Open Forum II
Key Issues in TB Drug Development
London, 12-13 December, 2006

Challenges in Studying and treating MDR and XDR-TB: Extent of the problem

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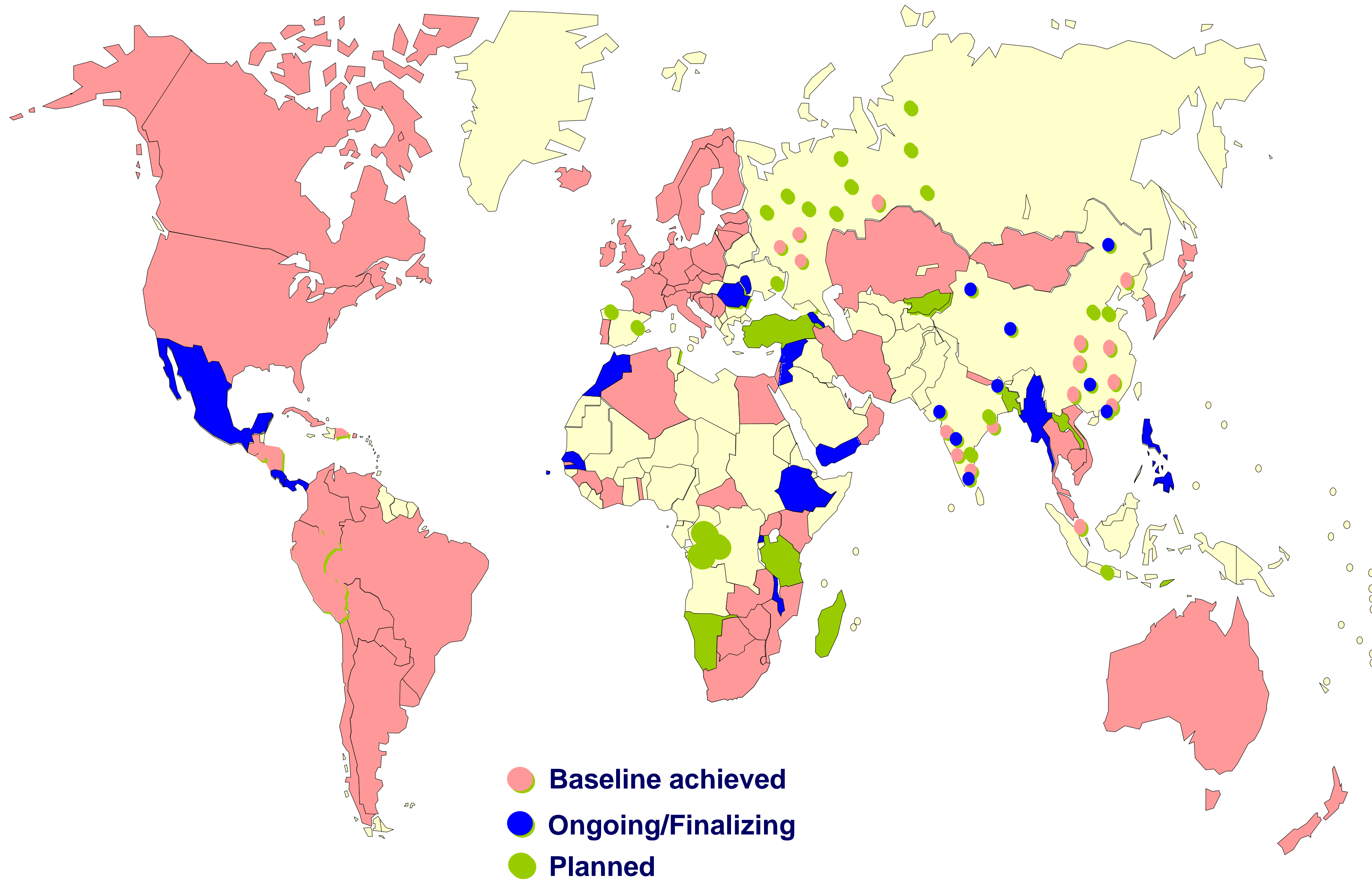
Drug resistance survey coverage 2005



