MDR-TB and XDR-TB: Mechanisms, epidemiology, and treatment

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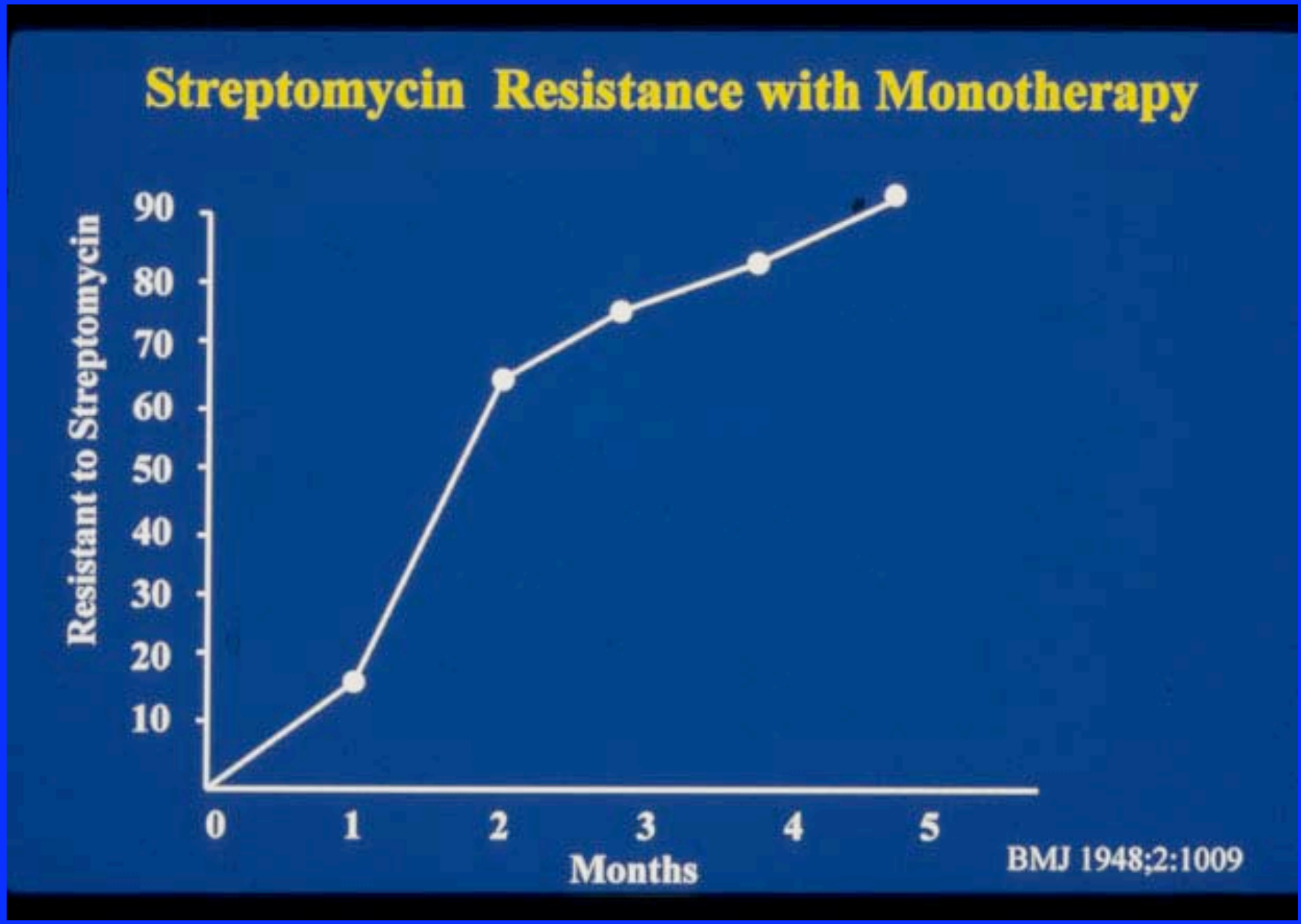
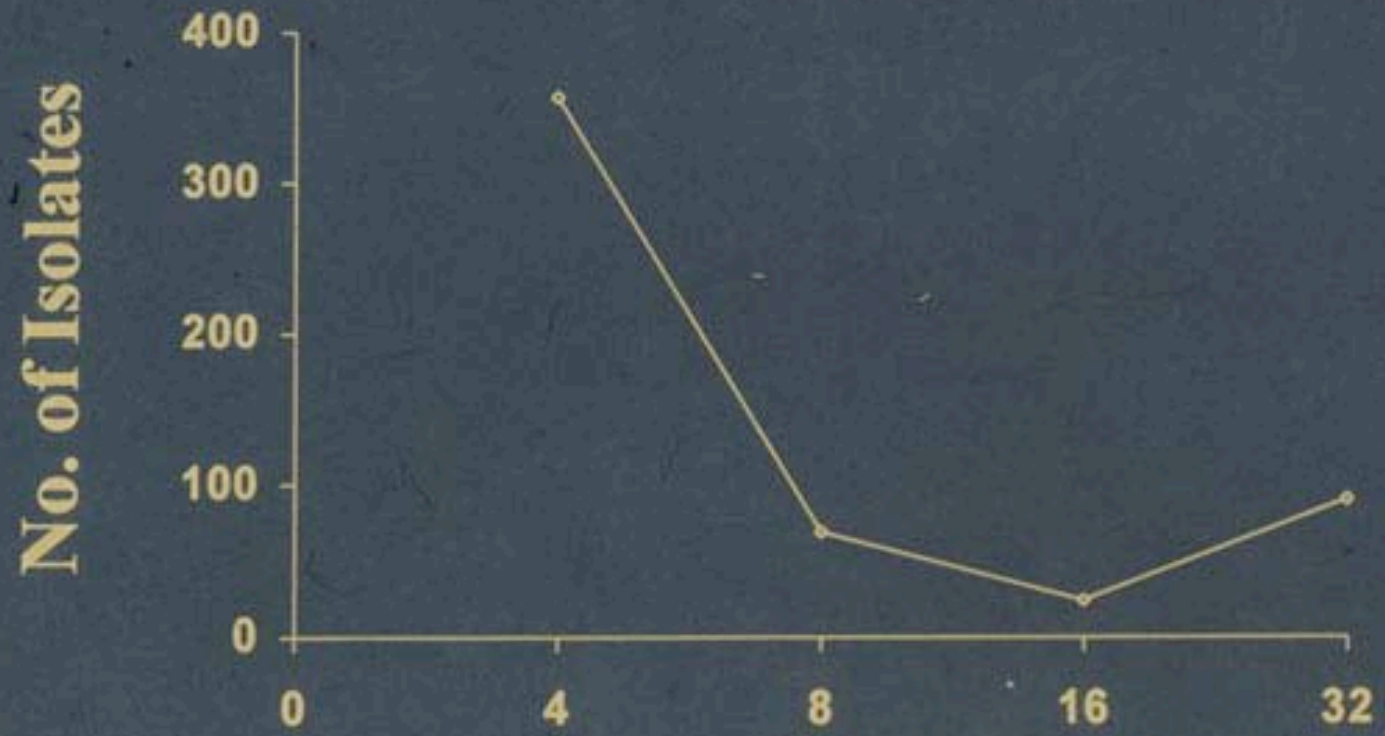
Streptomycin Resistance with Monotherapy



