24 Mars1882 : annonce de la découverte du bacille de la tuberculose

Tuberculose multi-résistante (MDR-TB)

Vincent Jarlier
Hôpital Pitié-Salpêtrière
Paris, France

CNR mycobactéries Et résistance aux antituberculeux

Definitions

MDR-TB definition (WHO)

2 major antituberculous drugs :

Isoniazid (INH)

Rifampicine (RIF)

MDR =

resistance to INH and RIF

Definition XDR-TB (revised) October 2006

XDR = resistance to :

INH and RIF (MDR-TB)

and

amikacin, kanamycin or capreomycin

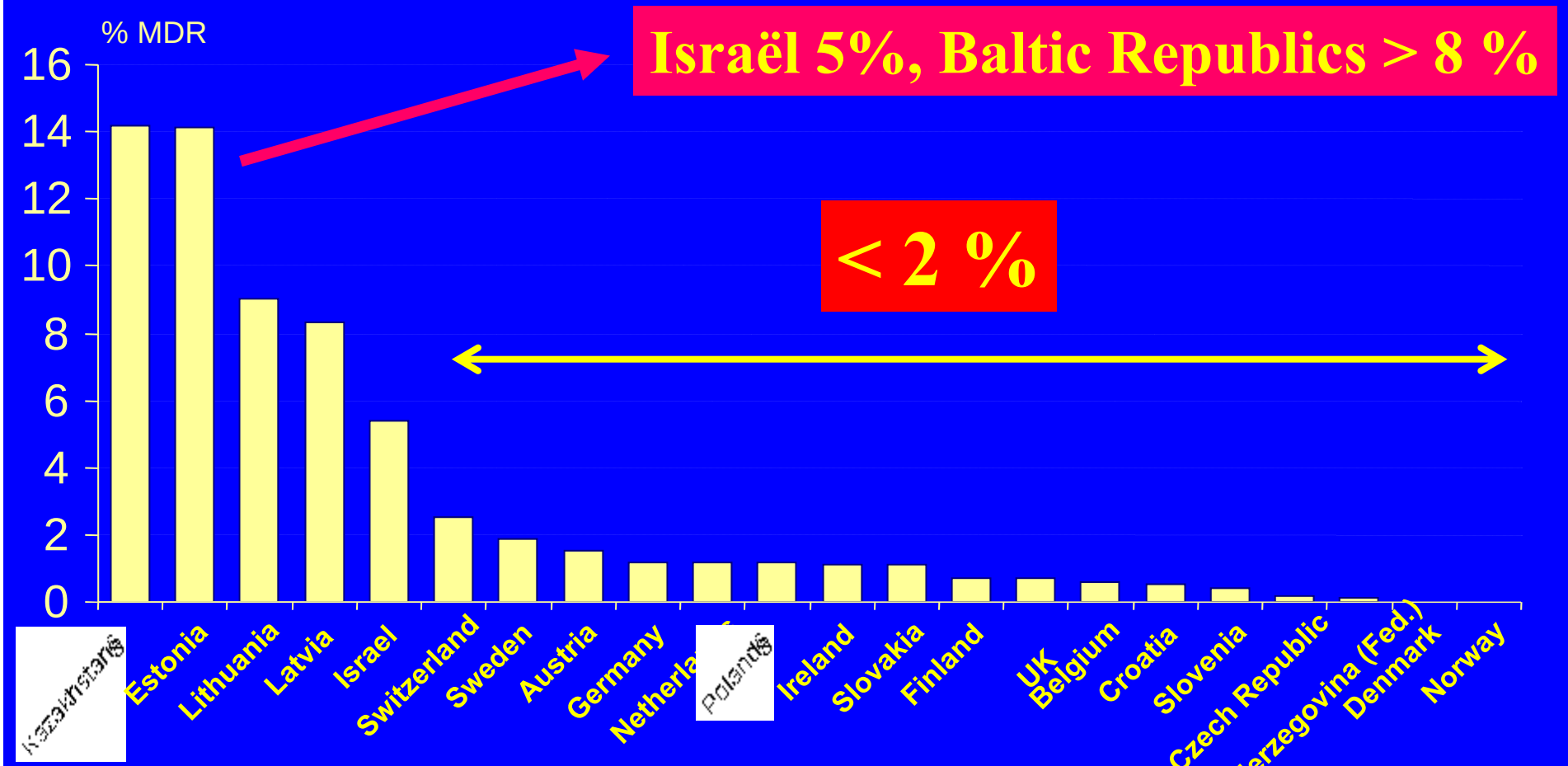
(aminoglycosides other than streptomycin)

and

fluroquinolones

MDR et XDR dans le monde

% MDR in new TB cases in Europe
EuroTB 2003



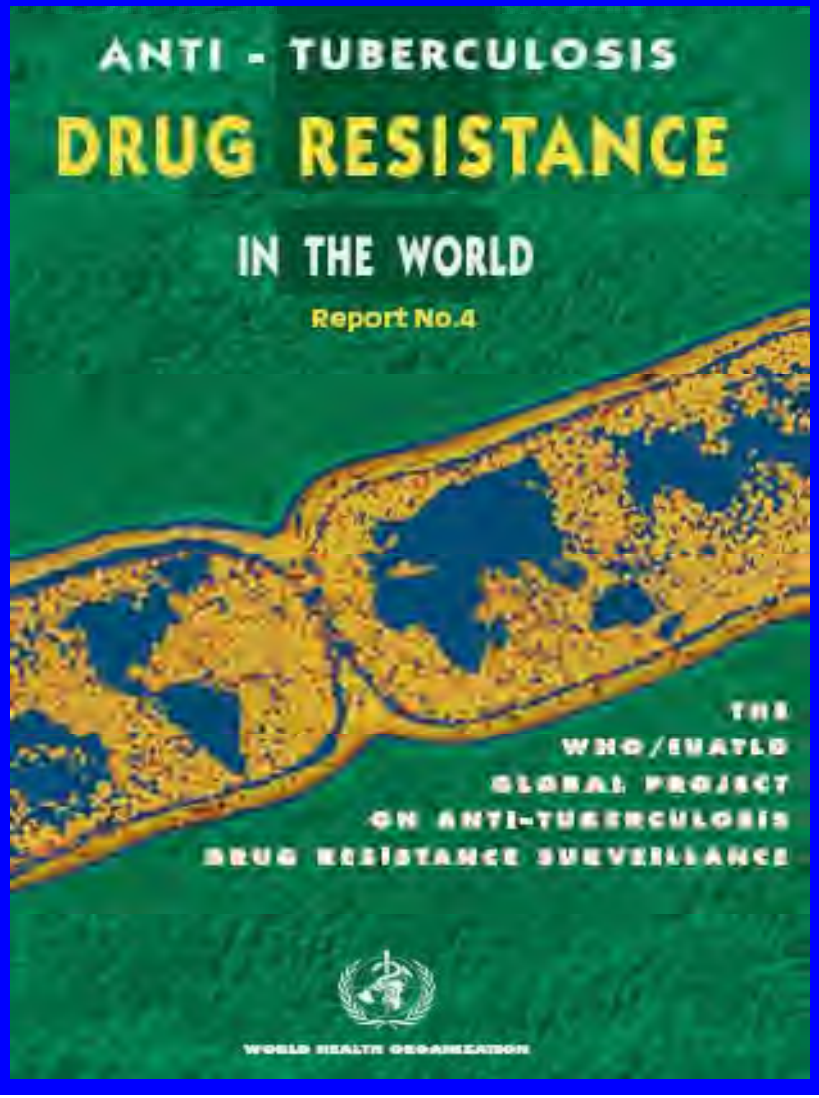
MDR-TB in the world
WHO 3rd report 2004

- **Estimation : 424 000 cases/year**
- **(~ 4% of ~ 10 millions cases)**
- **Primary : 243 000 (3% of new cases)**
- **Secondary : 181 000 (19% of prev. treated cases)**
- **China, India, Russia** : 261 000 (= **62% of total MDR cases**)
- **> 10% MDR** : Estonia (17%), Georgia (16%), Azerbaïdjan (15%), Moldavia (15%), Kazakhstan (14%), Ouzbekistan (13%)

TB drug resistance in the world
WHO 4th report 2008

- 138 countries/regions
- data on drug susceptibility tests for **91,577 patients** in 81 countries, years **2002-06**

n.b. previous reports 1997, 2000, 2004



MDR TB
key findings 4th report 2008 (**global**)

- Estimated MDR cases in 2006 :

489 139

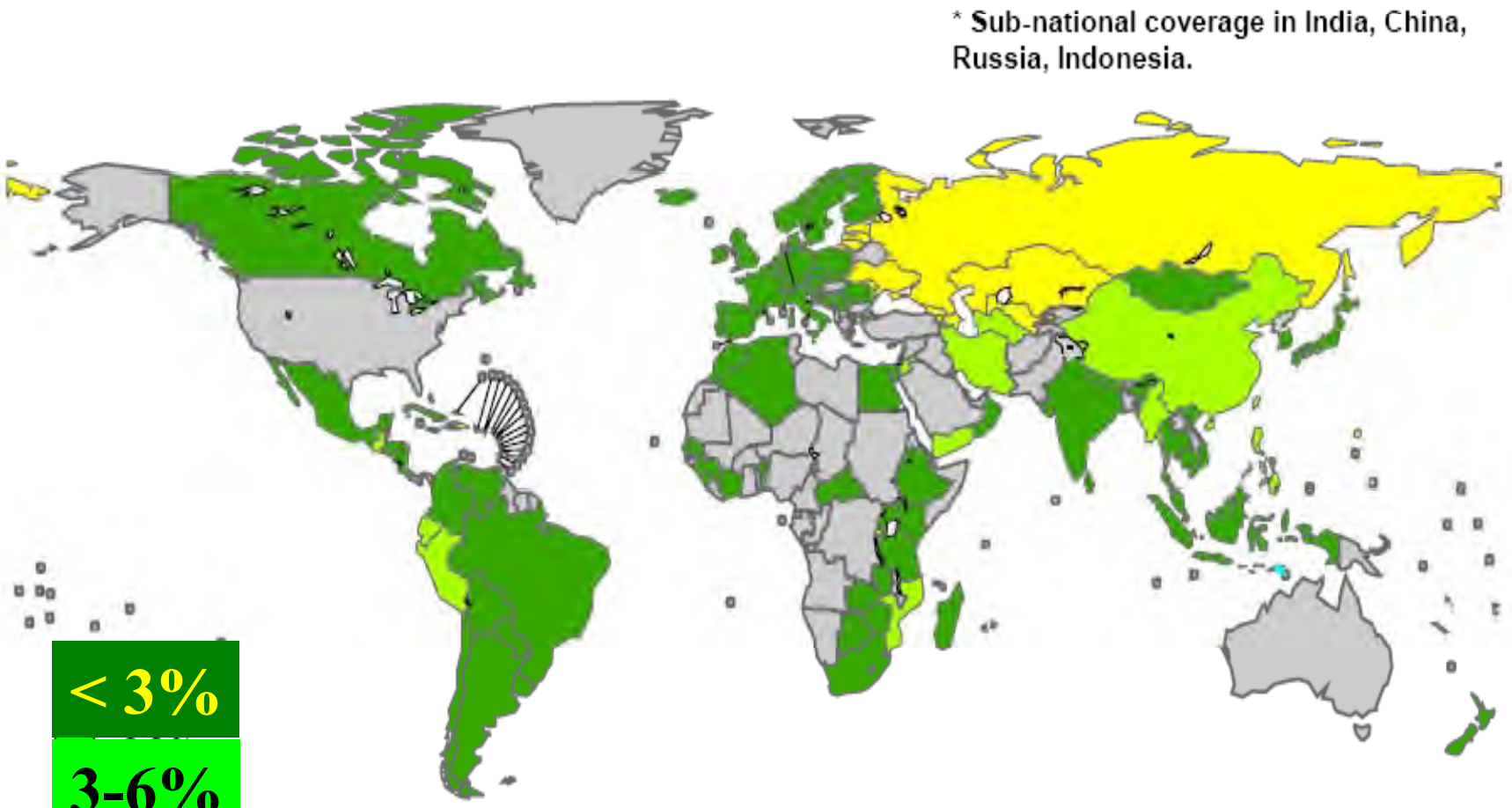
(95% CLs, 455,093 to 614,215)

- Global proportion of MDR among all cases :

4.8 %

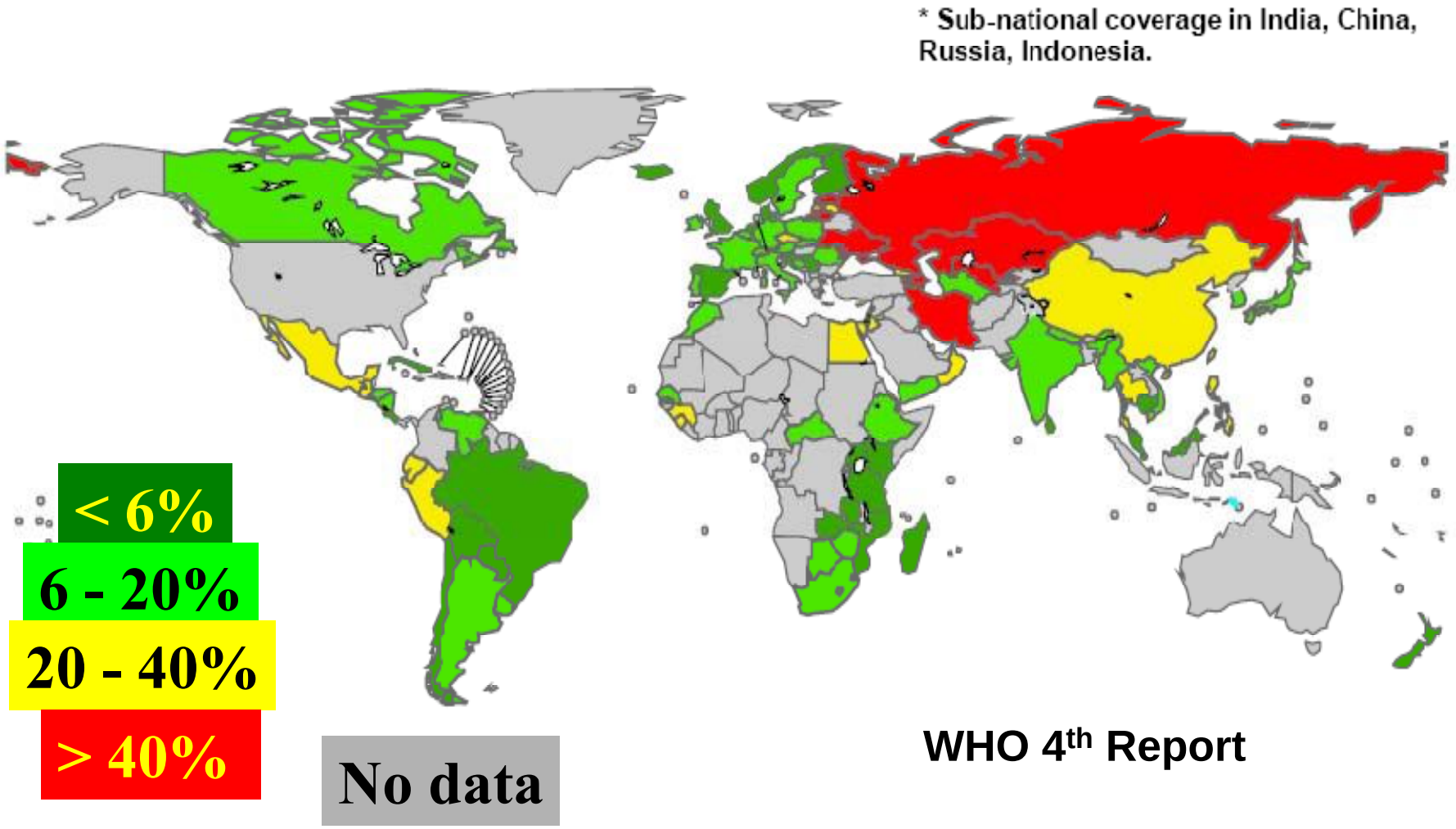
(95% CLs, 4.6 to 6.0)

MDR-TB **in new cases** 1994-2007 (in %)



WHO 4th Report 2008

MDR-TB in previously treated cases 1994-2007 (in %)



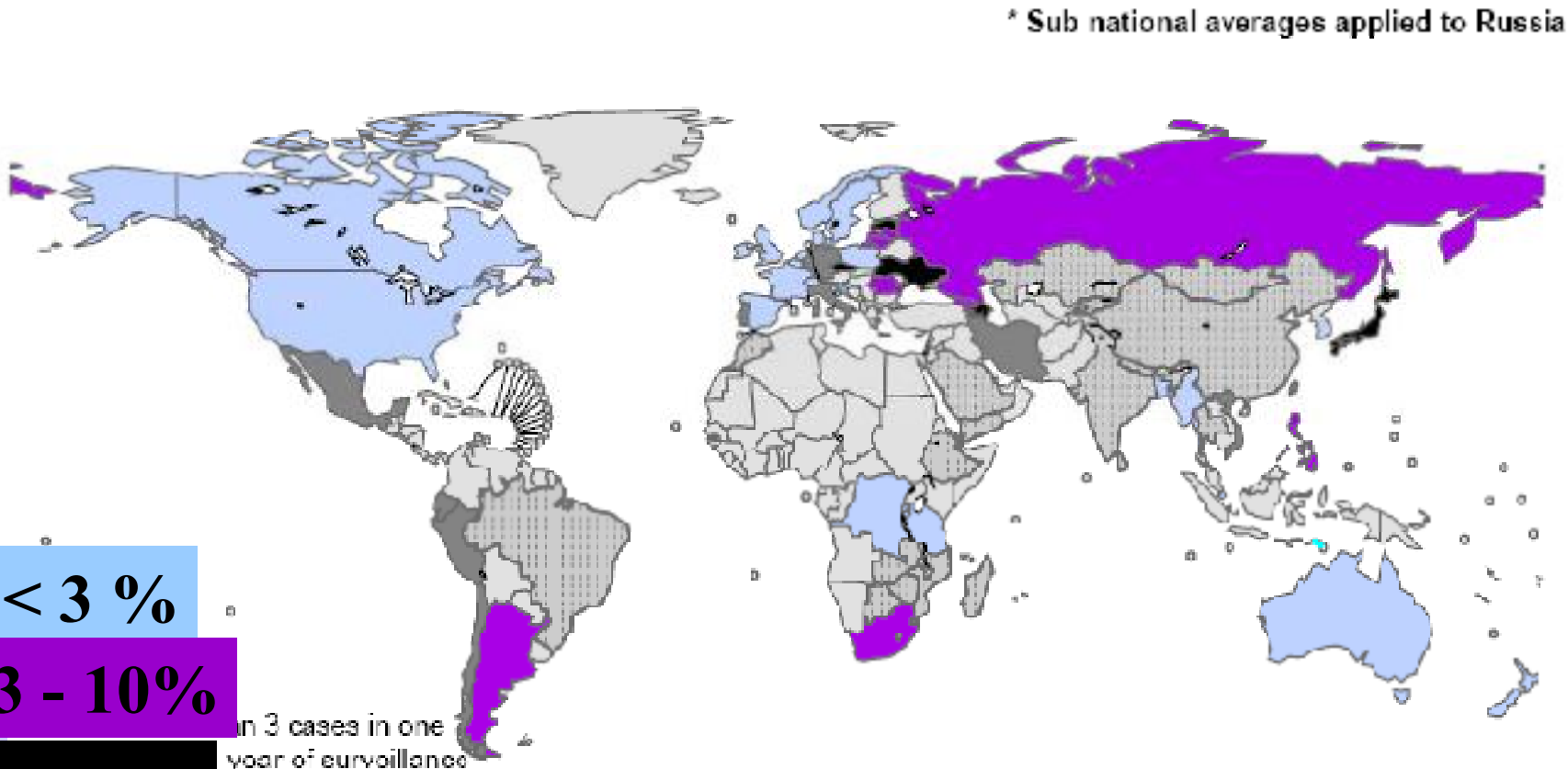
XDR-TB : key findings 4th report 2008

- Representative data for 39 countries or regions (24 in Europe)
- >> data for ~ 5.000 MDR TB cases 2002-07

% XDR TB among MDR TB :

- **0 - 1% in 14/39** (e.g. Canada, UK, France, Denmark)
- **2 - 10% in 15/39** (e.g. USA, Australia, Netherlands Sweden, Latvia, Romania, Moldova, Armenia, Georgia)
- **> 10% in 10/39** (33% Ireland, 33% Slovenia, 31 % Japan, 24% Estonia, 20% Czech, 15% H.Kong, 15% Ukraine, 14% Lithuania, 13% Azerbaijan)

XDR-TB (revised definition) in % of MDR cases (late 2000s)



WHO 4th Report 2008

XDR-TB : key findings 4th report 2008

- Representative data for 39 countries or regions (24 in Europe) for ~ 5.000 MDR TB cases 2002-07

Only 4 countries with 10-20 cases/year :

