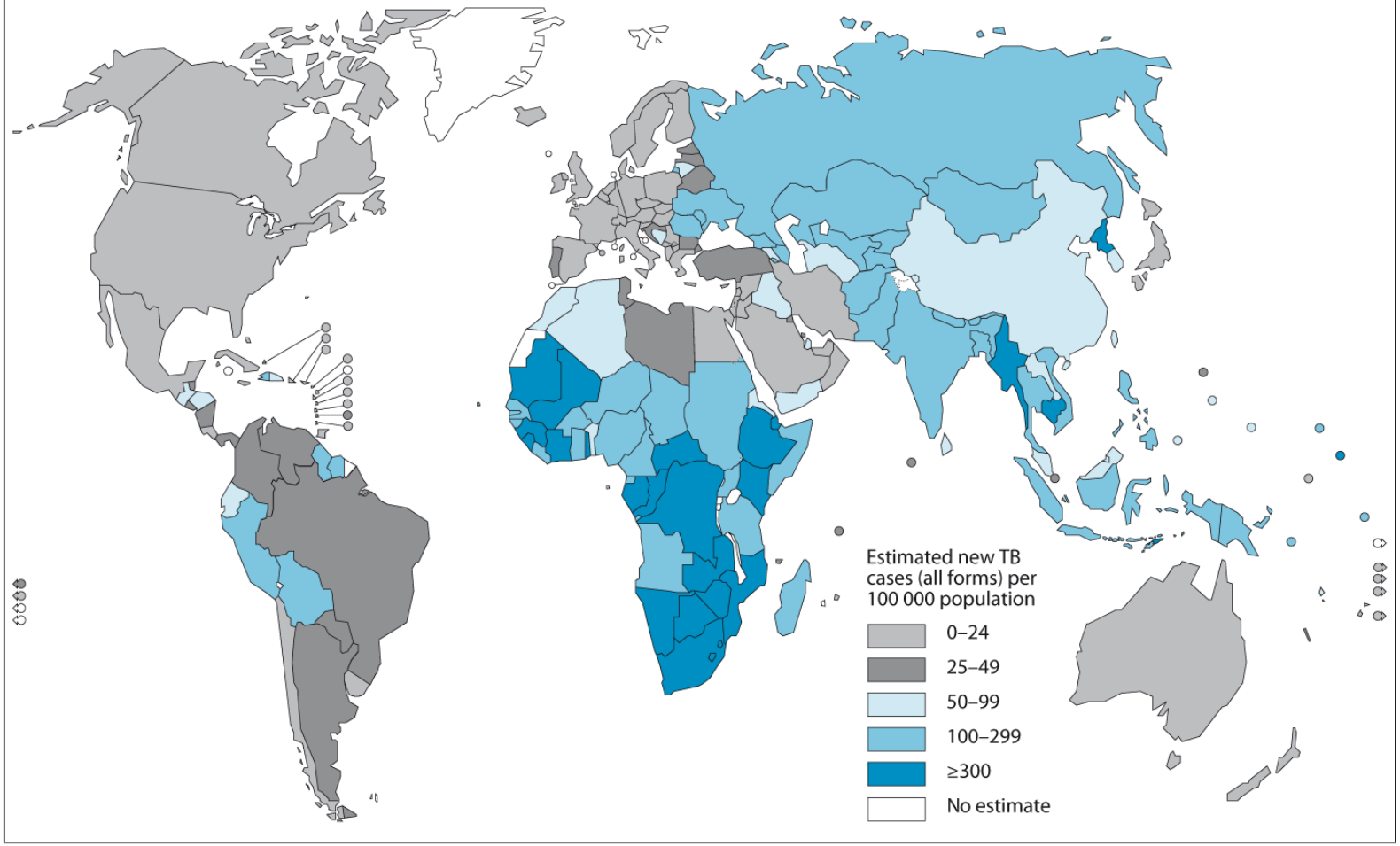
TUBERCULOSIS

Estimated TB incidence rates, by country, 2009



