

Fifth Regional Meeting on TB/HIV Collaborative Activities  
(*San José, Costa Rica, 7 November 2008*)

# Multidrug-Resistant and Extensively Drug Resistant Tuberculosis in the Era of HIV

Paul Nunn

*Stop TB* Department, WHO, Geneva



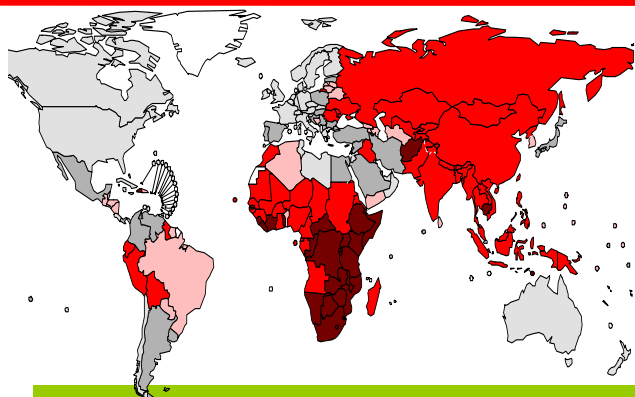
# Issues

- Epidemiology of MDR and XDR-TB
- Overlap with HIV
- Prevention and management of MDR-TB in the context of HIV

# Latest Global TB Estimates, 2006



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**Estimated  
number of  
cases**

**Estimated  
number of  
deaths**

**All forms of TB**  
Greatest number of cases in Asia;  
greatest rates per capita in Africa

**9.15 million**

**1.65 million**

**Multidrug-resistant  
TB (MDR-TB)**

**489,000**

**120,000**

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

**40,000**

**20,000**

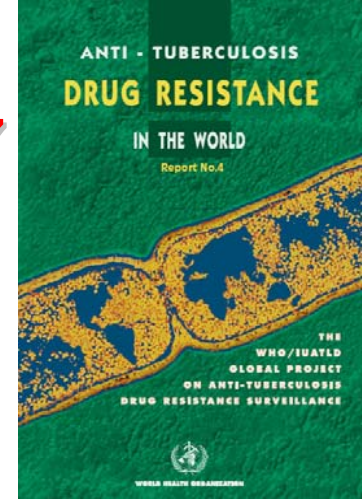
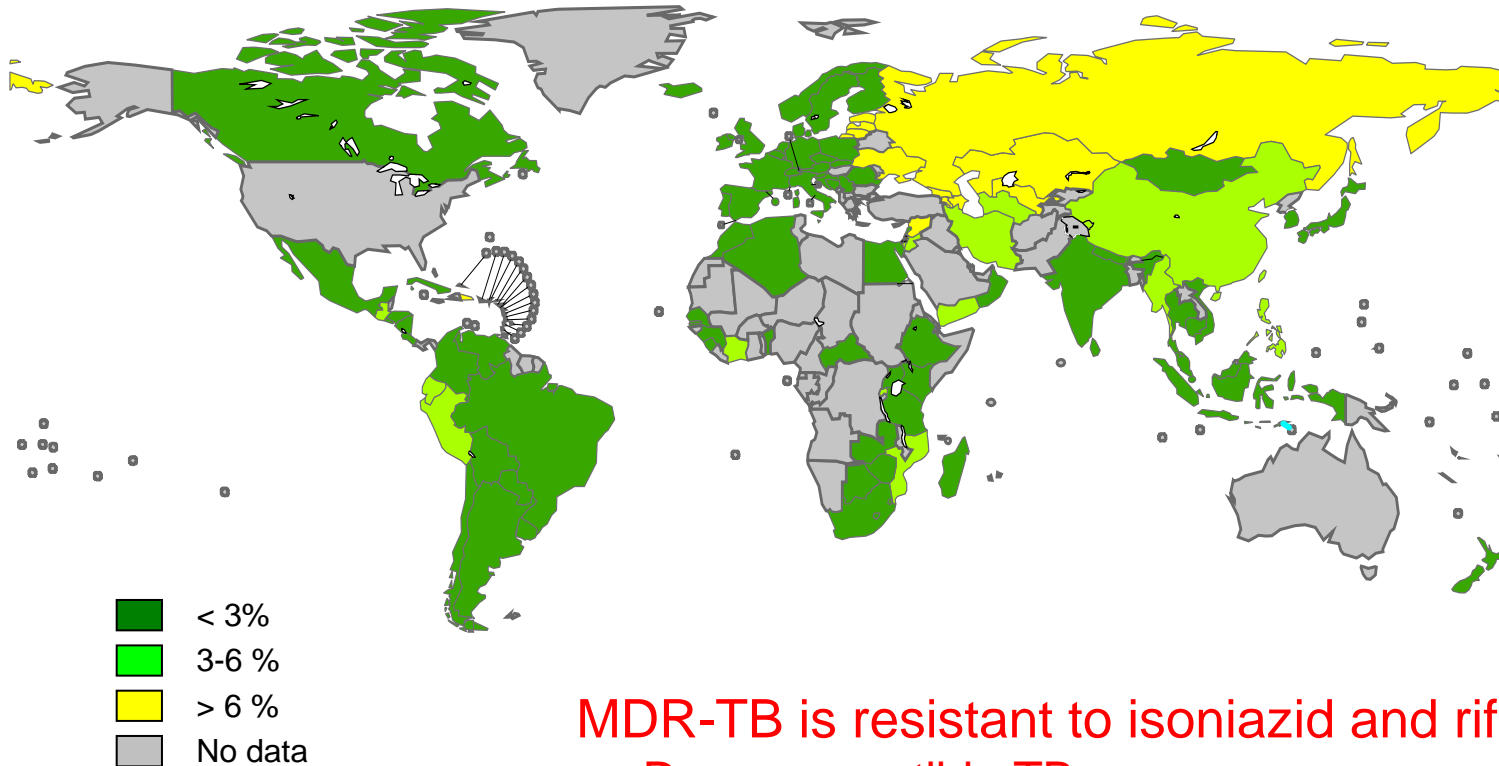
**HIV-associated TB**

**700,000**

**200,000**

# MDR-TB among new cases 1994–2007

\* Subnational averages applied to China, Russia, Indonesia.



