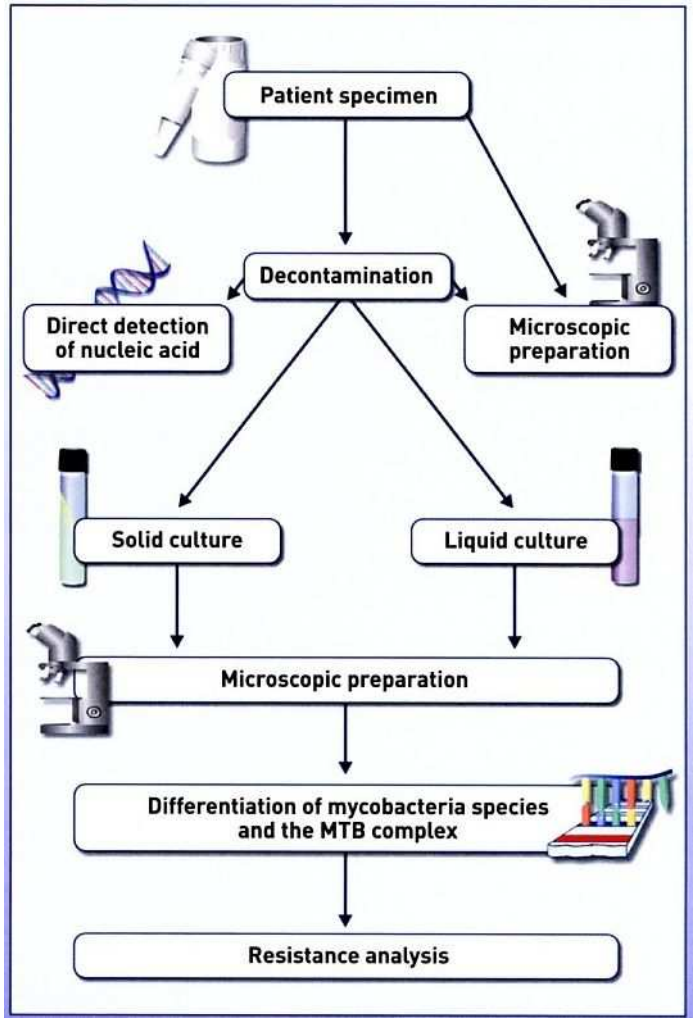
Diagnostic methods

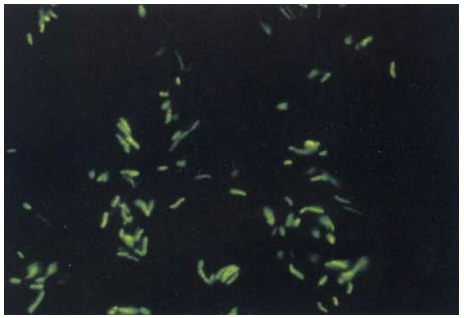
- **Classical methods:**
  - Direct microscopy of sputum samples (poor sensitivity 35-70% – Stengart et al., 2006)
  - Culture (higher sensitivity, but time-consuming)
    - in solid media (3-4 weeks)
    - in liquid media (10-14 days)
    - biosafety practices, laboratory and equipment are needed
    - high per-test price
  - Identification and resistance determination (even more time is needed)
- **Molecular techniques** (nucleic acid-based techniques)
  - Direct detection of *M. tuberculosis* complex and atypical mycobacteria from the samples
  - Identification and resistance gene detection from the isolated bacteria
  - Typing for epidemiological purposes
- **Interferon-γ release assay** for detection of latent TB cases

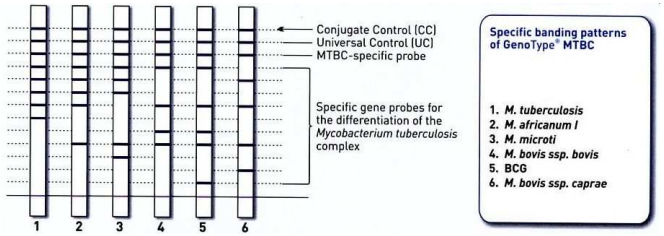
Susan E. Dorman (CID, S3, 2010)

Recommendation for the diagnostics of TB



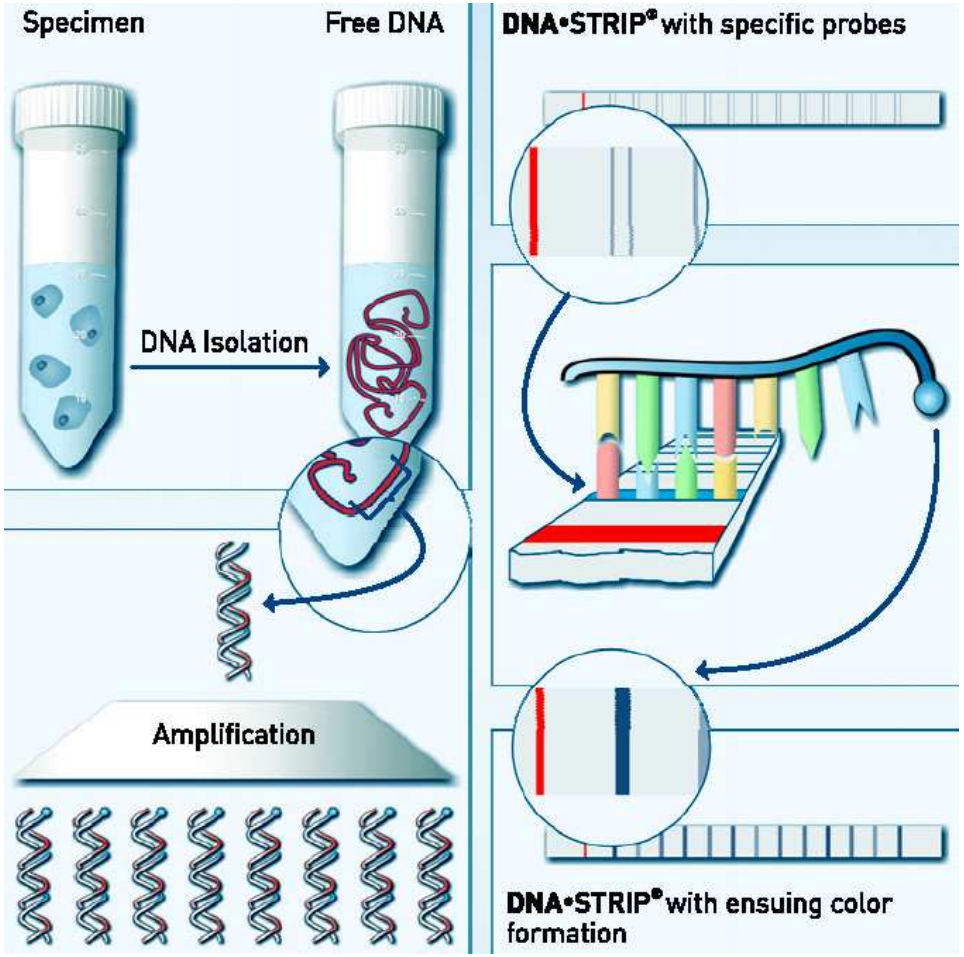






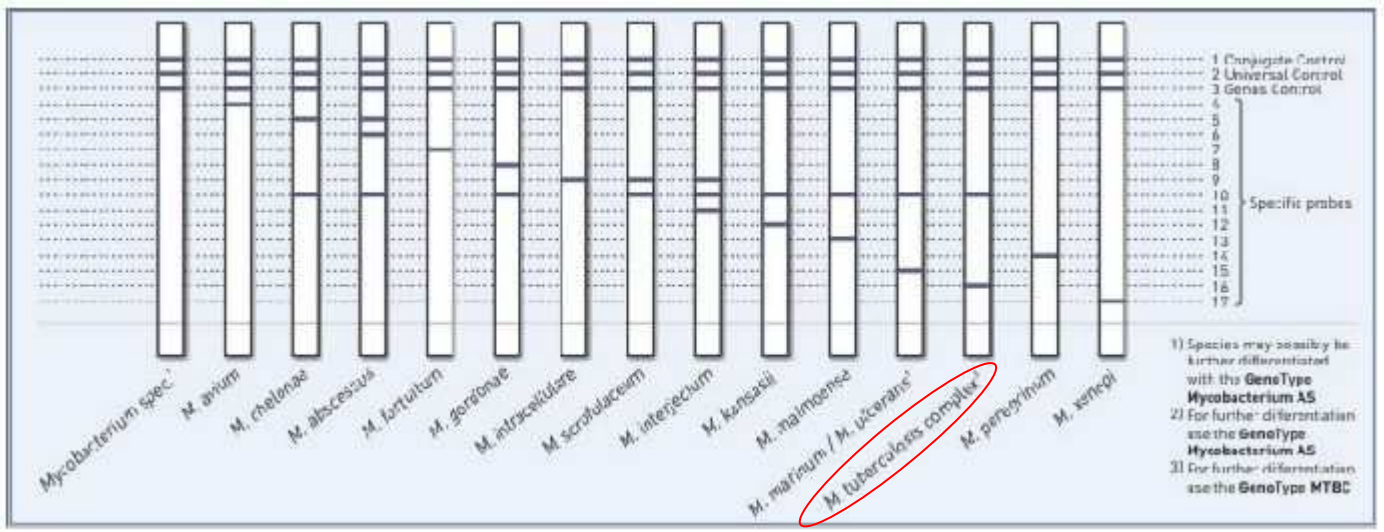
The 2008 WHO recommendation was to use molecular Line-Probe Assays for the rapid screening of patients at risk of MDR-TB

