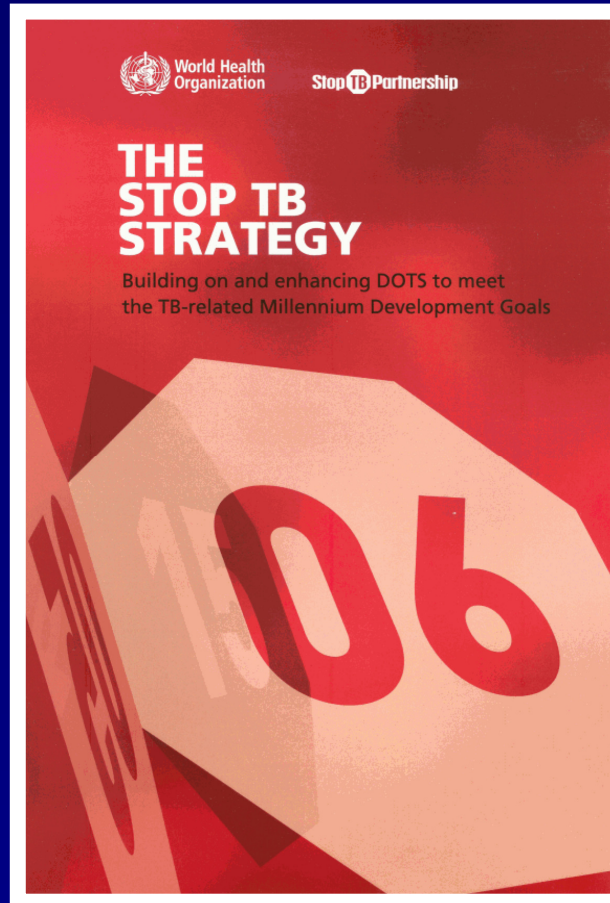


# What can be done against XDR-TB?



Dr Matteo  
Zignol

Stop TB Dep.  
World Health  
Organization  
Geneva



16<sup>th</sup> Swiss Symposium on tuberculosis  
Münchenwiler, 22 March 2007

# XDR-TB – Extensive Drug Resistance



  
**MMWR**<sup>™</sup>  
Morbidity and Mortality Weekly Report

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

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**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 the trend. Although the 2005 TB rate was the lowest recorded in the United States since national reporting began in 1953, the average annual decline has slowed during the past 3 years, multidrug-resistant TB remains a threat, and disparate rates of TB persist among certain racial, ethnic, and foreign-born populations.

Many states are 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>.

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

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**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).

**INSIDE**

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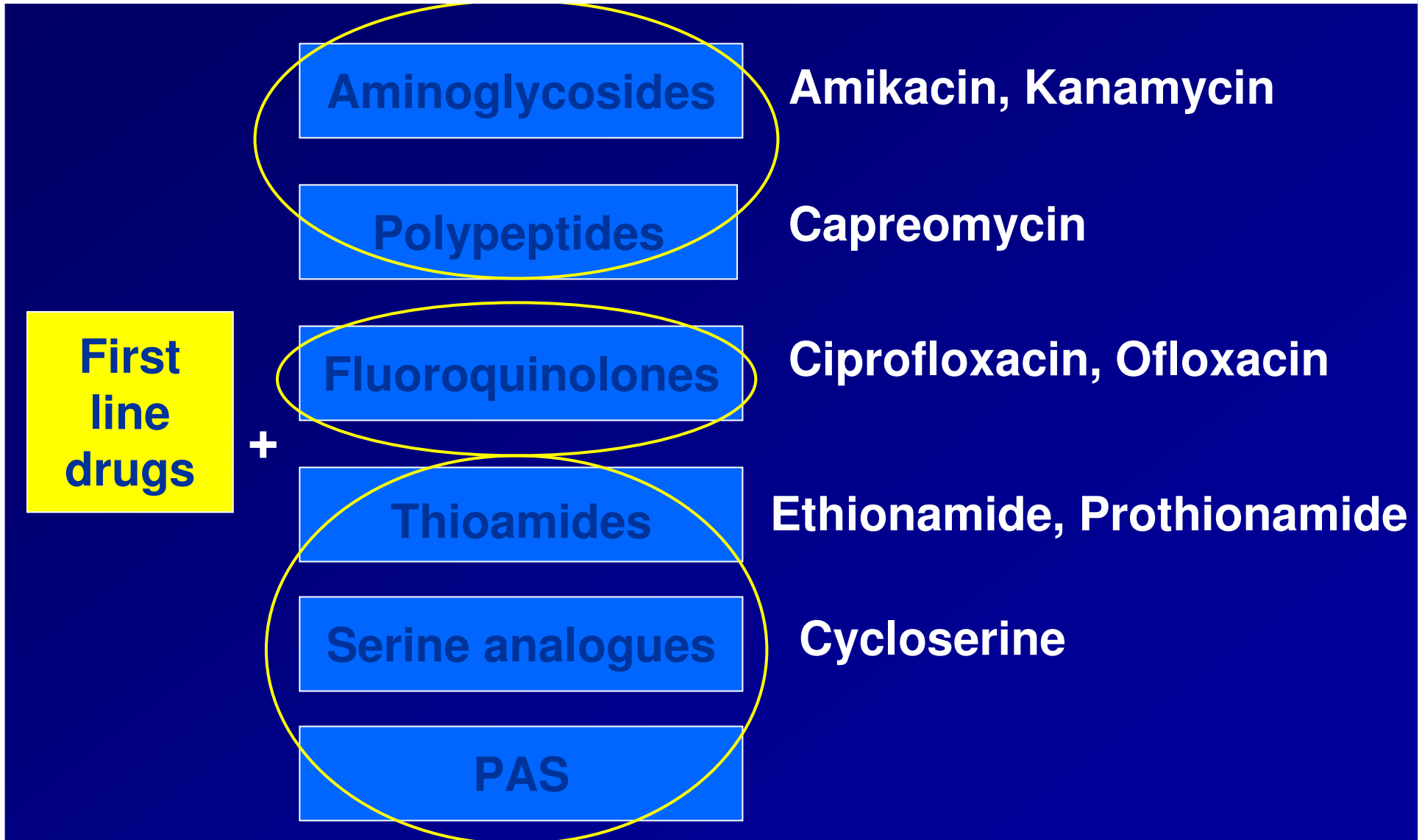
XDR = Resistance to at least INH and RIF (MDR) PLUS resistance to three of the six classes of second-line anti-TB drugs.

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

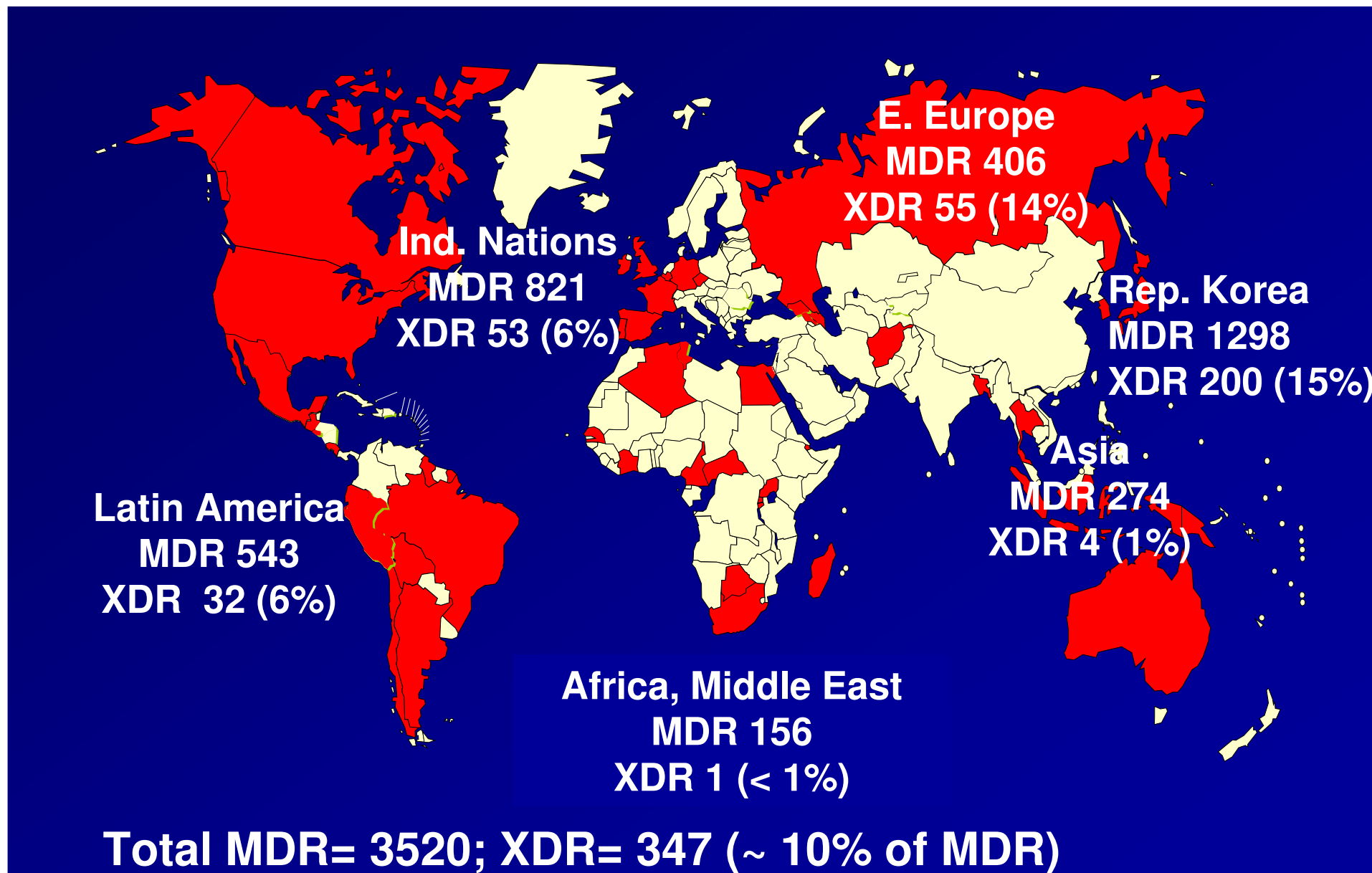
XDR found in  
Southern Africa  
associated with HIV

