

Principles of MDR-TB regimen design

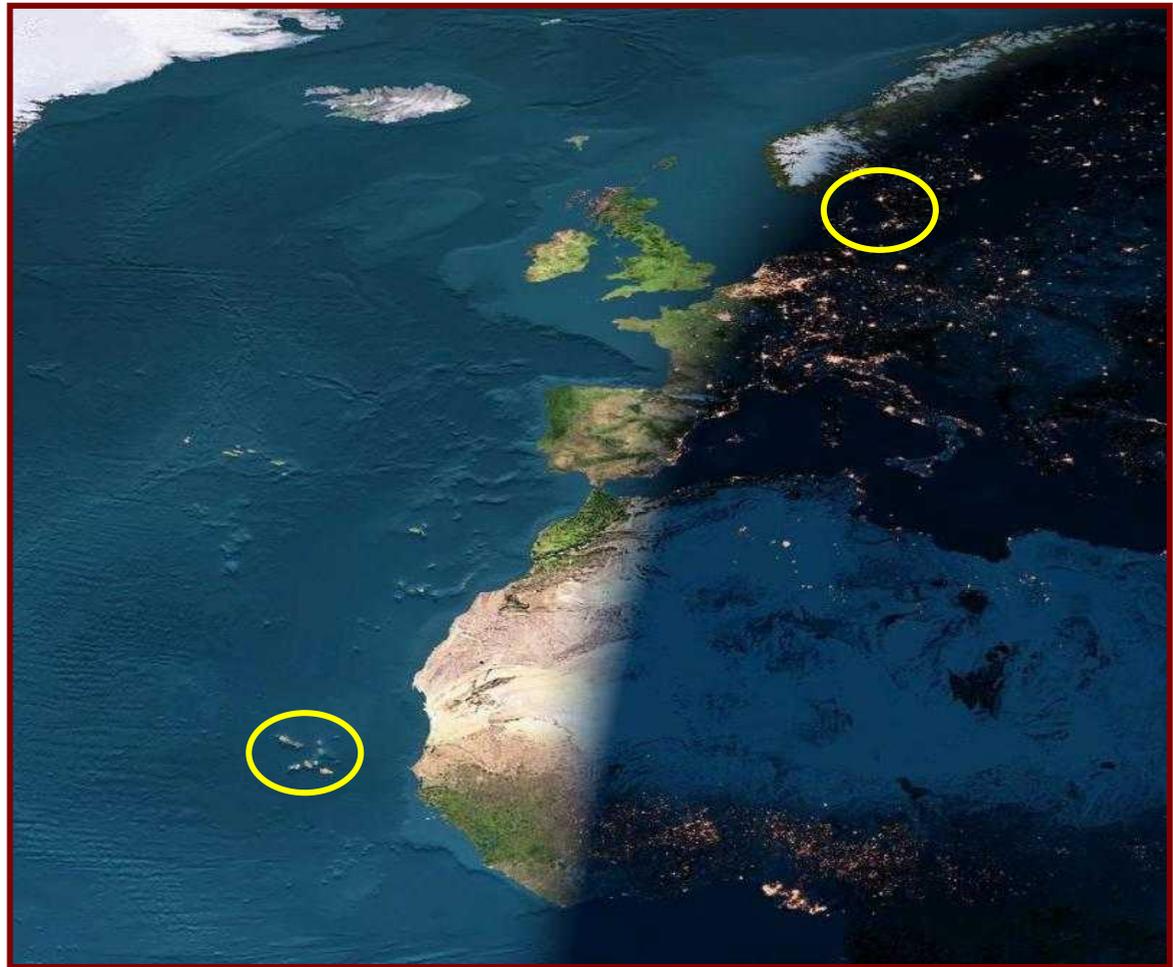
W.H.O.

***Second DOTS-Plus
Consultant Course***

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***The Union (IUATLD)
Canary Islands, Spain***



Principles of MDR-TB regimen design

Many Controversial Issues to Address

- ***There are **not Clinical Trials** comparing different Regimes and Drugs***
- ***There are only many **personal** experiences and Publications showing very different results***
- ***The **Recommendations** of the most important **Societies** have changed in the last decades and has not agreement***
- ***Currently there are very **controversial** issues, sometimes with difficult agreement***

Many *Controversial* Issues in MDR Treatment

- 1. How to approach *Diagnosis* of MDR?. Reliability of DST**
- 2. How *Many Drugs* to Treat MDR-TB ?**
- 3. *Rational* Use of the FLD and SLD**
- 4. Length of the *Injectable* (Intensive phase).**
- 5. Roll of the *Surgery* in the Treatment of MDR-TB**
- 6. Approach to the Ideal Regime in MDR-TB.
Standardized vs *Individualized* Regimes**

Treatment of multidrug-resistant tuberculosis: evidence and controversies

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* Hospital de Gran Canaria 'Dr Negrín', Las Palmas de Gran Canaria, Spain; † International Union Against Tuberculosis and Lung Disease, Paris, France

S U M M A R Y

In the last decade, multidrug-resistant tuberculosis (MDR-TB, defined as resistance to at least isoniazid and rifampicin) has become an epidemiological issue of first priority at the global level. Case management needs to be simplified and standardised, as in many countries MDR-TB cases cannot receive individualised attention from specialist physicians. However, before any decision can be made on standardisation, a careful analysis must first be made of the evidence and controversies behind the various published recommendations. Unfortunately, the controversies outweigh the evidence. The difficulties lie not only in the absence of controlled trials to validate specific recommendations, but also in the very different and even contradictory results found in the literature. It is therefore essential to analyse these discrepancies before developing rational, uniform recommendations. The analysis should encompass the most essential and

controversial issues regarding the management of MDR-TB patients: 1) confirmation of diagnosis in a suspected MDR-TB patient, and determination of the value of drug susceptibility testing; 2) the number of anti-tuberculosis drugs required to treat MDR-TB; 3) the most rational use of effective drugs against tuberculosis; 4) the advisable length of parenteral drug administration or of the initial phase of treatment; 5) the contribution of surgery to the management of MDR-TB patients; and 6) the optimal regimen for treating MDR-TB: standardised vs. individualised regimens. The evidence and controversies regarding each of the above questions are analysed with the aim of facilitating decision making in the treatment of these complex patients.

KEY WORDS: tuberculosis; multidrug resistance; MDR; management; treatment; standardised; individualised

How to approach **diagnosis** of MDR-TB?

... The selection of anti-TB agents is based upon the history of previous therapy and the results of reliable DST.

ATS. A Statement by the Committee on Therapy. Treatment Drug-Resistant TB. Am Rev Respir Dis 1966;94:125-7



Initiation of drug therapy in patients with proven MDR-TB requires assessment of the **history of treatment** as well as meticulous laboratory studies to characterize the susceptibility of the specific strain

...previous therapy with a drug for more than a month was associated with **diminished efficacy of that drug regardless of in vitro tests** indicating susceptibility. These results place a great premium on obtaining records of therapy



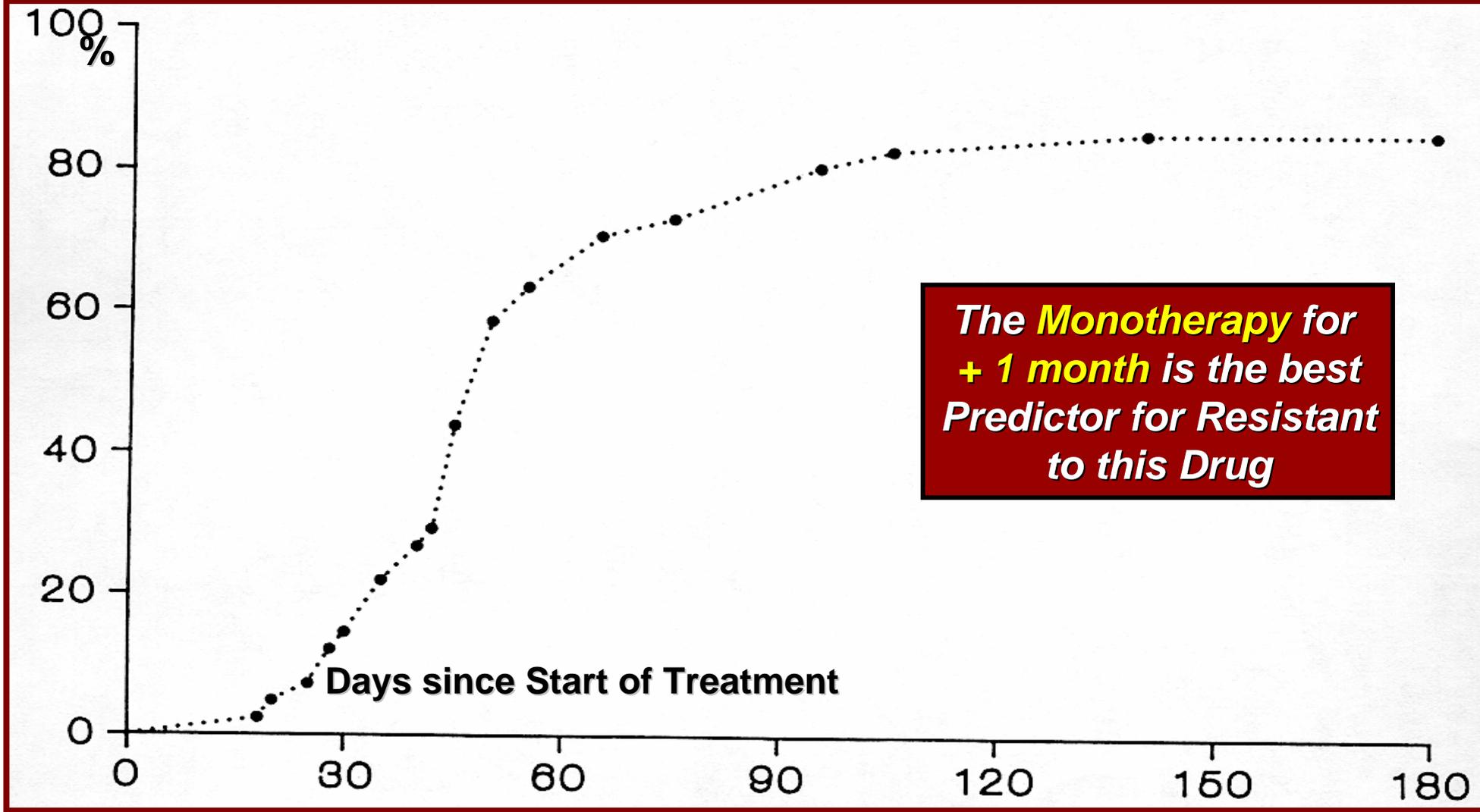
How to approach *Diagnosis* of MDR-TB?

- **History**, detailed and directed, of previous drugs, looking for:
 - Real or false monotherapies
- **Highly Qualified Specialist:**
 - Second-line drugs
 - History of drugs in country or region
 - Minimum 1 hour for first consultation
 - “Display of boxes and pills used in country”



Accumulative percentage of **SM Resistant Cultures**

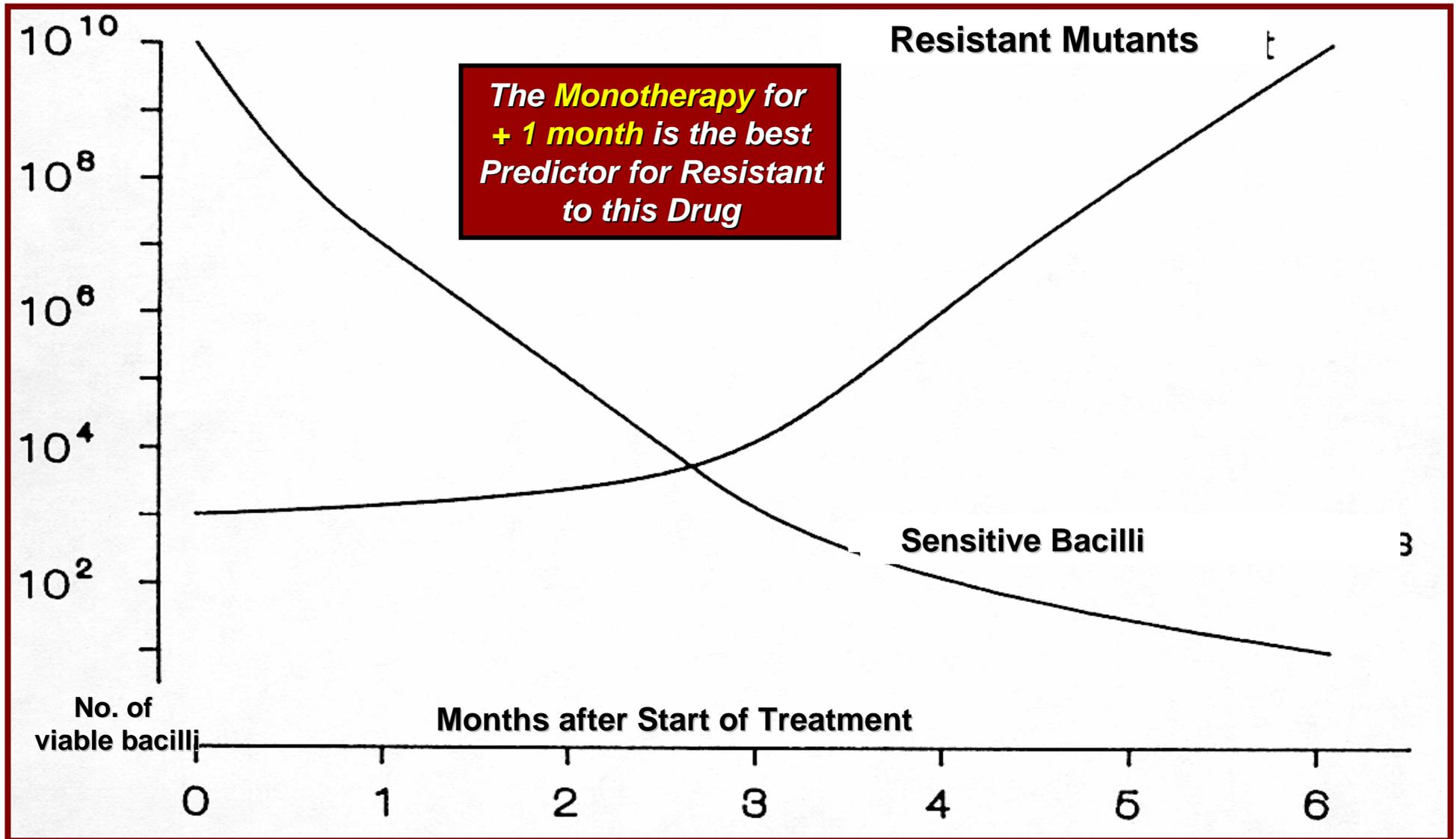
BMRC Study on SM, 1947



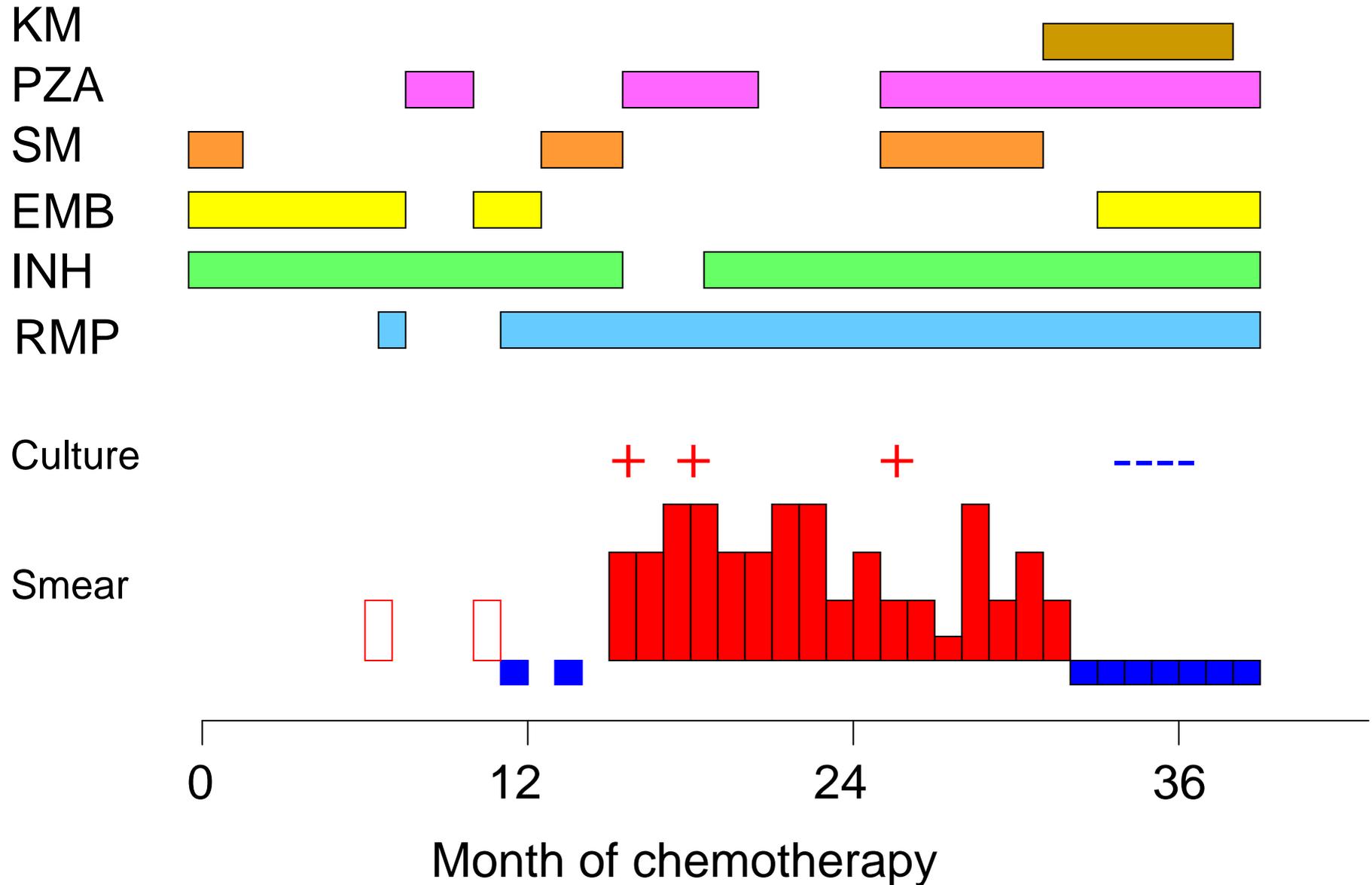
The Monotherapy for + 1 month is the best Predictor for Resistant to this Drug



Appearance of resistance to INH administered in Monotherapy



Creating Drug Resistance in a 49-Year-Old Patient





Model of Drug History

	Patient: Year											
Drug	January	February	March	April	May	June	July	August	September	October	November	December
H												
R												
Z												
E												
S												
Kn												
Ak												
Cp												
OfI												
Cip												
Eth												
Pth												
Pas												
Cs												
Cfz												
*												
*												
*												
*												
Culture**												
DST***												
	H: Isoniacida	R: Rifampicina	Z: Pirazinam.	E: Etambutol	S: Estreptom.	Kn: Kanamicina	Ak: Amikacina	Cp: Capreomic	OfI: Ofloxacina	Cip: Ciproflo.	Eth: Etionam.	Pth: Protionam
	Pas: PAS	Cs. Cicloserina	Cfz: Clofazim.	*: Otros								
	Cultivo: Reseñar el resultado del cultivo en la fecha realizada					*Sensib.: Reseñar el resultado del antibiograma en la fecha realizada						