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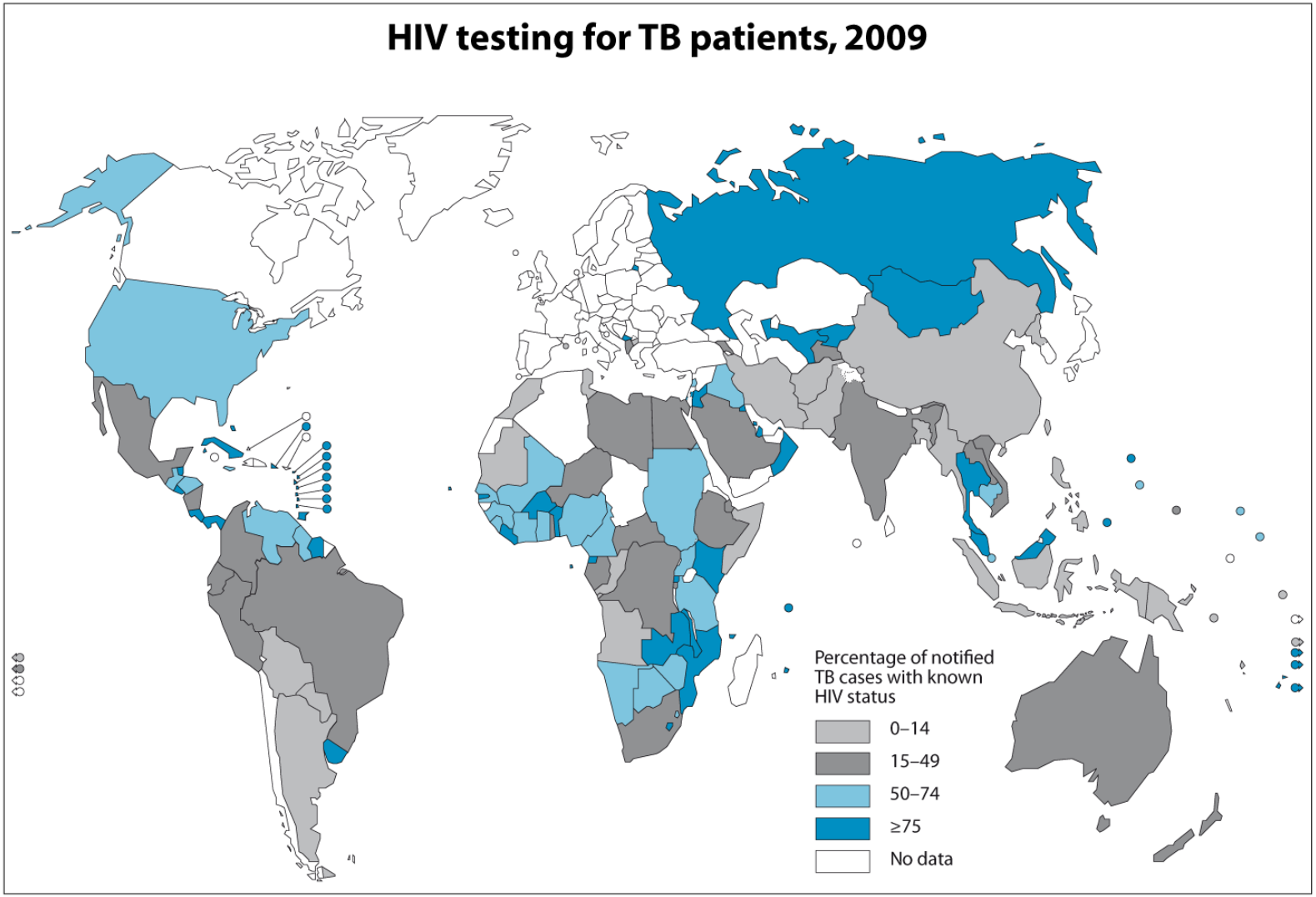
Source: *Global Tuberculosis Control 2010.* WHO, 2010.