# Second-Line Drug Classes for MDR TB Treatment



WHO. Guidelines for the programmatic management of drug-resistant tuberculosis. 2006.

# Number of MDR and XDR Cases, 2000–2004



# Global XDR-TB Task Force

## New definition



### Principles:

- Public health surveillance
- Reliable DST methodology
- Clinical relevance
- Relatively simple

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)

## THE LANCET.com

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

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

#### Summary

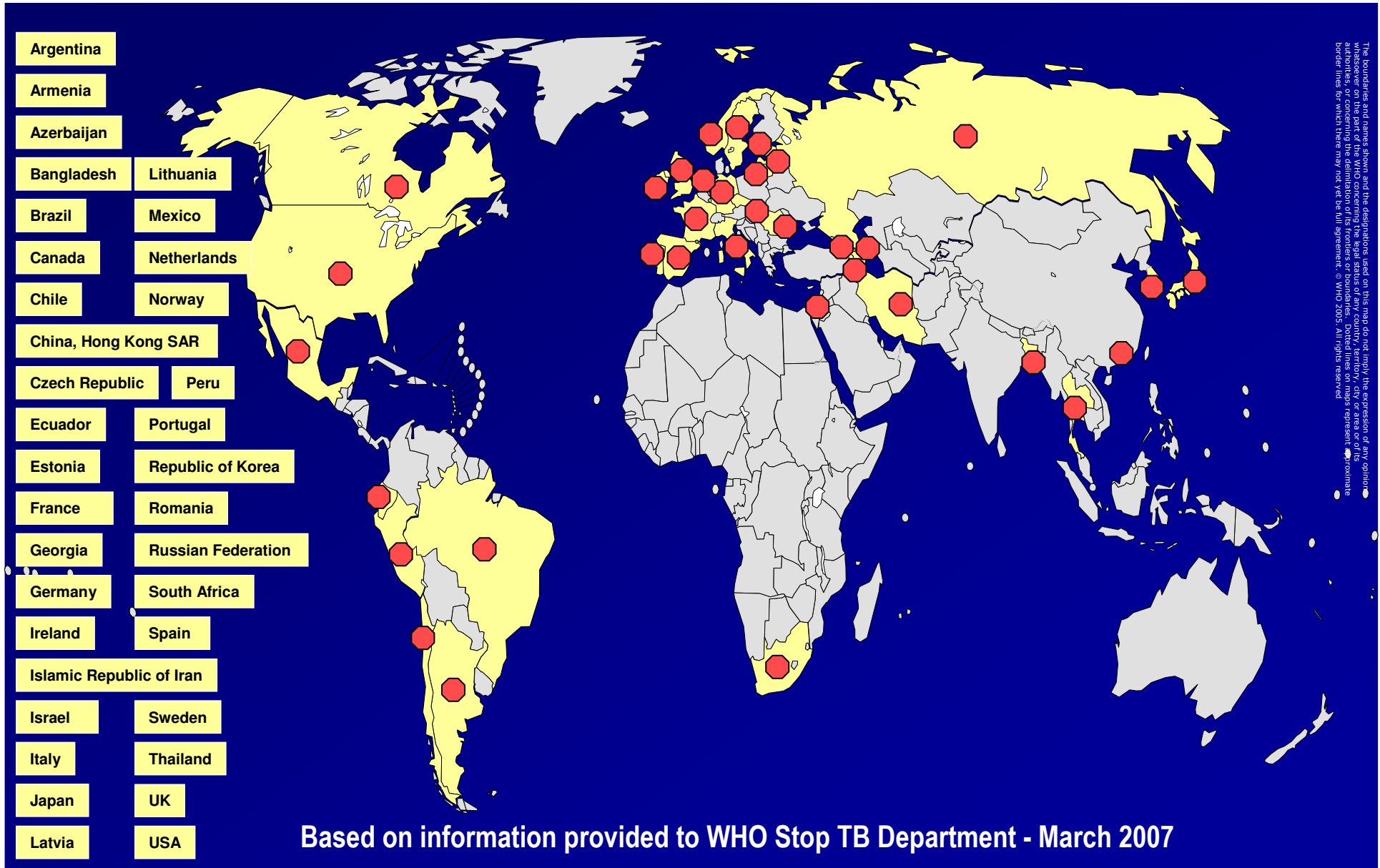
**Background** The epidemics of HIV-1 and tuberculosis in South Africa are closely related. High mortality rates in co-infected patients have improved with antiretroviral therapy, but drug-resistant tuberculosis has emerged as a major cause of death. We assessed the prevalence and consequences of multidrug-resistant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

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

**Results** From January, 2005, to March, 2006, sputum was obtained from 1539 patients. We detected MDR tuberculosis in 221 patients, of whom 53 had XDR tuberculosis. Prevalence among 475 patients with culture-confirmed tuberculosis was 39% (185 patients) for MDR and 6% (30) for XDR tuberculosis. Only 55% (26 of 47) of patients with XDR

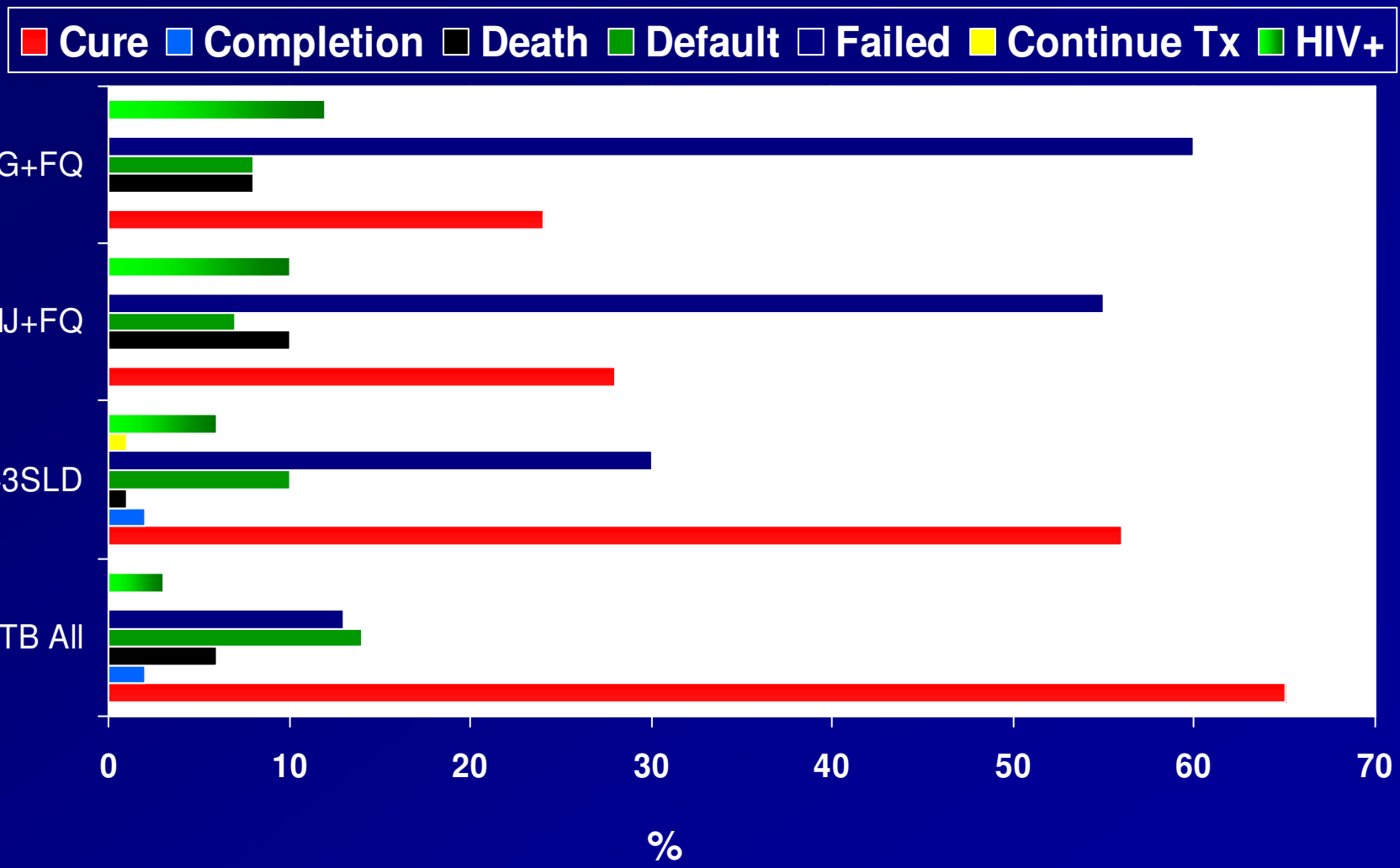
<u>Characteristics</u>	<u>No. (%)</u>
No prior TB Treatment	26 (51)
Prior TB treatment	
- Cure or Completed treatment	14 (28)
- Treatment Default or Failure	7 (14)
HIV-infected (44 tested)	44 (100)
Dead (includes 34% on ARV)	52 (98)
Identical <i>M. tb</i> spoligotype	26/30