Model of Drug History

Paciente D.: Pepe Caminero

Año 1996

Droga	Enero	Febrero	Marzo	Abril	Mayo	Junio	Julio	Agosto	Septiembre	Octubre	Noviembre	Diciembre
H												
R												
Z												
E												
S												
Kn												
Ak												
Cp												
Ofi												
Cip												
Eth												
Pth												
Pas												
Cs												
Cfz												
*												
*												
*												
*												
Cultivo**												
Sensib***												

H: Isoniacida R: Rifampicina Z: Pirazinam. E: Etambutol S: Estreptom. Kn: Kanamicina Ak: Amikacina Cp: Capreomic Ofi: Ofloxacin Cip: Ciproflo. Eth: Etionam. Pth: Protionam
 Pas: PAS Cs. Cicloserina Cfz: Clofazim. *: Otros

Cultivo: Reseñar el resultado del cultivo en la fecha realizada *Sensib.: Reseñar el resultado del antibiograma en la fecha realizada



Model of Drug History

Paciente D.: **Pepe Caminero**

Año **1998**

Droga	Enero	Febrero	Marzo	Abril	Mayo	Junio	Julio	Agosto	Septiembre	Octubre	Noviembre	Diciembre
H												
R												
Z												
E												
S												
Kn												
Ak												
Cp												
Ofi												
Cip												
Eth												
Pth												
Pas												
Cs												
Cfz												
*												
*												
*												
*												
Cultivo**												
Sensib***												

H: Isoniacida R: Rifampicina Z: Pirazinam. E: Etambutol S: Estreptom. Kn: Kanamicina Ak: Amikacina Cp: Capreomic Ofi: Ofloxacina Cip: Ciproflo. Eth: Etionam. Pth: Protionam
 Pas: PAS Cs. Cicloserina Cfz: Clofazim. *: Otros

Cultivo: Reseñar el resultado del cultivo en la fecha realizada *Sensib.: Reseñar el resultado del antibiograma en la fecha realizada



Model of Drug History

Paciente D.: **Pepe Caminero**

Año **1999**

Droga	Enero	Febrero	Marzo	Abril	Mayo	Junio	Julio	Agosto	Septiembre	Octubre	Noviembre	Diciembre
H												
R												
Z												
E												
S												
Kn												
Ak												
Cp												
Ofi												
Cip												
Eth												
Pth												
Pas												
Cs												
Cfz												
*												
*												
*												
*												
Cultivo**												
Sensib***												

H: Isoniacida R: Rifampicina Z: Pirazinam. E: Etambutol S: Estreptom. Kn: Kanamicina Ak: Amikacina Cp: Capreomic Ofi: Ofloxacina Cip: Ciproflo. Eth: Etionam. Pth: Protionam
 Pas: PAS Cs. Cicloserina Cfz: Clofazim. *: Otros

Cultivo: Reseñar el resultado del cultivo en la fecha realizada *Sensib.: Reseñar el resultado del antibiograma en la fecha realizada



Model of Drug History

Paciente D.: Pepe Caminero
 Año 2001

Droga	Enero	Febrero	Marzo	Abril	Mayo	Junio	Julio	Agosto	Septiembre	Octubre	Noviembre	Diciembre
H												
R												
Z												
E												
S												
Kn												
Ak												
Cp												
Ofi												
Cip												
Eth												
Pth												
Pas												
Cs												
Cfz												
*												
*												
*												
*												
Cultivo**												
Sensib***												

H: Isoniacida R: Rifampicina Z: Pirazinam. E: Etambutol S: Estreptom. Kn: Kanamicina Ak: Amikacina Cp: Capreomic Ofi: Ofloxacina Cip: Ciproflo. Eth: Etionam. Pth: Protionam
 Pas: PAS Cs: Cicloserina Cfz: Clofazim. *: Otros

Cultivo: Reseñar el resultado del cultivo en la fecha realizada *Sensib.: Reseñar el resultado del antibiograma en la fecha realizada

Drug Susceptibility Test (DST)



≠



How to approach **Diagnosis** of MDR-TB?

- Drug **Susceptibility** Test:



- *Information arrives quite late (3-4 Months)*
- *Correlation between “in vitro” and “in vivo” is not the ideal (except for H and R)*
- *Always should be done on first line drugs*
- ***Interpretation** of results is key*





SERIES "CONTROVERSIAL ISSUES IN TUBERCULOSIS"

Edited by A. Torres and J. Caminero

Number 4 in this Series

Drug-susceptibility testing in tuberculosis: methods and reliability of results

S.J. Kim

ABSTRACT: The demand for reliable drug-susceptibility testing (DST) increases with the expansion of antituberculosis drug-resistance surveillance, and with the need for an appropriate treatment of multidrug-resistant tuberculosis, whose incidence gradually increases in many parts of the world. However, the reliability of DST results obtained through widely used methods does not meet acceptable levels, except for DST to isoniazid and rifampicin.

In general, susceptibility results are highly predictable, while resistance results show low predictive values when the resistance prevalence is <10%. Poor reliability stems from a weak correlation with clinical response and a low reproducibility due to the poor standardisation of the complex and fragile test procedures. Therefore, *in vitro* criteria of resistance for susceptibility testing should be carefully determined with representative clinical samples of *Mycobacterium tuberculosis* isolated from patients never treated with any antituberculosis drug, and from patients having failed treatment with a regimen containing the tested drug; DST should then be carefully standardised to obtain reproducible results.

The critical concentration of some drugs is close to the minimal inhibitory concentration for wild susceptible strains and, thus, drug-susceptibility testing is prone to yield poorly reproducible results. These issues call for physicians' attention when using the results from drug-susceptibility testing for case management.

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Drug

Susceptibility

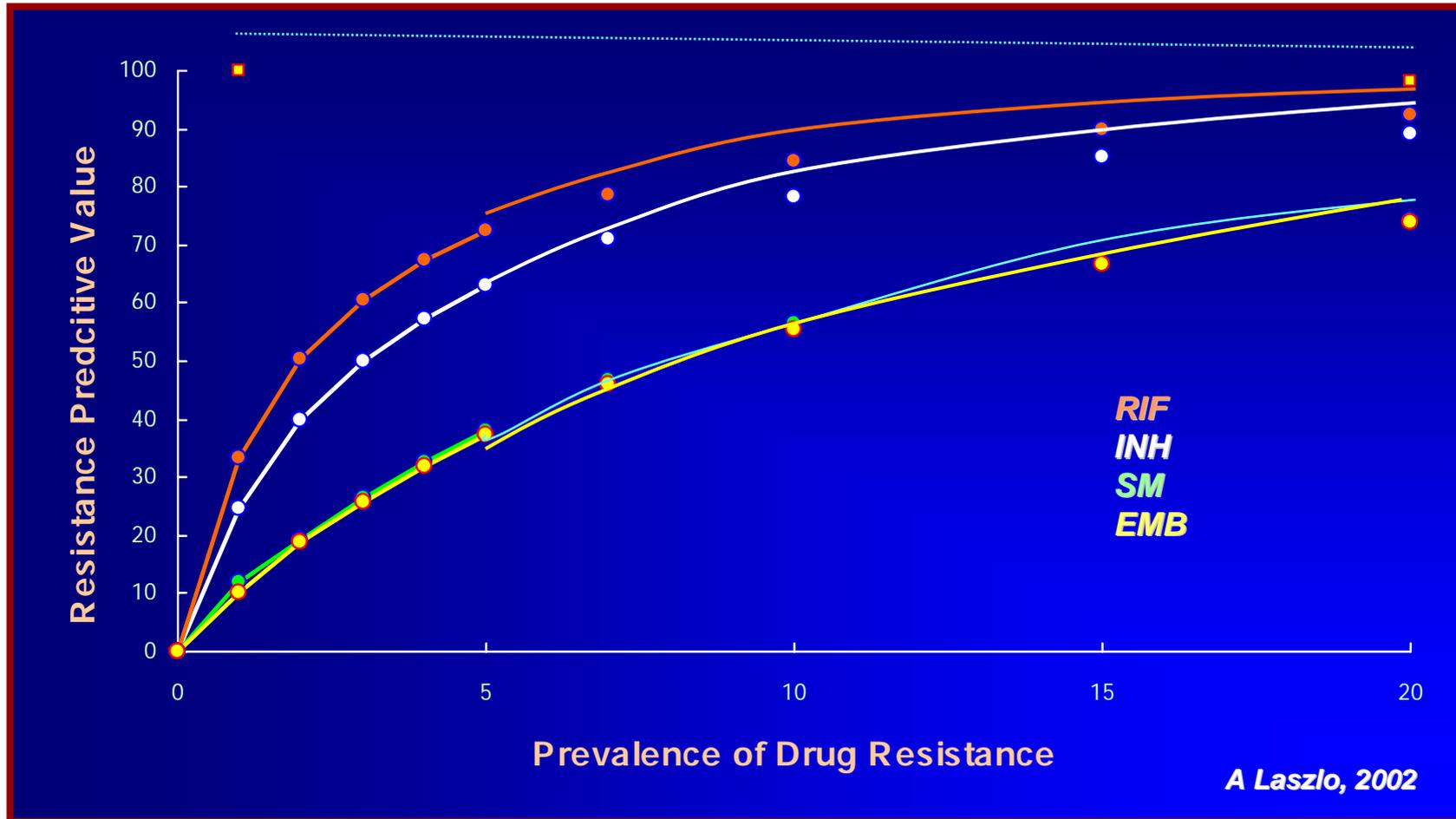
Test to First Line

Anti-TB Drugs



Drug Resistance Predictive Values

Based on SRLN Drug Susceptibility Testing



A Laszlo, 2002

Calibration of D.S.T.

To obtain clinically most relevant in vitro criterion of resistance

- Level of susceptibility of presumably susceptible strains***
- Determination of level of susceptibility at which treatment response changes***

Comparison of susceptibility of a sample of strains from never treated patients (PS) with that of a sample strains from patients who had been treated with the drug for at least 6 months (PR)

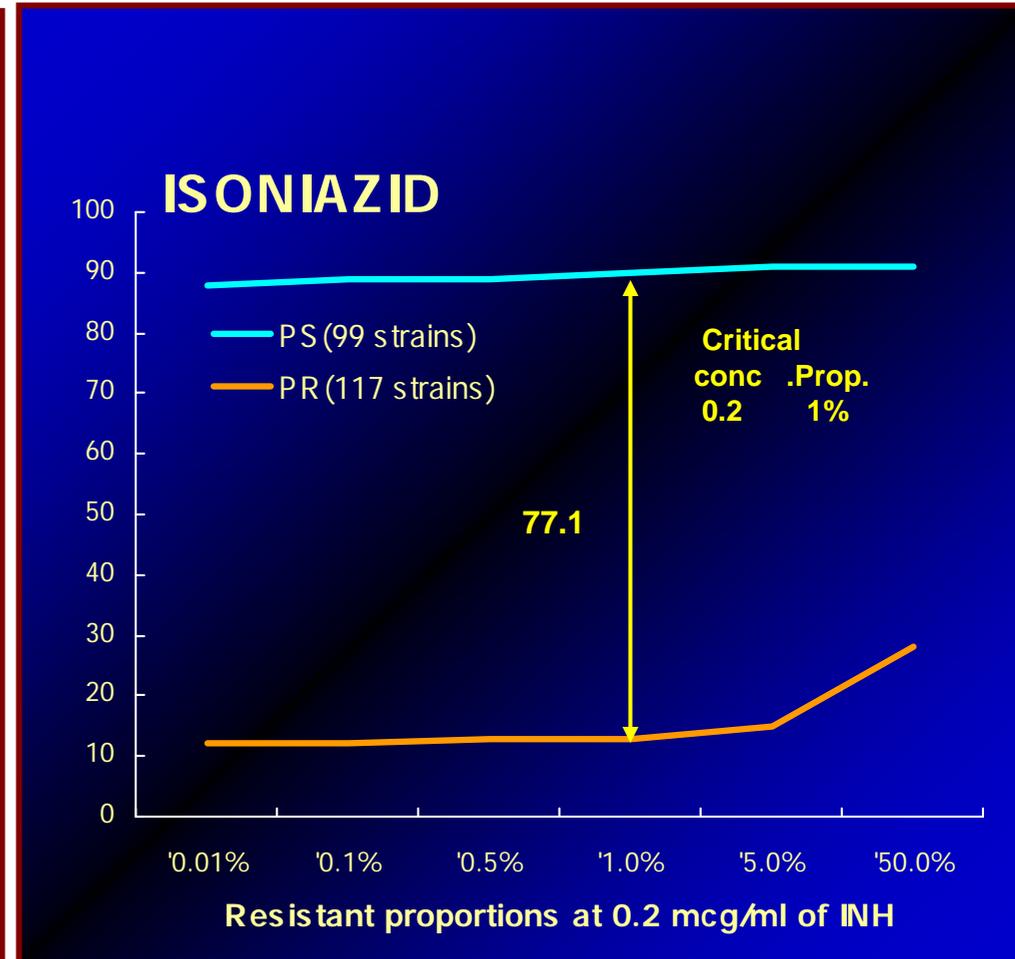
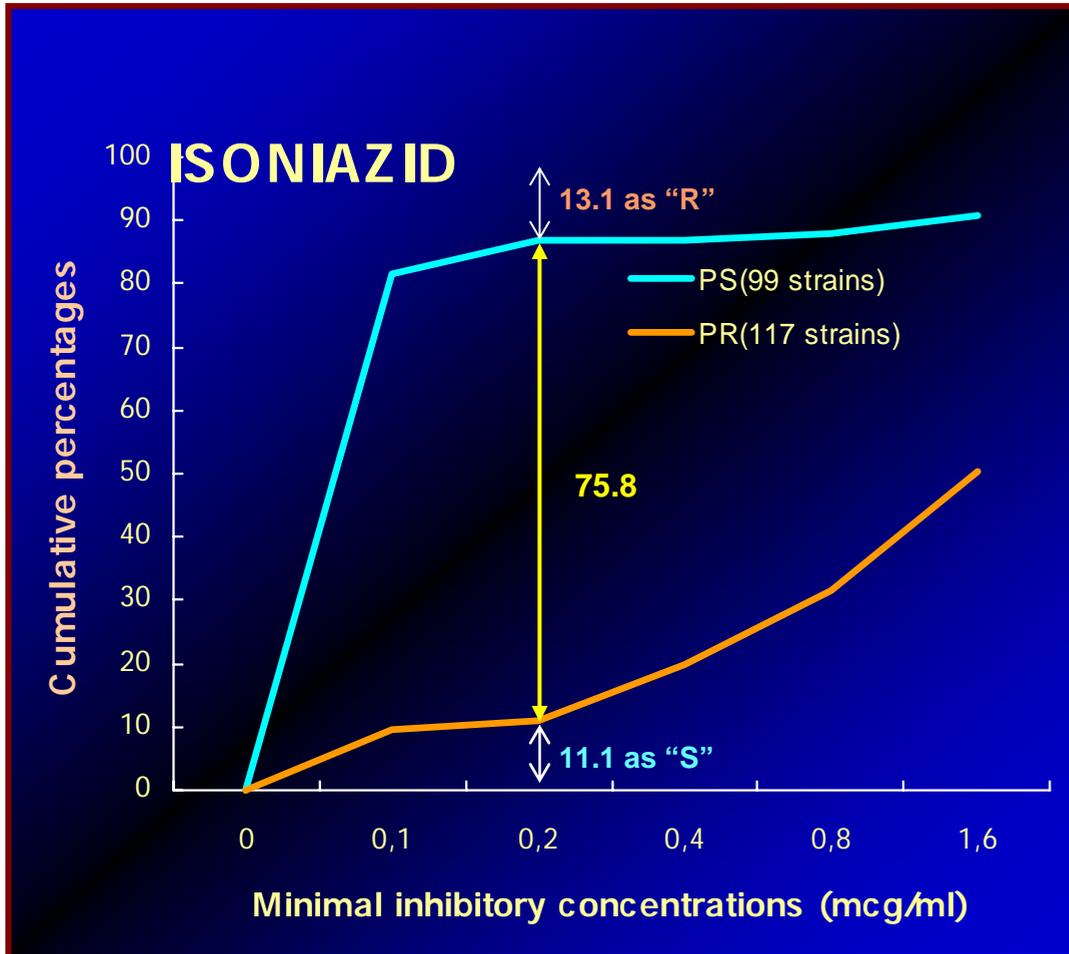
PS: >100 strains; PR: >50 strains



Cumulative Distribution of Susceptibility to INH



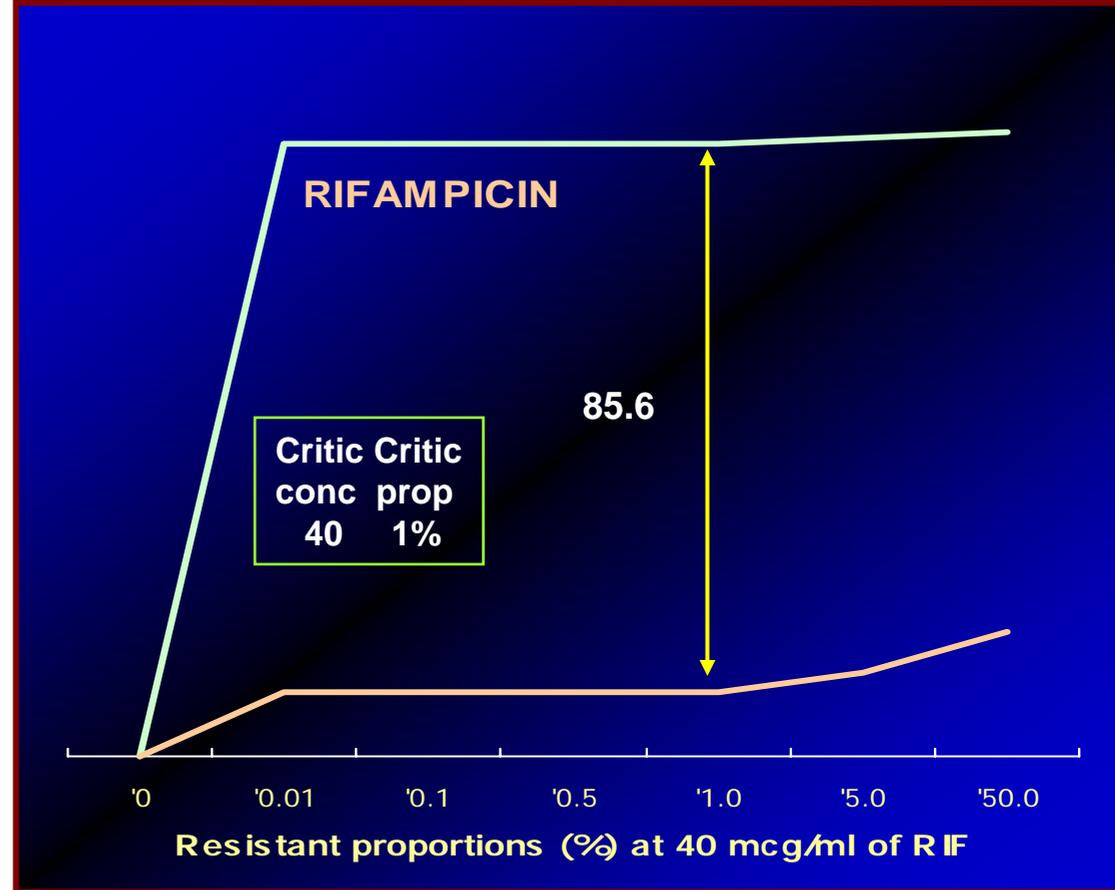
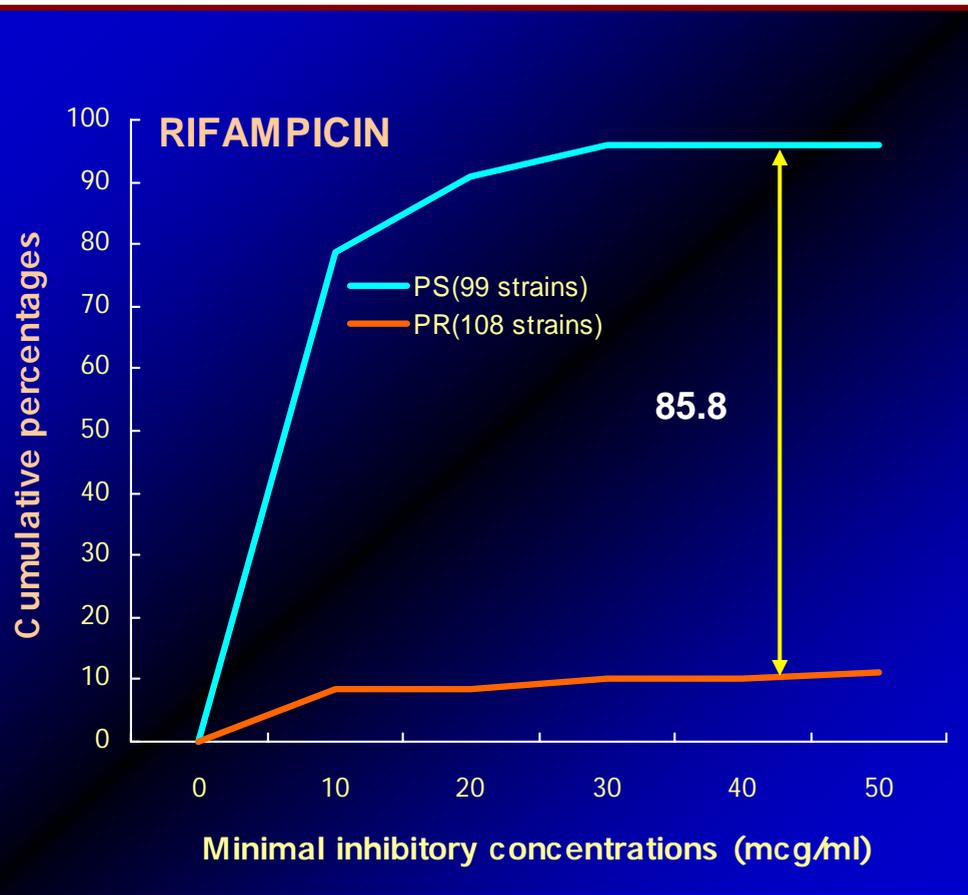
(Tests done in L-J medium using the absolute concentration method and proportion method)



