

Centralized management of MDR-TB

Manfred Danilovits
The Kai Koskela Seminar
St. Petersburg, May 29, 2008

MDR-TB FRAMEWORK APPROACH

1. Sustained Political commitment

2. Rational case-finding strategies using quality-assured culture and drug susceptibility testing (DST).

3. Appropriate treatment strategies that utilize second line drugs under proper management conditions.

4. Uninterrupted supply of quality assured anti-tuberculosis drugs.

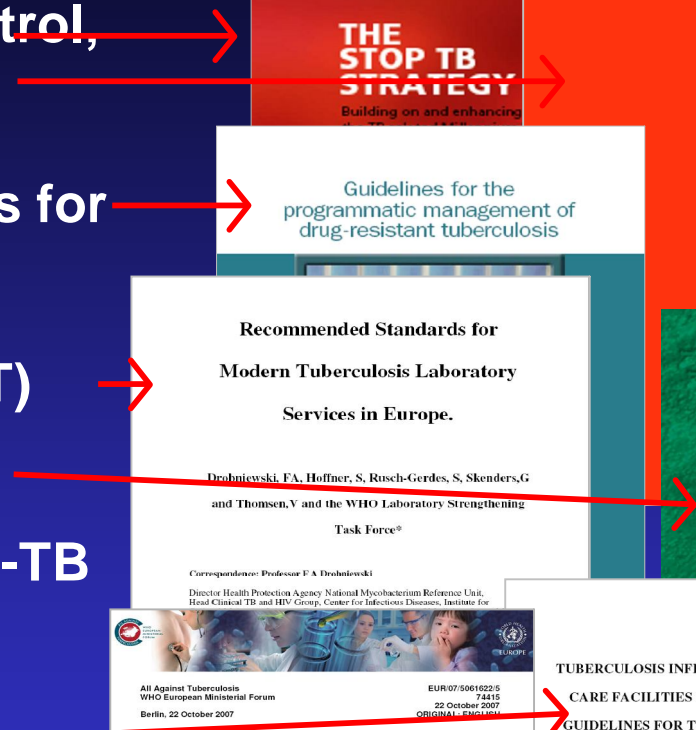
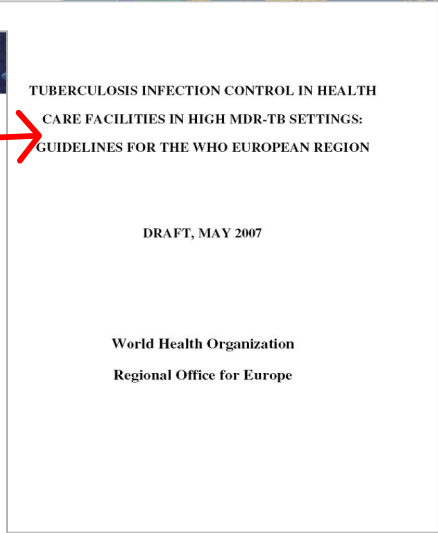
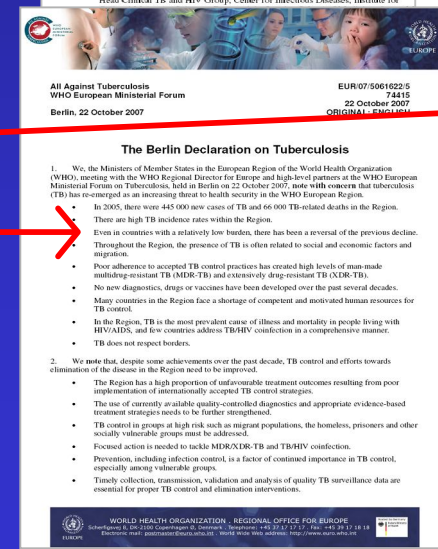
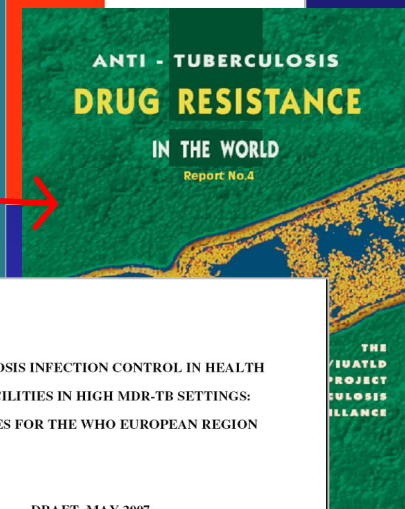
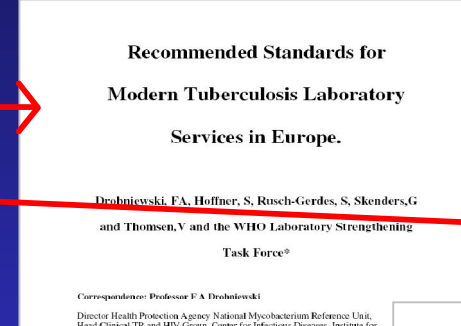
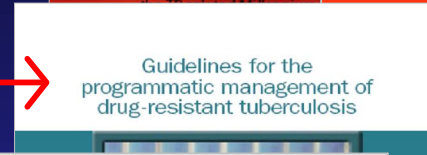
5. Recording and reporting system designed for MDR-TB program.