World Health Organization

HIV testing for TB patients, 2009



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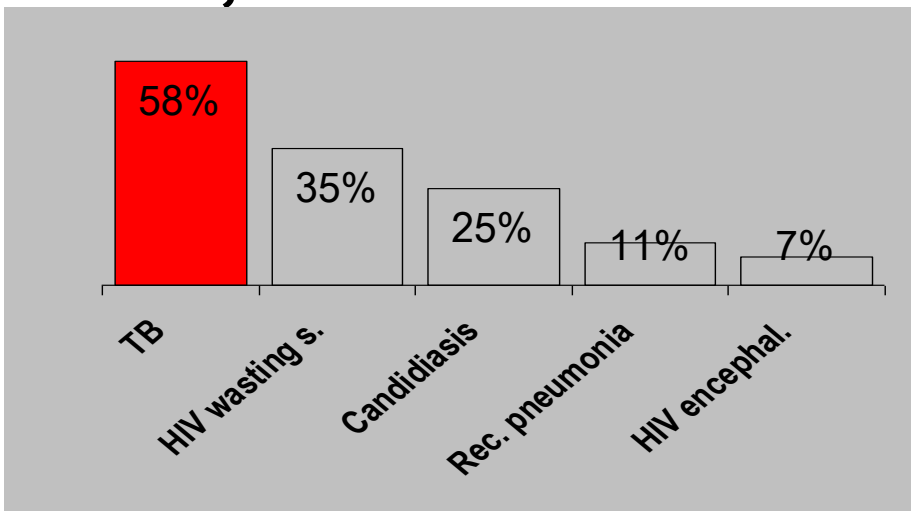
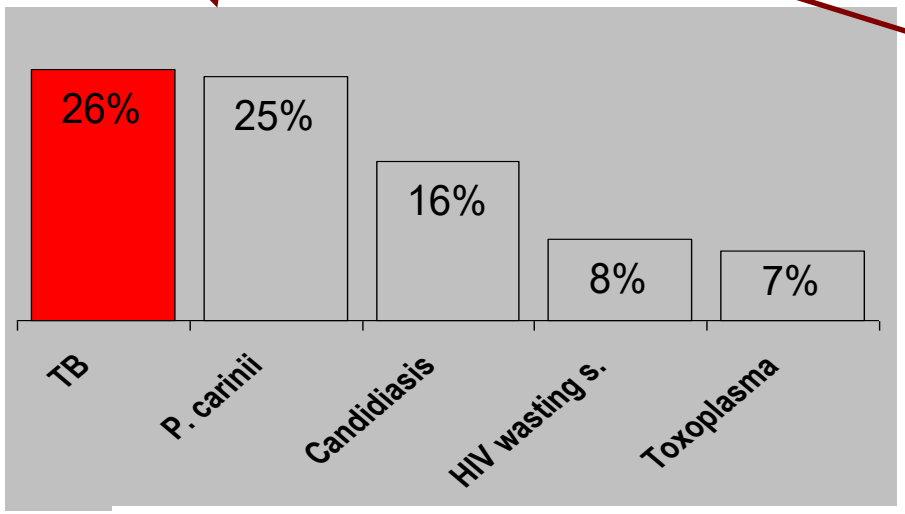
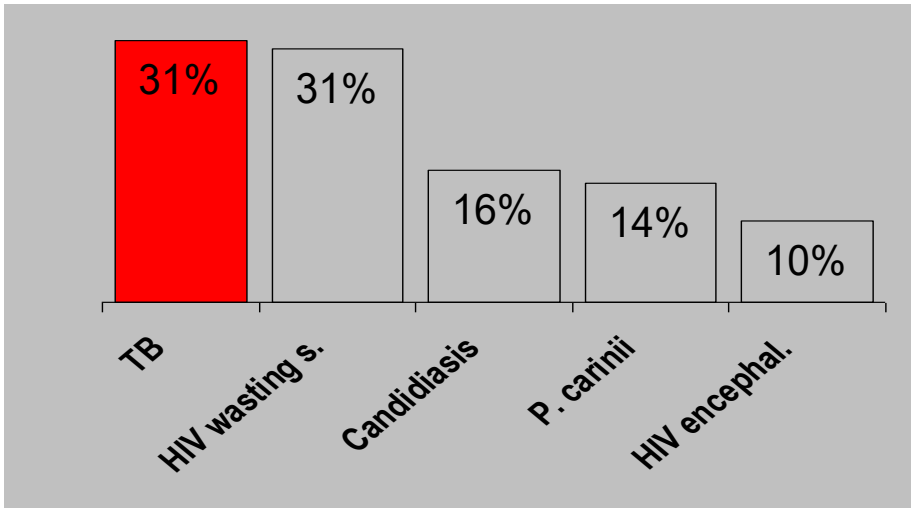
World Health Organization