# Countries with XDR-TB Confirmed cases to date



The boundaries and names shown and the designations used on this map do not imply the expression of any opinion on the part of WHO concerning the legal status of any country, territory, or sea area or its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement. © WHO 2005. All rights reserved.

# Treatment outcomes XDR-TB



Leimane V et al. First Global XDR TB Task Force Meeting. Oct 9, 2006  
(from N = 820 evaluated)

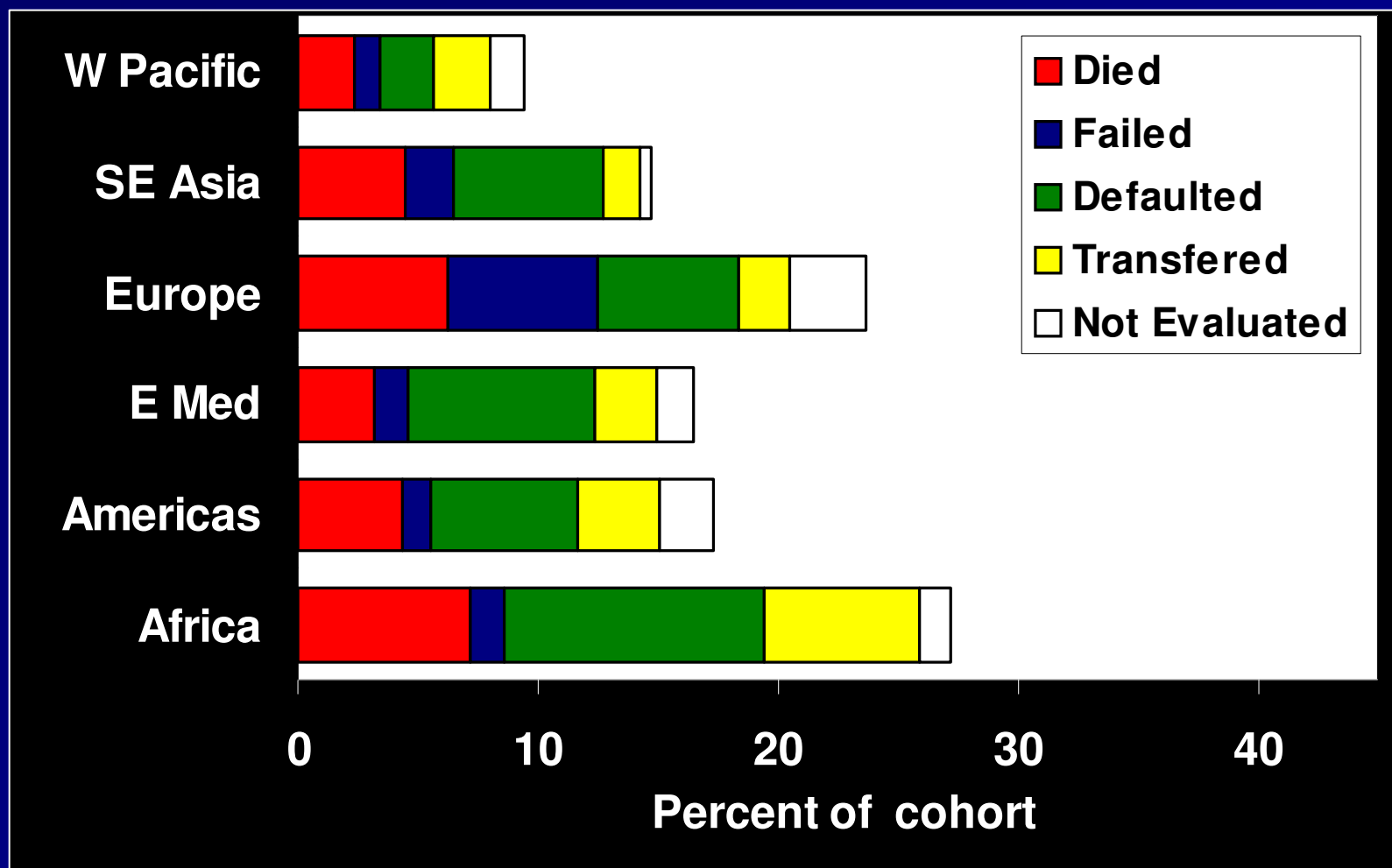
# What can be done against XDR-TB?



1. Strengthen basic TB and HIV/AIDS control, to avoid creation of MDR-TB and XDR-TB
2. Scale-up programmatic management of MDR-TB and XDR-TB
3. Strengthen laboratory services for adequate and timely diagnosis of MDR-TB and XDR-TB
4. Expand MDR-TB and XDR-TB surveillance
5. Introduce infection control, especially in high HIV prevalence settings
6. Strengthen advocacy, communication and social mobilization
7. Pursue resource mobilization at global, regional and country levels
8. Promote research and development into new diagnostics, drugs and vaccines

