

Tuberculose :
**Aspects fondamentaux ; traitements en
médecine humaine**

Académie Vétérinaire de France
Séance du 4 avril 2013

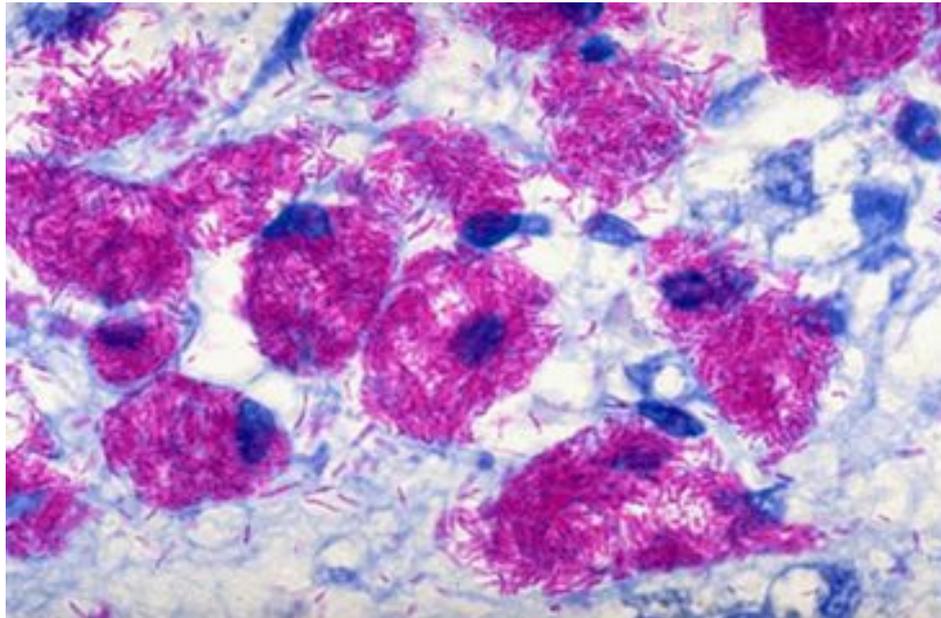
Henri-Jean Boulouis

Classification

- Classe : SCHIZOMYCETES
- Ordre : ACTINOMYCETALES
- Famille : *MYCOBACTERIACEAE*
- Genre : *MYCOBACTERIUM*