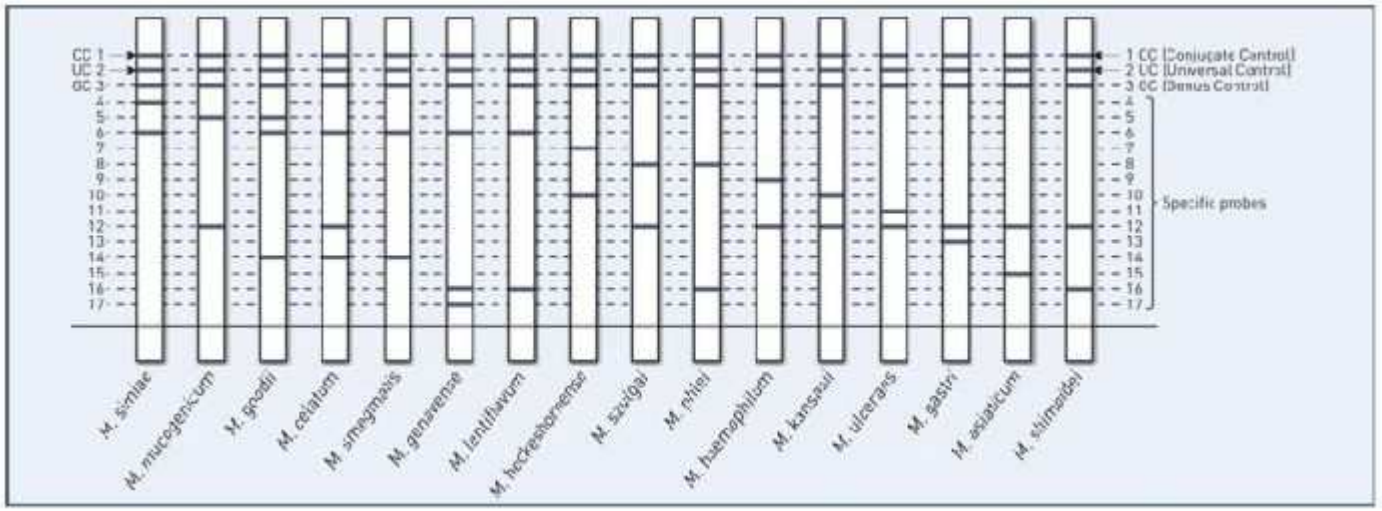
Direct detection from the specimen



Reverse hybridization of amplified nucleic acids to specific DNA probes bound on strips

For identification of MTC strains and NMT strains





GenoType®
Mycobacterium

(HAIN Lifescience)

Emerging resistance problems in TB

- Multidrug-resistant TB (MDR-TB):

  resistance to at least two of the best anti-TB drugs: isoniazid and rifampicin

- Extensively drug-resistant TB (XDR-TB):

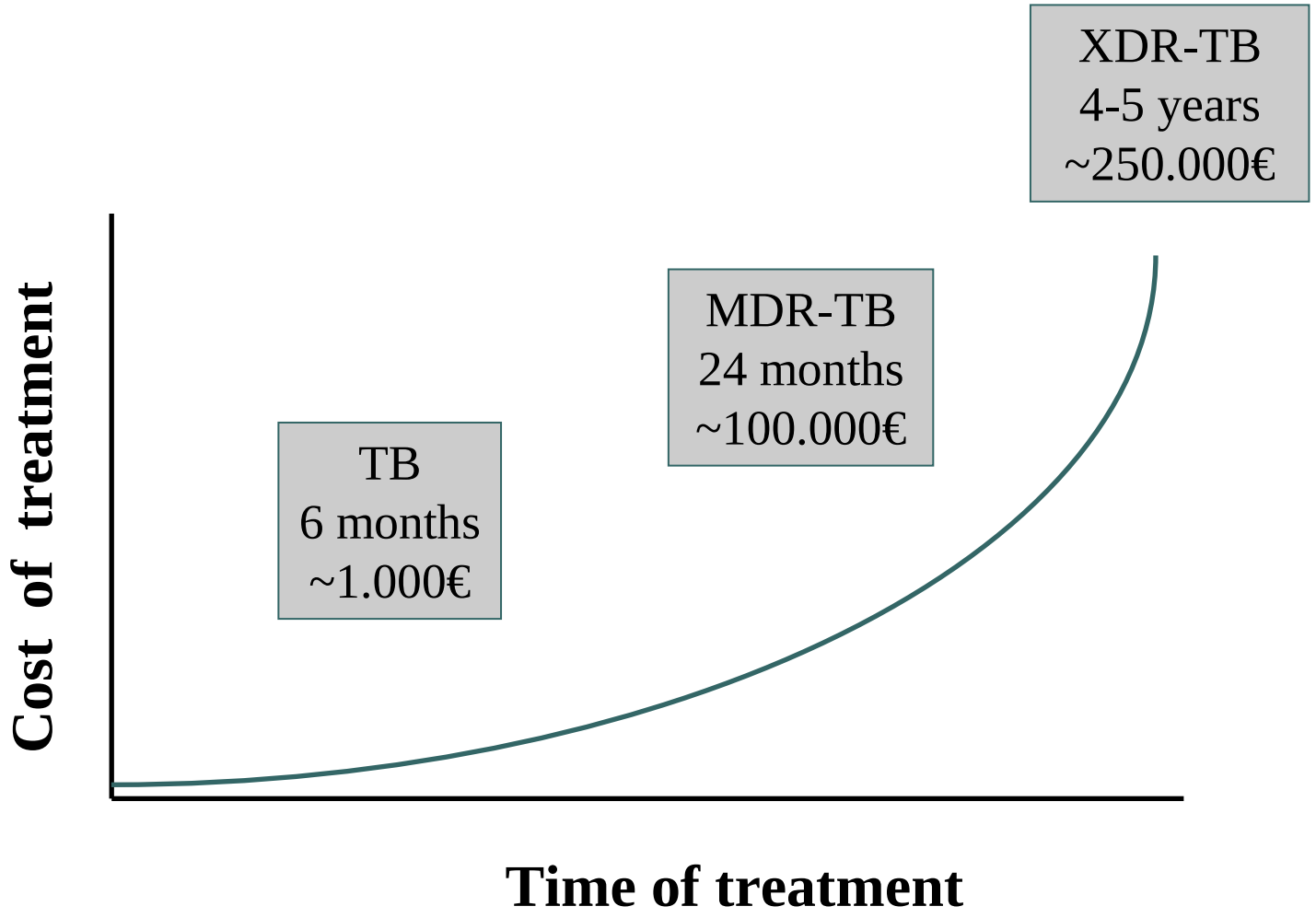
  resistant to isoniazid and rifampicin + any fluoroquinolone and at least one of the 3 injectable second-line drugs (i.e. amikacin, kanamycin or capreomycin)

- Extremely drug-resistant TB (XXDR-TB):

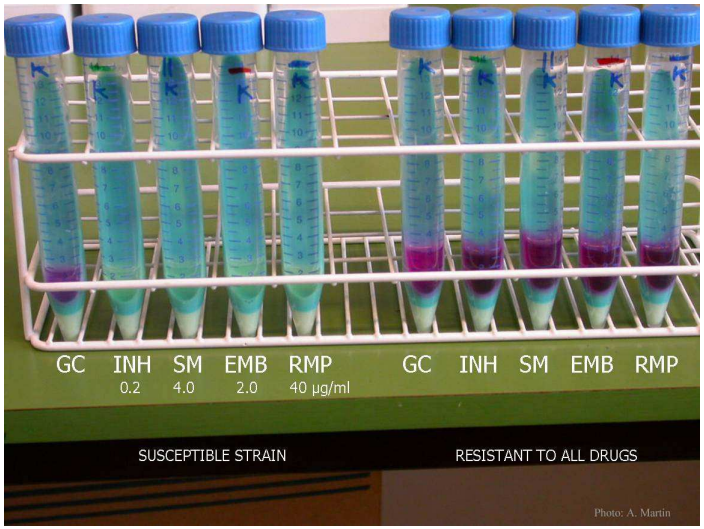
  bacteria are resistant to all tuberculosis drugs and the condition is generally fatal (2 in Italy*, 1 in US)

*Migliori GB et al. First tuberculosis cases in Italy resistant to all tested drugs. Eurosurveillance Weekly Release 12: 5, 2007.