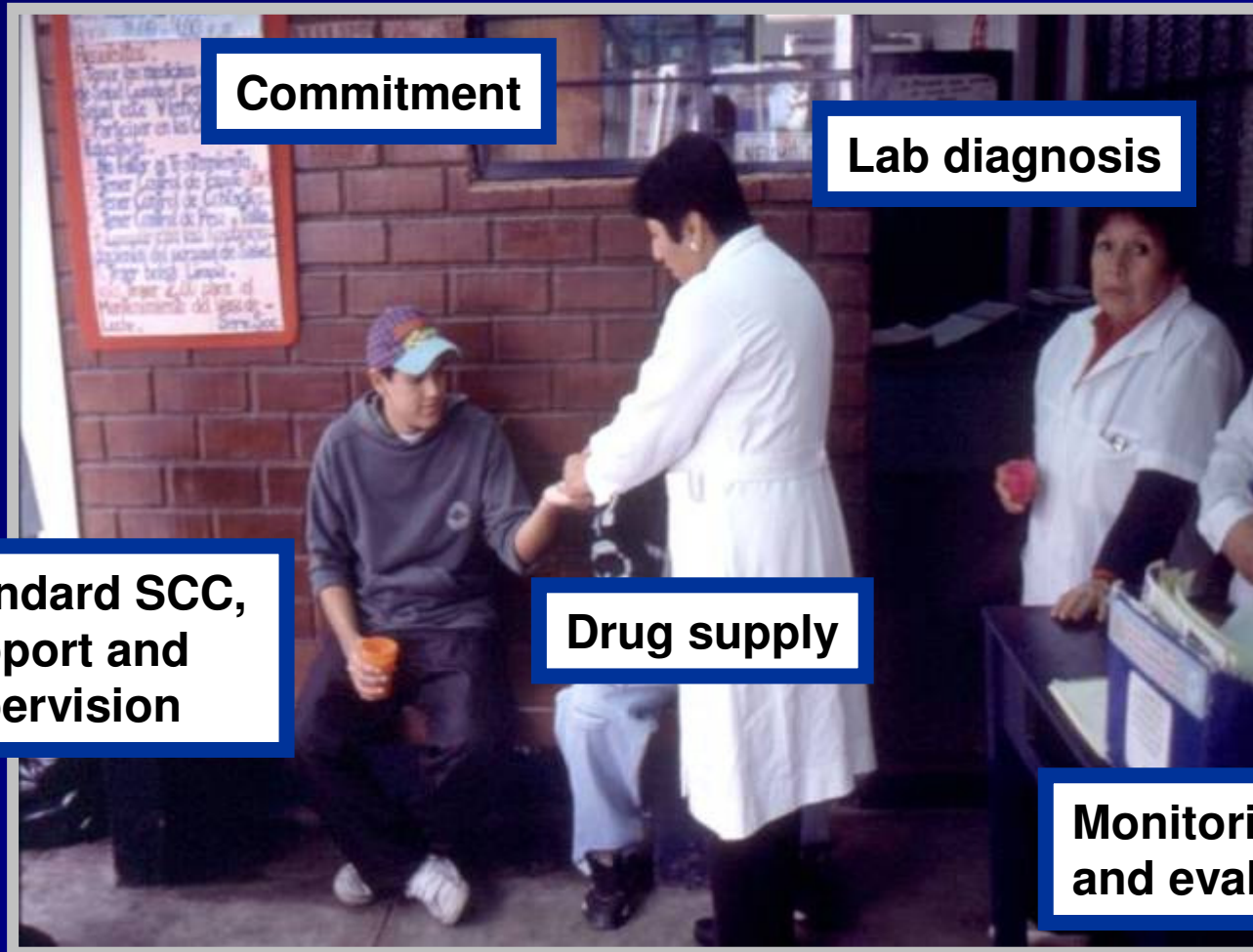
# 1. Strengthen basic TB control

## Reasons for failure



# 1. Strengthen basic TB control

DOTS on the ground + patient support = cure

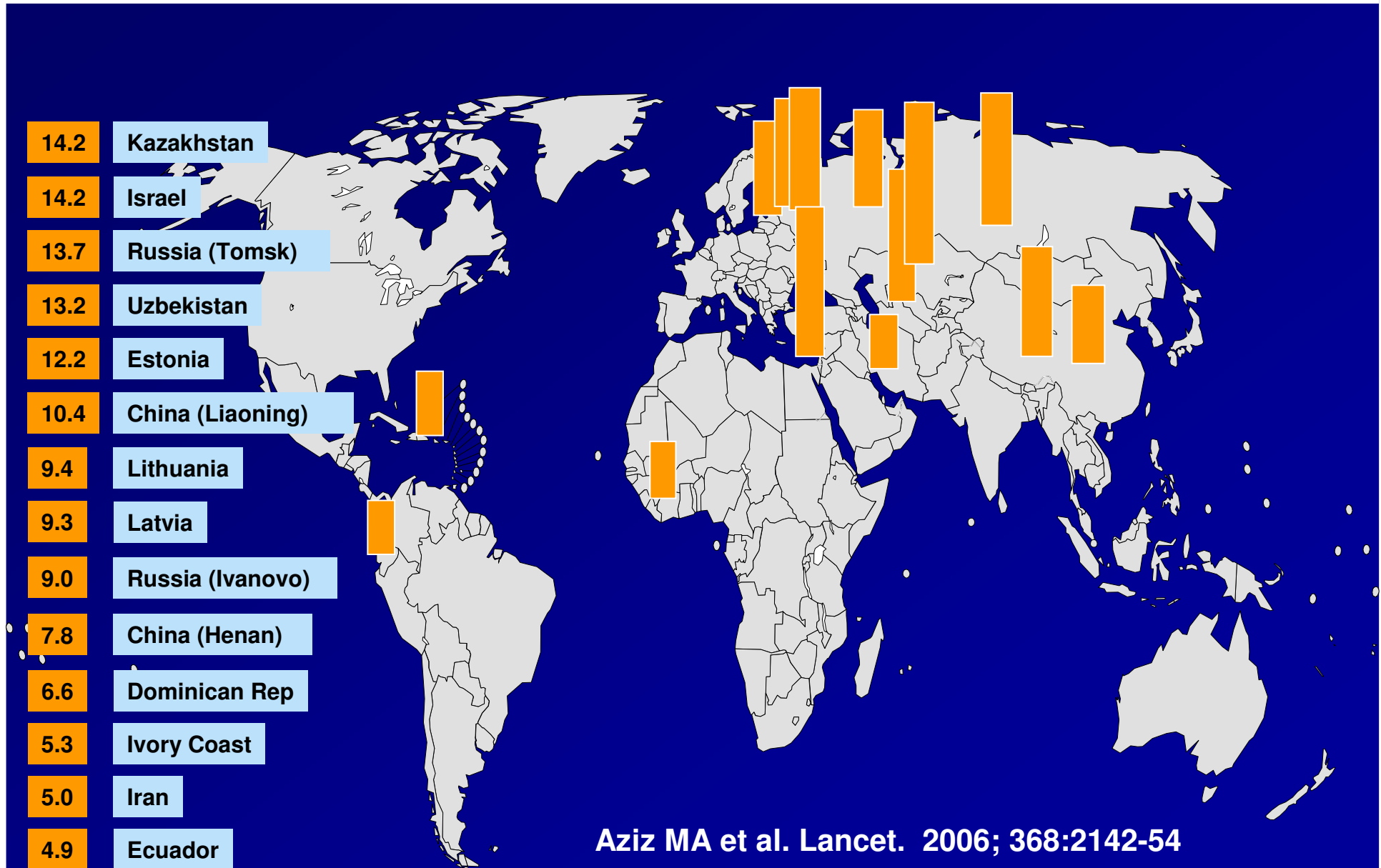


Centro de Salud Lima Norte, Peru

# 1. Strengthen basic TB control Involving all