Treatment of tuberculosis including MDR and XDR cases

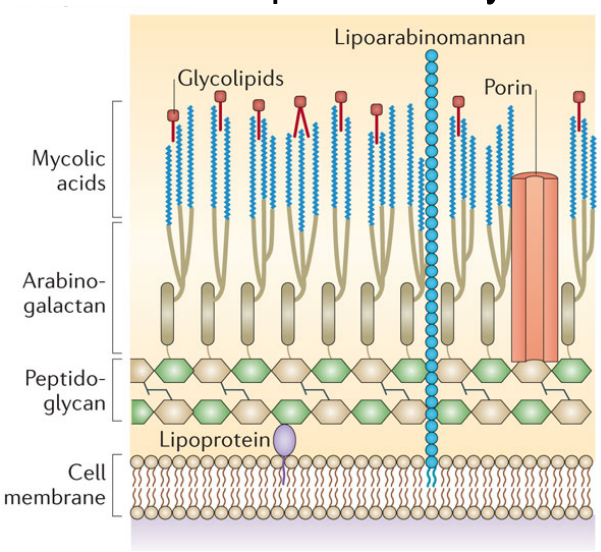
Pr Nicolas Veziris
CNR des Mycobactéries, Département de Bactériologie,
Hôpitaux Universitaires de l'Est Parisien , APHP
CiMi, INSERM, Sorbonne Université

Introduction : mycobacteria

	Stricts pathogens	≠	Opportunistic pathogens
Reservoir	Sick human or animal		Environnement
Transmission	Interhuman CONTAGIOUS		Not Interhuman
Species	-"tuberculosis" complex (*M.tuberculosis, M. bovis, M.africanum*) → **tuberculosis** -*M. leprae* → **lepropsy**		-200 species : 20 cause infections (*M. avium* …) =« non tuberculous mycobacteria »

Natural resistance

Impermeability



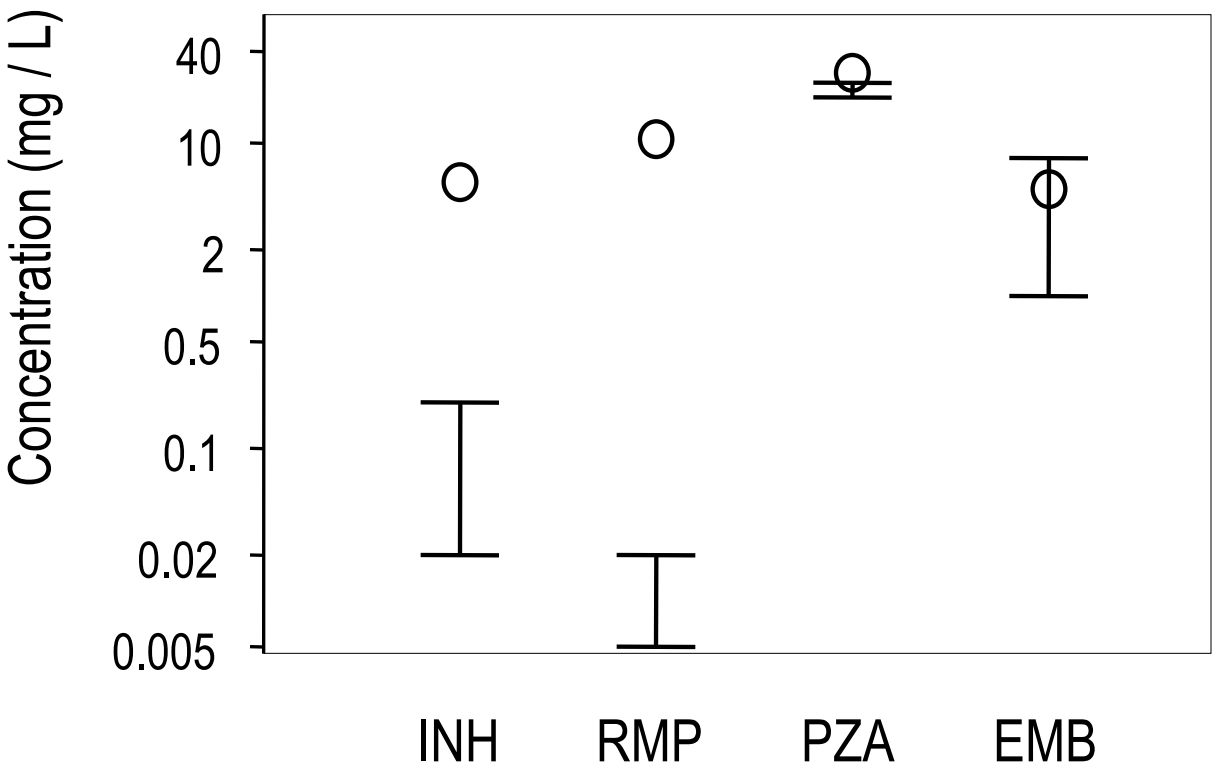
	mecanism	ATB
Target modification	*erm37* (methyltransferase)	macrolides
ATB modification	*blaC* (beta-lactamase)	beta-lactams

- Antibiotic tolerance (Aldridge, Microbiol Spectr 2014)
  - Dormancy regulon en hypoxie : DosR (Voskuil, J Exp Med 2003)
  - Biofilms
  - Efflux pumps (Adams, Cell, 2011)