Top 5 AIDS indicative diseases; EUR, 2003







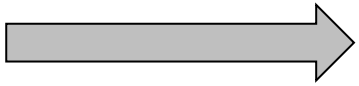
Source: EuroHIV. HIV/AIDS surveillance in Europe: End-year report 2003. Saint Maurice: Institute de Veille Sanitaire (France), 2004, N°70.

EPIDEMIOLOGY

- Every year TB infects up to 100,000,000 people
- 9,400,000 new cases of TB (137/100,000)
- 4,000,000 new cases of TB are smear positive
- 1,700,000 people (100,000 children) die from TB - 200 people/ hour are dying with TB
- 100 children die from TB every day
- 9 mln children are orphans as a result of parental deaths caused by TB

What happens next?

+ contact with IC



a healthy contact

LTBI

active TB

LATENT TB INFECTION (LTI)

Subclinical infection without clinical, bacteriological or radiological signs or symptoms of disease.

Positive TST or/and IGRA test

TUBERCULOSIS

Clinically, bacteriologically and/or radiographically confirmed disease

ETIOLOGY

Mycobacterium tuberculosis complex

Mycobacterium africanum

Mycobacterium bovis

Mycobacterium EAI (East African-Indian)

Beijing

Haarlem

LAM (Latin American and Mediterranea)

CAS (Central and Middle Eastern Asian)

European X family

European T family

TRANSMISSION

- Airborne
- Ingestion of unpasteurized milk (*M. bovis*)
- Inborne

PATHOGENESIS

- Clearance of the organism
- Rapid progressive disease (primary disease)
- Active disease many years after the infection
- Chronic or latent infection

Tuberculosis progression to active disease from latent infection

Age

- 43% in infants (children < 1year)
- 25% in children aged one to five years
- 15% in adolescents
- 10% in adults

Risk factors of TB infection

Household contact

Profession-due contact

Alcoholics, drug addicts, homeless people

Imigrants from high prevalence countries

Risk factors of developing TB disease

Immunosupresion (iatrogenic, HIV)

Malnutrition

Age < 5 years

Neoplastic disease

Chronic diseases: DM, chronic kidney failure, silicosis

Stomach resection

CLINICAL MANIFESTATIONS

- **Pulmonary disease** (lung parenchyma involved)
- **Extra-pulmonary disease**

Pleural effusion

Lymph node disease

CNS disease

Disseminated disease

Pericardilal disease

Genitourinary disease

Bone and joint disease

Abdominal and gastrointestinal disease

CLINICAL FEATURES

- Primary infection:
  - local inflammation with granuloma formation
  - lymphadenopathy (hilar,mediastinal)
  - lobar collapse due to bronchial compression (may lead to bronchectasis)
  - pleural effusion (lymphocytic exudate with high protein but low glucose concentration)
  - erythema nodosum