Cumulative Distribution of Susceptibility to RMP

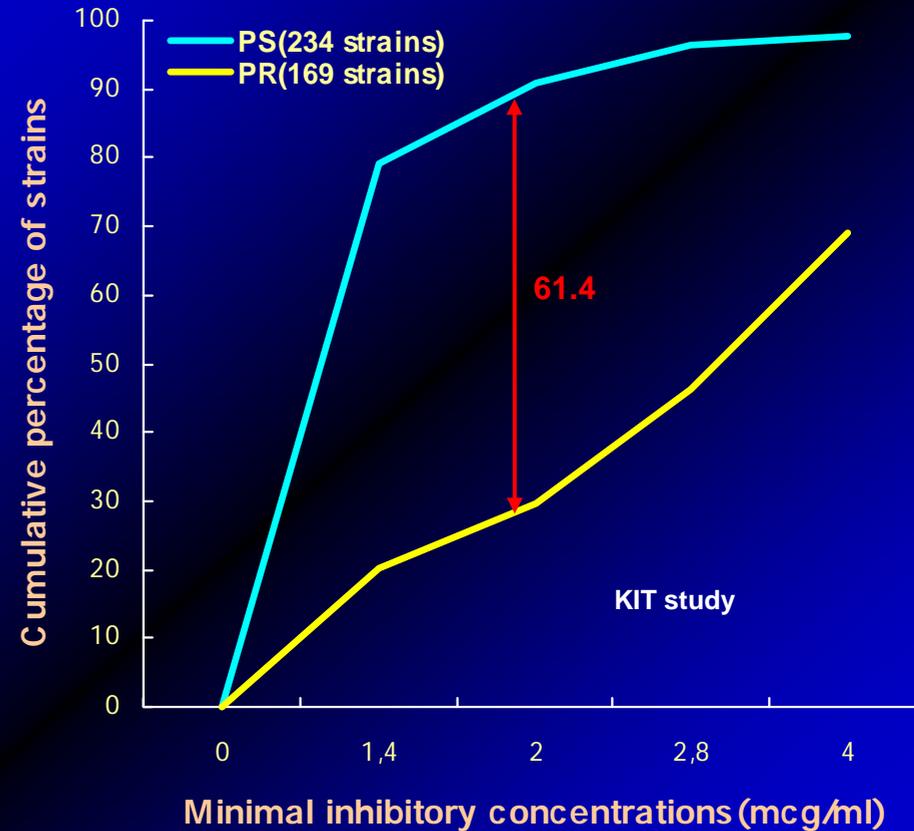
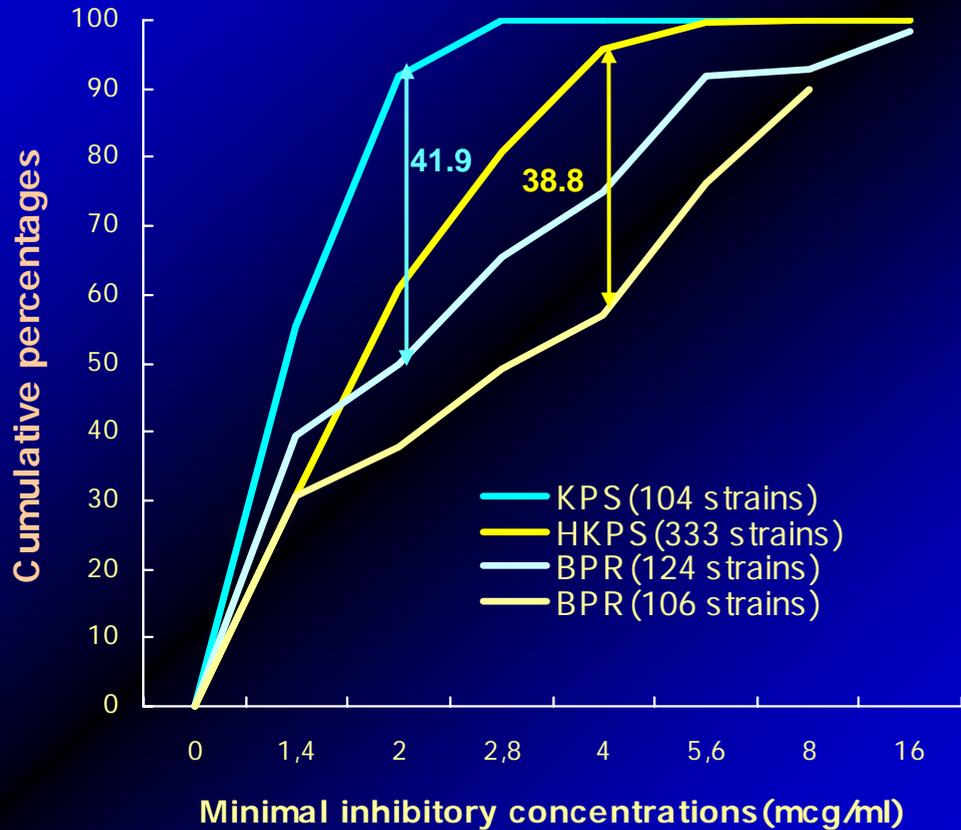


(Tests done in L-J medium using the absolute concentration method and proportion method)



Comparison of Critical Concentrations of Ethambutol Between Two Different Laboratories

(Tests done in L-J medium using the absolute concentration method)



KPS=Probably susceptible Korean strains; BPR=Probably resistant British strains;
HKPS=Probably susceptible Hong Kong strains

Courtesy: SJ Kim, NRL Korea, IUATLD

***Drug Susceptibility
Test to Second
Line Anti-TB Drugs***



DST to SLD. We do *Not Really Know*

- **Few studies published**
 - *Insufficiently in-depth*
 - *too few strains included*
 - *classification of strains as S or R: ??*
 - *emphasis on inter-lab precision, not accuracy*
 - *i.e. multi-centre study Pfyffer, JCM 1999*
- **STOP TB *project***
 - *Better definition of critical concentrations*

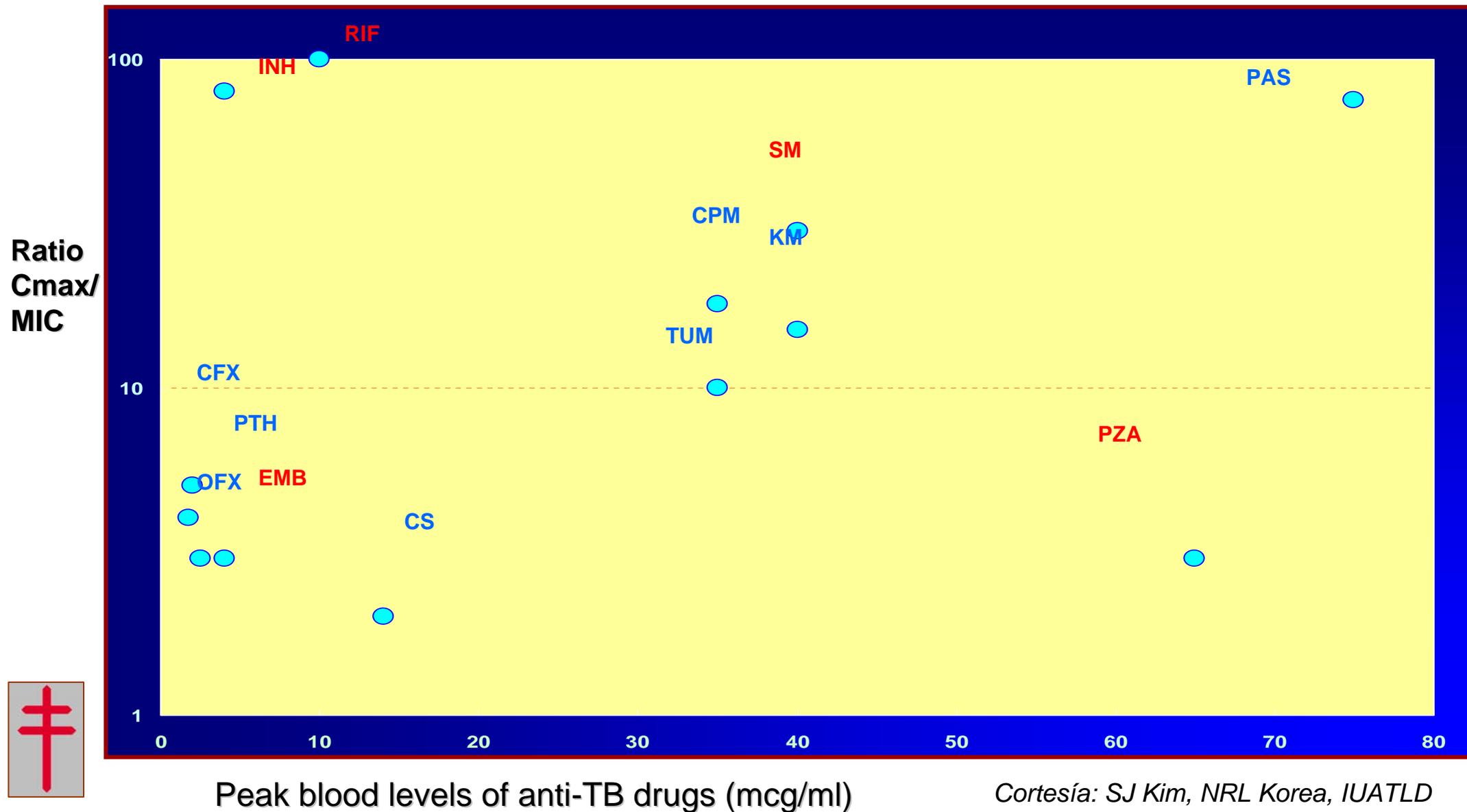




Factors Leading to Poor Reliability Results in DST to SLD

- 1. The *in vitro* resistance criteria may not reflect *clinical* response**
- 2. Attainable *drug concentration* in the lesions varies greatly and close to *MIC*; level of resistance may vary and close to *MIC* at which test may be difficult to distinguish Suscept. and Resistance**
- 3. *Fragility* of SLD to physicochemical test *environment***

Approximate Ratio of Cmax to Minimal Inhibitory Concentrations



Physicochemical Test Environment (Affecting DST Results): Drug potency / stability in medium

Drug: dissolution;
sterilization; dilution;
storage

Media preparation:

heat inactivation;
protein binding

Antagonists in medium:

Phospholipids ↔ SM;

D-alanine ↔ CS;

methionine ↔ PAS;

polyamines/ions ↔ EMB

pH: PZA (acidic);

SM (neutral)



Physicochemical Test Environment ***(Affecting DST Results)***

- Inoculum:

Size

Dispersion

Viability

Representativeness

- Incubation:

Time (period)



TDST to SLD. Discrepancy between the Supranat. Refer. Laboratories

Table Susceptibility testing for second-line anti-tuberculosis drugs

SRL No.	DTS systems			Culture media			Critical concentrations of drugs, µg/ml*					
	Conv. methods		Rapid growth methods	Egg-based	Agar-based	Broth	KM	CPM	ETH	CS	PAS	OFX
	PM	AC										
1	X			Ogawa			20.0 (1)		20.0 (1)	30.0 (1)	0.5 (1)	
2	X			LJ			20.0 (10)		20.0 (10)	30.0 (10)		2.0 (1)
3	X				7H11		6.0 (1)	10.0 (1)	10.0 (1)	30.0 (1)	8.0 (1)	2.0 (1)
4		X		LJ			40.0	40.0	40.0	30.0	1.0	2.0
5	X				7H11		6.0 (1)	10.0 (1)	10.0 (1)			4.0 (1)
6	X			LJ				20.0 (10)		30.0 (10)	0.5 (1)	
	X			LJ							0.5 (1)	
7		X		LJ			4.0 (1)		10.0 (1)			2.0 (1)
			BACTEC			X	16.0	32.0	56.0	28.0		2.4
8	X				7H10		5.0 (1)	10.0 (1)	10.0 (1)	30.0 (1)		2.0
			BACTEC			X	5.0	5.0	5.0	50.0		2.0
9			BACTEC			X		1.25	1.25		4.0	2.0
10			BACTEC			X		10.0	5.0	50.0	8.0	2.0

*Numbers in parentheses are critical proportions (%) of resistance.

DST = drug susceptibility testing; SRL = Supranational Reference Laboratory; Conv. = conventional; PM = proportion method; AC = absolute concentration method; KM = kanamycin; CPM = capreomycin; ETH = ethionamide; CS = cycloserine; PAS = para-aminosalicylic acid; OFX = ofloxacin (laboratory 8 tested ciprofloxacin).



Calibration of D.S.T.

To obtain clinically most relevant in vitro criterion of resistance

- Level of susceptibility of presumably susceptible strains***
- Determination of level of susceptibility at which treatment response changes***

Comparison of susceptibility of a sample of strains from never treated patients (PS) with that of a sample strains from patients who had been treated with the drug for at least 6 months (PR)

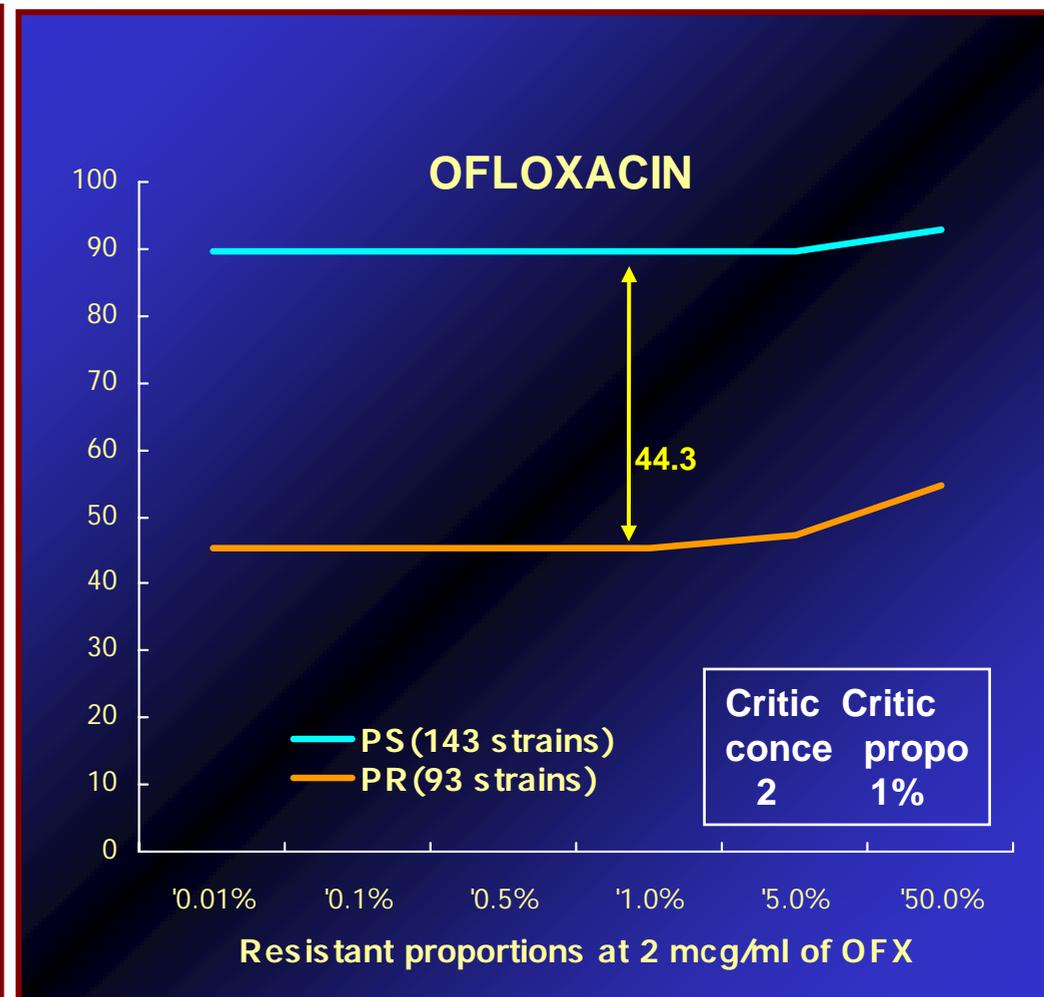
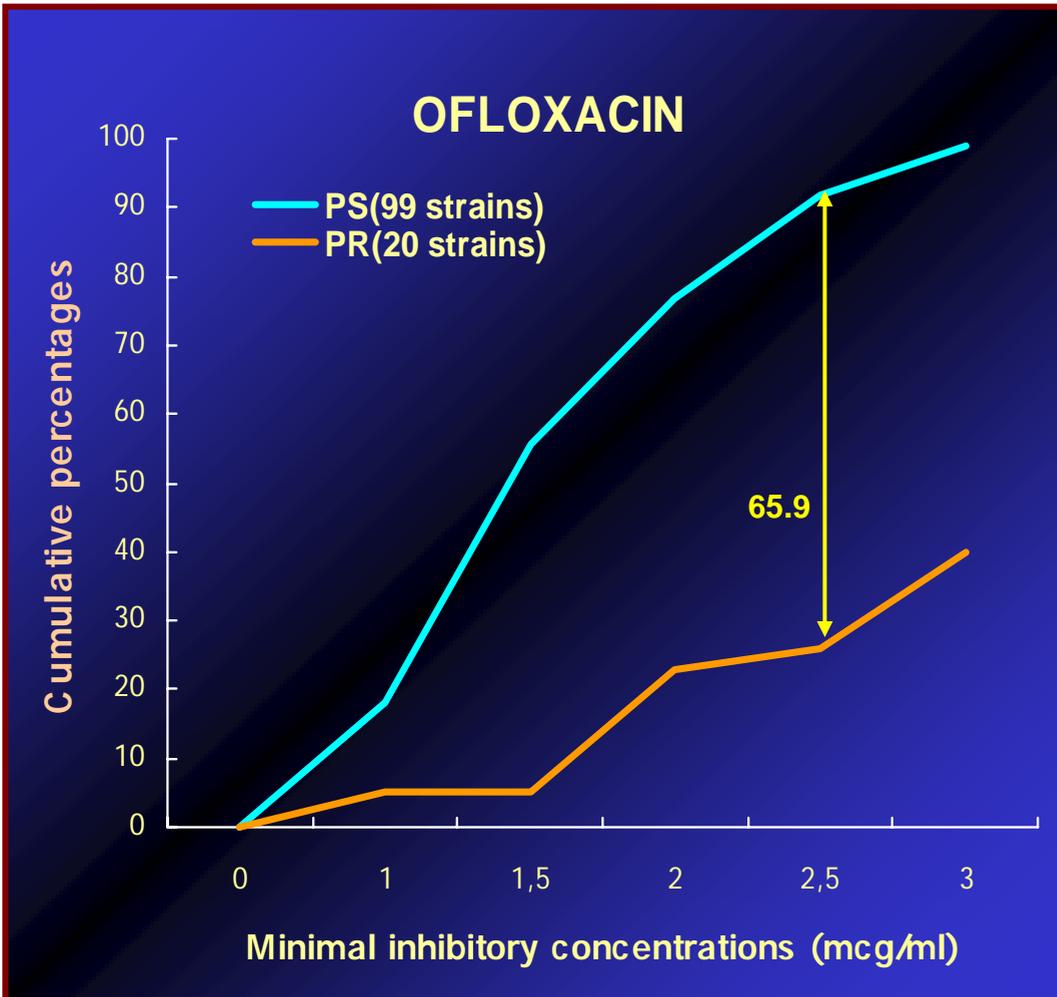
PS: >100 strains; PR: >50 strains



