

INTEGRATED DOTS/ DOTS PLUS IN LATVIA

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First DOTS Plus Consultants course 9-15 May,
Riga, Latvia

BACKGROUND: TB IN LATVIA

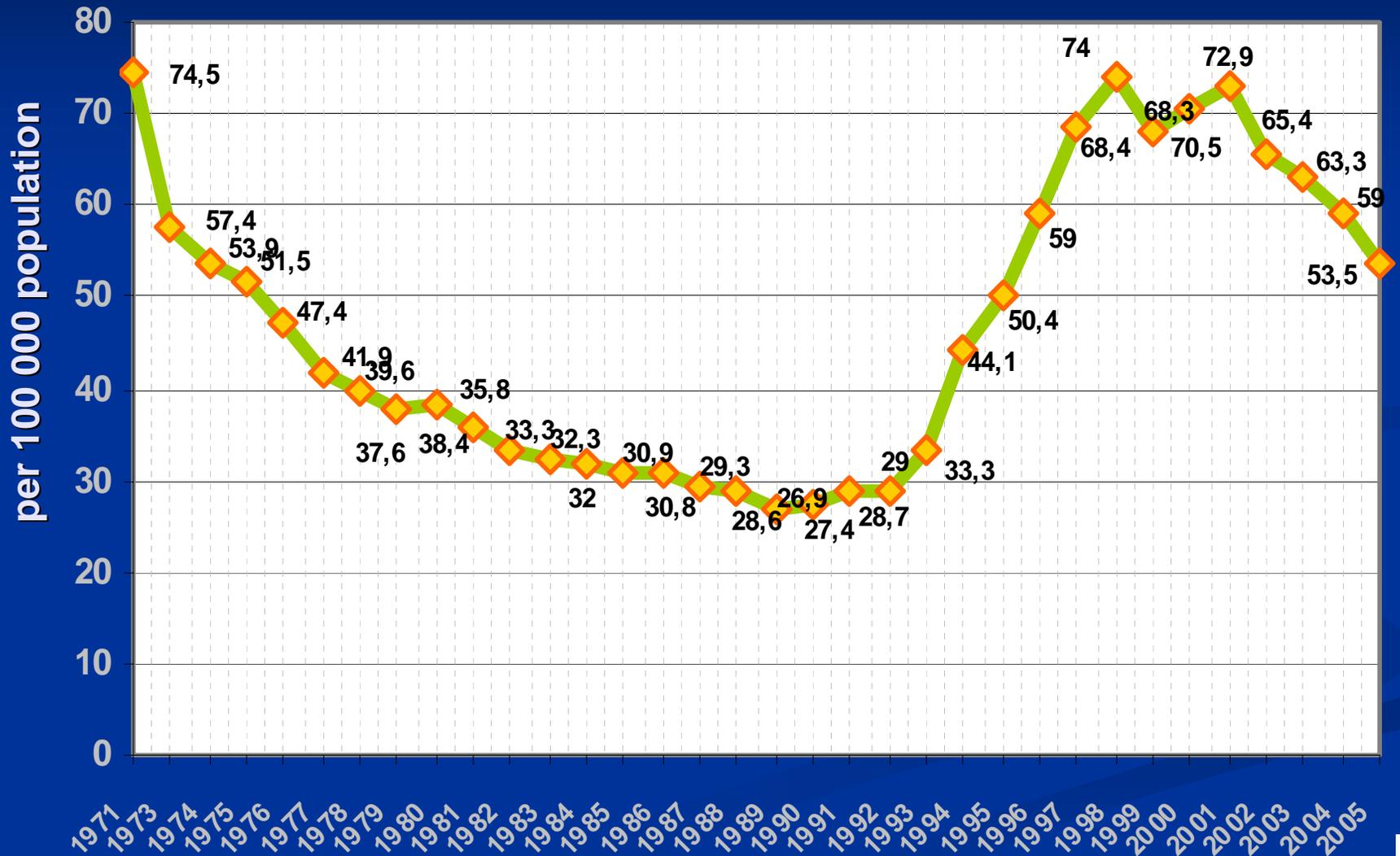
- Independent Baltic state since 1991
- DOTS implemented in 1996 countywide
- MDR-TB management started in 1997
- Latvia consistently ranked among countries with highest rates of MDR TB worldwide