.162 espèces

dont 8 tuberculeuses



M. tuberculosis

M. bovis

M. bovis BCG

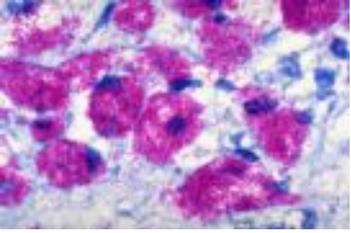
M. caprae

M. microti

M. pinipedii

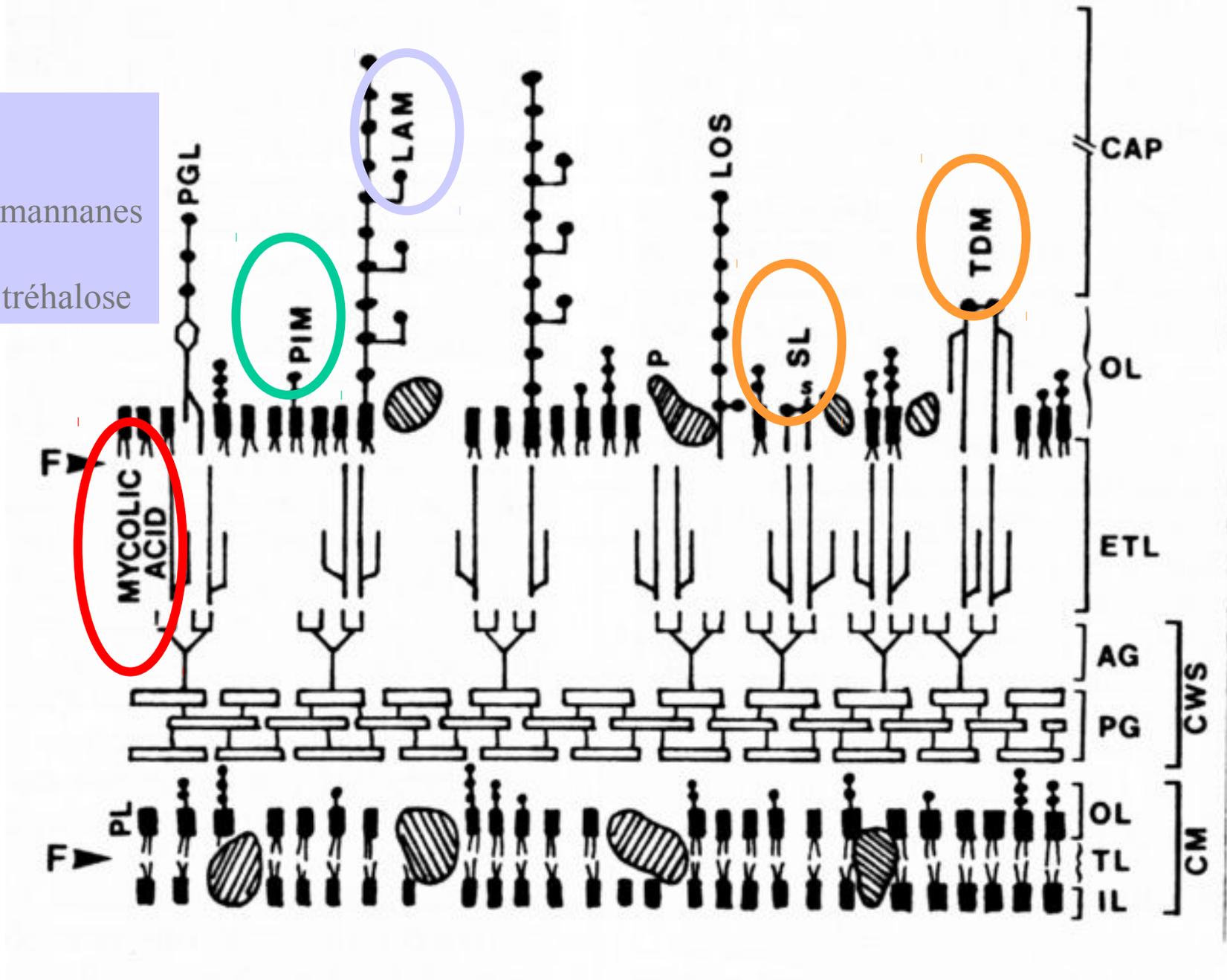
M. africanum

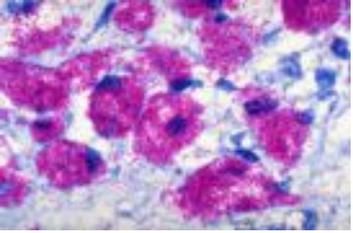
M. canettii



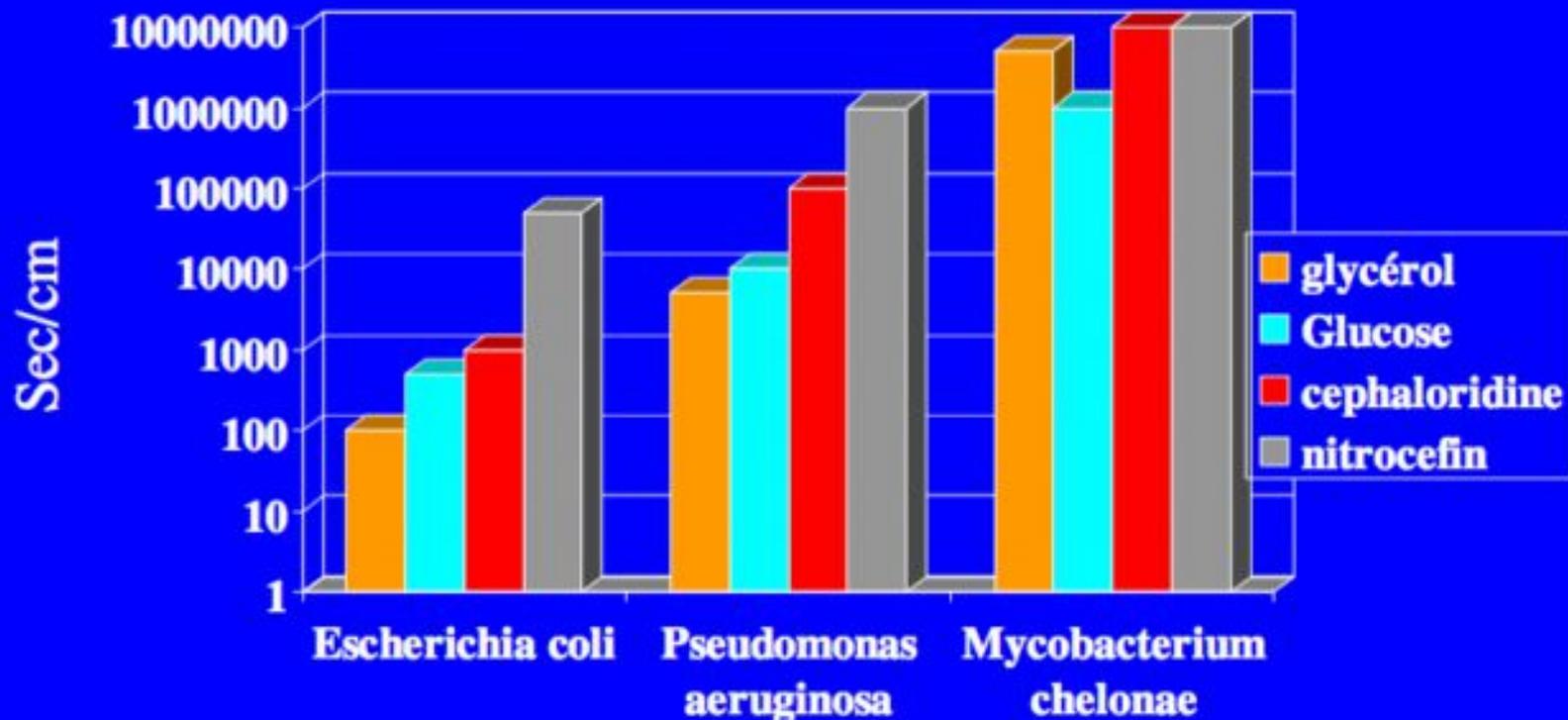
Structure de la paroi des mycobactéries

PG : peptidoglycane
 PIM : phospholipides
 LAM : lipido arabino mannes
 SL : sulfolipides
 TDM : dimycolate de tréhalose

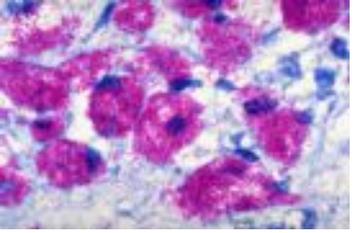




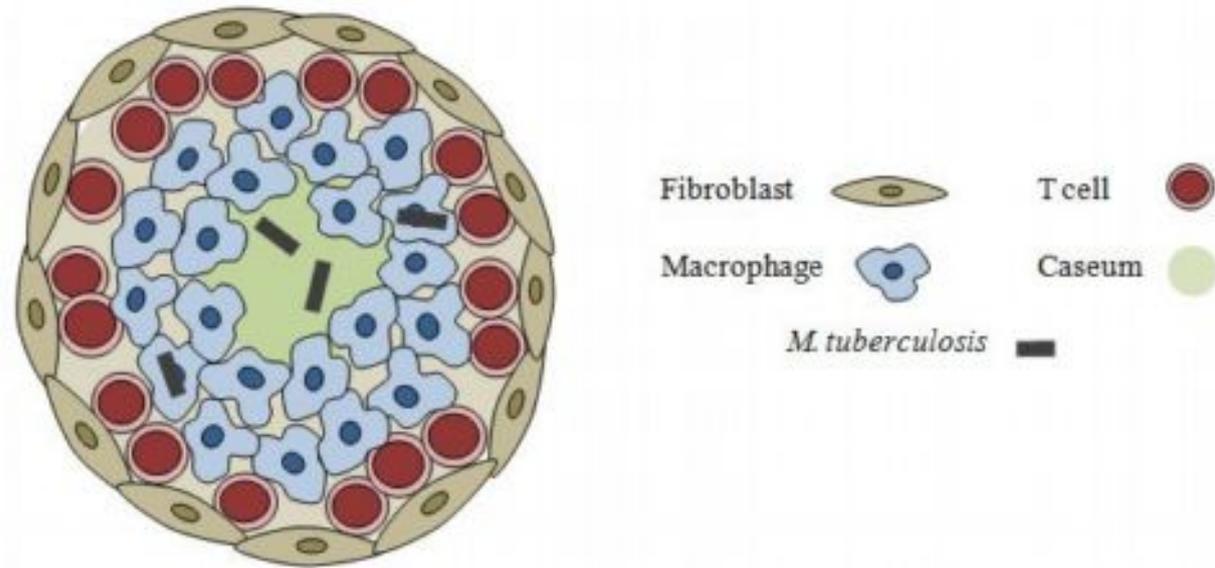
Imperméabilité naturelle de la paroi des mycobactéries