Constraints to scale up MDR-TB treatment

- **Political commitment and financial resources: slow to take off in key countries /donors.**
- **Capacity to deliver and absorb technical assistance and financial support**
- **Small and unreliable market of quality assured second-line anti-TB drugs, often coupled with poor drug management in many countries**
- **Limited laboratory capacity to diagnose and monitor response to treatment of MDR-TB and XDR-TB**
- **TB Infection control is an underdeveloped field in resource constrained regions**
- **Human resources: limited quantity of properly trained workforce and limited alternatives developed in-country**
- **Complex and lengthy diagnostic procedures and treatment difficult to deliver**

How to address MDR/XDR-TB effectively?

- ✓ Strengthen basic TB and HIV/AIDS control, to prevent drug resistance
- ✓ Mainstream MDR-TB into national plans for TB control
- ✓ Strengthen laboratory (culture and DST)
- ✓ Ensure drug resistance surveillance
- ✓ Increase access to quality 2nd line anti-TB drugs (GLC?)
- ✓ Reinforce TB infection control
- ✓ Increase advocacy and communication
- ✓ Promote operational research and basic research on new diagnostics, drugs and vaccines



All Against Tuberculosis
WHO European Ministerial Forum
Berlin, 22 October 2007

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22 October 2007
ORIGINAL - ENGLISH

The Berlin Declaration on Tuberculosis

1. We, the Ministers of Member States in the European Region of the World Health Organization (WHO), meeting with the WHO Regional Director for Europe and high-level partners at the WHO European Ministerial Forum on Tuberculosis, held in Berlin on 22 October 2007, note with concern that tuberculosis (TB) has re-emerged as an increasing threat to health security in the WHO European Region.

- In 2005, there were 445 000 new cases of TB and 66 000 TB-related deaths in the Region.
- There are high TB incidence rates within the Region.
- Even in countries with a relatively low burden, there has been a reversal of the previous decline.
- Throughout the Region, the presence of TB is often related to social and economic factors and migration.
- Poor adherence to accepted TB control practices has created high levels of multi-drug resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB).
- No new diagnostics, drugs or vaccines have been developed over the past several decades.
- Many countries in the Region face a shortage of competent and motivated human resources for TB control.
- In the Region, TB is the most prevalent cause of illness and mortality in people living with HIV/AIDS, and few countries address TB/HIV coinfection as a comprehensive issue.
- TB does not respect borders.

2. We note that, despite some achievements over the past decade, TB control and efforts towards elimination of the disease in the Region need to be improved.

- The Region has a high proportion of unfavorable treatment outcomes resulting from poor implementation of internationally accepted TB control strategies.
- The use of currently available quality-controlled diagnostics and appropriate evidence-based treatment strategies needs to be further strengthened.
- TB control in groups at high risk such as migrant populations, the homeless, prisoners and other socially vulnerable groups must be addressed.
- Focused action is needed to tackle MDR/XDR-TB and TB/HIV coinfection.
- Prevention, including infection control, is a factor of continued importance in TB control, especially among vulnerable groups.
- Timely collection, transmission, validation and analysis of quality TB surveillance data are essential for proper TB control and elimination interventions.

WORLD HEALTH ORGANIZATION - REGIONAL OFFICE FOR EUROPE
 11 rue des Saussaies, 75008 Paris, France
 Tel: +33 (0)1 42 93 12 14
 Fax: +33 (0)1 42 93 12 18
 Email: info@euro.who.int, eur@euro.who.int, eur@who.int, <http://euro.who.int>

TUBERCULOSIS INFECTION CONTROL IN HEALTH CARE FACILITIES IN HIGH MDR-TB SETTINGS: GUIDELINES FOR THE WHO EUROPEAN REGION

DRAFT, MAY 2007

World Health Organization
Regional Office for Europe

Short history about the TB program in Estonia

- NTP from 1998- 2007 (financed by Government)
New programm for 2008-2012 approved by the Minister of Social Affairs, February 20,
- **Main indicator** (compared to year 2006): BY year 2012, the incidence of TB in Estonia is 20 cases per 100 000 population (in 2006, the incidence was 27.8 cases per 100 000 pop.
- The prerequisite of achieving this target is to control TB epidemic among HIV-infected patients and stopping the spread of MDR-TB
-
- With currently applied methods, the incidence of TB has decreased during the last 6 years. In 2006, the incidence of TB was 27.8 per 100 000 pop.
- In 2007, the same number was 30.3 per 100 000 pop.