providers

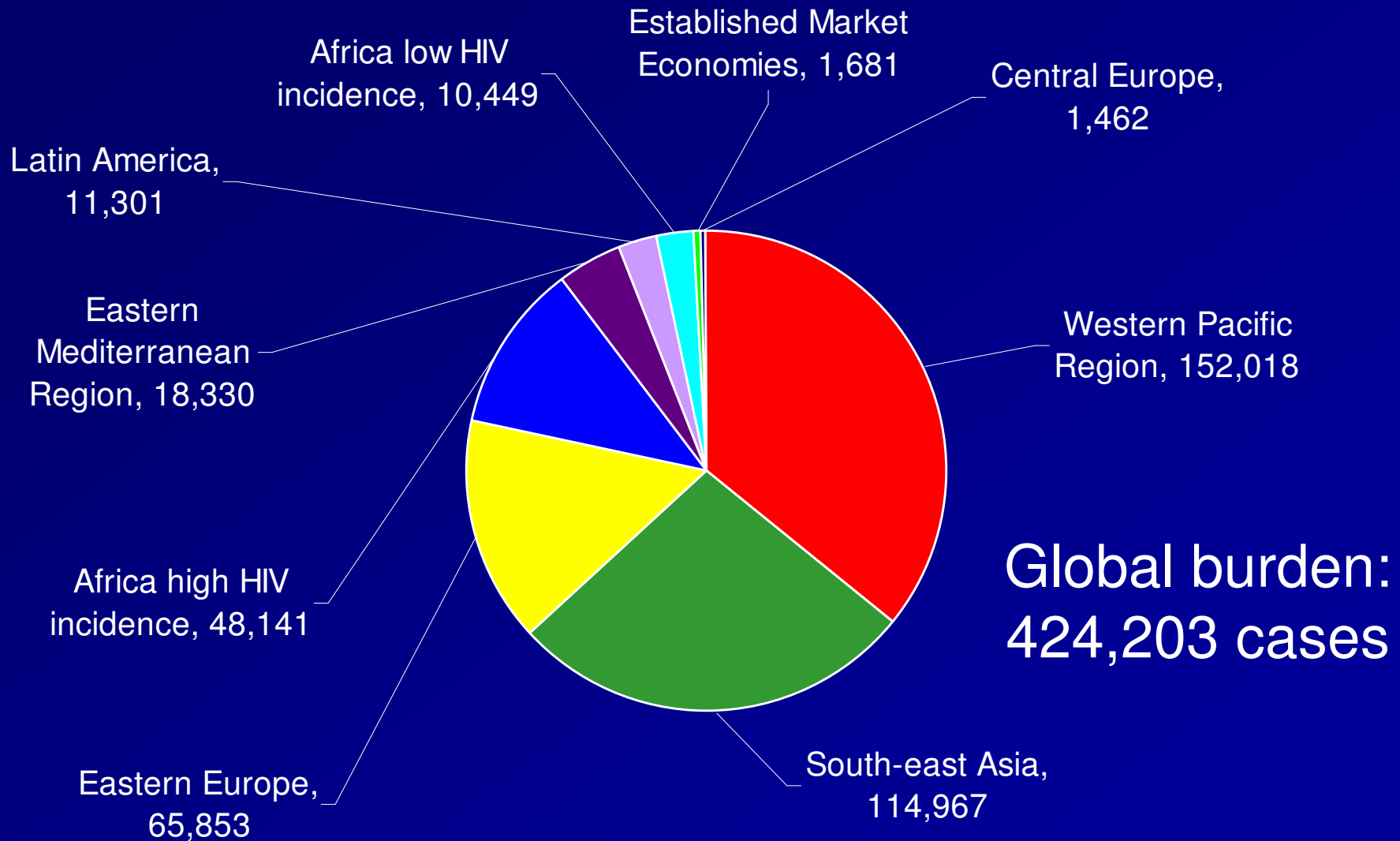


## 2. Scale-up programmatic management of MDR & XDR MDR-TB prevalence in new cases, 1994-2003



## 2. Scale-up programmatic management of MDR & XDR

### Estimated number of MDR-TB cases, 2004

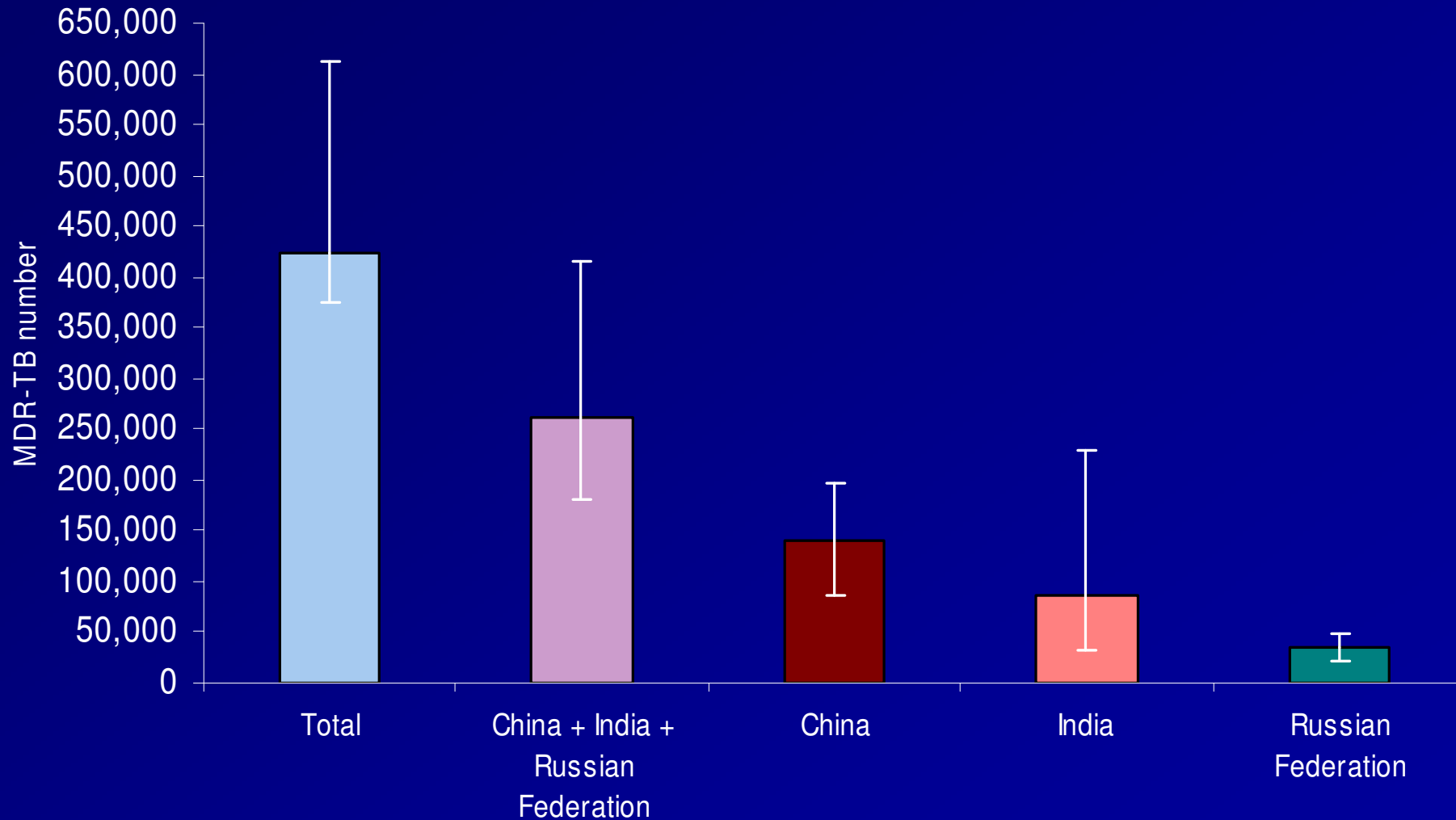