MIC of Streptomycin for M.tb



Bull WHO 1969;41:21

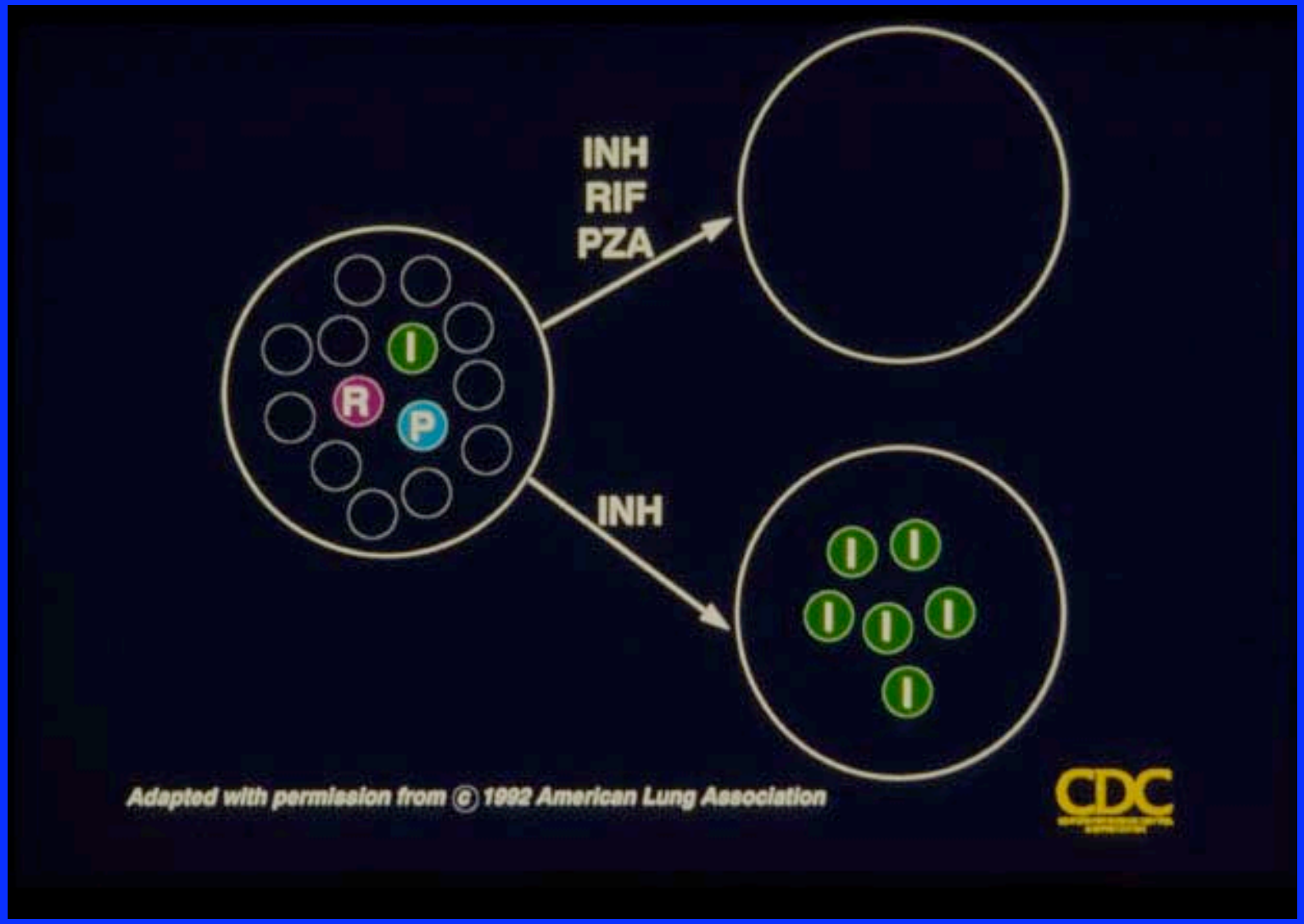
Spontaneous Mutations of *M. tuberculosis* and Drug Resistance

Drug	Average Resistance Mutation Rate	Resistant: Susceptible Ratio in bacterial populations
Isoniazid	2.56×10^{-8}	$1:10^{6}$
Rifampin	2.25×10^{-10}	$1:10^{8}$
Ethambutol	1.00×10^{-7}	$1:10^{5}$
Streptomycin	2.95×10^{-8}	$1:10^{6}$