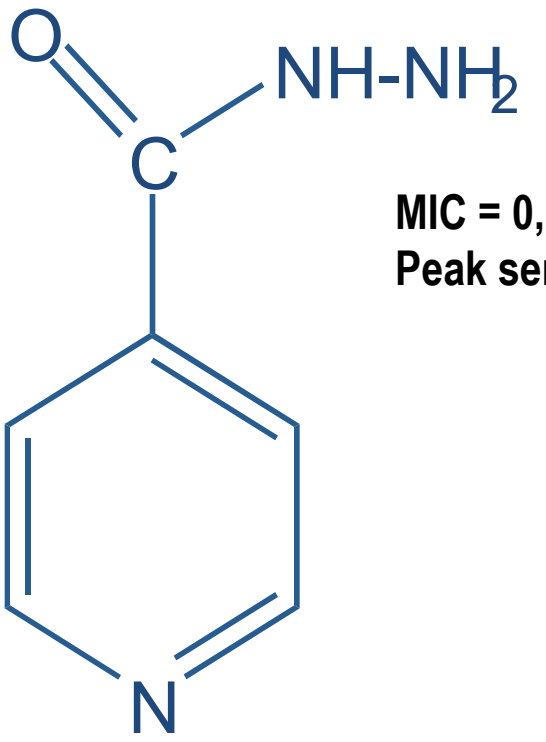
TRAITEMENT

MOLECULES

Drug serum levels and MICs



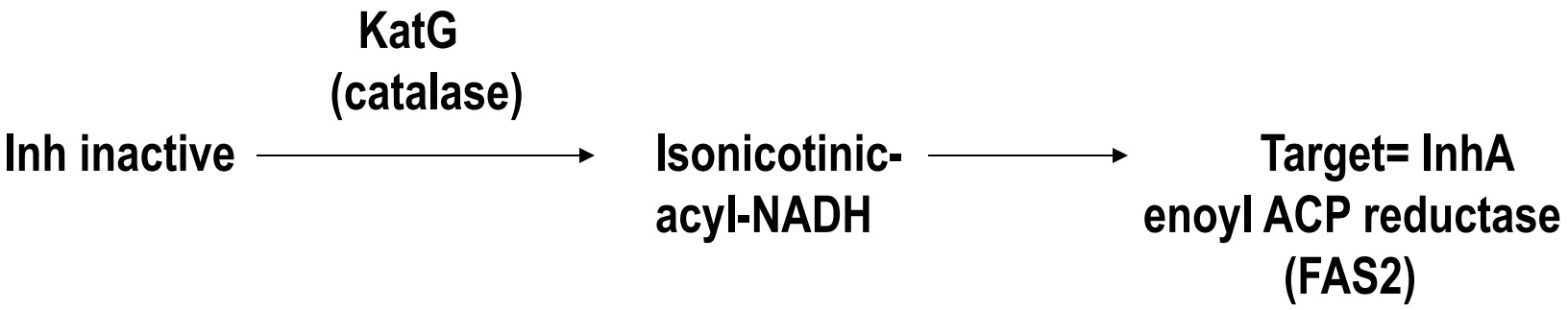
Isoniazid



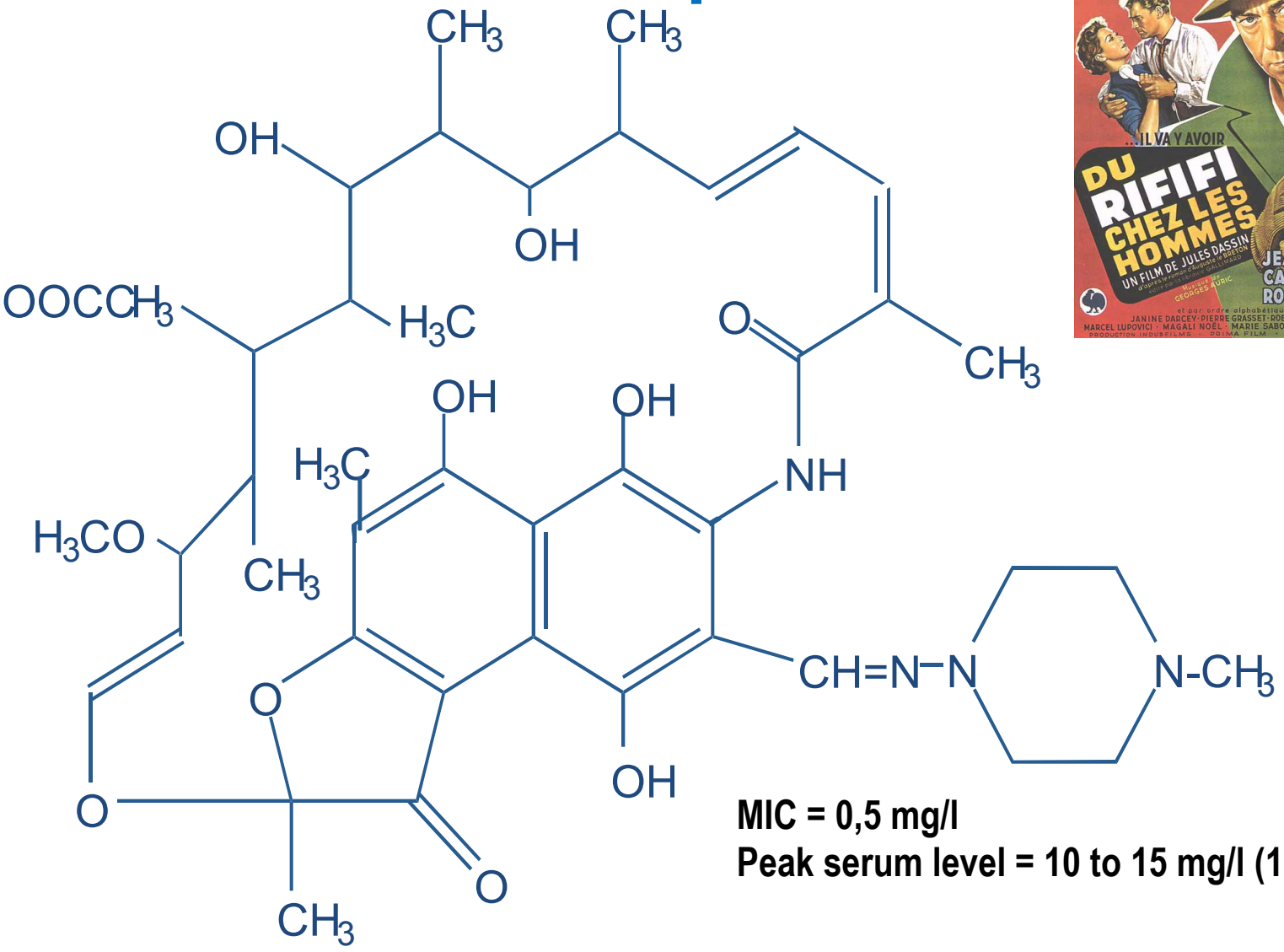
MIC = 0,05 mg/l
Peak serum level= 3 to 5 mg/l (5 mg/kg)

Meyer H, Mally J. Monatshefte Chemie 1912;33:393-414

Isoniazid : mechanism of action



Rifampin



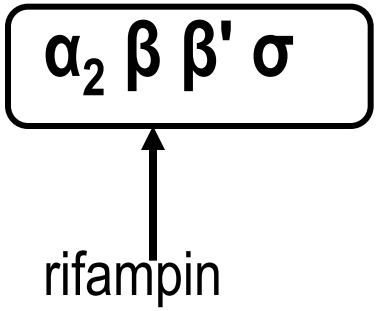
MIC = 0,5 mg/l

Peak serum level = 10 to 15 mg/l (10 mg/kg)