## 2. Scale-up programmatic management of MDR & XDR



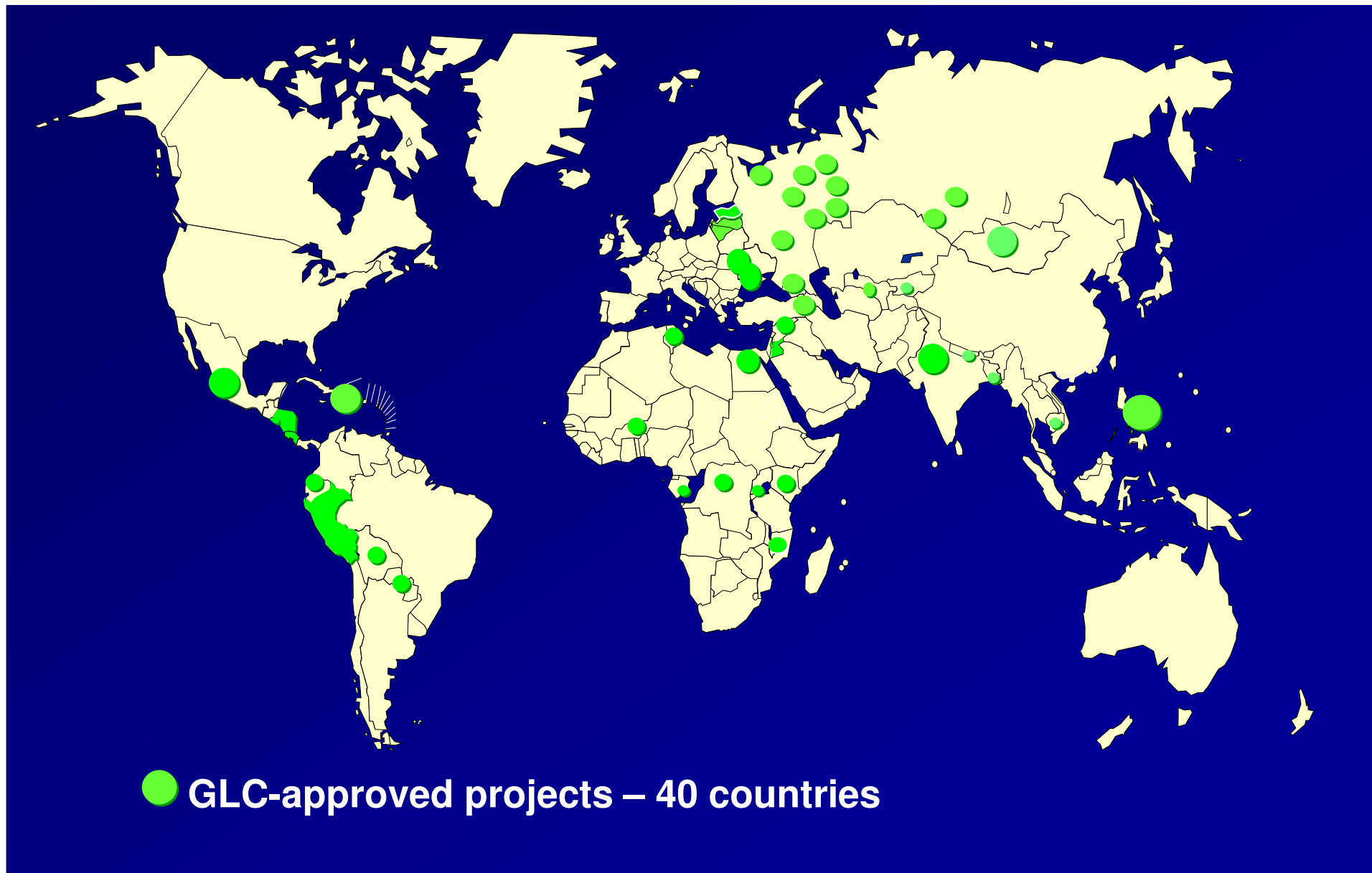
WHO

### Estimated number of MDR-TB cases, 2004



Zignol M et al. *JID*. 2006 194:479-85

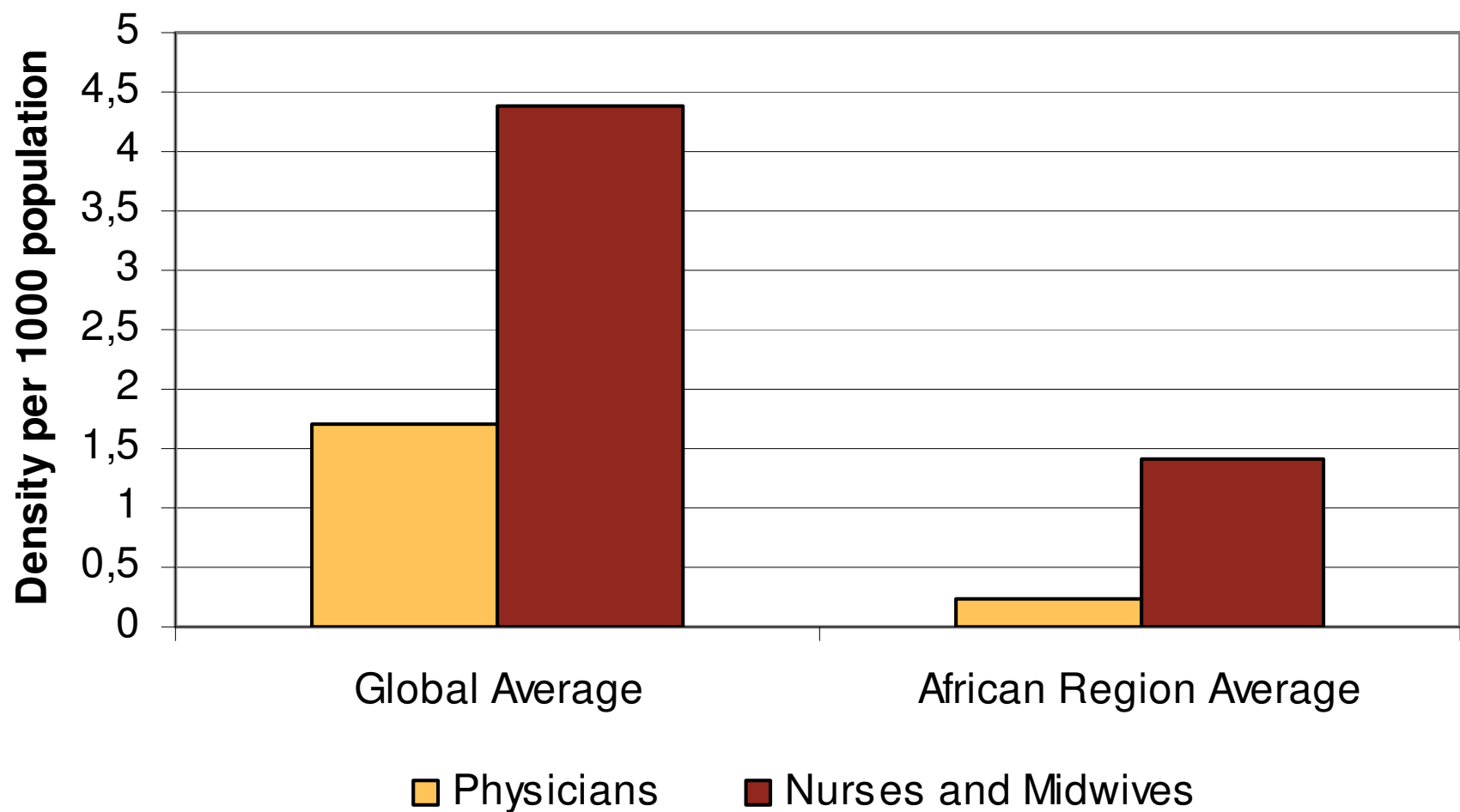
## 2. Scale-up programmatic management of MDR & XDR GLC-approve projects, end 2006