**MDR-TB is resistant to isoniazid and rifampicin**

**Drug susceptible TB**

**MDR-TB**

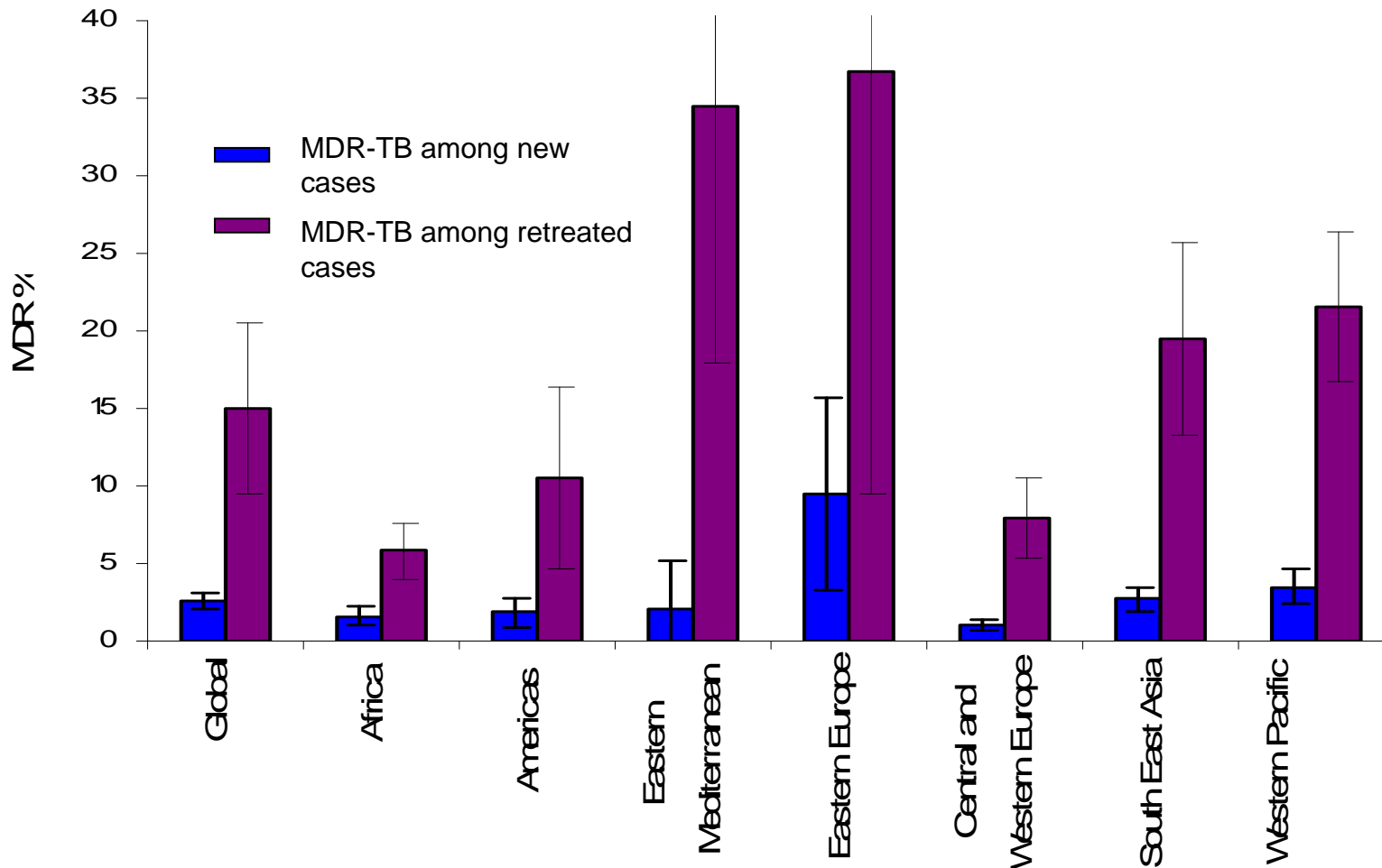
**Cure rate 95+%**

**Cure rate 67%**

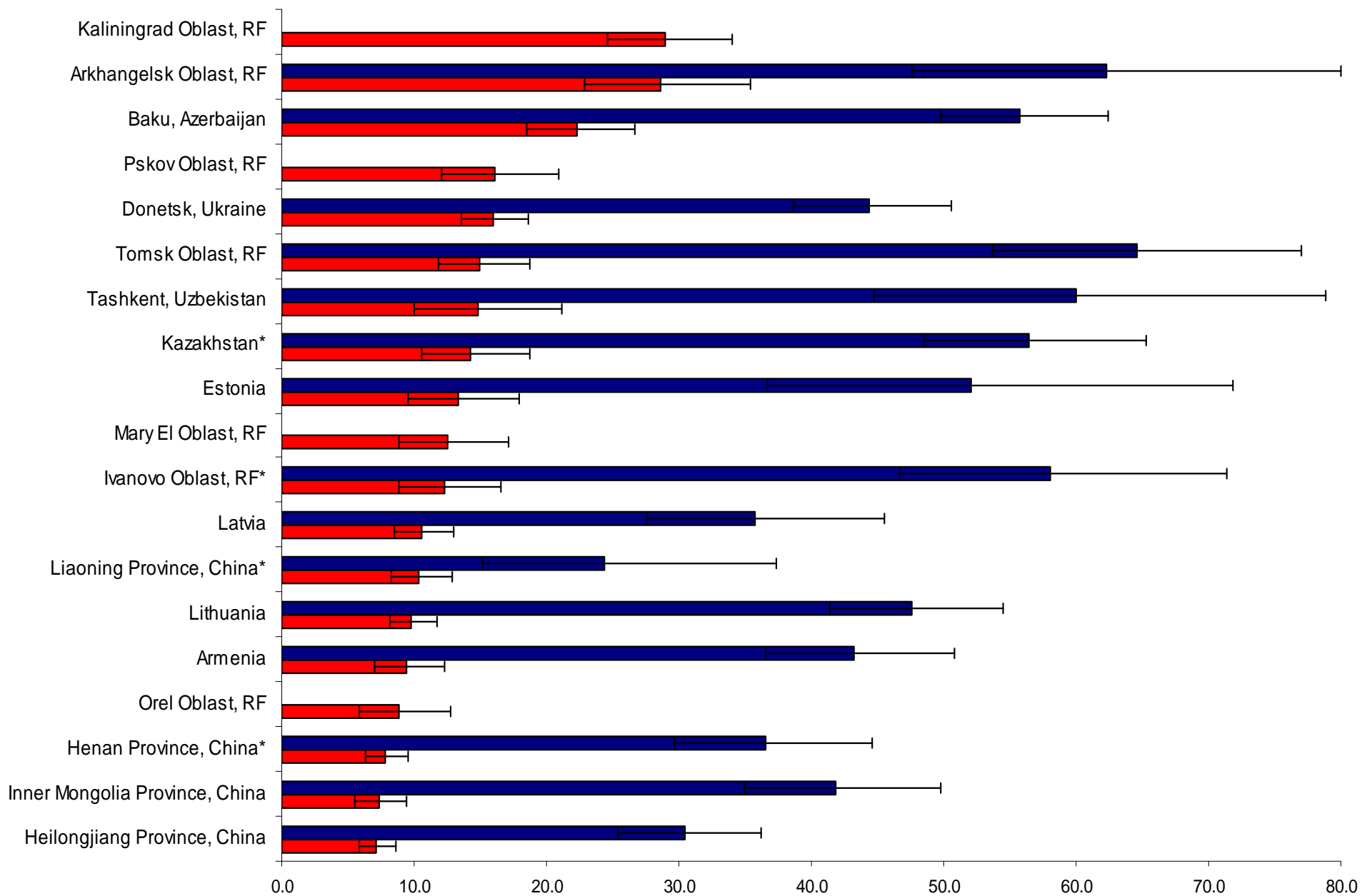
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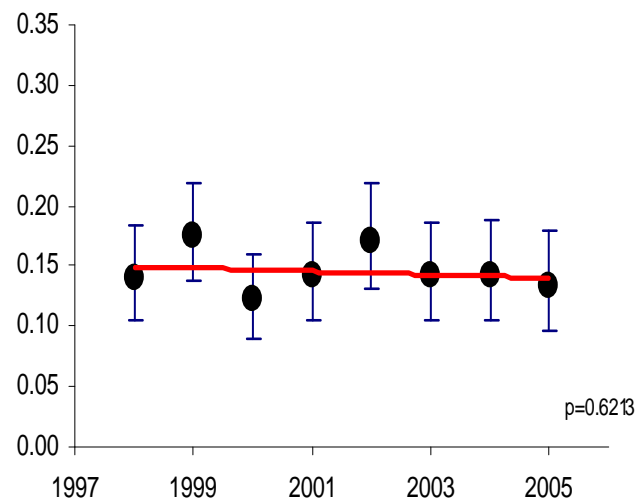
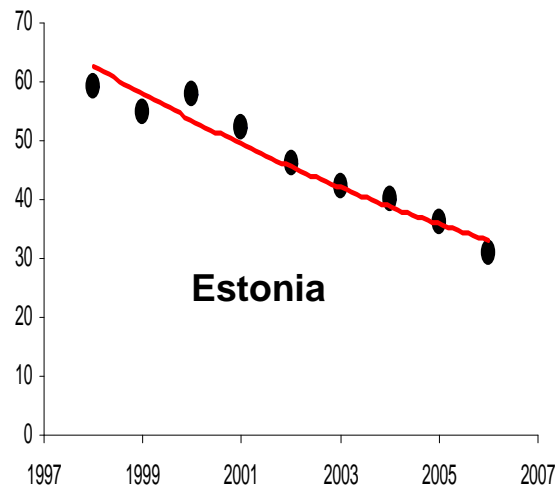