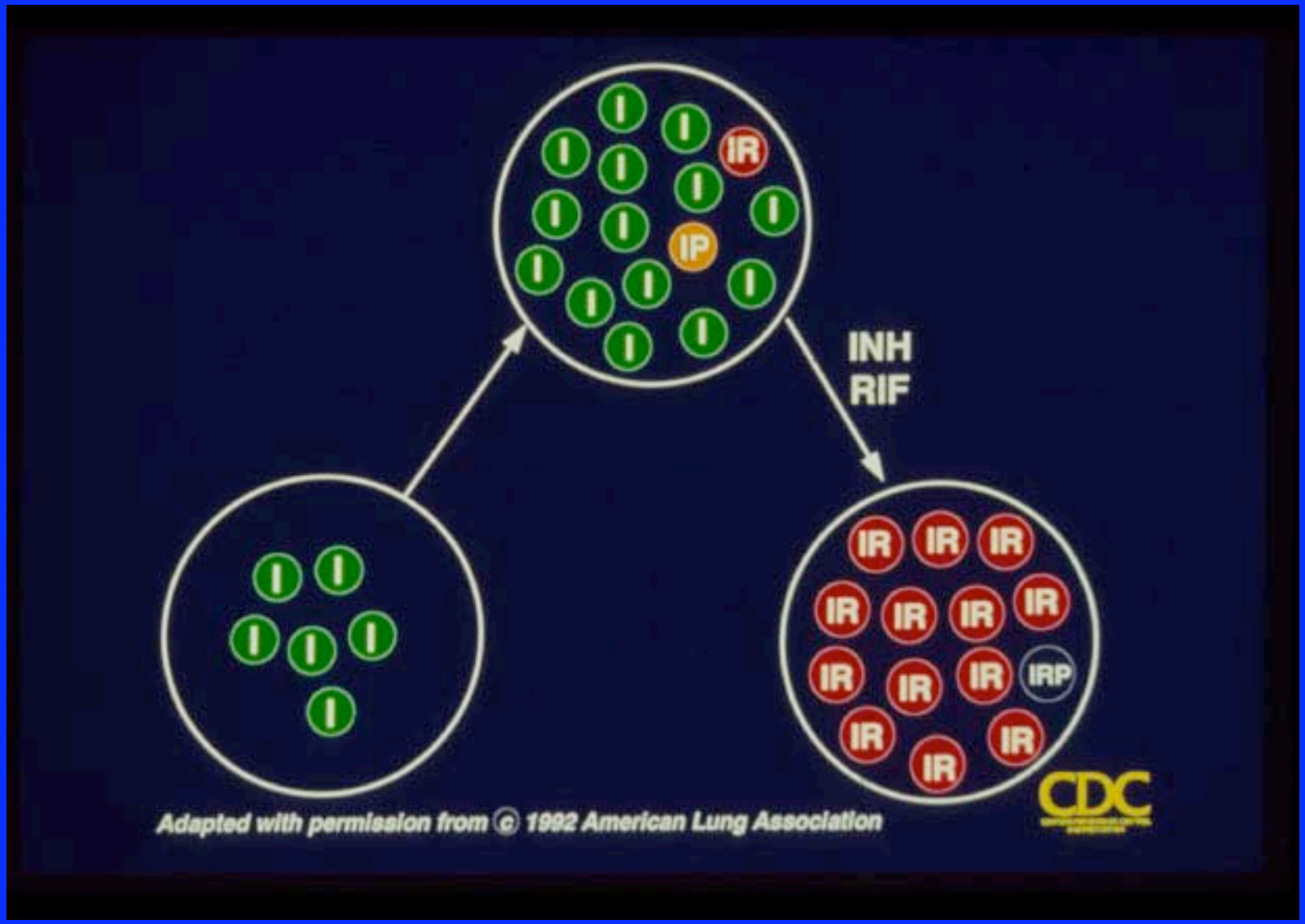
Mechanisms of *M. tuberculosis* Drug Resistance

	Target	
Drug	Gene	Enzyme
Isoniazid	*kat*G	catalase
	*inh*A	
Rifampin	*rpo*B	RNA polymerase ß
Streptomycin	*str*A	Ribosomal protein S12
	*t*RNA	16s rRNA
Ciprofloxacin	*gyr*A	DNA gyrase

Selection of Drug Resistance with Monotherapy



Selection of MDR with Monotherapy



Primary (Initial) Resistance

TB patient's initial population of *M. tuberculosis* is resistant to drug

Secondary (Acquired) Resistance

Drug resistant *M. tuberculosis* organisms in initial population selected by inappropriate drugs (inadequate Rx or failure to take Rx)