## 2. Scale-up programmatic management of MDR & XDR

### The challenge of Human resources



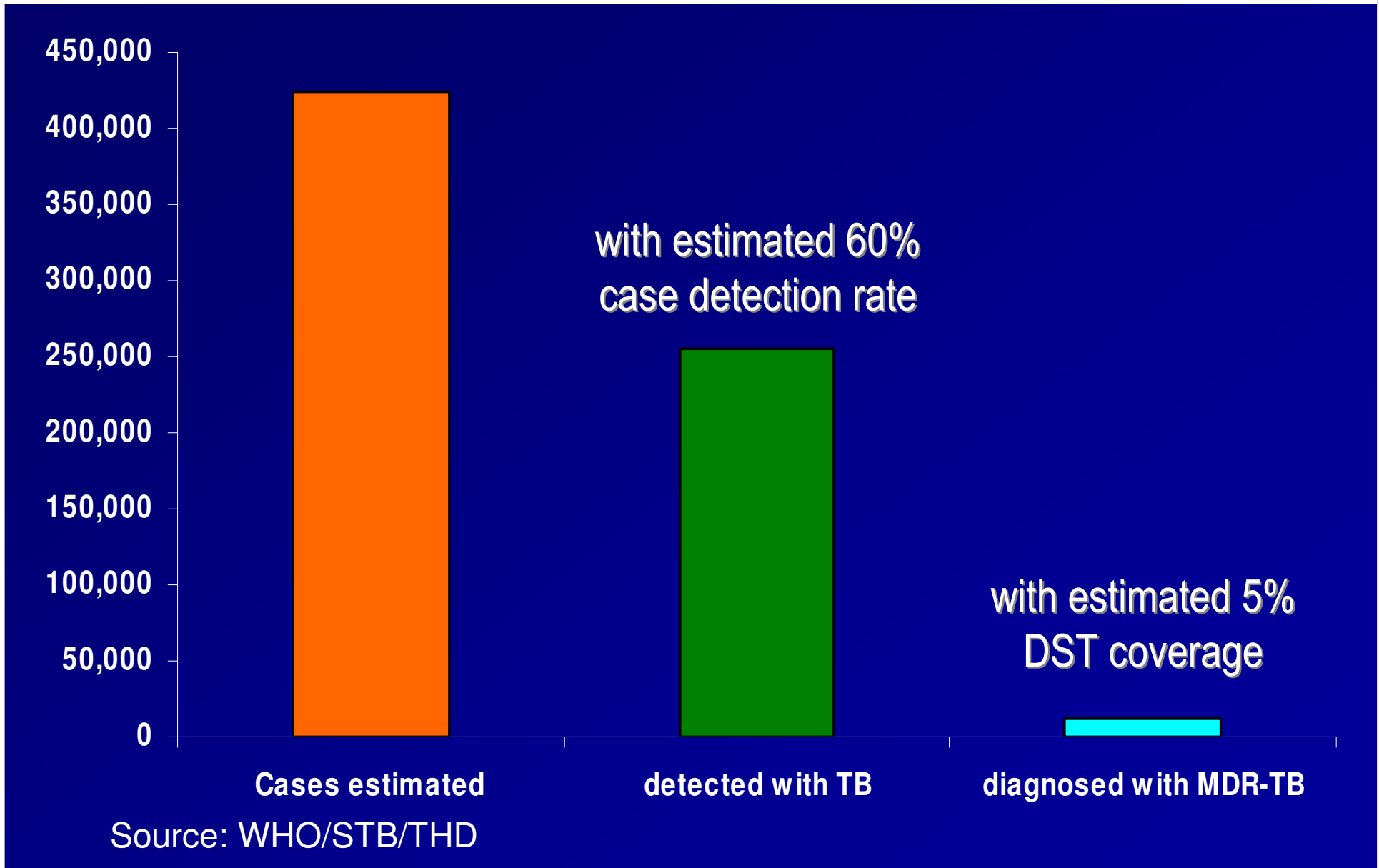
# 3. Strengthen laboratory services

## The Supranational Lab Network



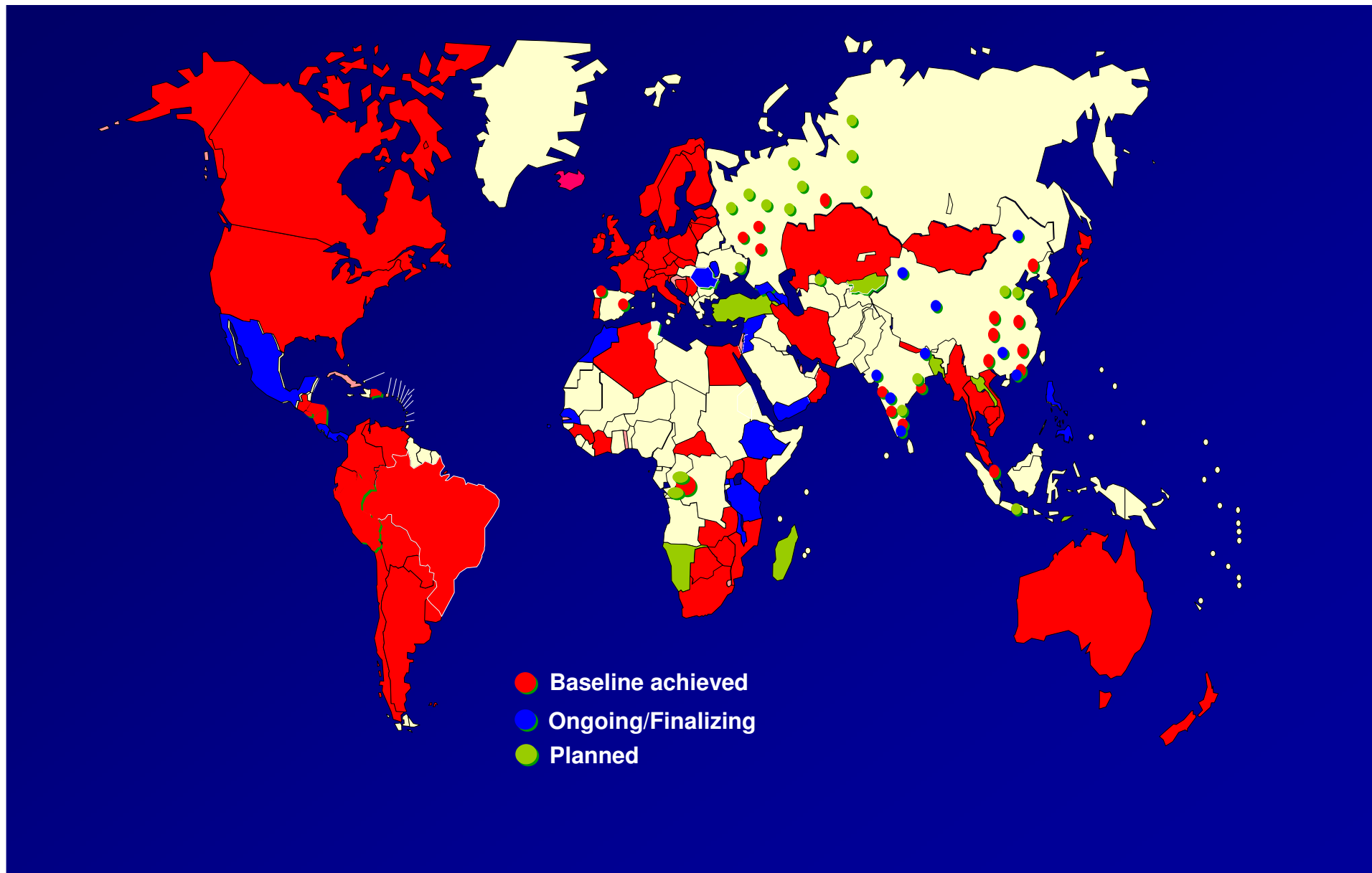
### 3. Strengthen laboratory services

#### The gap



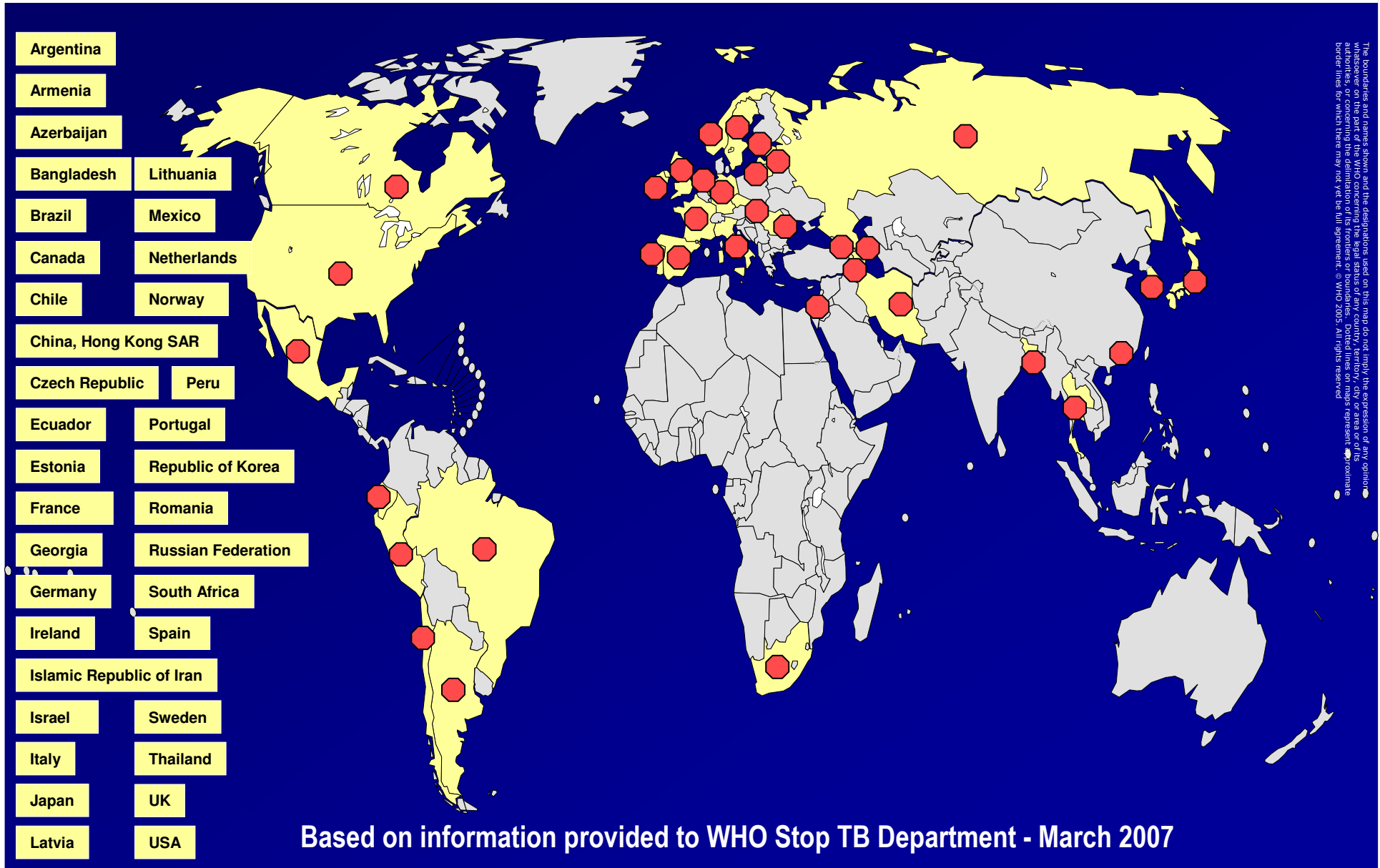
# 4. Expand MDR-TB and XDR-TB surveillance

