

XDR TB: The Myth and The Reality

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Preview

- **The myths: What XDR TB is not**
- **What can we learn from the emergence of XDR TB?**
- **The reality: What is XDR TB?**

The Myths: XDR TB is not...

- An alien species from another planet
- A government conspiracy
- A hyper-virulent “Andromeda Strain” of *M. tuberculosis*
- Only found in South Africa
- Only found in / lethal in HIV-infected persons
- Easily treatable with the “remaining” anti-TB drugs in most cases
- ...Unexpected

What is XDR TB?

- A subgroup of MDR TB even more highly drug-resistant than MDR TB itself
- Conceptually: MDR TB that is also resistant to the most important 2nd-line drugs used to treat MDR TB
- Specifically: MDR TB that is also resistant to:
 - any one of the fluoroquinolones
 - at least one of the 2nd-line injectable drugs

XDR TB is a subgroup of MDR TB

Culture confirmed TB
cases with adequate
DST Results

Cases with any
drug resistance

MDR
TB

XDR
TB

Concept Behind Definition of XDR TB: Analogy to MDR TB

		MDR	XDR
1st-line drugs	“2 most important”	isoniazid	isoniazid
		rifampicin	rifampicin
		pyrazinamide ethambutol	pyrazinamide ethambutol
2nd-line drugs	“2 most important”	“injectables”	“injectables”
		quinolones	quinolones
		ethionamide	ethionamide
		cycloserine	cycloserine
		PAS	PAS

The Devil in the Details...