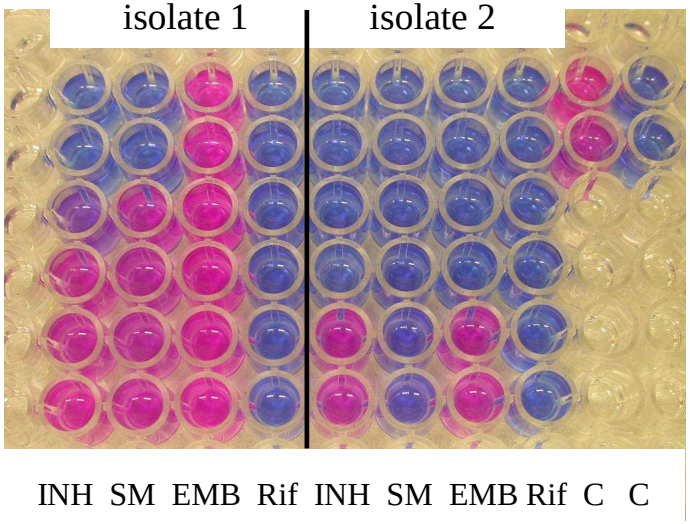
Finacial aspects of the spread of MDR-TB and XDR-TB in the population



Different methods to detect resistance (1)



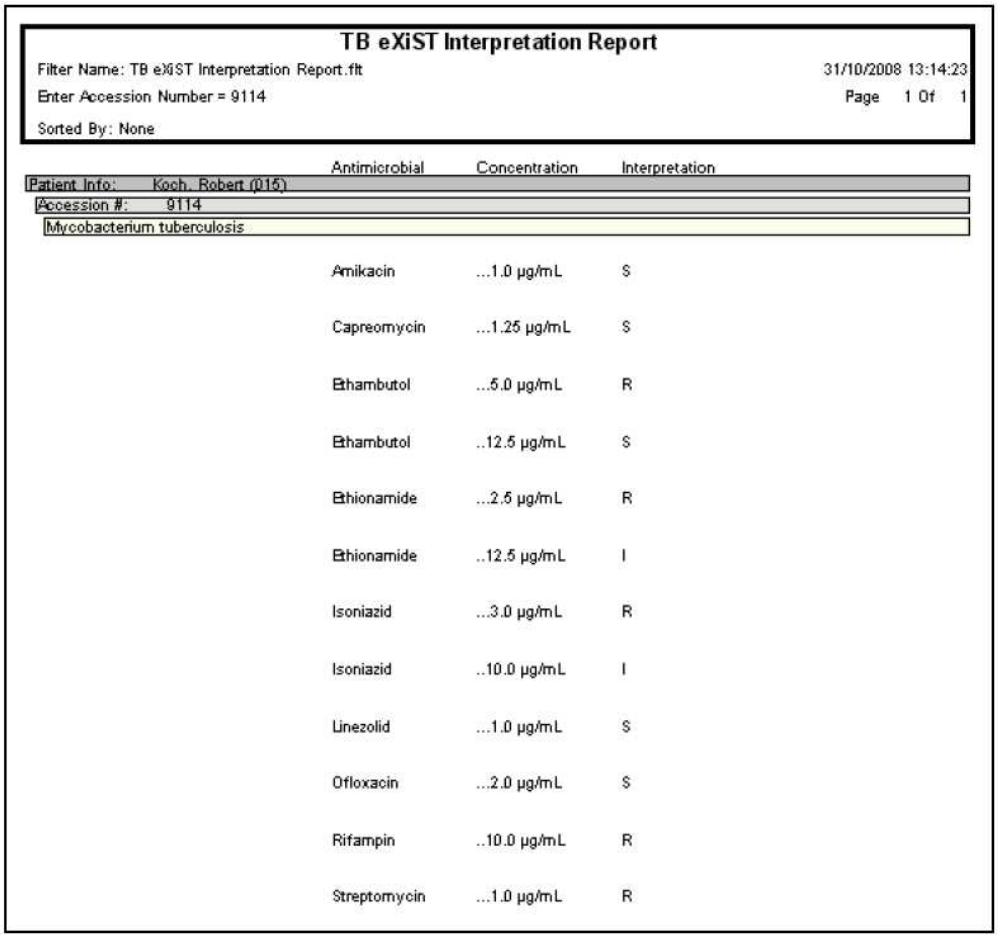
- Löwenstein-Jensen medium with different drugs
- Needs the previous positive culture
- Nitrate reduction detects growth
- Precise, inexpensive, but time-consuming
- No special safety problem



Decreasing concentration

- MIC determination for essential drugs in liquid medium
- Inexpensive, but time-consuming
- Only from pure culture
- Microtiter plate format, less safe

BD Migit 960 provides resistance determination for 12 drugs in liquid medium (2)



TB eXiST Interpretation Report

Filter Name: TB eXiST Interpretation Report.flt — 31/10/2008 13:14:23
Enter Accession Number = 9114 — Page 1 Of 1
Sorted By: None

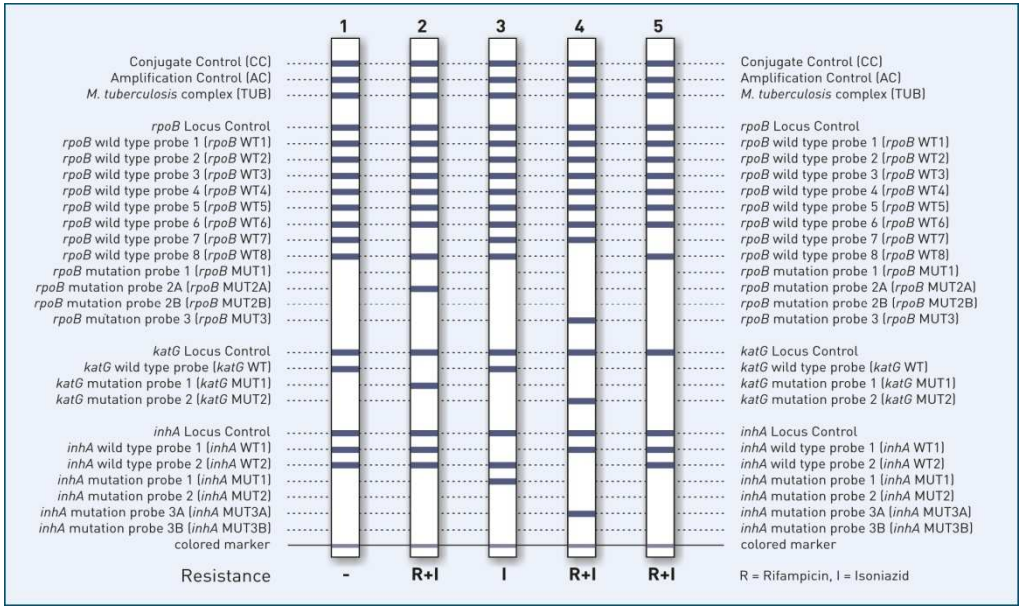
Patient Info: Koch, Robert (015)
Accession #: 9114
Mycobacterium tuberculosis

Antimicrobial	Concentration	Interpretation
Amikacin	...1.0 µg/mL	S
Capreomycin	...1.25 µg/mL	S
Ethambutol	...5.0 µg/mL	R
Ethambutol	..12.5 µg/mL	S
Ethionamide	...2.5 µg/mL	R
Ethionamide	..12.5 µg/mL	I
Isoniazid	...3.0 µg/mL	R
Isoniazid	..10.0 µg/mL	I
Linezolid	...1.0 µg/mL	S
Ofloxacin	...2.0 µg/mL	S
Rifampin	..10.0 µg/mL	R
Streptomycin	...1.0 µg/mL	R

Results appear in the BD EpiCenter TB eXiST system

Different methods to detect resistance (3)

LiPA pattern	Mutation	INNO-LiPA Rif. TB strip
Wild-type	None	
ΔS1	511cCg	
ΔS1	513cCa	
ΔS1	513Gaa	
ΔS2	516Tac	
ΔS2	516-517ΔGACCAG	
ΔS2	518ΔAAC	
R2	516gTc	
ΔS3	522tTg	
ΔS3	522CAg	
ΔS4	526Aac	
ΔS4	526ACc	
ΔS4	526cCc	
ΔS4	526cGc	
ΔS4	526cTc	
ΔS4	526TGc	
R4a	526Tac	
R4b	526Gac	
ΔS5	531tGg	
ΔS5	533cCg	
R5	531tTg	



HAIN GenoType® MTBDRplus

Cepheid Xpert ® MTB/RIF

INNO-LiPa Rif. TB Line-Probe Assay detects several mutations in the rifampicin gene

HIV-related TB

- HIV influences TB evolution: the risk of the development of TB is 5-15%/year in HIV-positive persons (5-10% for whole life in HIV-negative cases)

- HIV modifies TB presentation:
  - cavitary lesions are rare,
  - association of pulmonary & extra-pulmonary localizations is frequent
  - atypical myobacteria can cause infection