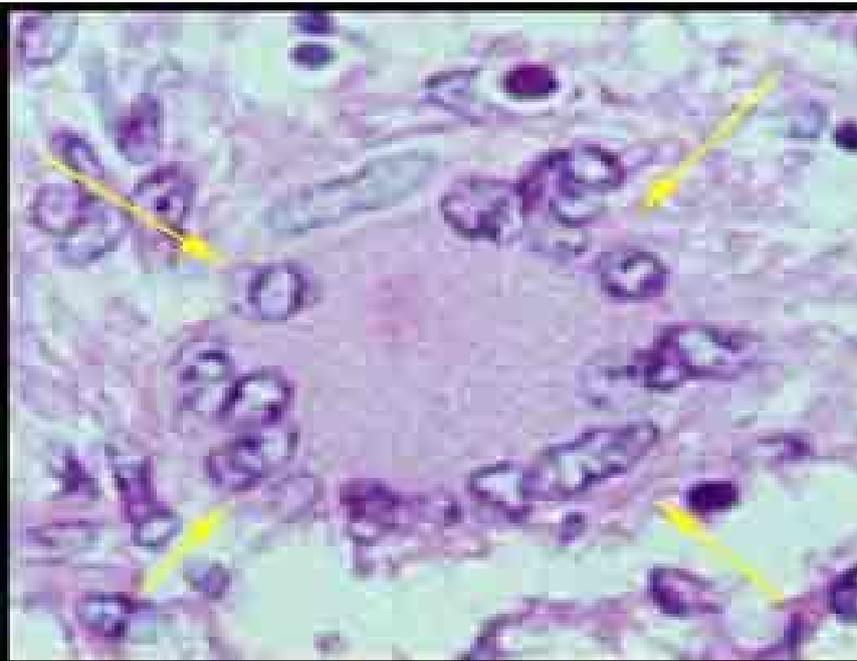
Jarlier et Nikaido 1990

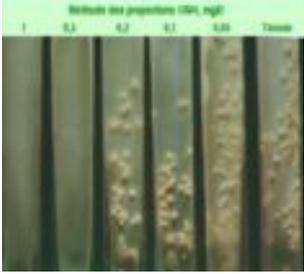


Physiopathologie



Tubercule

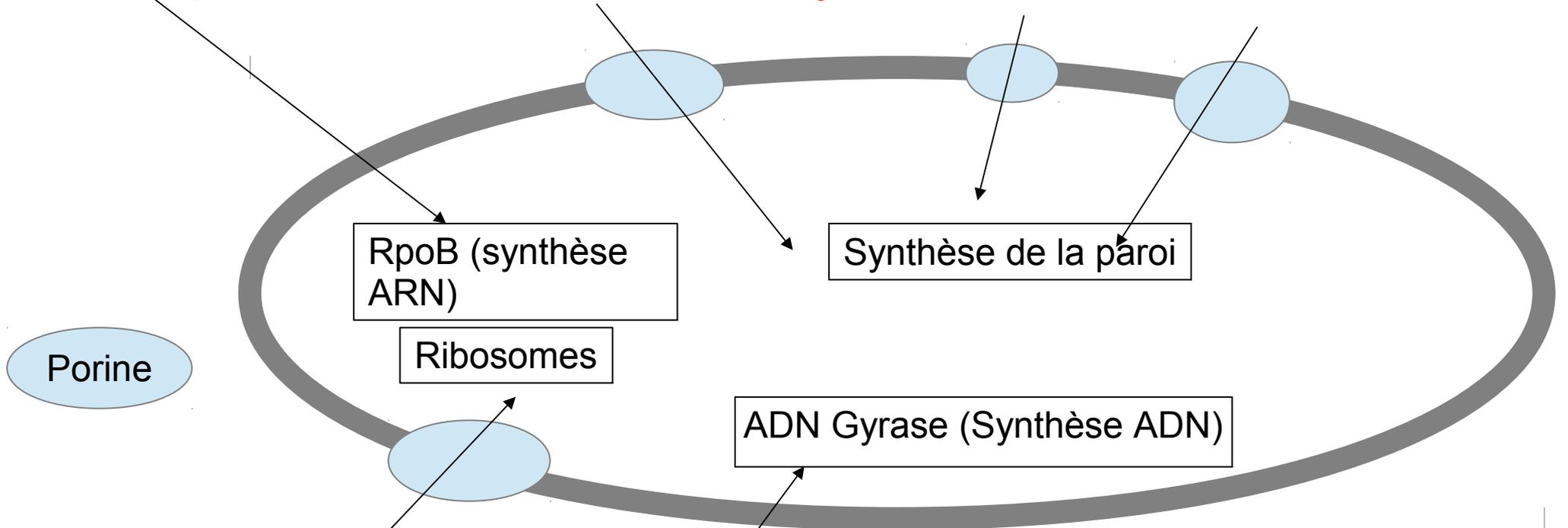




Mode d'action des anti tuberculeux

1ere ligne

Rifampicine Isoniazide Pyrazinamide Ethambutol



2ème ligne

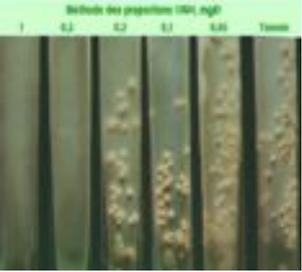
Aminosides

Quinolones

Ethionamide Rifabutine

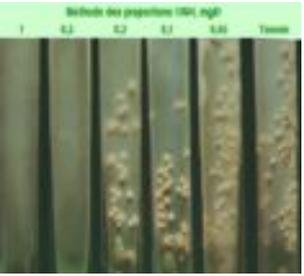
Clofazimine Cyclosérine

Capréomycine Thiacetazone

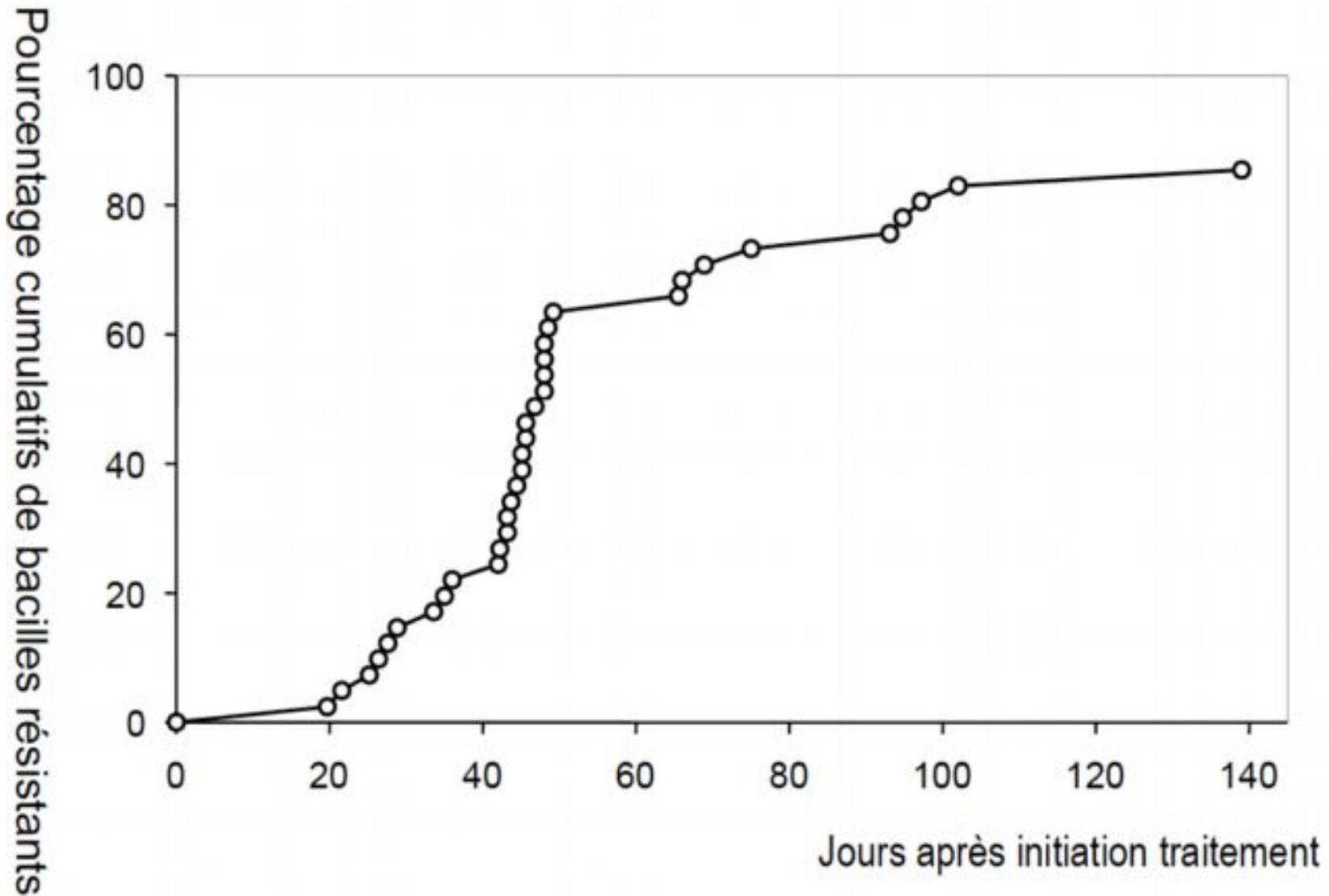


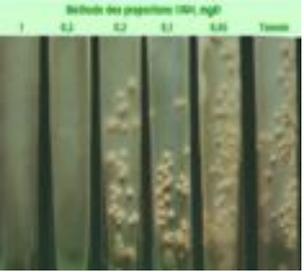
Historique des résistances acquises

Anti tuberculeux <i>M. tuberculosis</i>	Utilisation du traitement	Résistance in vivo	Références
Streptomycine	1946	1947	BMRC
Isoniazide	1952	1953	Fox
Rifampicine	1968	1968	Tsukamura
Ofloxacine	1985	1985	Tsukamura