MDR

~~Isoniazid~~

~~Rifampicin~~

Pyrazinamide

~~Ethambutol~~

Aminoglycosides

Capreomycin

Quinolones

Thioamides

Cycloserine

PAS

XDR

~~Isoniazid~~

~~Rifampicin~~

Pyrazinamide

Ethambutol

~~Aminoglycosides~~

~~Capreomycin~~

~~Quinolones~~

Thioamides

~~Cycloserine~~

~~PAS~~

rifabutin, rifapentene

streptomycin

kanamycin, amikacin

capreomycin, viomycin

cipro, oflo, levo, moxi

ethionamide, prothio-

cycloserine, terizidone



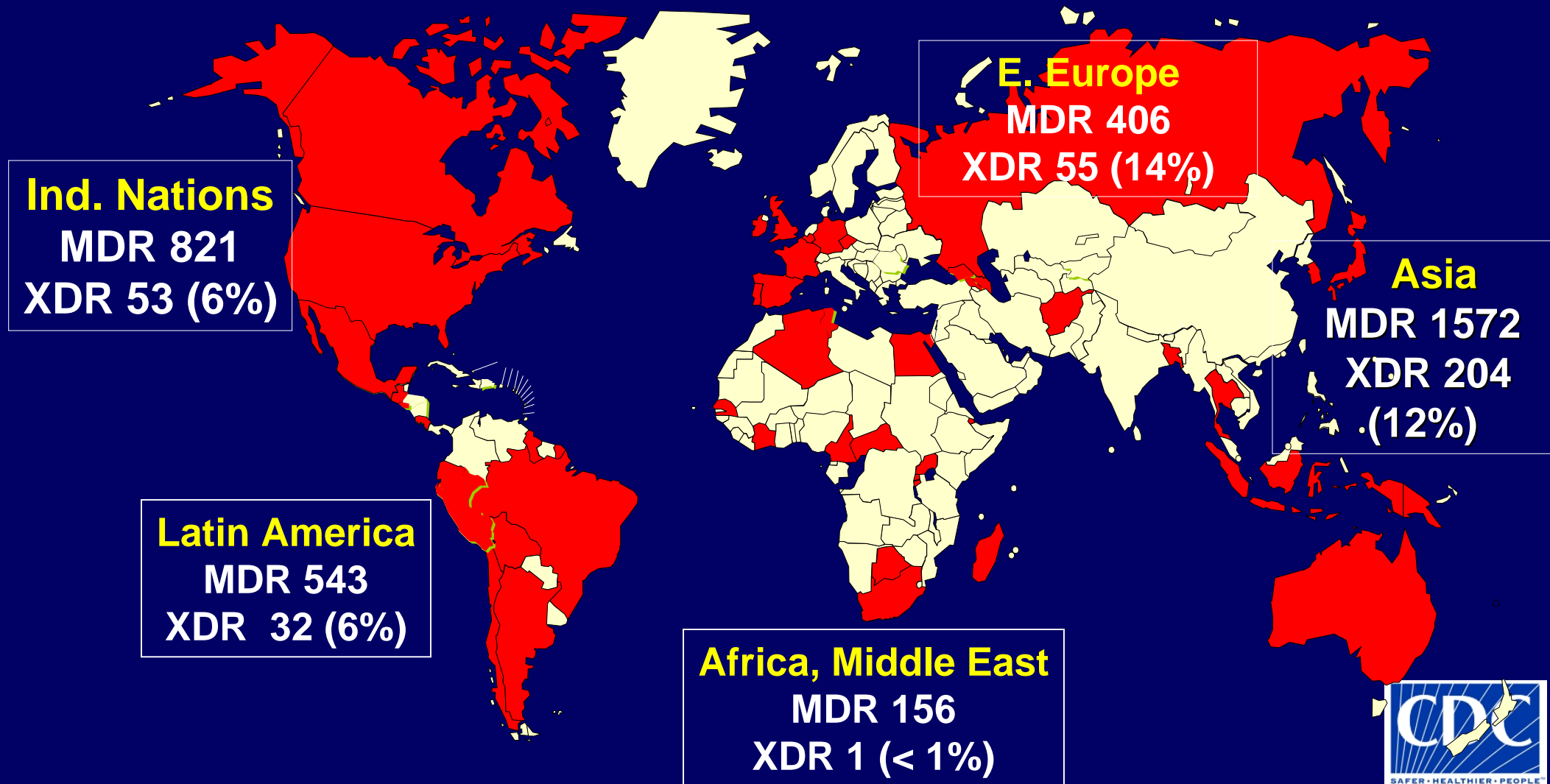
Resistance by definition



Resistance likely



**XDR TB is not limited to one country:
Distribution of XDR TB Cases Among Countries in the
Global Survey of Supranational Reference Labs, 2000–2004**



* Country unknown, MDR= 102; XDR= 2 (2%)



XDR TB in the U.S. 1993- 2005

TB cases with drug-susceptibility testing (DST)
results for isoniazid and rifampicin
N=180,324

Multidrug-resistant (MDR) TB cases
N=2,813 (1.6%)

MDR TB cases tested for at least 1
fluoroquinolone and 1 injectable 2nd-line drug
N=1,564 (55.6%)

Extensively drug-resistant (XDR) TB cases
N=47 (3.0%)



Characteristics of XDR TB in KZN

Infectiousness, Pathogenicity, and Lethality

<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)
● Previously hospitalized any reason	33 (64)
● Identical <i>M. tb</i> spoligotype	26/30
● HIV-infected (44 tested)	44 (100)
● Dead (Includes 34% on ARV)	52 (98)