World Health Organization

Global Estimate of MDR-TB

Incident MDR-TB cases 2004 is

424,203

(95% CI, 376,019–620,061),

which is 4.3% (95% CI, 3.8%–6.1%) of the total of new and previously treated cases notified in 2004

Zignol M et al (2006). Global Incidence of Multidrug-Resistant Tuberculosis, JID 2006:194 (15 August)

Highest MDR-TB rates

> 10% among new cases

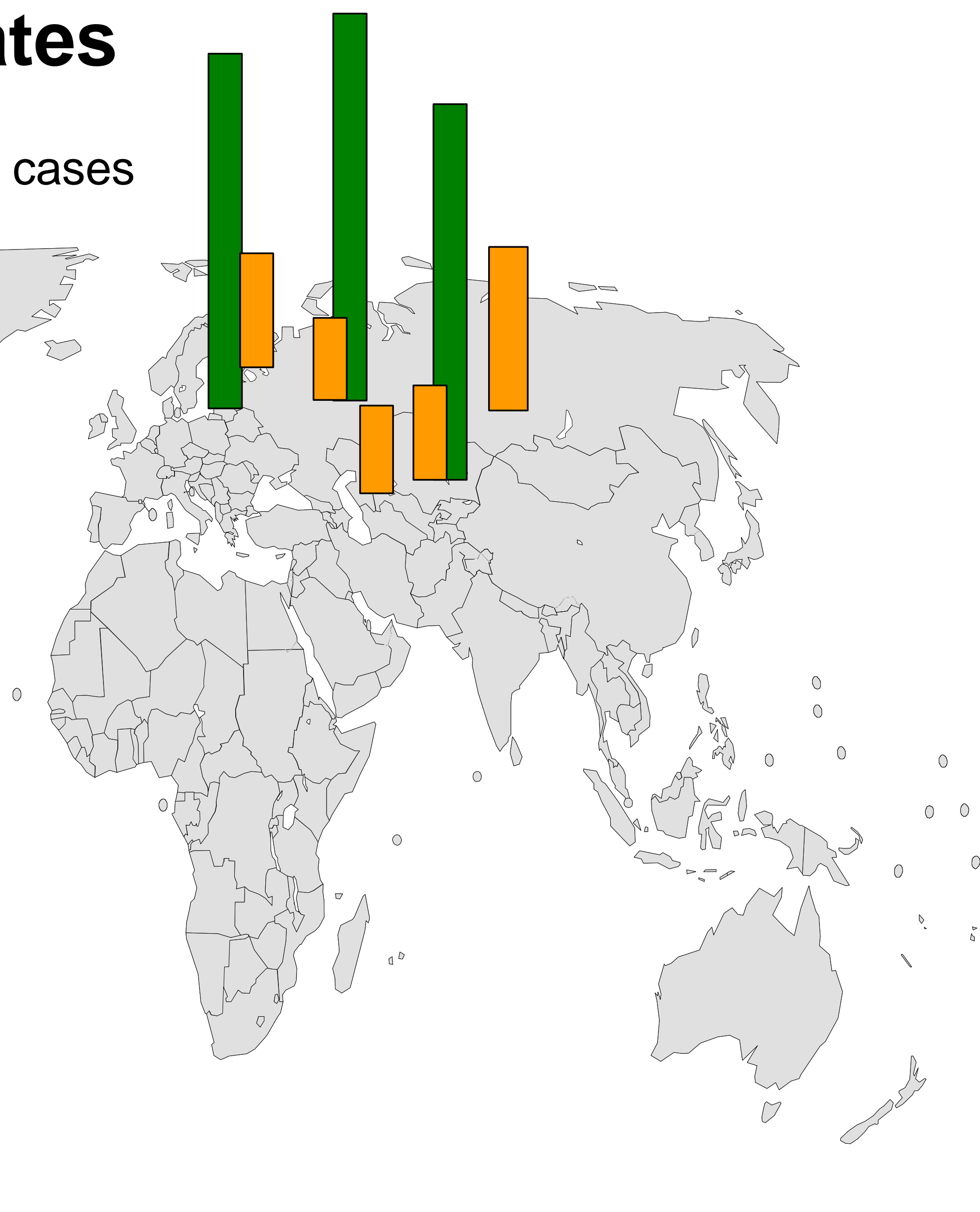
> 50% among previously treated cases

New cases

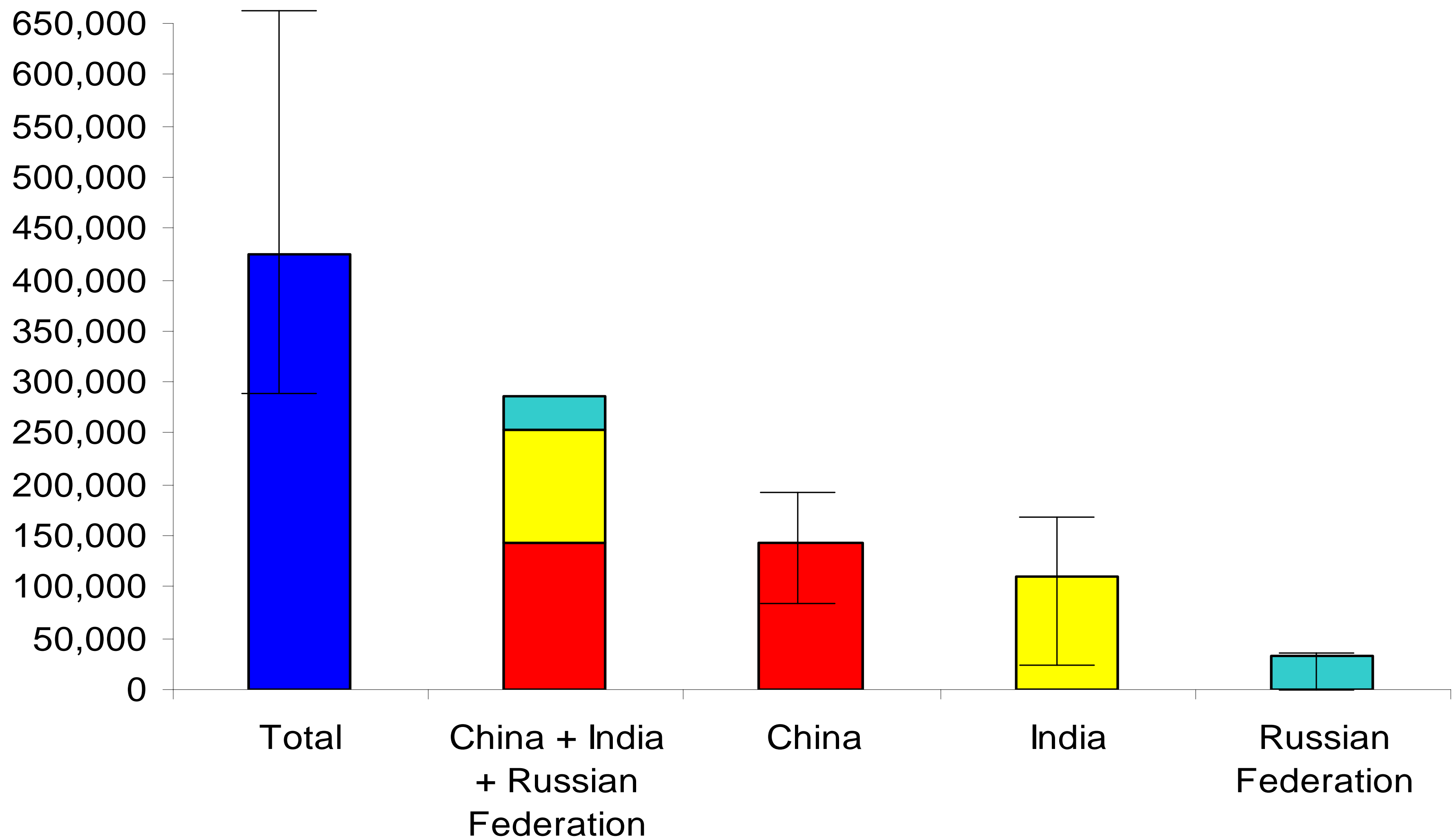
17.1	Estonia
14.2	Kazakhstan
13.7	Russia (Tomsk)
13.2	Uzbekistan
12.3	Russia (Ivanovo)