Japan, **Estonia**, **Latvia**, **Azerbaijan**

- Non representative data for **South Africa** 2004-07

200 cases / year

South Africa XDR-TB 2006

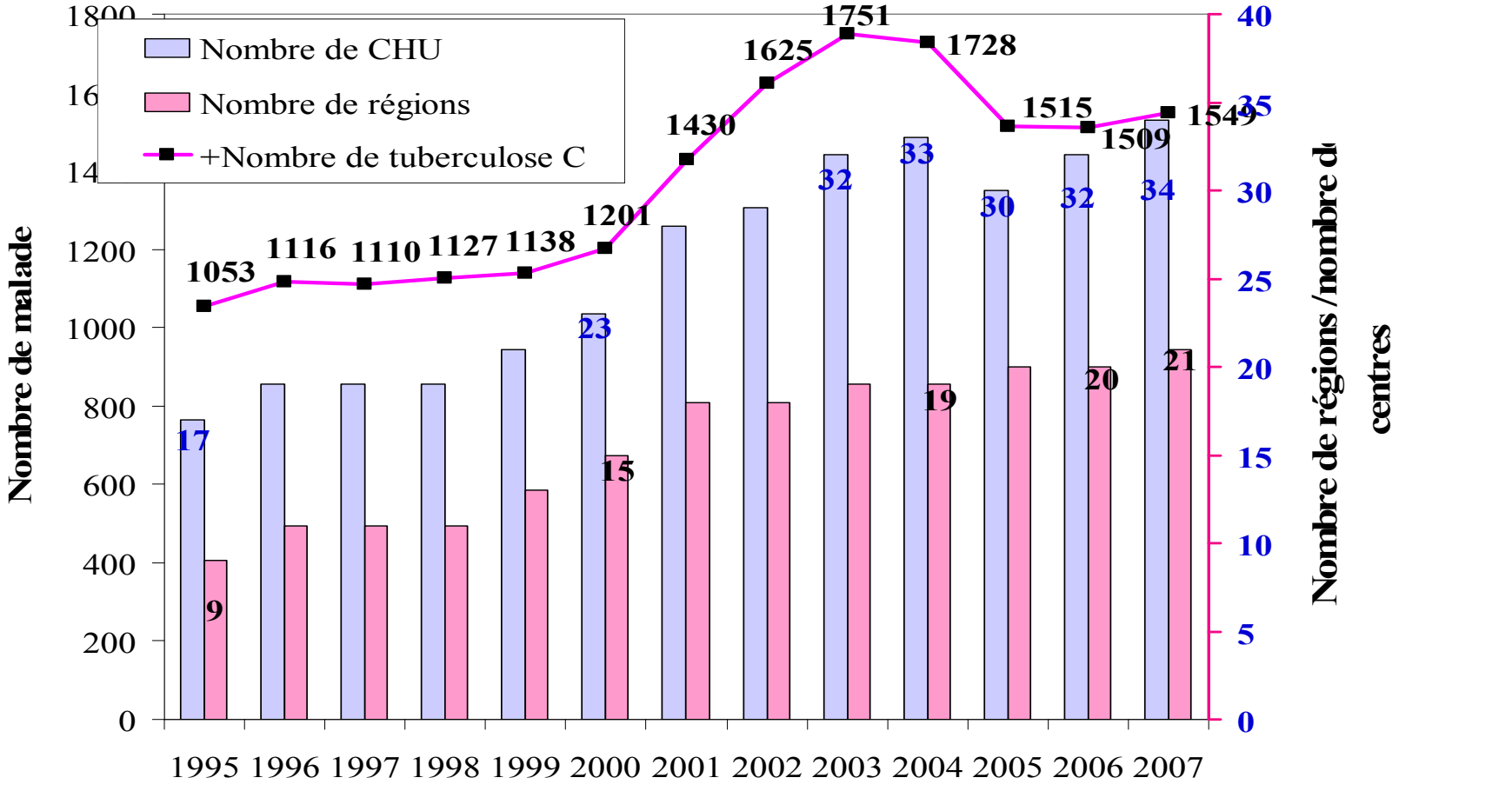
- Majority : no previous treatment
- Suggests newly infected with XDR
- 26 of 30 (87%) XDR isolates = **genetically similar**
- Nosocomial transmission in hospitals likely
- Transmission in community possible for 36% of the patients who had no prior hospitalizations
- 52 of 53 patients died
- All patients tested for HIV (n=44) : HIV +

Gandhi Lancet 2006

Résistance, MDR et XDR en France

Résistance en France : réseau AZAY mycobactéries (représentativité)

Réseau Azay-mycobactéries : évolution de la couverture 1992-2007



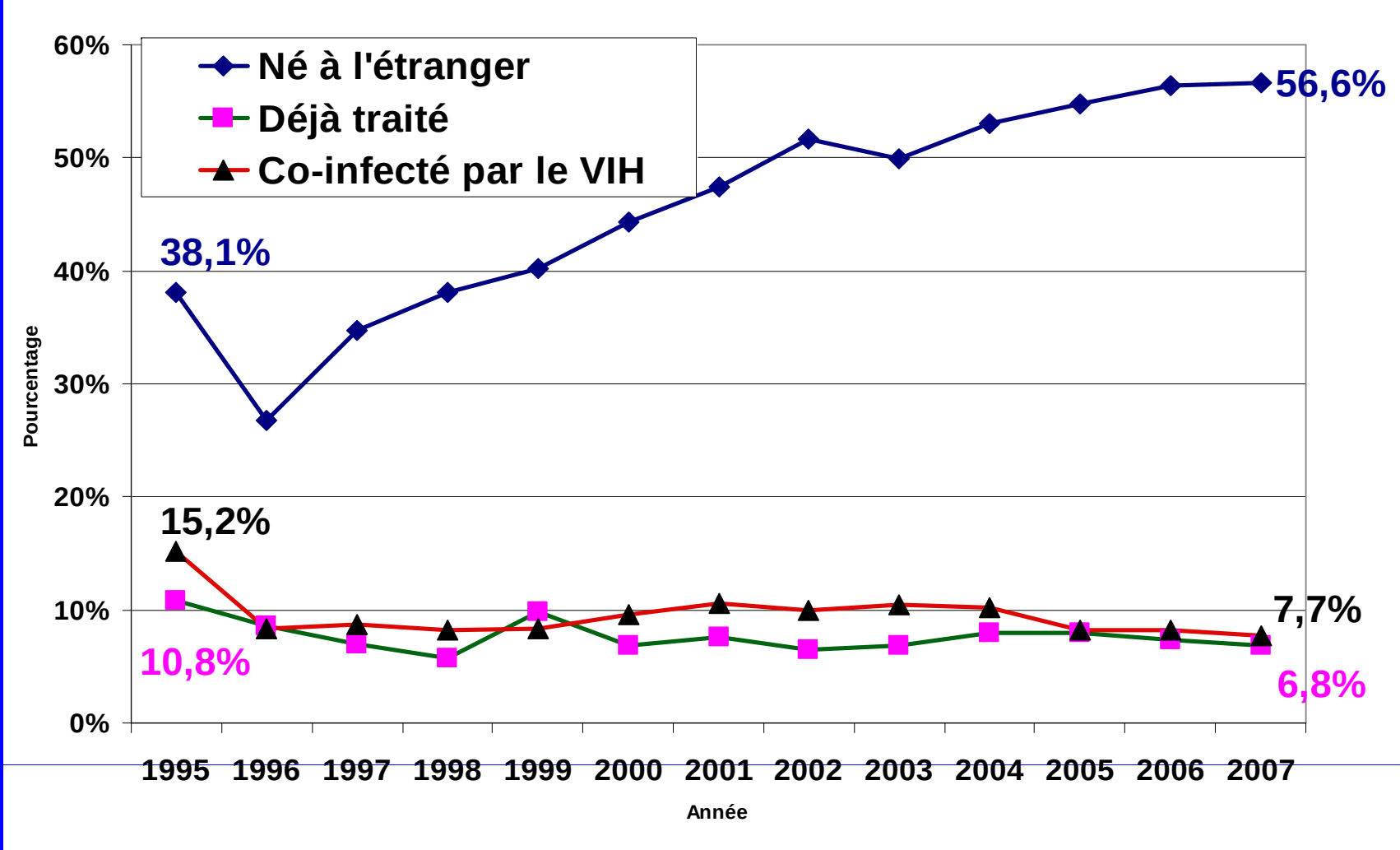
17 CHU
9 régions

1000 cas

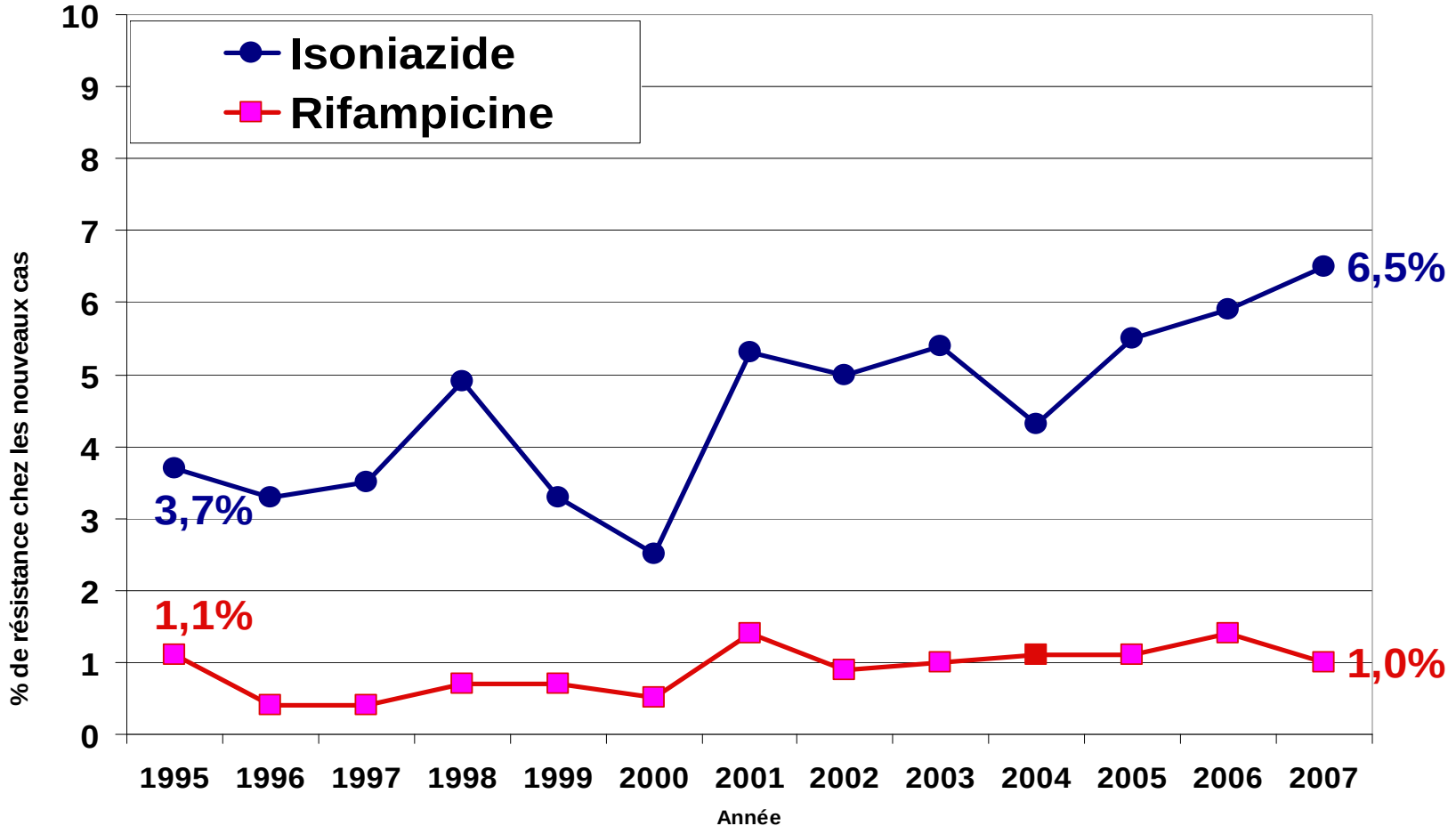
34 CHU
21 régions

1500 cas

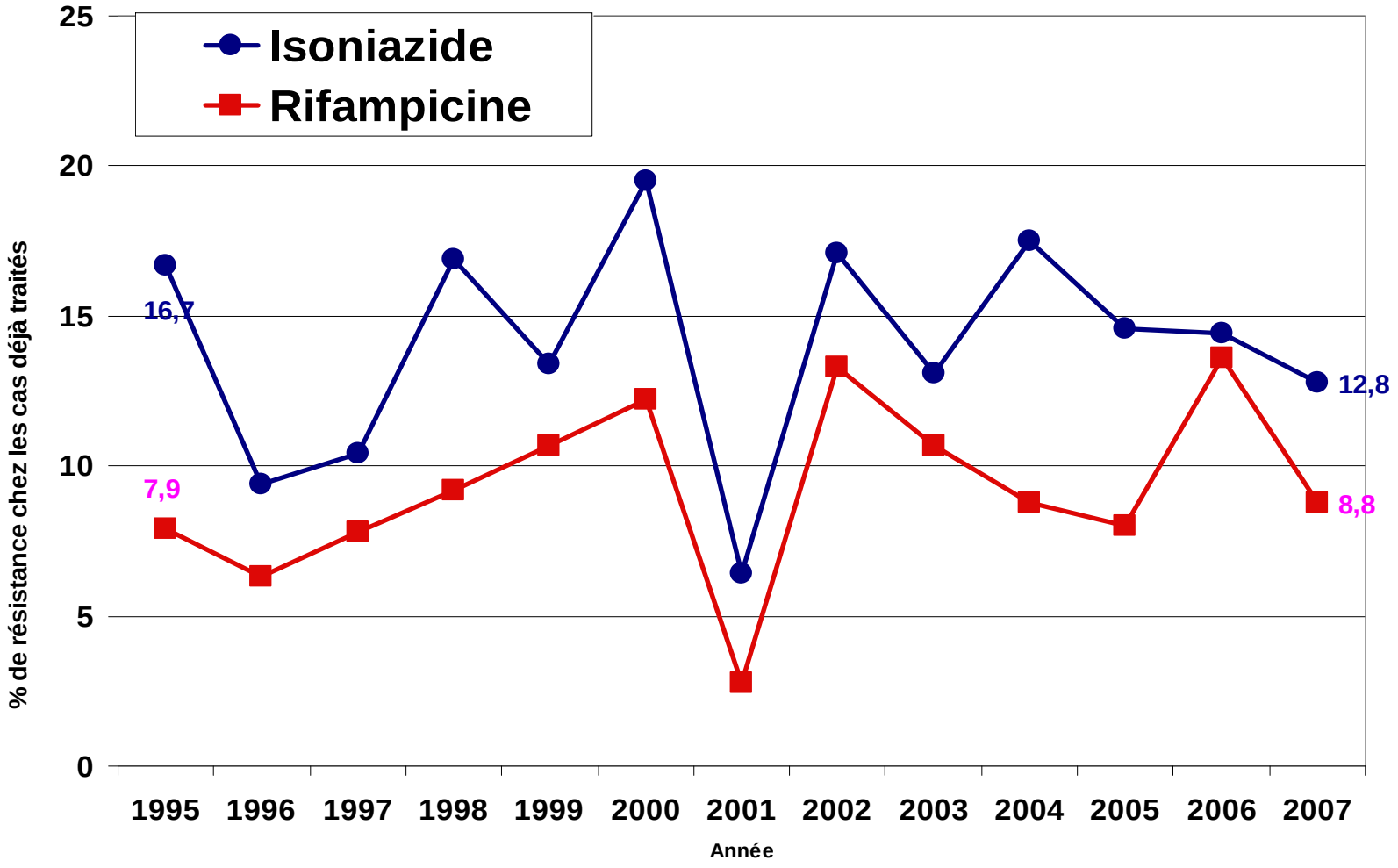
Caractéristiques des tuberculoses culture + AZAY mycobactéries 1995-2007



Résistance 1aire tuberculose AZAY mycobactéries 1995-2007

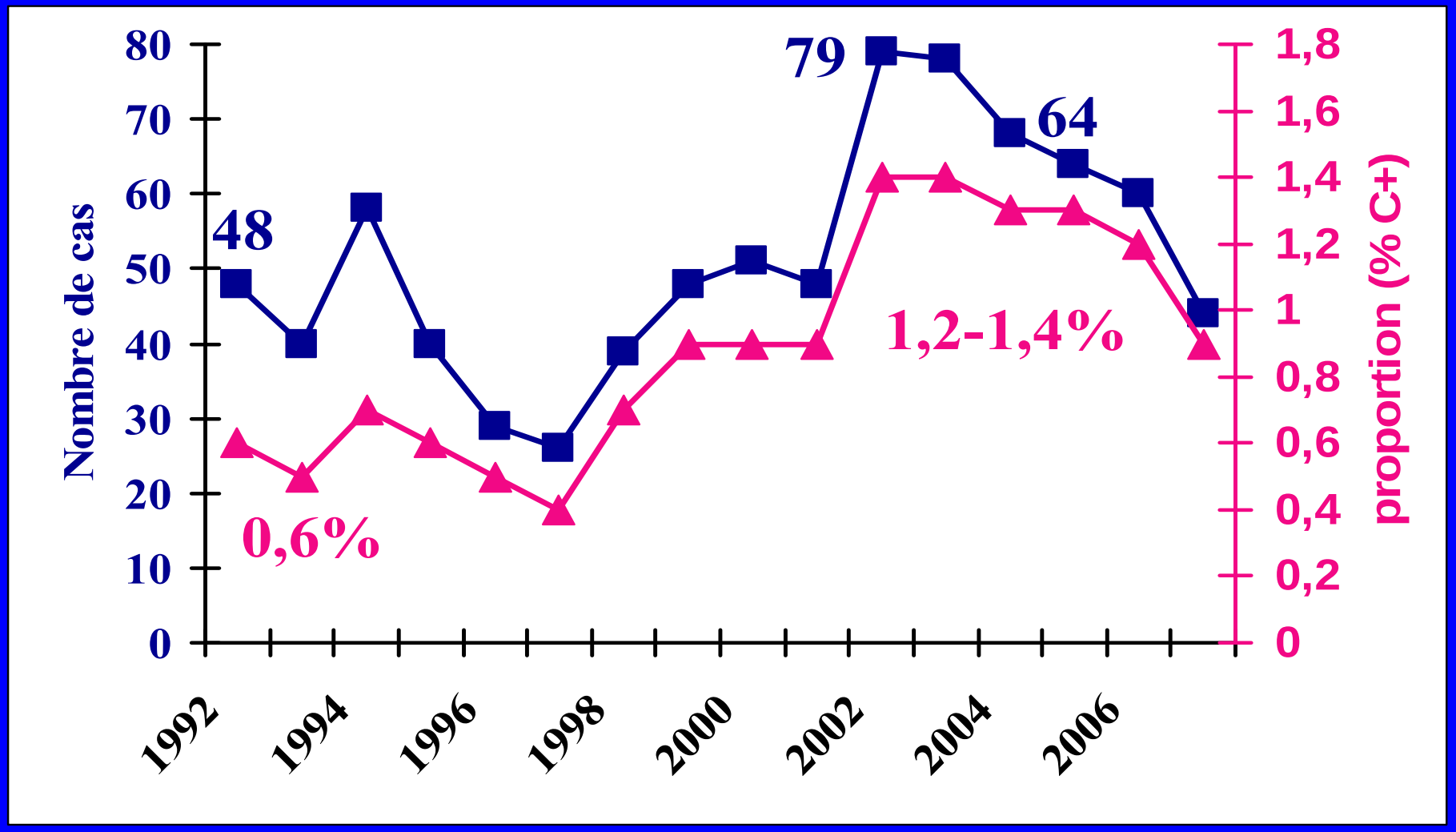


Résistance 2aire tuberculose AZAY mycobactéries 1995-2007



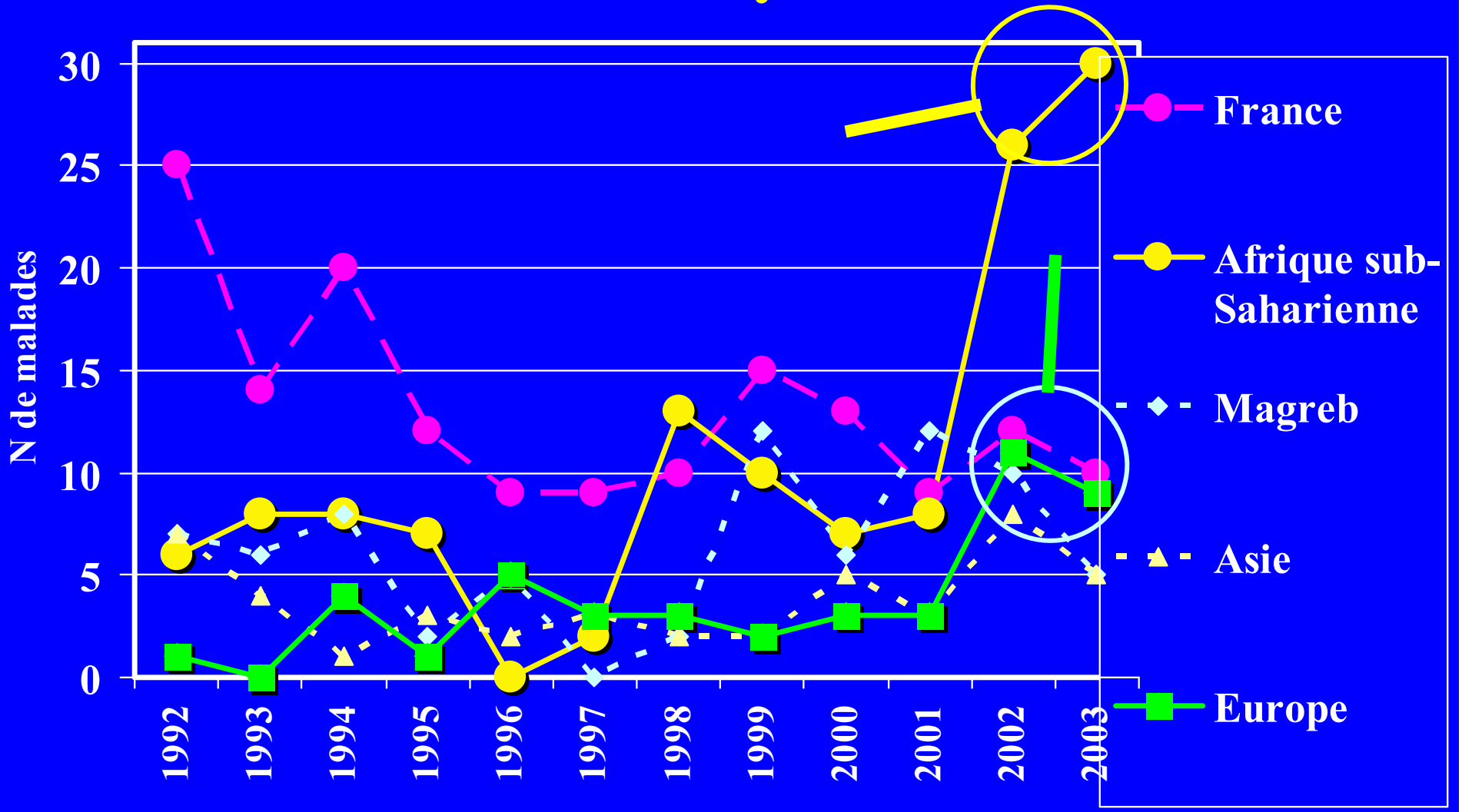
MDR et XDR en France : réseau du CNR (exhaustivité)

Multirésistance (INH-RMP) 1992-2007
Réseau CNR (~300 laboratoires)