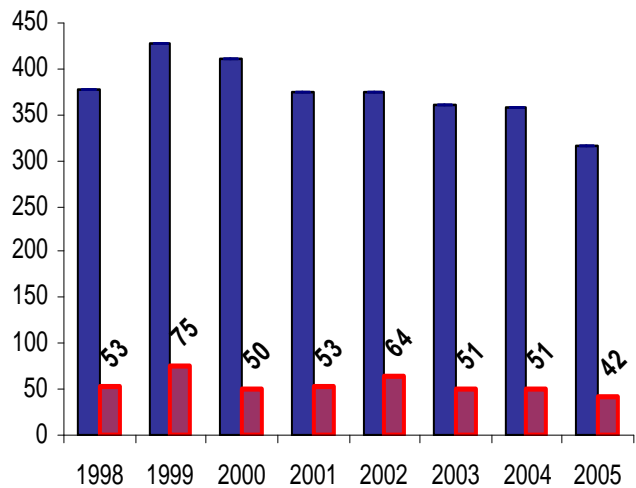
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# % MDR-TB among New and Previously Treated Patients, by Region



# % MDR among new and retreatment cases (1994–2006)

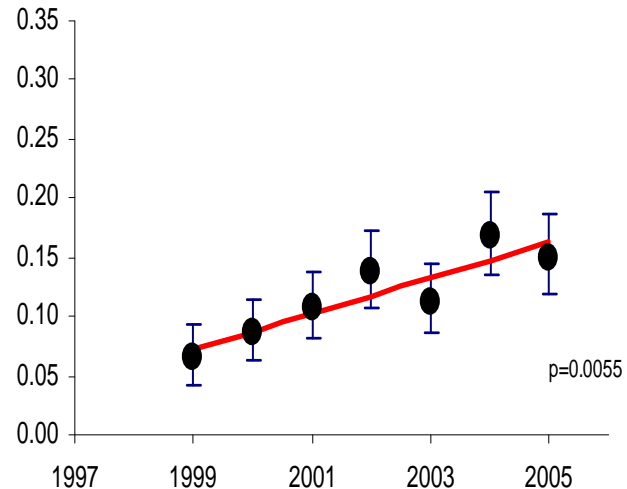
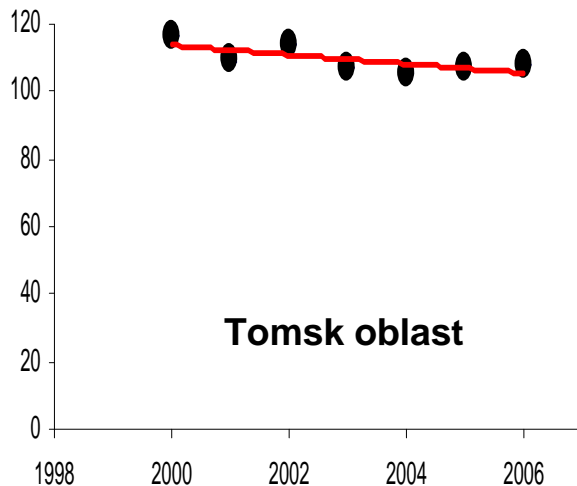
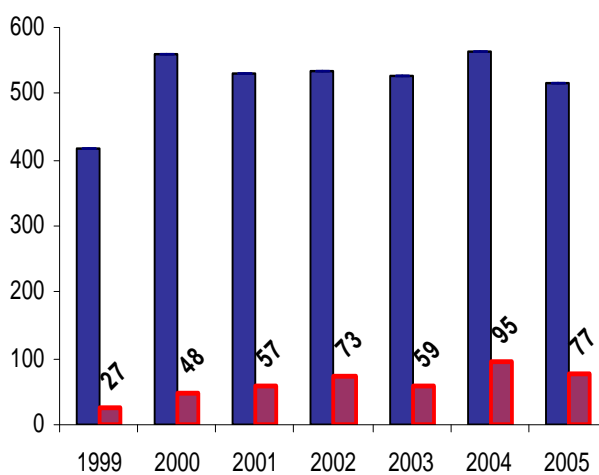