Cumulative Distribution of Susceptibility to Oflox

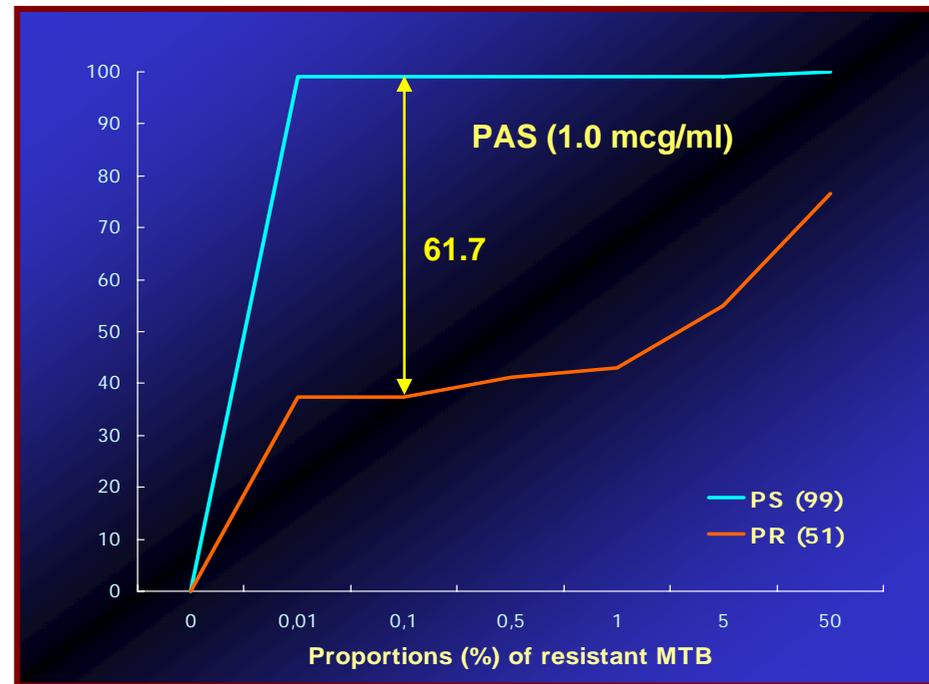
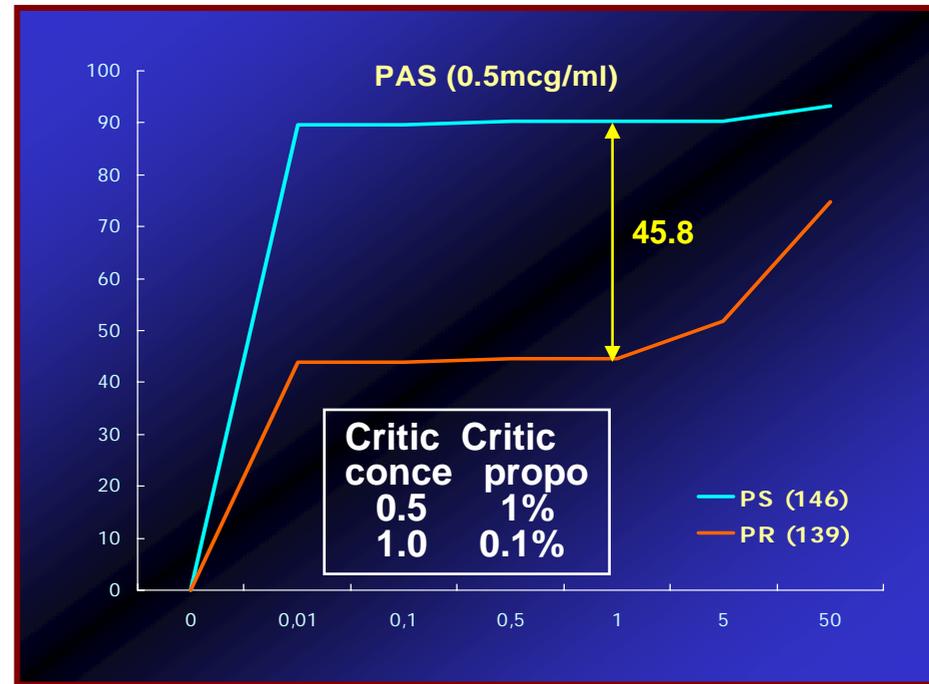
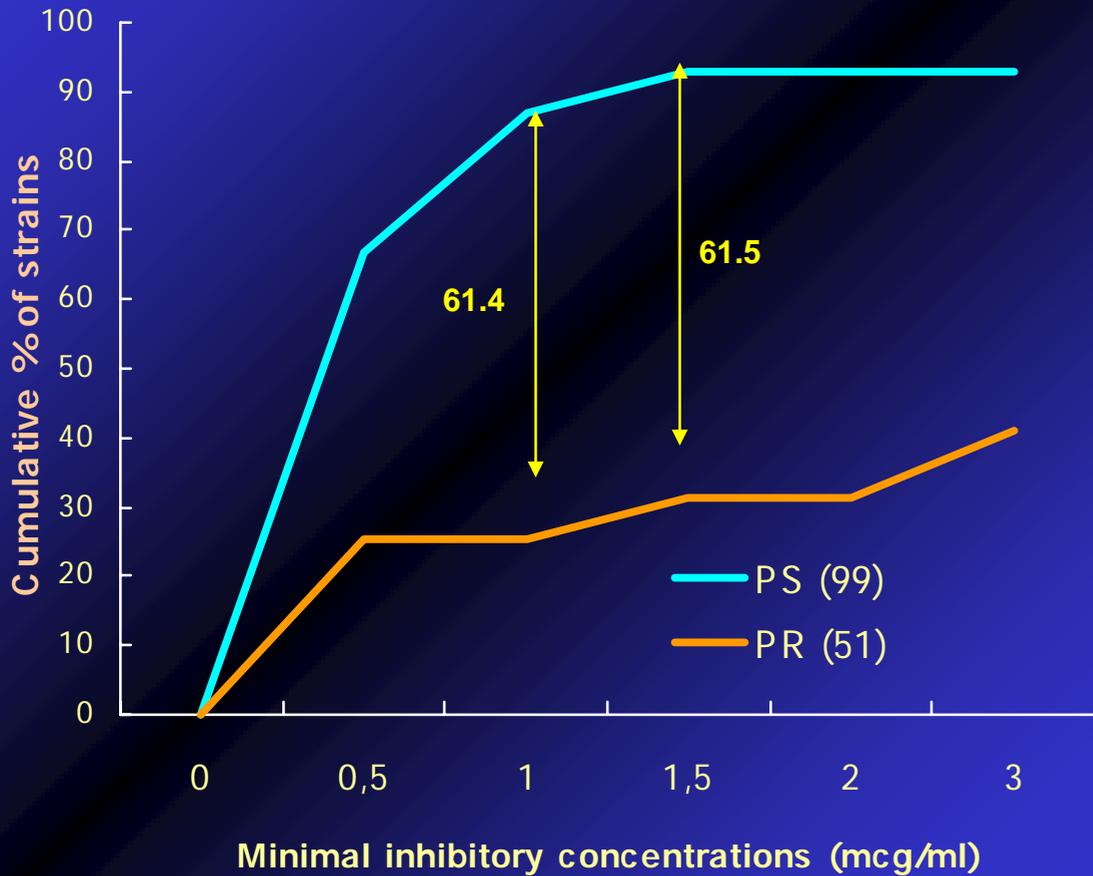


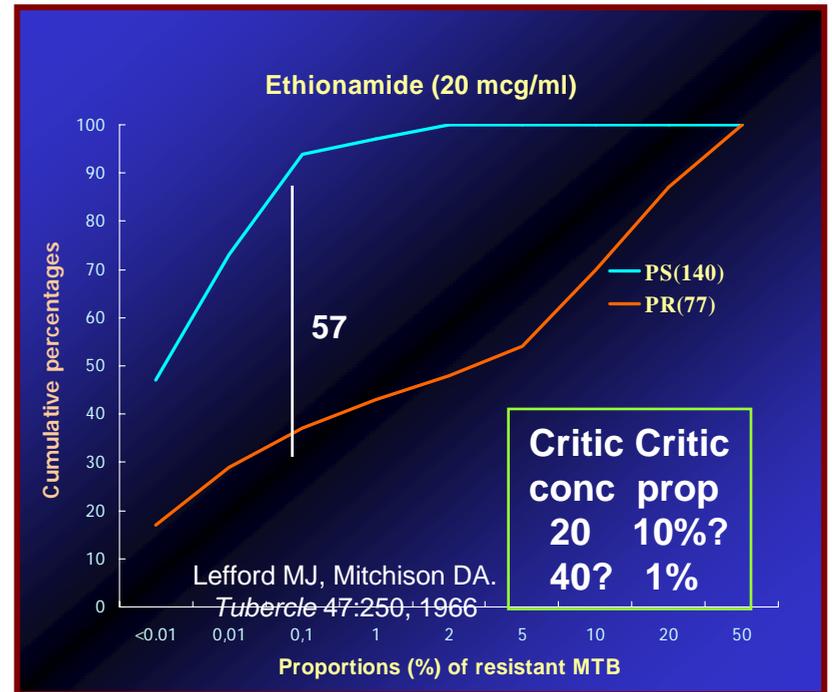
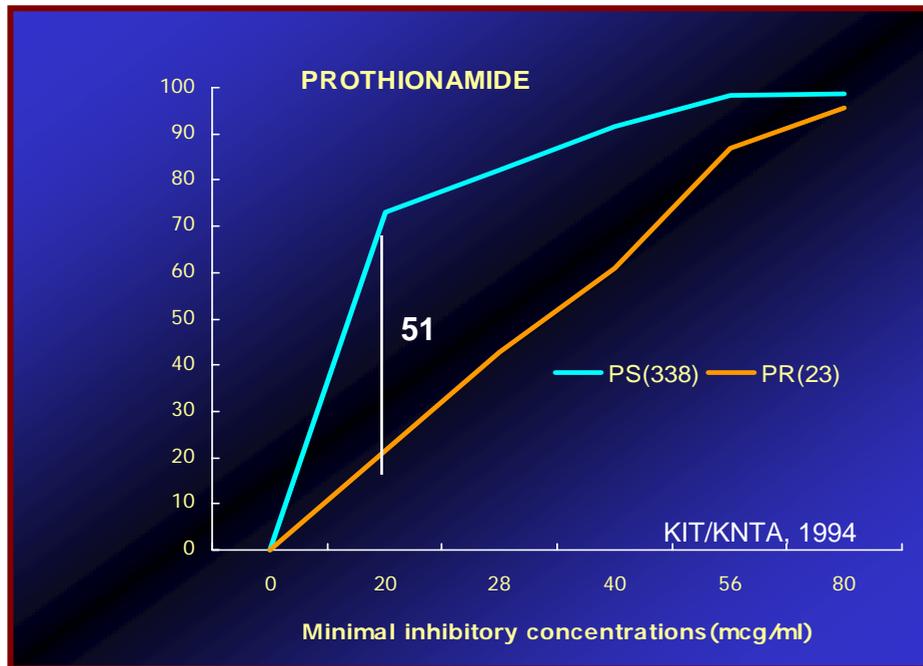
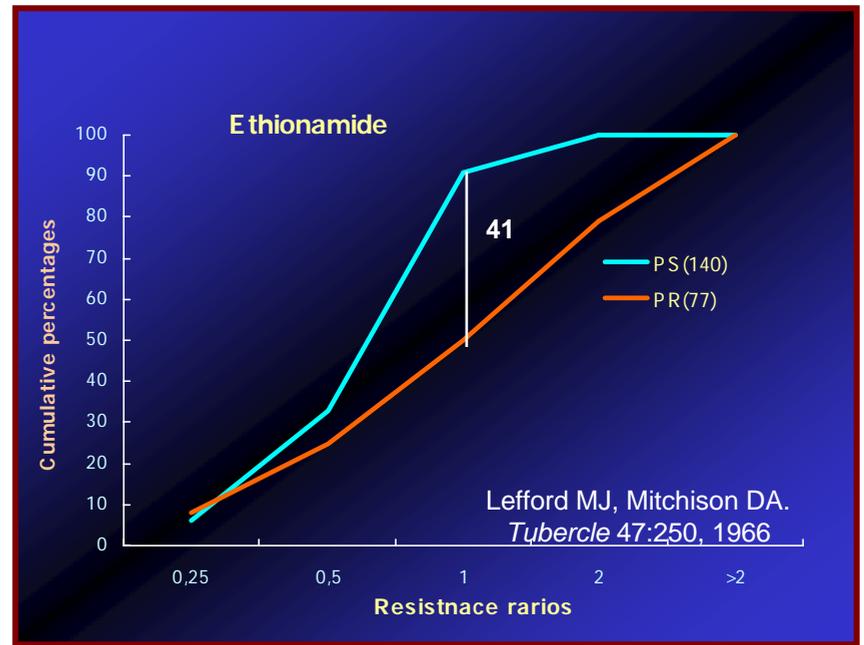
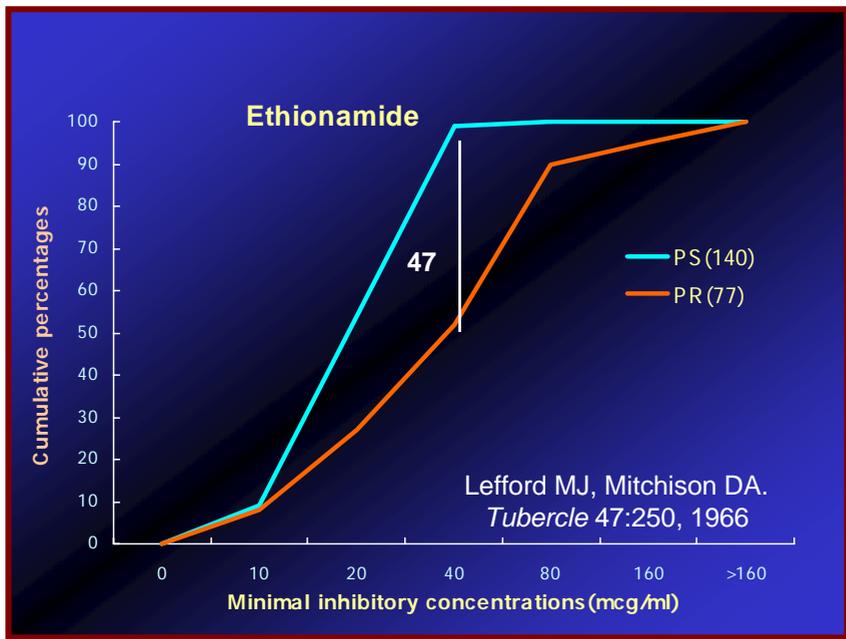
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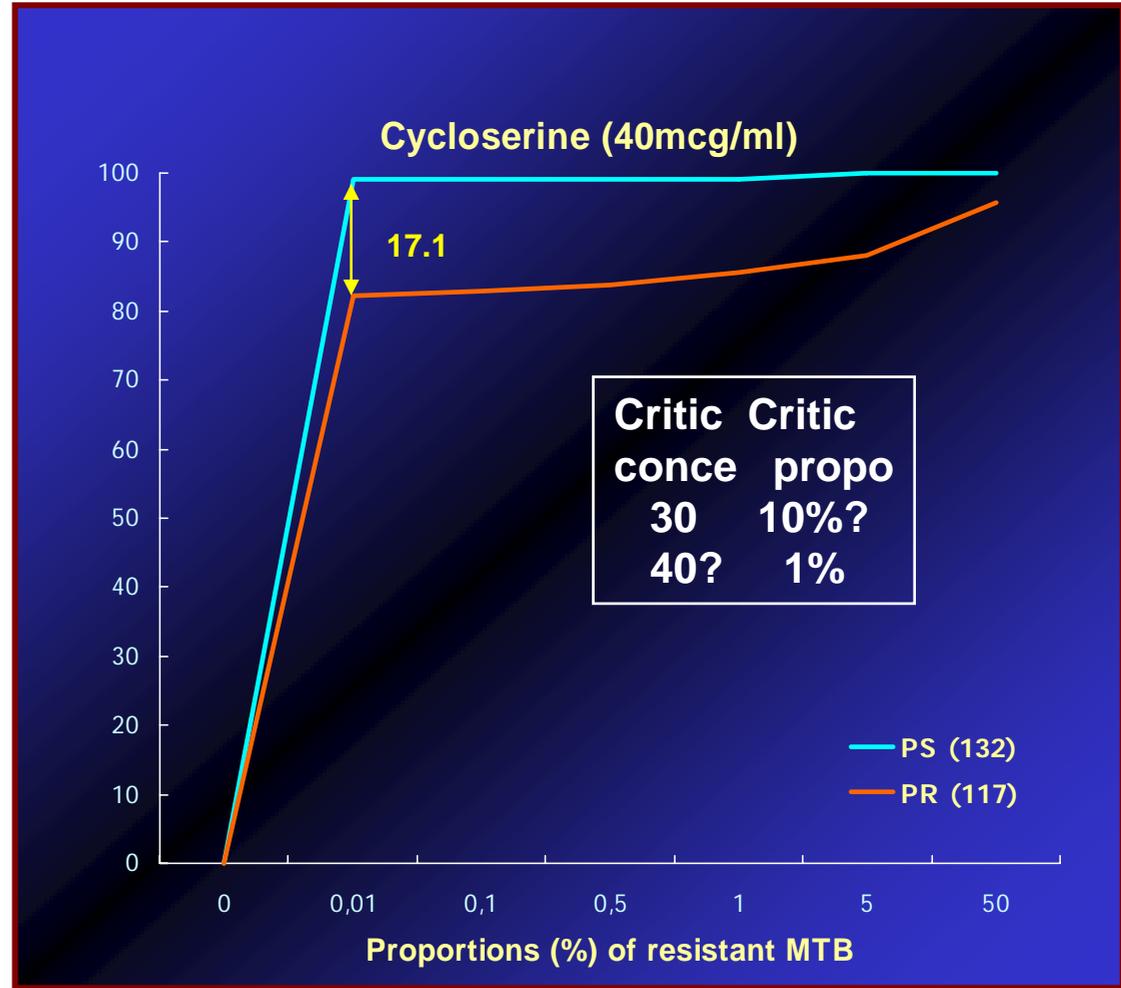
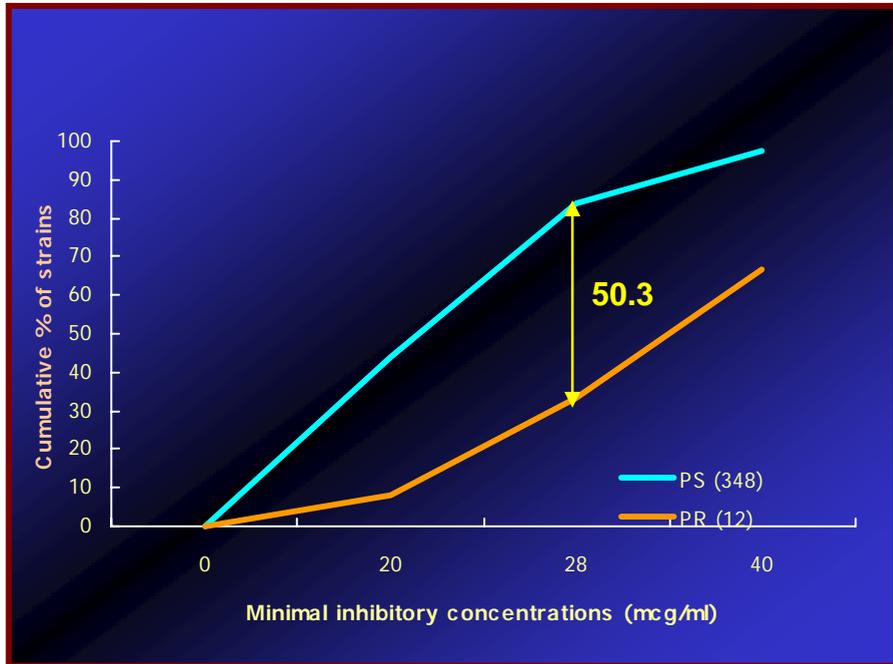
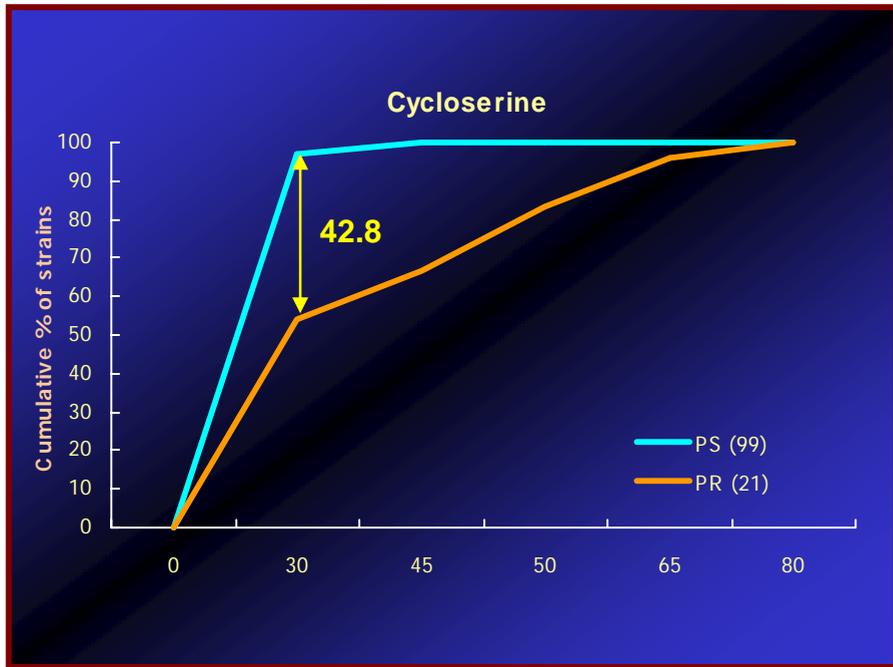