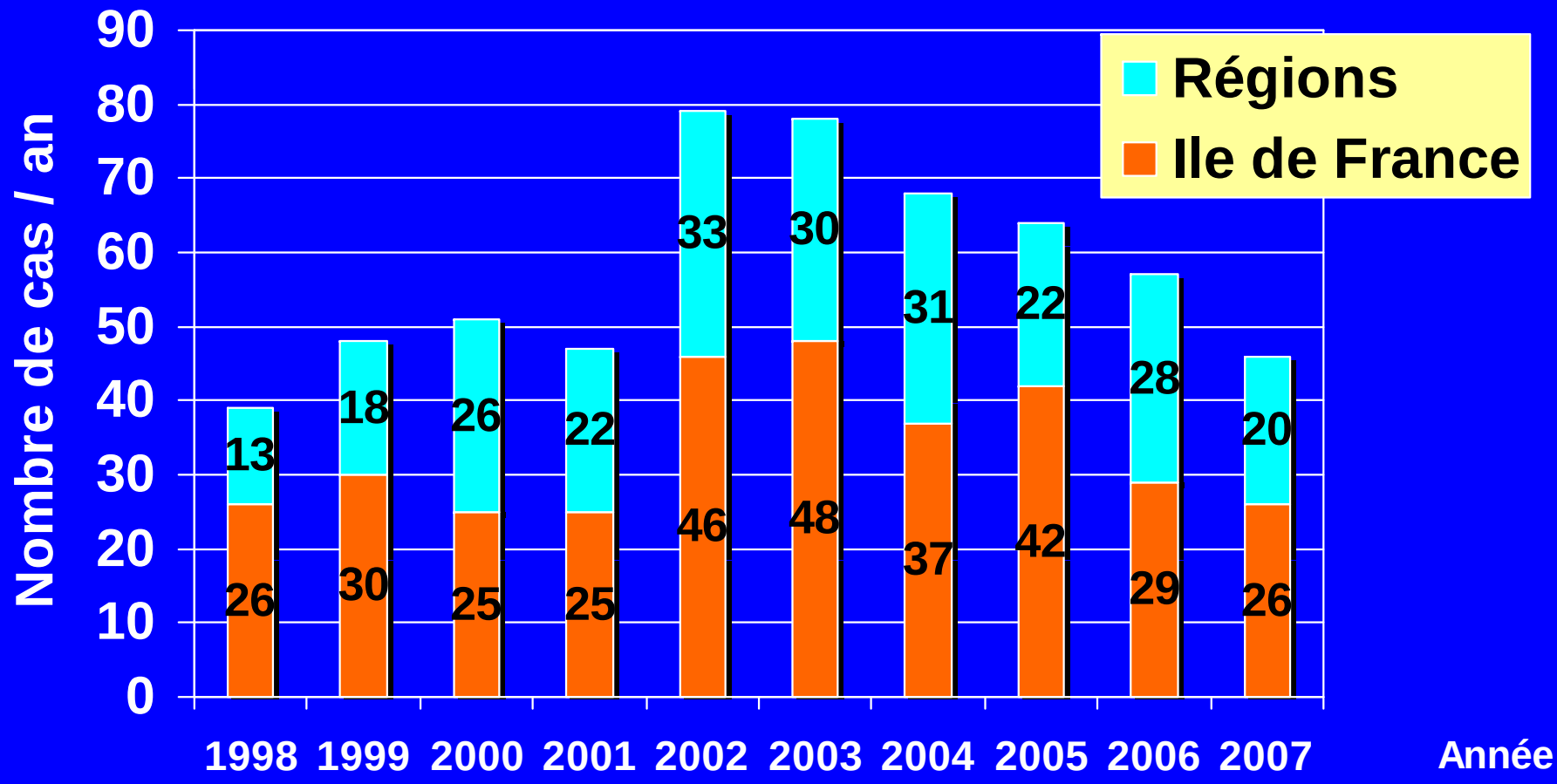


Robert, Eur Respir J 2003 ; rapport CNR 2008

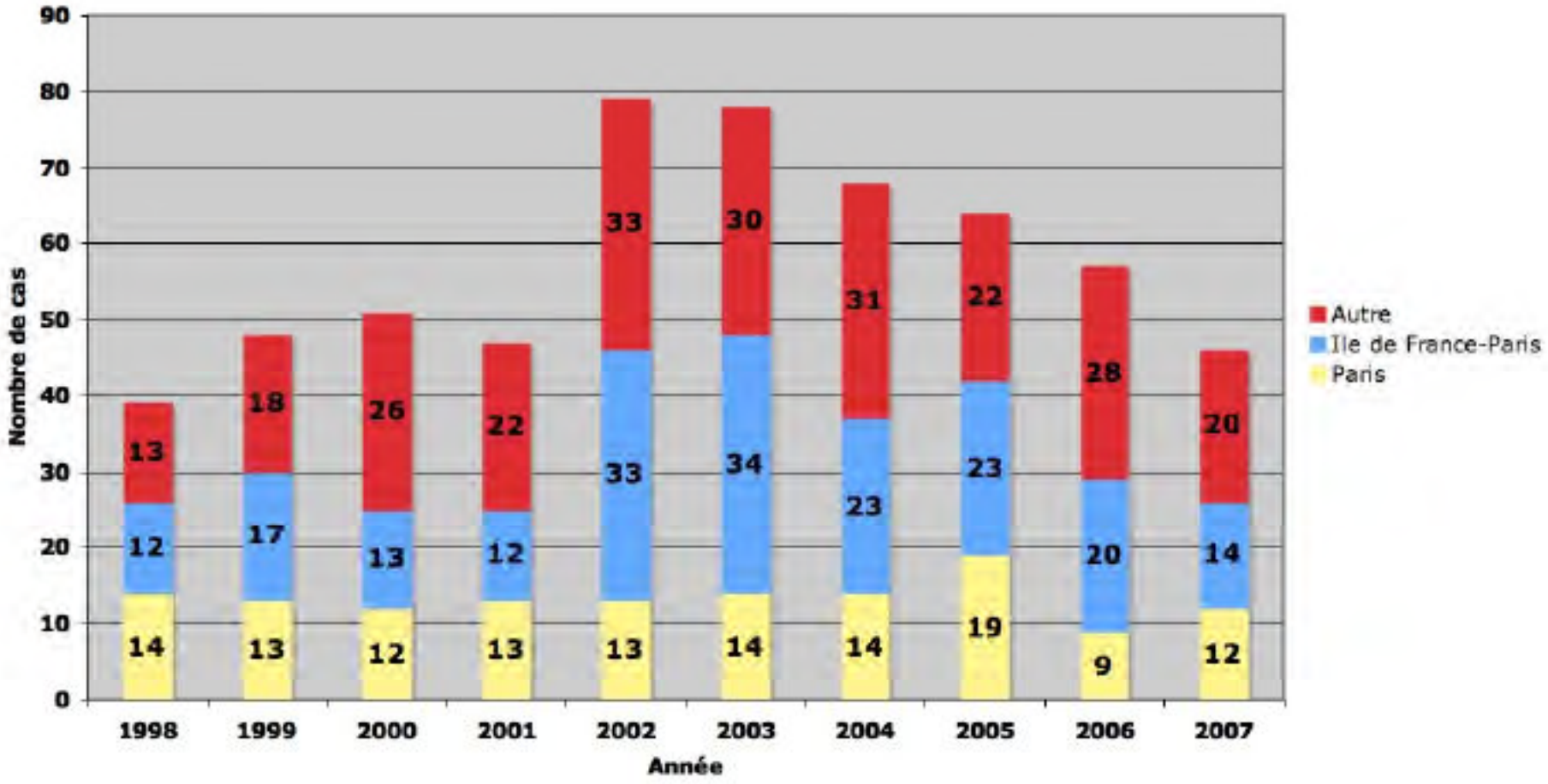
Tuberculose à bacilles multirésistants 1992 - 2003
Pays de naissance des cas
Réseau CNR Mycobactéries



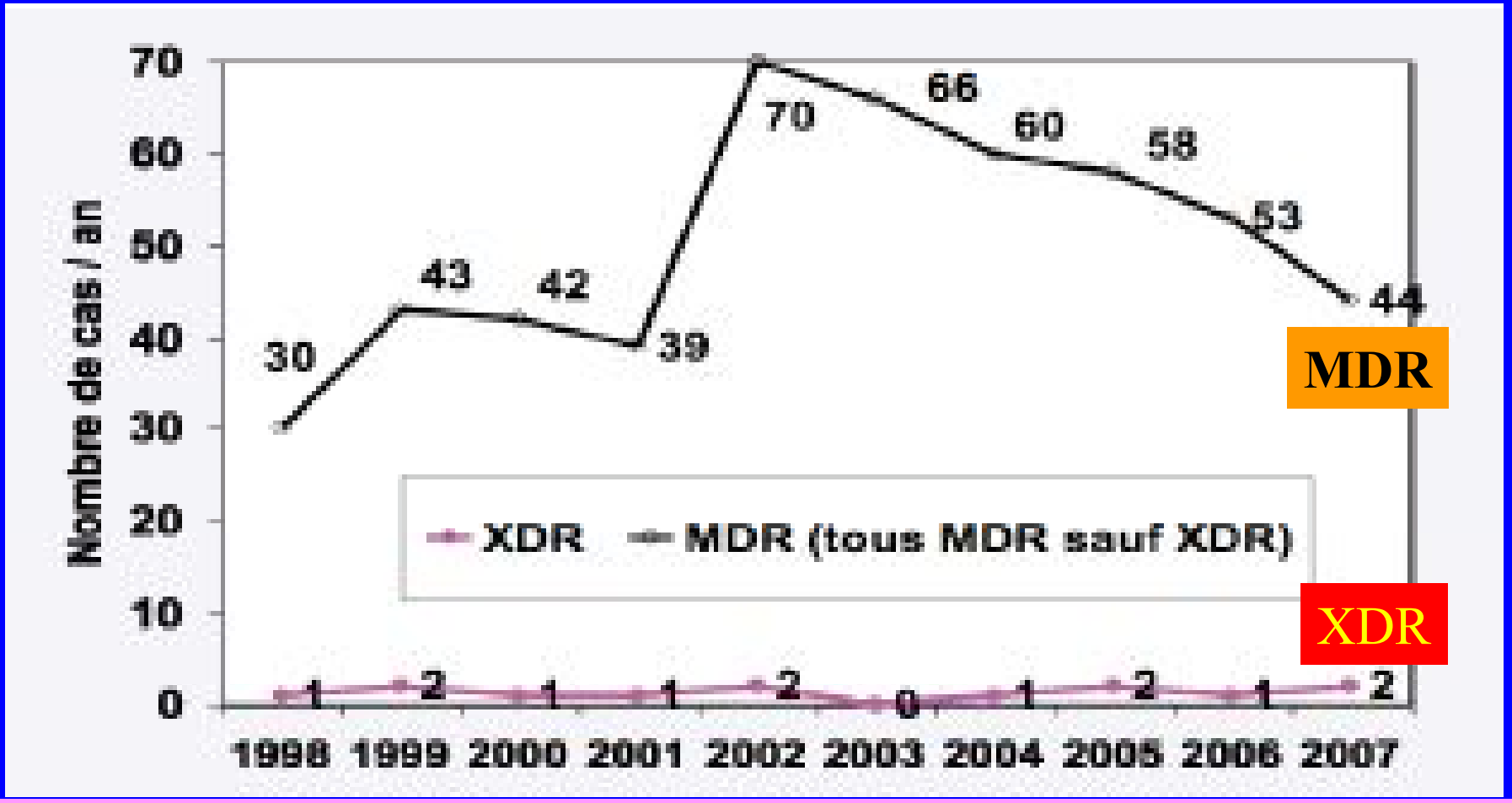
Distribution Ile de France/régions tuberculose multirésistante 1998-2007



Distribution Paris/reste Ile de France/régions tuberculose multirésistante 1998-2007



MDR-TB and XDR-TB in France
CNR mycobactéries 1998 - 2007



In 10 years :
517 MDR and 13 XDR (2,5% of MDR; 1 to 2 per year)

Evolution des caractéristiques des tuberculose MDR en France 1992-2005

	1992-99 (n=264)	2002-03 (n=137)	2004-05 (n=118)
< 24 ans	8	32	31
25-34 ans	30	39	38
35-44 ans	**25**	**18**	**13**
45-64 ans	**23** **62**	**16** **39**	**13** **27**
> 65 ans	**14**	**5**	**5**
Hommes	70	56	64
Né en France	**44**	**16**	**17**
VIH +	21	16	17
Formes pulm	85	89	91
Microscope +	59	64	56
R 2aire	**59**	**39**	**42**

Challenges of MDR TB

Optimize the treatment of MDR cases

Outcome of MDR cases background

Cure : 40 - 75 %

Failure : 10 - 30 %

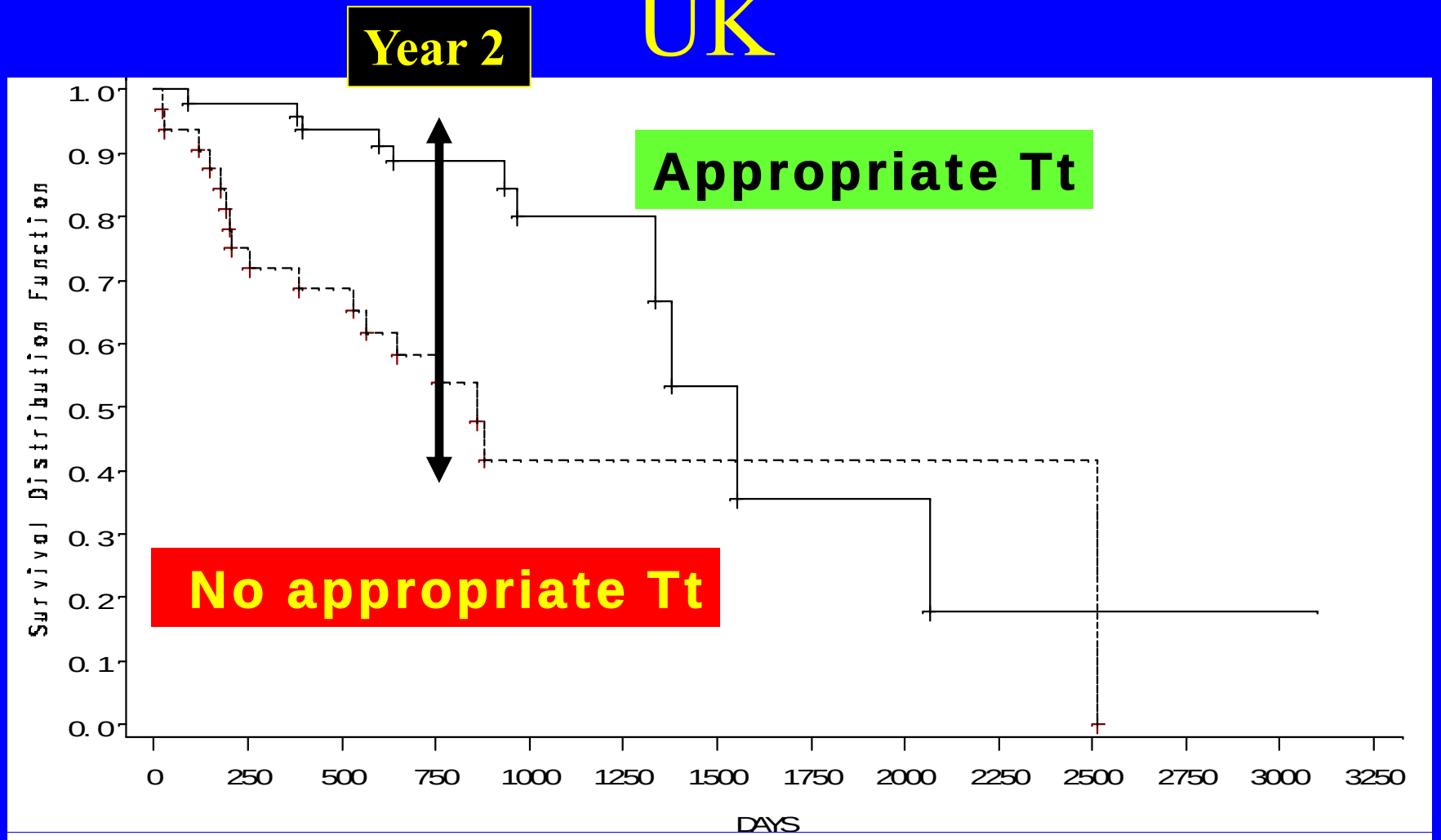
Death : 5 – 20 %

Death in HIV + : 80 %

Lost to follow-up : >= 10 %

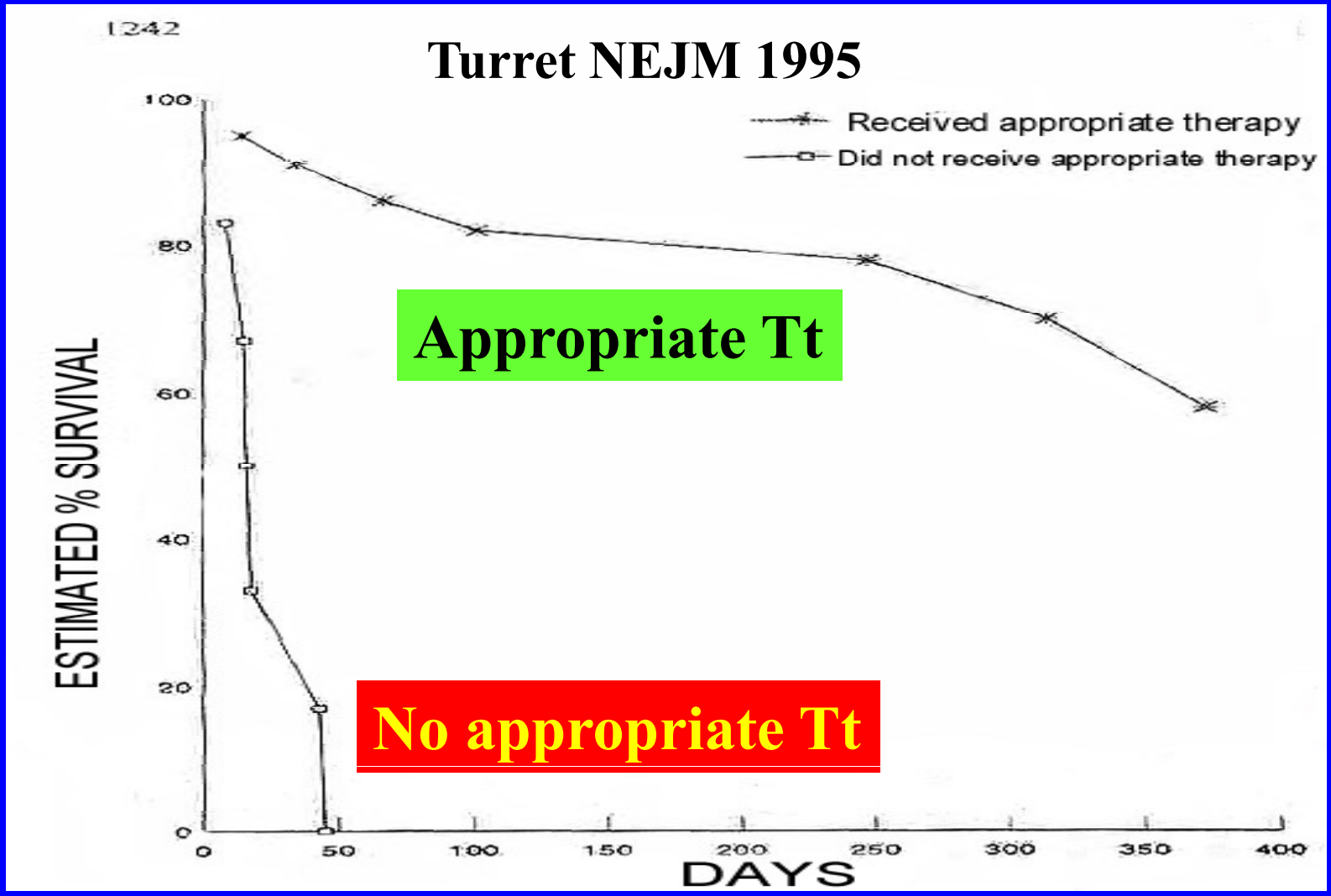
Suarez 2002, Tahaoglu 2001, Goble 1993, Frieden 1996, Chan 2004, Mitnick 2003