Essai streptomycine (1948)





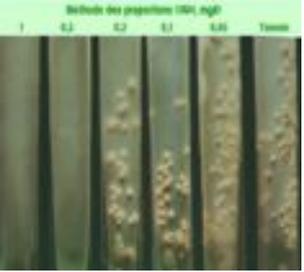
Résistance à la Streptomycine chez *M. tuberculosis*

Mutations ponctuelles

RspL/ prot L12

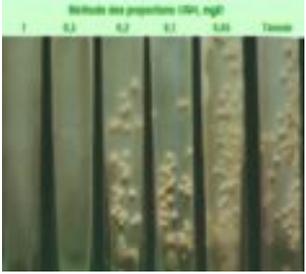
rrs (ARN 16S)

43	88	491	512, 513, 516	903,904
Lys	Lys			
Arg	Gln			
	Thr			
	55%		15%	



Résistance à l'amikacine et la capréomycine

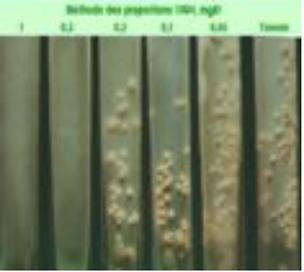
- rrs (ARN 16S) :A 1401 G
 - Résistance à l'amikacine et la capréomycine
- rrs (ARN 16S) :C 1401 T
 - Résistance à la capréomycine
- Autres mécanismes...



Résistance à la Rifampicine chez *M. tuberculosis*

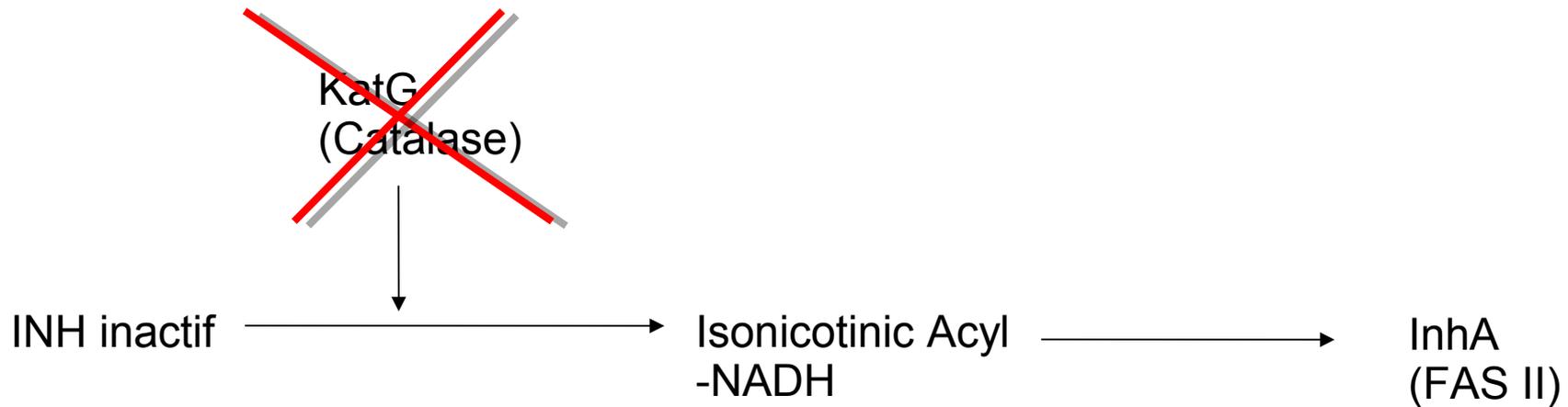
Mutations ponctuelles
(région 507-533 de rpoB)

511	513	516	521	526	531	533
Leu	Gly	Asp	Ser	His	Ser	Leu
Pro	Leu	Tyr	Leu	Tyr	Leu	Pro
	Pro	Val		Asp	Trp	
				Arg		
				Leu		
		10%		35%		45%



Résistance à l'isoniazide chez *M. tuberculosis*

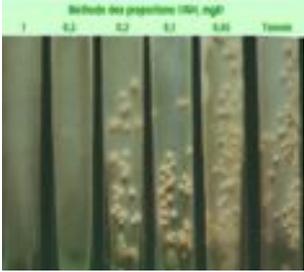
Deux mécanismes de résistance :



Mutations KatG (>50%) :

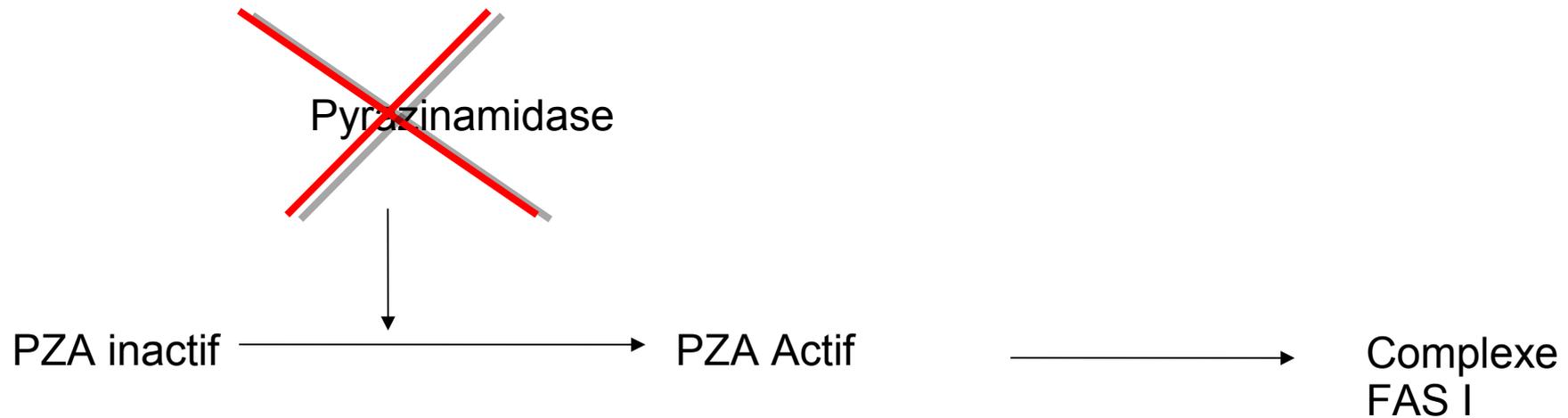
Ser 315 Thr (60%)
Arg 104 Leu, His 108 Gln
Thr 275 Pro

Mutations inhA

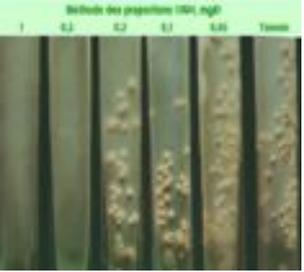


Résistance au Pyrazinamide chez *M. tuberculosis*

Deux mécanismes de résistance :



Mutations PncA (72-98%)

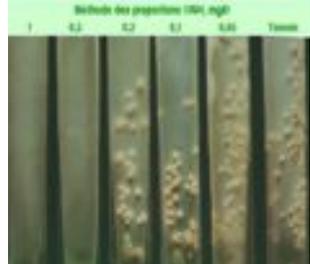


Mutations de l'ADN gyrase et résistance acquise aux FQ

	Ac. Aminés dans la sous unité A			
	81	83	84	87
<i>M. tuberculosis</i> WT	Gly	Ala	Ser	Asp
<i>M. tuberculosis</i>	Cys	Val	Pro	His
<i>M. bovis</i>				Tyr