## Coverage of the Global Project, 2006



# 4. Expand MDR-TB and XDR-TB surveillance

## Confirmed XDR-TB cases to date



## 5. Introduce infection control



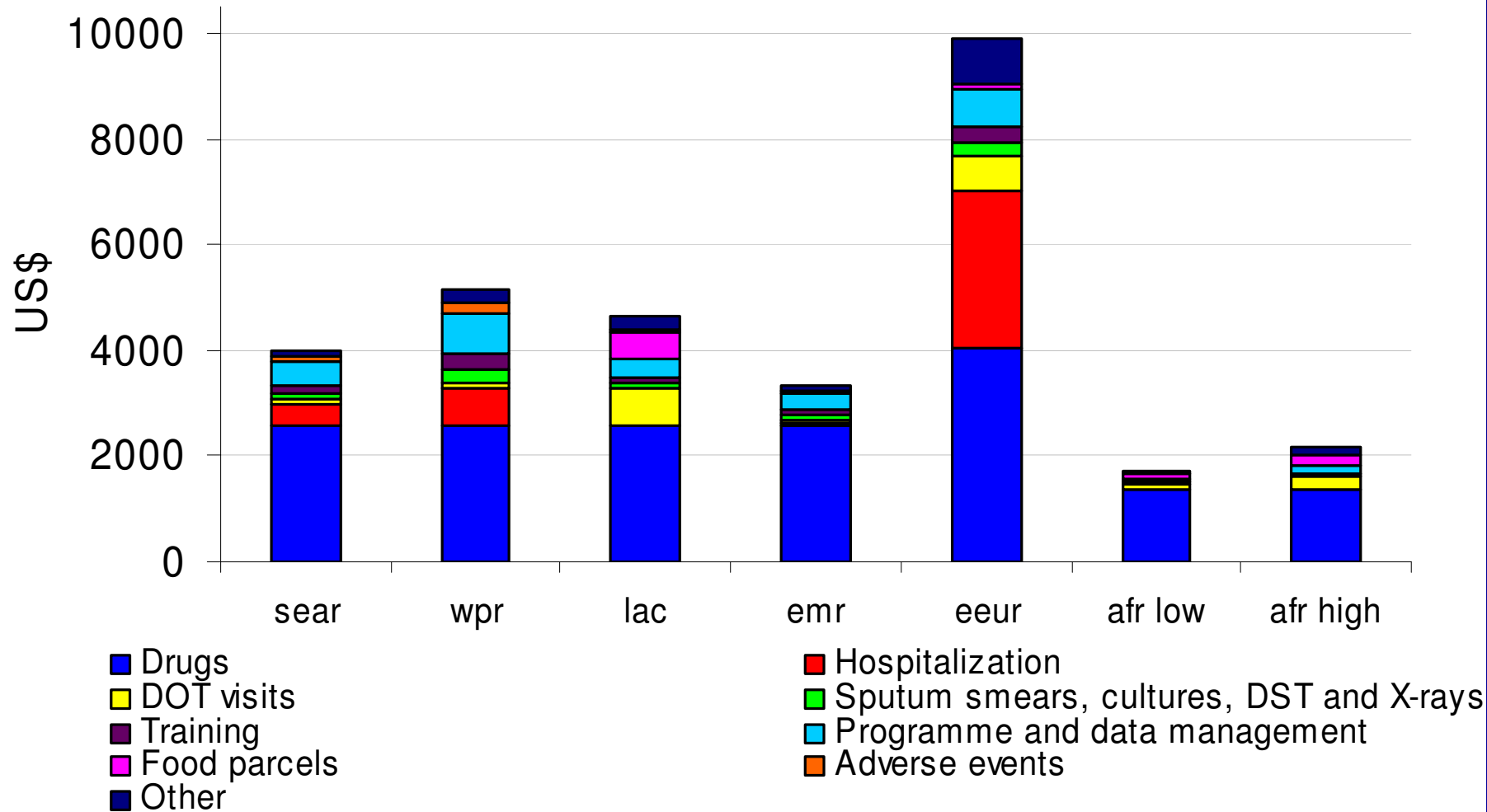
## 6. Strengthen advocacy, communication and social mobilization



**Role of community workers in TB control R.J. State, Brazil**

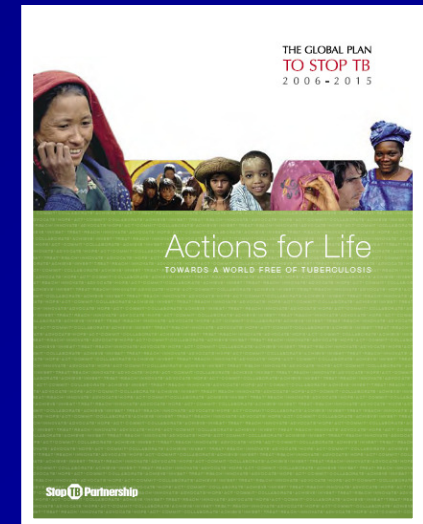
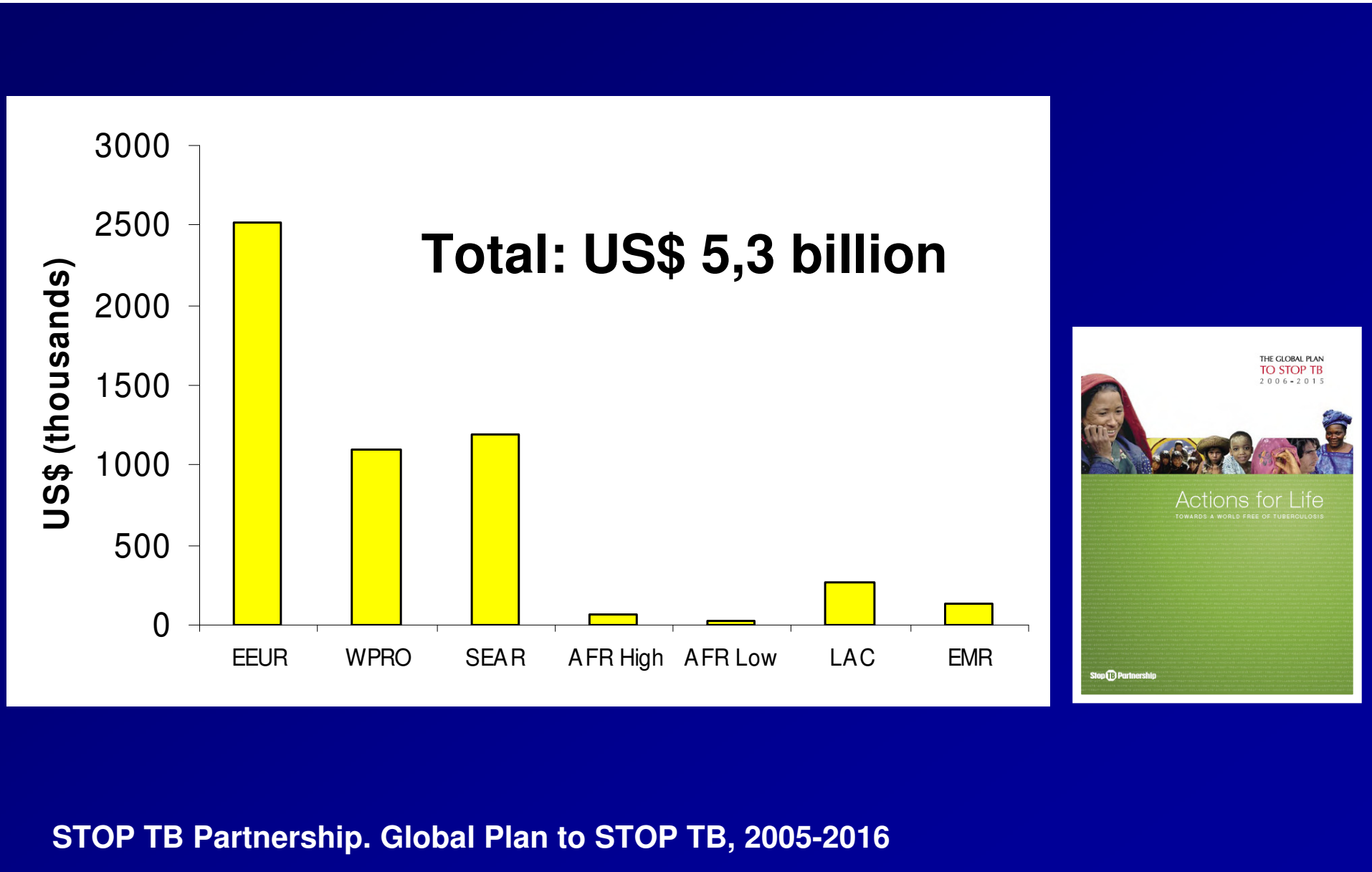
# 7. Pursue resource mobilization

## Cost per MDR-TB patient treated



# 7. Pursue resource mobilization

## Total amount needed to treat MDR-TB, 2006-2015



## 8. Promote research and development into new diagnostics, drugs and vaccines



No global "movement" attempting at convening basic scientists involved in upstream research or implementers involved in operational research

Scarcity of funds (1/10 of HIV R&D devoted to TB) and scarcity of coordination and debate world-wide

Without basic science, research in immunology, pathogenesis, genomics etc, scarcity of products to get into pipeline for development

Most people involved in control activities have no interest in advocating for intensified and well financed research

## 8. Promote research and development into new diagnostics, drugs and vaccines



MDR-TB and XDR-TB diagnosis based on long and old procedures, at times unreliable

- lack of new rapid culture and DST (in developing countries)

Defaulting a major issue in many programmes due to long duration of treatment

- long intermittency or shorter regimens not available
- no new drugs

MDR/XDR-TB/HIV co-infection

- interactions between 2<sup>nd</sup> line anti-TB drugs and ARVs largely unknown

A largely ineffective vaccine

# Conclusions

## The next steps to control XDR-TB



1. Strengthen basic TB and HIV/AIDS control, to avoid creation of MDR-TB and XDR-TB
2. Scale-up programmatic management of MDR-TB and XDR-TB
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