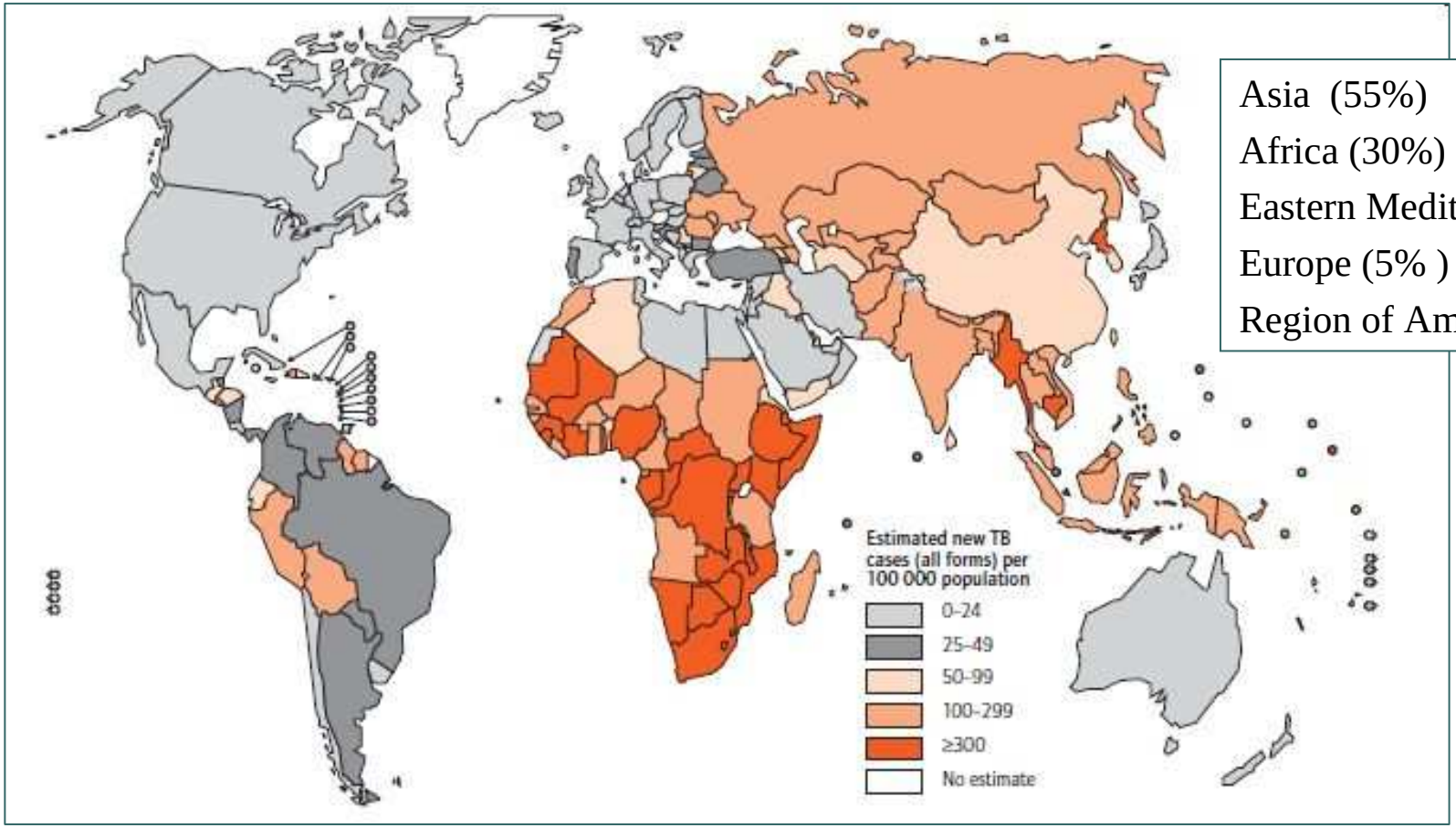
- TB occurs relatively early in the course of HIV infection

- TB worsens the prognosis of HIV infection and is a leading cause of HIV-related morbidity and mortality

- HIV is the most important factor fuelling TB epidemics in high HIV prevalence populations

The global burden of TB in 2008

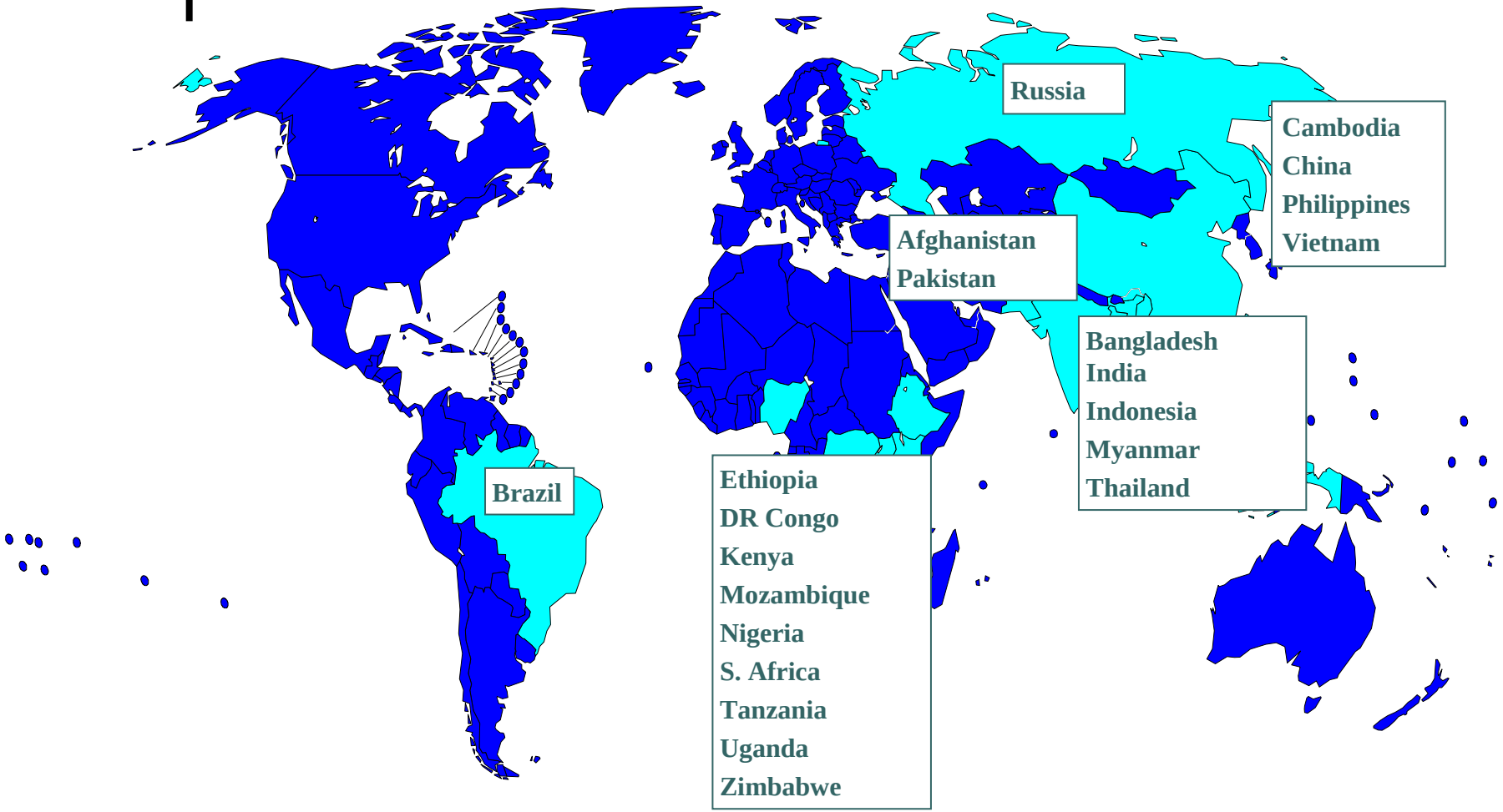
(according to the WHO data)



Asia (55%)
Africa (30%)
Eastern Mediterranean (7%)
Europe (5%)
Region of Americas (3%)

Estimated incidence in 2008: 9.4 million TB cases (= 139 cases/100 000 population)

22 high-burden countries totalling around 80% of world TB cases



Global Tuberculosis Control. WHO Report 2002. WHO/CDS/TB/2002.295

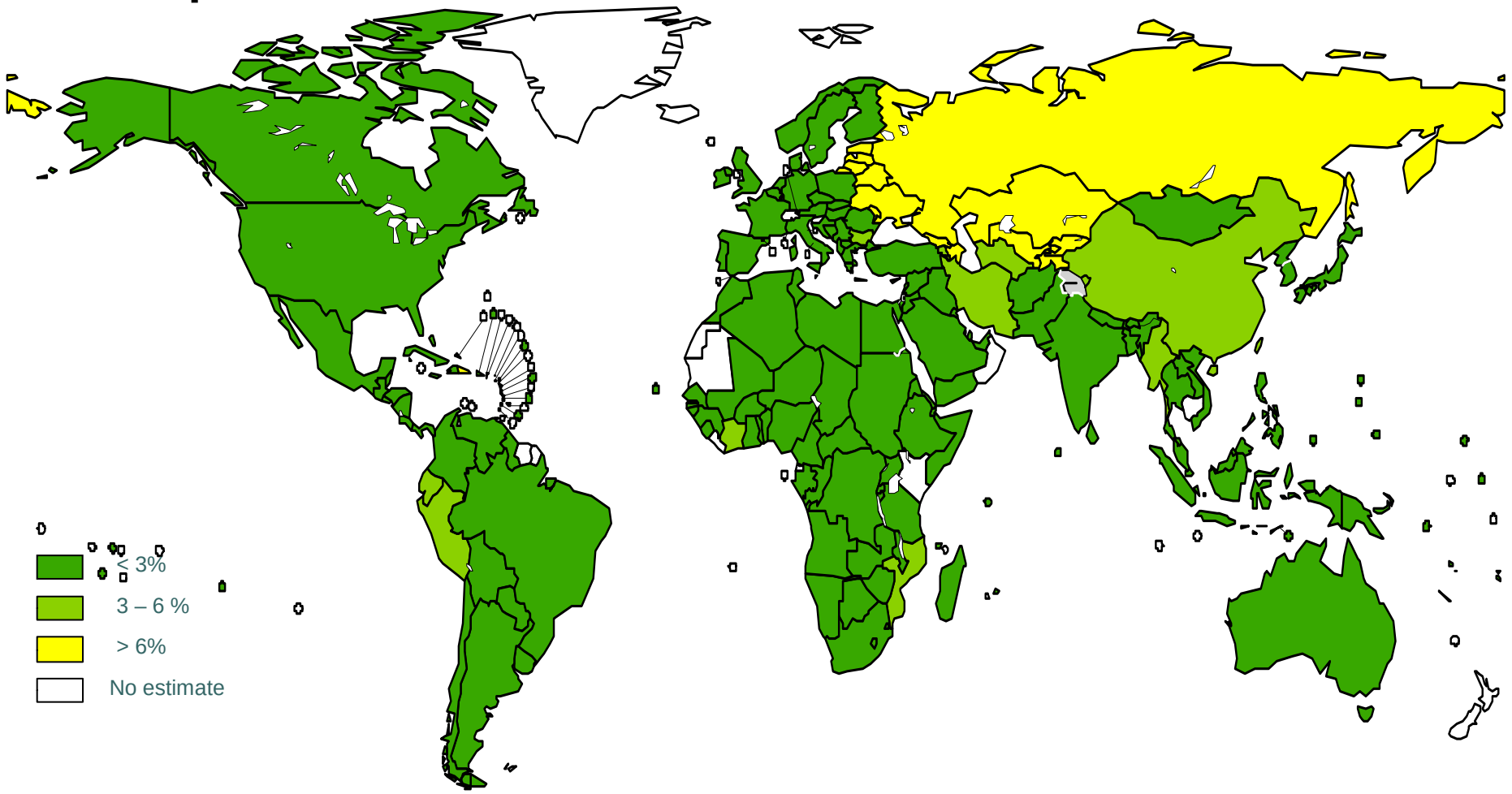
Number of new and relapse TB cases in 2008 in the „ high burden" countries and in the different regions worldwide