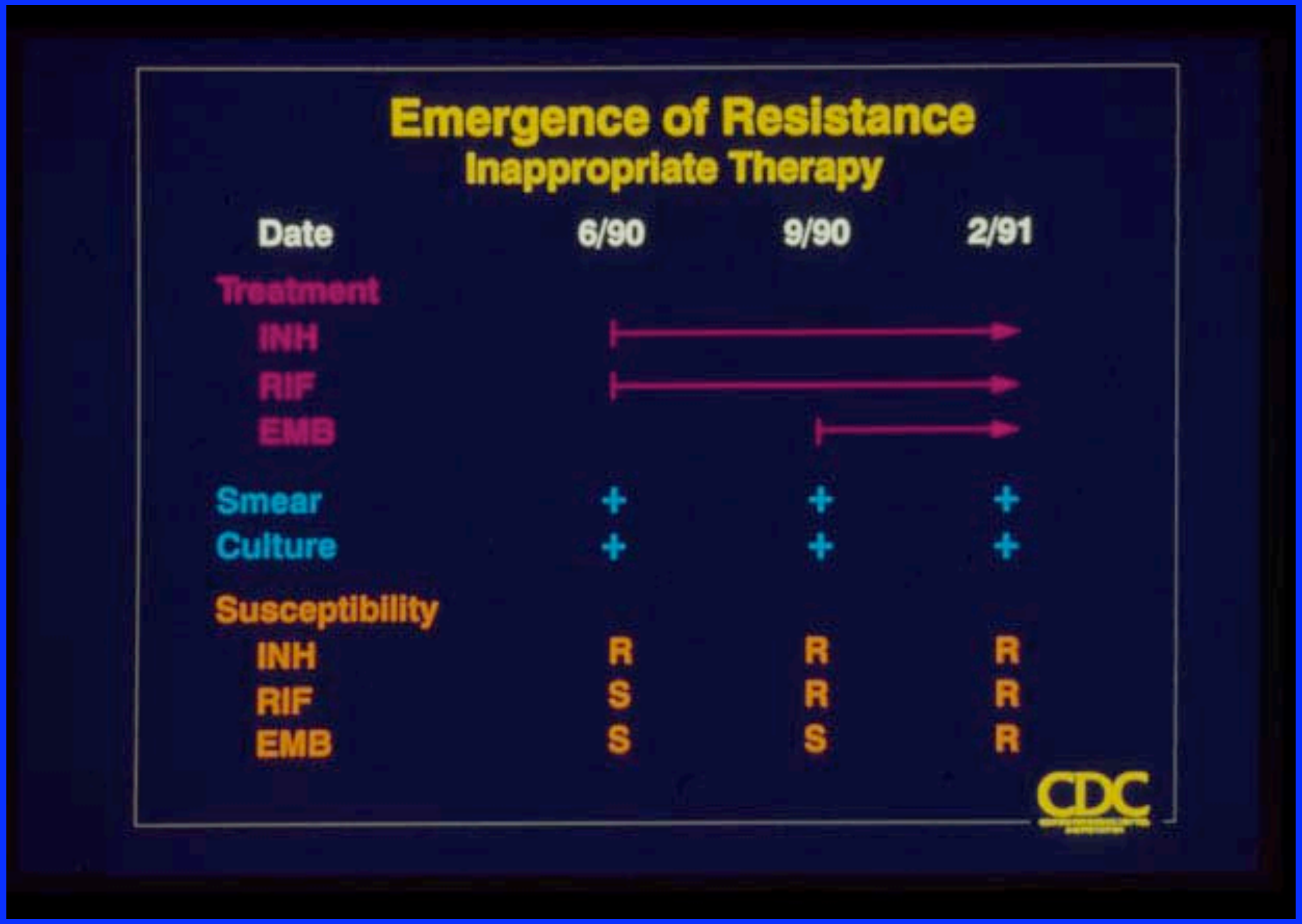
Multidrug-Resistant TB (MDR-TB):

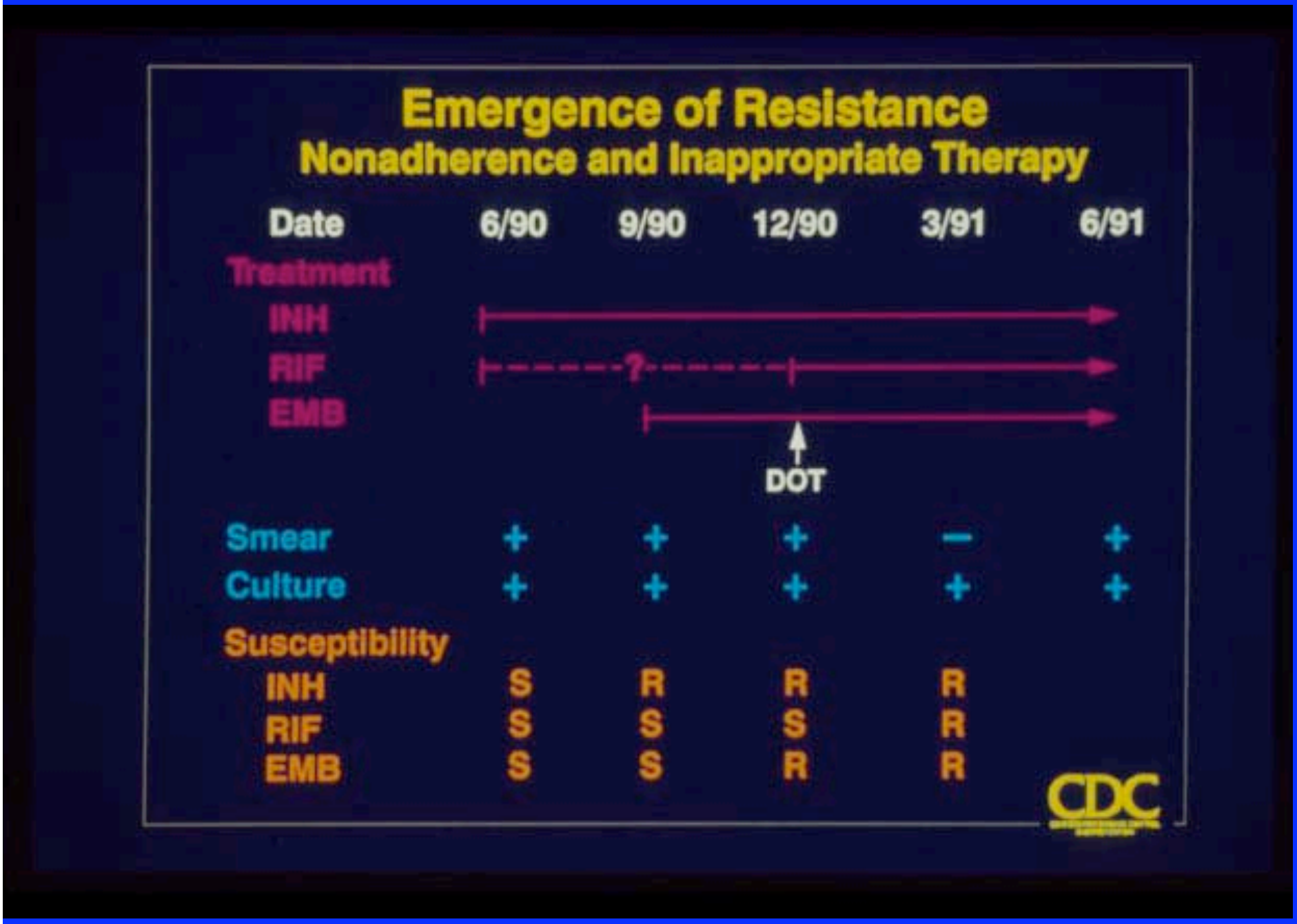
Tuberculosis disease caused by *M. tuberculosis* resistant to Isoniazid and Rifampin
(+/- other drugs)