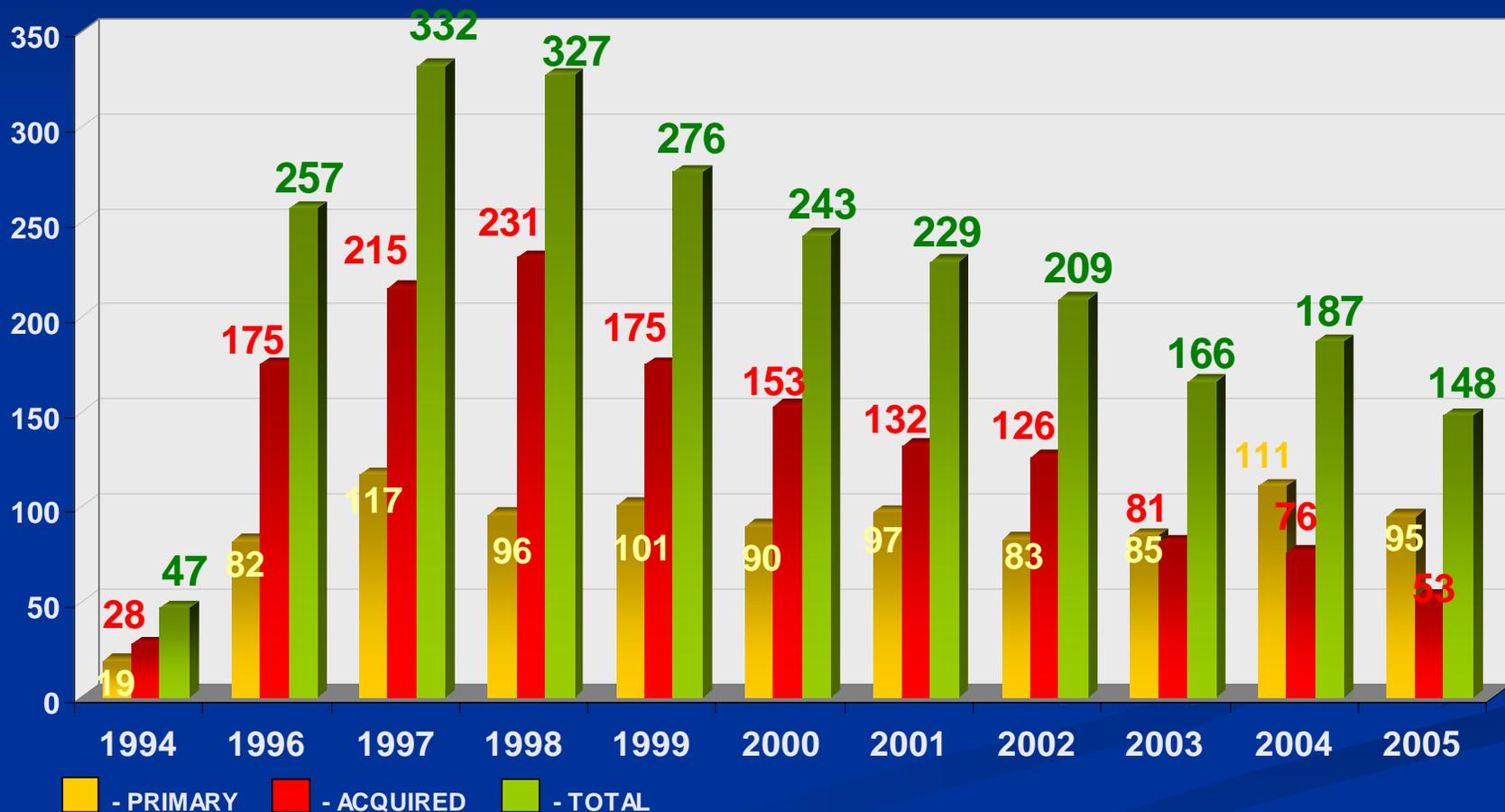
PRESENTATION OUTLINE

- EPIDEMIOLOGICAL SITUATION
- IMPLEMENTATION TB/MDR TB CONTROL PROGRAMS
- PROGRESS AND RESULTS IN TB CONTROL

TB incidence 1971-2005

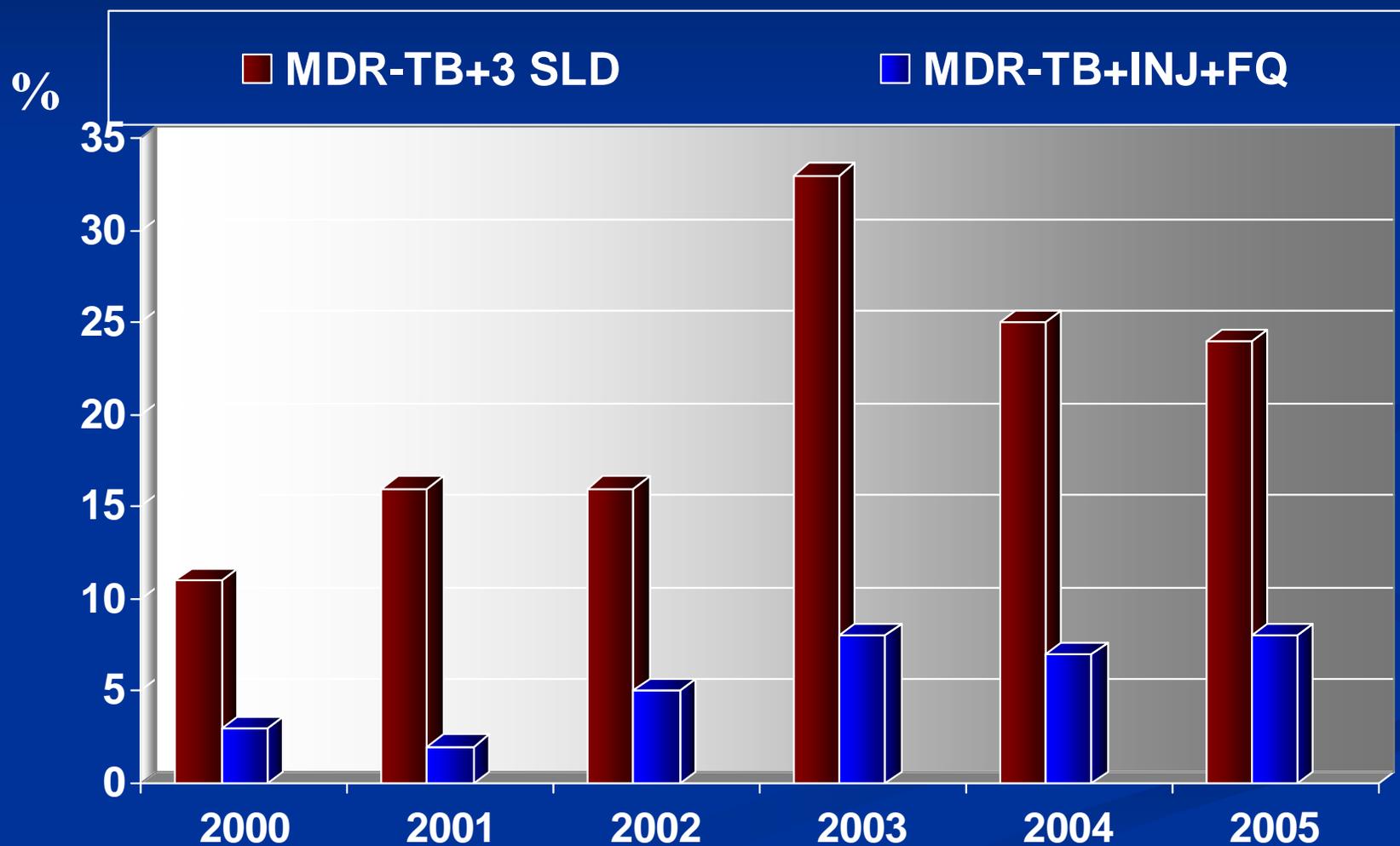


Primary and Acquired MDR TB Incidence Rates, 1994-2005



Since 1998 the total number of annually registered MDR TB cases decreased 2,2 times, for previously treated cases 4,4 times