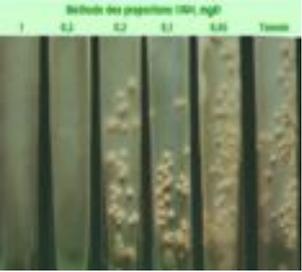
Drug(s) ^a	Yr of discovery	Drug mode of action	Gene	Target enzyme	Frequency of mutations (%) associated with resistance	References
INH*	1952	Inhibits cell wall synthesis	<i>katG</i>	Catalase peroxidase	30–60	52, 55, 88, 90, 101, 128
			<i>InhA</i>	Fatty acid enoyl acyl carrier protein reductase A	70–80	
			<i>ahpC</i>	Alkyl hydroperoxidase reductase	Not known	
			<i>kasA</i>	B-ketoacyl-ACP synthase	Not known	
			<i>ndh</i>	NADH dehydrogenase	9.5	
RIF*	1966	Inhibits RNA synthesis	<i>rpoB</i>	B subunit of RNA polymerase	95	88, 90, 108, 128
STR***	1944	Inhibits translation	<i>rpsL</i>	Ribosomal protein S12	65–67	77, 88, 128
			<i>rrs</i>	16S rRNA		
			<i>gidB</i>	7-Methylguanosine methyltransferase	33	
EMB*	1961	Inhibits cell wall synthesis	<i>embCAB</i>	Arabinosyl transferase	70–90	48, 88, 128
PZA*	1952	Disrupts plasmamembrane and energy metabolism	<i>pncA</i>	Pyrazinamidase	>70	62, 96, 128
				IS6110 insertion	Not known	
FQ**	1963	Introduces negative supercoils in DNA molecules	<i>gyrA</i>	DNA gyrase	42–85	16, 32, 33, 128
			<i>gyrB</i>			
KAN, AMI**	1957	Inhibits translation	<i>rrs</i>	16S rRNA	>60	2, 53, 105, 109, 128
CAP, VIO**	1957		<i>rrs</i>	16S rRNA	40–100	66, 105
			<i>tlyA</i>	rRNA methyltransferase	80	
ETH**	1956	Disrupts cell wall biosynthesis	<i>InhA</i>	Fatty acid enoyl acyl carrier protein reductase A	>60	7, 57, 69, 91, 128
			<i>ethA</i>	Flavin monooxygenase	>60	
			<i>ethR</i>	Transcriptional repressor	Not known	

^aAll drugs were hydrophilic. VIO, viomycin; ETH, ethionamide. *, first-line drug for treatment of TB; **, second-line drug for treatment of MDR-TB; ***, alternative first-line drug for retreatment TB cases. The FQ for treatment of MDR-TB consists of OFL-CIP-moxifloxacin.



Pompes à efflux et résistance aux anti tuberculeux

Pump	Gene	Transporter Family	Known Substrates	Known Inhibitors	Energy Source	Mycobacteria	Reference
-	<i>rv0194</i>	ABC	Ampicillin Chloramphenicol Streptomycin Novobiocin	Reserpine	ATP	<i>M. tuberculosis</i>	[25]
DrrAB	<i>drrA-drrB</i>	ABC	Doxorubicin	Verapamil Reserpine	ATP	<i>M. tuberculosis</i>	[71]
MmpL7	<i>mmpL7</i>	RND	Isoniazid	Reserpine CCCP	PMF	<i>M. tuberculosis</i>	[72]
Tap	<i>rv1258c</i>	MFS	Tetracycline Rifampicin	Piperine	PMF	<i>M. tuberculosis</i> <i>M. fortuitum</i>	[73-75]
P55^b	<i>rv1410c</i>	MFS	Rifampicin Clofazimine Aminoglycosides Tetracycline	CCCP Valinomycin	PMF	<i>M. tuberculosis</i> <i>M. bovis</i>	[76,77]
JefA	<i>rv2459</i>	MFS	Isoniazid Ethambutol Streptomycin	Verapamil CCCP	Not speculated	<i>M. tuberculosis</i>	[78]
EfpA	<i>rv2846c</i>	MFS	Not determined	-	PMF	<i>M. tuberculosis</i> <i>M. smegmatis</i> <i>M. leprae</i> <i>M. avium</i>	[67,79]
IniA^a	<i>iniA</i>	-	Isoniazid Ethambutol	Reserpine	Not speculated	<i>M. tuberculosis</i>	[80]
Mmr	<i>rv3065</i>	SMR	Erythromycin Thioridazine	CCCP	PMF	<i>M. tuberculosis</i>	[81,82]
Tet(V)	<i>tet(V)</i>	MFS	Tetracycline	CCCP	PMF	<i>M. smegmatis</i> <i>M. fortuitum</i>	[81]
LfrA	<i>lfrA</i>	MFS	Fluoroquinolones Doxorubicin	CCCP	PMF	<i>M. smegmatis</i>	[83]



Définitions

Résistance primaire : nouveau cas (jamais traité par anti tuberculeux)

Résistance secondaire : cas déjà traité par anti tuberculeux

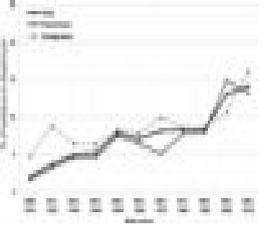
Multi résistance (MDR) : Résistance à INH et RMP)

Ultra résistance (XDR):

- . MDR

- + Résistance à FQ

- + Résistance à un aminoside autre que STP



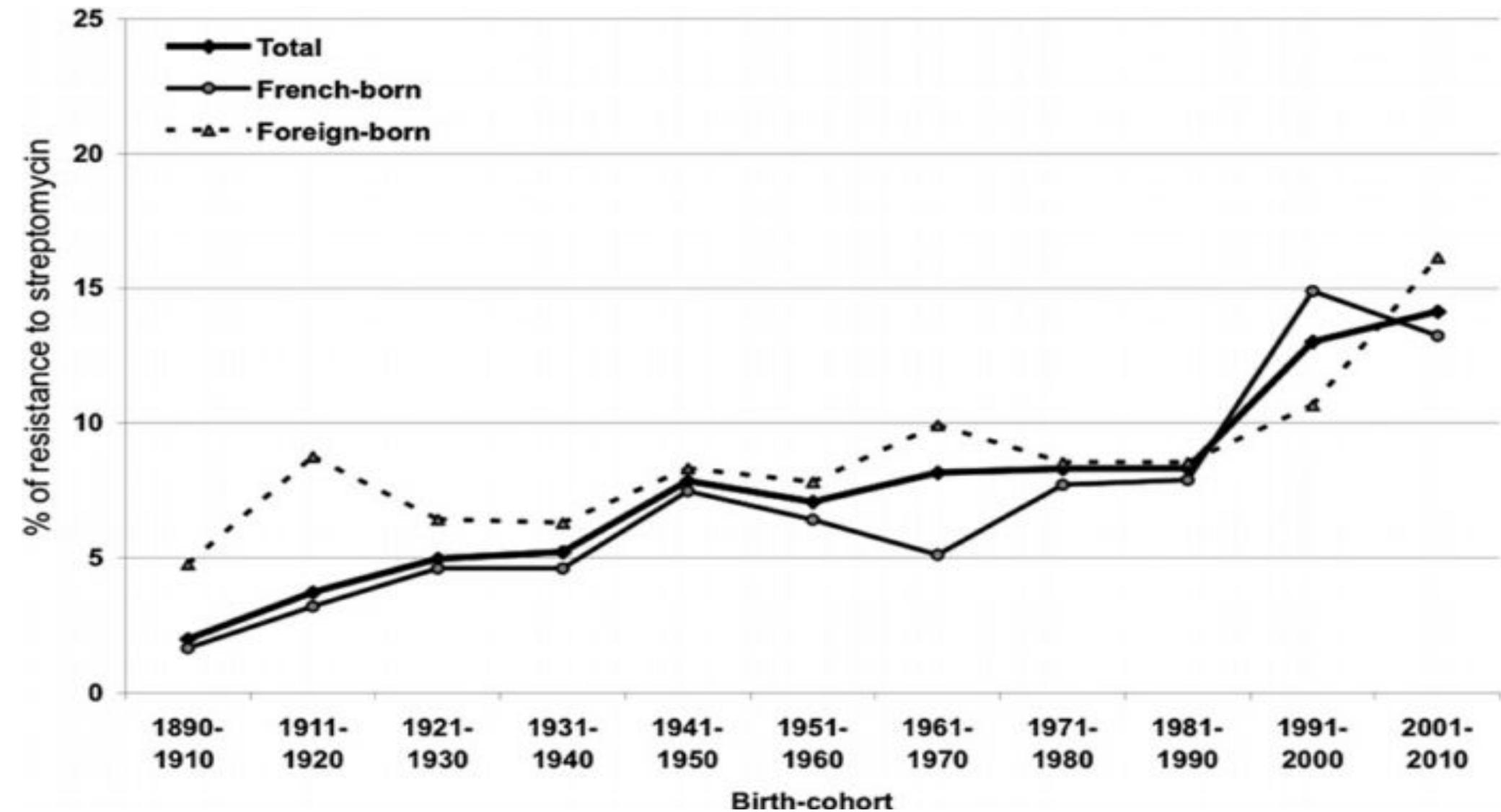
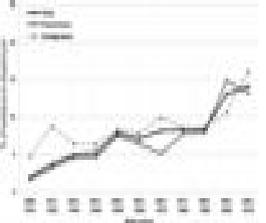
Épidémiologie des résistances