Para-aminosalicylic acid







What is the true value of the Drug Susceptibility Test?

First Line Drugs

- Very Good for H and R
- Less for S and E (More reliable the Susc. Result)
- Z needs BACTEC in many countries



What is the true value of the Drug Susceptibility Test?

Second Line Drugs

- *Relatively good for **Aminoglycosides**
and **Quinolones***
- *Low Reliability in the others, above all:*
 - *Eth/Pth, Cs, PAS*



Diagnosis of MDR-TB

Individual Management:

- ***History***, detailed and directed, of previous drugs taken in the past
- Supported by ***DST*** to H and R and, if possible, Kn and Of

N.T.P. Management:

- ***History*** of previous drugs administered, in the past, in the Country
- Supported by ***DST*** Surveillance above all to H and R



Many *Controversial* Issues in MDR Treatment

1. *How to approach Diagnosis of MDR?. Reliability of DST*

2. How *Many Drugs* to Treat MDR-TB ?

3. *Rational Use of the FLD and SLD*

4. *Length of the Injectable (Intensive phase).*

5. *Roll of the Surgery in the Treatment of MDR-TB*

6. *Approach to the Ideal Regime in MDR-TB.
Standardized vs Individualized Regimes*

***How Many Second
Line Drugs are
Necessary for Good
Re-Treatment?***

2, 3, 4, 5, 6, 7, 8, 9...

How Many Drugs to Treat MDR-TB?

History of *American Thoracic Society* Recommendations (1)

***...When resistance to S+H, or to all three primary drugs (S+H+P) is present. Reliance must be placed entirely on TWO or THREE other appropriate drugs.
Z, Et, Cs, Kn and Vi are available***

ATS. A Statement of the Committee on Therapy. Am Rev Respir Dis 1965; 92: 508-512

...However, in most instances, TWO or THREE drugs, to which the patient's organisms are susceptible and which have never been used, can be combined into a suitable regimen

ATS. A Statement by the Committee on Therapy. Treatment Drug-Resistant TB. Am Rev Respir Dis 1966;94:125-7

How many Drugs to Treat MDR-TB?

History of American Thoracic Society Recommendations (2)

Unfortunately, good data are not available on the relative effectiveness of various regimens and the necessary duration of treatment for patients with organisms resistant to both H+R. Moreover, many such patients will have resistance to other FLD when resistance is discovered. Because of the poor outcome in such cases, it is preferable to give AT LEAST THREE new drugs to which the organism is susceptible.

ATS. Treatment of Tuberculosis. Am J Respir Crit Care Med 1994; 149: 1359-1374

How many Drugs to Treat MDR-TB?

History of **American Thoracic Society** Recommendations (3)

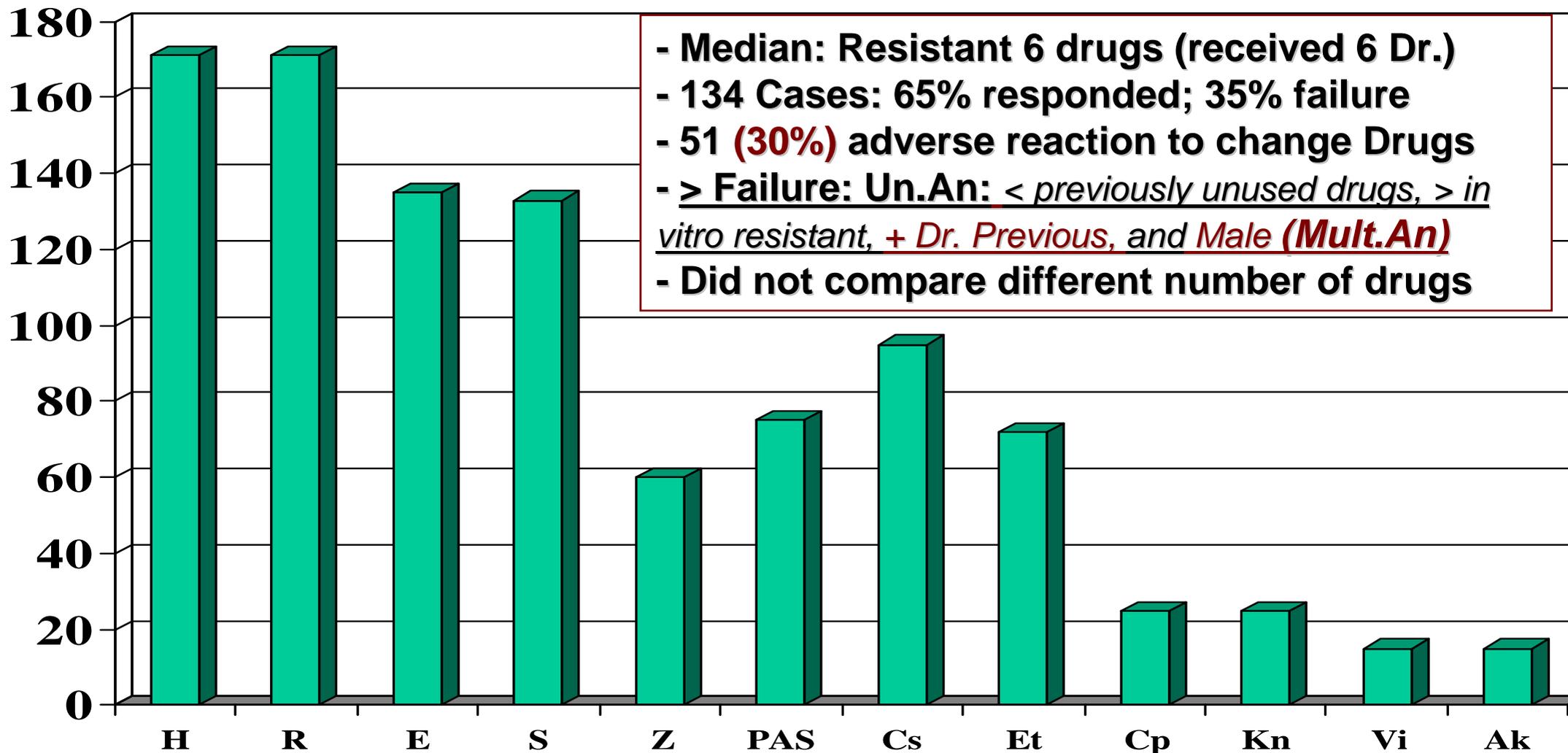
...always attempt to employ **at least three** previously unused drugs to which there is in vitro susceptibility (one an injectable agent)

Do not limit the regimen to three agents if other previously unused drugs that are likely to be active are available. In patients with MDR organisms in whom there is resistance to FLD in addition to H+R, regimens employing **FOUR** to **SIX** medications appear to be associated with better results (Goble, Park, Geerligs)

Treatment of **171 patients** with pulmonary tuberculosis resistant to Isoniazid and Rifampin

Goble M, et al. N Eng J Med 1993; 328: 527-32

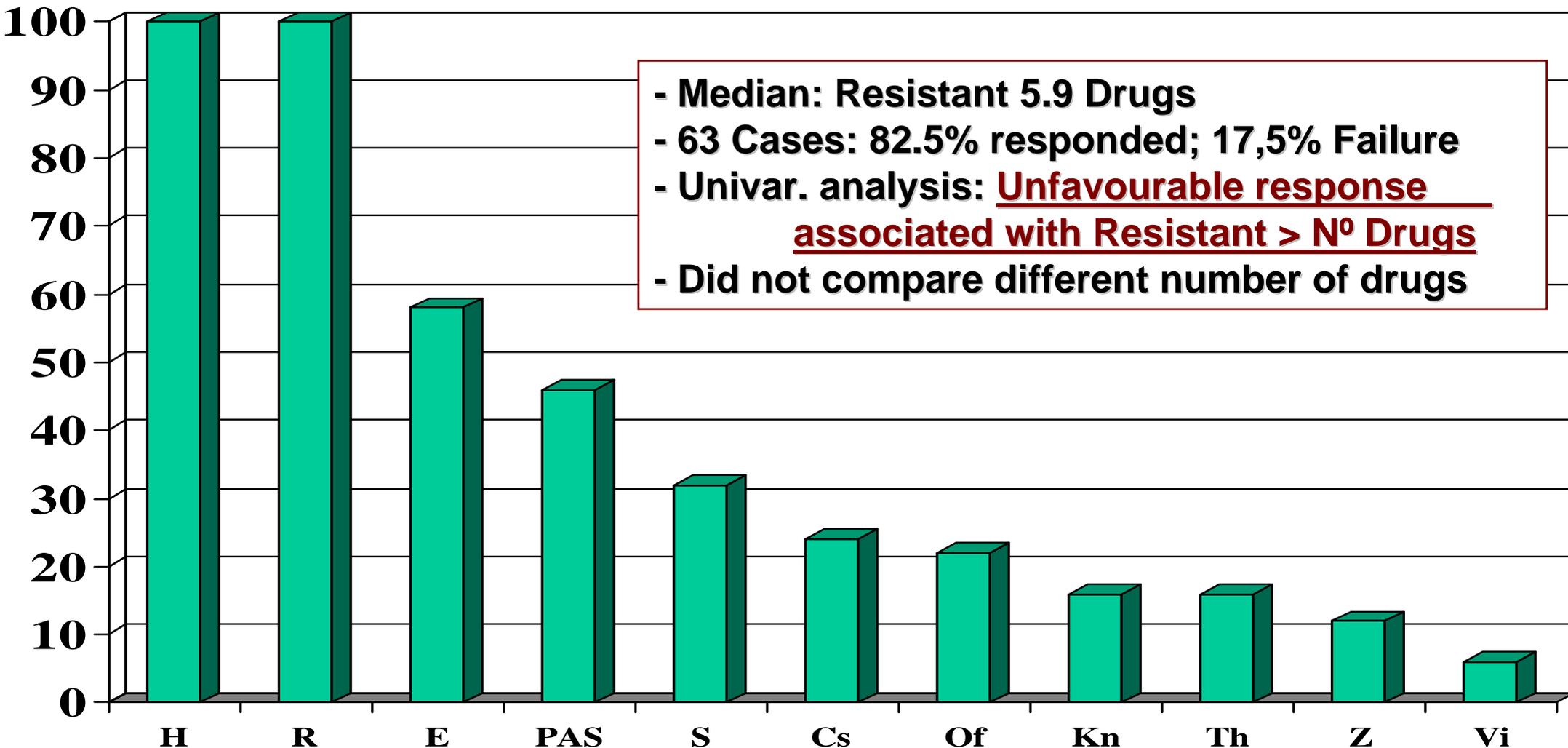
Resistant (Number)



Outcome of Chemotherapy in **107 Patients** with Pulmonary Tuberculosis resistant to Isoniazid and Rifampin

Park SK, et al. Int J Tuberc Lung Dis 1998; 2: 877-884

Resistant (%)

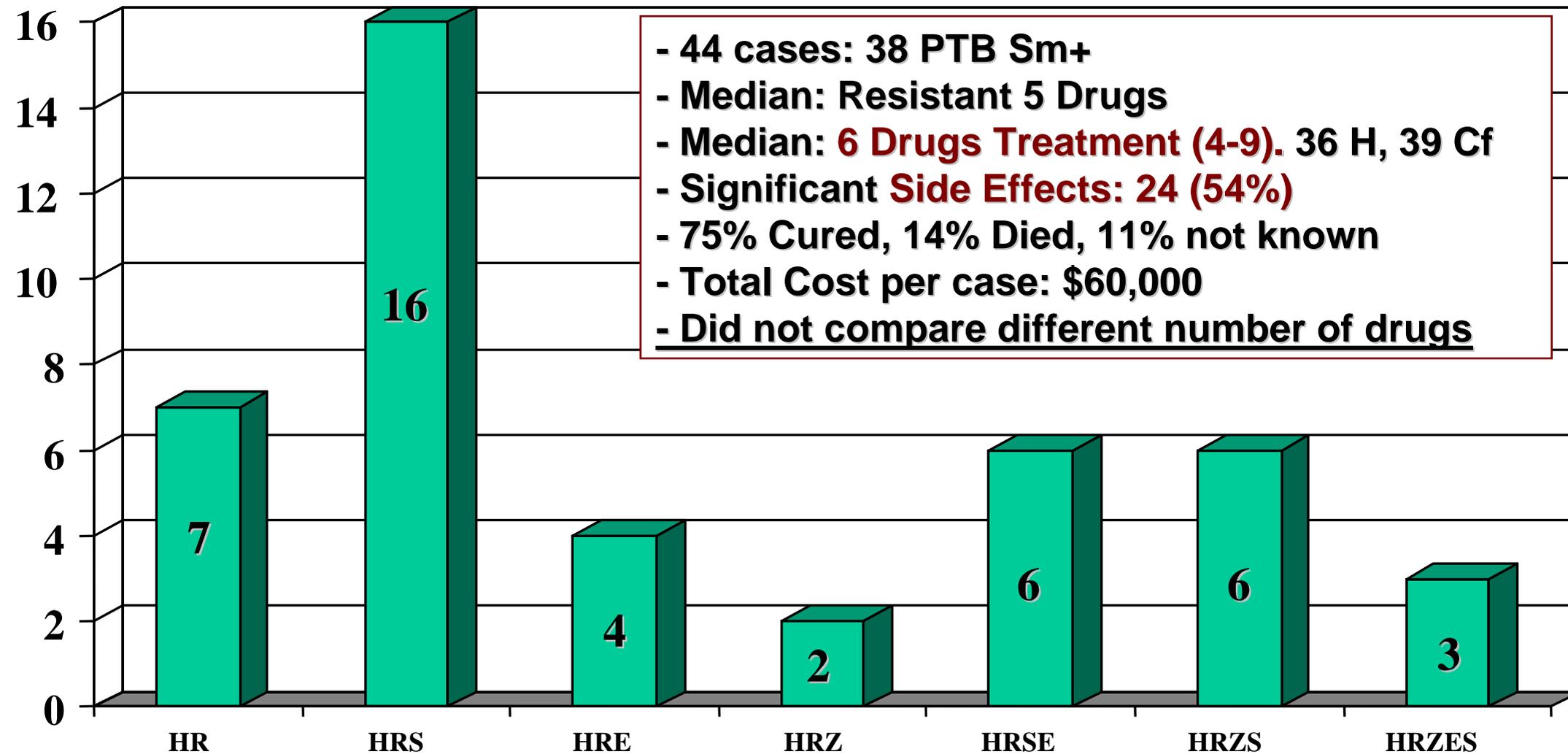


- Median: Resistant 5.9 Drugs
- 63 Cases: 82.5% responded; 17,5% Failure
- Univar. analysis: **Unfavourable response associated with Resistant > N° Drugs**
- Did not compare different number of drugs

Multidrug-resistant tuberculosis: long-term treatment outcome in the *Netherlands*

Geerligs WA, et al. Int J Tuberc Lung Dis 2000; 4: 758-764

Patterns of MDR



How many drugs to treat MDR-TB ?