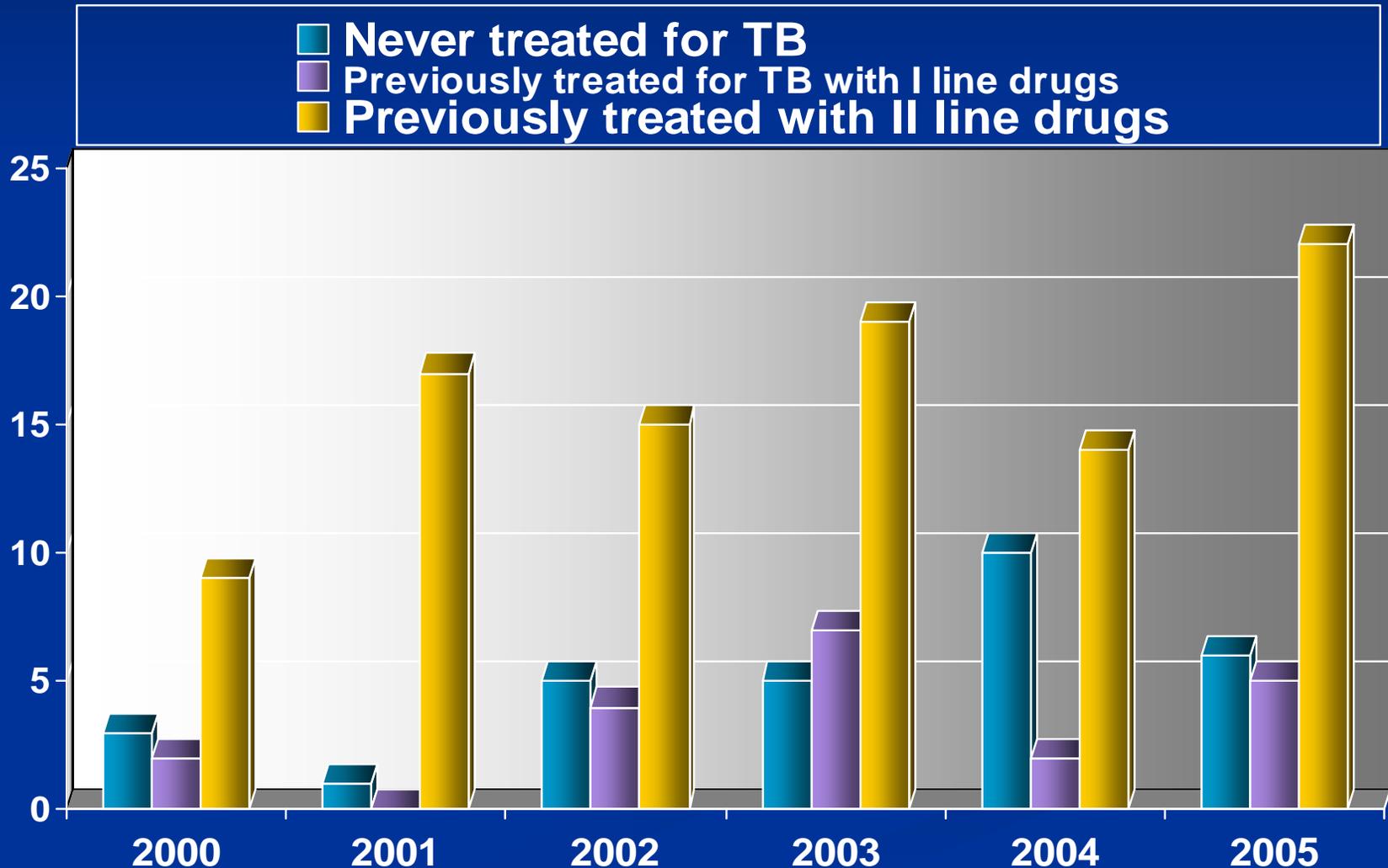
Proportion of Extensively Resistant Patients According to Patterns of Resistance



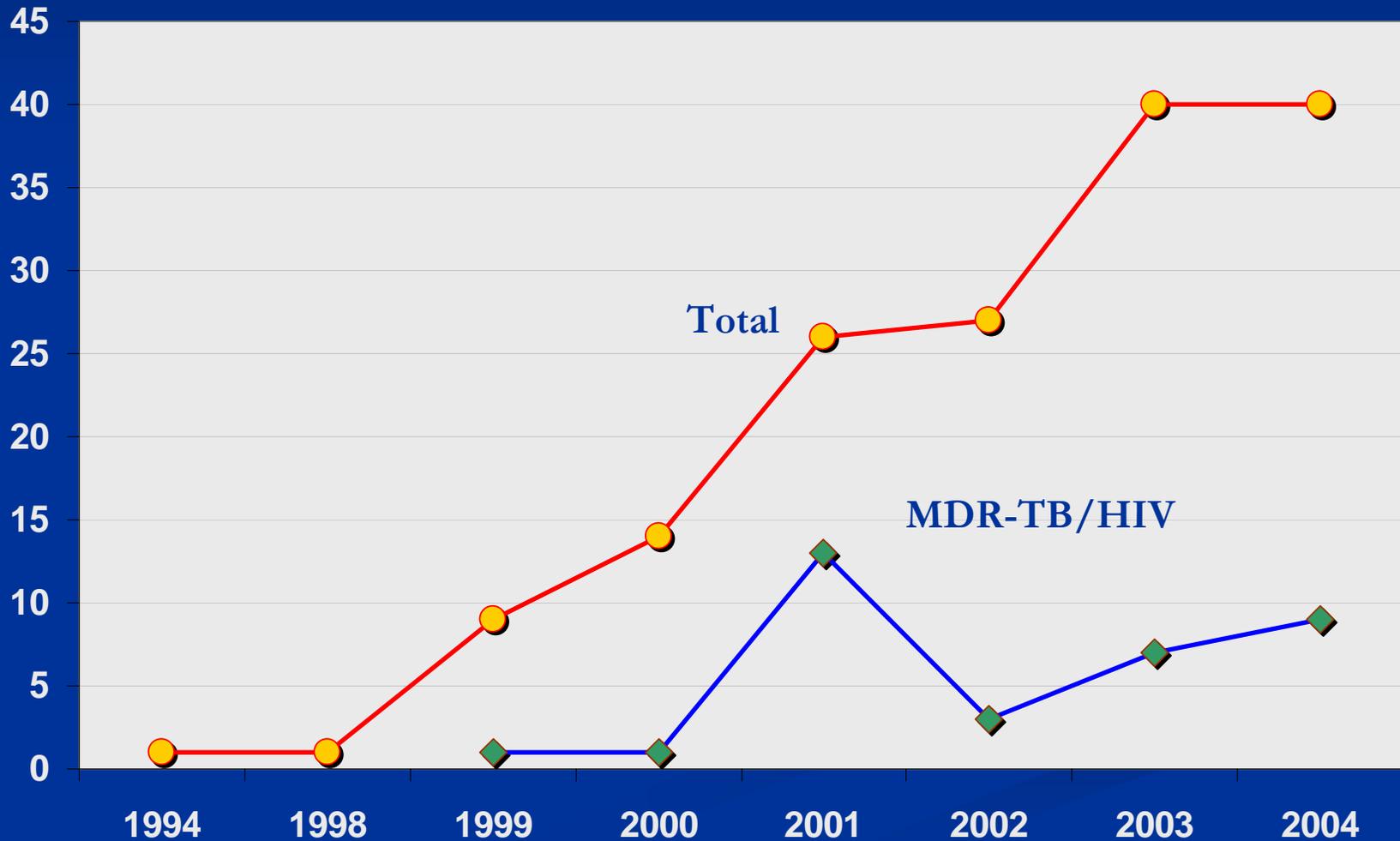
chi square test for trend = 12,4, $P < 0.001$

XDR-TB (MDR-TB+INJ+FQ)

Among 3 Patient Categories

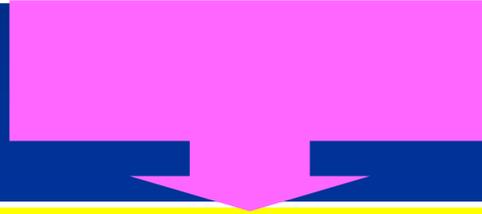


Number of TB/HIV Patients (Including Prisoners), 1994-2004



Ministry of Health of Latvia

SUSTAINED POLITICAL COMMITMENT



National TB Program (Financed by Government)
within the Health Care reform

- Well functioning DOTS program with additional treatment of MDR TB (within resources available)
- Collaboration and coordination between community, local governments, social services and international agencies
- Established centralized procurement and distribution of all anti-tuberculosis drugs