Previously treated cases

58.1	Russia (Ivanovo)
56.4	Kazakhstan
53.3	Lithuania



HIV epidemic worsening in the areas with the highest number of MDR-TB cases estimated in 2004



Source: WHO/STB/THD

Progress in addressing MDR-TB

- 42 countries using the Green Light Committee mechanism
- GFATM MDR-TB programmes in India, China, Russia
- Increasing number of trained consultants in MDR-TB management
- Supranational Reference Laboratory Network expansion
- MDR-TB cure rate reaching 80% in the first GLC-approved projects
- Increasing number of drug manufacturers submitting dossiers to the WHO Prequalification programme
- Drug resistance survey (DRS) of second line TB drugs underway within routine DRS

Emergence of XDR-TB

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 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.

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 = Multidrug-resistant TB (MDR-TB) plus resistance to (i) any *fluoroquinolone*, and (ii) at least 1 of 3 injectable second-line drugs *capreomycin, kanamycin, amikacin* (new definition agreed October 2006)

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

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

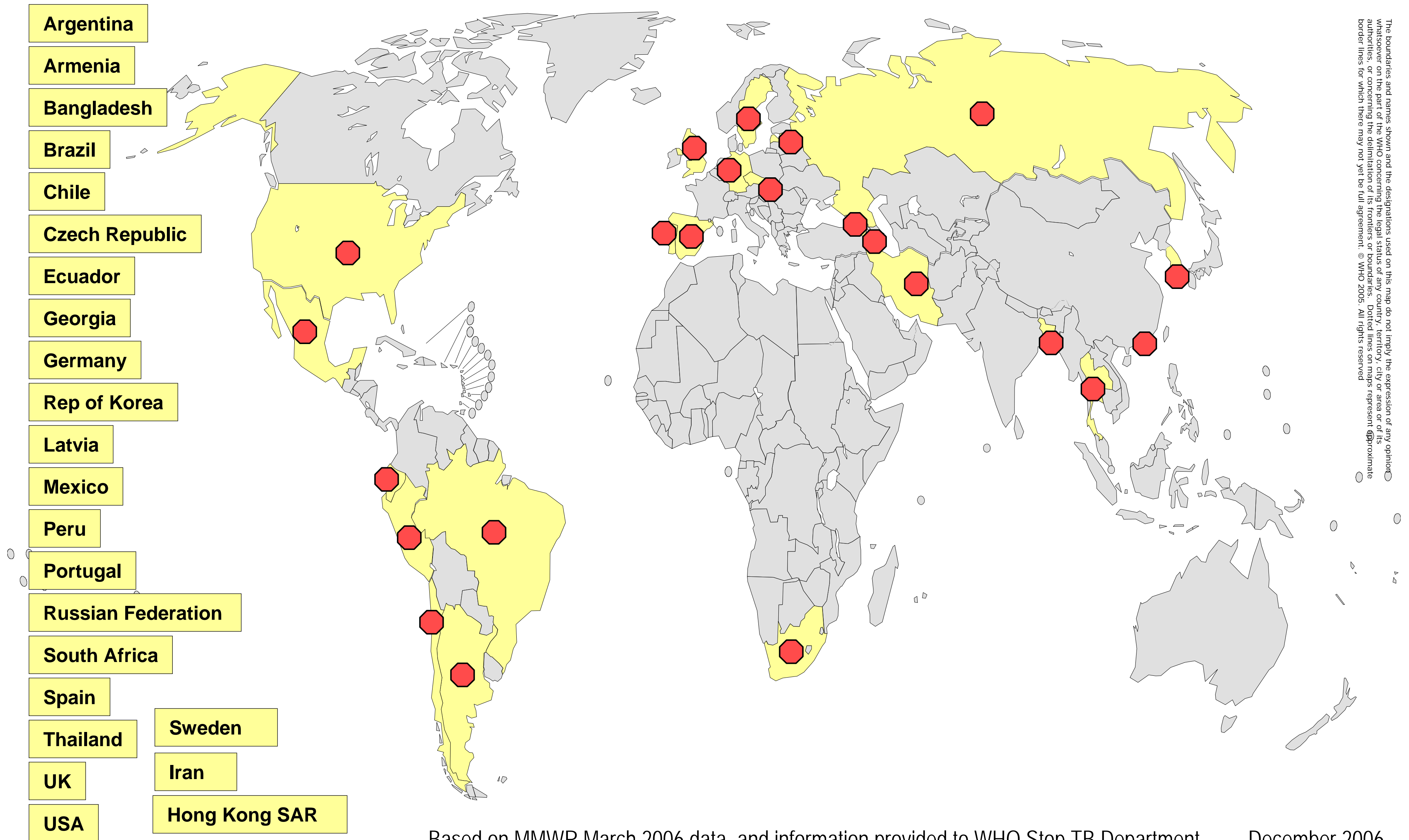
Revised WHO Case Definition for XDR TB

Goals

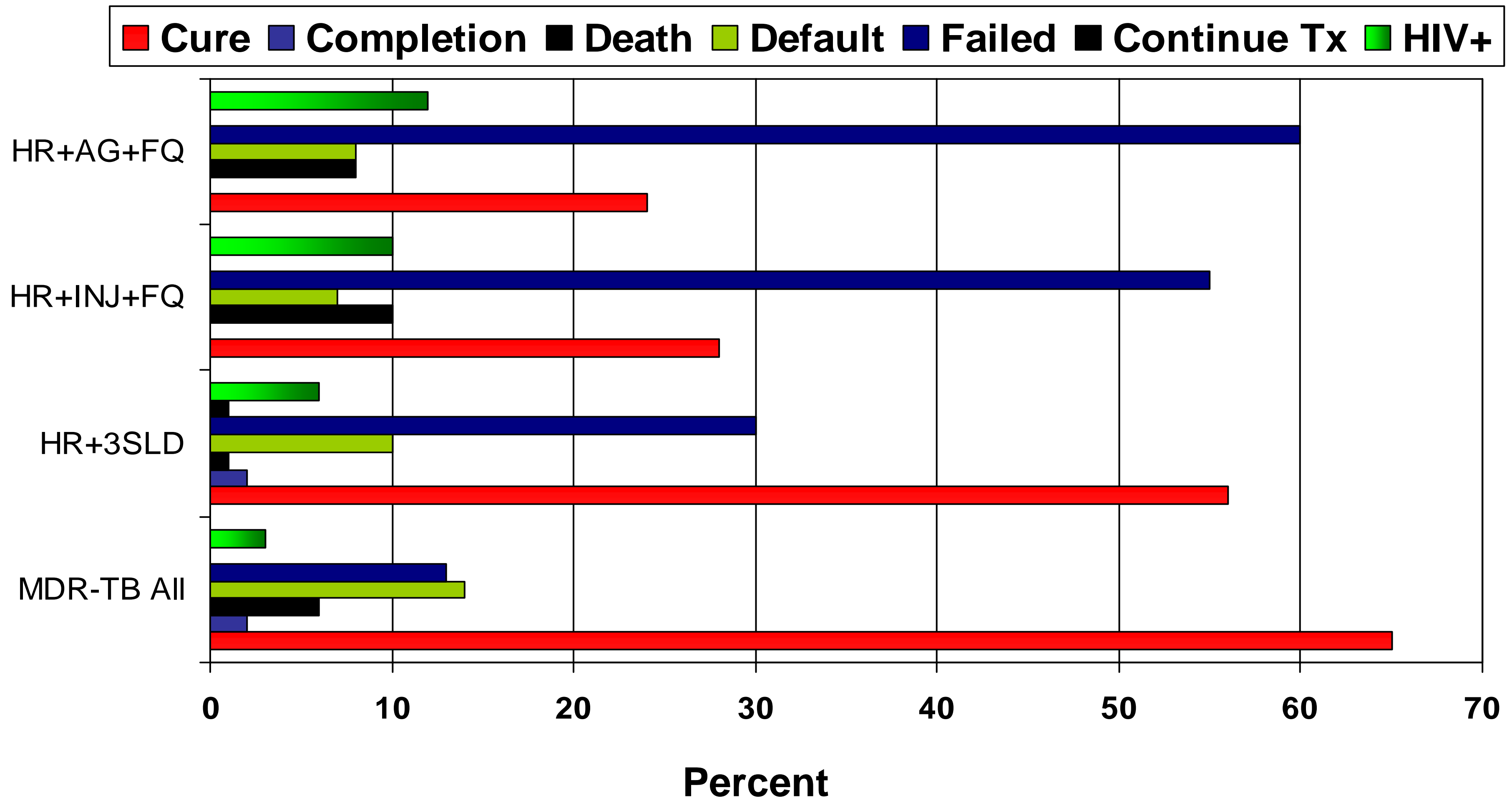
- Public health surveillance
- Reliable DST methodology
- Clinical relevance
- Relatively simple