Tableau Résistance aux antituberculeux de première ligne en France en 2010 (réseau du Groupe Azay-Mycobactéries) / *Table* Resistance to first-line anti-tuberculosis drugs in France in 2010 (Network of the Azay-Mycobactéries Group)

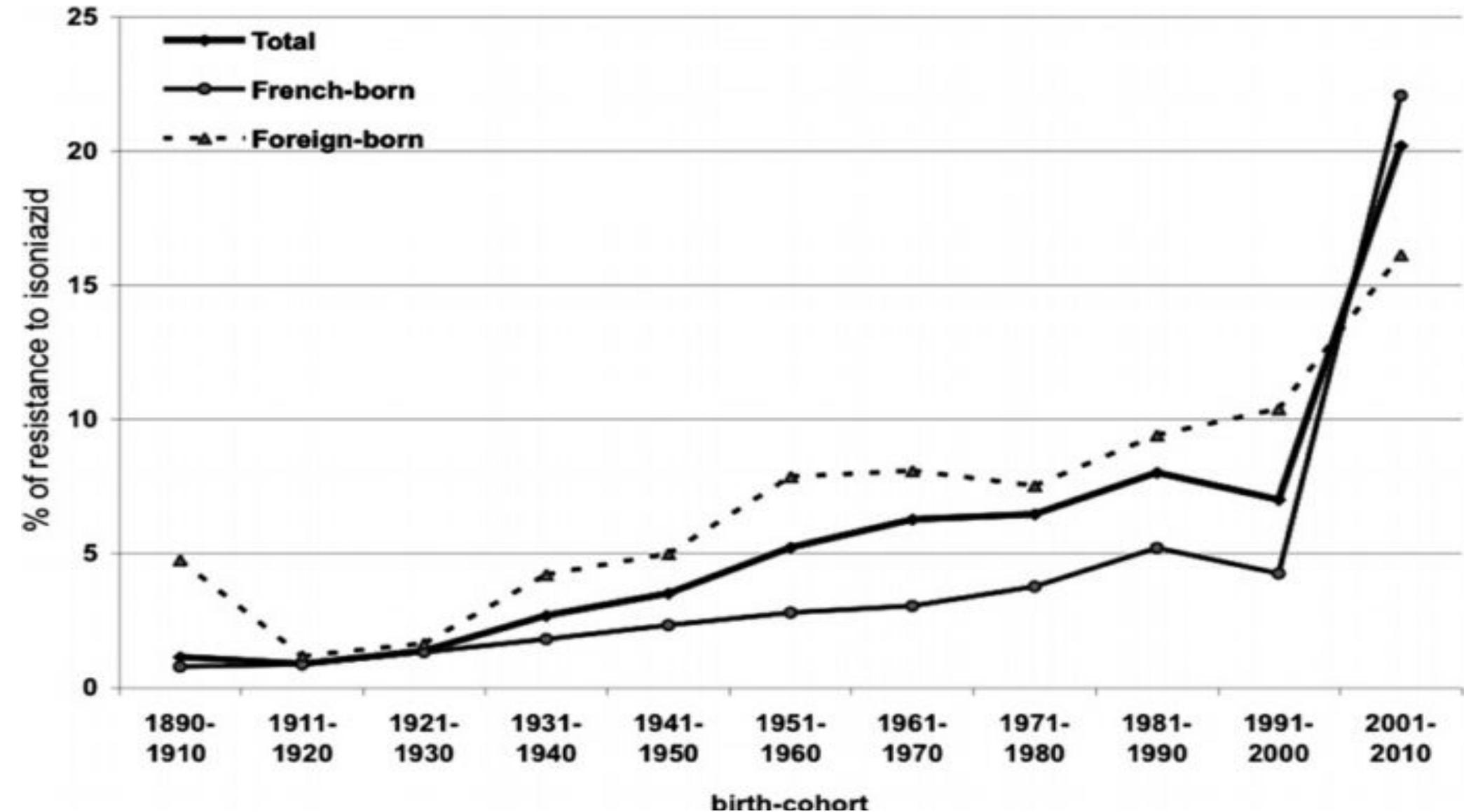
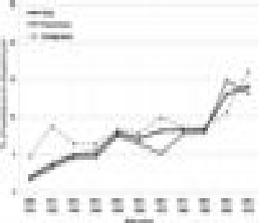
Profil de sensibilité	Nouveaux cas		Malades déjà traités		Antécédents inconnus	
	N	%	N	%	N	%
Souches testées	1 187	100,0	91	100,0	195	100,0
Sensibles	1 072	90,3	72	79,1	168	86,2
Résistantes	115	9,7	19	20,9	27	13,8
- dont au moins à :						
SM	71	6,0	12	13,2	17	8,7
INH	64	5,4	16	17,6	12	6,2
RMP	15	1,3	8	8,8	5	2,6
EMB	10	0,8	7	7,7	5	2,6
INH+RMP	13	1,1	8	8,8	2	1,0

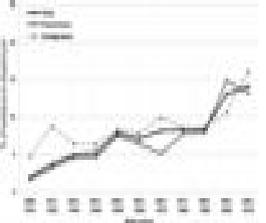
SM : streptomycine ; INH : isoniazide ; RMP : rifampicine ; EMB : éthambutol ; INH+RMP : multirésistance (définition OMS).

Evolution du taux de résistance à la streptomycine par cohorte de naissance en France.



Evolution du taux de résistance à l'isoniazide par cohorte de naissance en France.