TB and MDR-TB Control in Latvia

Includes



NATIONAL TB CONTROL PROGRAM

Accepted first NTP, based on WHO-

recommended DOTS strategy

ALL FIVE ELEMENTS

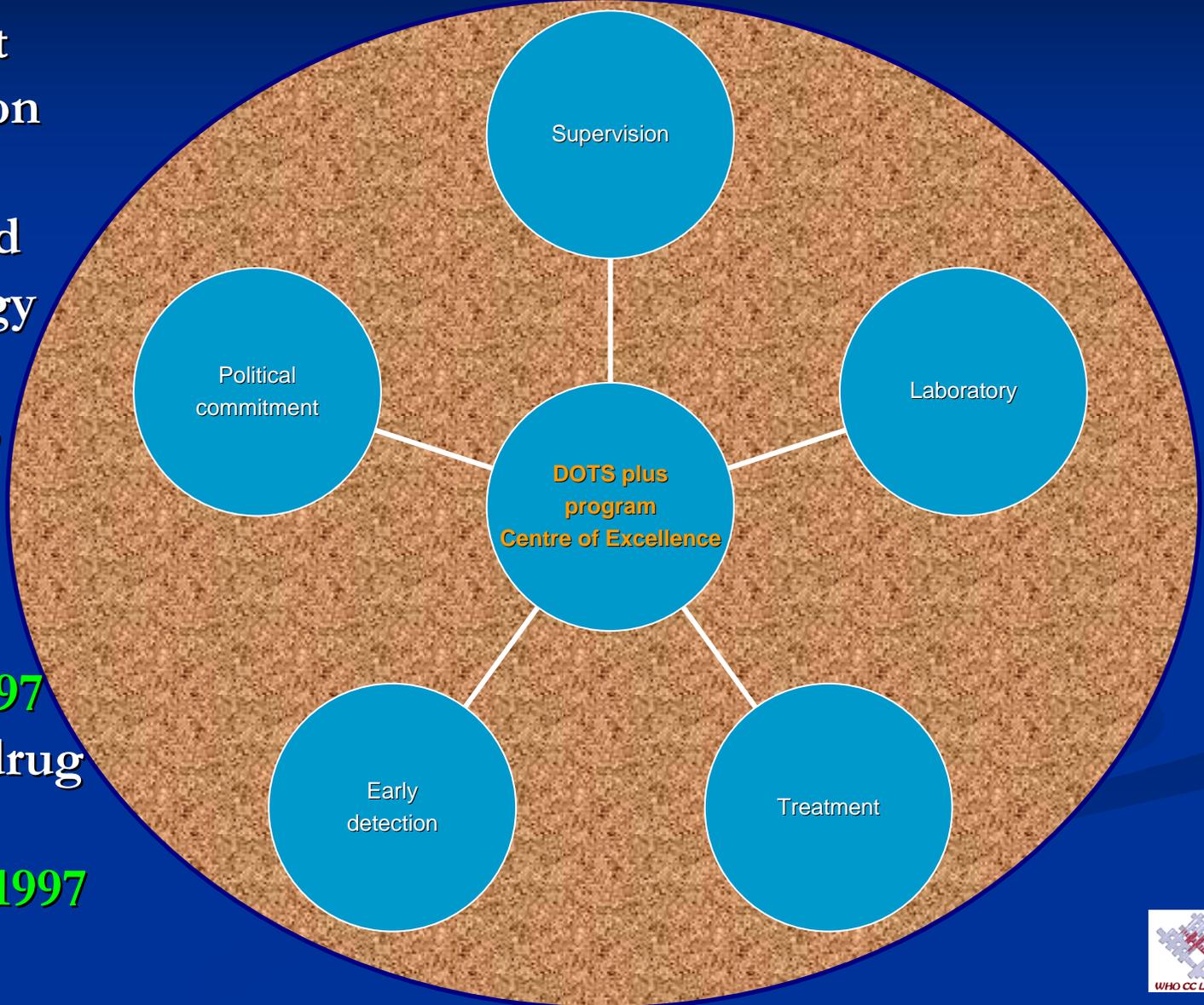
in 1995

Treatment of MDR TB

patients in 1997

Established drug resistance

surveillance 1997



DOTS PLUS IMPLEMENTATION

- **DOTS-plus project accepted by WHO Green Light Committee in January 2001**
 - Approval for 350 patients for drugs
 - Full coverage with treatment
- **Center of Excellence founded in 2000**
 - International training centre for treatment and management for MDR TB
 - First training course in **January 2001**
- **Established MDR-TB database, data management, and information system 2002 -2003**