Resistance to at least isoniazid and rifampin (MDR) plus resistance to fluoroquinolones and one of the second-line injectable drugs (amikacin, kanamycin, or capreomycin)

Countries with XDR-TB confirmed cases to date



TB Treatment Outcomes, by Selected Drug Resistance Patterns, Latvia, 2000-2003*



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

The threats of XDR-TB

- Present in all regions – but distribution unknown
- High case fatality rate (95-97% in PLHIV), median survival time 16-43 days
- Cure rates of up to 50-60%
- Not a single strain, thus indicates systemic failures in health sector and/or in TB control
- Diagnostic capacity to detect XDR-TB only in a few countries
- Threatens progress towards MDG

Urgent need of answer to key questions

- What are factors in the TB control strategy and programmes contributing to the creation of XDR-TB?
- What is the geographical distribution?
- What is the rate among those without HIV compared to those with HIV, in different settings?
- What is the case fatality rate in XDR-TB compared to MDR-TB, in those with and without HIV? What are the survival times?
- What are the cure rates among those with and without HIV?

WHO GLOBAL TASK FORCE ON XDR-TB

Geneva, 9-10 October 2006

- Preventing XDR-TB through strengthening TB and HIV control
- Management of XDR-TB suspects in high and low HIV prevalence settings:
- Programme management of XDR-TB and treatment design in HIV negative and positive people:
- Laboratory XDR-TB definition:
- Infection control and protection of health care workers with emphasis on high HIV prevalence settings:
- Immediate XDR-TB surveillance activities and needs:
- Advocacy, communication and social mobilization

Progress in addressing XDR-TB

- Budget for the immediate response to XDR-TB submitted to donors
- Request for technical assistance and plans of action submitted to WHO by 6 southern African countries; delivery of technical assistance is underway
- Rapid drug resistance surveys ongoing in South Africa and Lesotho; plan underway for surveys in five other countries in January 2007
- First MDR-TB management training workshop in Africa took place in Tanzania, October 2006; further training will take place early in 2007
- FIND demonstration sites for rapid rifampicin testing to start in South Africa and Lesotho in early 2007
- Update of WHO Guidelines on TB infection control ready