History of **British Thoracic Society** Recommendations

...In cases with MDR resistance affecting both RIF and INH, treatment should be started with at least **THREE** drugs to which the organism is sensitive and continued until sputum cultures become negative, after which TWO should be continued for at least nine months more

Recommendation of BTS. Chemotherapy and management of TB in the UK. Thorax 1990; 45: 403-408

... Treatment of MDR-TB should start with **FIVE** or **MORE** drugs to which the organism is, or is likely to, susceptible and continued until sputum cultures become negative. Drug treatment then has to be continued with at least three drugs for a minimum of nine further months and perhaps to 24 months (Iseman NEJM 1993: 329: 784)

BTS Guidelines. Recommendations 1998. Thorax 1998; 53: 536-548

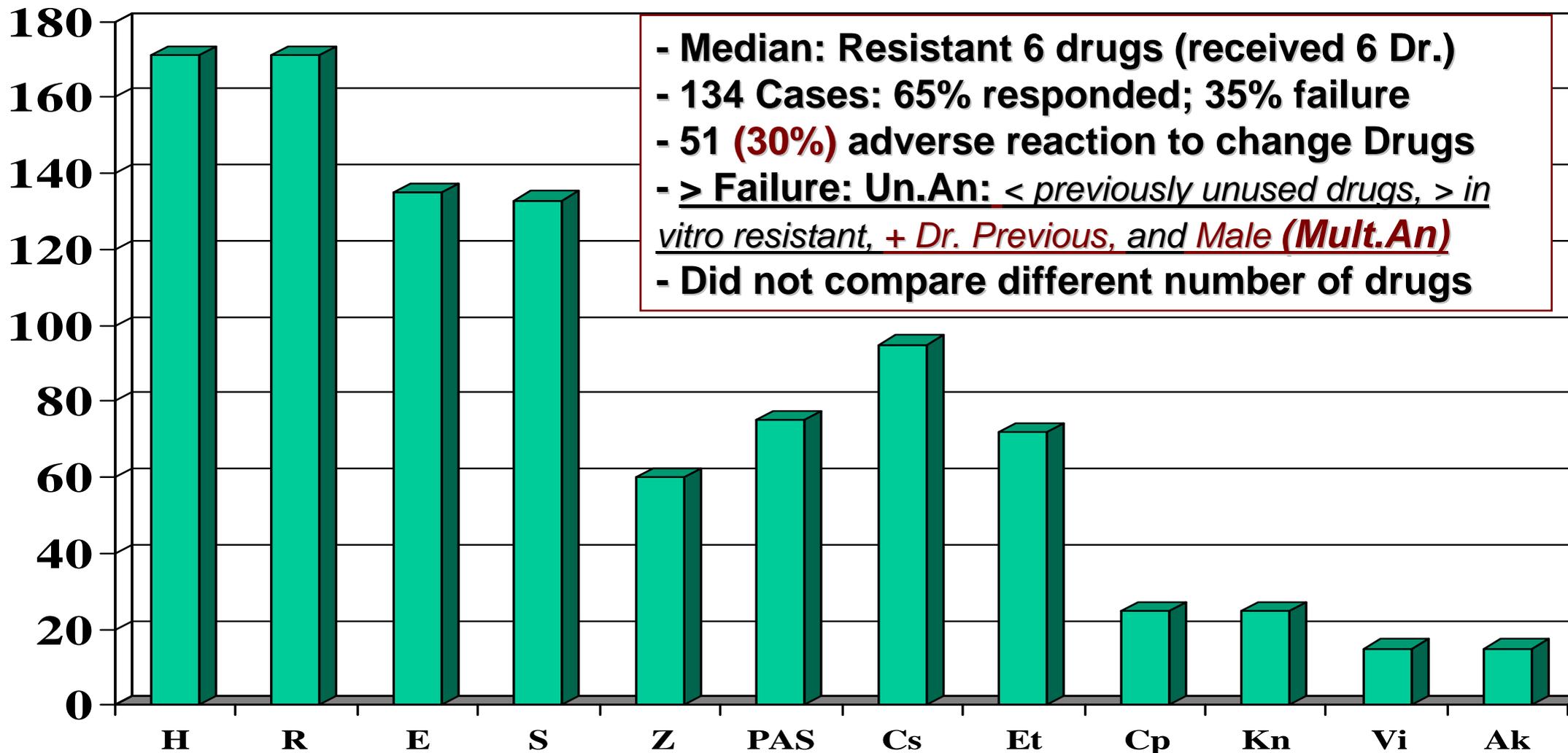
A tuberculosis retreatment regimen should always include at least **FOUR** but possibly as many as SIX or SEVEN drugs.

The number of drugs used varies depending on the extent of disease and the potency of the available agents

Treatment of **171 patients** with pulmonary tuberculosis resistant to Isoniazid and Rifampin

Goble M, et al. N Eng J Med 1993; 328: 527-32

Resistant (Number)



***But, what **Evidence** exists
about this theme ?***

***Most of the articles were
published **before** the
introduction of **RIF**, in those
with organisms **Resistant to**
H+S***

How Many Drugs are Necessary for Re-Treatment without **H+R**?

Re-Treatment with only **3 Drugs (1)**

Reference	Drugs	Follow-up (m)	N° Cases	Sm Conversion
USA. Schwartz <i>JAMA 1962; 181:134</i>	Kn-Z-Eth-Cs	6-12	64	57 %
UK. Pines <i>Chest 1962; 53: 163</i>	Z-Eth-Cs-Vi-Th	12-24	39	100 %
Morocco. Chicou <i>RevTuberc1962;26:867</i>	Kn-Eth-Cs-Vi-P	4-12	31	67,7 %
USA. Kass <i>Tubercle1965;46:151-80</i>	Kn-Z-Eth-Cs E-Cm-Th	21-37	98	94,8 %
Germany. Schütz <i>PraxisPneum1964;18:288</i>	Eth-Cs-P	6	34	85 %

How Many Drugs are Necessary for Re-Treatment without **H+R**?

Re-Treatment with only **3 Drugs** (2)

Reference	Drugs	Follow-up(m)	N° Cases	Sm Conversion
Hungary. Böszörményi <i>Tubercle</i> 1965;46:143	Z-Eth-Cs	3	31	51,6 %
USA. Lester <i>AmRevRespirDis</i> 1968;97:392-8	Kn-Z-Eth-Cs-	6-60	146	83.5 %
Poland. Zierski <i>Tubercle</i> 1964;45:96	Z-Eth-Cs	3-9	65	92,4 %
Czechosl. Tousek <i>Tubercle</i> 1967;48:27	Z-Eth-Cs	60-84	55	96 %
Spain. March <i>RevClinEsp</i> 1968;109:117	Z-Eth-Cs-Vi-E	6-18	33	93,4 %

Clinical outcome of individualised treatment of multidrug-resistant tuberculosis in Latvia: a retrospective cohort study

Lancet 2005; 365: 318–26

Vaira Leimane, Vija Riekstina, Timothy H Holtz, Evija Zarovska, Vija Skripconoka, Lorna E Thorpe, Kayla F Laserson, Charles D Wells

State Centre of Tuberculosis and Lung Diseases, Riga, Latvia

(V Leimane MD, V Riekstina MD, E Zarovska MD, V Skripconoka MD); and Division of Tuberculosis Elimination, (T H Holtz MD, L E Thorpe PhD, K F Laserson ScD, C D Wells MD) and Epidemic Intelligence Service, Epidemiology Program Office (L E Thorpe), Centers for Disease Control and Prevention, Atlanta, Georgia, USA

Correspondence to: Dr Vaira Leimane, Latvia State Centre of Tuberculosis and Lung Diseases, PO Cekule, Stopinų p, Riga Region, Latvia
vaira@tuberculosis.lv

Summary

Background Latvia has one of the highest rates of multidrug-resistant tuberculosis (MDRTB). Our aim was to assess treatment outcomes for the first full cohort of MDRTB patients treated under Latvia's DOTS-Plus strategy following WHO guidelines.

Methods We retrospectively reviewed all civilian patients who began treatment with individualised treatment regimens for pulmonary MDRTB in Latvia between Jan 1, and Dec 31, 2000. We applied treatment outcome definitions for MDRTB, developed by an international expert consensus group, and assessed treatment effectiveness and risk factors associated with poor outcome.

Findings Of the 204 patients assessed, 55 (27%) had been newly diagnosed with MDRTB, and 149 (73%) had earlier been treated with first-line or second-line drugs for this disease. Assessment of treatment outcomes showed that 135 (66%) patients were cured or completed therapy, 14 (7%) died, 26 (13%) defaulted, and treatment failed in 29 (14%). Of the 178 adherent patients, 135 (76%) achieved cure or treatment completion. In a multivariate Cox proportional-hazards model of these patients, independent predictors of poor outcome (death and treatment failure) included having previously received treatment for MDRTB (hazard ratio 5·7, 95% CI 1·9–16·6), the use of five or fewer drugs for 3 months or more (3·2, 1·1–9·6), resistance to ofloxacin (2·6, 1·2–5·4), and body-mass index less than 18·5 at start of treatment (2·3, 1·1–4·9).

Interpretation The DOTS-Plus strategy of identifying and treating patients with MDRTB can be effectively implemented on a nationwide scale in a setting of limited resources.

How *Many Drugs* are Necessary for Re-Treatment without *H+R*?

- **From a Bacteriological point of view, with *3 good SLD* could be enough (natural resistant mutants $>10^{15}$)**
- **However, many times in the field some drugs can be compromised, or they are very weak**
- **For this reason, in NTP conditions, a SLD regime should haveat least *FOUR* drugs...**
- **Sometimes, when several drugs could be compromised or are very weak, could be justified More than Four**

Many *Controversial* Issues in MDR Treatment

1. *How to approach Diagnosis of MDR?. Reliability of DST*

2. *How Many Drugs to Treat MDR-TB ?*

3. *Rational* Use of the FLD and SLD

4. *Length of the Injectable (Intensive phase).*

5. *Roll of the Surgery in the Treatment of MDR-TB*

6. *Approach to the Ideal Regime in MDR-TB.
Standardized vs Individualized Regimes*

ANTIMYCOBACTERIAL DRUGS

1. ISONIAZID

3. PYRAZINAMIDE

5. STREPTOMYCIN

7. KANAMYCIN

9. ETHION. – PROTHIONAMIDE

11. P.A.S.

13. QUINOLONES:

- CIPROFLOXACIN

- OFLOXACIN - LEVOFLOX. - MOXIFLOX

2. RIFAMPICIN

4. ETHAMBUTOL

6. CAPREOMYCINE

8. AMIKACIN

10. CYCLOSERINE-TERIZ.

12. THIAETAZONE

14. CLOFAZIMIDE

15. Others:

- MACROLIDES, CLAVULANATE., Etc

AT LEAST 4 FOR GOOD RETREATMENT!



Rational Classification of Anti-TB Drugs

Group 1: First Line Drugs, Oral (H,R,E,Z) → **All Possible**

Group 2: Injectables: Sm, Km, Ak, Cm → **1**

Group 3: Quinolones: Cp, Of, Lf, Mox., Gat → **1**

Group 4: Other Second Line Drugs: → **Until 4 New**
Et, Pth, Cs, PAS

Group 5: Reinforcement Drugs (poor) : → **Exceptional If < 4**
Am/Cl, Clof, Clar., Th, >> INH



Many *Controversial* Issues in MDR Treatment

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Lenght of the *Injectable* in MDR-TB Regime

RE-TREATMENT OF PATIENTS WITH ISONIAZID-RESISTANT TUBERCULOSIS^{1, 2, 3}

Analysis and Follow-Up of 146 Cases

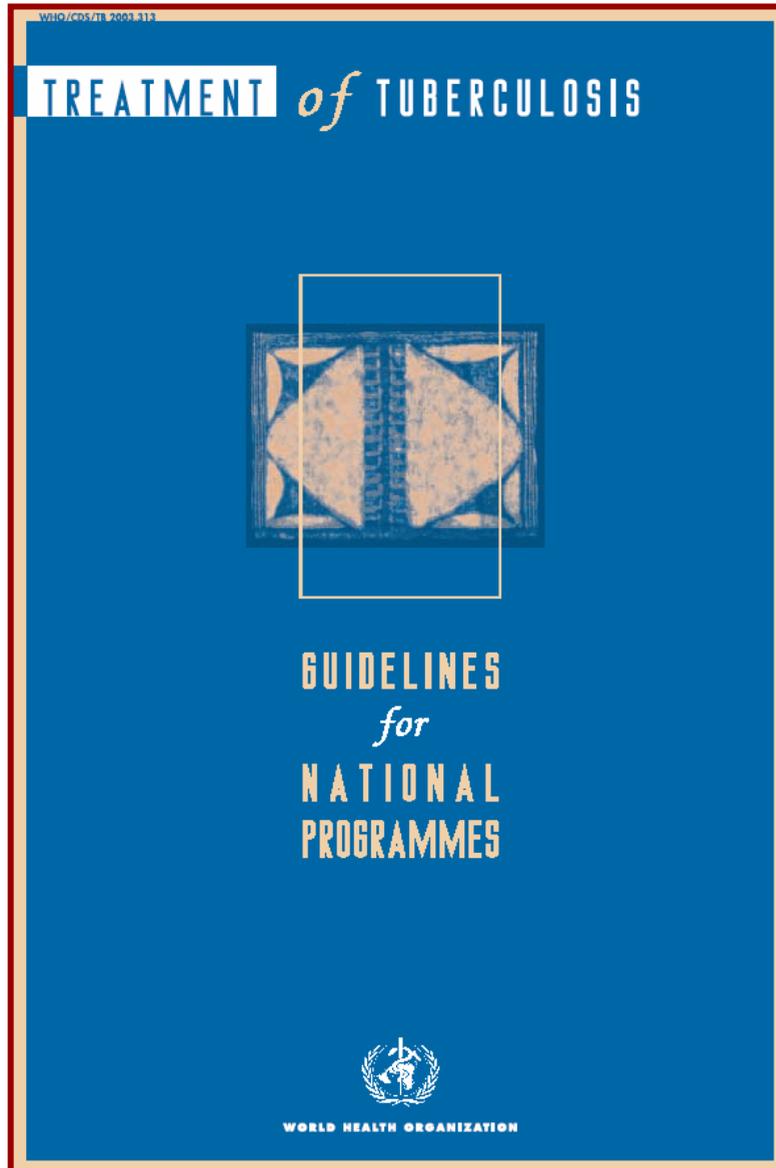
D. A. FISCHER, WILLIAM LESTER, WILLIAM E. DYE, AND
THOMAS S. MOULDING

Am Rev Respir Dis 1968; 7:392-398

**83,5% Sputum Conversion at 4^o Month,
using only 3 Drugs including Kn during
16-24 Weeks**

The results of treatment and follow-up of 146 patients with isoniazid-resistant tuberculosis are reported. Patients were started on re-treatment chemotherapy programs between January 1, 1960 and December 31, 1962. They continued a re-treatment chemotherapy regimen for a minimal period of 120 days. The median month of follow-up of the survivors was 46. The regimens used and the number of patients in each were as follows: kanamycin, ethionamide, and pyrazinamide, 63; kanamycin, ethionamide, and cycloserine, 17; other regimens, 66. After 120 days of treatment, the sputum of 122 (83.5 per cent) of the 146 patients was noninfectious. There were only 7 patients who failed to respond to therapy. Thirty patients (20.5 per cent) have experienced bacteriologic relapse during the period of observation. Relapses occurred at a median time of 12 months after the start of treatment. The median "conversion" time for patients who became noninfectious was the forty-seventh day of chemotherapy. Significant toxic reactions were encountered in 42 per cent of patients on the previously mentioned regimens, and appeared after a median duration of more than 60 days of treatment with any specific drug. Of the surviving patients in this series whose status was known as of January 1966, 88 per cent remained consistently noninfectious.

Based in its Theoretically only *Extracellular* action, the WHO and the IUATLD recommend only *2 Months* in the Category II



MANAGEMENT OF TUBERCULOSIS

A Guide For
Low Income Countries

Fifth edition
2000

Donald A Enarson, Hans L Rieder, Thuridur Arnadottir, Arnaud Trébuçq

International Union Against Tuberculosis
and Lung Disease

68 boulevard Saint-Michel, 75006 Paris, France

Inhibition by Streptomycin of Tubercle Bacilli within Cultured Human Macrophages¹⁻³

A. J. CROWLE, J. A. SBARBARO, F. N. JUDSON, G. S. DOUVAS, and M. H. MAY

SUMMARY The strategy for using streptomycin against tuberculosis assumes that it is not effective intracellularly. But according to animal cell experiments, this is probably incorrect. We retested this assumption with a new experimental model using cultured human macrophages infected with tubercle bacilli so that the results would be directly relevant to human disease. At 5 and 50 $\mu\text{g/ml}$, streptomycin inhibited the bacilli strongly and killed some; at the lowest tested concentration of 0.5 $\mu\text{g/ml}$, it inhibited them weakly. It was acting intracellularly, because it could inhibit even when added 2 days after the macrophages had been infected and washed free of extracellular bacilli, and because in our experimental model the bacilli were shown to be unable to multiply extracellularly. However, as has been reported for animal macrophages, the antibiotic was quantitatively more than 2 orders of magnitude less effective in human macrophages than in simple bacteriologic medium. Probably this is because streptomycin is concentrated within lysosomes where low pH greatly inhibits it. The human macrophage-tubercle bacillus chemotherapeutic bioassay we describe here for the first time could be a superior patient-consonant new method for testing antituberculosis agents and treatment regimens. It retains important *in vivo* features, the complete host cell-parasite relationship for instance, without giving up the *in vitro* advantages of rapidity and objectivity.

Lenght of the **Injectable** in **MDR-TB Regime**

CONCLUSSIONS

- **There are not Studies comparing different Length in the the aminoglycoside, as in efficacy as in toxicity**
- **There are some studies showing good results with only **16-24 Weeks****
- **Although only Extracellular action has been assumed, it is possible good **Intracellular** action**

Preferable until culture (-) or **6 Months, but it could be prolonged if the Regime is week after stopping the Injectable**

Many *Controversial* Issues in MDR Treatment

1. *How to approach Diagnosis of MDR?. Reliability of DST*
2. *How Many Drugs to Treat MDR-TB ?*
3. *Rational Use of the FLD and SLD*
4. *Length of the Injectable (Intensive phase).*
- 5. Roll of the *Surgery* in the Treatment of MDR-TB**
6. *Approach to the Ideal Regime in MDR-TB.
Standardized vs Individualized Regimes*

*What is the role of **SURGERY** in the treatment of **MDR-TB** ?*



Treatment and Outcome Analysis of 205 Patients with Multidrug-resistant Tuberculosis

Edward D. Chan, Valerie Laurel, Matthew J. Strand, Julianie F. Chan, Mai-Lan N. Huynh, Marian Goble, and Michael D. Iseman

Department of Medicine, Program in Cell Biology and Division of Biostatistics, National Jewish Medical and Research Center; Division of Pulmonary Sciences and Critical Care Medicine and Division of Infectious Diseases, University of Colorado Health Sciences Center; Denver Veterans Administration Medical Center, Denver, Colorado; and Wilford Hall USAF Medical Center, San Antonio, Texas

Am J Respir Crit Care Med Vol 169. pp 1103–1109, 2004

Multidrug-resistant tuberculosis, a disease caused by *Mycobacterium tuberculosis* strains that are resistant at least to rifampin and isoniazid, entails extended treatment, expensive and toxic regimens, and higher rates of treatment failure and death. We retrospectively analyzed the outcomes in 205 patients treated at our center for multidrug-resistant tuberculosis, with strains resistant to a median of six drugs, and compared the results with those of our previous series. Logistic regression and survival analysis were used to evaluate short- and long-term outcomes, respectively. Initial favorable response, defined as at least three consecutive negative sputum cultures over a period of at least 3 months, was 85% compared with 65% in the prior cohort. The current cohort had greater long-term success rates, 75% versus 56%, and lower tuberculosis death rates, 12% versus 22%, than the earlier one. Surgical resection and fluoroquinolone therapy were associated with improved microbiological and clinical outcomes in the 205 patients studied after adjusting for other variables. The improvement was statistically significant for surgery and among older patients for fluoroquinolone therapy.

comparable drug resistance and extent of disease. Some of the results of these studies have been previously reported in the form of an abstract (8).