STRUCTURE OF DOTS-PLUS PROGRAM

EXPERT CONSILIUM

**TREATING
PHISICIANS**

PHARMACY

LABORATORY

**TB/MDR TB
REGISTRY**

NURSES

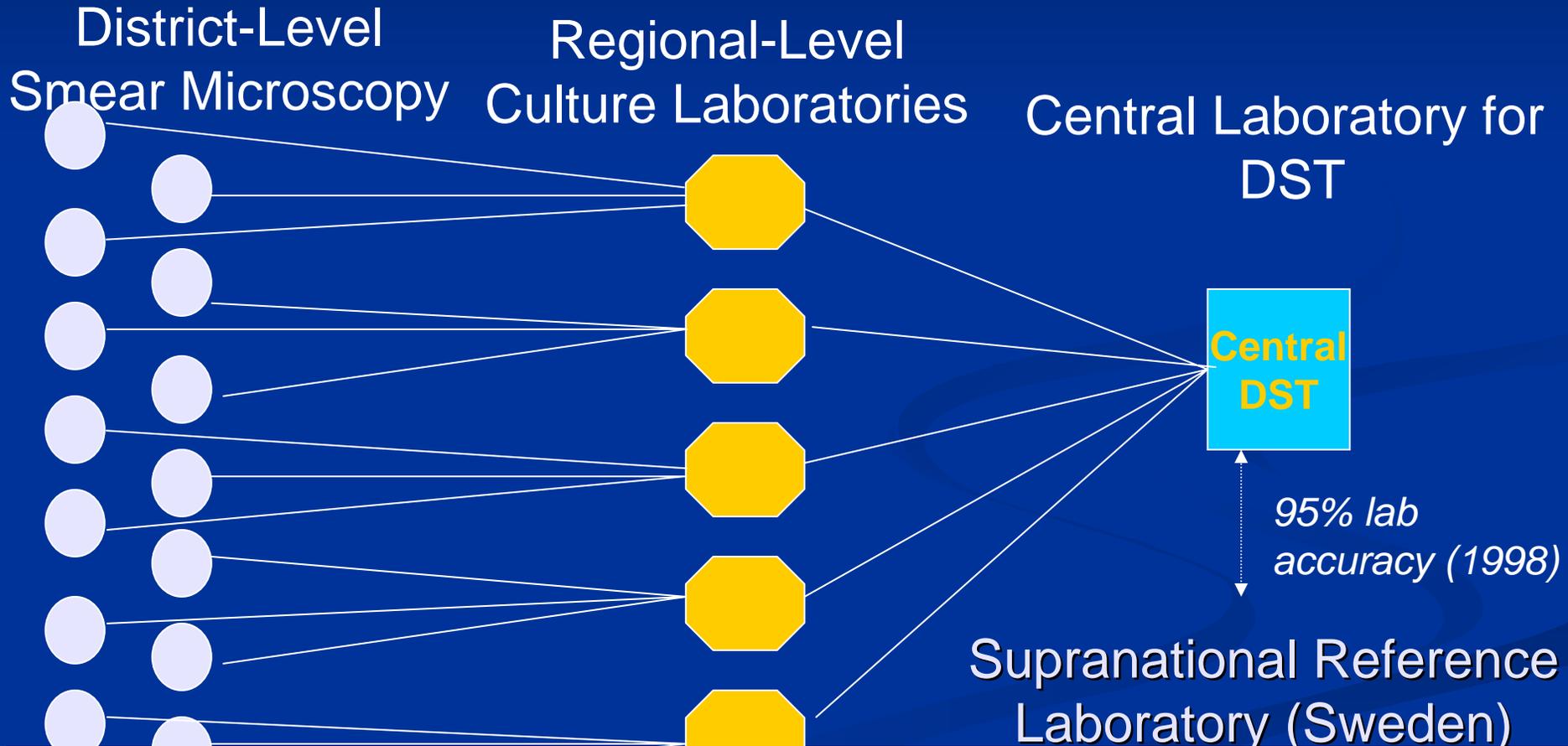
HOSPITALS

**AMBULATORY
TREATMENT**

**SOCIAL
WORKERS**

**SUPERVISION
BOARD OF EXPERTS**

NATIONAL LABORATORY NETWORK



Proficiency testing were provided once for OF and other second line drugs

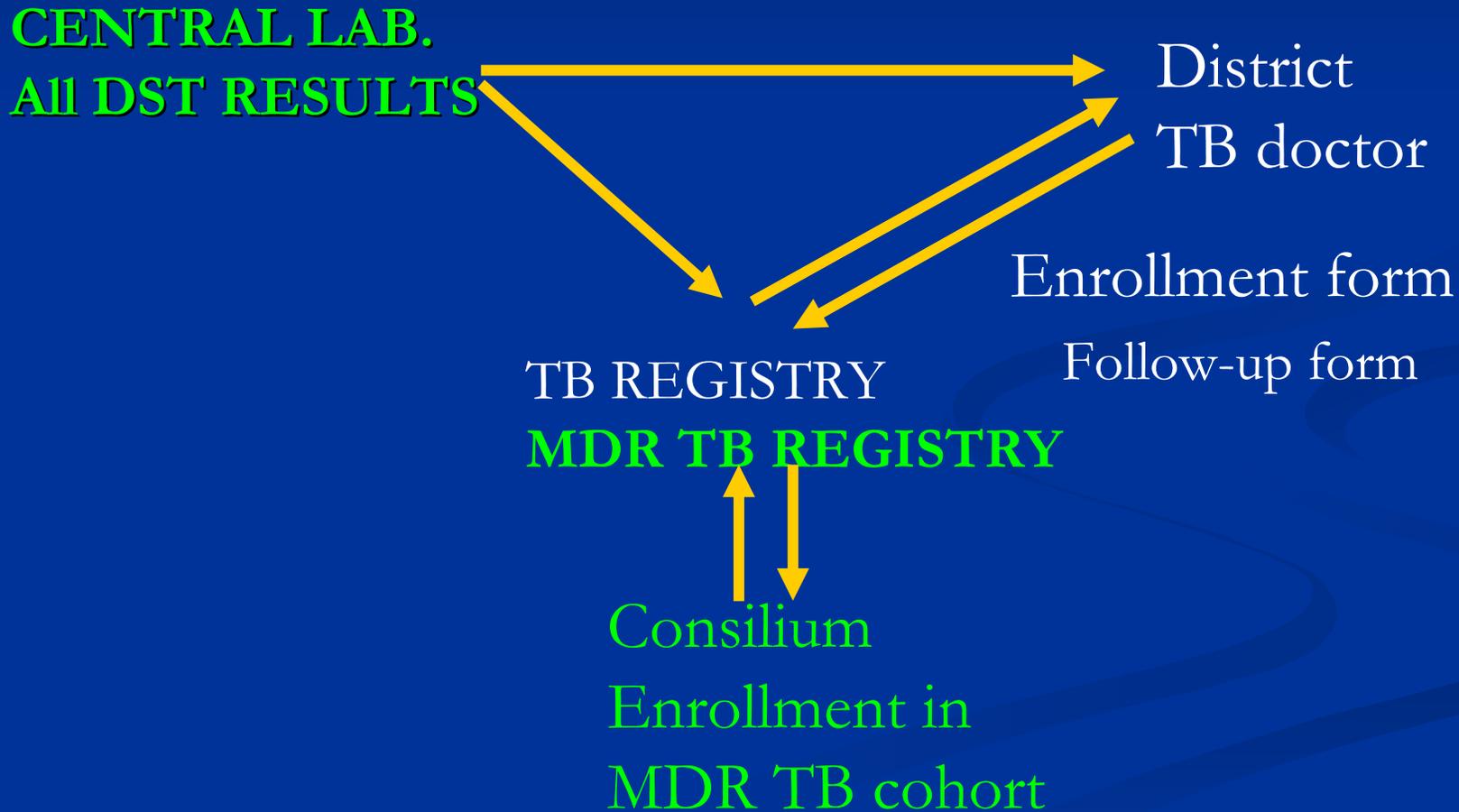
USE OF LABORATORY DIAGNOSTIC METHODS FOR– DST

- **DST** provide for all cc+ patients on L/J – absolute concentration method
- **BACTEC/MIGIT**
 - Priority I - for high MDR-TB risk patient SS (+)
 - Priority II – all SS+ cases for better infection control purposes
- **INNO Lipa test** – from direct specimen for SS+ high risk for MDR-TB patients

DST for MDR-TB treatment management

- ✓ DST to second line drugs perform when DST to I line drugs shows MDR-TB
- ✓ Repeat DST to I line drugs from specimen obtained before start of MDR-TB Tx to detect resistance amplification during Tx with I line drugs
- ✓ During MDR-TB treatment DST repeat if conversion not achieved after 4-6 months of treatment

MDR TB REPRTING AND RECORDING



SECOND LINE DRUGS USED AND DST

DST available

- Aminoglycoside
 - Streptomycine
 - Kanamycine
- Capreomycine
- Ofloxacin, Ciprofloxacin