## New DST, New MDR

## TB Notification Rate

## % MDR among New Cases



# 2006 - extensively Drug Resistant Tuberculosis (XDR-TB)



## 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*.

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

During the 1990s, multidrug-resistant (MDR) tuberculosis and rifampin- and isoniazid-resistant (XDR) tuberculosis emerged in the United States. The United States requires the use of second-line drugs, more toxic, and more expensive, than first-line drugs. The Green Light Committee (GLC) of the Centers for Disease Control and Prevention (CDC) has increased drug resistance through the use of multiple drugs. To assess the prevalence of extensively drug-resistant (XDR) tuberculosis, the National Tuberculosis (WHO) Reference and Surveillance Centres (NTRSC) in 10 laboratories. This study determined that 20% of MDR isolates, 20% were extensively drug-resistant (XDR) based data.

resistant to isoniazid (aminoglycosides, rifampin, and para-

005  
United States,  
March 5–11, 2006

## THE LANCET.com

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

Nzel R Gandhi, Anthony Mall, A Wilton Stearn, Robert Pawinski, Thulashini Govender, Umeshi Jeeoo, Kimberly Zeller, Joann Andrus, 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

XDR = Resistance to at least INH and RIF (MDR) PLUS resistance to fluoroquinolones, AND one of the second-line injectable drugs (amikacin, kanamycin, or capreomycin)

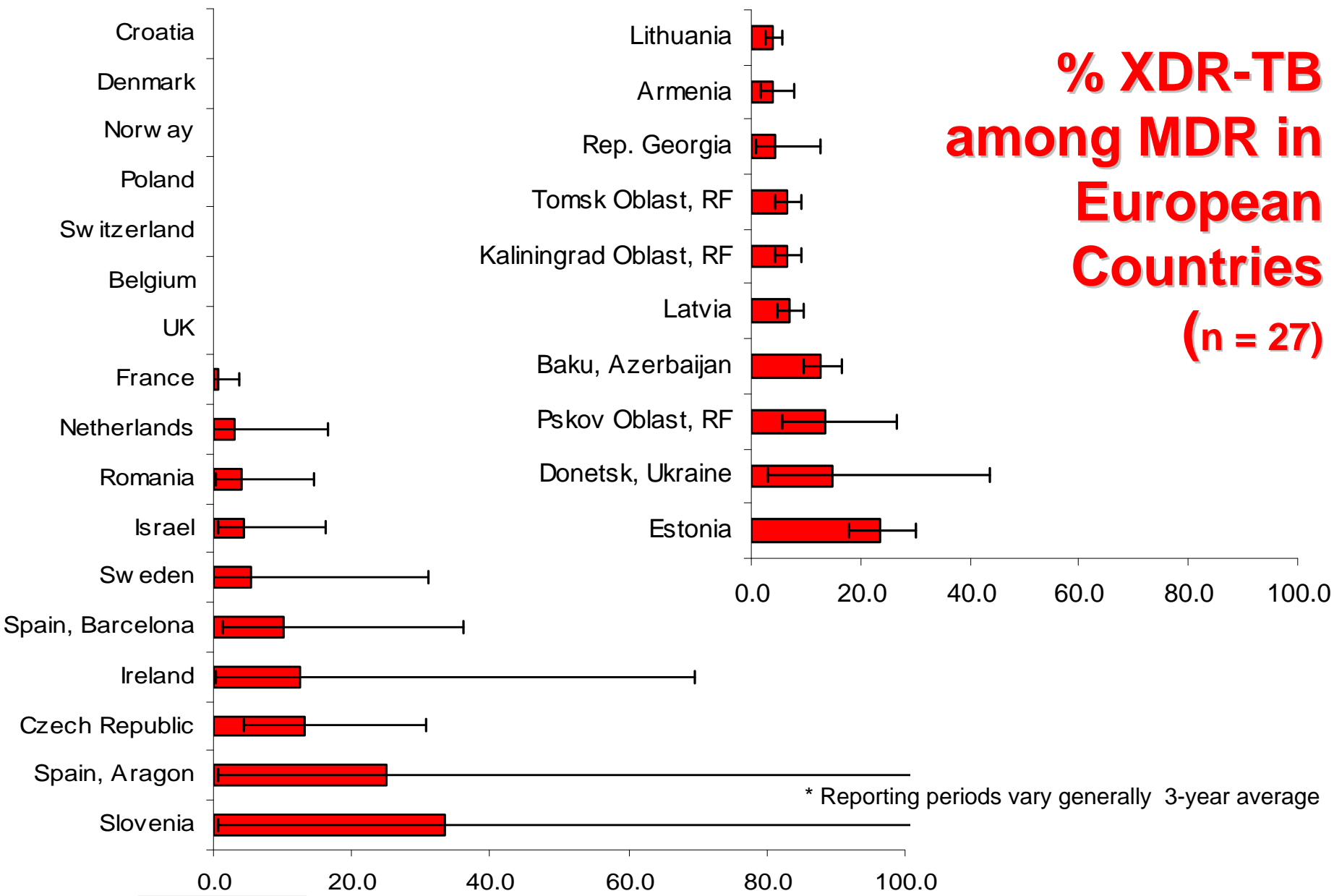
Of 17,690 isolates from 49 countries during 2000-2004 20% were MDR and 2% were XDR