- Case detection rate:
  - highest in European Region and the Region of the Americas,
  - followed by Western Pacific Region
  - lowest rate in African Region

	NEW AND RELAPSE
Afghanistan	28 301
Bangladesh	151 062
Brazil	73 395
Cambodia	38 927
China	975 821
DR Congo	104 426
Ethiopia	141 157
India	1 332 267
Indonesia	296 514
Kenya	99 941
Mozambique	39 261
Myanmar	124 037
Nigeria	85 674
Pakistan	245 635
Philippines	139 603
Russian Federation	128 263
South Africa	343 855
Thailand	55 252
Uganda	42 178
UR Tanzania	60 490
Viet Nam	97 772
Zimbabwe	36 650
High burden countries	4 640 481
AFR	1 329 581
AMR	218 249
EMR	392 633
EUR	336 443
SEAR	2 078 238
WPR	1 363 479
Global	5 718 623

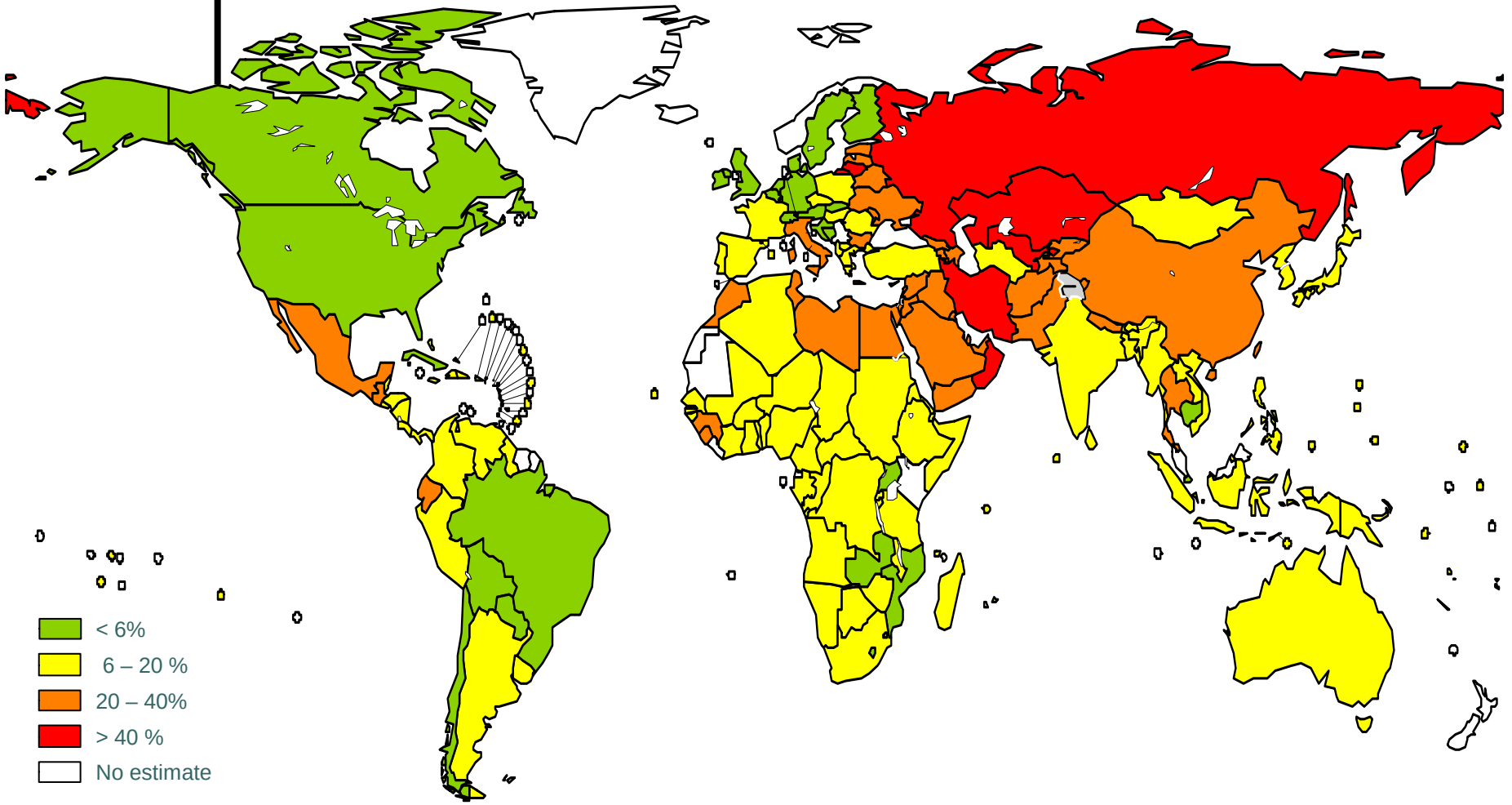
80.1%

Rates of MDR among new TB cases



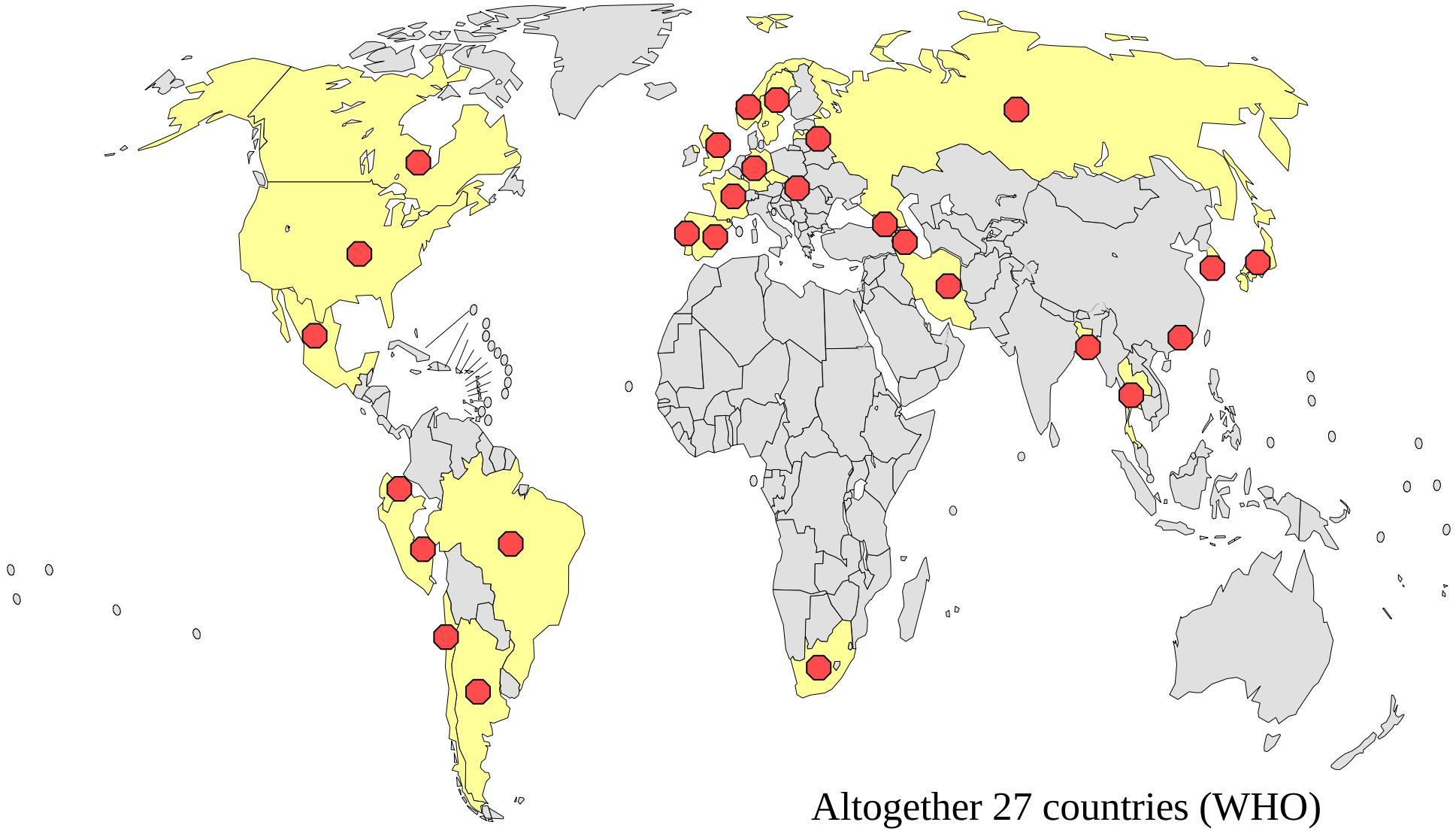
Data from WHO (2006)