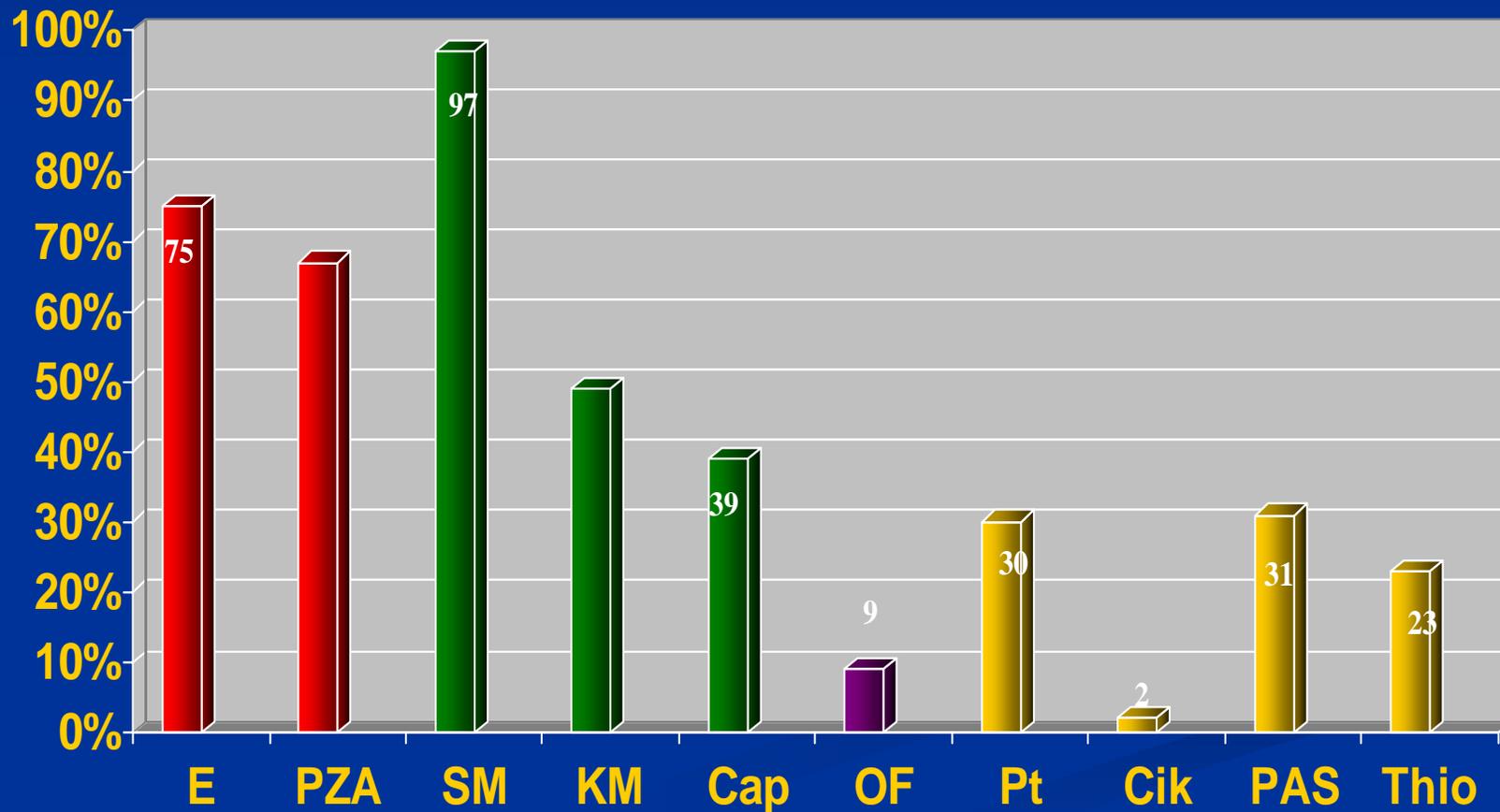
DST available

- Prothionamide
- Cycloserine, Terzindon
- Para-aminosalicylic Acid
- Thiacethasone

DST not available:

Clarithromycine; Amoxicillin/Clavulanate;

RESISTANCE TO INDIVIDUAL DRUGS (%) 2003-2005



MDR-TB Treatment Strategy - I

- ✓ ETR based on DST to I line drugs until DST to 2nd line drugs becomes available
 - ✓ Use 5-7 most powerful drugs available
- ✓ ITR based on DST to II and II line drugs
 - ✓ Injectables drug use
 - ✓ Daily until culture conversion confirmed
 - ✓ Continue at least 6 months after culture conversion
 - ✓ Use 12 month if TX regimen contains only 4 drugs
 - ✓ Use entire course of TX if extensive lung damage and/or week TX regimen