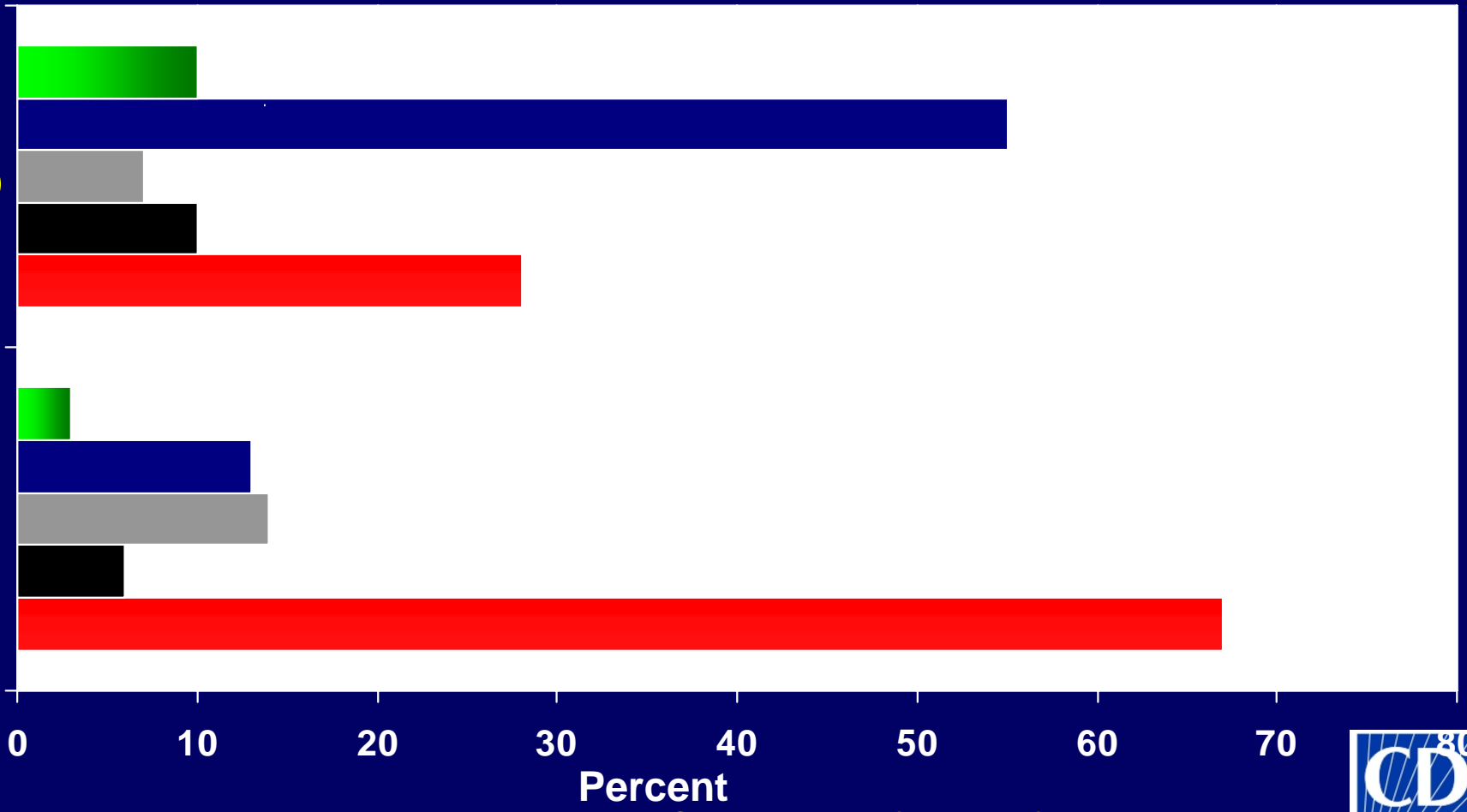


TB Treatment Outcomes in 820 TB Patients, Latvia, 2000-2003

■ Cure ■ Death ■ Default ■ Failed ■ HIV+

XDR TB only

MDR-TB All



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



XDR TB vs. MDR TB in the U.S., 1993-2005

	Characteristic	XDR TB N=47 (%)	MDR TB N=2766 (%)	P-value
Prior TB	Yes	7 (15)	498 (18)	0.80
	No	38 (81)	2247 (81)	
HIV status	Positive	16 (34)	700 (25)	0.15
	Negative	10 (21)	839 (30)	
	Unknown/Missing	21 (45)	1227 (45)	
Chest X-ray	Abnormal	37 (79)	2425 (88)	0.08
	Cavitary	9 (26)	798 (33)	0.33
Type of TB	Pulmonary	32 (68)	2235 (81)	0.43
	Extrapulmonary	6 (13)	283 (10)	
	Both P & EP	9 (19)	247 (9)	
Outcome	Completed therapy	15 (38)	1344 (56)	
	Died	13 (28)	685 (25)	

Initial resistance to 1st line drugs among XDR TB cases as reported to the U.S. National TB Surveillance System

Resistance To:	N (%)
INH + RIF	47 (100)
INH + RIF + EMB	38 (81)
INH + RIF + SM	39 (83)
INH + RIF + PZA*	16 (40)
INH + RIF + EMB + SM	35 (74)
INH + RIF + EMB + PZA*	11 (28)