Risk Factors for Multi-Drug resistant TB

- Prior therapy for TB

- Birth outside the US (especially Africa, Asia, S. America)
- Recent travel to a country with MDR-TB
- Recent exposure to someone with MDR-TB


Emergence of Resistance
Inappropriate Therapy
Date
6/90
9/90
2/91
Treatment
INH
RIF
EMB
Smear
Culture
Susceptibility
INH
RIF
EMB
+
+
+
+
+
+
R
R
R
S
R
R
S
S
R
CDC


Emergence of Resistance
Nonadherence and Inappropriate Therapy
Date
6/90
9/90
12/90
3/91
6/91
Treatment
INH
RIF
?
EMB
DOT
Smear
+
+
+
−
+
Culture
+
+
+
+
+
Susceptibility
INH
S
R
R
R
RIF
S
S
S
R
EMB
S
S
R
R
CDC

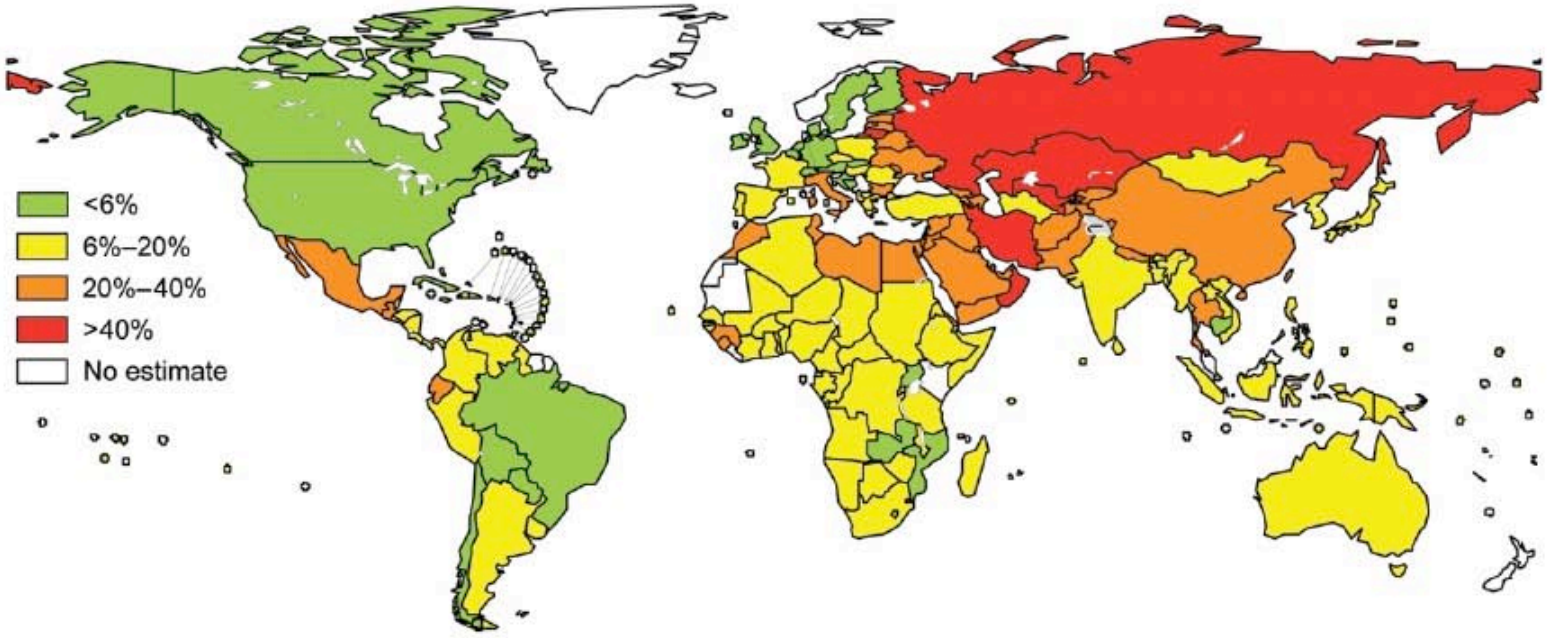
Numbers and Proportions of MDR- TB cases, 2004

Region	All cases No.*	All MDR cases	
		No.* (95% CI)	% (95% CI)
Established market	113	1.7 (1.3–2.1)	1.5 (1.3–1.8)
Central Europe	51	1.5 (0.7–4.5)	2.8 (1.5–8.6)
Eastern Europe	428	65 (52–88)	15 (14–20)
Latin America	386	11 (9.5–14)	2.9 (2.6–3.5)
Eastern Mediterranean	555	18 (12–45)	3.3 (2.2–8.1)
Africa, low HIV	519	10 (9.2–22)	2.0 (1.8–4.3)
Africa, high HIV	2,356	48 (39–95)	2.0 (1.7–4.0)
Southeast Asia	3,300	115 (62–265)	3.5 (2.0–7.7)
Western Pacific	2,170	152 (100–214)	7.0 (5.7–8.5)
All countries (*n* = 184)	9,880	424 (367–620)	4.3 (3.8–6.1)