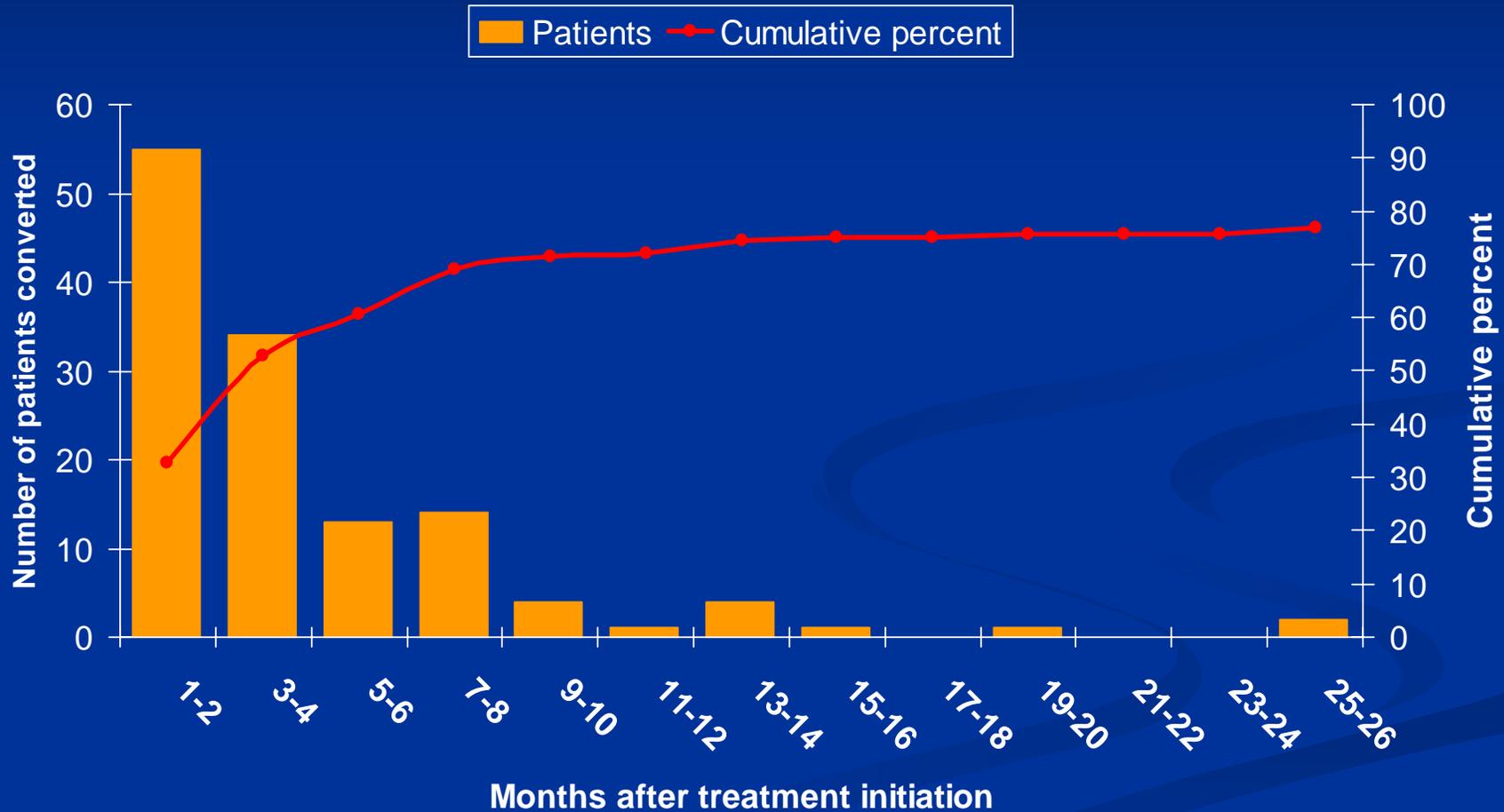
MDR-TB Treatment Strategy II

- ✓ Four oral drugs with preliminary susceptibility if possible, continue until completion of treatment
- ✓ Treatment duration after culture conversion
 - 12 – 18 months
- ✓ Treatment in hospital until culture conversion
- ✓ Ambulatory treatment DOT 5-6 times per week

TREATMENT CHARACTERISTICS

- 107 distinct regimens
- Median treatment duration: 18 months (1 – 38 mos)
- Median of 6 drugs used (range 3 - 8) for 3 months or more
 - Most common were ofloxacin, prothionamide, thiacetazone, pyrazinamide, ethambutol
- Use of injectable drugs
 - kanamycin, capreomycin, streptomycin
 - Median duration of use 12 months
 - Range of use 1-36 months
 - After culture conversion, median 9 months of use
- Defaulting patients with median treatment time of 7 months (range 2 – 16)

Initial sputum culture conversion in 129 patients of 167 culture positive patients who had culture conversion



15% (37) patients had negative culture at Tx start

Duration of Treatment for Good Outcomes - 135

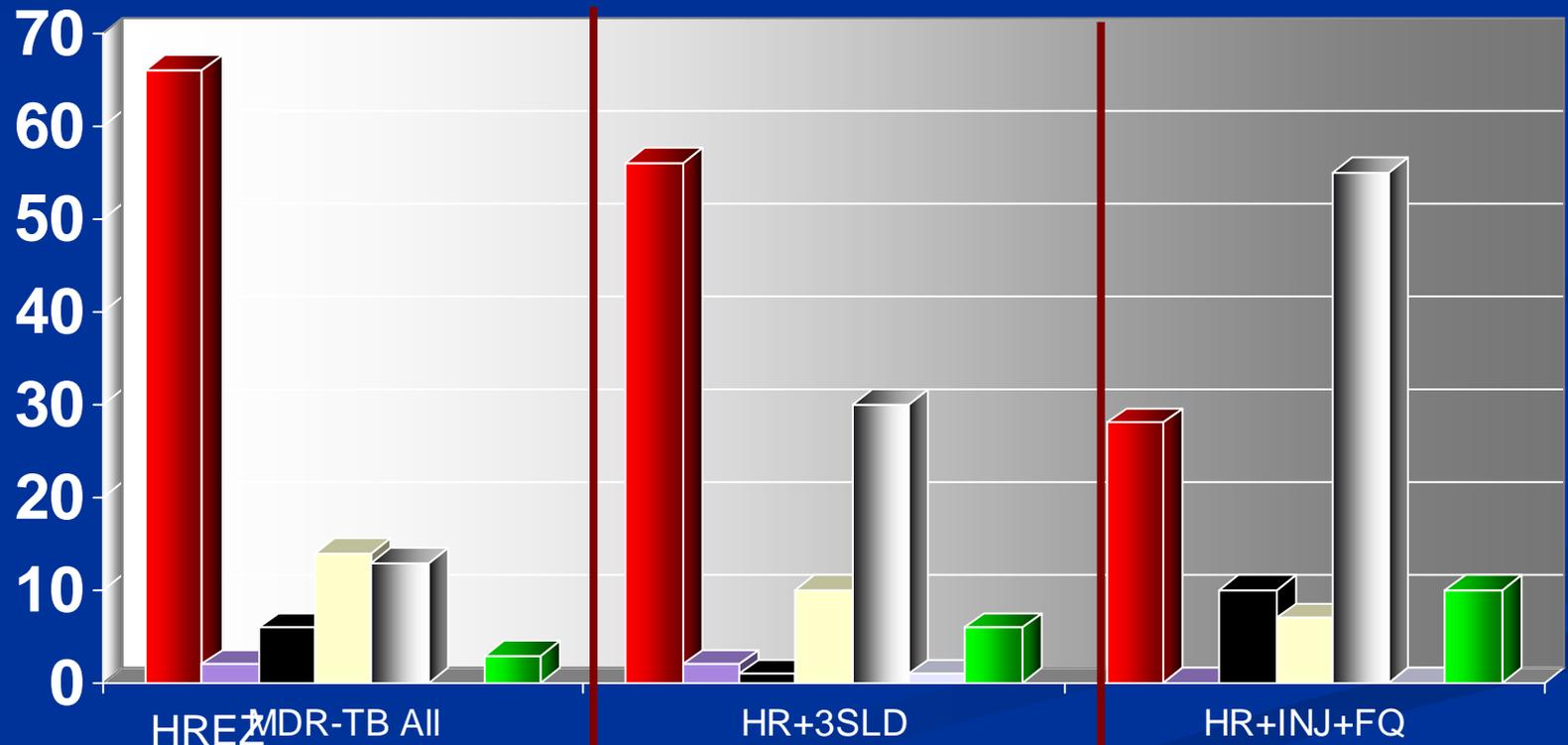


Treatment duration

- After culture conversion - Median 18 months, range 12-28
- No adherent defaulted after median 7, ranged 2-16 m.