METHODS

Study Population and Data Collection

The National Jewish Medical and Research Center (NJMRC) specializes in the treatment of MDR-TB. We reviewed the records of 205 such patients who were treated on the inpatient service and discharged between January 1, 1984, and December 31, 1998. Records were reviewed for (1) demographics; (2) previous number of drugs taken for TB (defined as the administration of an agent for 3 or more months) and other potential risk factors for development of MDR-TB; (3) susceptibilities to the anti-TB drugs; and (4) drugs used, drug toxicity, surgical intervention, results of sputum cultures, and clinical outcomes.

Medical and Surgical Treatment

In vitro susceptibility testing was used to guide therapy of MDR-TB

130 MDR-TB Treated with Surgery (63%). Mortality by the Surgery: 10 (8%)

Treatment of Multidrug-Resistant Tuberculosis in San Francisco: An Outpatient-Based Approach

Clin Infect Dis 2005; 40: 968-75

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¹Department of Internal Medicine, Division of Infectious Diseases, University of New Mexico, and Department of Medicine, Albuquerque Veterans Affairs Medical Center, Albuquerque, New Mexico; ²Division of Pulmonary and Critical Care Medicine, San Francisco General Hospital, and University of California, San Francisco, and ³Tuberculosis Control Section, San Francisco Department of Public Health, San Francisco, California

Background. Treatment of patients with multidrug-resistant tuberculosis requires prolonged therapy, often involving long hospital stays. Despite intensive and costly therapy, cure rates are relatively low.

Methods. We reviewed the outcomes for all patients with multidrug-resistant tuberculosis treated in San Francisco, California, during 1982–2000 and identified billing charges for patients treated during 1995–2000. *Mycobacterium tuberculosis* isolates were genotyped by IS6110-based restriction fragment–length polymorphism analysis.

Results. Forty-eight cases were identified with resistance to a median of 3 drugs (range, 2–9 drugs). The median age of the patients was 49.5 years (range, 22–78 years); 36 (75%) of 48 patients were foreign born, 11 (23%) were human immunodeficiency virus (HIV) seropositive, and 45 (94%) had pulmonary tuberculosis. Thirty-two (97%) of the 33 HIV-seronegative patients were cured, with only 1 relapse occurring 5 years after treatment. All 11 HIV-seropositive patients died during observation. Twenty-one patients (44%) required hospitalization, with a median duration of stay of 14 days (range, 3–74 days). The estimated inpatient and outpatient aggregate cost for the 11 patients treated after 1994 was \$519,928, with a median cost of \$27,752 per patient. No secondary cases of multidrug-resistant tuberculosis were identified through population-based genotyping.

Conclusions. Treatment of multidrug-resistant tuberculosis in HIV-seronegative patients largely on an outpatient basis was feasible and was associated with high cure rates and lower cost than in other published studies. Patients with underlying HIV infection had very poor outcomes.

Only 3 HIV- surgical procedures (2 drainages in empyema TB and 1 resection)

Received: 2002.04.05
Accepted: 2002.09.24
Published: 2002.12.27

Authors' Contribution:

- A** Study Design
- B** Data Collection
- C** Statistical Analysis
- D** Data Interpretation
- E** Manuscript Preparation
- F** Literature Search
- G** Funds Collection

Role of surgery in pulmonary tuberculosis

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Background:

The purpose of our study was to analyze current indications for surgery in tuberculosis (TB). We present our experience with TB patients presenting with indications for surgery between 1990 and 1998.

Material/Methods:

The indications for surgical intervention included 25 cases of pulmonary aspergilloma, 19 cases of pneumothorax, 16 cases of pulmonary nodes and masses without histological diagnosis, 15 cases of bronchiectasis, 12 cases of massive hemoptysis, 12 cases of pleural empyema, and 33 cases of other complications. No patients with multidrug-resistant tuberculosis required surgical intervention, although 56 were treated during this period.

Results:

The techniques utilized included lobectomy in 45 cases, pleural drainage in 32 cases, segmental pulmonary resection in 32 cases, surgical procedures on the thoracic wall in 17 cases, pneumonectomy in 10 cases, pleuropulmonary decortication in 8 cases, mediastinoscopy in 6 cases, and thoracoscopy in 5 cases. In 25 cases two or more procedures were performed on the same patient. In 36 cases (27.3%) there were complications, of which persistent air leakage after pulmonary resection was the most frequent (n=10). There was a mortality rate of 5.3% (7 cases).

Conclusions:

In our experience, surgery in the treatment of TB is indicated to resolve sequelae or complications, since cases of simple or multidrug-resistant TB can be managed pharmacologically. The morbidity and mortality rates in our series were acceptable.



Role of **SURGERY** in MDR-TB

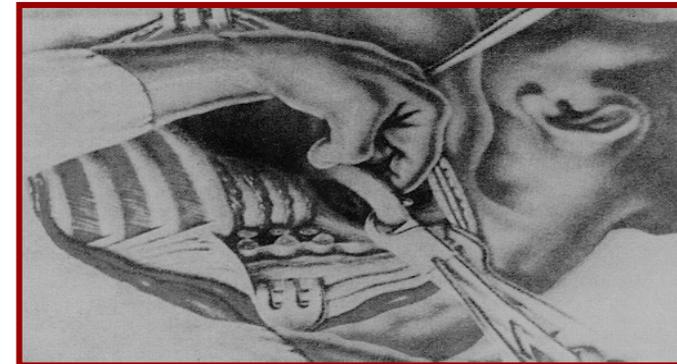
- Only indicated if :

- There are not 4 drugs available (rare)**
- The lesion is localised (very rare)**
- There is sufficient respiratory reserve (very rare)**

- Even in this situation, it must be remembered:

- High morbidity-mortality**
- Lesions are not sterilised**

Only indicated in very exceptional circumstances!

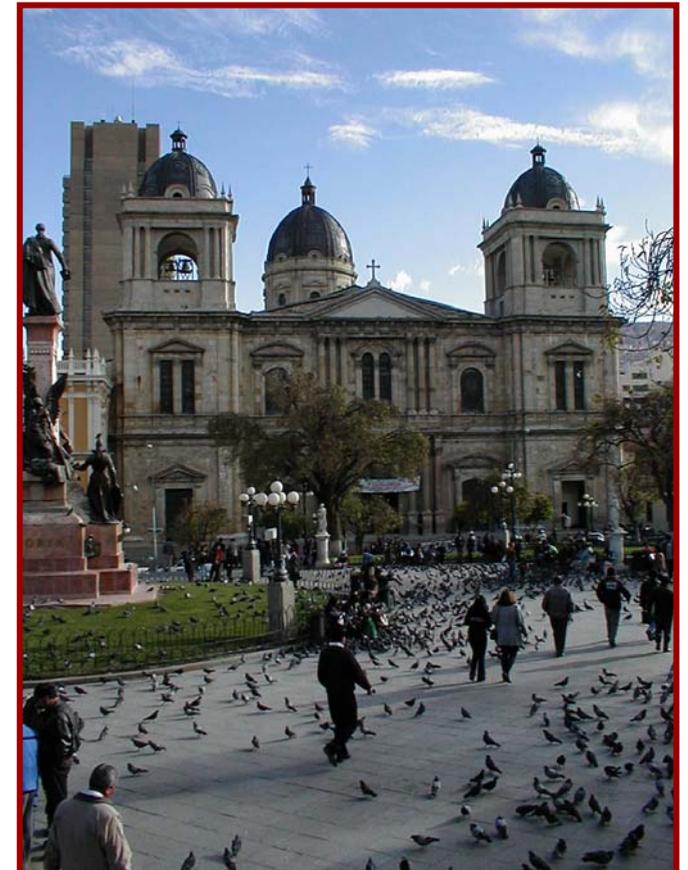


Many *Controversial* Issues in MDR Treatment

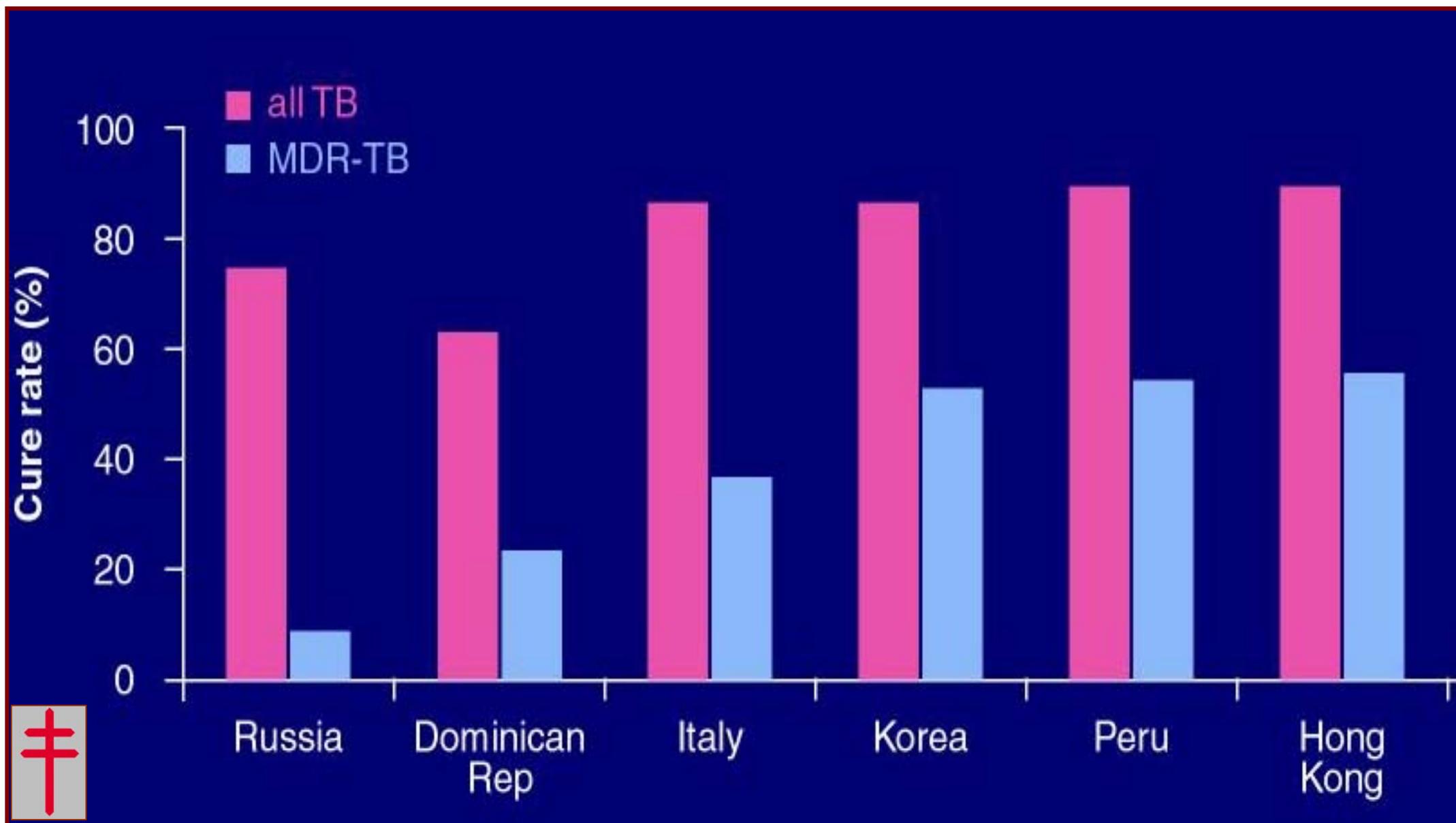
- 1. How to approach Diagnosis of MDR?. Reliability of DST*
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- 3. Rational Use of the FLD and SLD*
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- 6. Approach to the Ideal Regime in MDR-TB.
*Standardized vs Individualized Regimes***

MDR-TB Treatment

Low and Middle Income Countries



Influence of *MDR* in the Cure of *Untreated* Cases



NTP Most Important Problems with MDR

*What should they do in the Suspect of Res. **Waiting DST Results***

- 1. What should we do with Patients who **FAIL** with the Initial St. Treatment ? **2 HRZE/4 HR (6HE)*****
- 2. What should we do with Patients who **FAIL** with the Standardised Retreatment Scheme with First-Line Drugs? **2 HREZS / 1 HRZE / 5 H₃R₃E₃*****
- 3. What should we do with Patients who **FAIL** with a lot of Regimes and they have received many drugs and associations?***



In N.T.P. Conditions
it is necessary
Simplify the complex
Management of
MDR-TB Cases



A very Important NTP Problem

*1. What should we do with Patients who **FAIL** with the Initial St. Treatment ?*
2 HRZE / 4 HR (6HE)

*Risk to **AMPLIFY** Resistance with
Cat. II Regime: : 2 HRZES / 1HRZE / 5H₃R₃E₃*



**The Risk to Amplify Resistance in the Failures to Cat. I
receiving Category II Regime (1)**

2 HRZE/4 H₃R₃

FAILURE

**1. Susceptibility to all FLD (20-80%)
(Operational Failure ?)**

**Not Problem Cat. II: 2HRZES / 1HRZE / 5(HRE)₃
(Not Risk to Amplify Resistance)**



The Risk to Amplify Resistance in the Failures to Cat. I receiving Category II Regime (2)

2 HRZE/4 H₃R₃

FAILURE



2. Initial Resistance to H (+%)

~~2~~ ~~HRZE~~/~~4~~ ~~H₃~~~~R₃~~

MDR, but suscpt. Z+E

~~2~~~~HRZES~~/~~1~~~~HRZE~~/~~5~~~~H₃~~~~R₃~~~~E₃~~

**Risk to Amplify Resistance E
(Avoidable if DST before 3rd Month)**

The Risk to Amplify Resistance in the Failures to Cat. I receiving Category II Regime (3)

2 HRZE/4 H₃R₃

FAILURE



3. Initial M.D.R. (-%)

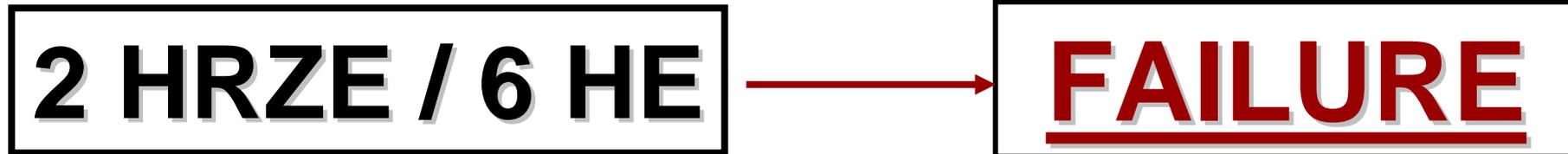
2 ~~HRZE~~/4 ~~H₃R₃~~

Resistance to HR+E+Z

2~~HRZE~~S/1~~HRZE~~/5~~H₃R₃~~E₃

Risk to Amplify
Resistance to S

The Risk to Amplify Resistance in the Failures to Cat. I receiving Category II Regime (1)



**1. Susceptibility to all FLD (20-80%)
(Operational Failure ?)**



**Not Problem Cat. II: 2HRZES / 1HRZE / 5(HRE)₃
(Not Risk to Amplify Resistance)**



The Risk to Amplify Resistance in the Failures to Cat. I receiving Category II Regime (2)

2 HRZE / 6 HE

FAILURE



2. Initial Resistance to H (+%)

~~2 HRZE/4 HE~~

Res. HE, but suscpt. R+E

~~2HERZS/1HERZ/5H3E3R3~~

Very Low Risk to Amplify Res. R
(Avoidable if DST before 3rd Month)

The Risk to Amplify Resistance in the Failures to Cat. I receiving Category II Regime (3)

2 HRZE / 6 HE

FAILURE



3. Initial M.D.R. (-%)

2 ~~HRZE~~ / 4 ~~H₃R₃~~

Resistance to HR+E+Z

2 ~~HRZE~~ / 1 ~~HRZE~~ / 5 ~~H₃R₃E₃~~

Risk to Amplify Resistance to S

Frequent Case: Initial **INH** Resistance



Prudent approach

2 EHRZ / 6 EH

**Failure / relapse:
relatively frequent**

2 SEHRZ / 6 ERHZ

**Failure = MDR
Relatively infrequent**

Risky approach

2 EHRZ / 4 RH

**Failure / relapse:
relatively infrequent**

2 SEHRZ / 1 ERHZ / 5 ERH

**Failure = MDR
Relatively frequent**

Failures of failures: appropriate numerator

1. What should we do with Patients who *FAIL* with the Initial St. Treatment ?
2 HRZE / 4 HR ?

1. Category II (2 HRZES / 1 HRZE / 5 H₃R₃E₃)

2. Standardised S.L.D* Regime



* Every Country should adapt concerning History of Drugs used in the past and Availability

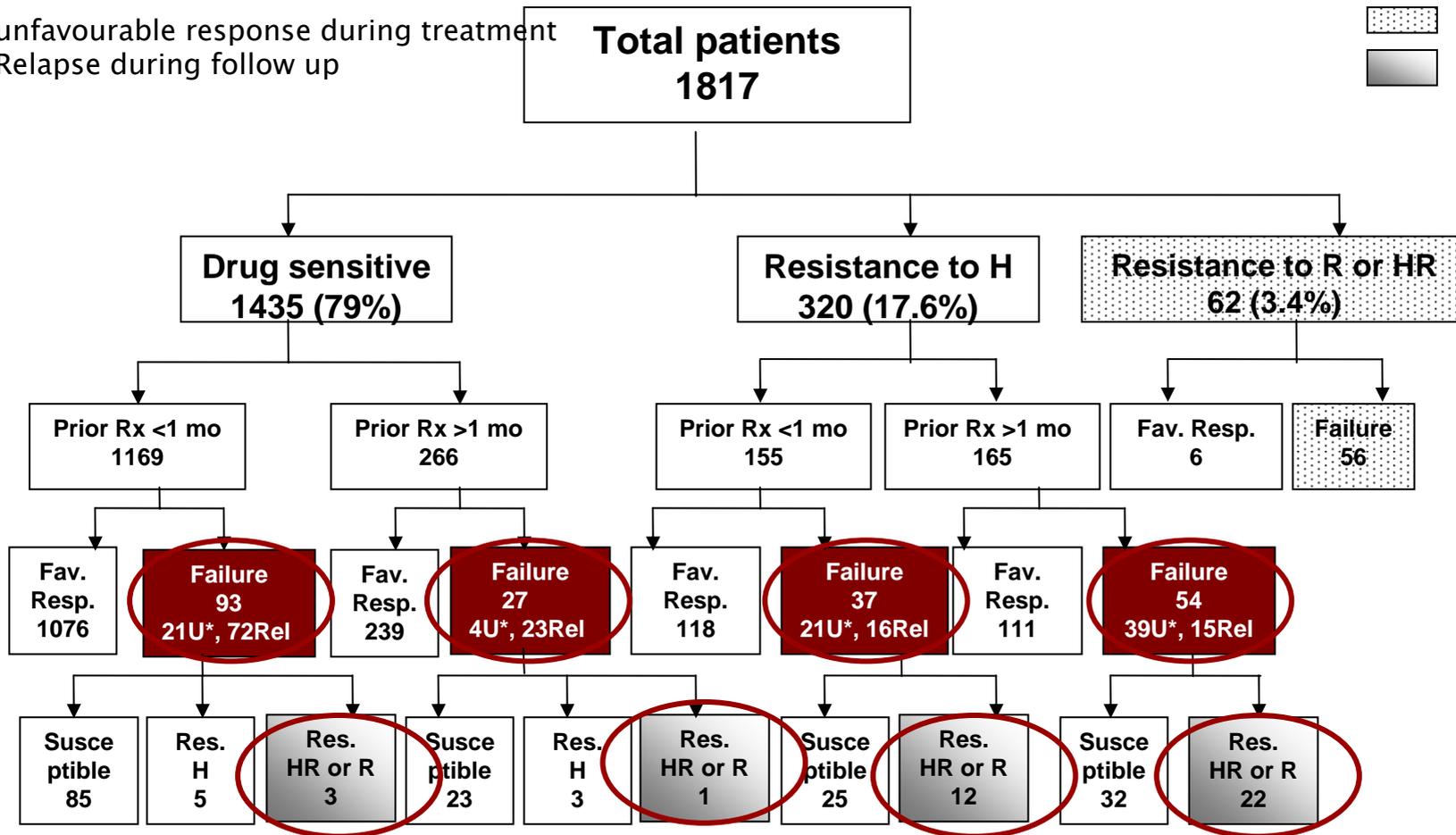
Treatment **outcome** with SCC in relation to prior treatment.