Maggi N, Pasqualuci C, Ballotta R, Sensi P.
Chemotherapy 1966;11:285-92

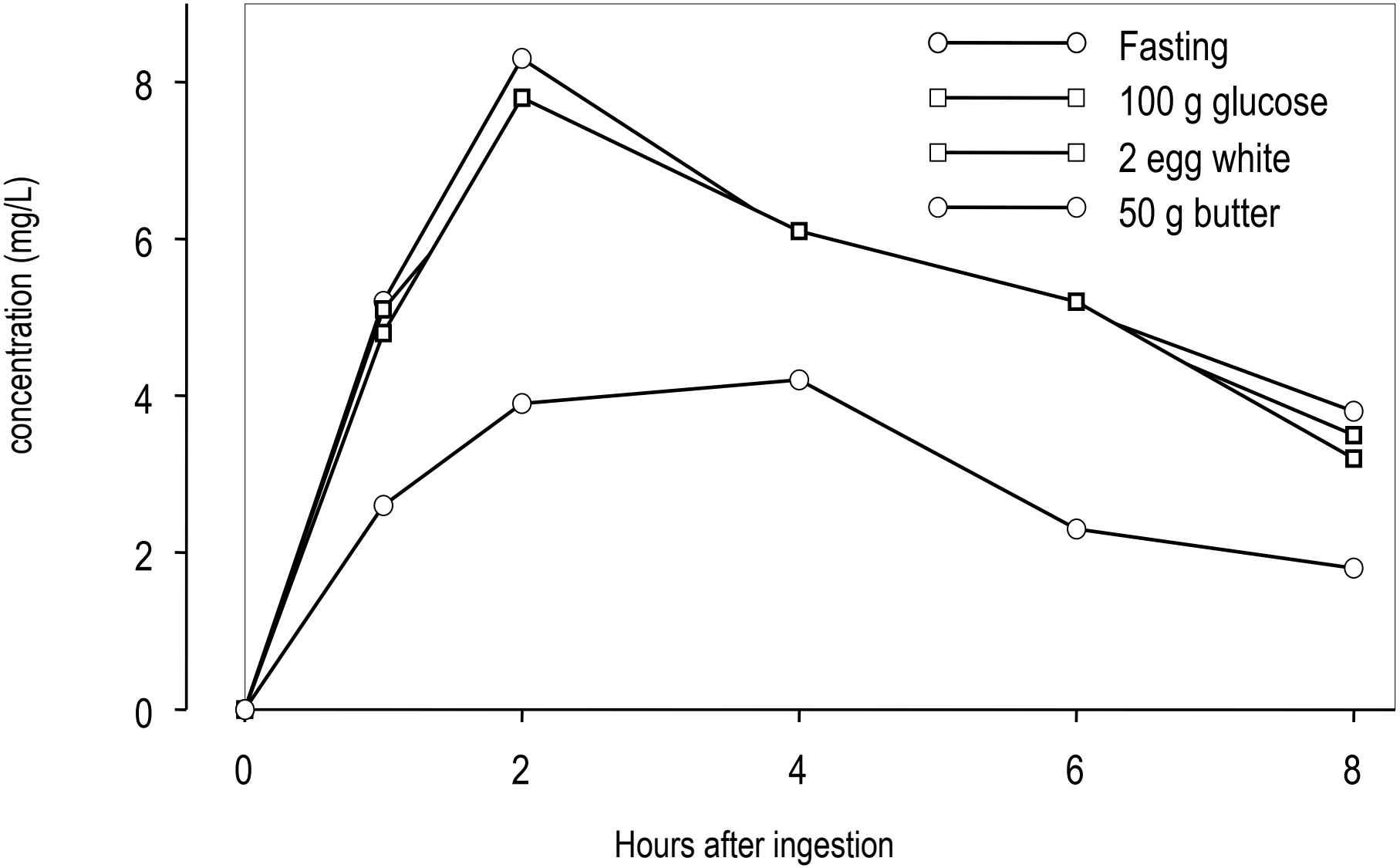
Rifampin : mechanism of action

– Binds to beta sub-unit of RNA polymerase :

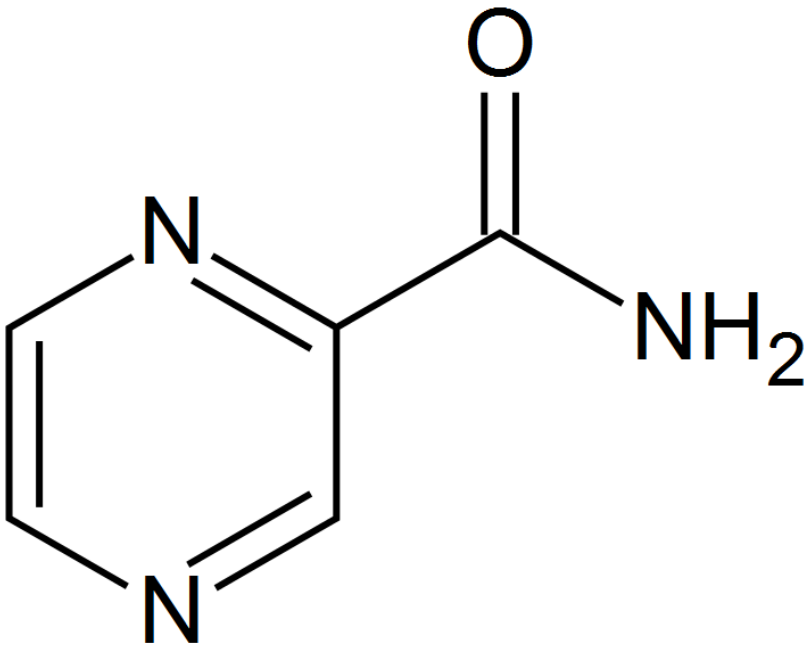


– Blocks transcription

PK of Rifampin



Pyrazinamide



MIC= 6 to 50 mg/l at pH 5,5
Peak serum level = 30 mg/l (20 mg/kg)

Kushner S, et al. Am J Chem Soc 1952;74:3617

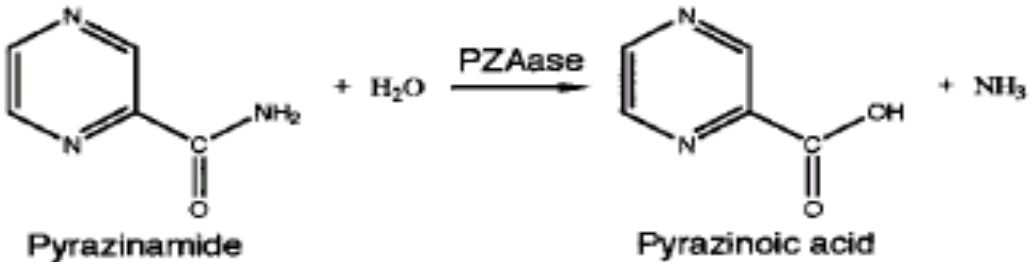
Pyrazinamide : mode of action

- *Zhang, Int J Tuberc Lung Dis, 2003*

H57D
Natural resistance
M. bovis

Pyrazinamidase (*pncA*)

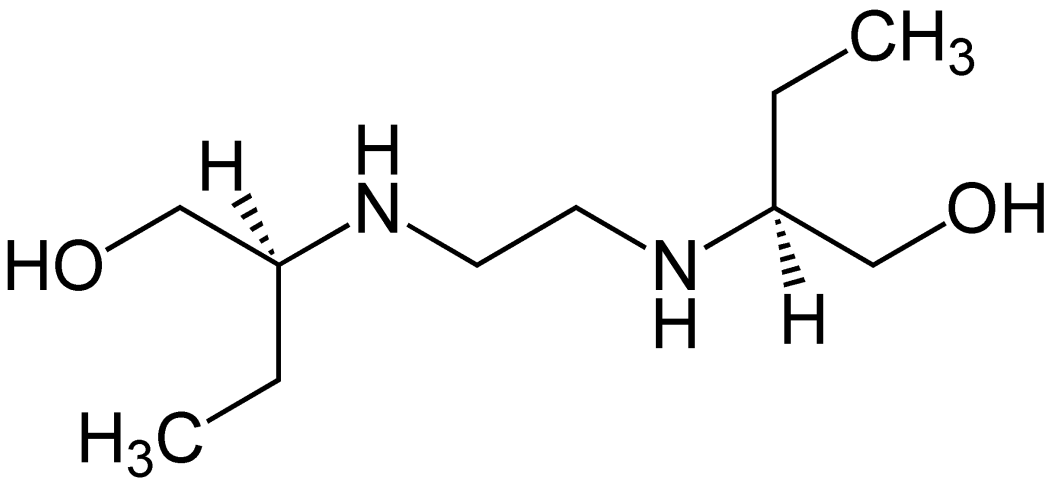
Pyrazinamide → Pyrazinoïc acid



– Target : FAS1 ("fatty acid synthetase")