Main strategies, cooperation

- **The aims and measures of the NTP are connected to the main targets of the National HIV/AIDS Prevention Strategy for Years 2006 – 2015 and the National Strategy for the Prevention of Drug Abuse until 2012.**
- **To strengthen political commitment , the Government also created a high-level multisectorial «Governmental HIV and AIDS Committee» and coordinating body between NTP and HIV/AIDS program.**
- **Detailed connections between the strategies have been outlined in the action plan of the TB program for years 2008 – 2012.**
- **In frame of two programmes there is co-operative management of TB/HIV patients**
- **The National Institute for Health Development is playing an active role to coordinate joint activities between TB and HIV programmes.**
- **TB services can be the entry point for HIV patients and vice-versa**

Political and financial support from Government

**National Institute for Health Development
National TB programm**

**Human resources, public health capacity, TB
treatment network
existing drug management system, DOT**

Cooperation with HIV programm

**MDR-TB
GLC approved
country-wide
treatment project**
To advise on the
specific areas for
MDR-TB
interventions

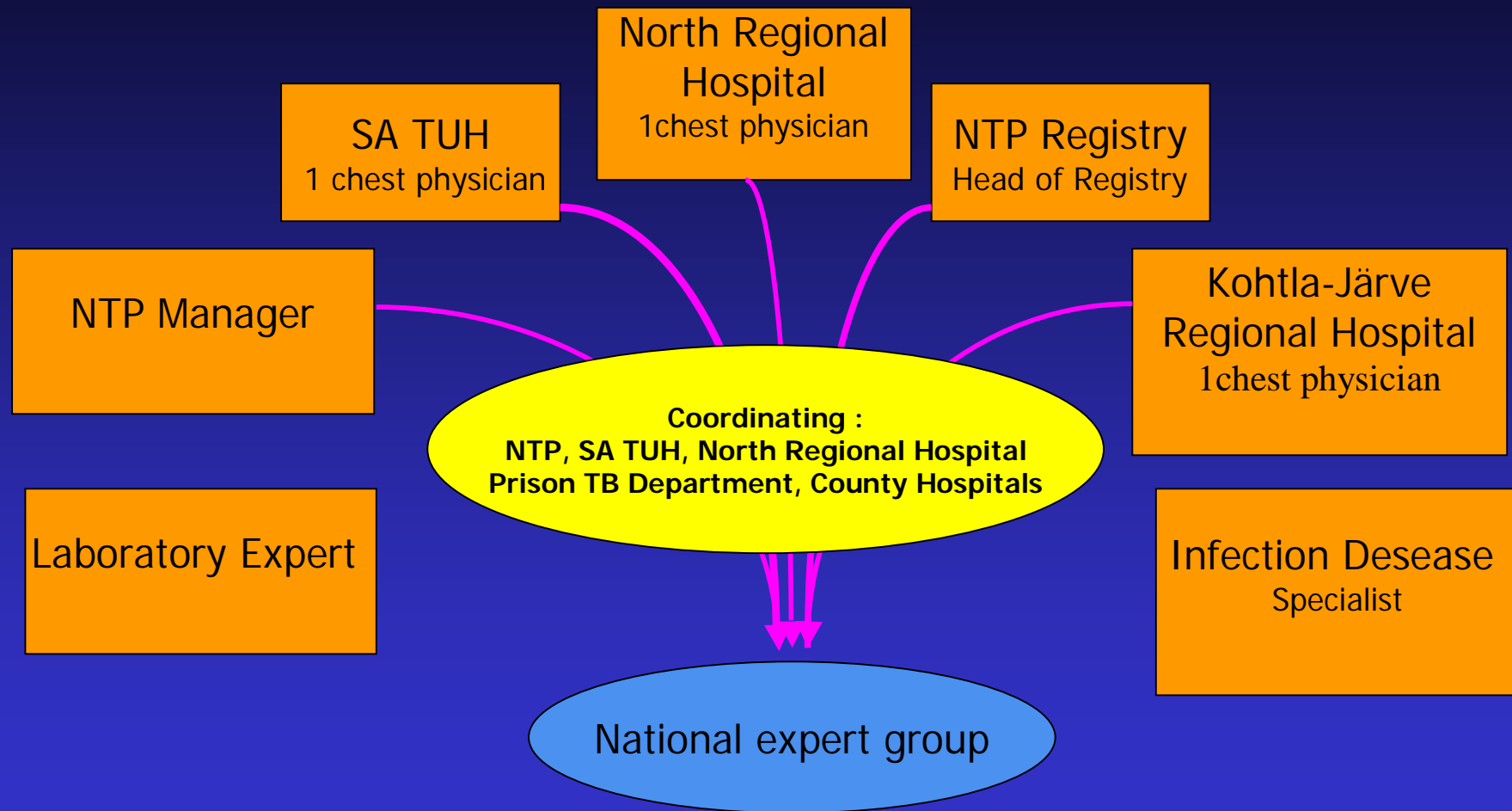
**Case based TB register
Drug-resistance
surveillance together
with treatment outcome
monitoring, integrated
with lab data**