Rates of MDR among previously treated TB cases



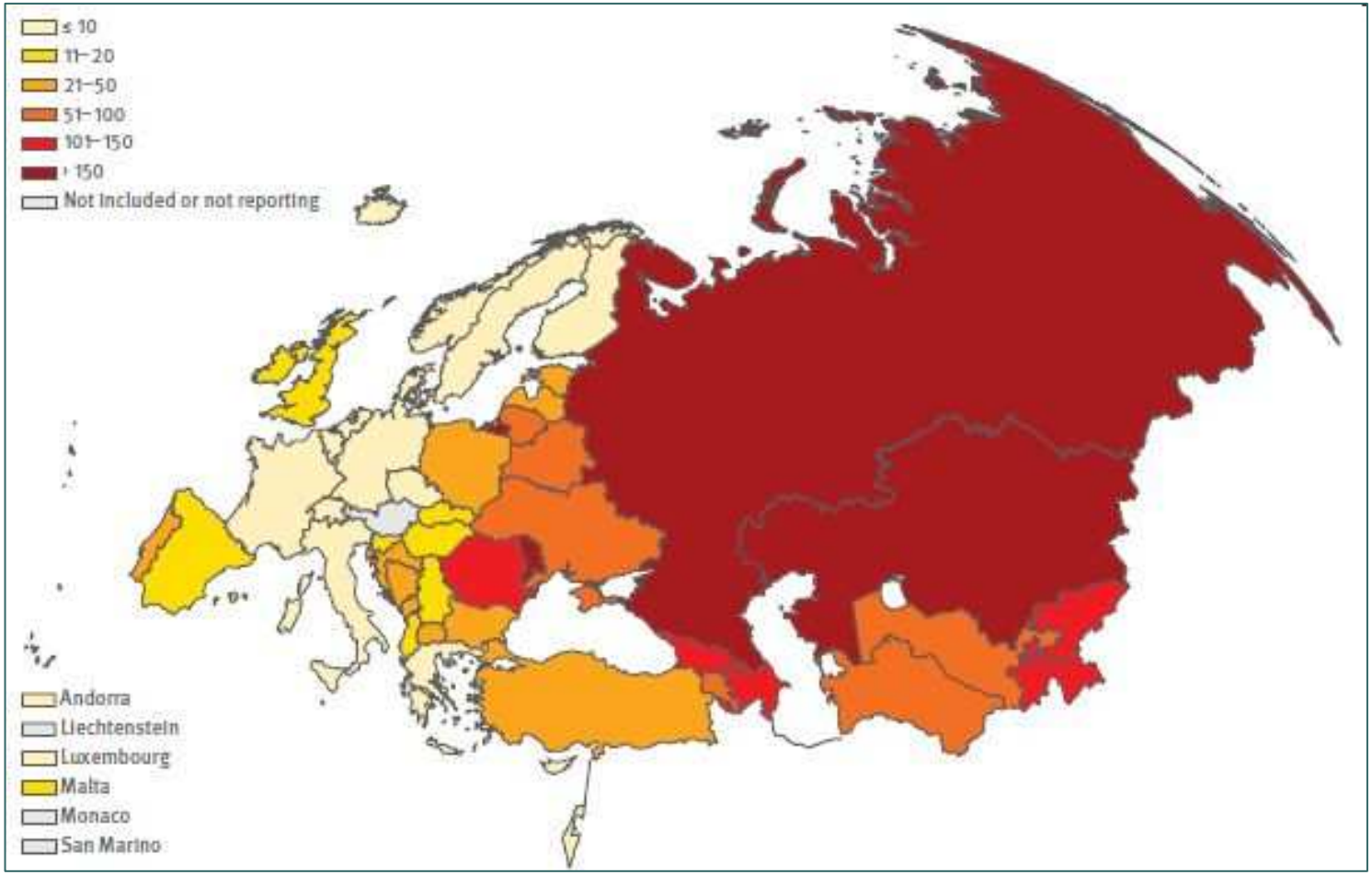
Data from WHO (2006)

Countries with confirmed XDR-TB cases as of 02. 2007



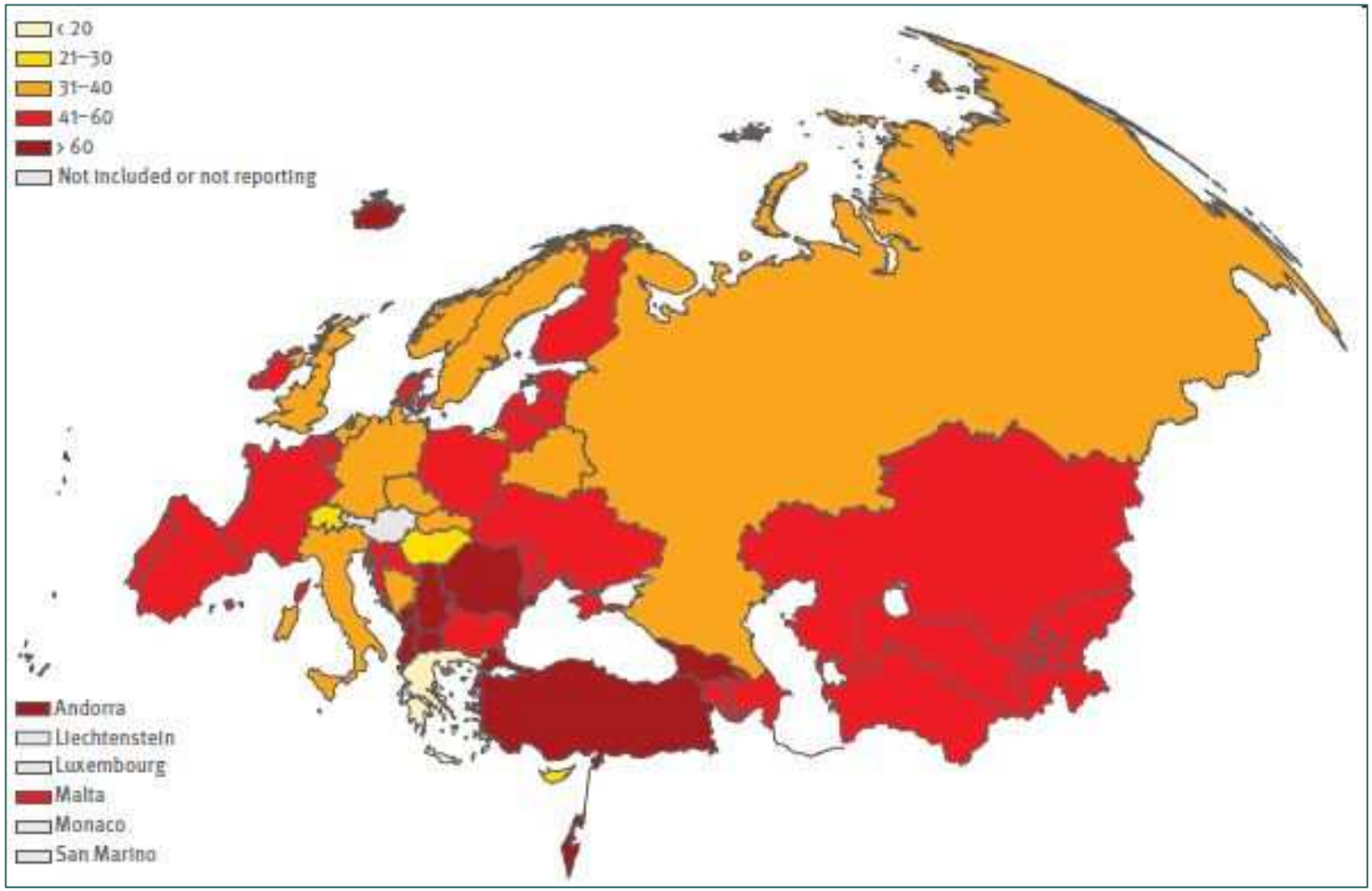
Altogether 27 countries (WHO)