XDR found in:  
USA: 4% of MDR  
Latvia: 19% of MDR  
S Korea: 15% of MDR

Source: MMWR Morb Mortal Wkly Rep 2006; 55:301-5

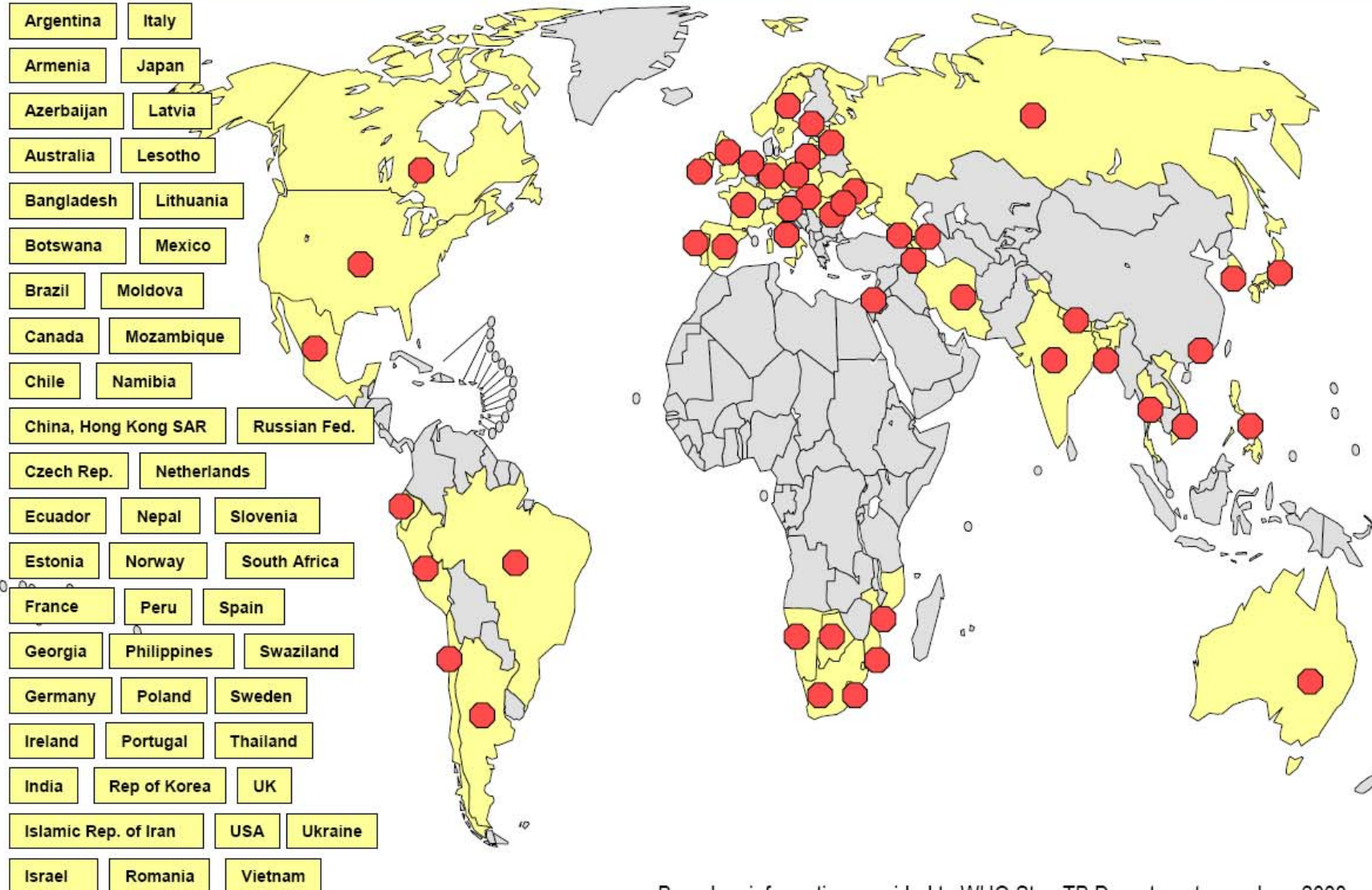


# % XDR-TB among MDR in European Countries (n = 27)



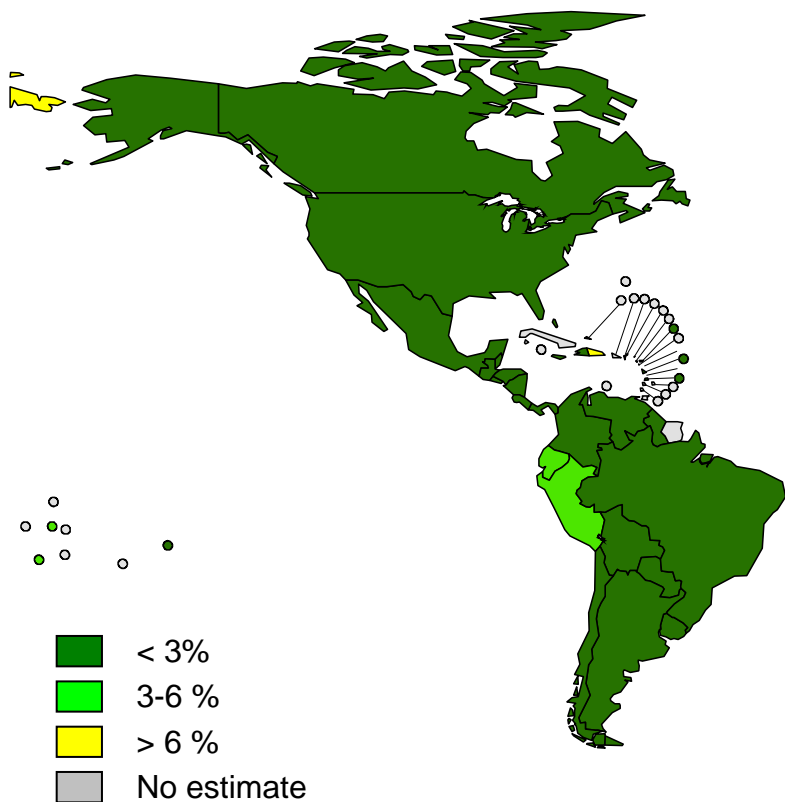
\* Reporting periods vary generally 3-year average

# Countries with Confirmed Cases of XDR-TB as of November 2008

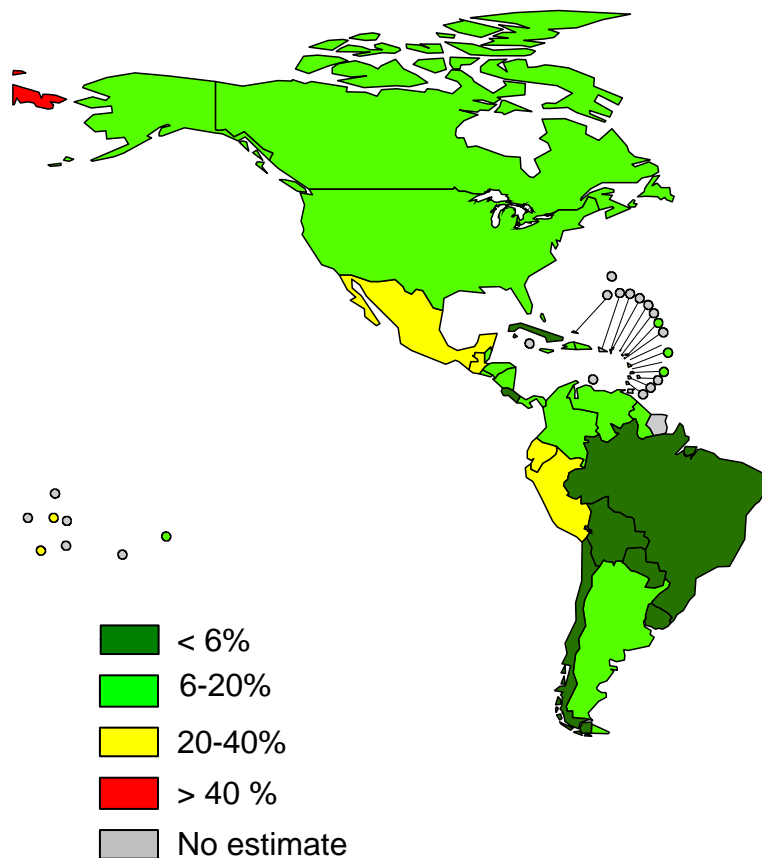


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## Estimated % MDR among New TB cases