Zimhony et coll., Nature Med, 2000

Ethambutol



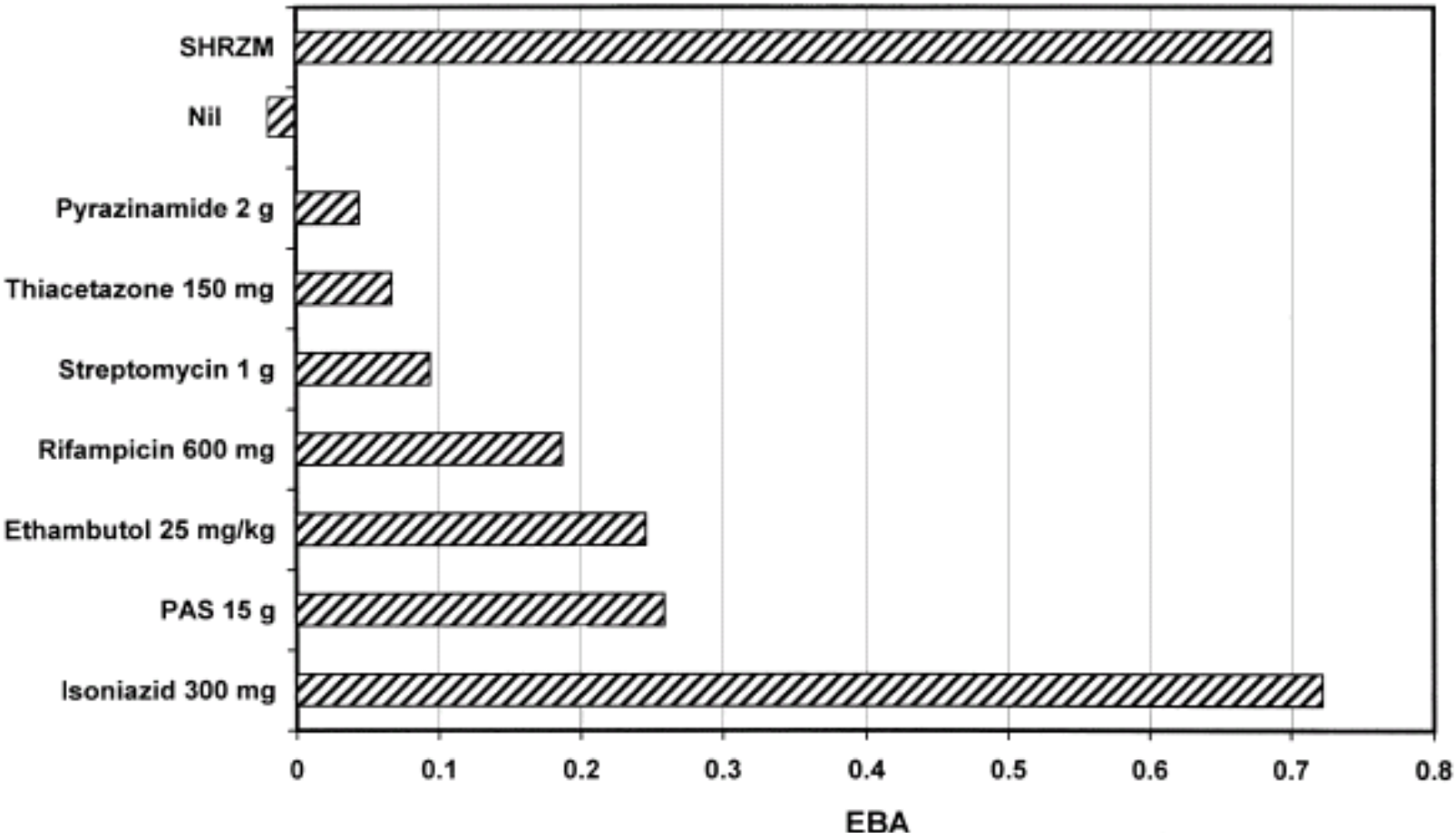
Inhibits
Arabinogalactane synthesis
= cell wall

MIC= 0,5 to 2 mg/l
Peak serum level = 2 to 3 mg/l (25 mg/kg)

Thomas JP, et al. Am Rev Respir Dis 1961;83:891-3

The role of antituberculous drugs

Early bactericidal activity

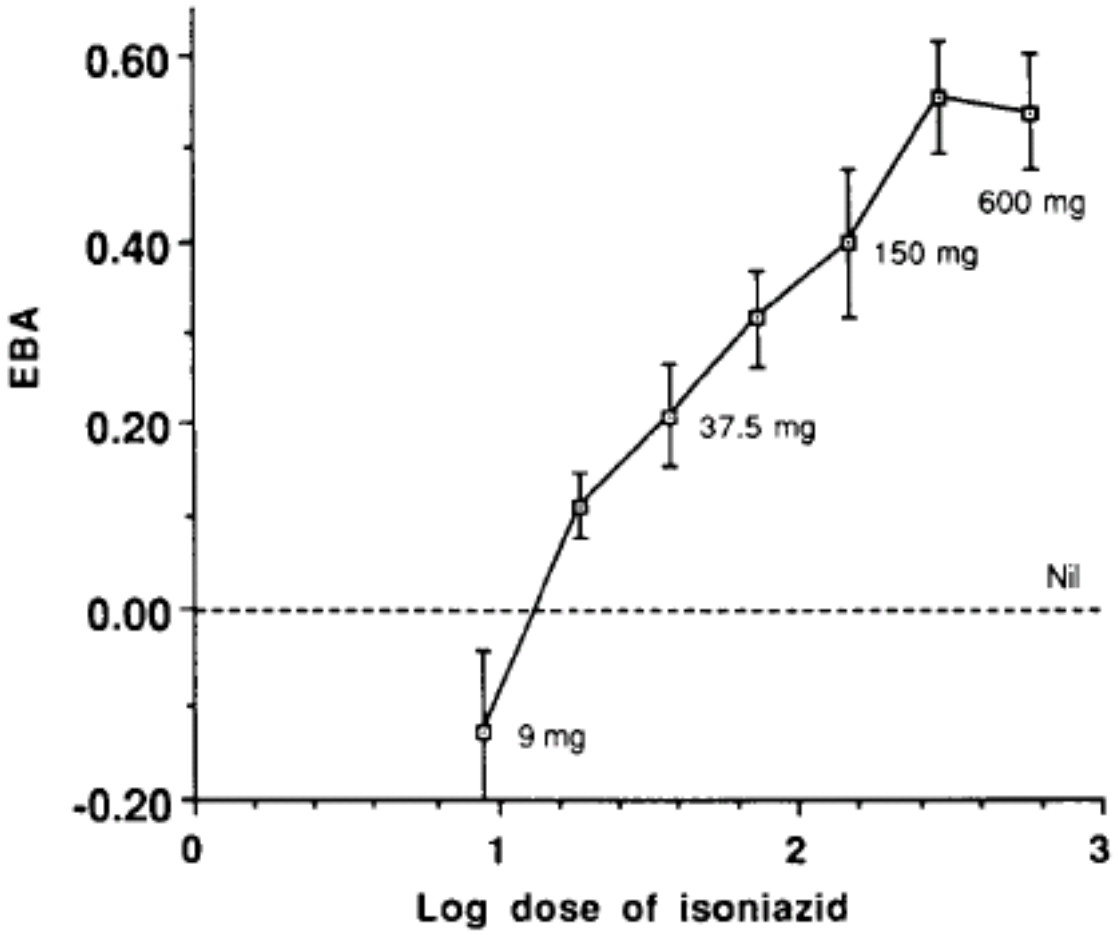


SHRZM : streptomycin+isoniazid+rifampicine+pyrazinamide+ethambutol

Nil : no treatment

Jindani, 1980

Isoniazid EBA depending on dosing



Serum level (mg/l)	EBA (log10)
0-0,5	-0.034
0,5-1	0.342
1-,1,5	0.455
1,5-2	0.390
2-3	0.609
3-6	0.633
≥6	0.526