Clinical Trial. Tuberculosis Research Centre. India

Int J Tuberc Lung Dis. 2001 Jan;5(1):40-

U* = unfavourable response during treatment
 Rel = Relapse during follow up

 Initial HR Resistant
 Acquired HR Resistant



Very Low Rate MDR in Failures and Unfavourable Response
 ----> **Low Risk of Amplification with Category II**



Percentages of **MDR-TB** in the different re-treatment categories

Retreatment Group	Vietnam	Malawi	Benin	Nicaragua	Thailand	Brazil	Peru
	HE	HE	HT	HT	HR	HR	HR
Failures of Category I with HR					19/22 (86%)	29/91 (33%)	80/91 (88%)
Failures of Category I with HE	32/40 (80%)	0/11 (0%)					
Failures of Category I with HT			2/9 (22%)				
Relapse of Category I with HR					2/18 (11%)	2/37 (6%)	
Relapse of Category I with HE	3/39 (8%)						
Relapse of Category I with HT			1/23 (4%)				
Return after default of Category I with HR					1/19 (5%)		
Failures of retreatment with Category II				34/38 (89%)		49/78 (65%)	298/344 (87%)

Possibilities in the **FAILURES** to Cat. I Regime (1)

(2 HRZE / 4 HR)

1. **Category II** (2 HRZES / 1 HRZE / 5 H₃R₃E₃)

- Only Possibility in very **Low** Income Countries

- Good Results in Good NTP and few use of FLD out of the NTP
 - Initial MDR < 1%
 - More 50% of Failures Susceptible to all FLD
- Only Risk to Amplify Resistance to 1 Drug (E ó S) in the rest

- To Evaluate in **Middle** Income Countries. Conditions:

- History of Good NTP and Few use of FLD out of the NTP
- Initial MDR < 1% -----> Rate of Failures with Cat. I < 2%
- MDR < 25-50% in FAILURES to Initial Category I Regime



Possibilities in the **FAILURES** to Cat. I Regime (2)

(2 HRZE / 4 HR)

2. **Standardised S.L.D. Regime***

* Every Country should adapt concerning History of Drugs used in the past and Availability

- (#) Until Sm (-)
- (&) Until 18 M if Sm- before 6 M
Until 24 M if Sm- after 6 M

Advised

(#) **Kn-Z-Of-Et-E / (&) Of-Et-E**

- It is possible use E if the Cat. II has been not used + Susc. in DST
- Cheaper. It use the most studied associations
- It use the best tolerated and lest toxic associations (?)
- This scheme makes Drug availability easier and avoids **“Improvisations”** (Chest physicians like them)





1. What should we do with Patients who **FAIL with the Initial St. Treatment ? **2 HRZE / 4 HR****

- The decision should be based concerning the *rate* of **MDR in the **Failures** to Cat. I in the Country**

- 1.- Low rate MDR ---> Not Problem with **Category II** (2 HRZES / 1 HRZE / 5 H₃R₃E₃)
- 2.- High rate MDR ---> Standardised **S.L.D.** Regime

It is Pivotal to perform DST to all the Failures to Cat. I

If possible → Culture and **DST** to the **Sm+** in 2-3 m.

2. What should we do with Patients who **FAIL with the Standardised Retreatment Scheme with First-Line Drugs?**

2 HREZS / 1 HRZE / 5 H₃R₃E₃

We could Assume **MDR-TB** and Resistance to E, but probable **Susceptibility** to All **S.L.D.**



How *Standard* the Management of TB-MDR?

Initial MDR

Failure Category I ?

Failures Category II

INCIDENTS (New) MDR, in Good NTP

Standardised S.L.D. Regime*

* Every Country should adapt concerning History of Drugs used in the past and Availability

Advised

(#) Until Sm (-)

(&) Until 18 M if Sm- before 6 M. // 24 M if Sm- after 6 M



(#) *Kn-Z-Of-Et-Cs(E)* / (&) *Of-Et-CS(E)*

3. What should we do with Patients who **FAIL with a lot of Regimes and they have received many drugs and associations?**

It is necessary accept **MDR-TB, and also **Resistance** to some SLD**



How **Standard** the Management of TB-MDR?

Failure Standardised SLD

(In NTP Conditions)

MDR Prevalents cases

(Many SLD received)

TB-MDR PREVALENTS (Chronic) Cases

(Obligatory Confirm Resistance to H+R in DST)

INDIVIDUALIZED S.L.D. Regime*

* Duration = Criteria that Standard Regime (18-24 M)

- Only **4 new Drugs** (or without suspect of Res) are necessary, and always 1 aminog. in First Ph
- Based on the Drug **History** (Patient and Country) and, if possible, DST to Q + Kn
- If not possible 4 New Drugs ---> May be more Drugs
- **WARNING**: More Drugs ---> More Side effects and More Expensive
- Use the sequence: **Z, E, S, Kn, Ak, Cp, Of, Eth, Cs, PAS, Th, Cf**



MDR-TB Cases *Classification*

Approach to the *Ideal Regime*

1. *Initial MDR-TB Cases*

- **Never (<1 month) have received Anti-TB Drugs**

2. *MDR-TB cases receiving only FLD*

3. *MDR-TB Cases receiving FLD and SLD*

- **Receiving only 1-2 SLD (injectable and/or Quinol.)**
- **Receiving Many SLD**

It will Condition *Different Therapeutic Strategies*



Approach to the Ideal **Regime** in the Initial MDR-TB

1. Do not Modify the Category I

***2. Individualized SLD Regime based in
the pattern of Resistance of the Index
Case and DST***

Treatment Outcome of New TB Cases According Resistance

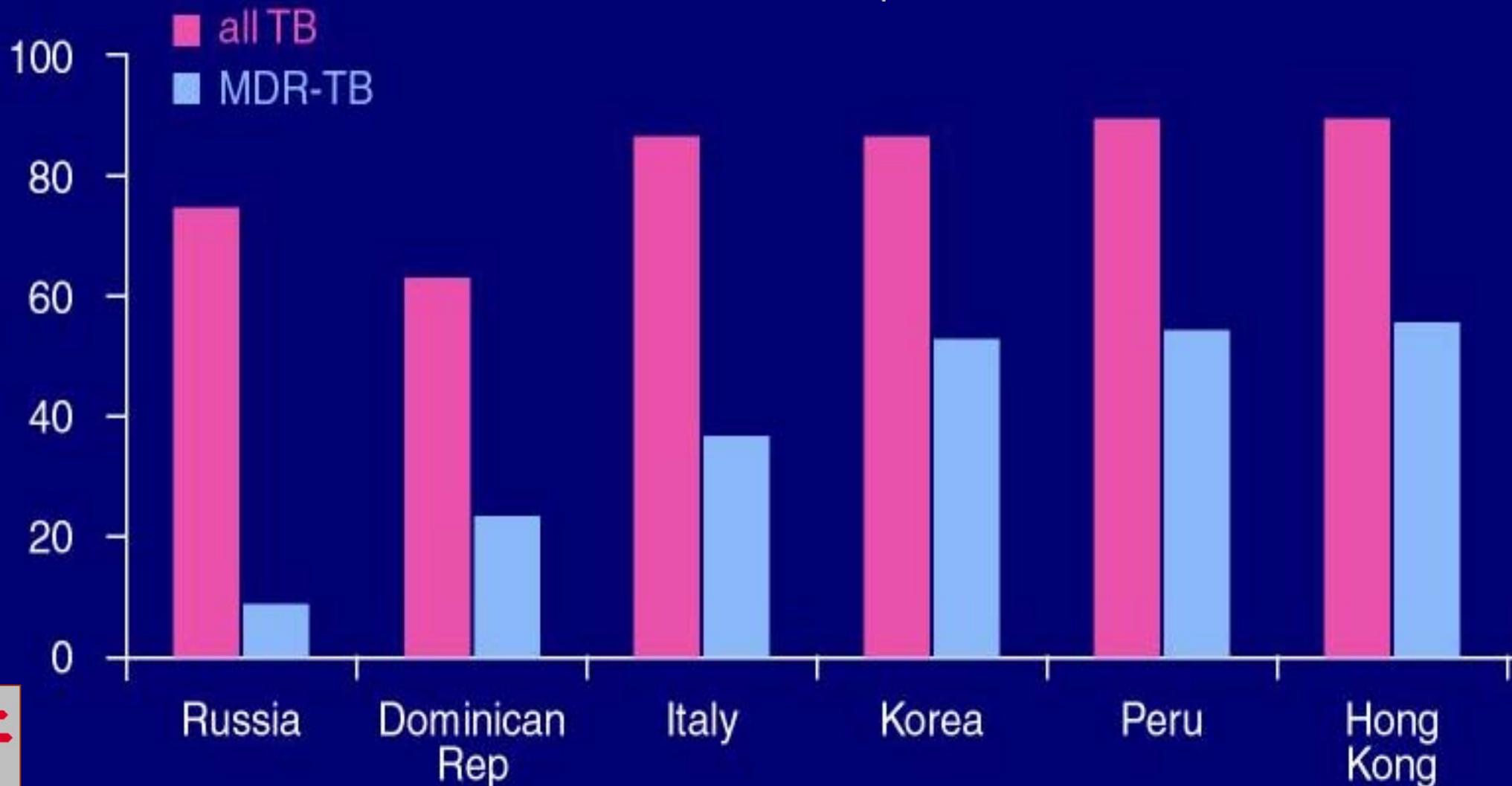
Espinal et al. JAMA 2000; 283: 2537-45

Treatment Outcome, No. (%)

Region	Cured	Treatment Completed	Died	Failure	Default	Transfer	Total	Treatment Success
Any Resistance*								
Republic of Korea	124 (87)	0	2 (1)	10 (6)	8 (5)	12 (8)	156	124 (80)
Peru	123 (83)	6 (4)	6 (4)	5 (3)	8 (5)	1 (1)	149	129 (87)
Hong Kong†	329 (84)	10 (3)	7 (2)	1 (0.2)	6 (1)	38 (10)	391	339 (87)
Ivanovo Oblast‡	18 (29)	16 (26)	5 (8)	12 (19)	7 (11)	4 (7)	62	34 (54)
Dominican Republic	21 (22)	43 (47)	0	8 (8)	18 (19)	4 (4)	94	64 (68)
Italy	46 (41)	50 (45)	1 (1)	0	7 (6)	8 (7)	112	96 (86)
Total	661 (68)	125 (13)	21 (2)	36 (4)	54 (6)	67 (7)	964	786 (81)
Multidrug Resistance								
Republic of Korea	20 (56)	0	1 (3)	11 (31)	0	4 (11)	36	20 (56)
Peru	13 (54)	1 (4)	4 (17)	6 (25)	0	0	24	14 (58)
Hong Kong†	41 (59)	1 (1)	6 (9)	3 (4)	5 (7)	14 (20)	70	42 (60)
Ivanovo Oblast‡	1 (6)	1 (6)	4 (22)	8 (44)	3 (17)	1 (6)	18	2 (11)
Dominican Republic	5 (26)	5 (26)	1 (5)	3 (16)	4 (21)	1 (5)	19	10 (53)
Italy	6 (35)	1 (6)	0	8 (47)	2 (12)	0	17	7 (41)
Total	86 (47)	9 (5)	16 (9)	39 (21)	14 (7)	20 (11)	184	95 (52)
Any Rifampicin Resistance*								
Republic of Korea	10 (71)	0	0	2 (14)	1 (7)	1 (7)	14	10 (71)
Peru	15 (75)	1 (5)	0	3 (15)	1 (5)	0	20	16 (80)
Hong Kong†	10 (66)	2 (13)	0	1 (7)	0	2 (13)	15	12 (80)
Ivanovo Oblast‡	5 (31)	4 (25)	2 (12)	3 (19)	2 (13)	0	16	9 (56)
Dominican Republic	8 (27)	14 (47)	0	4 (13)	3 (10)	1 (3)	30	22 (73)
Italy	10 (50)	5 (25)	0	0	4 (20)	1 (5)	20	15 (75)
Total	58 (50)	26 (23)	2 (2)	13 (11)	11 (9)	5 (4)	115	84 (73)

Influence of **MDR** in the Cure of **Untreated** Cases

Espinal et al. JAMA 2000; 283: 2537-45



Rates of **MDR-TB** among **Contacts** of MDR-TB patients

<i>Study</i>	<i>Country</i>	<i>Number of contacts</i>	<i>Percentage of patients with MDR-TB (# of TB case/total # with active TB)</i>
<i>Kritski et al. (1996)</i>	<i>Brazil</i>	218	<u>62%</u> (8/13)
<i>Schaaf et al. (2000)</i>	<i>South Africa</i>	149	<u>83%</u> (5/6)
<i>Texeira et al. (2001)</i>	<i>Brazil</i>	133	<u>83%</u> (5/6)
<i>Schaaf et al. (2002)</i>	<i>South Africa</i>	119	<u>75%</u> (3/4)
<i>Bayona et al (2003)</i>	<i>Peru</i>	945	<u>84%</u> (35/42)



Approach to the Ideal **Regime** in the Initial MDR-TB

1. Do not Modify the Category I

- Only justified when is too long the delay in the DST result (3-4 m.) and the clinical and bacteriological response is good

2. Individualized SLD Regime based in the pattern of Resistance of the Index Case and DST → Usually Best Option

2. MDR-TB Cases only Receiving **FLD** in the past

Others

Failure Category I ?

Failures Category II

INCIDENT MDR, in good NTP

Standardised SLD regimen*

* Every Country should adapt concerning History of Drugs used in the past and Availability
- Add FLD if DST shows susceptibility

(#) Until Sm / Cult (-) /// (&) Until 18 M if Sm- before 6 M. // 24 M if Sm- after 6 M

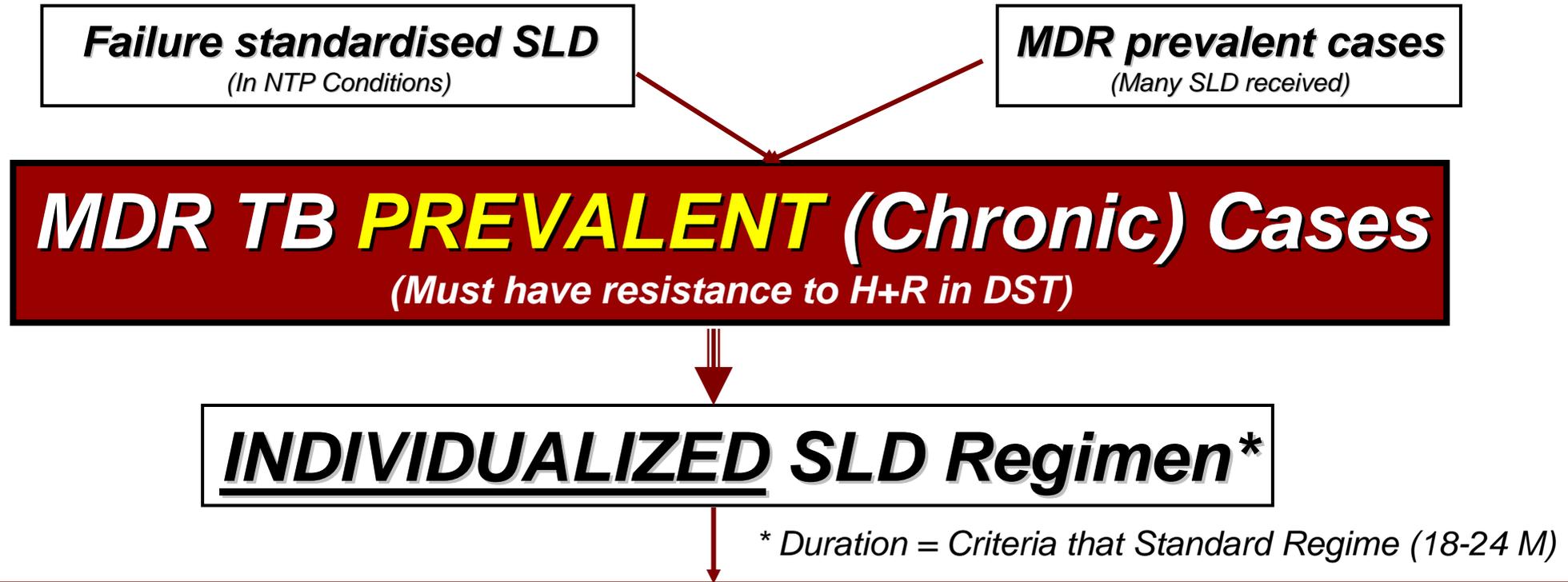
(E) Could be used in the Failures to Cat. I, not in the Failure to Cat II

advised



(#) Kn-Z-Of-Et-Cs(E) / (&) Of-Et-CS(E)

3. MDR-TB Cases Receiving **FLD** and **SLD** in the past



- At least **4 new drugs** (or with unlikely Res) are necessary, and always 1 inject. in first phase.
- Based on the drug **history** (patient and country) and, if possible, DST to Quin.+ Kn
- If not possible 4 new drugs ---> Maybe more drugs used previously
- **WARNING**: More drugs ---> More side effects and more expensive
- Use the sequence: **Z,E,S,Kn,Ak,Cp,Of,Eth,Cs,PAS,Th,Cf**



MDR-TB Cases *Classification*

Approach to the *Ideal Regime*

1. *Initial MDR-TB*

Based in the same Pattern of Resistance of *Index Case*

2. *MDR-TB Cases only receiving *FLD**

Standardized SLD Regime

3. *MDR-TB Cases receiving *FLD* and *SLD**

Individualized SLD Regime

Principles of MDR-TB regimen design

Many Controversial Issues to Address

1. How to approach ***Diagnosis*** of MDR?. Reliability of DST
2. How ***Many Drugs*** to Treat MDR-TB ?
3. ***Rational*** Use of the FLD and SLD
4. Length of the ***Injectable*** (Intensive phase).
5. Roll of the ***Surgery*** in the Treatment of MDR-TB
6. Approach to the Ideal Regime in MDR-TB.
Standardized vs Individualized Regimes

Addressing these Controversial Issues we have *reasoned***
the Most Important ***Principles*** of the MDR-TB Regime Design**

***All the NTP should develop
a Network to Treat all the
Patients in Different Levels***

***Including a **Network** to Treat
the patients with Suspected or
Confirmed **MDR*****