## Estimated % MDR among Previously treated TB cases

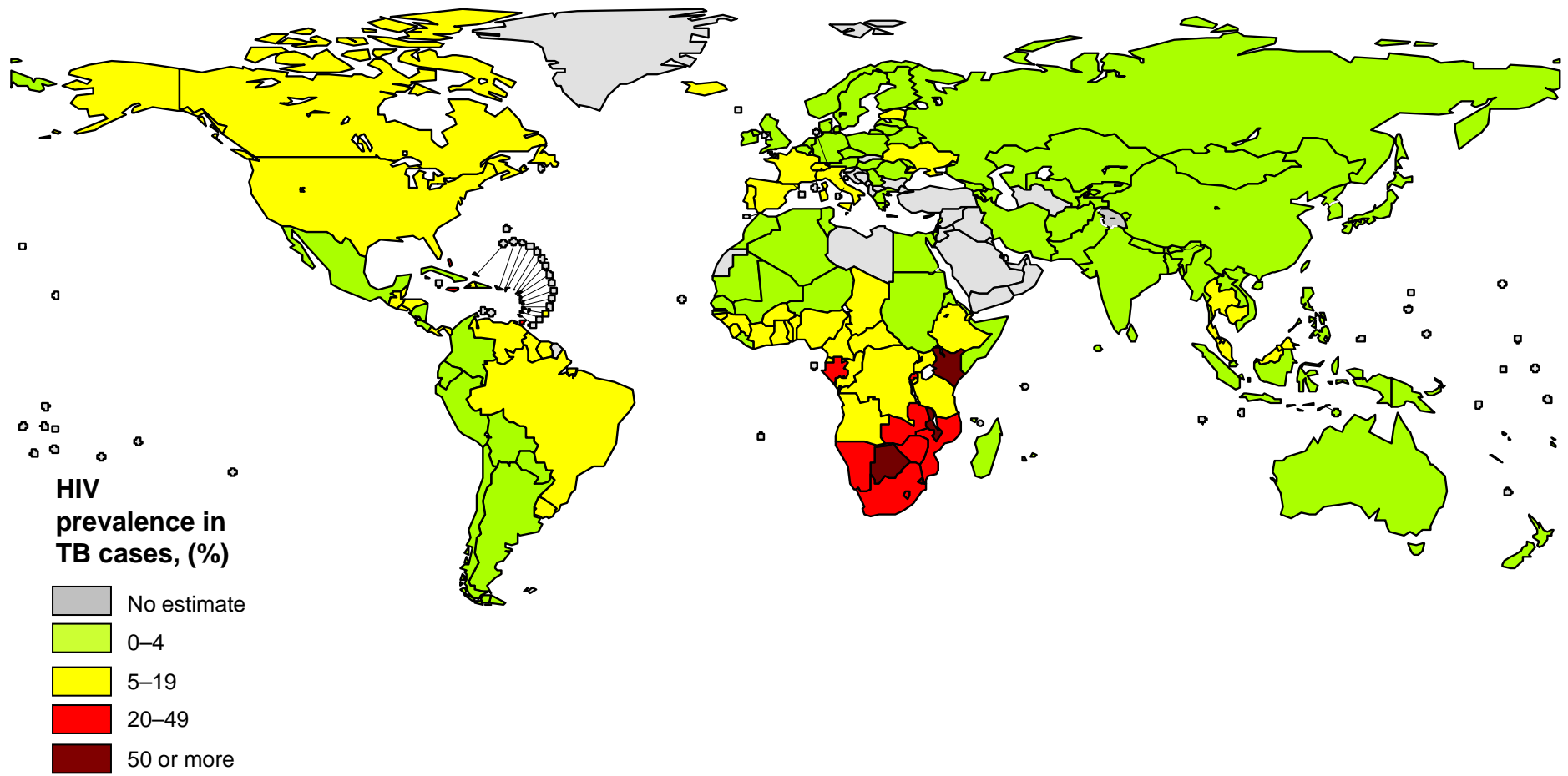


# Anti-TB Drug Resistance: Status as of 2008

- Highest rates in FSU, with MDR rates among new cases higher ( 29%) as DRS expands
- Up to 10% MDR in new cases in China and India
- China, India and Russia account for 60% global MDR-TB burden – but response in all 3 is inadequate
- Baltic states addressing the problem, Estonia reducing all cases and % MDR-TB
- Mortality of M and XDR-TB remains very high
- What is the impact of HIV on MDR?



# Estimated HIV Prevalence in New TB Cases, 2006



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# HIV-associated MDR-TB Outbreaks

- 1980s and 1990s: Outbreaks in Buenos Aires, London, Milan, New York City etc
- Periodic surveys, especially in Africa, did not detect higher rates of HIV among those with drug resistance
- However, prevalences of both HIV and drug resistance are relatively high in many countries, and rising in some
- Further outbreaks MDR and XDR-TB associated with HIV are predictable



# Outbreak of XDR-TB in Tugela Ferry, KZN, South Africa

- 119 patients in TB/ARV integration study
  - 14 deaths
  - 10 (71%) of 14 with MDR-TB
- Suggestive of probable extensive drug resistant TB in hospital
  - 6/10 MDR-TB resistant to all tested first and second line drugs (SLD) for TB
    - Isoniazid, rifampicin, ethambutol, streptomycin
    - Ciprofloxacin and kanamycin
- Prompted survey January 2005 to March 2006

\* Moll A, et al. HIV associated Extensively Drug-Resistant TB (XDR-TB) in Rural KwaZulu-Natal (South Africa MRC Expert Consultation Sept 8, 2006)