Donald, 2004

⟹ At least 2 mg/l peak serum level

Rifampin EBA depending on dosing

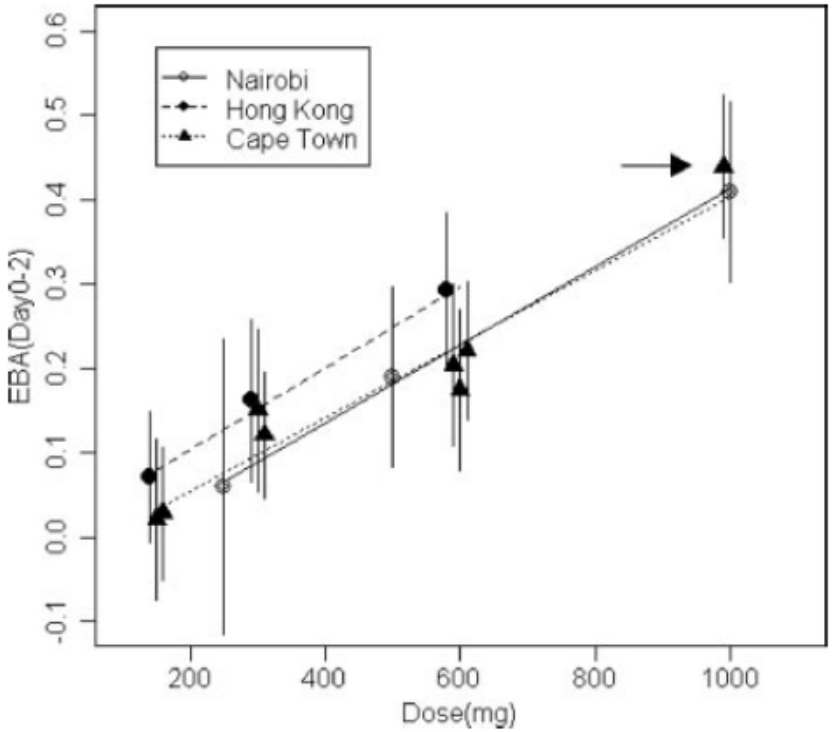
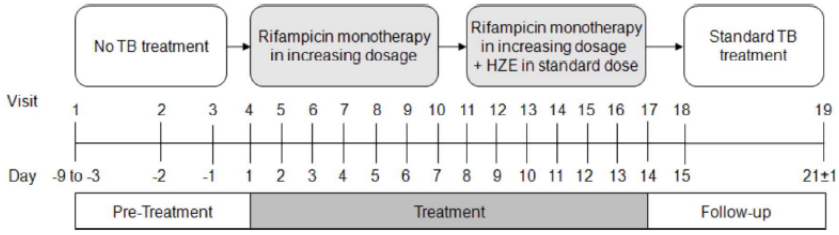
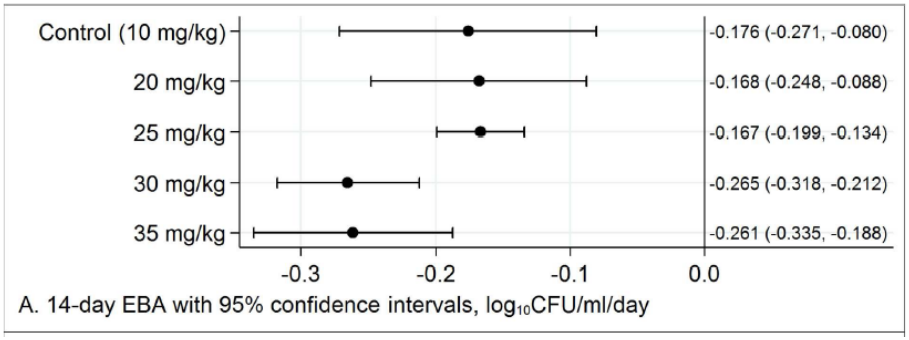


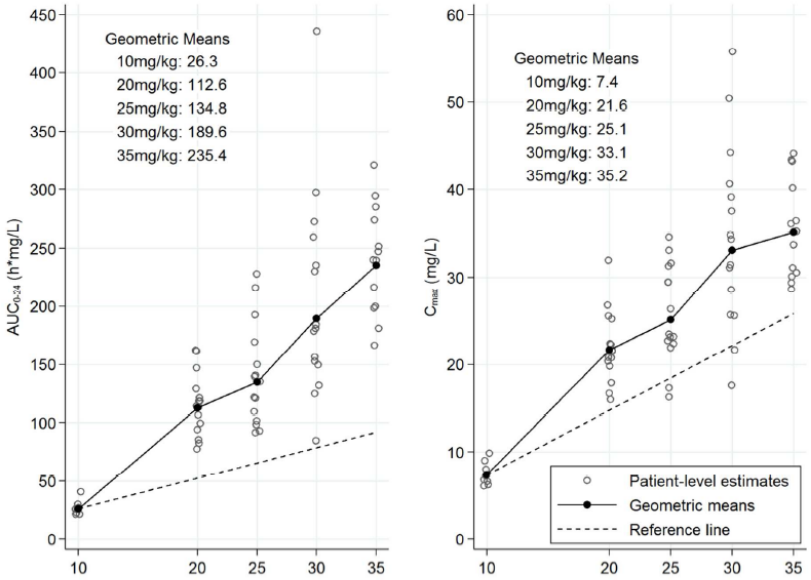
FIG. 2. EBA data from studies performed in Hong Kong (3), Nairobi (6), and Cape Town (15–17), including the present study (arrow). For comparison, the doses of RMP are normalized to a patient weighing 50 kg. Data are means ± 2 standard errors. The standard error is calculated using a pooled estimate of standard deviation from all studies, where available, and the number of subjects in the study.

20 mg/kg more active than 10 mg/kg

Rifampin high dosing







Boeree, AJRCCM 2015

EBA increases over 30 mg/kg
No toxicity after 2 weeks
Confirmed at 12 weeks (Boeree, LID 2017)