  In children manifestation may be scarce and non-specific

POST PRIMARY TUBERCULOSIS

- Direct progression of primary infection
- Hematogenous spread
- Reactivation of primary disease
- Exogenous reinfection

CLINICAL FEATURES

- Post-primary tuberculosis:
  - Pulmonary symptoms
    - Cough
    - Sputum
    - Hemoptysis
    - Chest pain
    - Dyspnoea
  - General symptoms
    - Fever
    - Night sweat
    - Weight loss

CLINICAL SIGNS OF PULMONARY TB

- Reduced breath sounds and consolidation
- Wheezing in bronchial narrowing
- Signs of extrapulmonary involvement

SPECIAL SITUATIONS: CHILDREN

- Higher risk of severe primary progressive disease after infection
- Higher proportion of disseminated and extrapulmonary disease
- Unreliable symptoms and signs
- Bacteriological examination difficult

TIMETABLE OF DISEASE AFTER PRIMARY INFECTION IN CHILDREN

- **3-8 weeks**:
  - TST response
  - Erythema nodosum
- **1-3 months**:
  - Hematogenous spread (meningitis and miliary in infants)
- **3-7 months**:
  - Bronchial disease (< 5 years)
  - Pleural effusions (>5 years)
- **1-3 years:**
  - Osteo-articular disease
  - Calcifications
  - Adult-type disease

SPECIAL SITUATIONS: HIV

- Higher frequency of extrapulmonary TB
- Higher frequency of atypical localisation
- Greater frequency of general symptoms
- Shorter duration of symptoms before diagnosis

DIAGNOSTIC MATERIALS

- gastric aspirate
- bronchial washings
- cerebrospinal fluid
- pleural fluid
- urine
- sputum (more useful in adults)
- other body fluid

DIAGNOSTIC TESTS

- AFB smears
- Culture: solid media up to 10 weeks, liquid media up to 6 weeks
- PCR

CULTURE

GOLD STANDARD TO CONFIRM TUBERCULOSIS

DIAGNOSTIC PROBLEMS

- **Active disease**

- *M. tuberculosis* is difficult to isolate: even with good microbiological facilities, the bacillus is recovered in 50-60% of cases in adults and up to 40% in children

- **Latent infection**

- *M. tuberculosis* cannot be cultured from latently infected individuals: no gold standard

IMMUNOLOGICAL TESTS

- **The tuberculin skin test** – can not differentiate between latent and active disease. Tool available for diagnosis of TB infection

- **IGRA (interferon gamma release assay) -** Cell mediated immunity **–** circulating lymphocytes are extracted from the venous blood and exposed to antigens of *M. tuberculosis* and after 6-24 hrs the production of interferon gamma is measured.

- **Serology** –blood tests to measure the humoral response to *M. tuberculosis*

Tuberculin skin test

Positive TST	Active TB disease
	Latent TB infection
	Recent exposure to *M. tuberculosis*
	Exposure to environmental mycobacteria
	(BCG-vaccination)

TST does not distinguish among all these different clinical situations

Positive TST

Interpretation

TST interpretation depends on two factors:

-diameter of the induration;

- person's risk of being infected with TB and risk of progression to disease if infected.