# Tugela Ferry MDR-XDR TB Survey

1539 isolates tested

**544 (35%) Cx+**  
***M. tuberculosis***

**995 (65%) Cx Negative**

**221 (41%) MDRTB**

**323 (59%) Susceptible**

**53 (10%) XDR-TB**  
**(24% of MDR-TB)**



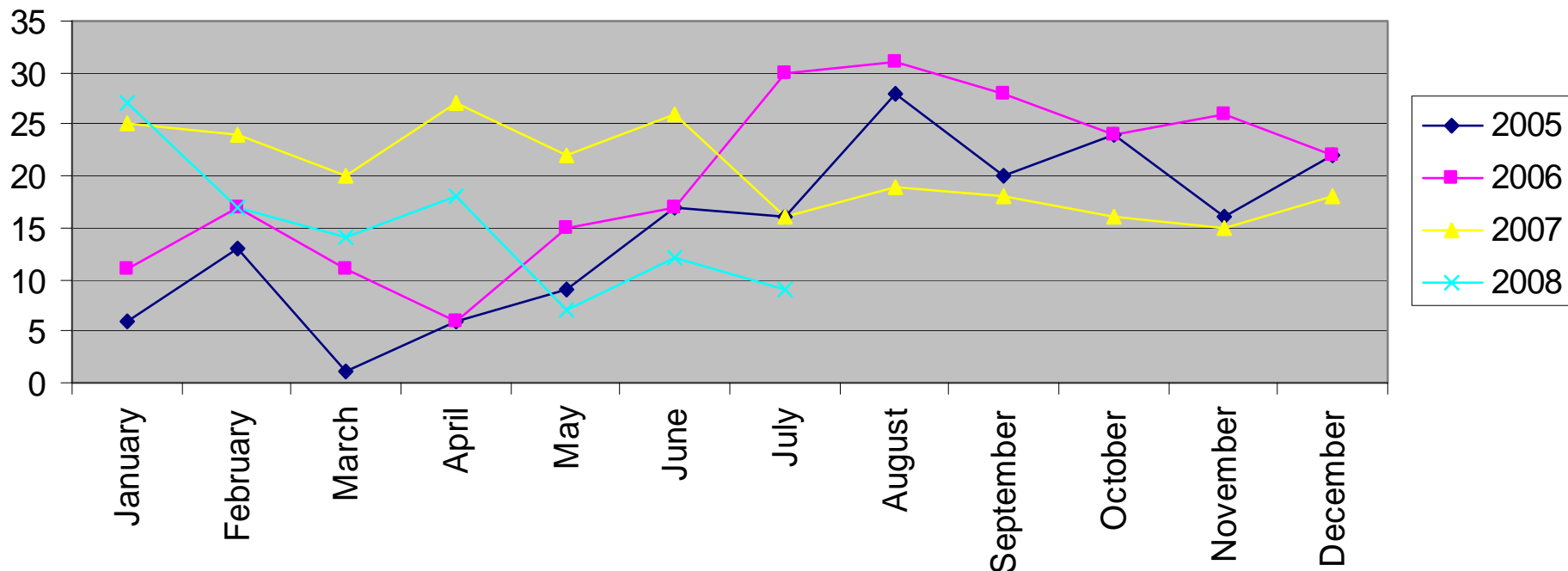
# XDR-TB in Tugela Ferry, South Africa



<i>Study characteristics (53 patients)</i>	<i>No. (%)</i>
■ No prior TB treatment	26 (51)
■ Prior TB treatment	
– Cure or completed treatment	14 (28)
– Treatment Default or Failure	7 (14)
■ HIV-infected (44 tested)	44 (100)
■ Healthcare workers	2
■ Deaths (includes 34% on ARV)	52 ( <b>98</b> )
■ Median survival	16 days
■ Number of TB strains	4+

# MDR and XDR-TB Diagnosed in CoSH, by month, 2005–2008

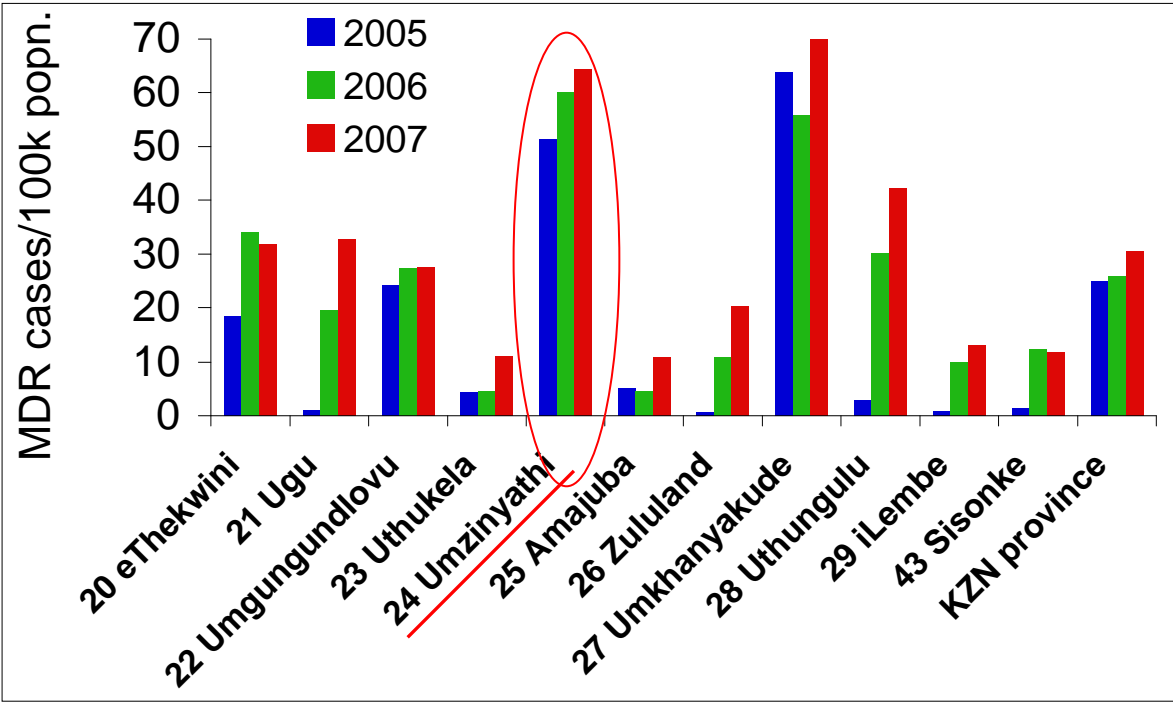
Monthly MDR and XDR Cases (2005–2008)