**Laboratory network
Use of new laboratory
techniques (DNA
fingerprinting and
molecular typing)
Training activities**

**International cooperation
WHO, IUATLD, CDC, FILHA
Participation in expert
network.
International training for
doctors/nurses**

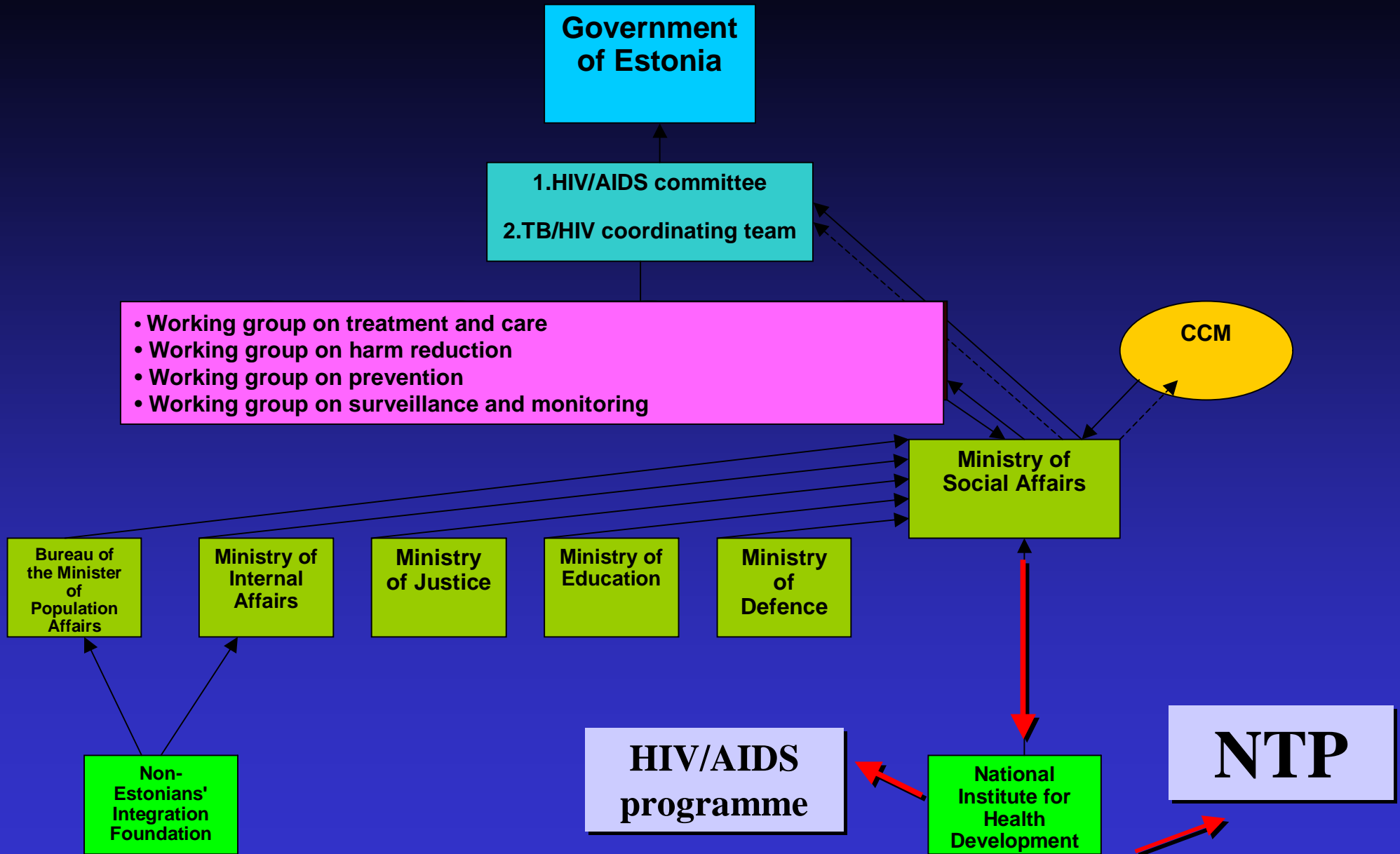
**Clinical trials
for new TB
drugs and
treatment
methods**

National expert group for TB treatment



The role and tasks of the expert group

- To develop and maintain expertise on management of MDR-TB cases inc. TB/HIV co-infected patients
- To follow treatment of HIV-TB, MDR- and XDR-TB-cases and assist/guide in choices of regimens and other decisions inc. the **antiretroviral therapy for patients with TB/HIV**
- Meets 1per month, consultations also between the meetings