Activity against «dormant» bacilli: isoniazid and rifampin

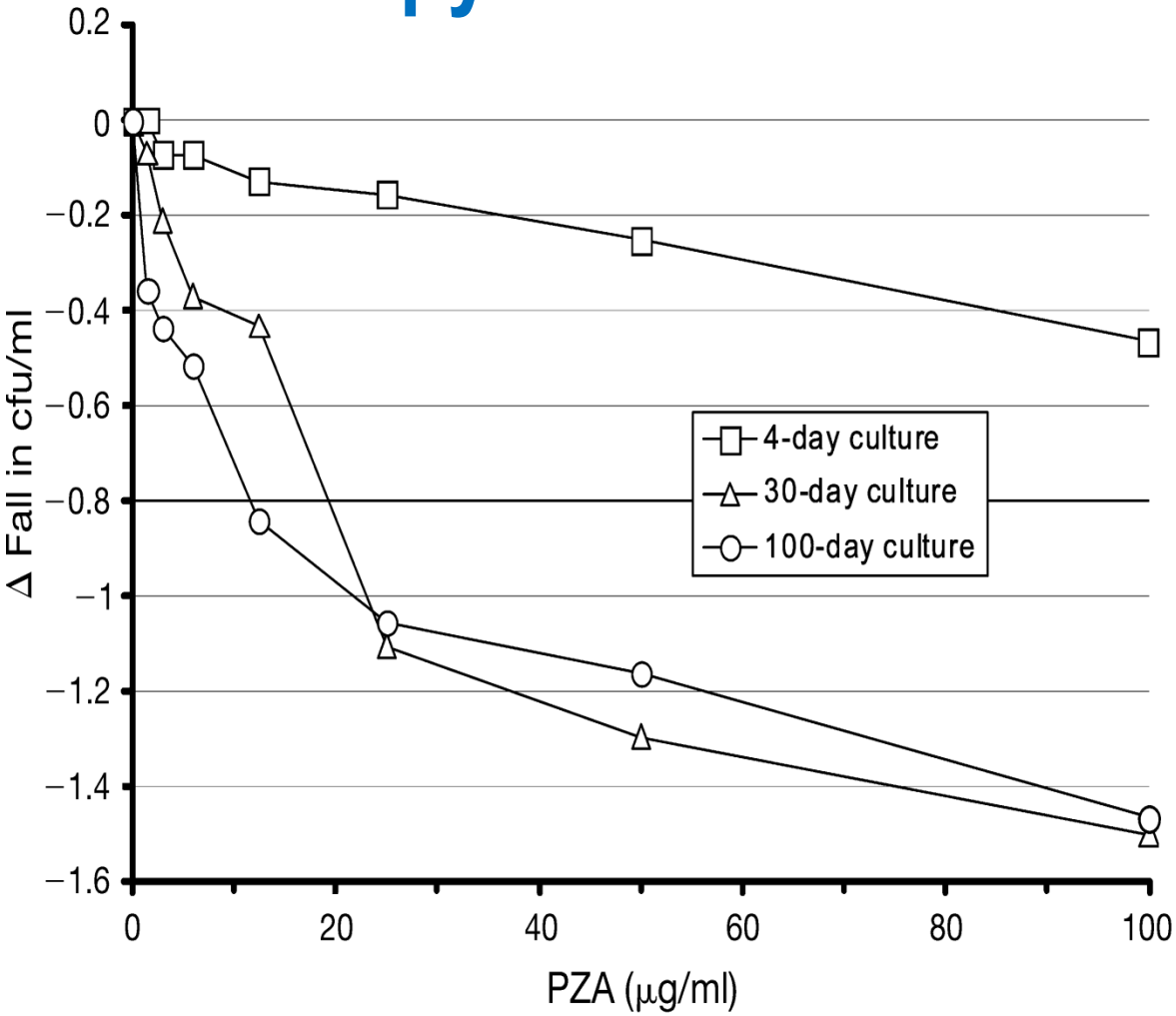
- Bacilli « dormant » in vitro by reducing temperature to 8°C
  - isoniazid and rifampin inactive

- Bacilli at 8°C then temperature raised at 37°C for 1h
  - isoniazid inactive
  - rifampin active

→ Rifampin active dormant bacilli with short periods of metabolic acitivity
= <u>sterilizing activity</u>

Dickinson, 1981

Activity against «dormant» bacilli : pyrazinamide



Hu, 2006

→ pyrazinamide active against dormant bacilli = sterilizing activity

TREATMENT

Choice of a therapeutic regimen

2 caracteristics of treatment

- Many antibiotics
- Long treatment

BRITISH MEDICAL JOURNAL

LONDON SATURDAY OCTOBER 30 1948

STREPTOMYCIN TREATMENT OF PULMONARY TUBERCULOSIS

A MEDICAL RESEARCH COUNCIL INVESTIGATION

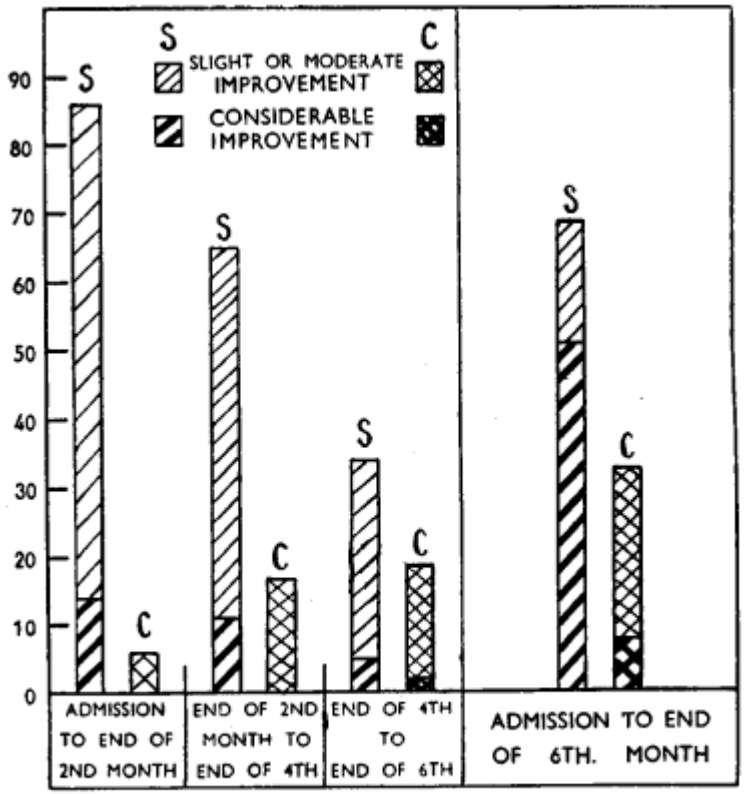


TABLE XIII.—*Presence of Tubercle Bacilli*

Results on Admission	Total	Deaths	Results in Third Month: Direct Smear Strongly Positive	Direct Smear Weakly Positive	Smear Negative Culture Positive	Culture Negative
S Cases:						
Smear strongly positive	40	0	16	12	10	2
Smear weakly positive ..	11	0	1	3	1	6
Smear negative, culture positive	3	0	1	0	0	2
C Cases :						
Smear strongly positive	29	5	19	3	1	1
Smear weakly positive ..	17	1	6	8	2	0
Smear negative, culture positive	4	0	1	1	2	0
			Results at End of 6 Months			
S Cases:						
Smear strongly positive	40	4	24	1	7	4
Smear weakly positive ..	11	0	3	3	2	3
Smear negative, culture positive	3	0	1	0	1	1
C Cases:						
Smear strongly positive	29	11	15	2	0	1
Smear weakly positive ..	17	3	4	7	3	0
Smear negative, culture positive	4	0	0	1	2	1

Despite initial improvment, smear again strongly positive at 6 months

What happened?