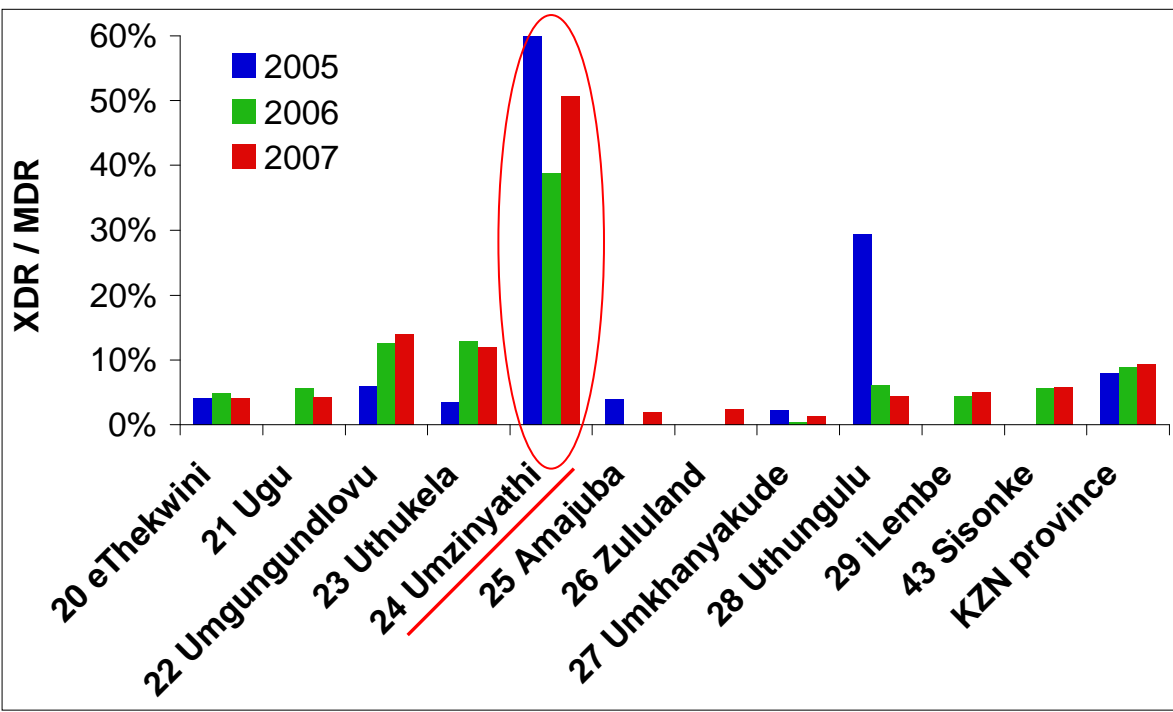
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# MDR cases per 100 000 population (top)



# XDR/MDR-TB (bottom)



(Data for Uthungulu for 2005 excluded)



# MDR-TB and HIV in the Ukraine

	Civilian sector		Penitentiary sector	
	New cases n=924	Previously treated cases n=369	New cases n=78	Previously treated cases n=125
MDR rates (95% CLs)	15.5 (13.1 to 17.8)	41.5 (36.4 to 46.5)	21.8 (12.4 to 31.2)	52.8 (43.9 to 61.7)

- **Independent predictors for MDR-TB**

*History of previous treatment: OR: 4.0 (95%CLs 3.1-5.1)*

*Imprisonment: OR: 1.5 (95%CLs 1.1-2.0)*

- **HIV status: OR: 1.7 (95%CLs 1.3-2.3)**



# Summary Situation of MDR-TB and HIV

- HIV reactivates MDR-TB latent infection, and HIV-infected susceptible to infection by MDR strains, so ...
- HIV is causing outbreaks of MDR-TB
- HIV probably increasing community transmission of MDR-TB, especially where MDR-TB already circulating in community
- Epidemics of HIV (focus: Africa) and MDR (focus: Eastern Europe) now overlap

# TB/HIV Collaborative Activities

## Establish mechanisms for collaboration

- Set up a coordinating body for TB/HIV activities
- Conduct surveillance of HIV prevalence among tuberculosis patients
- Carry out joint TB/HIV planning
- Conduct monitoring and evaluation

The "3 Is"

## Decrease the burden of tuberculosis in people living with HIV/AIDS

- Establish intensified tuberculosis case-finding
- Introduce isoniazid preventive therapy
- Ensure tuberculosis infection control in health care and congregate settings

## Decrease the burden of HIV in tuberculosis patients

- Provide HIV testing and counselling
- Introduce HIV prevention methods
- Introduce co-trimoxazole preventive therapy
- Ensure HIV/AIDS care and support
- Introduce antiretroviral therapy

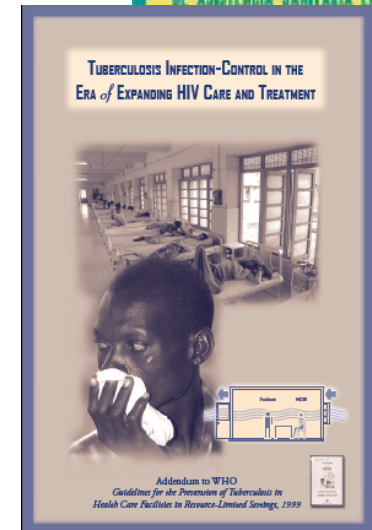


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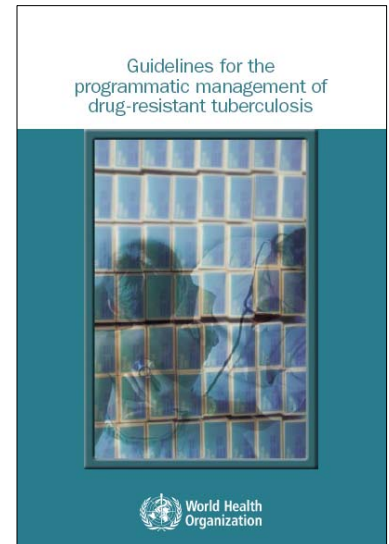
# Prevention of MDR-TB in the Context of HIV

- Involve community representatives in design of care and prevention
- Ensuring high quality basic TB control
- Infection control
  - HIV and ART clinics
  - Guidelines, and WHO policy of January 2009
- Preventive therapy problematic



# Management of MDR-TB in the Context of HIV

- Ensuring rapid diagnosis and management of TB in HIV clinics
  - Intensified case finding
  - Laboratory capacity for MDR-TB diagnosis
    - Culture, solid and liquid
    - Molecular tests, eg line probe assays, now WHO policy
    - DST for all patients?
- Empirical treatment for MDR-TB
  - Avoid thiacetazone



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# Management of MDR-TB in the Context of HIV (II)

- ART
  - When to start
  - Drug interactions
  - Immune reconstitution inflammatory syndrome
- HIV care and support, but remember infection control
- Centres of excellence
- Isolation facilities/involuntary detention
- Care in the community
- Special teams



# THE LANCET

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[www.thelancet.com](http://www.thelancet.com)

“Failure to act now to contain the threat posed by XDR-TB will have devastating consequences for patients with TB, particularly those co-infected with HIV/AIDS.”

See Editorial page 964

## Articles

H5N1 vaccine: phase I trial  
See page 1001

## Articles

FRISC-II: early invasive strategy outcomes at 5 years  
See page 938

## Articles

Burden of valvular heart diseases  
See page 1445

## Articles

Identification of diagnostic markers by proteomic fingerprinting for tuberculosis  
See page 1012

## Seminar

Panic disorder  
See page 1023

# Acknowledgements

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