Total TB notification rates per 100 000 population, Europe, 2008



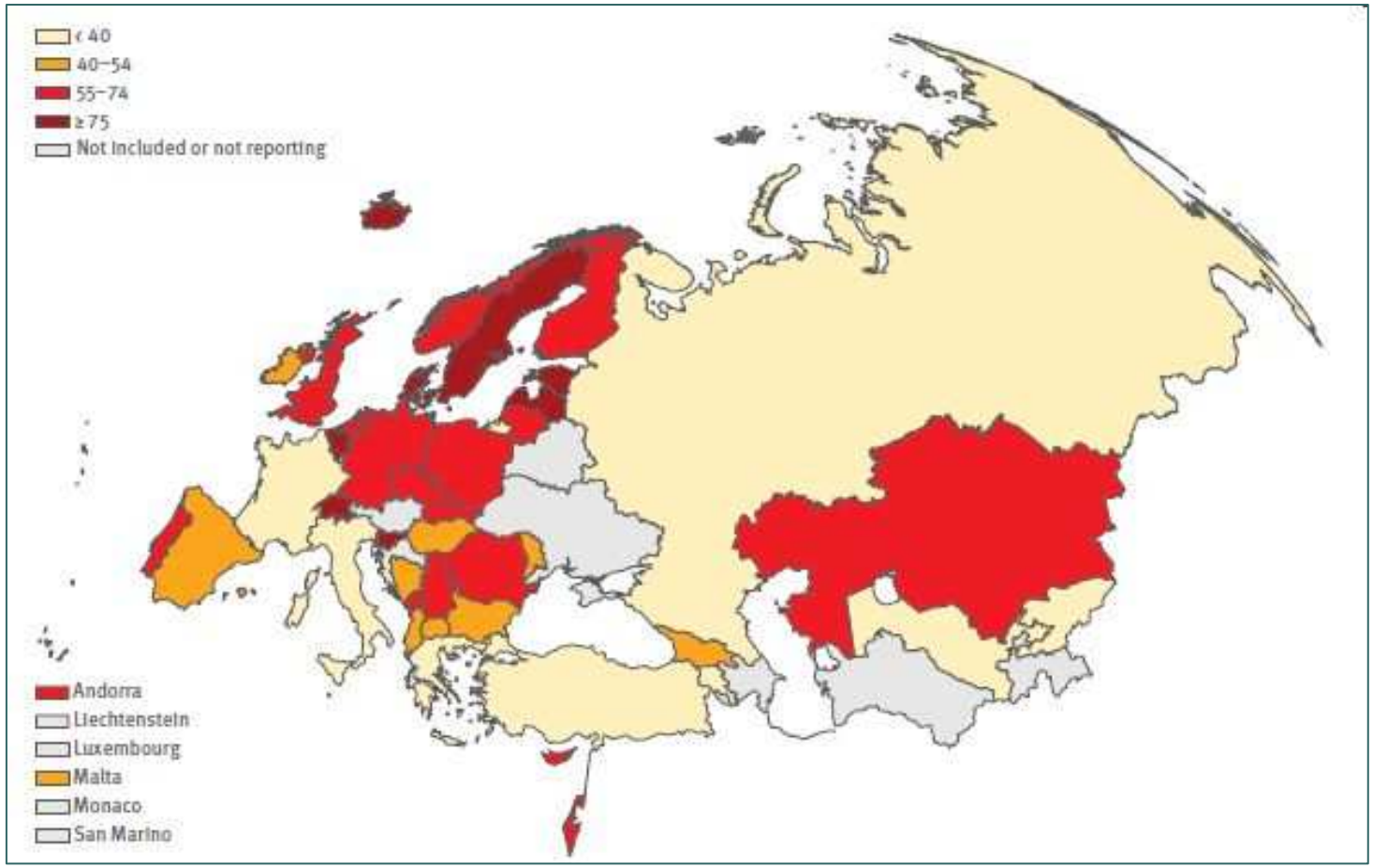
www.ecdc.europa.eu

Percentage of smear-positive cases among pulmonary TB cases



www.ecdc.europa.eu

Percentage of TB cases confirmed by culture, Europe, 2008



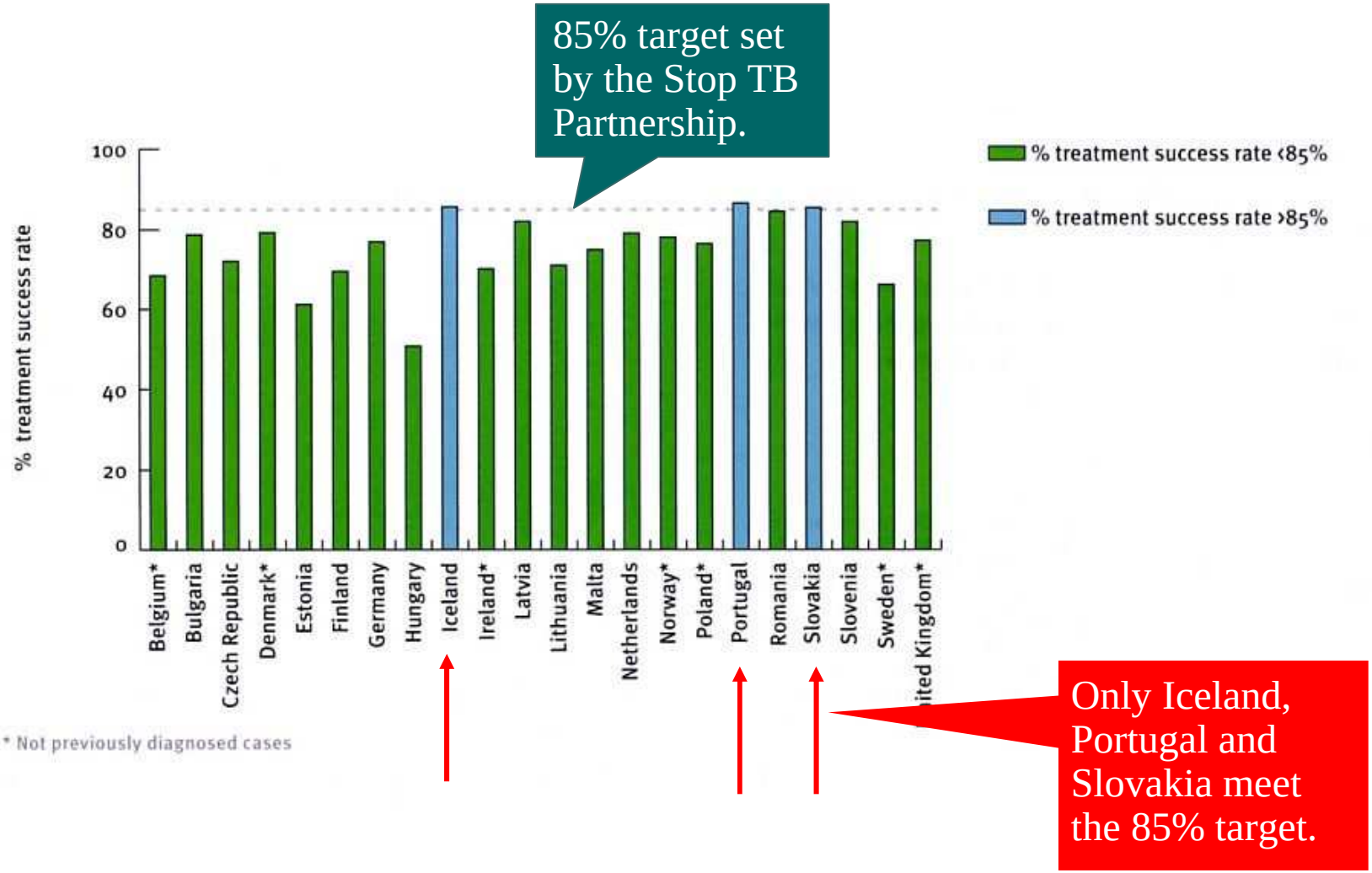
www.ecdc.europa.eu

World Tuberculosis Day 2010

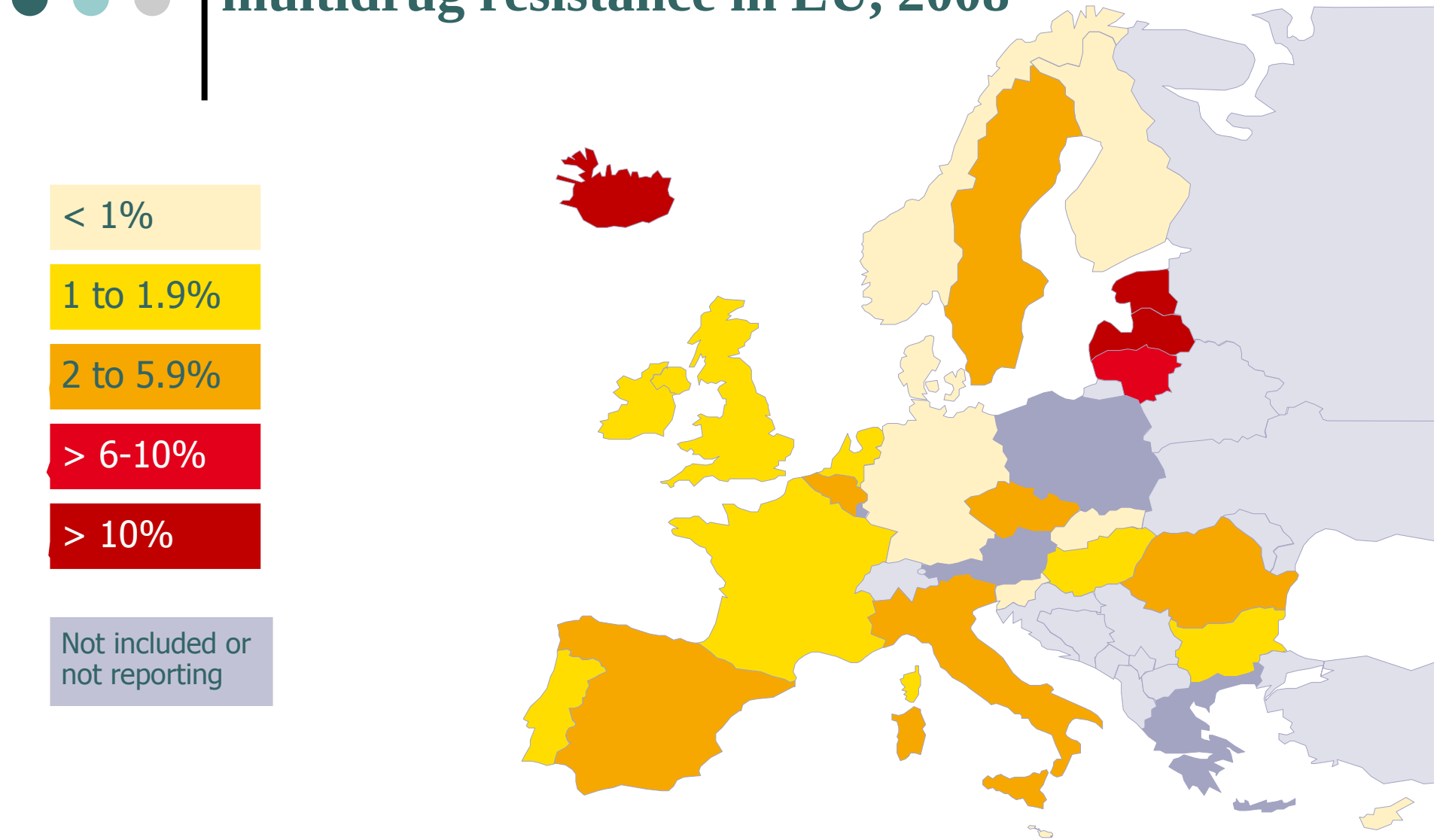
(European Centre for Disease Prevention and Control
Stockholm, 24 March 2010)

- **Three key messages on tuberculosis control**
  - The treatment success rate in the EU is too low to meet global targets !!
  - Multidrug-resistant tuberculosis **(**MDR-TB) remains a problem in the EU !!
  - The decline in tuberculosis has levelled off in the EU !!