*** In 1000s**

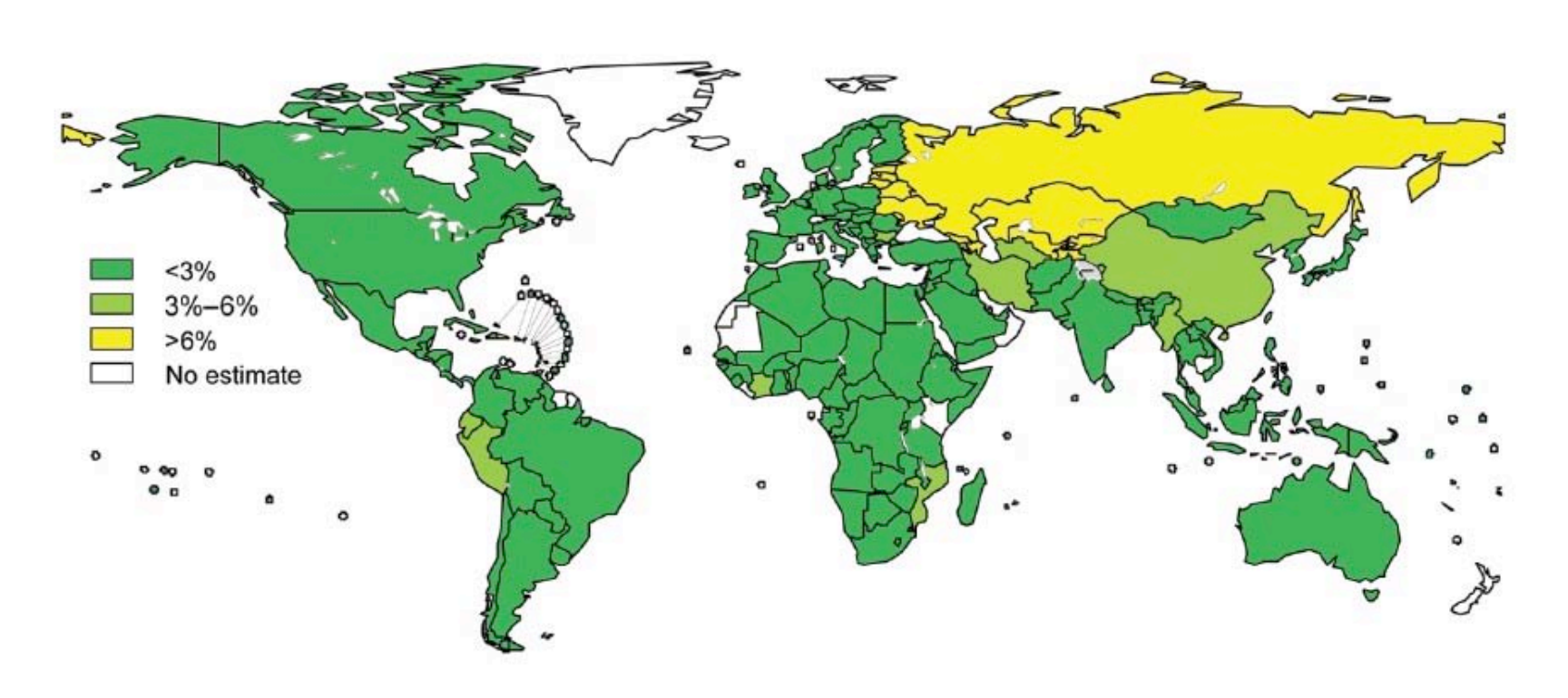
J Infect Dis 2006;194:484

Distribution of MDR-TB rates among previously treated cases.



JID 2006;194:479

Distribution of MDR-TB rates among new cases



JID 2006:194:479

Extensively Drug-resistant TB (XDR-TB)

M. tuberculosis resistant to:

- Isoniazid
- Rifampin
- Fluoroquinolone

  and

- An injectable second-line agent (kanamycin, capreomycin or amikacin)

XDR-TB, KwaZulu-Natal, 2006

	No	%
Drug Susceptible	323	59.4%
MDR	168	30.9%
XDR	53	9.7%

- All 53 XDR cases were HIV-infected.
- 52 (98%) died.
- Average Survival 25 days

Lancet 2006; 368:964

XDR TB Among MDR Isolates, 2000-2004

Geographic region	No. Isolates Tested	No. MDR Patients (%)	No. XDR Patients (% of MDR)
Established Market	2,499	821 (32.9)	53 (6.5)
Latin America	985	543 (55.1)	32 (5.9)
Eastern Europe and Russia	1,153	406 (35.2)	55 (13.6)
Africa and Middle East	665	156 (23.5)	1 (0.6)
Asia (other than Republic of Korea)	391	274 (70.1)	4 (1.5)
Republic of Korea	11,939	1,298 (10.9)	200 (15.4)
Total		3,418	345 (10.1)

Emerging Infect Dis 2007;13:385

Countries with Confirmed XDR-TB Cases, March 2007

Source: WHO

Drugs Used to Treat Multidrug - Resistant Tuberculosis

Pyrazinamide
Ethambutol
Streptomycin

Capreomycin
Kanamycin
Amikacin

Ofloxacin
Ciproflaxcin
Levofloxacin

Ethionamide
Cycloserine
Clofazamine
Thiacetazone
Para-aminosalicylic Acid (PAS)

Clinical Trials for INH-monoresistant TB before the availability of RIF

Regimen	Duration	Culture conversion at end of course
SM+PZA	6 months	58%
SM+PZA	12 months	90%
SM+PZA	18 months	94%
SM+PZA+PAS	12 months	94%