Evolution du taux de résistance à la rifampicine par cohorte de naissance en France

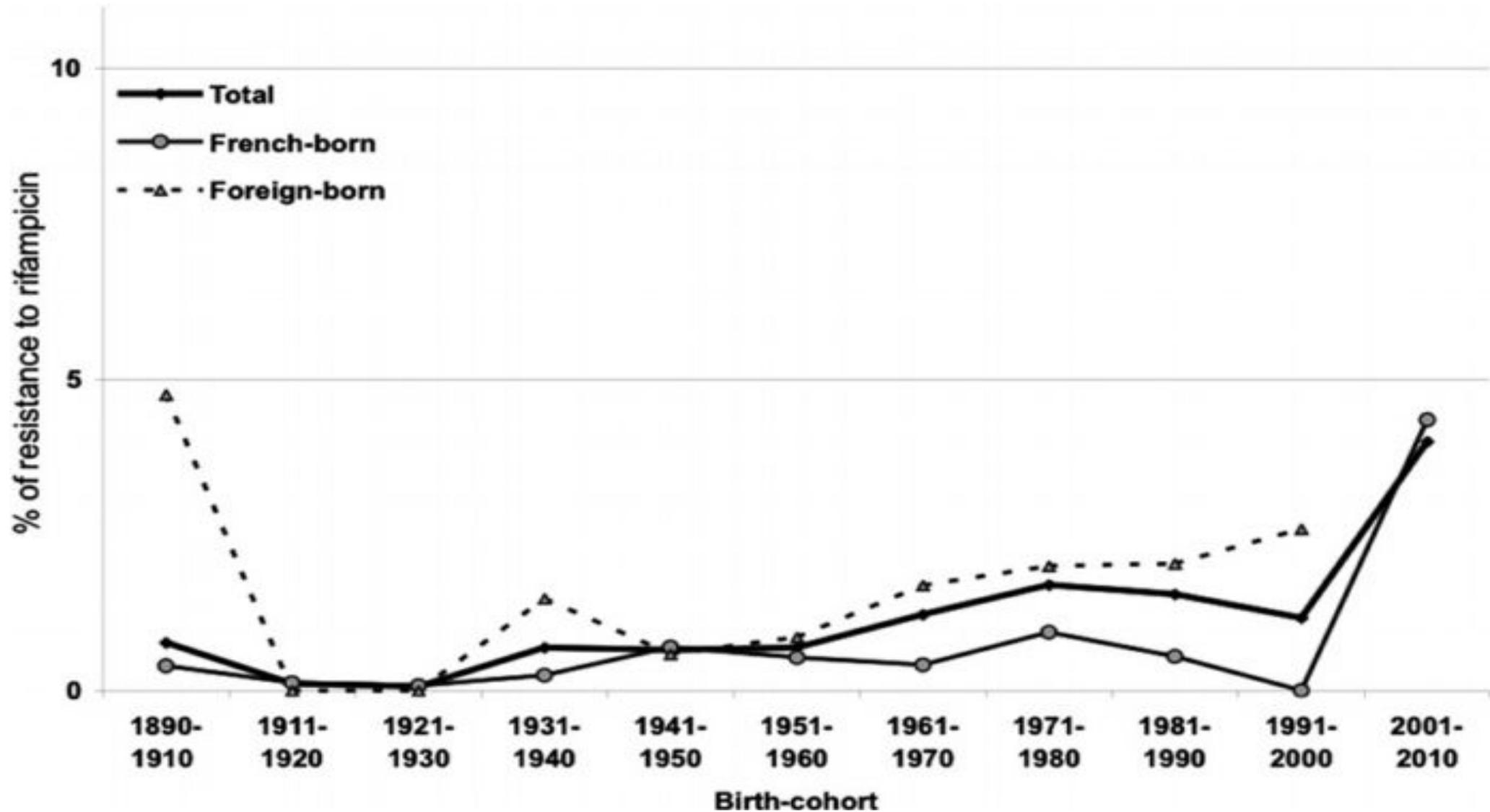


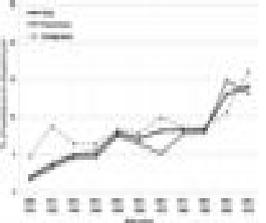
TABLE 1

Combined (previously untreated and retreatment) anti-tuberculosis drug resistance in EU/EEA countries, 2008

Country	Total number of cases	Culture-positive cases	Cases with DST results to at least rifampicin and isoniazid ¹	Cases resistant to at least:					
				Isoniazid	Rifampicin	Isoniazid and rifampicin (multidrug resistant)	Ethambutol	Streptomycin	Cases resistant to any anti-TB drug
				N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Austria	-	-	-	-	-	-	-	-	-
Belgium	1,006	812 (80.7)	773 (95.2)	56 (7.2)	24 (3.1)	22 (2.8)	22 (2.8)	4 (0.5)	62 (8.0)
Bulgaria	3,151	1,361 (43.2)	938 (68.9)	121 (12.9)	43 (4.6)	32 (3.4)	84 (9.0)	55 (5.9)	179 (19.1)
Cyprus	50	36 (72.0)	36 (100.0)	4 (11.1)	1 (2.8)	1 (2.8)	0 (0.0)	3 (8.3)	6 (16.7)
Czech Republic	868	561 (64.6)	520 (92.7)	26 (5.0)	14 (2.7)	11 (2.1)	7 (1.3)	29 (5.6)	41 (7.9)
Denmark	367	283 (77.1)	281 (99.3)	11 (3.9)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	12 (4.3)
Estonia	444	347 (78.2)	347 (100.0)	103 (29.7)	74 (21.3)	74 (21.3)	78 (22.5)	122 (35.2)	130 (37.5)
Finland	360	248 (68.9)	247 (99.6)	12 (6.0)	2 (0.8)	1 (0.4)	0 (0.0)	6 (2.4)	15 (6.4)
France	5,812	2,296 (39.5)	1,556 (67.8)	103 (6.6)	32 (2.1)	27 (1.7)	18 (1.2)	112 (7.2)	171 (11.0)
Germany	4,343	3,112 (71.7)	2,983 (95.9)	197 (6.7)	33 (1.1)	43 (1.5)	43 (1.5)	134 (4.3)	187 (10.7)
Greece	669	252 (37.7)	-	-	-	-	-	-	-
Hungary	1,606	766 (47.7)	611 (79.8)	48 (7.9)	18 (2.9)	16 (2.6)	19 (3.1)	37 (6.1)	71 (11.6)
Iceland	6	5 (83.3)	5 (100.0)	2 (40.0)	1 (20.0)	1 (20.0)	0 (0.0)	1 (20.0)	2 (40.0)
Ireland	470	209 (44.5)	146 (69.9)	9 (6.2)	4 (2.7)	3 (2.1)	2 (1.4)	5 (3.4)	13 (8.9)
Italy	4,418	1,529 (34.6)	1,932 (95.4)	244 (12.6)	89 (4.6)	71 (3.7)	71 (3.7)	238 (12.3)	381 (20.3)
Latvia	1,070	838 (78.3)	828 (98.8)	257 (31.0)	132 (15.9)	129 (15.6)	115 (13.9)	242 (29.2)	285 (34.4)
Liechtenstein	-	-	-	-	-	-	-	-	-
Lithuania	2,250	1,616 (71.8)	1,616 (100.0)	469 (29.0)	287 (17.8)	276 (17.1)	167 (10.3)	412 (25.5)	513 (31.7)
Luxembourg	28	-	-	-	-	-	-	-	-
Malta	53	25 (47.2)	25 (100.0)	2 (8.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (20.0)	5 (20.0)
Netherlands	997	728 (73.0)	728 (100.0)	55 (7.6)	14 (1.9)	13 (1.8)	3 (0.4)	0 (0.0)	56 (7.7)
Norway	324	227 (70.1)	227 (100.0)	36 (15.9)	6 (2.6)	4 (1.8)	6 (2.6)	29 (12.8)	48 (21.1)
Poland	8,081	5,094 (63.0)	-	-	-	-	-	-	-
Portugal	2,995	2,007 (67.0)	1,641 (81.8)	121 (7.4)	29 (1.8)	28 (1.7)	17 (1.0)	156 (9.5)	213 (13.0)
Romania	24,786	14,762 (59.6)	5,547 (37.6)	1,126 (20.3)	873 (15.7)	816 (14.7)	297 (5.4)	229 (4.1)	1,187 (21.4)
Slovakia	633	383 (60.5)	383 (100.0)	10 (2.6)	4 (1.0)	4 (1.0)	2 (0.5)	3 (0.8)	12 (3.1)
Slovenia	213	201 (94.4)	195 (97.0)	3 (1.5)	2 (1.0)	2 (1.0)	1 (0.5)	5 (2.6)	6 (3.1)
Spain	8,214	4,493 (54.7)	1,628 (36.2)	161 (9.9)	88 (5.4)	76 (4.7)	32 (2.0)	77 (4.7)	191 (11.7)
Sweden	552	436 (79.0)	423 (97.0)	49 (11.6)	13 (3.1)	12 (2.8)	15 (3.5)	9 (2.1)	52 (12.3)
United Kingdom	8,655	4,870 (56.3)	4,808 (98.7)	288 (6.0)	71 (1.5)	53 (1.1)	35 (0.7)	186 (3.9)	405 (8.4)
Total	82,611	47,497 (57.5)	28,404 (66.4)	3,513 (12.4)	1,876 (6.6)	1,717 (6.0)	1,037 (3.7)	2,159 (7.6)	4,343 (15.3)