Achievements in TB control in Baltic States

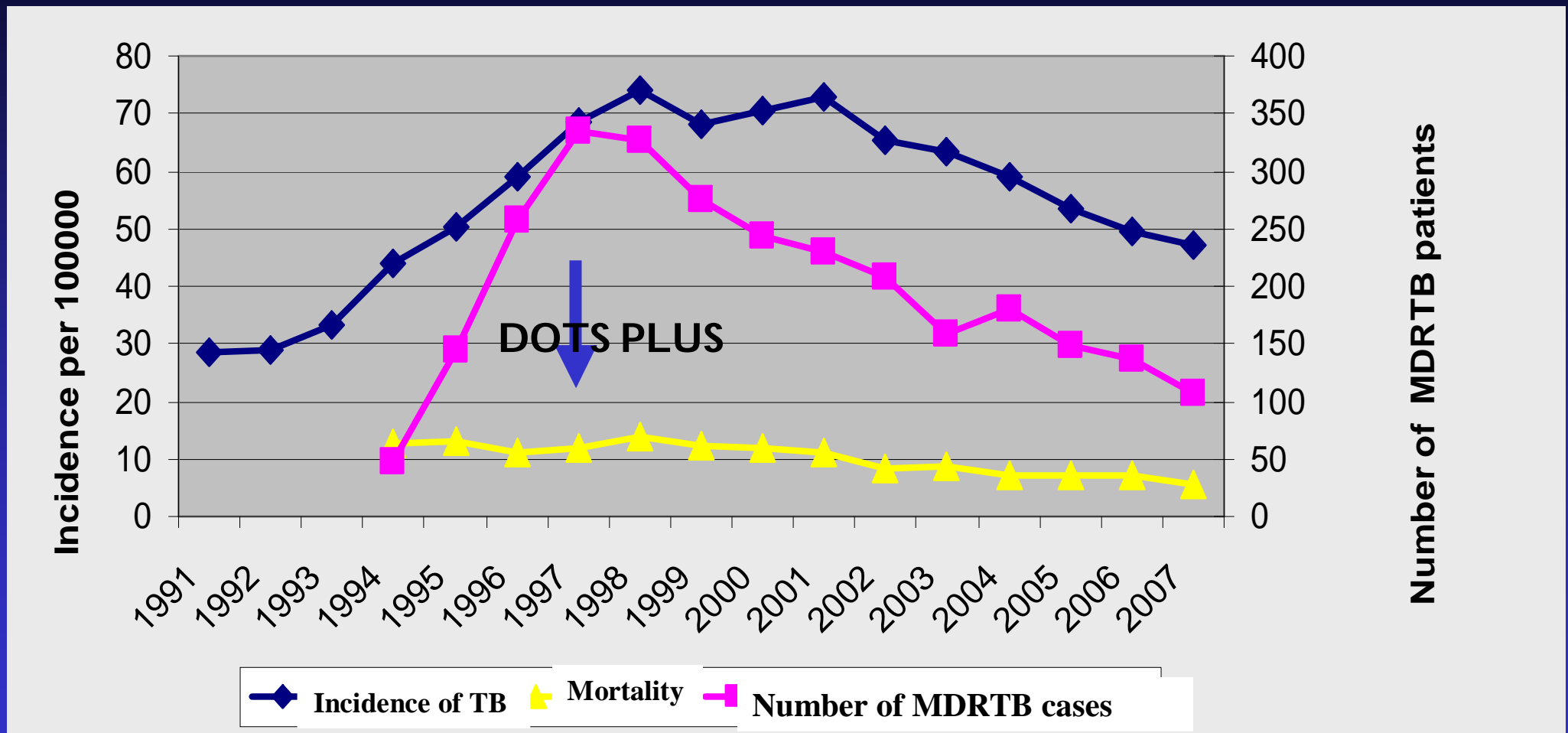
TB

- **Sustainable political commitment for TB control at country level**
- **Incidence of TB have been decreased**
- **DOTS-Plus for MDR-TB treatment in Estonia (2001), Latvia (1997), Lithuania (2007) according to GLC approved projects**
- **Human resources for MDR-TB**
 - **Development of guidelines and training modules**
 - **International Training Centers for NTP managers, consultants pulmonary specialists and nurses (Latvia, Estonia)**

TB/HIV

- **Policy for collaborative TB/HIV activities in country level started in 2005**
- **All Baltic countries have special government budget for both HIV/AIDS and TB control**

Impact of MDR TB Management on TB Case Detection and mortality in Latvia 1991-2007