Groups are not mutually-exclusive; 7 isolates no PZA results reported



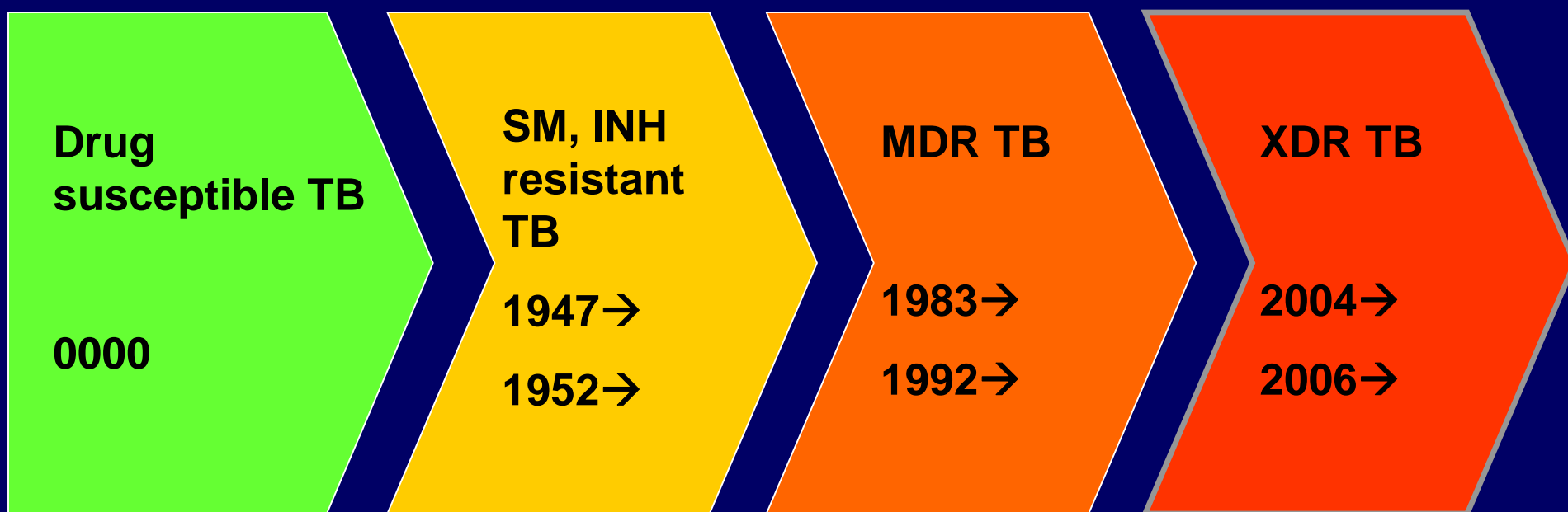
Initial resistance to 2nd-line drugs among XDR TB cases as reported to the U.S. National TB Surveillance System

Resistance To:	# Resistant / # Reported (%)
SM	40/47 (85)
Ethionamide	23/44 (52)
Cycloserine	8/34 (24)
PAS	20/31 (65)
Both KAN + CAP	14/41 (34)
Both AMK + CAP	10/39 (26)

Additional 2nd-line drug resistance among XDR TB cases in the Global Survey of Supranational TB Reference Labs

Resistance To:	N (%)
Ethionamide	217 (66)
PAS	94 (27)
Both AG + CAP	90 (26)
Both AG + CAP + ETA	127 (37)