Treatment success rate among previously untreated, laboratory-confirmed pulmonary TB cases in 2007

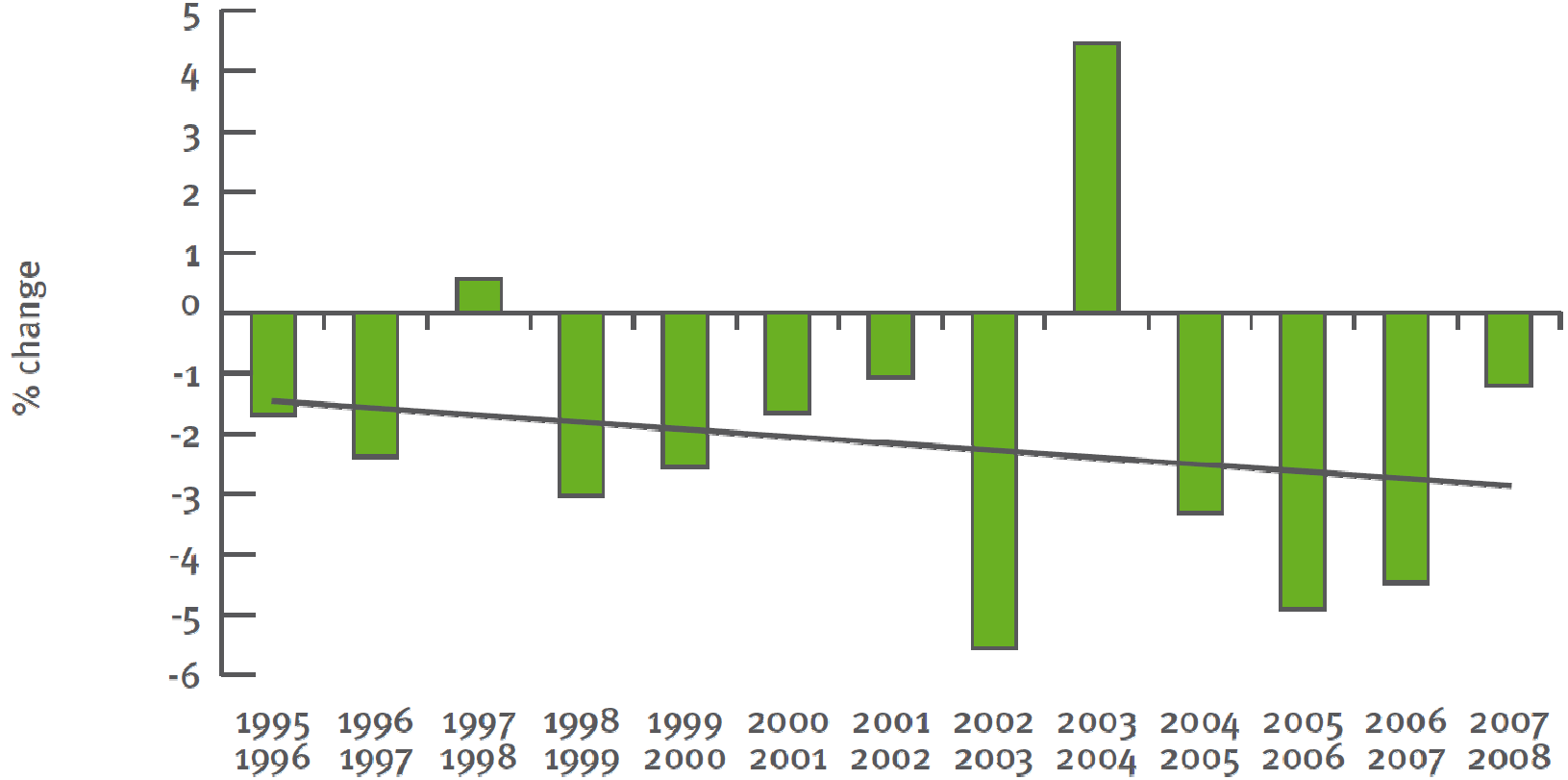


Proportion of notified TB cases with primary multidrug resistance in EU, 2008



Percentage annual change in TB notification rates in EU 1996–2008

Between 2007 and 2008, the TB notification rate decreased by only 1.2%, the lowest in four years.



Directly observed therapy (DOT) in MDR-TB

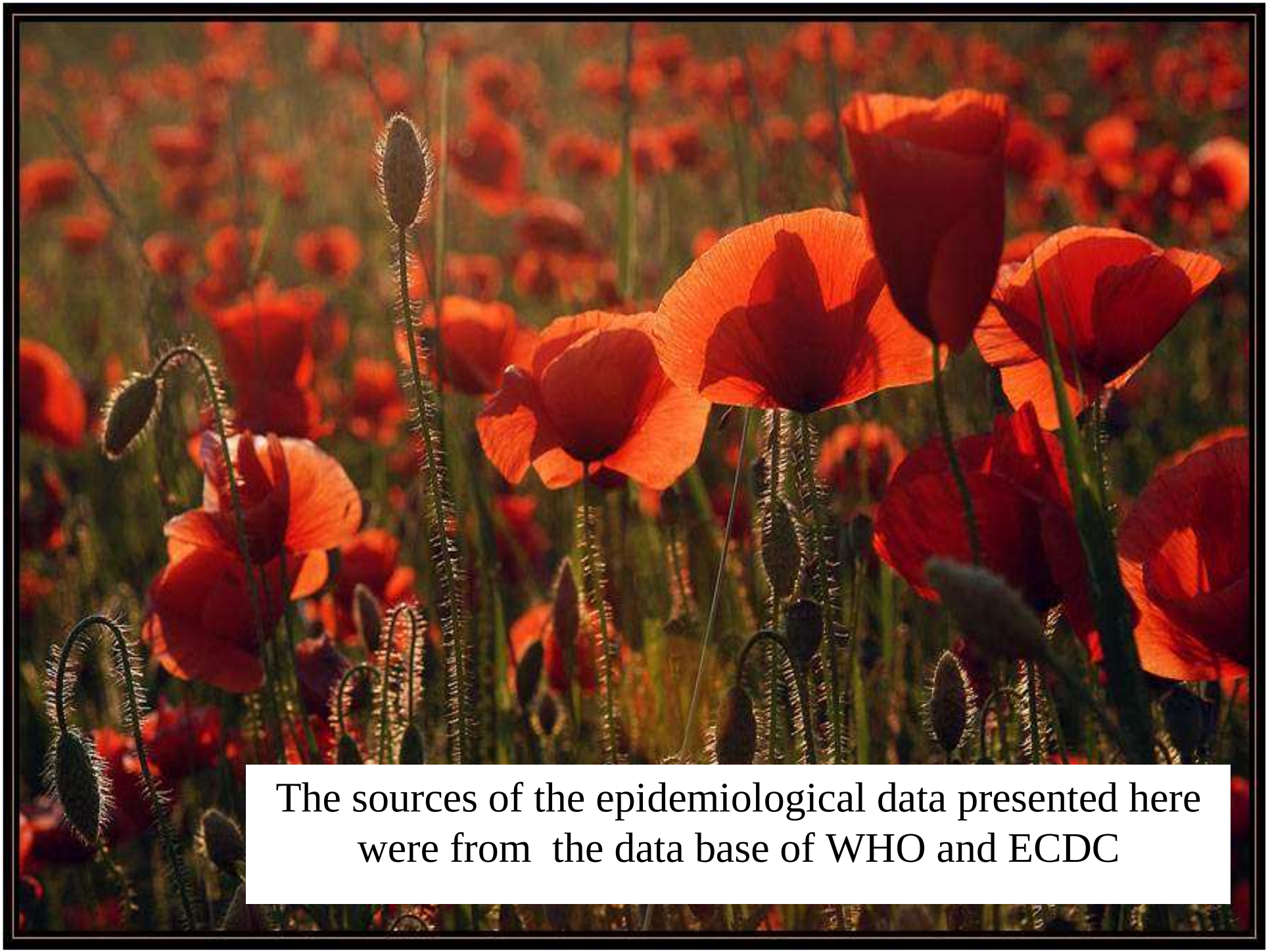
- Prevents the increase of drug resistance
- Ensures adherence to treatment
- Helps in detecting adverse drug reactions
- Prevents trafficking of costly second-line drugs

No compromise on DOT in MDR-TB management !

The Global Plan to Stop TB 2006-2015

- Detection of 84% of active TB cases globally by 2015
- A treatment success rate among smear-positive cases of 87% by 2015
- Access to quality TB diagnosis and treatment for all
- By this 14 million lives will be saved
- 50 million people treated for TB in total
- 3 million TB patients, co-infected with HIV, put on anti-retrovirals
- Nearly one million people should be treated for MDR-TB
- The first new TB drug in 40 years by 2010
- A new vaccine by 2015
- Rapid and inexpensive diagnostic tests at the point of care.

WHO 2006


The sources of the epidemiological data presented here were from the data base of WHO and ECDC