Survival of MD-RTB in the 1990s UK

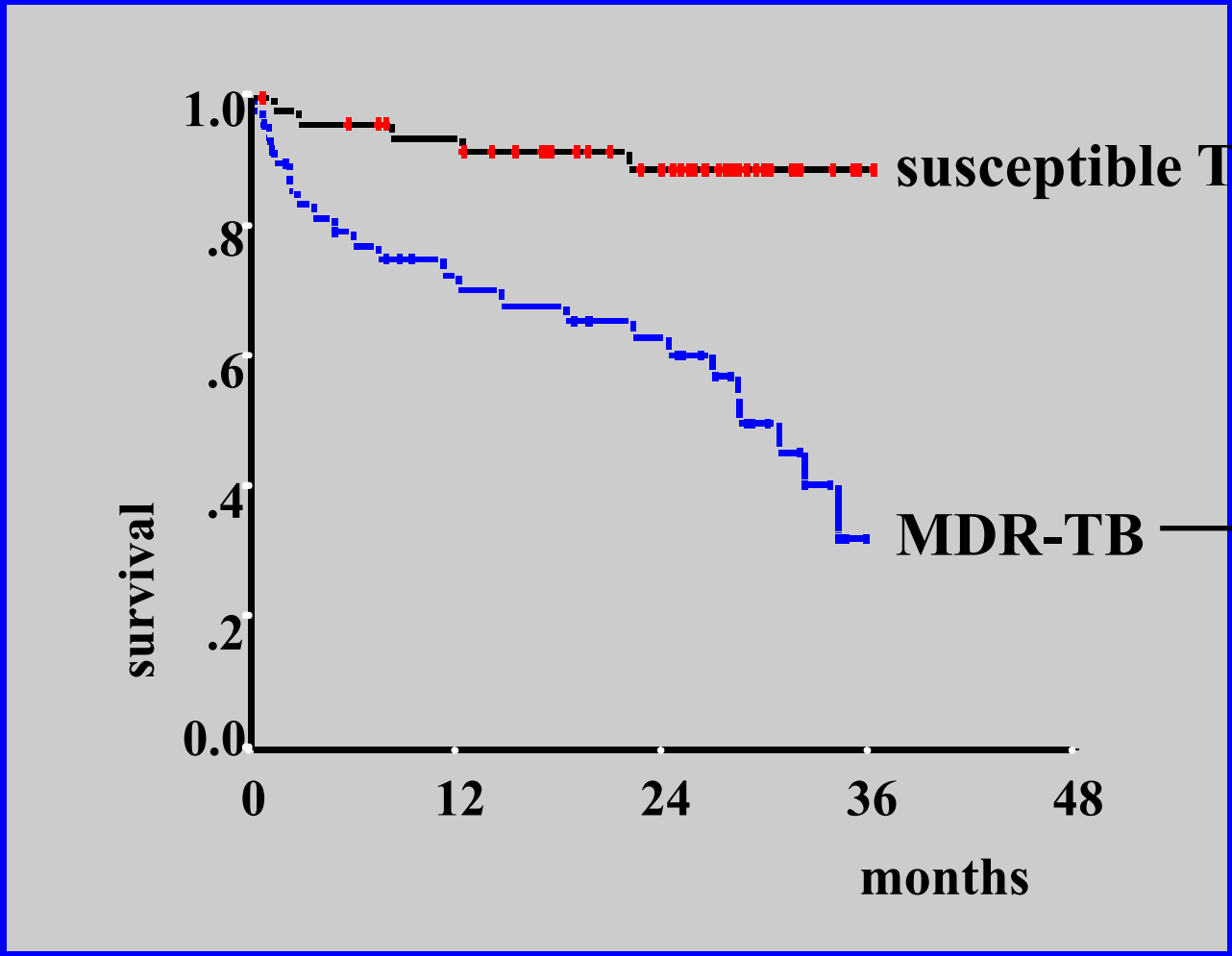


Drobniewski, Thorax 2002, 90 MDRTB patients

Survival of HIV-associated MDR-TB in the 1990s New York city, USA



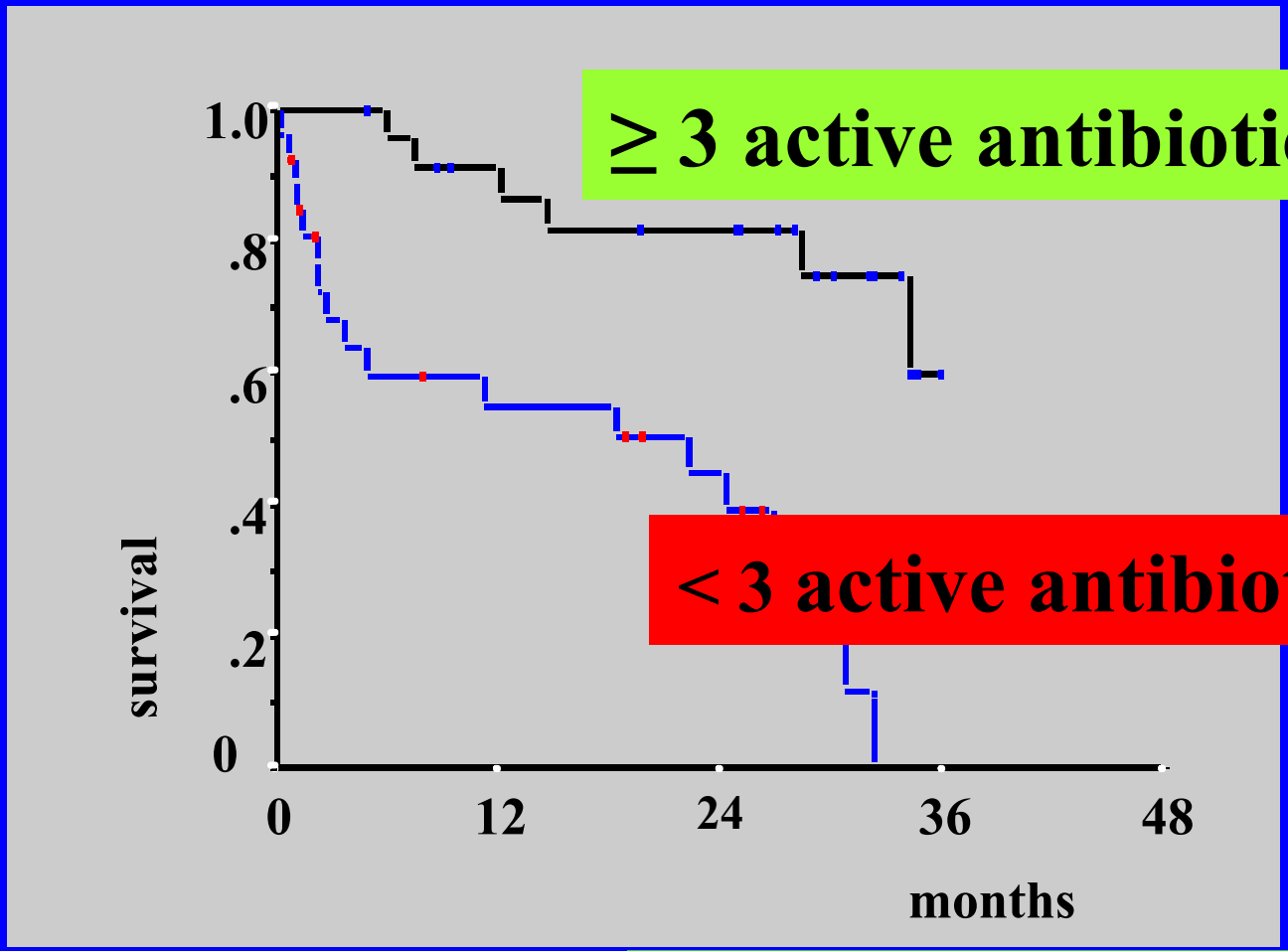
Outcome of MDR cases diagnosed in 1994 in France (n=51)



Deaths at 2 years 40 %

Flament-Saillour AJRCCM 1999

Outcome of MDR cases diagnosed in 1994 in France (n=51) depending on the number of active drugs used



Flament-Saillour AJRCCM 1999

Outcome of MDR-TB France

	1994 (n=51)*	1999 (n= 45)**	2006 (n= 53)***
No of tested drugs (including STR, EMB)	5	8	11
Treatment with > 3 active drugs	47%	84%	85%
Succes	41%	67%	evaluated in 2009

* Saillour Am Resp Crit Care Med 1999 : non specialized teams

** Uffredi Inter J Antibiot 2006 : specialized team (lab/physicians)

*** Veziris 2008 : specialized team (idem but systematic)

Appui aux cliniciens pour les 53 cas MDR 2006

- **45 cas :** traitement défini en collaboration entre CNR et clinicien en charge du malade
- **11 cas** : traitement défini par le « Groupe thérapeutique des infections à mycobactéries résistantes »
- **7 cas** : pris en charge à la Pitié-Salpêtrière

TB MDR 1992-2005 : cas chroniques

Année	N	% total	% chroniques	Cas déclarés pour la première fois en													
				92	93	94	95	96	97	95	99	00	01	02	03	04	05
1992	48	0.6	-	48													
1993	40	0.5	17	7	33												
1994	58	0.7	24	8	6	44											
1995	40	0.6	35	3	7	4	26										
1996	29	0.5	28	1		3	3	22									
1997	26	0.4	35	2	1	1		4	18								
1998	39	0.7	21	1		2	1	1	3	31							
1999	48	0.9	8	1			1			2	44						
2000	51	0.9	18	2			2			3	2	42					
2001	48	0.8	15								1	6	41				
2002	79	1.3	9		1				1			2	3	72			
2003	78	1.4	16										1	11	65		
2004	68	1.4	12											3	5	60	
2005	64	1.3	9				1						1			4	58

Management of MDR cases

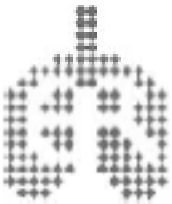
Speeding up identification
and susceptibility tests
(including directly on sputum)

Recommended standards for modern TB laboratory services

Laboratories should aim to identify TB and rifampicin resistance in over 90% of smear + cases **directly from smear + sputum** where resources are available for this…

… rapidly within 1-2 days

Eur Respir J 2006; 28: 1–7
DOI: 10.1183/09031936.06.00064906



Recommended standards for modern tuberculosis laboratory services in Europe

F.A. Drobniewski*, S. Hoffner#, S. Rusch-Gerdes¶, G. Skenders+, V. Thomsen§ and the. WHO European Laboratory Strengthening Task Force

Performances of genomic identification tests by classical PCR **in smear + sputum**

(meta-analysis by Sarmiento, JCM 2003)

- **Sensitivity** : **95-100 %**
- **Specificity** : **95-98%**
- **PPV** : very high (>99%) due to :
  - good specificity
  - **high prevalence of TB in smear + patients** (> 90%)

« Typing PCR »

(ATS 1997, AJRCCM 155:1804-14)

Identification of *M.tuberculosis* in smear + sputum by using marketed DNA amplification and strip assay

- **INNO-LIPA mycobacteria (Innogenetics) :**

  spacer 16s-23s : 16 species (including Mtb complex)

- **Genotype mycobacterium (Hain Lifescience) :**

  23s gene : 13 species (including Mtb complex)

- **Genotype MTBC (Hain Lifescience)** :

  23s, RD1, *gyrB* : species within Mtb complex

Resistance detection in *M.tuberculosis*

- **Rifampicin (surrogate for MDR)**
- (Isoniazid)

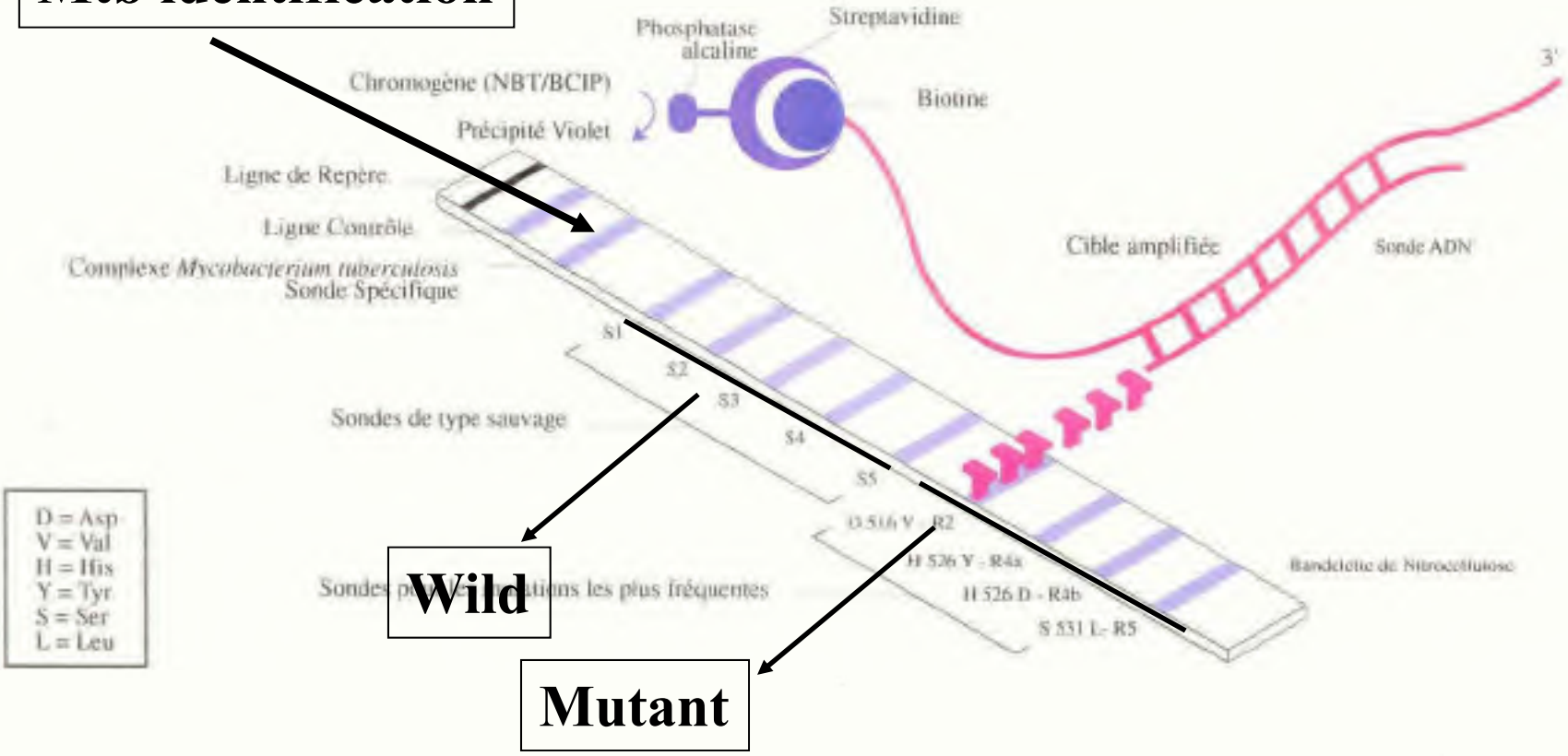
Genomic resistance detection in *M. tuberculosis* directly in Smear positive specimens

- DNA source : smear + specimen
- Sometimes requires additional specimen
- May require double PCR (nested)
- Technologies : hybridation strips, chips, others…

INNO-LiPA - Rif-TB

Sondes pour les mutations les plus fréquentes

Mtb identification



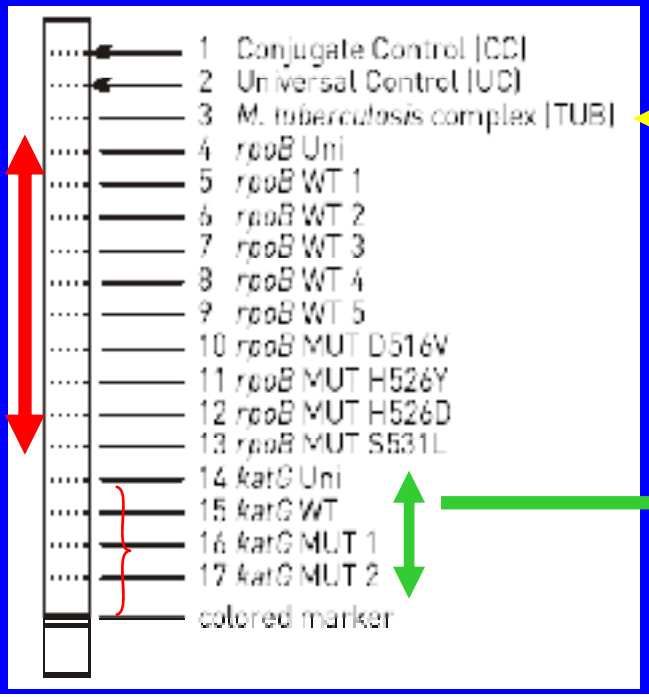
Performances of InnoLiPA RIF. TB® (Innogenetics)

95-100 % of detection

in RIF-R strains

Rossau 1997, Cooksey 1997, Marttila 1898, Matsiota 1998, Watterson 1998, Gamboa 1998, Kiepela 1998, Sintchenko 1998, Gonzalez 1999, Hirano 1999, Traore 2000……..

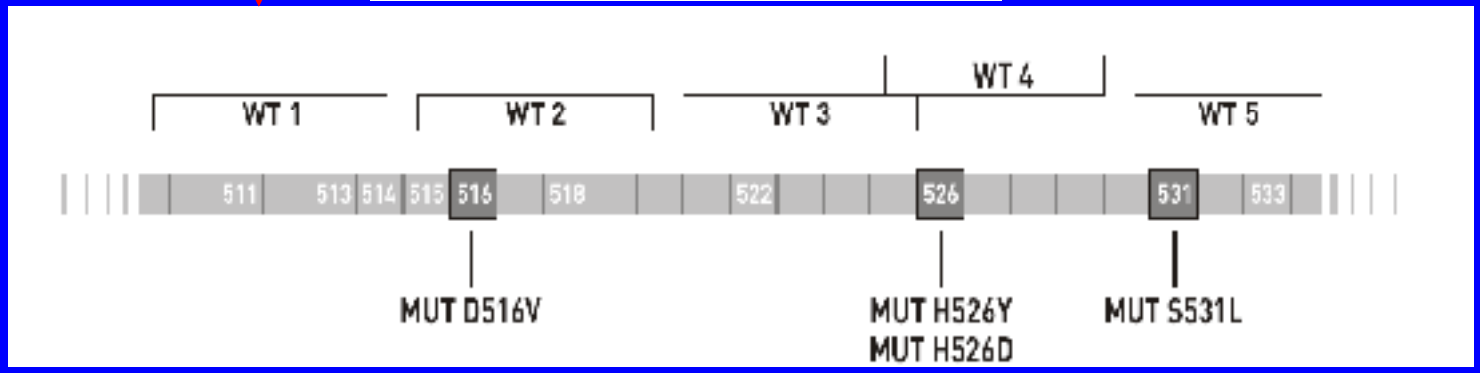
DNA strip assay MTBDR®



Mtb identification

Rifampicine
rpoB

INH
***katG* 315**



From D. Hilleman et coll., J Clin Microbiol, 2005.

Strip DNA assay MTBDR® for detecting rifampicine resistance (77 R strains, France)

Région étudiée	Mutations MTBDR		Séquençage	N souches (%)
	MUT WT[a]	MUT[b]		
511-513	MUT WT1		Q513K	1
			Q513P	1
514-516	MUT WT2		D516Y	3
			M515I+D516Y	2
		MUT1:D516V	D516V	4 (5%)
522	MUT WT3		S522L	2
526	MUT WT4		H526A	1
			H526L	3
			H526R	3
		MUT2B:H526D	H526D	8 (10%)
		MUT2A:H526Y	H526Y	6 (8%)
531-533	MUT WT5	MUT3 :S531L	S531L	37 (48%)
			S531W	2
			S531T	1
			L533P	2
	MUT WT5+WT1		S531C+L511P+F505L	1

100% detection of rifampicine-R

Brossier 2006 JCM
Brossier Int J Tub Lung Dis 2008

Strip DNA assay MTBDR® plus for detecting INH resistance (96 R strains, France)

		% mutation among Inh^R	Inh^R High level	Inh^R Low level
katG :	S315	68 %	60	5
inhA promotor :	-15c->t	19 %	3	15
Other *inhA* or *katG*		13 %	4	9

KatG 315 and InhA promotor
87 % detection of INH-R
(NPV still too low if high prevalence)

Brossier
Int J Tub Lung Dis
2008

Détection moléculaire de la résistance à l'isoniazide (n = 95 souches INH-R)

		% mutations	R haut niveau	R bas niveau
katG	S315T	64 %	59	3
	autres	9 %	4	5
promoteur *InhA*	-15c->t	29%	13	15
	autres	4%	4	
InhA	S94A	7%		7
R non détectée		3%	1	3

97% des souches INH-R détectées par séquence de 2 gènes (3 kb !) (83% par bandelette hybridation!!)

Brossier 2006
J Clin Microbiol

Phenotypic susceptibility test directly from Smear + specimen

- **Possible when > 1 afb/microscopic field**
- Source of bacilli : specimen itself (homogeneized and decontaminated)
- Dilutions according to afb count
- Requires technical training
- Results obtained at the same time as primo-cultures

Particularly important for 2nd line drugs (can be done as soon as genotypic test proves RMP-R)

Management of MDR cases

Design and organize treatment

WHO ranked classification of second line antituberculosis drugs according to their effectiveness (1997)

rank		activity
1	**AMINOGLYCOSIDES**	Bactericidal
a	Streptomycine	
b	Kanamycine/ Amikacine	
c	Capreomycine	
2	**ETHIONAMIDE**	Bactericidal
3	**PYRAZINAMIDE**	Bactericidal acidic pH
4	**OFLOXACINE**	Bactericidal
5	**ETHAMBUTOL**	Bacteriostatic
6	**CYCLOSERINE**	Bacteriostatic
7	**P.A.S.**	Bacteriostatic

« Simple » MDR cases (susceptible to all second line drugs)

At least 3 months of initial intensive phase :

Amikacin or kanamycin

Moxifloxacine

Ethionamide

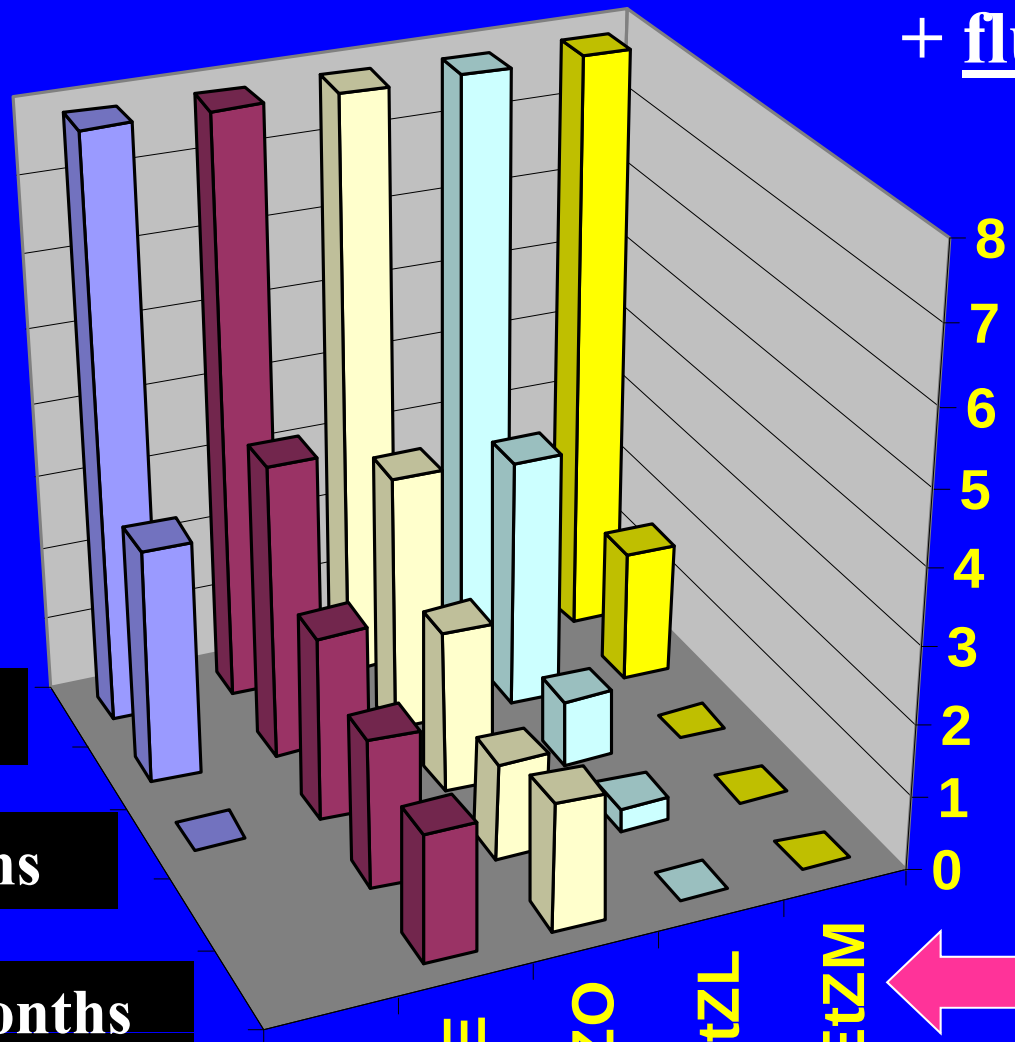
Pyrazinamide

+ Ethambutol (if S)