The Evolution of Resistance



Adapted from Paul Nunn, Global Task Force on XDR TB, Geneva, 2006



Global Response to Drug-Resistant TB

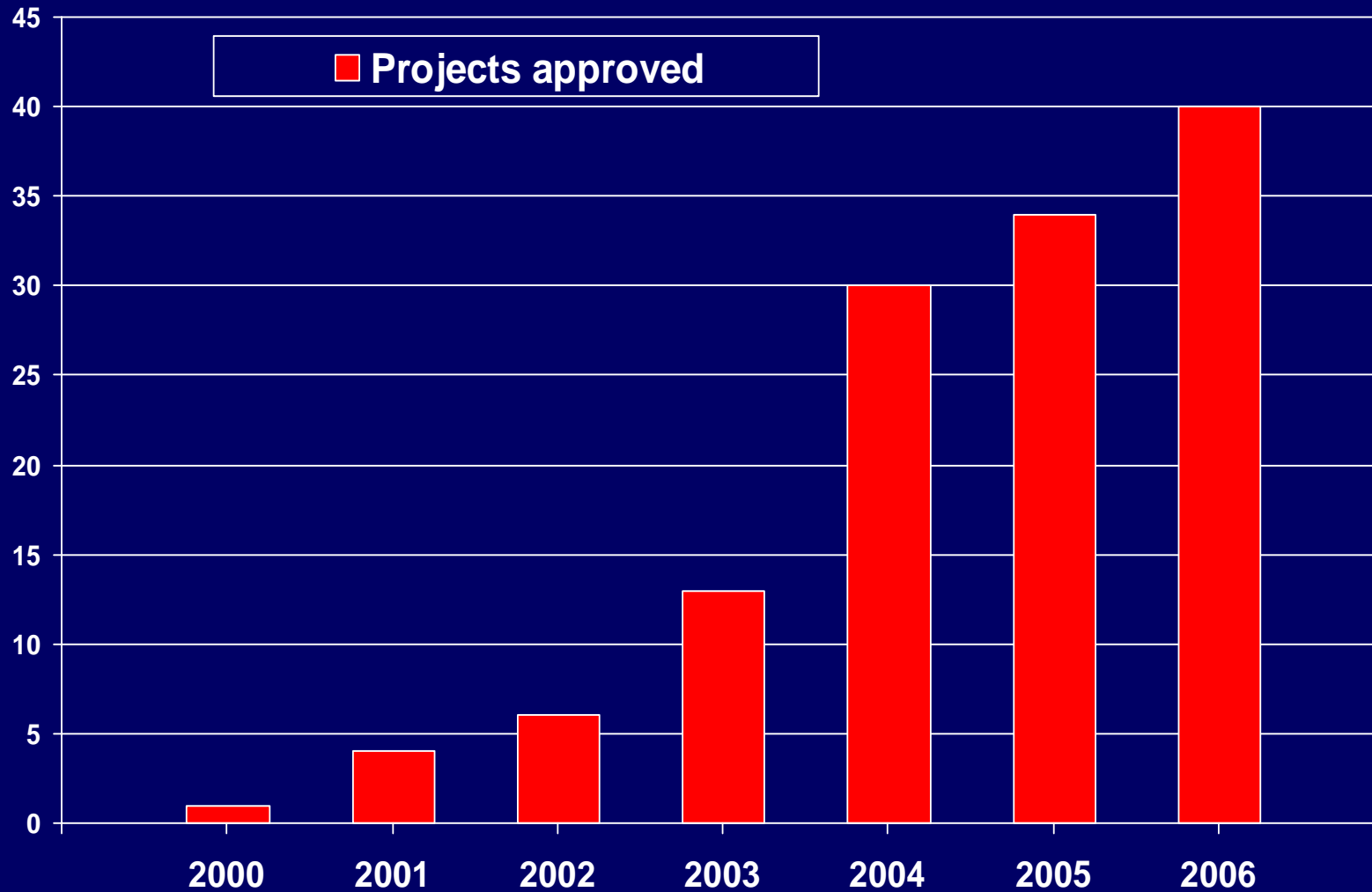
- Global drug resistance surveys
- “Green Light Committee”
- “DOTS-Plus” pilot projects demonstrate feasibility
- GFATM reduces financial barrier, requires GLC approval for 2nd-line drugs
- Transformation of global policy recommendations
 - ALL TB patients should receive best treatment
 - WHO Guidelines on drug-resistant TB (2006)
- DOTS-Plus moves into expansion phase
- Global Plan to Stop TB, 2006-2015



Green Light Committee (GLC)