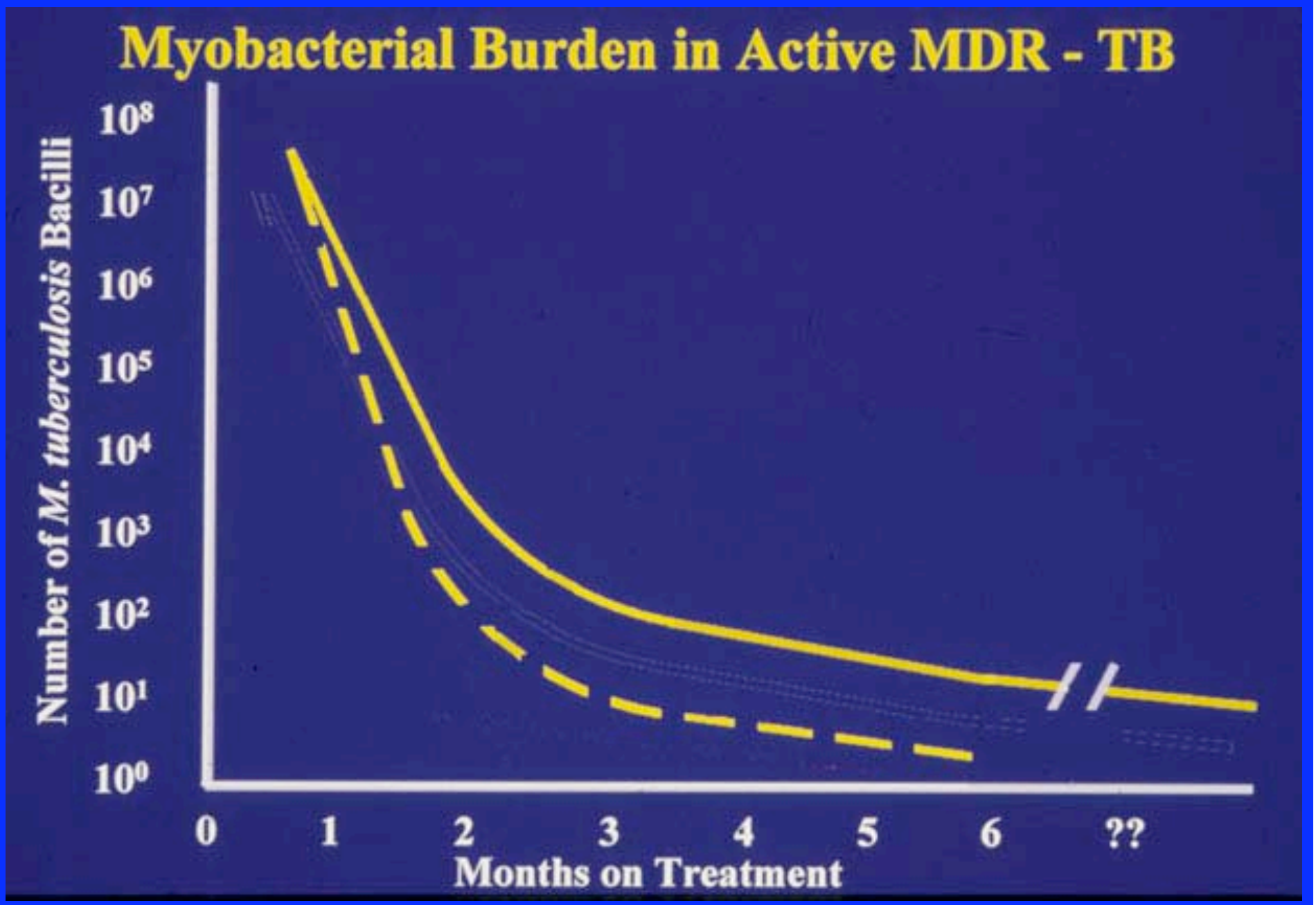
Tubercle 50;81, 51;359, 52;191

Current Recommendations for Treatment of MDR-TB

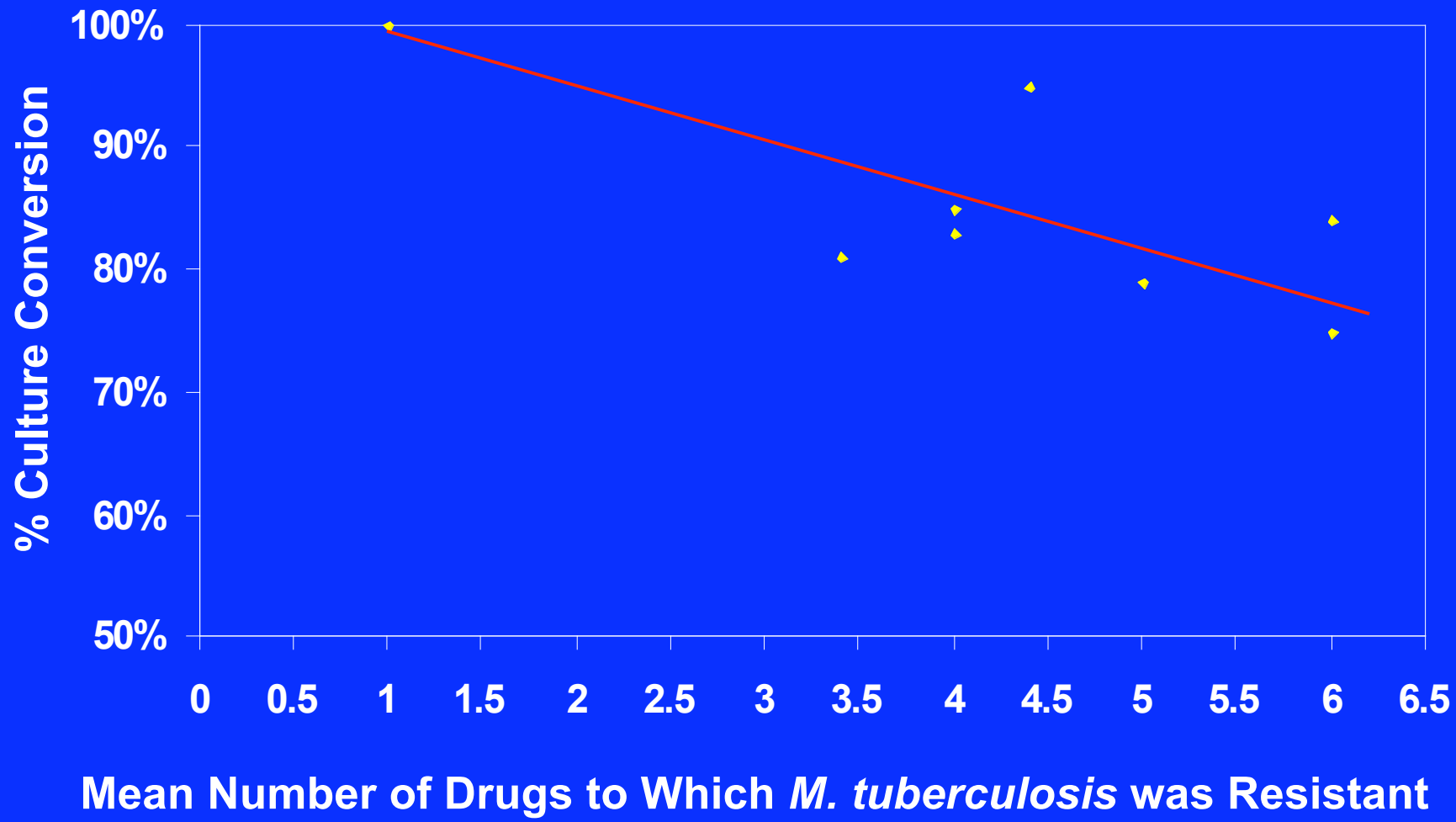
Resistance Pattern	Regimen	Duration
HR+3rd drug	4 drugs*	18-24 months
HR+3rd,4th drugs	5 drugs*	Conversion+24months
HR+3rd,4th,5th drugs	5 drugs*	Conversion+24months