At least 12 months of continuation phase (stop aminoglycoside after culture negativation)

Moxifloxacin in MDR TB treatment in the mice

amikacin + ethionamide + pyrazinamide (AEtZ) + fluoroquinolone



Mean UFC in lungs

Day 0

6 months

12 months

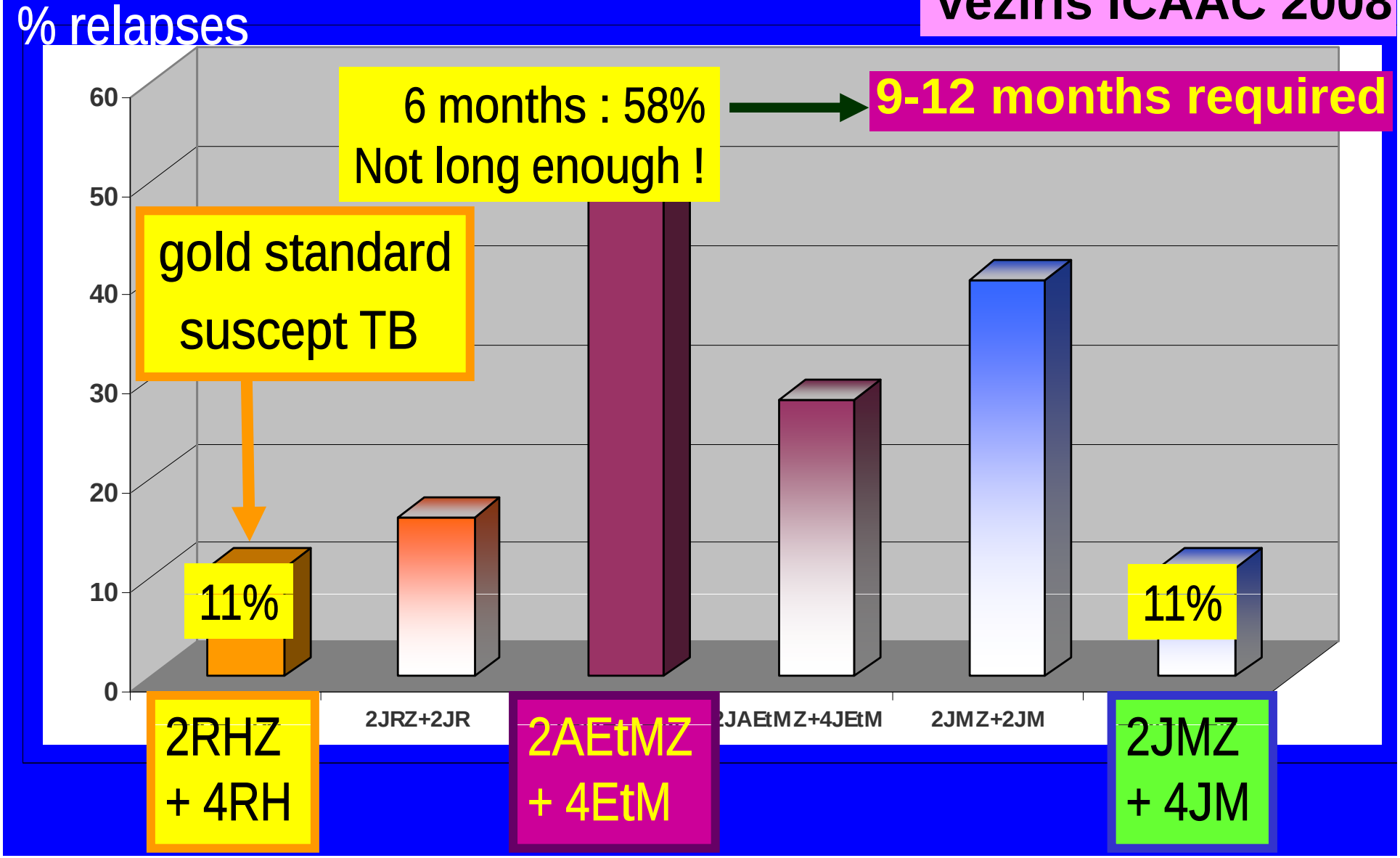
WHO standard

Moxifloxacin

Veziris AAC 2003

Sterilizing activity in MDR TB (mice) : relapse 3 months after end of treatment

Veziris ICAAC 2008



« Complicate » MDR cases (e.g. R to ethionamide, pyrazinamide..) and XDR cases

- « Hand tailored » treatment designed by an expert team
- Last chance for patient survival

Outcome (%) of MDR et XDR Lithuania (old and new definitions)

	cure*	**failure**
MDR	67	**13**
XDR (old definition**)	58	**30**
XDR (new definition***)	28	**55**

- completed treatment

** R to 3 2nd line drugs

*** R to FQs and 1 injectable

Lemaine UICT 2006

Devenir des 4 malades XDR de 2004-06

- **Cas 1 : S à** PAS, cyclosérine, linézolide

  > décès
- **Cas 2 :** S à amikacine, capréomycine, PAS, linézolide

  > vivant
- **Cas 3** : S à éthionamide, pyrazinamide, PAS, cyclosérine, linézolide

  > décès (à l'arrivée en France, avant traitement)
- **Cas 4** : S à éthionamide, pyrazinamide, éthambutol, PAS, cyclosérine, linézolide

  > vivant

Curb the genesis of new cases

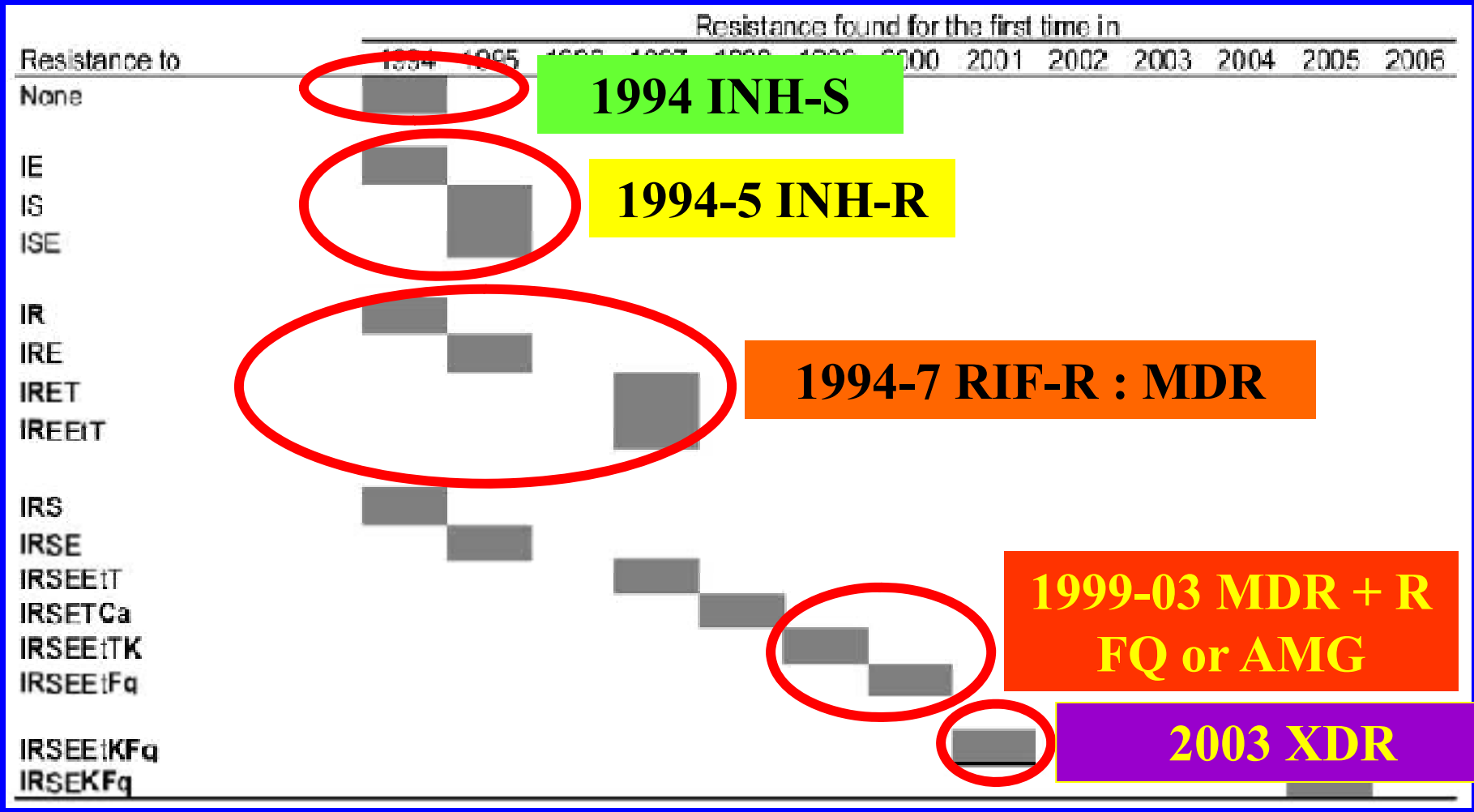
Prevent transformation of MDS-TB in MDR-TB (and of MDR-TB in XDR-TB)

Prevent transformation of MDS-TB in MDR-TB

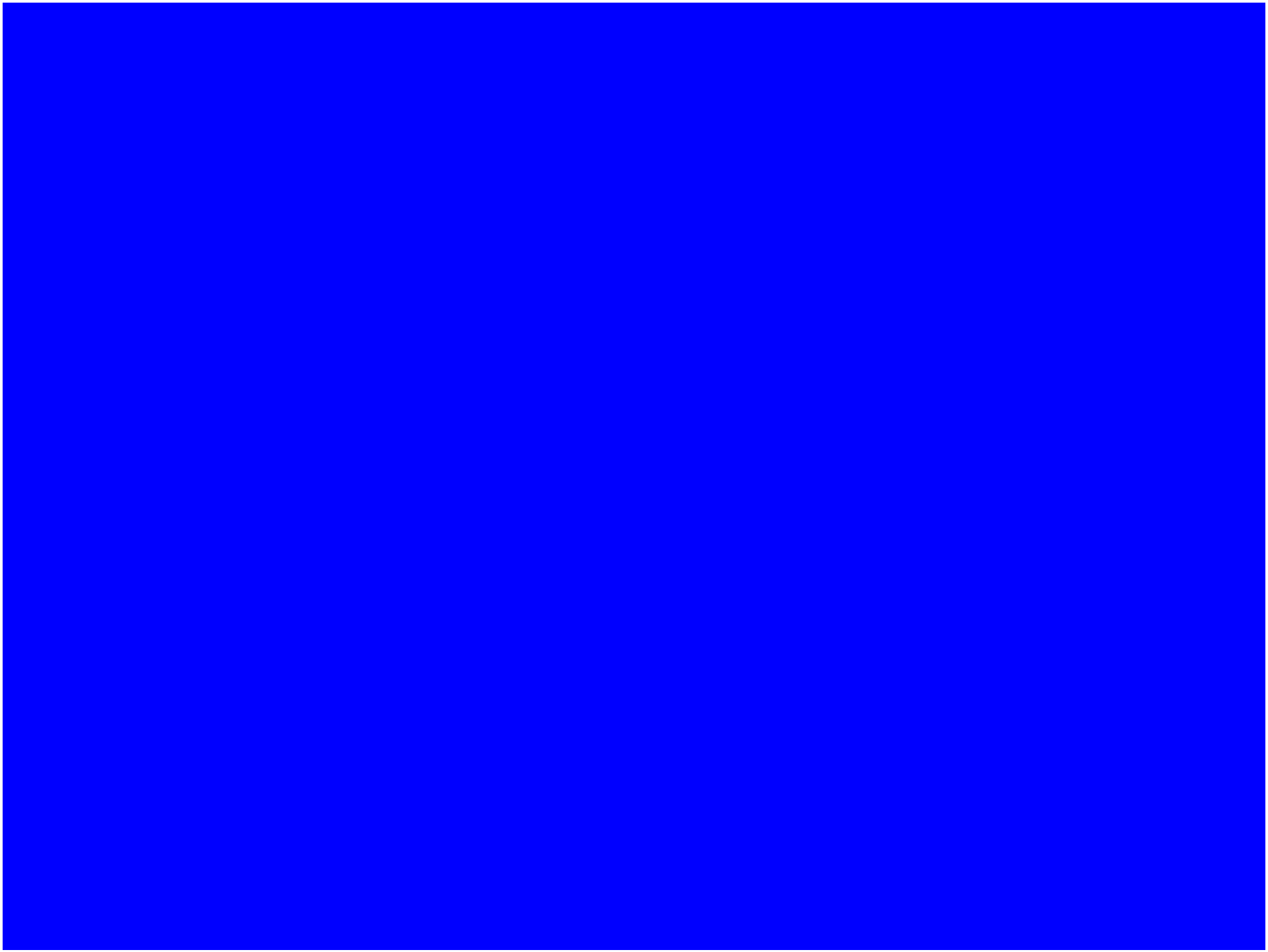
- TB program
- Resources and expertise
- Standardized protocols (DOT, **combined drugs : do not forget ethambutol !!!!! , particularly if smear +**)
- Organization
- Training
- Evaluation (indicators : % completed treatment, % cases with previous treatment, resistance rates…)

Commitment : health authorities, medical community

Stepwise resistance in strain F15/LAM4/KZN in South Africa



Pillay CID 2007



Management
of MDR cases

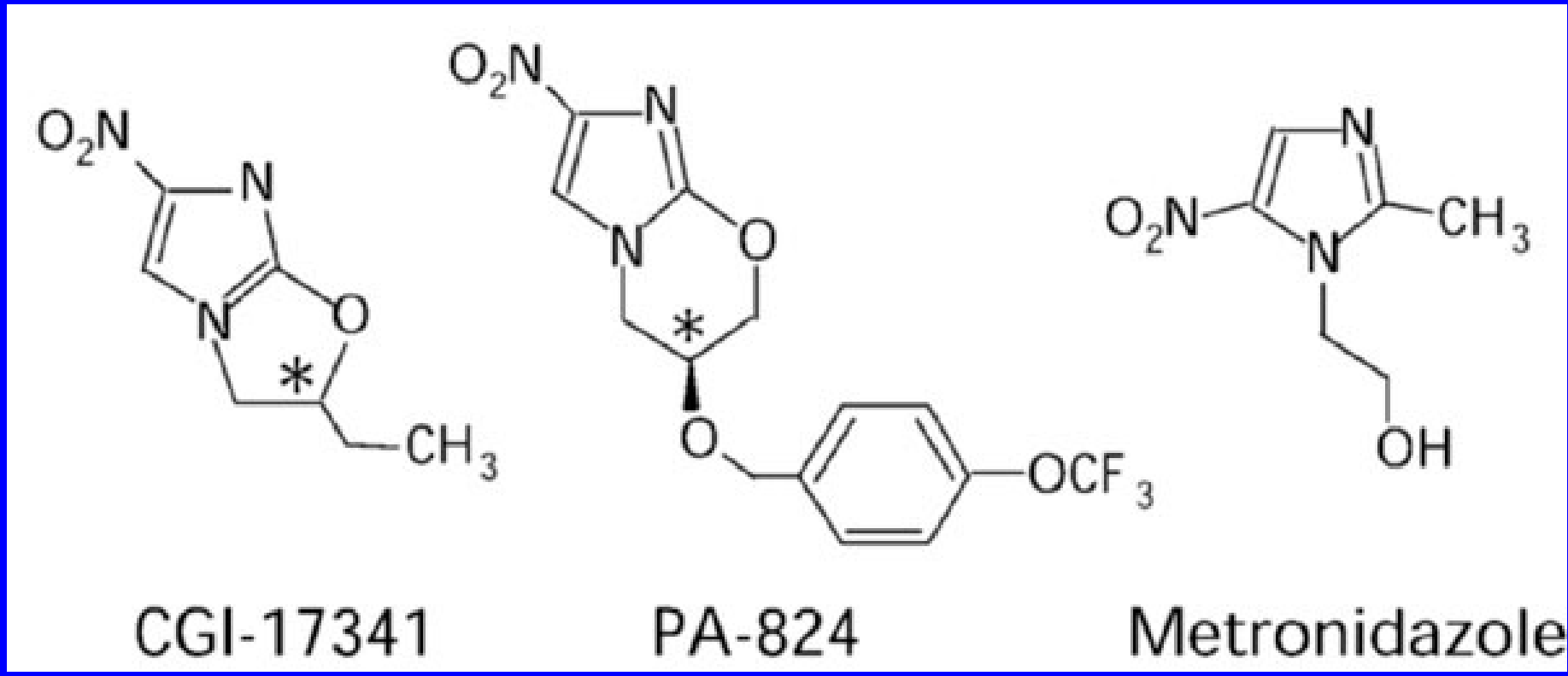
Discover and evaluate
new antituberculous
agents

Discover and evaluate new antituberculous agents

- Screening of drug libraries
- (design based on new targets identified by genomics or proteomics)
- In vitro testing
- Target identification
- Identification of acquired mechanisms of resistance
- In vivo testing : animal model (mice)
- Trials in human

Nitro-imidazoles : PA-824 (PathoGenesis Corp. >> global Alliance against TB)

MIC on *M.tuberculosis* : 0.06 - 0.1 mg/L



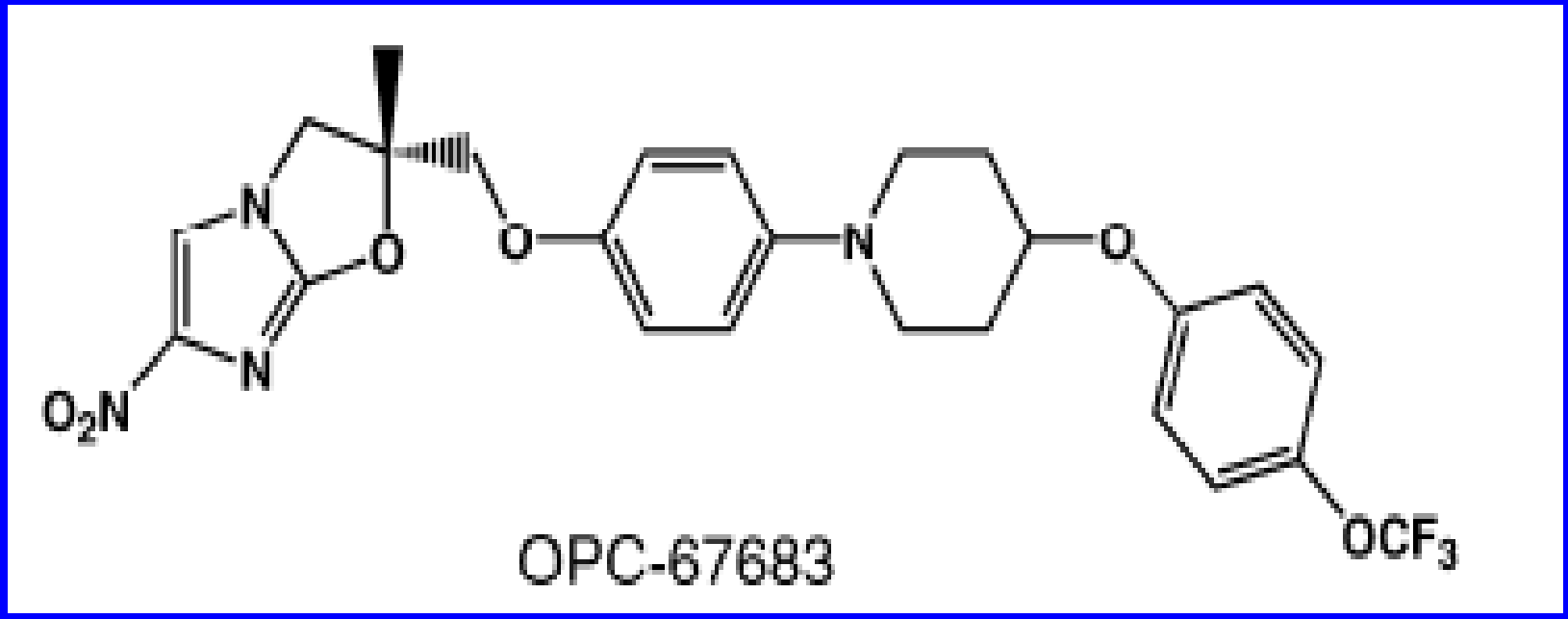
Target unclear

Stover Nature 2000

Nitro-imidazoles : OPC-67683

(Otsuka Pharmaceutical, Tokushima)

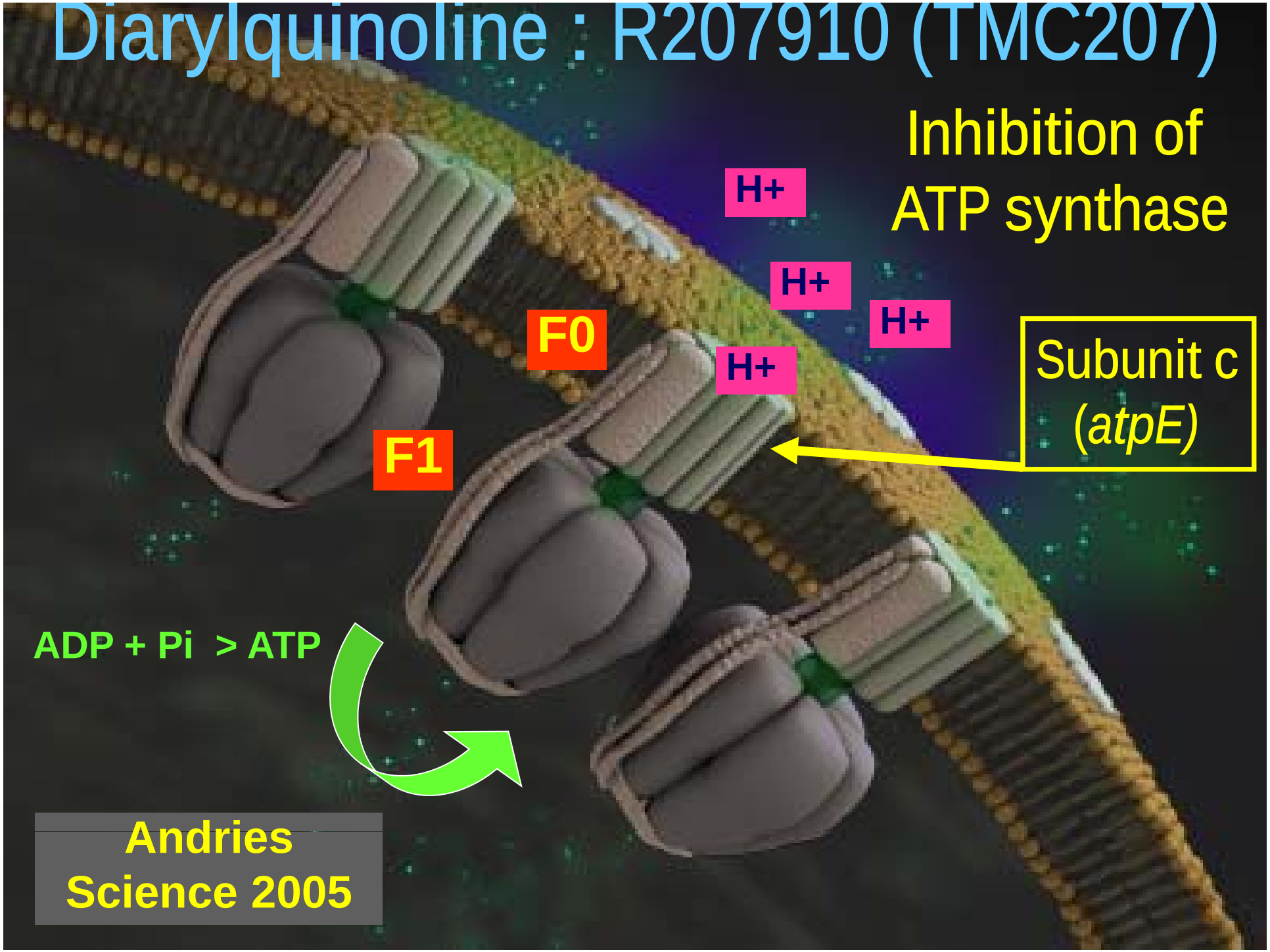
MIC on *M.tuberculosis* : 0.01 mg/L



OPC-67683

Target unclear

Matsumoto PLos Medicine 2006


Diarylquinoline : R207910 (TMC207)
Inhibition of ATP synthase
H+
H+
H+
H+
F0
F1
Subunit c (atpE)
ADP + Pi > ATP
Andries Science 2005

Task 2
Decrease the number of MDR cases :

Curb the genesis of new cases

Curb the genesis of new cases

Prevent cross transmission

South Africa (Tugela Ferry)
XDRTB and HIV

Fears of 'extreme' TB strain

New drug-resistant infection is 'nightmare' say health experts

by Robin McKie

Science Editor

HEALTH EXPERTS are to hold an emergency meeting in Johannesburg this week, following the discovery of a deadly new strain of tuberculosis.