TST

Causes of false negative TST results:

Incorrect administration or interpretation of test
Incorrect interpretation of test
HIV infection BCG vaccination
Improper storage of tuberculin
Infection with nontuberculous mycobacteria
Viral infections (e.g. measles, varicella)
Vaccinated with live viral vaccines (within 6 weeks)
Malnutrition
Bacterial infections (e.g. typhoid, leprosy, pertussis)
Immunosuppressive medications (e.g. corticosteroids)
Neonatal patient
Primary immunodeficiencies
Diseases of lymphoid tissue (e.g. Hodgkin disease, lymphoma, leukaemia, sarcoidosis)
Low protein states
Severe TB

Causes of false positive TST results:

Incorrect interpretation of test

BCG vaccination

Infection with nontuberculous mycobacteria

BASIC PRINCIPLES OF TREATMENT

- Combination of antibiotics
  - Rapid killing of mycobacteria
    - Interruption of the chain of transmission
  - Prevention of drug resistance
- Long duration of treatment
  - Sterilisation of lesions
    - Prevention of relapse

FIRST LINE ANTYTUBERCULOSIS DRUGS

- Isoniazid (INH, H)
- Rifampicin (RMP, R)
- Pyrazinamide (PZA, Z)
- Ethambutol (EMB, E)
- Streptomycin (SM, S)

ISONIAZID

- Highly bactericidal against replicating mycobacteria
- 5 mg/kg daily or 10 mg/kg 3 times weekly
- AE: transient rise in hepatic transaminases, hepatitis, peripheral neuropathy
- Interaction with some antiepileptic drugs (phenytoin, carbamazepin)

RIFAMPICIN

- Bactericidal against replicating and intermittently active mycobacteria, sterilizing effect
- 10 mg/kg daily or 600 mg 3 times weekly
- AE: influenza-like syndrome, skin rash, hepatitis
- Interactions with drugs metabolized in the liver (oral contraceptives, anticoagulants, corticosteroids)

STREPTOMYCIN

- Bactericidal against mycobacteria in extracellular environment
- 15 mg/kg daily or 3 times weekly by injection
- AE: nephrotoxicity, impairement of vestibular function, toxic during pregnancy

PYRAZINAMIDE

- Weak bactericidal but potent sterilizing activity against mycobacteria within acidic environment (inflammation, macrophages)
- 25 mg/kg daily or 35 mg/kg 3 times weekly
- AE: gastrointestinal disturbances, rise in liver transaminases, arthralgias, skin rash

ETHAMBUTOL

- Bacteriostatic, delays the emergence of resistant strains
- 15-20 mg/kg daily or 30 mg/kg 3 times weekly
- AE: dose-dependent optic neuritis (visual acuity and color vision)

Chemoprophylaxis: Treatment of infection with *M. tuberculosis* to prevent progression to active TB

Preventive chemotherapy: Treatment of individuals at risk of acquiring TB who are not infected

RATIONALE TREATMENT STANDARD

- Intensive phase (2 months)
  - rapid killing

- Continuation phase (4-6 months)
  - sterilization

TREATMENT GUIDELINES

WHO

IUATLD

ATS/CDC

European

NICE (UK)