*to which isolate is susceptible

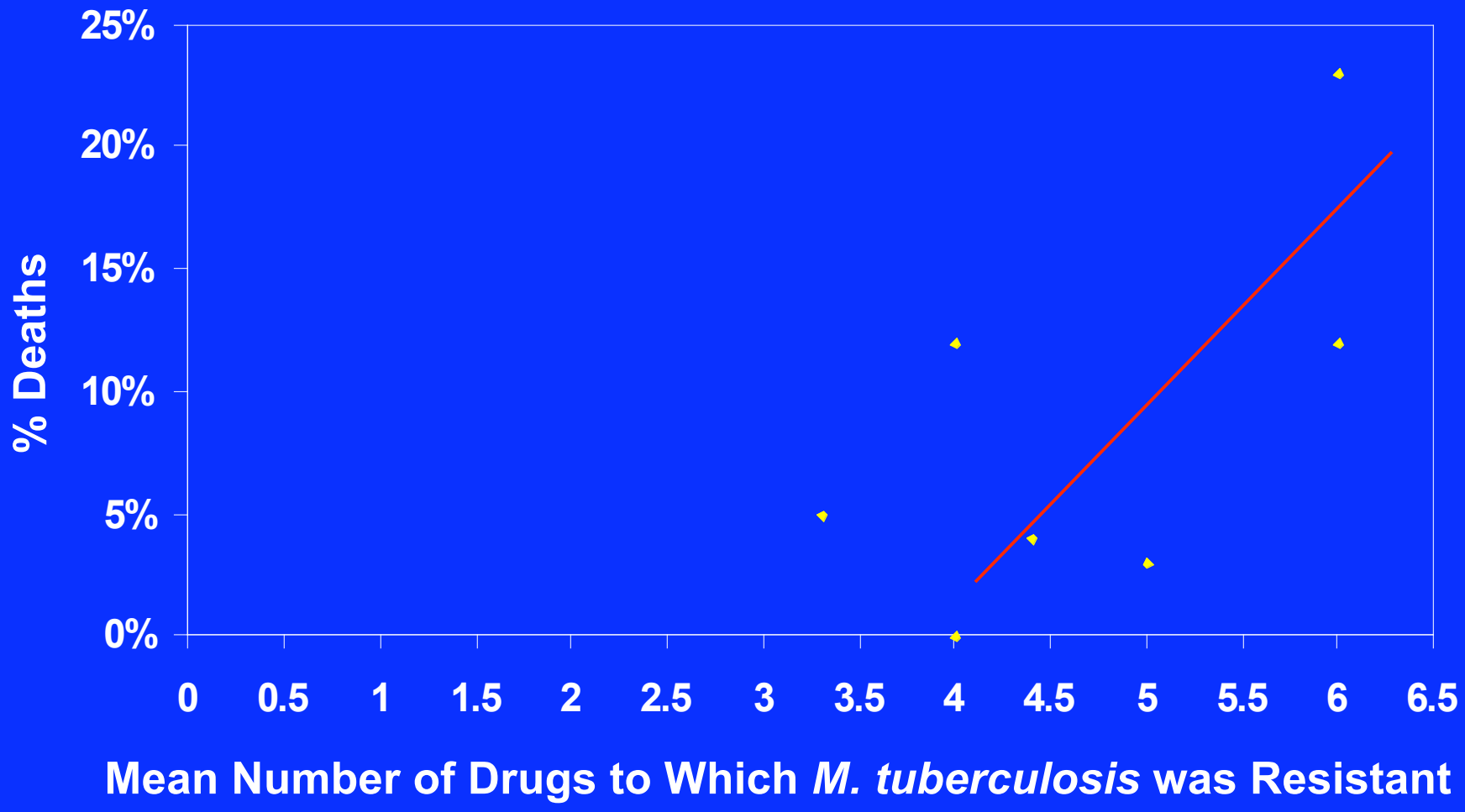
Adapted from NEJM 1993;329:788


Myobacterial Burden in Active MDR - TB
Number of M. tuberculosis Bacilli
10⁸
10⁷
10⁶
10⁵
10⁴
10³
10²
10¹
10⁰
0
1
2
3
4
5
6
??
Months on Treatment

Culture Conversion of Patients with DR-TB



Survival of Patients with DR-TB



Conclusions

1. Resistance to antituberculosis drugs is a growing global problem
2. Currently available drug regimens for MDR-TB have limited efficacy, require prolonged treatment, and have substantial toxicity
3. New drugs and new regimens for treatment of MDR-TB are urgently needed.