BRITISH MEDICAL JOURNAL

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STREPTOMYCIN TREATMENT OF PULMONARY TUBERCULOSIS

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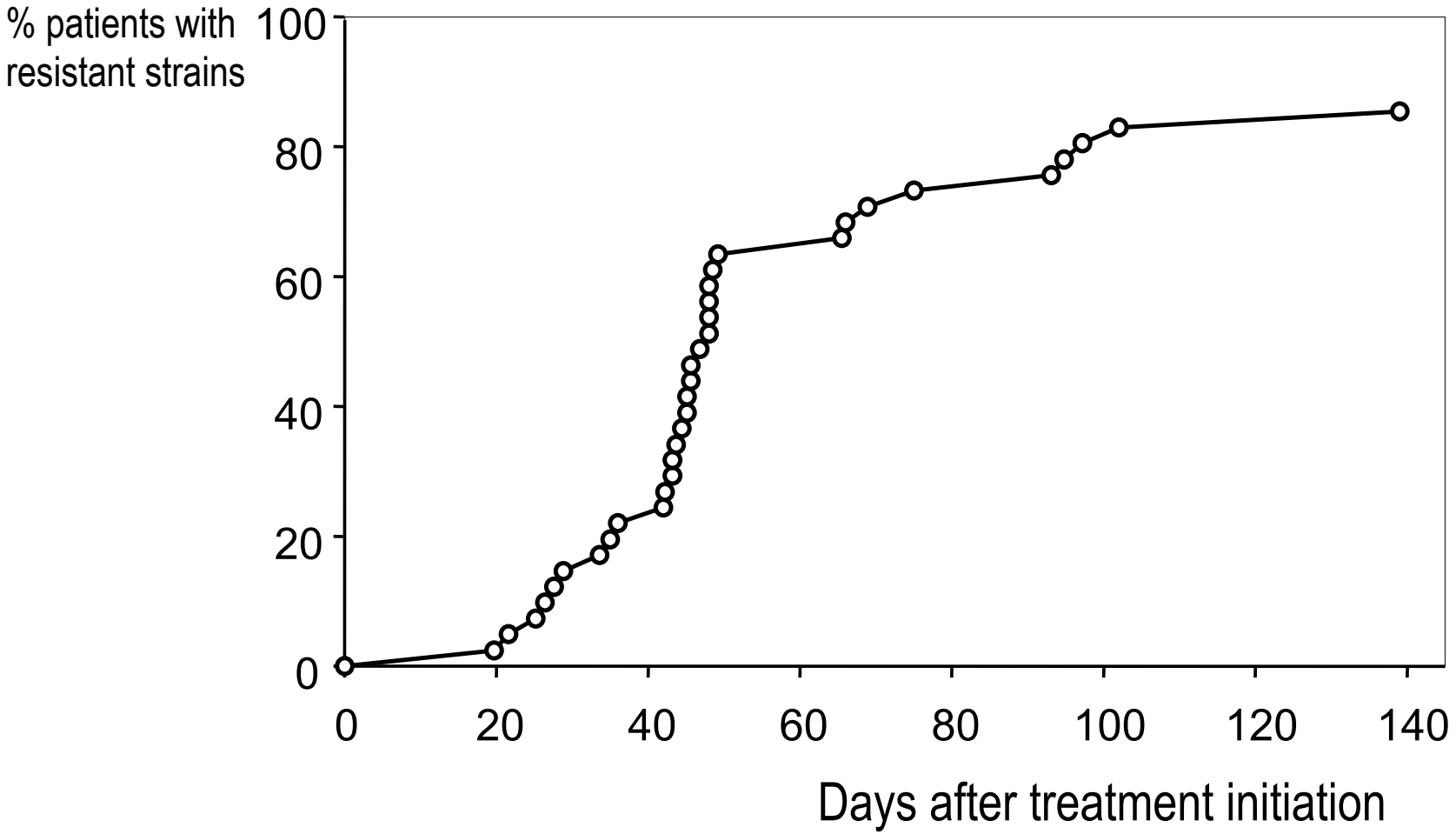
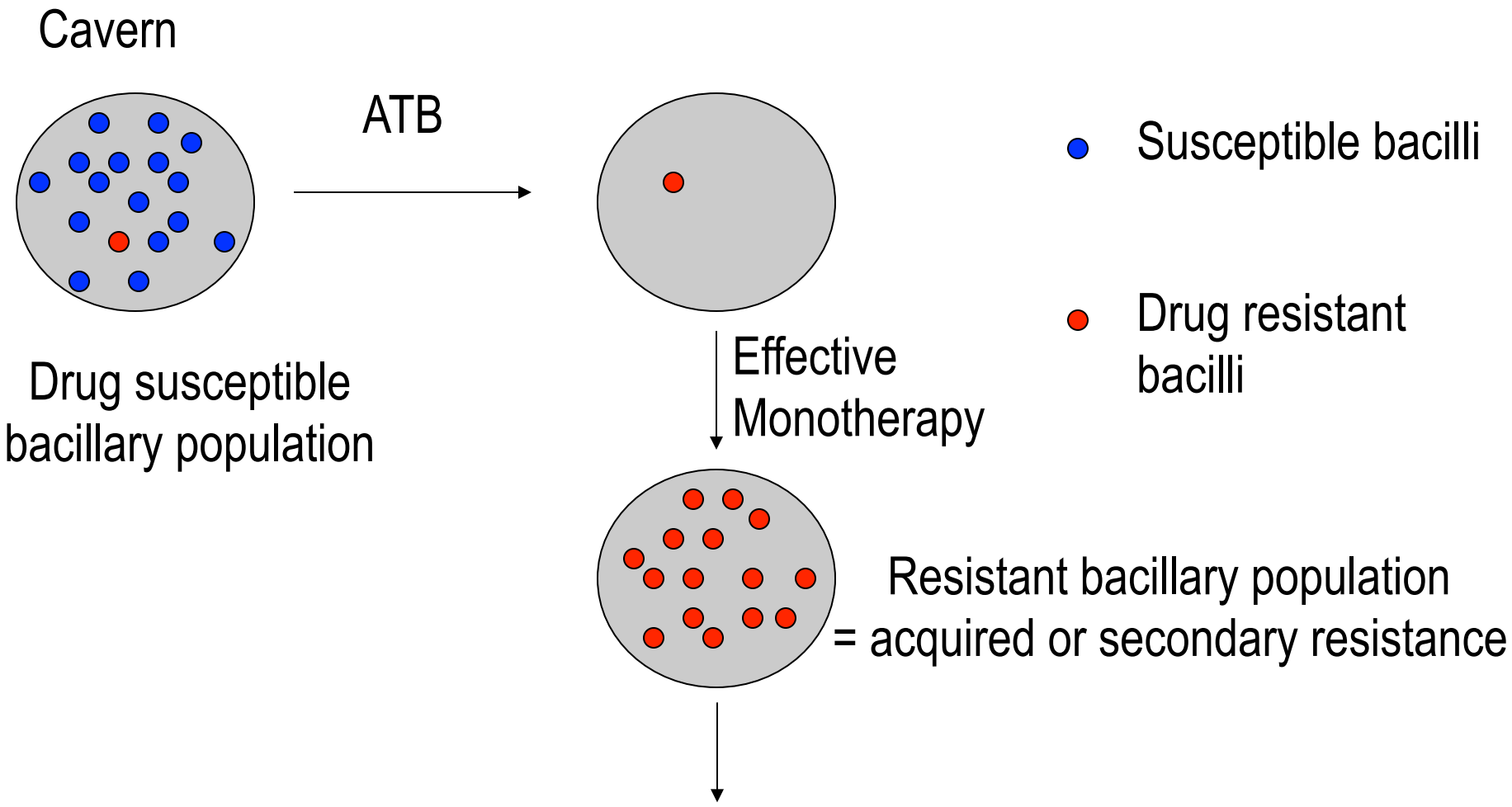
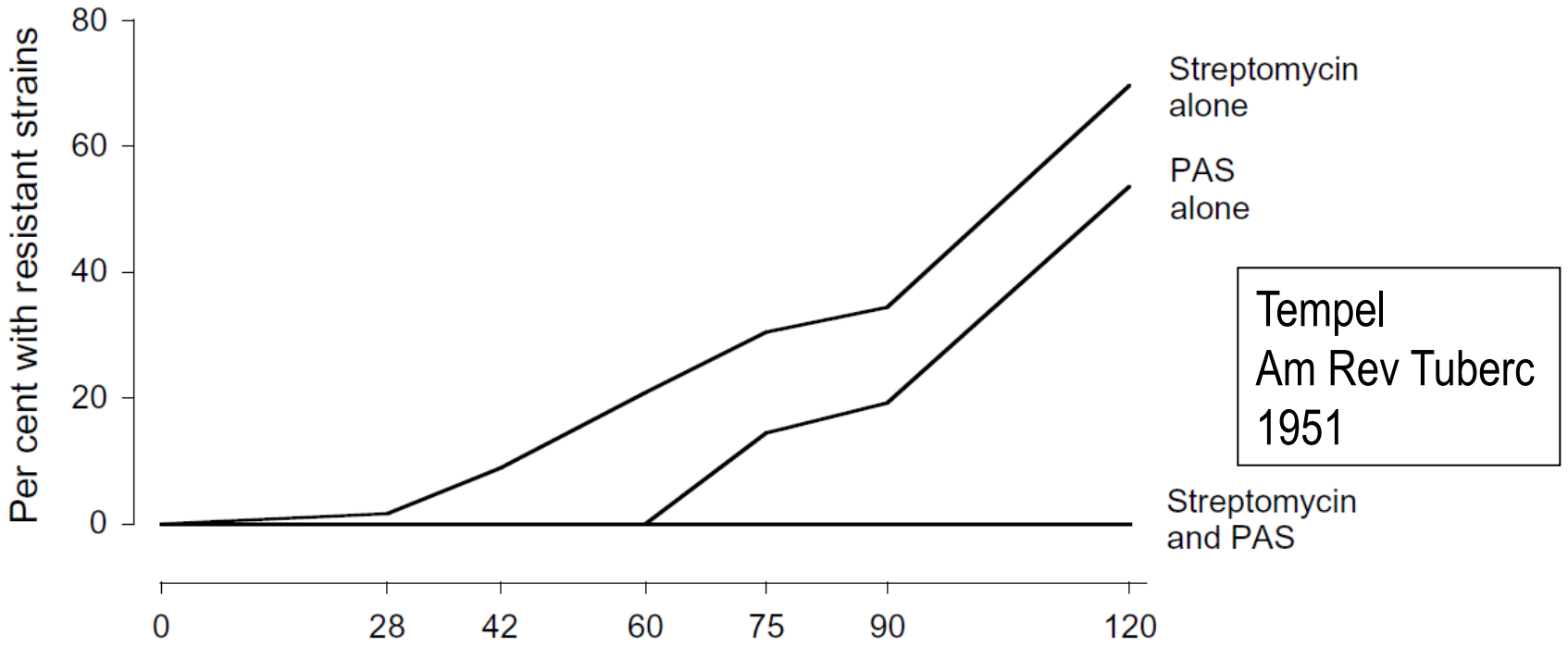