The strain – known as extreme drug-resistant TB – has horrified World Health Organisation doctors. In one outbreak in South Africa, 52 of 53 patients died within weeks of becoming infected.

'This new strain leaves us facing a nightmare,' said Paul Nunn, coordinator of the WHO's drug-resistance unit. 'It is resistant to nearly every drug in our arsenal. We are now on the threshold of the appearance of a strain of TB that is resistant to every medicine known to science.'

The strain was originally discovered by scientists earlier this year. They looked at cases of multiple drug-resistant TB – which has developed over the past decade in many parts of the world – and discovered that among these a worrying new 'extreme' strain had evolved.

'Mainstream drugs are ineffective against multiple drug-resistant TB,' said Nunn. 'However, there are half a dozen second-line medicines that can be used to tackle it. Now this new extreme resistant strain has appeared. It is not only resistant to our principal anti-TB drugs, but to many of our second-line defences. In short, we are now on the last line of our defences against tuberculosis.'

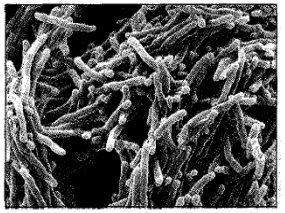
Among the areas found to have been affected by extreme drug-resistant TB are Latvia and South Africa. Scientists discovered the strain last month among HIV-infected patients in the Kwazulu-Natal region. 'Fifty two of the 53 infected people are already dead, and the last may well have died by now,' added Nunn.

An estimated 4.5 million people in South Africa have HIV. Extreme drug-resistance TB could devastate the population. 'If countries don't have the diagnostic capacity to find these patients, they will die without proper treatment,' said Nunn.

As a result, WHO is to hold its emergency meeting in Johannesburg to help establish measures that will lead to the rapid diagnosis of the new strain.

'It appears to kill within a few weeks and that does not give us a lot of time to spot it and treat it with the right drugs,' added Nunn. The few classes of drugs that are still effective against this strain of TB are expensive and can be toxic.

The meeting will be attended by officials from WHO and its partners, including the South African Medical Research Council and the US Centers for Disease Control and Prevention.



A new super-TB is threatening Latvia.

Gandhi Lancet 2006

Prevent cross transmission of MDR-TB

- Out-patients dispensaries
- Hospital
- Prisons
- ……

Prevent transformation of MDS-TB in MDR-TB

- TB program
- Resources and expertise
- Standardized protocols (DOT, **combined drugs**)
- Organization
- Training
- Evaluation (indicators : % completed treatment, % cases with previous treatment, resistance rates…)

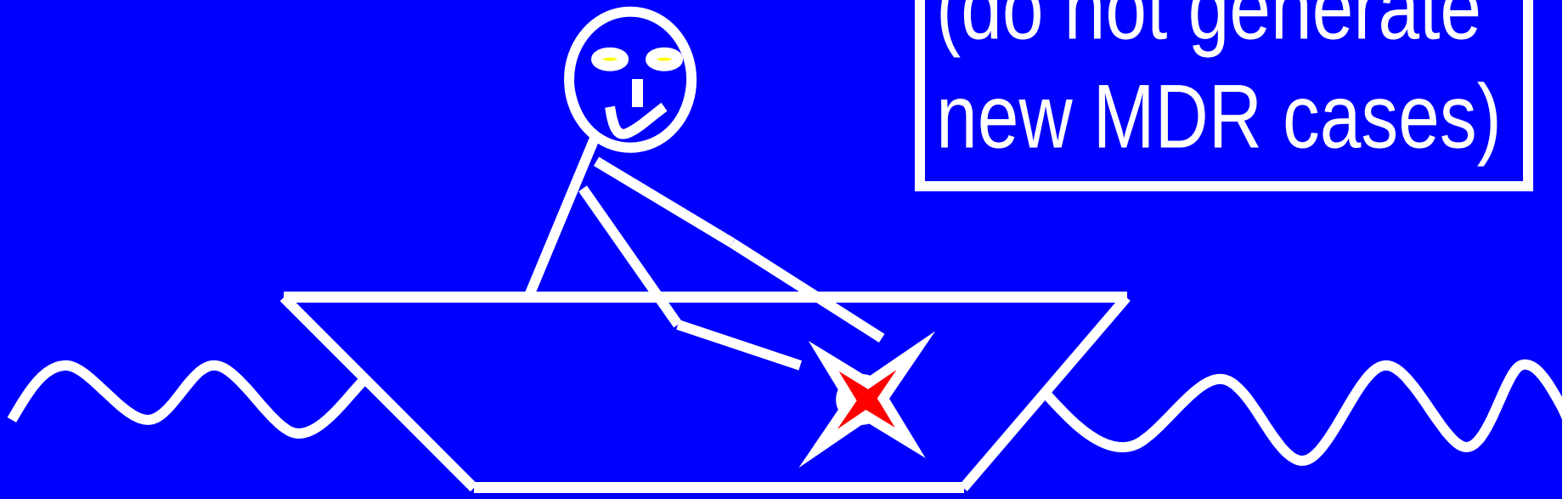
Commitment : health authorities, medical community

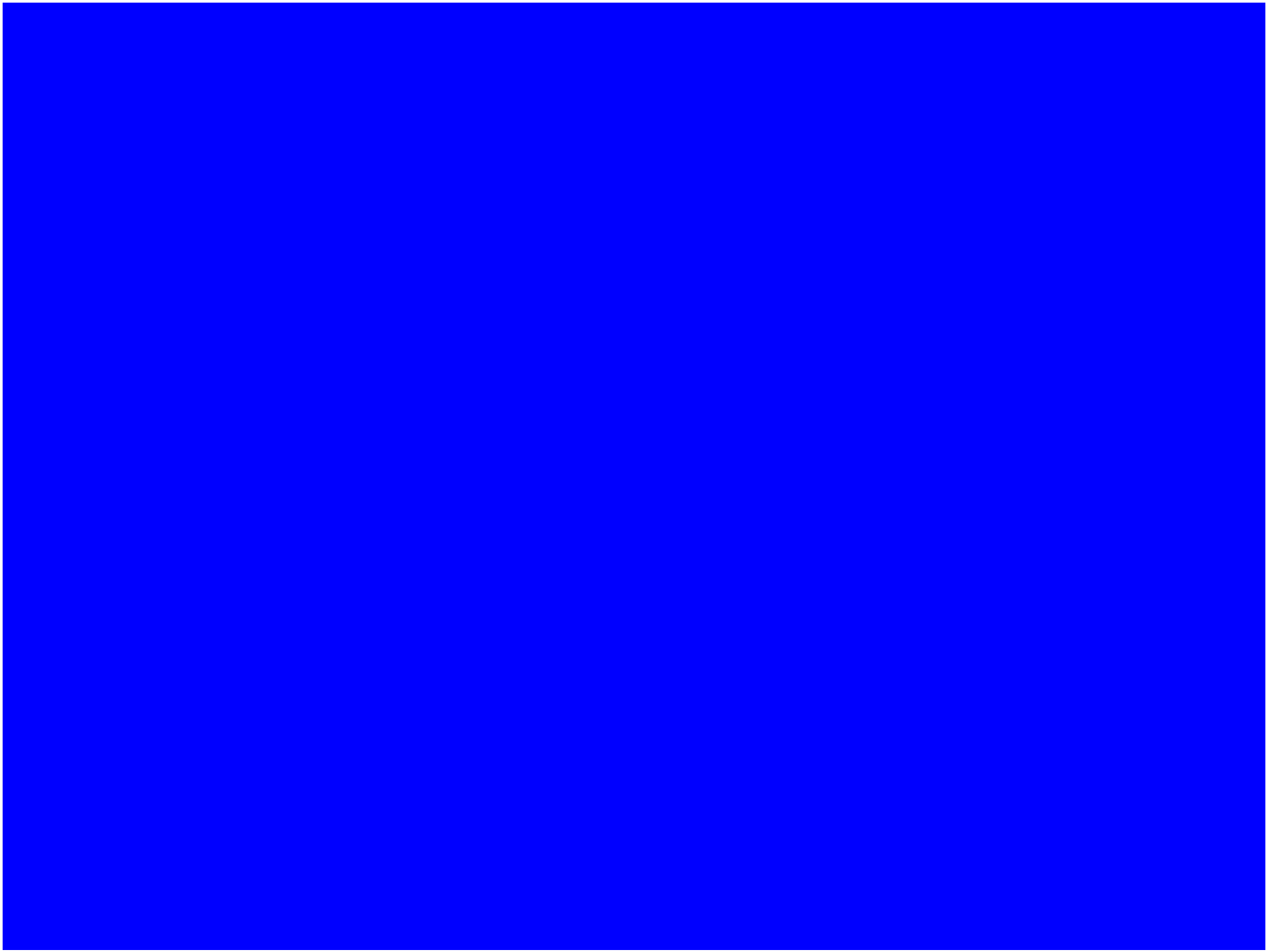
Conclusion

When your boat is sinking…

….but most crucial

Seale the hole
(do not generate
new MDR cases)





Actions and recommendations

- **Implement WHO *Guidelines for the programmatic management of drug-resistant tuberculosis***

- **Green Ligth Committee (GLCs) to facilitate access to high-quality second-line drugs**

Strip DNA assay MTBDR® for detecting INH resistance (96 R strains, France)

		% mutation among Inh^R	Inh^R high level	Inh^R low level
katG :	S315	68 %	60	5
inhA promotor :	-15c->t	19 %	3	15
Other *inhA* or *katG*		13 %	4	9

With KatG 315 only only 68 % detection of INH-R

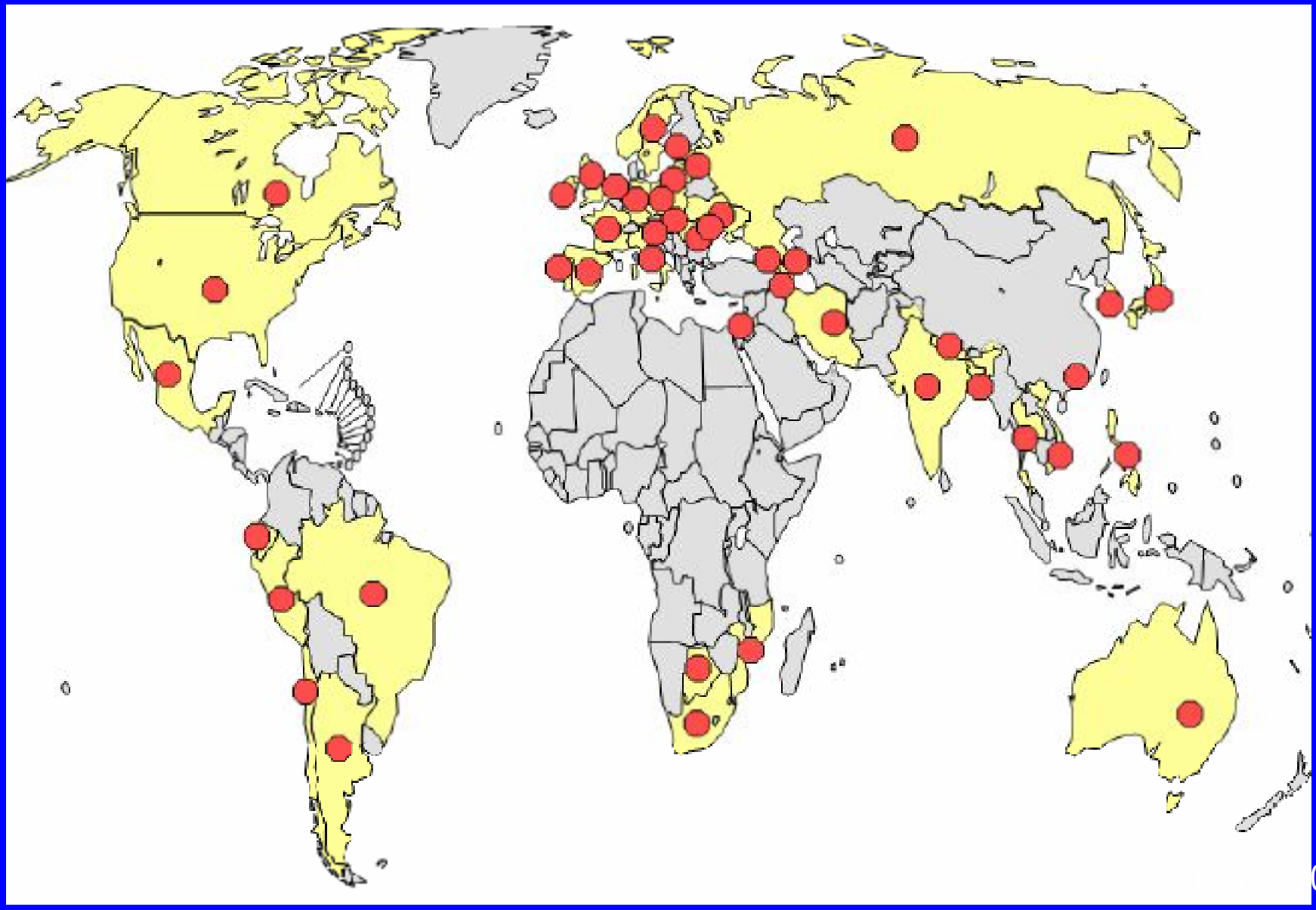
Brossier 2006 JCM

Strip DNA assay MTBDR® plus directly in Smear + sputum (MDR context, South Africa)

- 536 consecutive specimens
- 97 % of results interpretable in 2 days
- Rifampicine :
  - **Sensitivity 99 %**
  - **Specificity 99 %**
- Isoniazid :
  - Sensitivity 94 % (but many clonal strains !)
  - Specificity 99 %

Barnard Am J Resp Crit Care Med 2008

Pays ayant déjà signalés des cas de tuberculoses XDR



MDR TB
key findings 4th report 2008
(new cases)

- of the 20 settings with the highest proportion of MDR-TB in new cases
- 14 are countries of the former Soviet Union (FSU)
- 4 are in China

MDR TB
key findings 4th report 2008
(previously treated cases)

Highest MDR proportions :

Tashkent, Uzbekistan 60%

Baku, Azerbaijan 56%

Comparative outcome of MDR-TB and XDR-TB (old definition) (MMWR 2006)

		MDR		XDR	
Latvia 2000 -02	Total	N=490		N=115	
	Failures	N=83	**17 %***	N=30	**26 %***
USA 1993-02	Total	N=1,513		n=64	
	Deaths	N=275	**25 %****	N=21	**33 %****

* RR = 1.5 (1.1-2.2) p = 0.02 ** RR = 1.6 (1.2-2.2) p = 0.01

Principles of MDR treatment (WHO)

- (3 to) 5 active drugs :
  - Based on 2nd line drugs susceptibility tests (DST)
  - If no DST : drugs never given to the patient
- Include aminoglycoside in the initial intensive phase
- Maintain initial intensive phase till culture negativation
- Team(s) of experts : TB specialists + reference laboratory working together

XDR TB en France 1992-2006

- **Total : 14 cas en 15 ans (m= 1 par an)**
- **XDR = 3 % des 439 cas MDR** pour lesquels fluoroquinolones et amikacine ont été testés (total : 743 MDR cas)
- **XDR = 4 % des 53 MDR de 2006**

Appui aux microbiologistes pour les cas de tuberculose MDR

Appui microbiologique pour les tuberculoses MDR : tests phénotypiques

- **Tests phénotypiques de sensibilité aux antituberculeux de 2 ligne**

  pas de matériel commercialisé (« cousu main »

- **Idem, directement sur les prélèvements** :

  « antibiogramme direct »

  prérequis techniques (parfois impossible)

Tests de résistance aux antibiotiques par biologie moléculaire

- **Confirmer ou affirmer le statut MDR (ou monorésistant rifampicine) :**
  - Rifampicine (*rpoB*)
  - Isoniazide (*katG*, promoteur *inhA*, *inhA*)
- **En cas de MDR, sensibilité à :**
  - Pyrazinamide (*pncA*)
  - Quinolones (*gyrA*, *gyrB*)

Mutations dans le gène *rpoB* des 53 souches MDR de 2006

Codon	Mutation	N souches
516	D > V	9
	D > Y	4
526	H > D	3
	H > Y	2
	H > L	2
	H > R	1
	H > N	1
	H > S	1
531	S > L	26
	S > W	1
533	L > P	3

100% des rifampicine-R sont détecteés par séquence de 100 bp (ou bandelette hybridation)

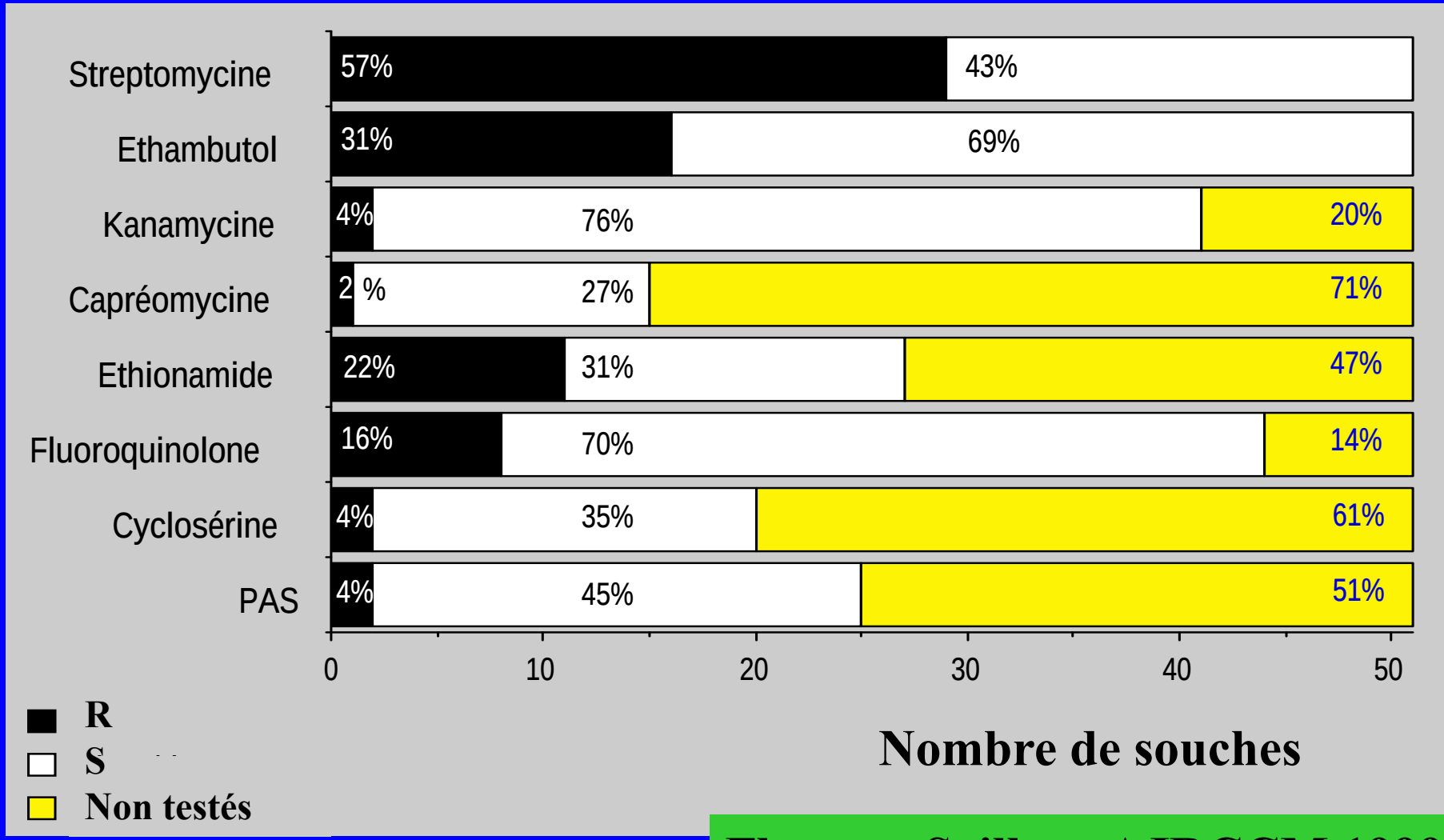
Génotypage des 53 souches MDR de 2006 : 3 groupes RFLP