DST: drug sensitivity testing; EEA: European Economic Area; EU: European Union; TB: tuberculosis.

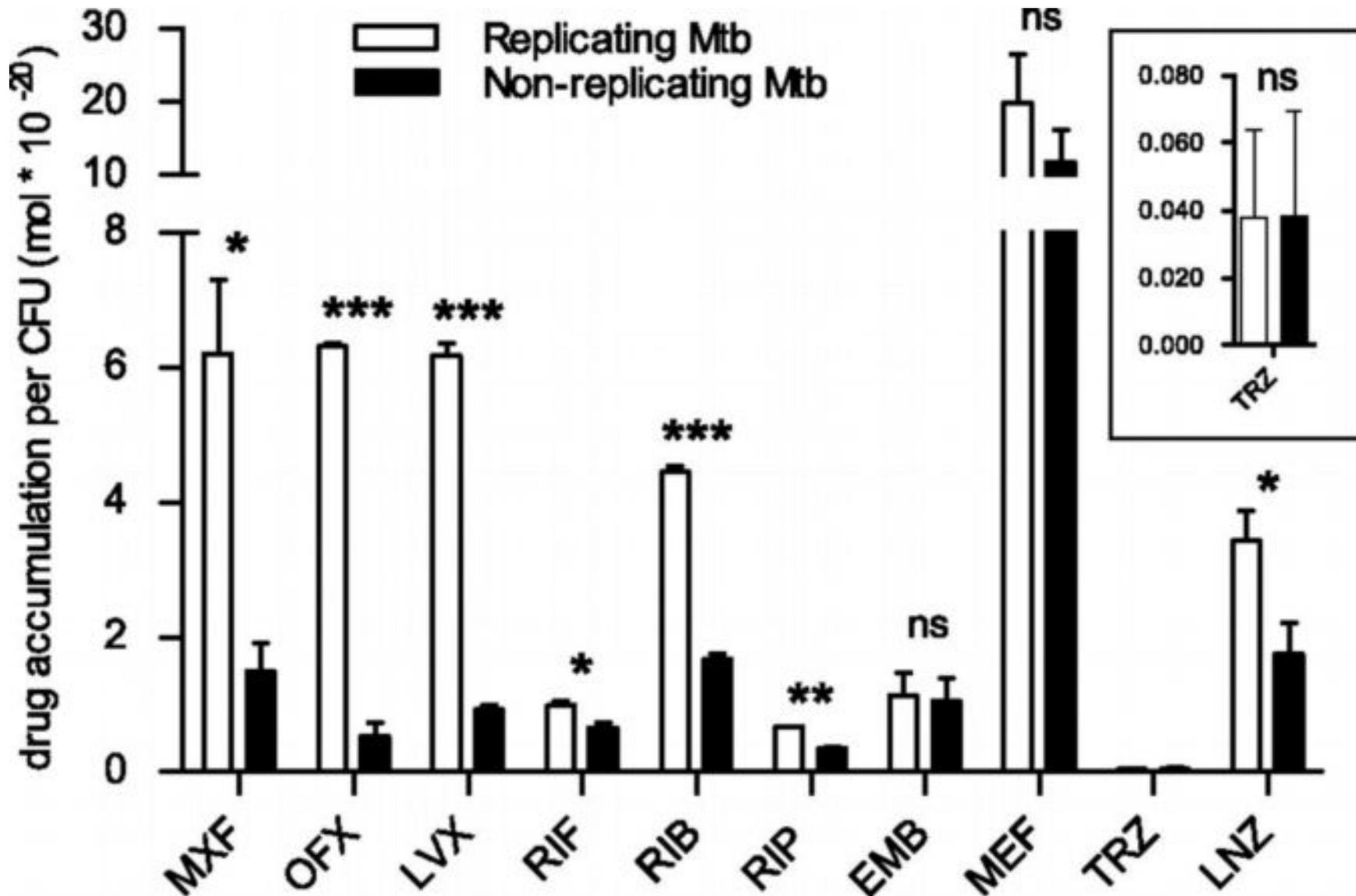
¹ Any resistance to isoniazid, rifampicin, ethambutol or streptomycin, expressed as a percentage of cases with available DST results at least to isoniazid and rifampicin. Testing for ethambutol and streptomycin not routine in all countries.



Resistance des autres Mycobactéries tuberculeuses

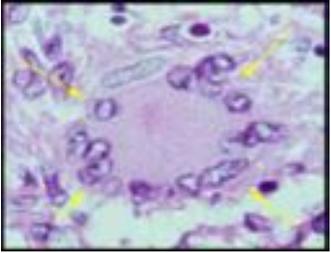
- *M. microti* : sur 10 souches testées, 3 sont résistantes uniquement à PZA (Panteix G. et al, JMM 2010)
- *M. bovis* BCG : résistance bas niveau à INH et ethionamide

Intracellular amounts of antituberculosis agents in exponentially growing and nutrient-starved nonreplicating *M. tuberculosis* (Mtb) following a 30-min incubation period at 10 μ M.



Sarathy J et al. Antimicrob. Agents Chemother. 2013;57:1648-1653

Antimicrobial Agents and Chemotherapy



Traitement antituberculeux chez l'homme

Bonne pénétration intracellulaire :

Isoniazide : activité bactéricide initiale

Rifampicine : activité stérilisante et bactéricide

Activité dans les vacuoles de phagocytose à pH 5,5

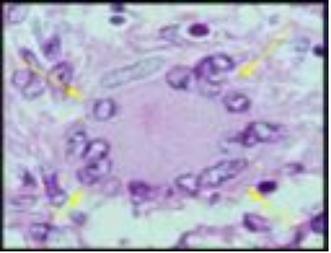
streptomycine

pyrazinamide (activité stérilisante)

Antituberculeux mineurs :

Ethambutol et fluoroquinolones

Autres : kanamycine, D-cyclosérine, PAS, (éthionamide),



Traitement antituberculeux chez l'homme

Association d'antibiotiques = obligatoire

- Traitement décidé avant lecture de l'antibiogramme : tri ou tétrathérapie : RMP + ETB + INH + PYR
- Ajustements ultérieurs éventuels selon l'antibiogramme.
Lorsque la charge bactérienne a beaucoup diminué, on ne donne plus que 2 antibiotiques

Durée

- 2 mois de tri ou tétrathérapie
- Puis 4-6 mois/10-12 mois de bi thérapie

Cout

Conclusion

Traitement long et couteux

Traitement nécessitant un contrôle

- concentration sanguine des antibiotiques
- observance