International Standards of Care

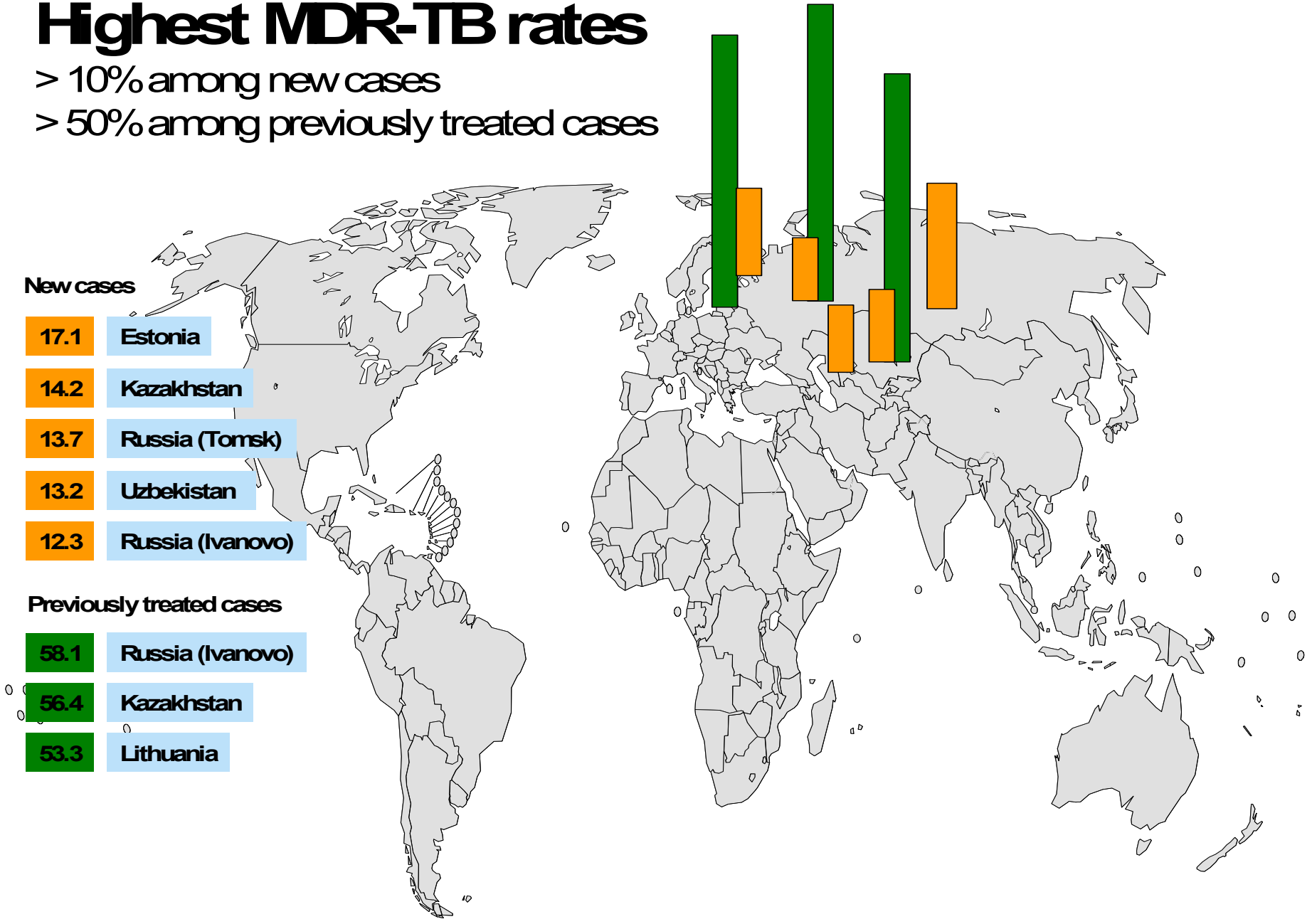
DOT AND DOTS

- DOT: Directly Observed Therapy
  - Recommended by WHO for all cases, at least in the intensive phase
- DOTS: Directly Observed Therapy, Short-Course

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

MDR-TB

In 2010, the largest WHO MDR-TB survey reported the **highest rates ever of MDR-TB, with peaks of** up to 28% of new TB cases in some settings of the former Soviet Union

BCG VACCINE

- The BCG vaccine is a live vaccine prepared from attenuated strains of M. bovis.
- Is used to prevent disseminated and other life-threatening infections of M. tuberculosis in infants and young children.
- Is used in more than 100 countries.

NEW DEVELOPMENTS

Global Plan 2006-2015 STOP TB

	By 2006	By 2010	By 2015
vaccines	3 vaccines in phase I trials	9 candidates in phase II trials; at least 2 vaccines in "proof of concept" trials; beginning phase III trials	4 phase III trials carried out; one safe, effective vaccine available
drugs	27 new compound sin the pipeline	1-2 new drugs registered; treatment shortened to 3-4 months	7 new drugs; treatment shortened to 1-2 months
diagnostics	rapid culture for case detection	point of care, rapid culture, improved microscopy, phage detection	predictive test for LTBI