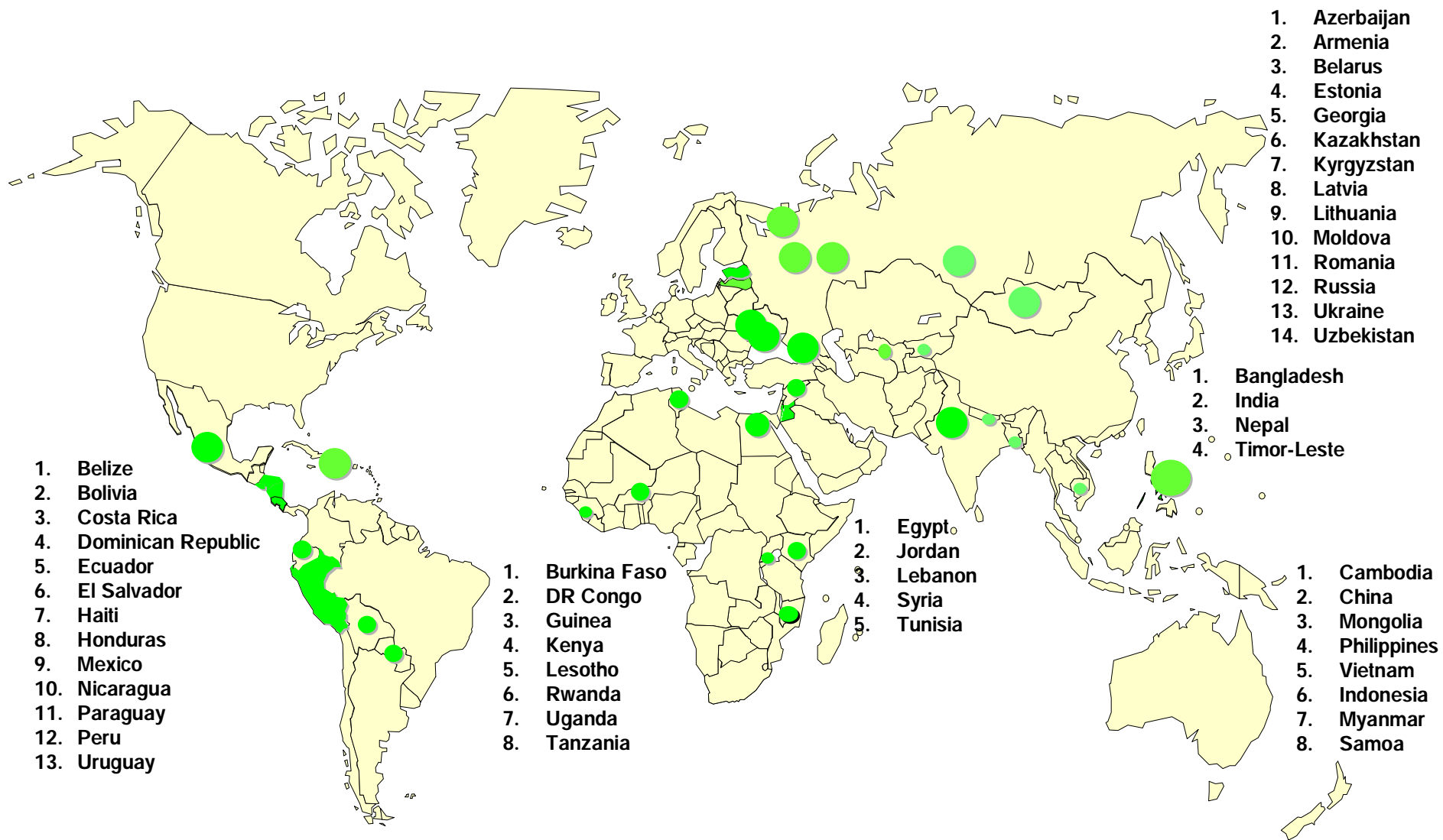


Source: Latvian National TB Control Program, published Eurosurveillance, March 2006

Green Light Committee

- **Members:** WHO, CDC, IUATLD, Latvia/Estonia NTPs, University of Harvard, MSF, KNCV, Hospital F.J. Muniz – Argentina, World Care Council. Former members include Medical Research Council (South Africa) and NTP Peru.
- **Task:** To review project applications and determine if projects are in compliance with WHO guidelines. Projects that meet the requirements will benefit from reduced-priced 2nd line drugs and technical assistance.

GLC approved projects by April 2008



GLC-approved projects in 52 countries
More than 37'000 patients approved for enrolment

GLC Initiative: components and products

Policy development

Technical assistance

Application review
Monitoring and evaluation

Access to drugs

- High-level expertise on the management of MDR-TB programmes based on best available evidence and collective experience;
- technical assistance through a wide network of technical partners;
- peer support and knowledge sharing in communication with other GLC-approved programmes;
- independent external monitoring and evaluation of your programme.
- high-quality drugs to treat MDR-TB at considerably lower than market prices;

Applying to the Green Light Committee

- As the NTP was unable to treat the DR patients due to the high cost of second-line anti-TB drugs (SLD) **and lack of coordinated MDR-TB management**, the NTP applied to the Green Light Committee (GLC) for the countrywide project on management of DR-TB in 2001, which started on 1st of August the same year.
- Second application for next cohort of 200 patients was sent to GLC in May 2004 and approved in July 2004.
- **In April 2008 GLC approved the cohort expansion for next 300 patients**

Estonia: % of NTP budget spent on second-line drugs



MDR TB cohorts in Estonia

Treatments started:

- 1. cohort 2001 157 (93 new cases+relapses)
- 2. cohort 2002 139 (95)
- 3. cohort 2003 106 (78)
- 4. cohort 2004 90 (70)
- 5. cohort 2005 81 (69)
- 6. cohort 2006 67 (47)

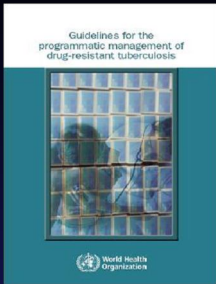
Treatment cost (drugs)

- **Susceptible case** 20-60 \$
- **Case of MDR-TB** 1500-4000 \$
- **XDR-TB** 20 000-30000 \$

Cost per patient, DOTS-plus

Cost Item	Cost	% total
Drug regimen	2094	25
Hospitalization (59 days @ €32 per day and 133 days @ €18 per day)	4238	50
DOT (171 ambulatory visits @ €5 each and 0.4 home visits @ €6.7 each)	841	10
Programme management	580	7
Payment for sick leave	213	3
Sputum smears, cultures, DST	184	2
Training	121	1
X-rays and clinical laboratory tests	112	1
Adverse events	11	0.1
Other*	75	1
TOTAL	8469	100

Other = specialist visits, bronchoscopies, audiometry, surgery, ECG



Management of MDR-TB patients in Estonia

- MDR-TB treatment as NTP policy, DOTS strategy accepted and political commitment in place
- Diagnosis of MDR-TB through quality assured culture and DST
- MDR management team
- Treatment started and followed according to decision of “consilium”
- Centralized drug management
- Individualized treatment
- Infection control in place
- Management of side-effects
- Centralized TB registry
- Treatment follow-up and monitoring by pulmonary physicians with cooperation of PHC services



with

Drugs used in Estonia for MDR-TB

- **Amikacin**
- **Kanamycin (GLC)**
- **Capreomycin (GLC)**
- **Ofloxacin**
- **Prothionamide**
- **Cycloserine (GLC)**
- **Para-amino-salicylic acid (GLC)**
- **Amoxicillin clavulanic acid***
- **Clarithromycin***

- Ministry of Social Affairs and NTP are responsible for drug procurement inc. drugs for side-effects managements
- No TB drugs in pharmacy
- All drugs are free of charge for a patients

First 5 XDR-TB patients on Linezolid and moxifloxacin

Principles of DOTS-Plus regimen design

- **Include first-line drugs to which infecting strain is susceptible**
- **Not rely on drugs to which resistance is suspected**
- **Include a minimum of five (5-7) drugs**
- **Utilize parenteral therapy for extended period (six month after culture conversion)**
- **Treatment period 18-24 month**
- **Observe all doses**

Infection control problems

- Administrative controls to reduce risk of exposure, infection, and disease through policy and practice;
- Environmental (engineering) controls to reduce concentration of infectious bacilli in air in areas where contamination of air is likely; and
- Respiratory protection to protect personnel who must work in environments with contaminated air



Approach to adverse effect management

- **Inadequately managed adverse effects are risk factors for poor treatment outcome**
- **Some adverse reactions are life-threatening if timely identification and treatment is not achieved**
- **Mild adverse effects are common and are to be anticipated**
- **Aggressive management of adverse effects is a central component of DOTS-Plus**
- **Adverse effects are not contraindications to adequate MDRTB therapy**
- **Use of protocols and guidelines**
- **Medications and services related to adverse effect management should be provided as part of DOTS-Plus programs**

- **The majority of adverse reactions are mild**
- **can be managed without compromising antituberculosis therapy**
- **There have been fewer problems due to side effects than expected**
- **Dose reduction or drug elimination is a last option for side effect management**
- **Complete clinical evaluation prior to MDR –TB treatment, informing the patients**
- **Follow-up/recording of the side effects during the treatment**

Adverse effects

- **Central nervous system**
- **Peripheral nervous system**
- **Ototoxicity**
- **Psychosis**
- **Depression**
- **Hypothyroidism**
- **Gastrointestinal**
- **Hepatitis**
- **Renal**
- **Musculoskeletal**
- **Ocular**

Research challenges in Estonia

- **Cost-effectiveness of different approaches to managing MDR-TB**
- **Molecular epidemiology- Drug resistance surveillance**
- **Rapid, cost-effective diagnosis of MDR-TB (HAIN MTBDRPlus Assay)**
- **Potential site for clinical trials**
- **Role of different regimens (duration of treatment, intermittent treatment)**
- **Extrapulmonary tuberculosis**
- **Patients and doctors delay in cases of TB diagnosis**

WHO European Region, 2007

EUROPEAN UNION (EU) (dark blue)

Austria
Belgium
Bulgaria
Cyprus
Czech Republic
Denmark
Estonia
Finland
France
Germany
Greece
Hungary
Ireland
Italy
Latvia
Lithuania
Luxembourg
Malta
Netherlands
Poland
Portugal
Romania
Slovakia
Slovenia
Spain
Sweden
United Kingdom

WEST, non-EU (light blue)