- **G1 (n=3)** : **2 cas familliaux**, 1 cas non lié (même pays origine mais arrivée récente, mutation *pncA* ≠
- **G2 (n=3)** : pas de lien récent : nés en RD Congo, arrivée après 2000, villes ≠, profil R ≠, mutations *pncA* et *gyrA* ≠
- **G3 (n=2)** : pas de lien récent : nés en Guinée Cky, arrivée en 2001 et 2006, mutations *pncA* ≠

2 sur 53 = 4% de cas secondaires

Appui aux cliniciens pour la prise en charge des cas de tuberculose MDR

Sensibilité des 51 souches des cas de tuberculose à bacilles multirésistants diagnostiqués en 1994 en France



Flament-Saillour AJRCCM 1999

« Groupe thérapeutique des infections à mycobactéries résistantes »

- Pr Bertand Dautzenberg (Pneumologie, Pitié-Salpêtrière, Paris)
- Pr Eric Caumes (Maladies Infectieuses, Pitié-Salpêtrière, Paris)
- Dr Mathilde Frechet-Jachym et Dr Nathalie Metivier (Sanatorium, CMC Bligny, Briis-sous-Forges)
- Dr Marie Saillour (Pneumologie, Max Fourestier, Nanterre)
- Dr Katarina Chadelat (Pédiatre, Trousseau, Paris)
- **Coordination : Dr Nicolas Veziris (pneumologue, bactériologiste, CNR-MyRMA)**

Résistance aux antituberculeux des 53 souches MDR de 2006

	Testés	R	% R
Pyrazinamide	53	25	47%
Ethambutol	53	31	58%
Streptomycine	53	40	75%
Kanamycine	53	8	15%*
Amikacine	53	3	6%*
Capréomycine	53	5	9%*
Fluoroquinolones	53	8	15%*
Ethionamide	53	18	34%
PAS	52	8	15%
Cyclosérine	50	5	10%
Linezolide	38	0	0%

*** 2 souches XDR (4 % des MDR)**

Prise en charge des Tb MDR en France

	1994 (51)*	1999 (45)**	2006 (53)
ATB testés (dont streptomycine et éthambutol)	**5**	**8**	**11**
Traitement > 3 ATB actifs	**47%**	**84%**	**85%**
Succès	**41%**	**67%**	**évalués en 2008**

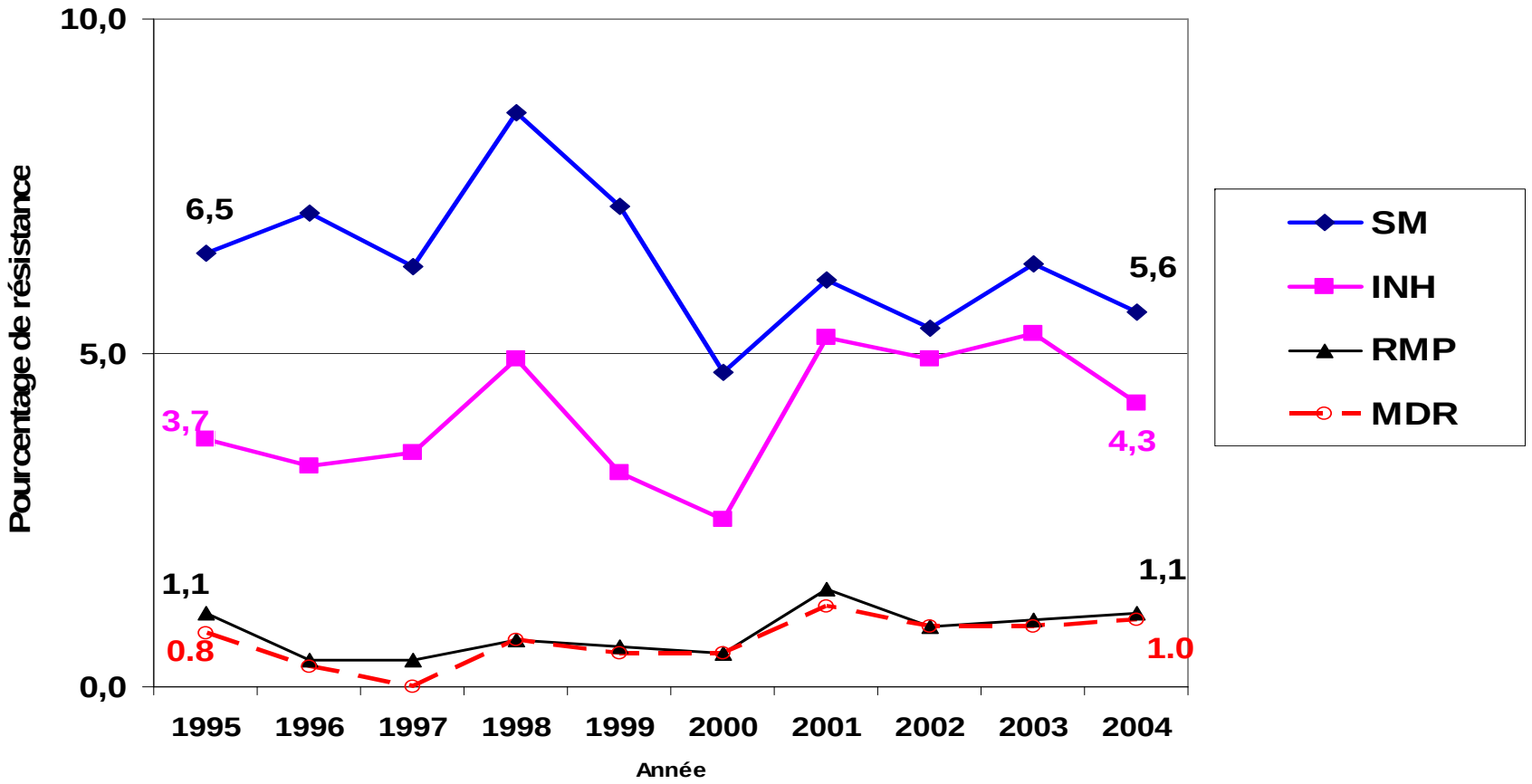
*** Saillour Am Resp Crit Care Med 1999**
**** Uffredi Inter J Antibiot 2006**

Principes généraux de management de la multirésistance

- Ne pas convertir une TB sensible en TB résistante : appliquer strictement le traitement standard OMS pour les nouveaux cas
- Ne pas convertir une TB résistante en TB MDR : appliquer strictement les shémas de retraitement
- Ne pas convertir une TB MDR en TB XDR : équipe spécialisée (traitement efficace = denière chance de survie du malade)

Devenir des cas MDR 2004-05

Figure 3: Evolution de la résistance aux antituberculeux de première ligne chez les nouveaux malades



Risk factors for MDR TB in Europe

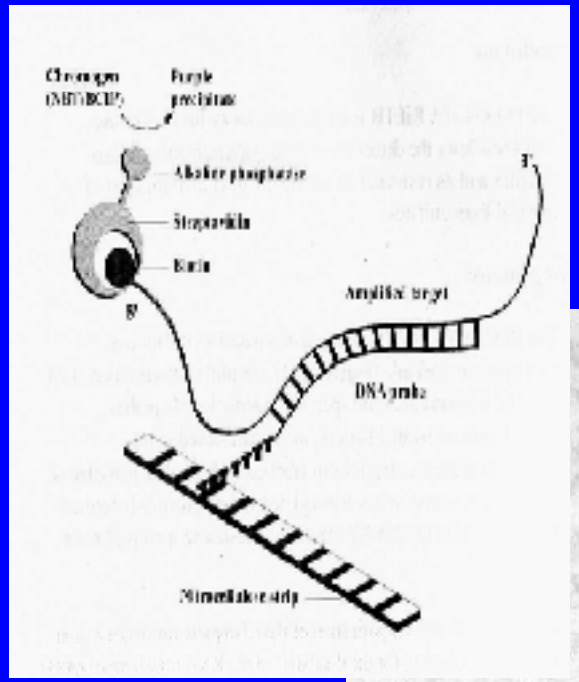
- Review 29 studies in Europe
- Pooled risk for MDRTB 10.2 in previous treated vs never treated
- 6 national studies in: MDRTB more likely to be foreign born, younger than 65, male and HIV positive
- Faustini Thorax 2006; 61:158-163.
- Samara, Russia
- Prior TB therapy (OR-7.4)
- Presence of cavities (OR-2.6)
- History of imprisonment (OR-2.1) (between 1 and 23 treatment cycles)
- Recreational drug use (OR-3.0)
- HIV not associated with resistance (OR-0.3)
- Ruddy 2005 Thorax; Drobniewski JAMA 2005

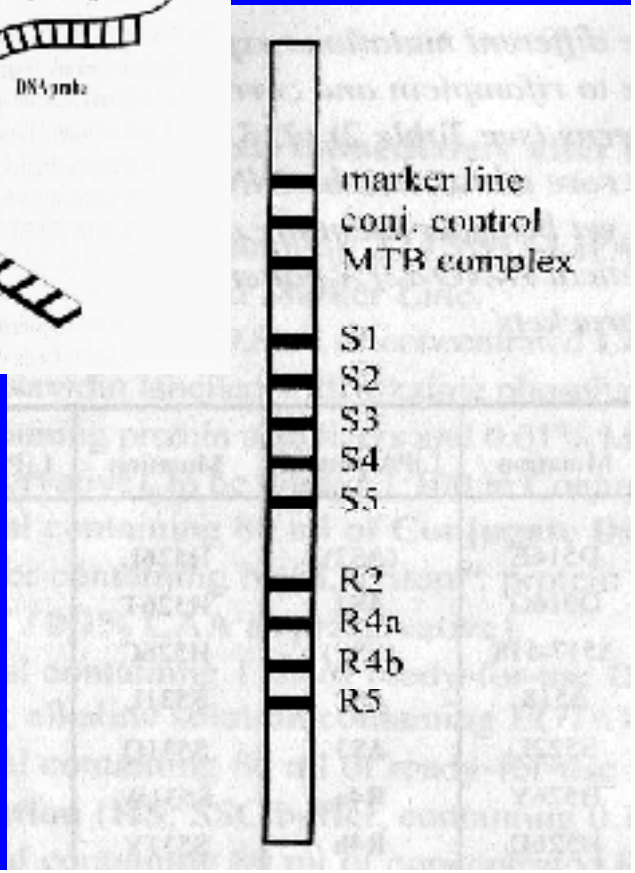
Actions and recommendations (1) Epidemiology and surveillance

- **Surveillance of XDR-TB must be included in existing drug resistance surveillance systems to increase access to second-line DST**
- **Rapid ‘rough’ surveys to rapidly determine the geographical distribution and extent of XDR-TB, and association with HIV**
- **anti-TB drug resistance surveillance should include HIV testing**
- **use of rapid rifampicin tests should be explored**

Molecular methods for drug resistance testing PCR+hybridization

- amplification of genes fragments involved in acquired resistance
- hybridization with oligonucleotide probes immobilized on membranes
- Commercial kits
- high sensitivity and specificity





HAIN GenoType® MTBDR Plus

- **125 clinical isolates and 72 smear-positive sputa**
- **106 RIF(r)/INH(r), 10 RIF(s)/INH(r), and 80 RIF(s)/INH(s) strains**
- **71 of 72 results for smear-positive sputa and all 125 results for clinical isolates were interpretable**
- **Compared to conventional DST both assays identified RMP resistance correctly in 74 of 75 strains (98.7%) and 30 of 31 specimens (96.8%)**
- **Correct detection INH resistance in 69/75 (92.0%) INH-resistant strains and**
- **37/41 (90.2%) among specimens growing INH-resistant strains.**

Hilleman et al J Clin Microbiol. 2007

HAIN GenoType® MTBDR Plus Africa

- **Rapid detection RIF and INH resistance directly on 536 consecutive smear-positive sputum specimens (patients at increased risk of MDR-TB**
- **97% smear-pos specimens interpretable results**

- **Sensitivity, specificity, PPV and NPV :**
- **98.9%, 99.4%, 97.9% and 99.7% for RIF resistance;**
- **94.2%, 99.7%, 99.1% and 97.9% for INH resistance;**
- **98.8%, 100%, 100% and 99.7% for MDRTB**

Barnard et al Am J Respir Crit Care Med. 2008

Second line drug susceptibility

World Health Organisation
Guidelines for drug susceptibility testing for second-line anti-TB drugs for DOTS-Plus.
WHO/CDS/TB/2001.288

MDRTB treatment

- Start with 5 or more drugs to which the organism is, or is likely to be sensitive.
- Once sensitivities are available and there has been clinical response a minimum of 3 or 4 drugs are needed for consolidation Rx.
- 18/12 is the current standard recommended treatment duration.

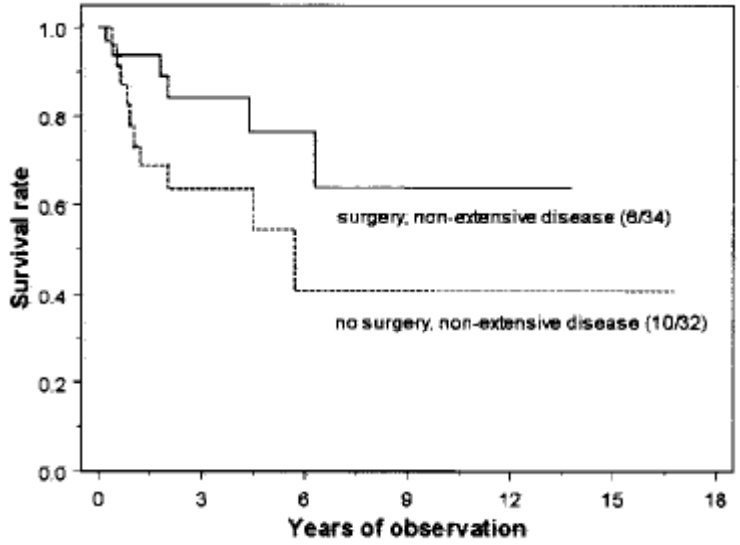
MDRTB treatment

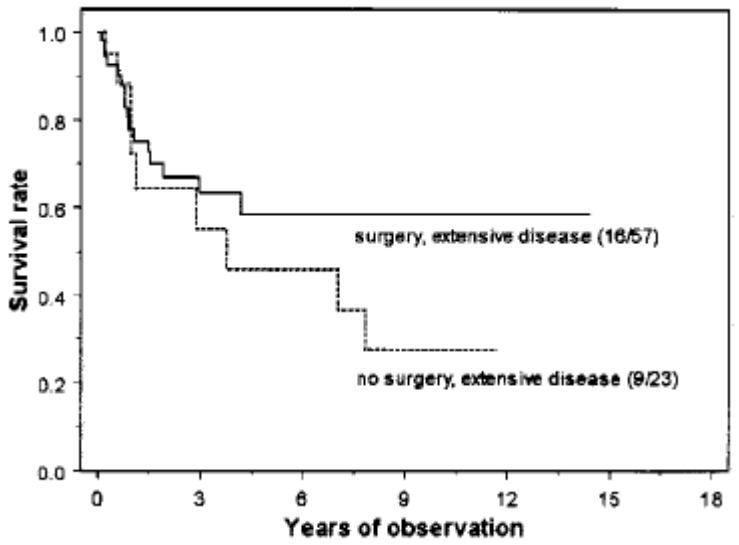
- Choice of Agents:
  - Initially from 1st line drugs
  - Then, in order:
    - Aminoglycoside
    - Fluroquinolone
    - Prothionamide
    - Cycloserine
    - PAS
- Clarithromycin has weak anti Mtb activity but is useful to prevent further resistance.

MDRTB treatment –role of surgery

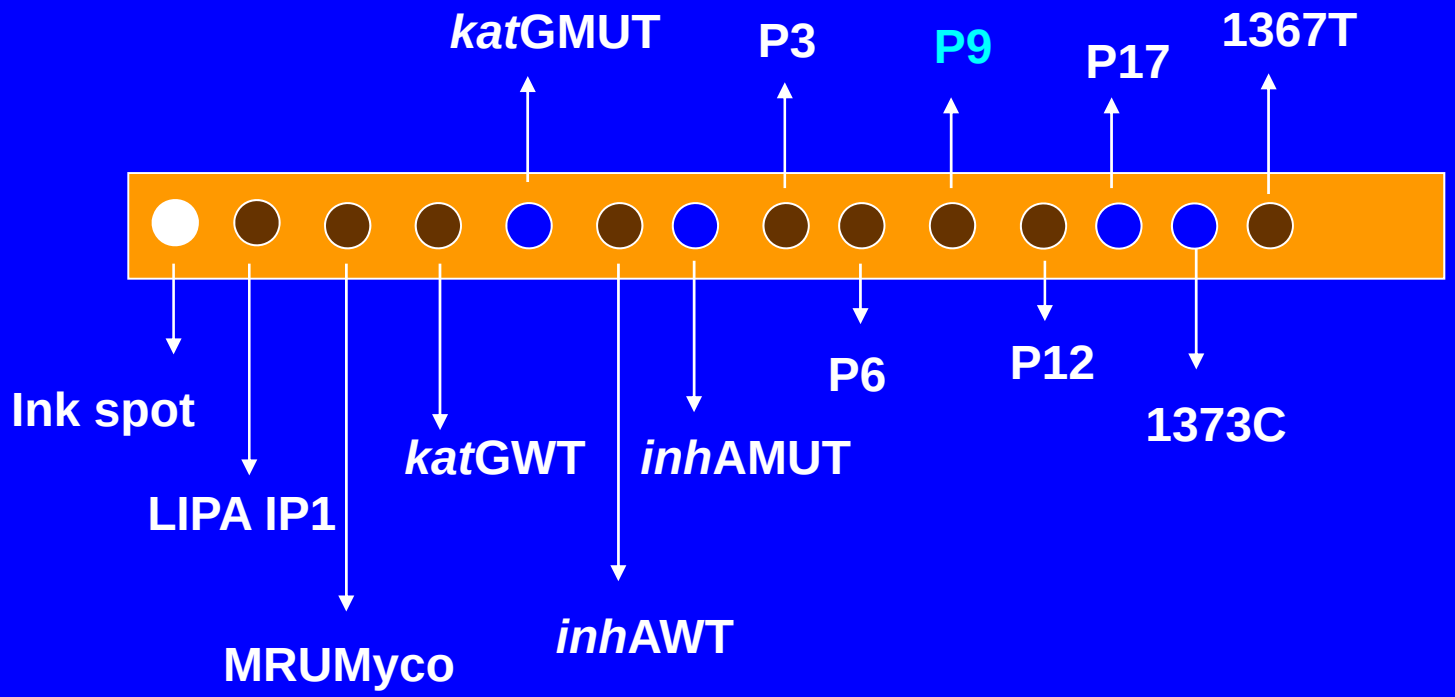
Treatment and Outcome Analysis of 205 Patients with Multidrug-resistant Tuberculosis

Edward D. Chan, Valer Am J Respir Crit Care Med Vol 169. pp 1103–1109, 2004 nh, Marian Goble, and Michael D. Iseman





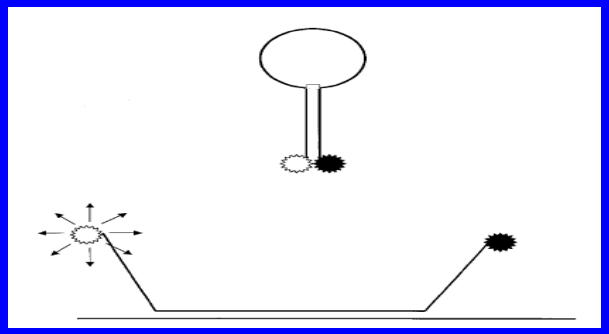
MRU:Identification of MDR-TB isolates using low density array technology

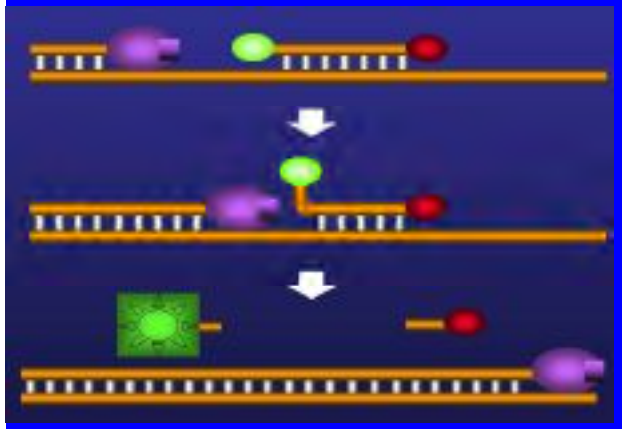


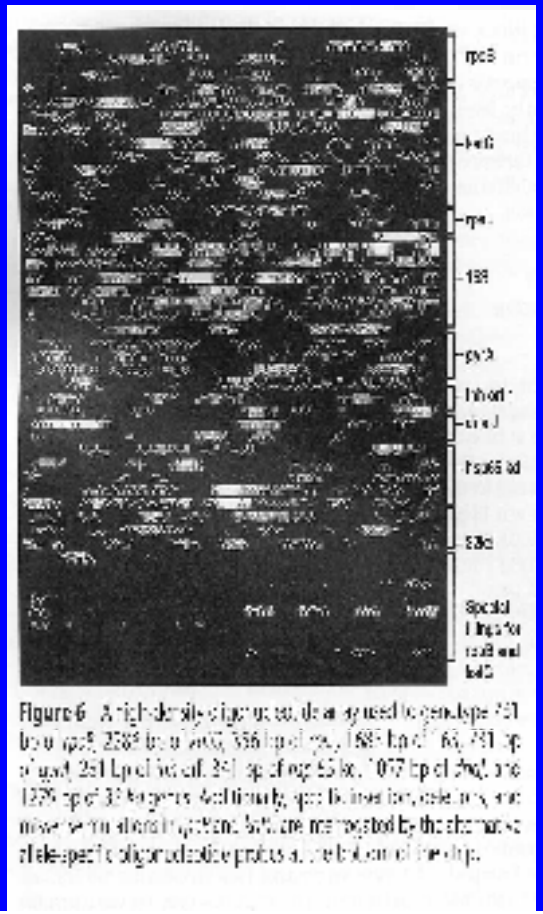
Drobniewski et al Emerg Inf Dis 2002; 8:1320-1326; Nikolayevskyy et al J Clin Micro 2004; 42:4498–4502; Brown et al J Microbiol Methods 2006;65: 294– 300; Nikolayevskyy et al Clin Microbiol Infect. 2007;13(2):129-38 and Mokrousov et al J Microbiol Methods. 2004;57(3):323-35

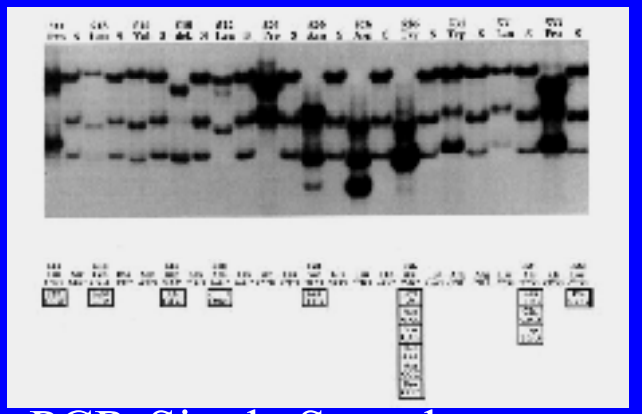
Molecular methods for drug resistance testing – PCR-based methods

Molecular Beacons
Piatek et al; Alland et al.