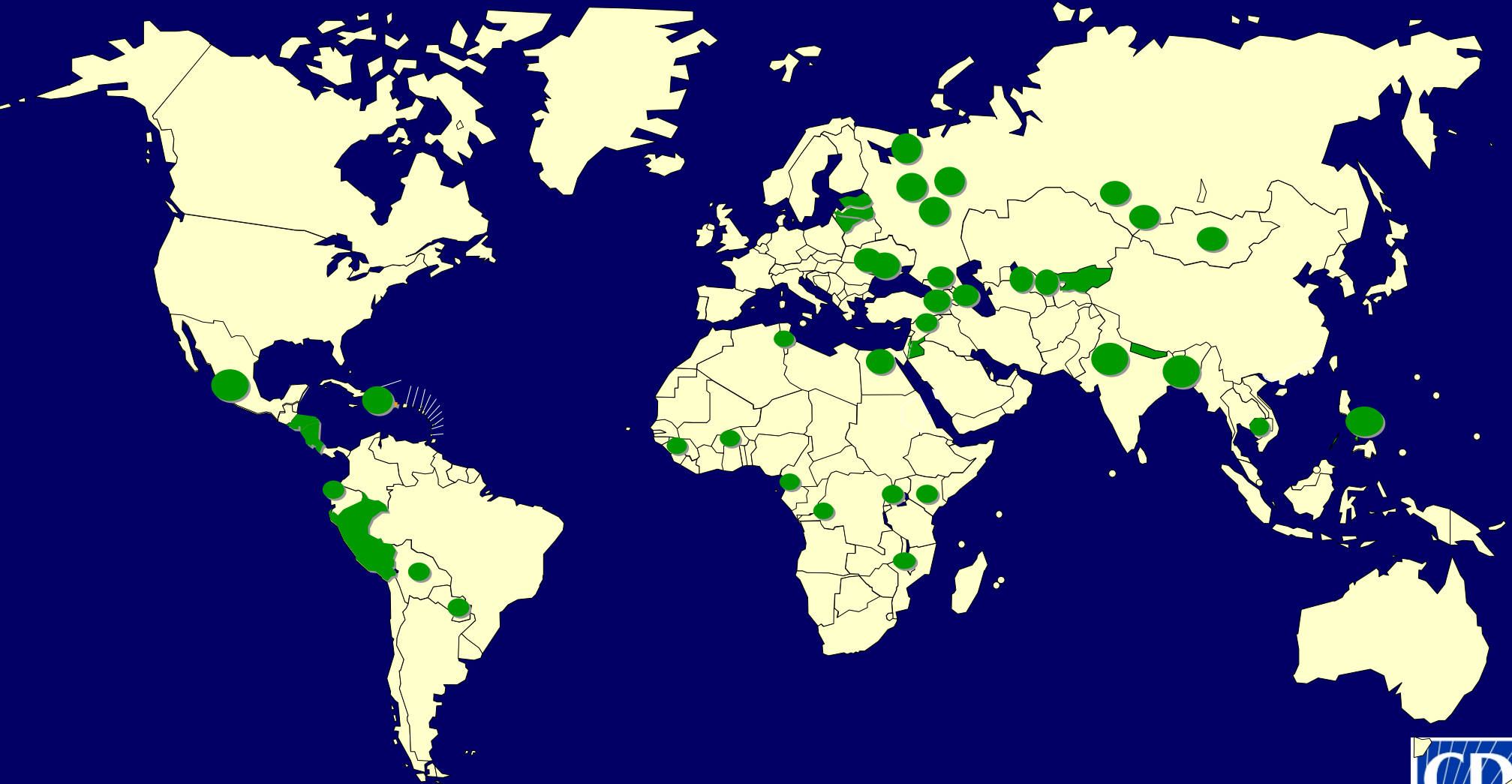
- Independent advisory committee of 6 agencies, anchored by WHO
- Provide quality-assured 2nd-line drugs at deeply reduced cost
- Technical assistance and training
- External monitoring and evaluation
- Improved clinical, programmatic drug use
- Creation of broad evidence base for policy development