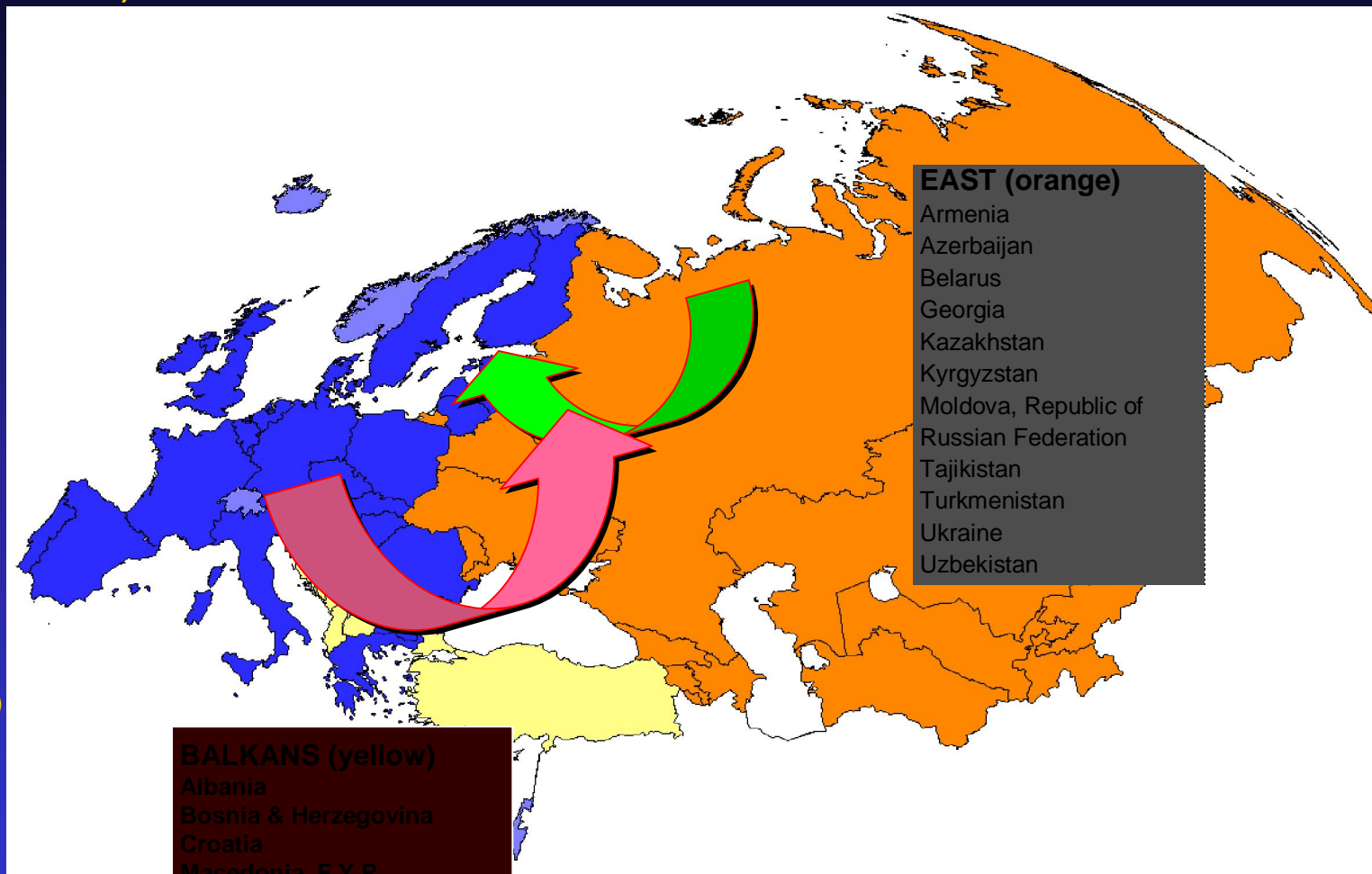
Andorra
Iceland
Israel
Monaco
Norway
San Marino
Switzerland

BALKANS (yellow)

Albania
Bosnia & Herzegovina
Croatia
Macedonia, F.Y.R.
Montenegro
Serbia
Turkey

EAST (orange)

Armenia
Azerbaijan
Belarus
Georgia
Kazakhstan
Kyrgyzstan
Moldova, Republic of
Russian Federation
Tajikistan
Turkmenistan
Ukraine
Uzbekistan



Conclusions

- **XDR-TB and rising numbers of TB /HIV cases can compromise the considerable progress already made in Estonia**
- **Programmatic management of MDR-TB has decreased the risk of TB transmission in society**
- **The impact of immigration in Estonia has been insignificant and role of foreign people from high-incidence countries still has not influenced TB epidemiology**
- **After the implementation of effective TB control strategy, all people in Estonia in regard to TB have equally free access to medical care independently of their employment status and nationality**
- **Sustainable political/financial commitment will support to TB control**