- PCR-Single Strand Conformation Polymorphism (PCR-SSCP) (Telenti et al., 1993)
- Mutations cause alterations in conformation of single-strand DNA fragments and it is registered in non-denaturizing PAGE

Torres J Clin Microbiol 2000

Fastrack: Molecular amplification methods for primary specimens

- Analysis national molecular Fastrack Jan1999 to Dec 2002
- Consecutive specimens from 2110 patients
- For detection of rifampicin resistance in specimens yielding MTBC on culture,
    - 99.1%, concordance
    - 95.0%, sensitivity
    - 99.6%, specificity
    - 92.7%, PPV
    - 99.7% NPV

- **Sam *et al*. EID 2006 12(5) 752-759**

Rapid Automated Culture Systems

JOURNAL OF CLINICAL MICROBIOLOGY, Mar. 2006, p. 811–818 Vol. 44, No. 3
0095-1137/06/$08.00+0 doi:10.1128/JCM.44.3.811–818.2006

Evaluation of MGIT 960-Based Antimicrobial Testing and Determination of Critical Concentrations of First- and Second-Line Antimicrobial Drugs with Drug-Resistant Clinical Strains of *Mycobacterium tuberculosis*

Annika Krüüner,[1,2] Malcolm D. Yates,[1] and Francis A. Drobniewski[1]*

Health Protection Agency, Mycobacterium Reference Unit, Clinical Research Centre, Barts and the London School of Medicine, Queen Mary College, University of London, 2 Newark Street, London, United Kingdom E1 2AT,[1] and Tartu University Clinics, United Laboratory, Department of Mycobacteriology, Tartu, Estonia[2]

JOURNAL OF CLINICAL MICROBIOLOGY, Mar. 2006, p. 688–692 Vol. 44, No. 3
0095-1137/06/$08.00+0 doi:10.1128/JCM.44.3.688–692.2006

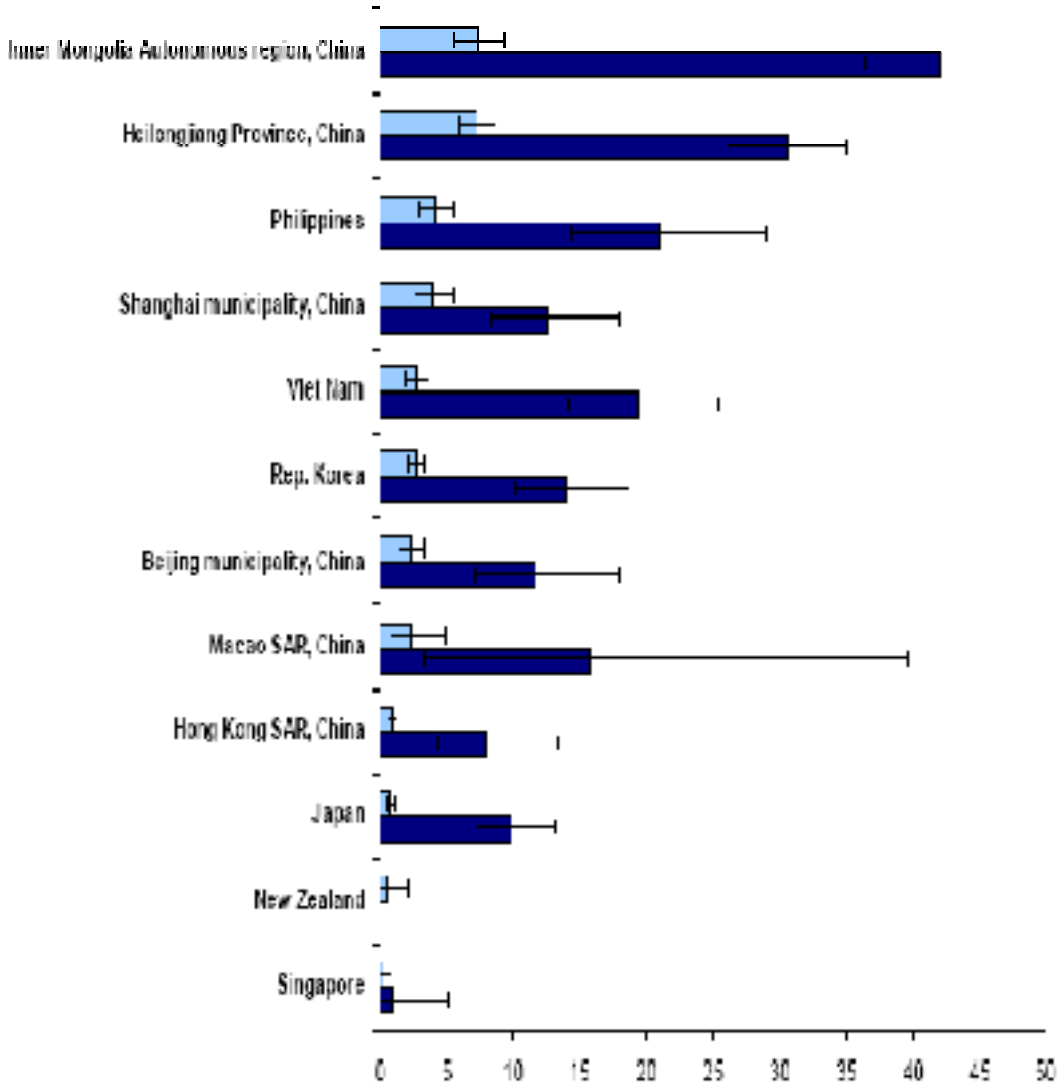
Multicenter Laboratory Validation of the BACTEC MGIT 960 Technique for Testing Susceptibilities of *Mycobacterium tuberculosis* to Classical Second-Line Drugs and Newer Antimicrobials

Sabine Rüsch-Gerdes,[1]* Gaby E. Pfyffer,[2] Manuel Casal,[3] Maureen Chadwick,[4] and Salman Siddiqi[5]

National Reference Center for Mycobacteria, Forschungszentrum Borstel, Borstel, Germany[1]; Department of Medical Microbiology, Luzern General Hospital, Lucerne, Switzerland[2]; Mycobacteria Reference Center, Faculty of Medicine, University of Cordoba, Cordoba, Spain[3]; Royal Brompton Hospital, London, United Kingdom[4]; and Becton Dickinson Diagnostic Systems, Sparks, Maryland[5]

MDR TB
key findings 4th report 2008

- China, India, and Russia : highest **number of new MDR cases**
- **MDR rates** ranged from 0 % in 8 countries to 19 % in the Republic of Moldova and 22 % in Azerbaijan



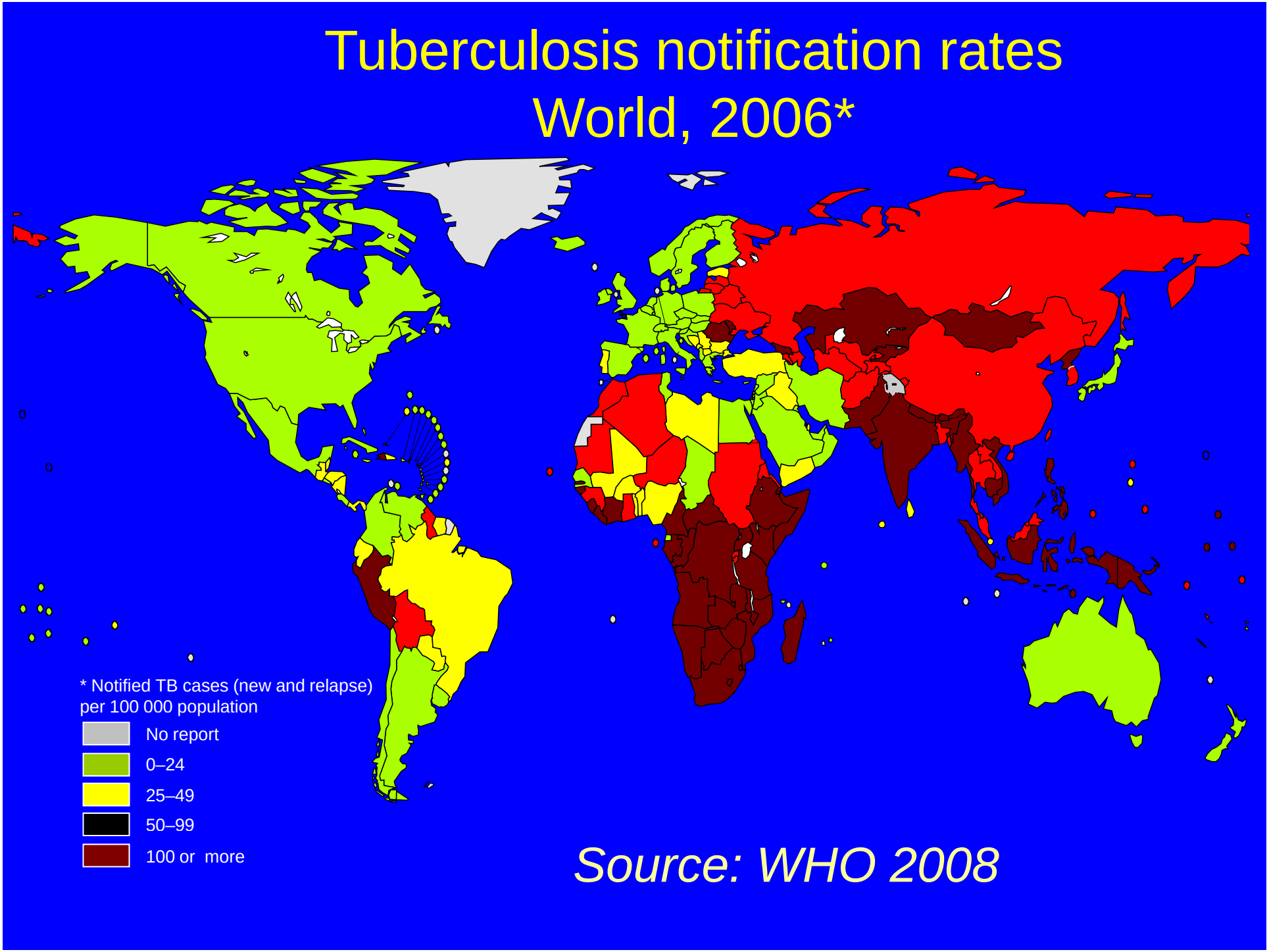
XDR* (% of MDR)
WHO, IUATLD, CDC 2000-2004

Established market	**6**
Central and south America	**6**
Eastern Europe	**14**
Africa	**1**
Asia	**1**

* old definition (R to 3 2nd line drugs)
new definition (R à FQs + injectable) : 1/3 to ½ of these %

MMWR March 24, 2006

Tuberculosis notification rates
World, 2006*



XDR and Survival (old definition)

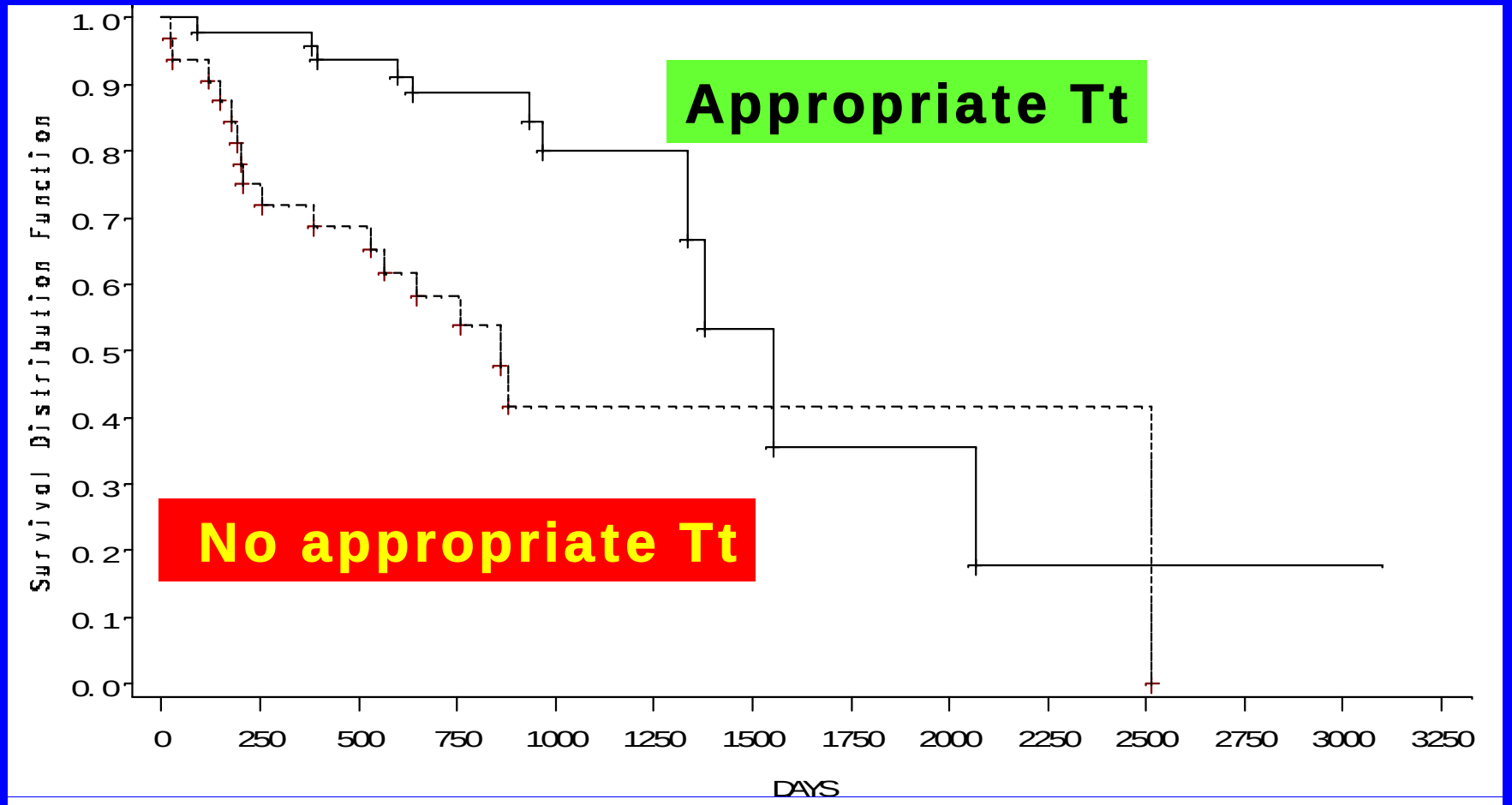
TABLE 2. Tuberculosis treatment outcomes among patients with extensively drug-resistant tuberculosis (XDR TB) and multidrug-resistant tuberculosis (MDR TB) — Latvia, 2000–2002, and United States, 1993–2002*

Outcome	XDR TB No. (%)	MDR TB No. (%)	Relative risk (95% CI†)	p-value
Latvia§¶				
Total	**115**	**490**		
Cure/Completion	70 (61)	339 (69)	Referent	
Death/Failure	30 (26)	83 (17)	1.5 (1.1–2.2)	0.02
Death	3 (3)	35 (7)		
Failure	27 (23)	48 (10)		
United States¶**				
Total	**64**	**1,513**		
Completion	20 (31)	828 (55)	Referent	
Death	21 (33)	375 (25)	1.6 (1.2–2.2)	0.01

* Inclusion in this cohort was truncated at December 2002 to allow time for MDR TB treatment completion and reporting.
† Confidence interval.
§ Outcome definitions used are based on international standards (*5*).
¶ Excludes 83 patients (15 with XDR TB and 68 with MDR TB) from Latvia and 333 patients from the United States (23 with XDR TB and 310 with MDR TB) for whom treatment outcome was unknown.
** Among persons who were alive at time of TB diagnosis and who initiated therapy with more than one anti-TB drug.

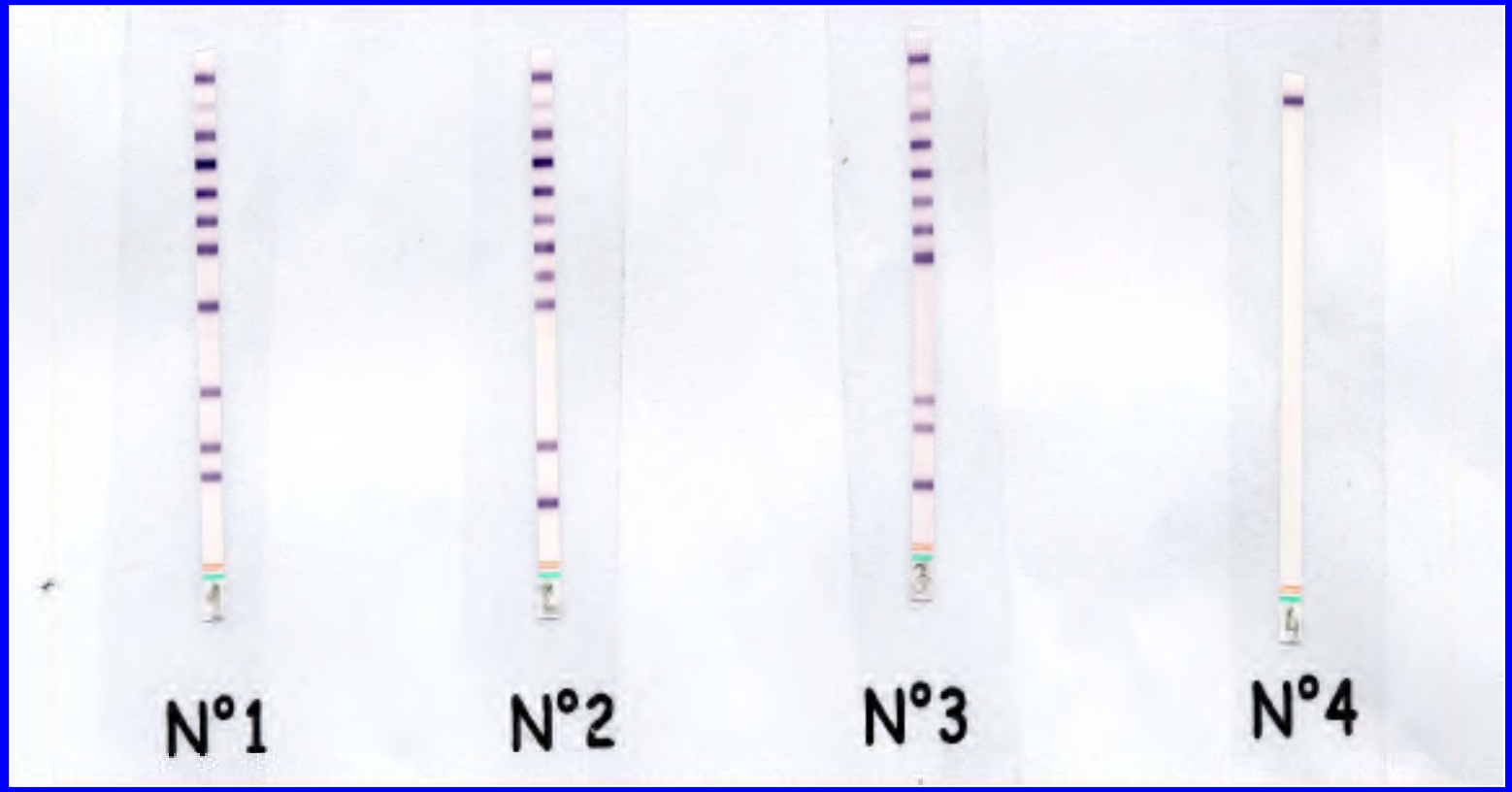
MMWR 2006

Survival of MD-RTB in the 1990s UK



Drobniewski, Thorax 2002, 90 MDRTB patients

DNA strip assay MTBDR®



N°1	N°2	N°3	N°4
Rmp R (His526Asp)	Rmp S	Rmp R (Ser531Leu)	control
INH S	INH R (Ser315Thr1)	INH R (Ser351Thr1)	

Fluoroquinolone activity

- In the mice (Lalande AAC 1993, Ji AAC 1995, Ji AAC 1998)

FQ	J0	CFU reduction (log) at week 4 (spleen)
Ofloxacin 200 mg/kg	7,4	- 0,9
Levofloxacin 200 mg/kg	7,4	- 2,4
Sparfloxacin 100 mg/kg	6,8	- 4,3
Moxifloxacin 100 mg/kg	6,8	- 4,8

Man : early bactericidal activity : (EBA) equivalent to that of RMP but less than that of INH (Gosling AJRCCM 2003)

Main antituberculous drugs for MDR (WHO, decreasing activity)

Aminoglycosides

Fluoroquinolones

Ethionamide

Ethambutol

Pyrazinamide

PAS

Cycloserine

Published results

Benefit of fluoroquinolones in MDR treatment

- Chan AJRCCM 2004 : significant on bacteriological and clinical outcome
- Tahaoglu NEJM 2001: trend on clinical outcome