Scaling up MDR-TB treatment through the GLC

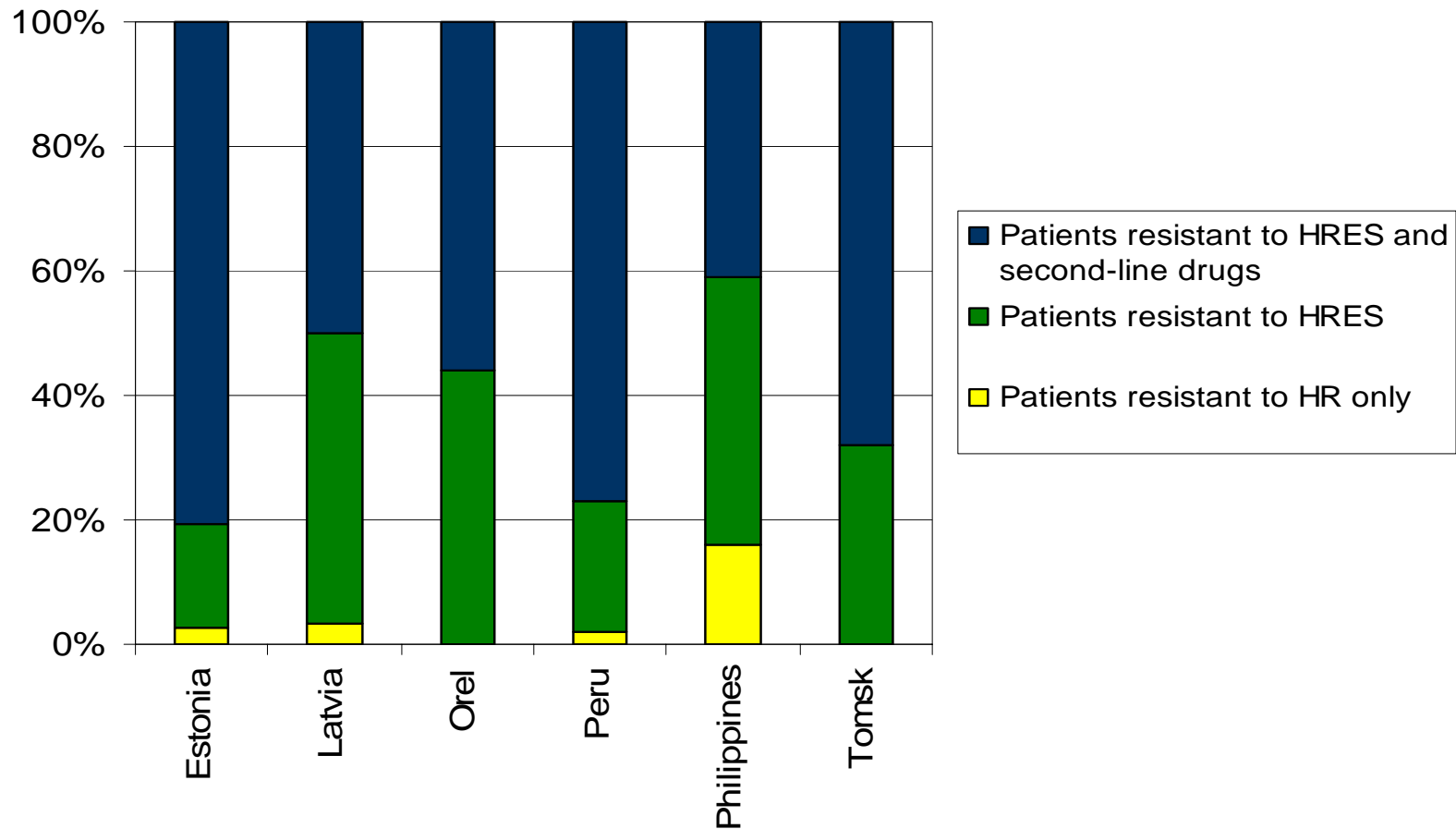


**40 projects
and
~23,000
patients
approved
in 6 years**

GLC approved countries / projects as of September 2006



TB Drug Resistance in DOTS-Plus Pilot Projects



Nathanson et al, EID 2006



Second-line TB Drug Use by Region, 2004

	Widely used	SLDs not available	No data
US, Can, WEur, Aus, NZ	14		6
Central / Eastern Europe	5		25
Latin America	17		7
Africa	10	3	38
N Africa / Middle East	4	13	
South and SE Asia	36	1	11
East Asia	2		4
Total	88	17	81

Source: WHO, 2004

What lessons can we draw from the parallels between MDR TB & XDR TB?

- MDR TB
 - INH 1952
 - RIF approved 1972
 - MDR TB outbreaks reported 1992
 - Global DRS reveals MDR TB worldwide starting in 1994-2002
 - 460,000 MDR TB cases per year (~5% of incident TB cases)
- XDR TB
 - KAN, CAP 1950s
 - FQ 1980s
 - XDR TB outbreak reported 2005
 - Survey of SRLs reveals global XDR TB
 - What does this suggest about the true magnitude of XDR TB?

The Reality: XDR TB is...

- Infectious
 - Pathogenic
 - Deadly
 - Distributed worldwide
 - Difficult to treat
- In both HIV-infected and –uninfected populations*
- An inevitable consequence of 2nd-line drug use
 - Likely to be more common than we realize and increasing because 2nd-line drug use increasing
 - A huge lever to increase resources for TB control