TREATMENT OUTCOMES STRATIFIED BY RESISTANCE PATTERNS 2000-2003, 820 PATIENTS

■ Cure
 ■ Completion
 ■ Death
 ■ Default
 ■ Failed
 ■ Continue Tx
 ■ HIV+



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RISK FACTORS FOR POOR OUTCOME AMONG 172 ADHERENT PATIENTS

Cox Proportional-Hazards Multivariate Regression Model*

Factor	Adjusted hazard ratio (95% CI)	P value
Male gender	0,9 (0,4-2,2)	0,77
Female	Ref	
Age over 40	1,4 (0,7-2,6)	0,31
Less than 40	Ref	
Low body-mass index <18,5	2,3 (1,1-4,9)	0,03
>18,5	Ref	
Resistance to ofloxacin	2,6(1,2-5,4)	0,01
No	Ref	
Category of MDR TB		
3 previously treated for MDR-TB	5,7(1,9-16,6)	0,002
2 previously treated for TB	1,9 (0,7-5,1)	0,19
1 never treated for TB	Ref.	--

*n=172. Missing values and defaulters excluded.

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RISK FACTORS FOR FASTER TIME TO CULTURE CONVERSION

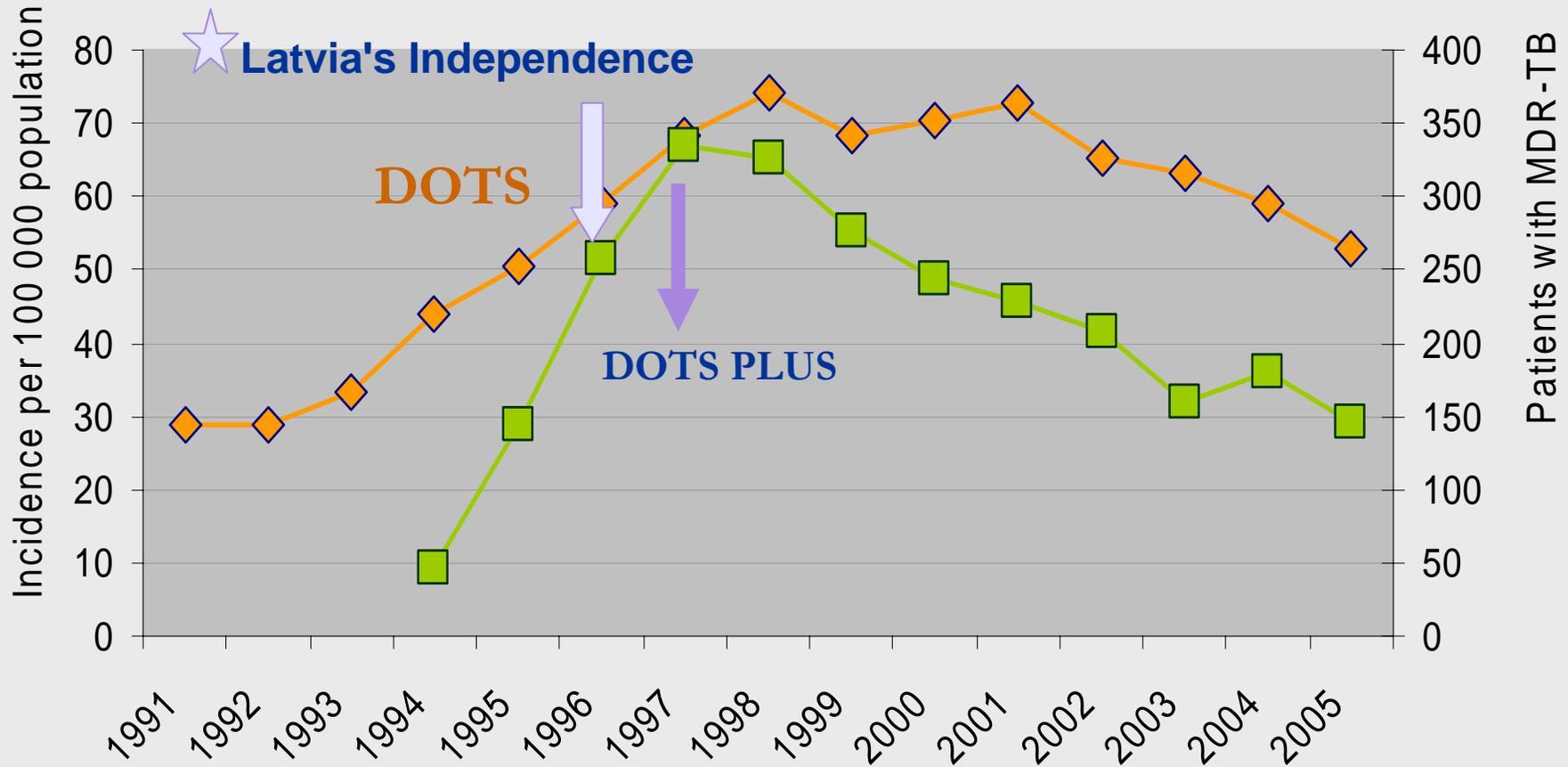
Weibull Proportional-Hazards Multivariate Regression Model*

*n=168. Those starting culture-negative were excluded.

Factor	Adjusted HR	95% CI	P value
Sensitivity to ofloxacin	6.1	3.2 - 11.7	<0.001
Sensitivity to PZA	1.9	1.3 – 2.7	0.001
No history of heavy alcohol use	1.5	1.1 – 2.2	0.02
Use of streptomycin in combination	2.1	1.1 – 4.4	0.048

In addition severity of disease – X-ray cavities, bacillary load, with low BMI – converts more slowly

THE IMPACT OF MDR-TB MANAGEMENT ON CASE DETECTION RATE 1991-2005



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

YEARLY CUMULATIVE DATA ON MDR-TB (01.01.2004)

YEAR	Completed treatment - 2003	Continue treatment 2004	Palliative treatment	Defaulted still on follow up 2003	Died in 2003
2002	181 (23%)	348 (44%)	101 (13%)	64 (8%)	101 (13%)
2004	156 (24%)	303 (46%)	85 (13%)	51 (8%)	67 (10%) (59 of TB)

Conclusions

- Acquired MDR-TB is decreasing in Latvia
- 2/3 of patients who started treatment in DOTS plus was cured
- Addressing treatment default could improve DOTS Plus program effectiveness
- XDR-TB is increasing, particularly for patients who has been treated with II line drugs before
- Cure rate of XDR –TB decrease to 28% for patients with XDR = INJ+ FQ comparatively 58% XDR = MDR + 3SLD and 66% for All MDR-TB

CHALLENGES TO PREVENT AND CONTROL DR-TB IN LATVIA

- Strengthening DOTS, improving Tx outcomes for drug sensitive cases
- Rapid diagnosis of MDR-TB and isolation
- MDR-TB in children
 - Contact investigation
- Treatment defaults and interruptions
 - Improving compliance
 - Compulsory treatment
- Infection control
 - In health care settings
 - Isolation of patients on palliative care
- Genotyping to detect chain of transmission is the next steps to improve MDR TB control in Latvia
- New drugs and treatment regimens
- HIV/AIDS and MDR-TB