Selection of drug resistant mutants



How to prevent drug resistance

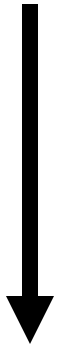
- 1949 : streptomycin + PAS



⇒Drug combination prevents selection of drug resistant mutants

Is a 2 drugs combination enough?

Isoniazid + rifampin



?

A 2 drugs combination is not enough

Isoniazid + rifampin

Isoniazid resistant strain

4% in France among patients not having been treated before

rifampin alone

⇒ **MDR!**

3 drugs combination

Isoniazid + rifampin **+ ethambutol**

Isoniazid
resistant
strain

2 drugs combination

⇒ **No MDR**

3 drugs combination

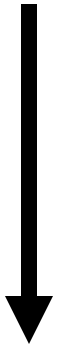
Isoniazid + rifampin **+ pyrazinamide**

Isoniazid
resistant
strain

?

Not all 3 drugs combinations

Isoniazid + rifampin **+ pyrazinamide**



Isoniazid resistant strain

⇒ MDR risk !

Active at acidic pH

not active against actively multiplying bacilli

⇒ Not active against bacilli of the caverna which are at risk of selection of drug resistance

A real case

- 30 years old man, born in Tunisia
- Wegener disease, deeply immunosupressed
- Disseminated TB (positive blood culture)
- Standard 4 drugs therapy
  - isoniazid and ethambutol resistant strain !
- Clinical improvment

- 2 months later, relapse sur un gluteal asbcess
  - **MDR strain!**

⇒ **Pyrazinamide does not prevent selection of drug resistant mutants**

Pyrazinamide not active?

- Int J Tuberc Lung Dis. 1997
- Tuberculosis Research Centre, Madurai, Inde.
- 1203 patients

	Isoniazid-R cases
	End of treatment Unfavorable outcome
Isoniazid+rifampin+pyrazinamide+ethambutol **2 months** puis Isoniazid+rifampin+ethambutol **4 months**	12/59 (20%)
Isoniazid+rifampin+pyrazinamide **2 months** puis Isoniazid+rifampin **4 months**	46/74 (62%)

$p<0.05$

2 caracteristics of treatment

- Many antibiotics **in order to prevent selection of drug resistant mutants**

- Long treatment

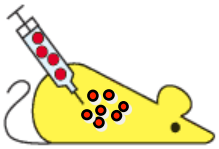
Lenght of treatment

- Isoniazid + streptomycin + PAS
  - 1 year : 22% relapses
  - 2 or 3 years : 4% relapses

- Long treatment required

MRC, Tubercle, 1962

Dormant bacilli: the Cornell model



Isoniazid + pyrazinamide

Mice cured

3 months without treatment

1/3 RELAPSES

THE FATE OF MYCOBACTERIUM TUBERCULOSIS IN MOUSE TISSUES AS DETERMINED BY THE MICROBIAL ENUMERATION TECHNIQUE

II. The Conversion of Tuberculous Infection to the Latent State by the Administration of Pyrazinamide and a Companion Drug*

By ROBERT M. McCUNE, Jr.,‡ M.D., RALPH TOMPSETT, M.D., and WALSH McDERMOTT, M.D.

(*From the Departments of Medicine and Public Health and Preventive Medicine, The New York Hospital—Cornell Medical Center, New York*)

(Received for publication, July 5, 1956)

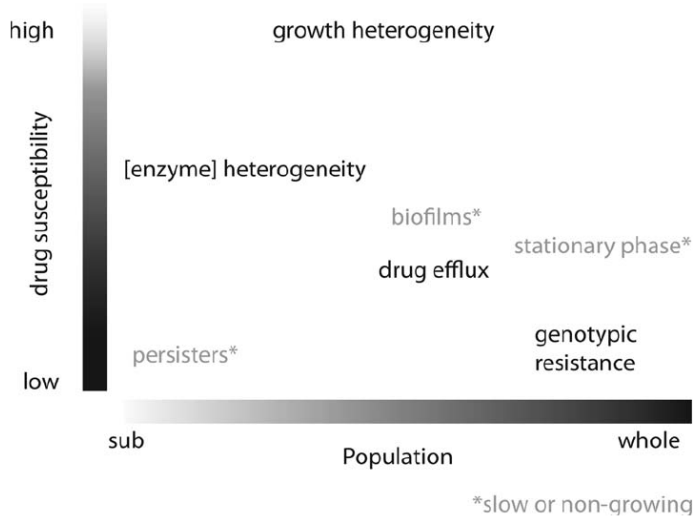
Influence of Sequential Administration Pyrazinamide and Isoniazid on Microbial Populations (H37Rv) in Mouse Tissues during 12 Weeks of Treatment. Effect of Discontinuing Treatment for an Additional 12 Weeks

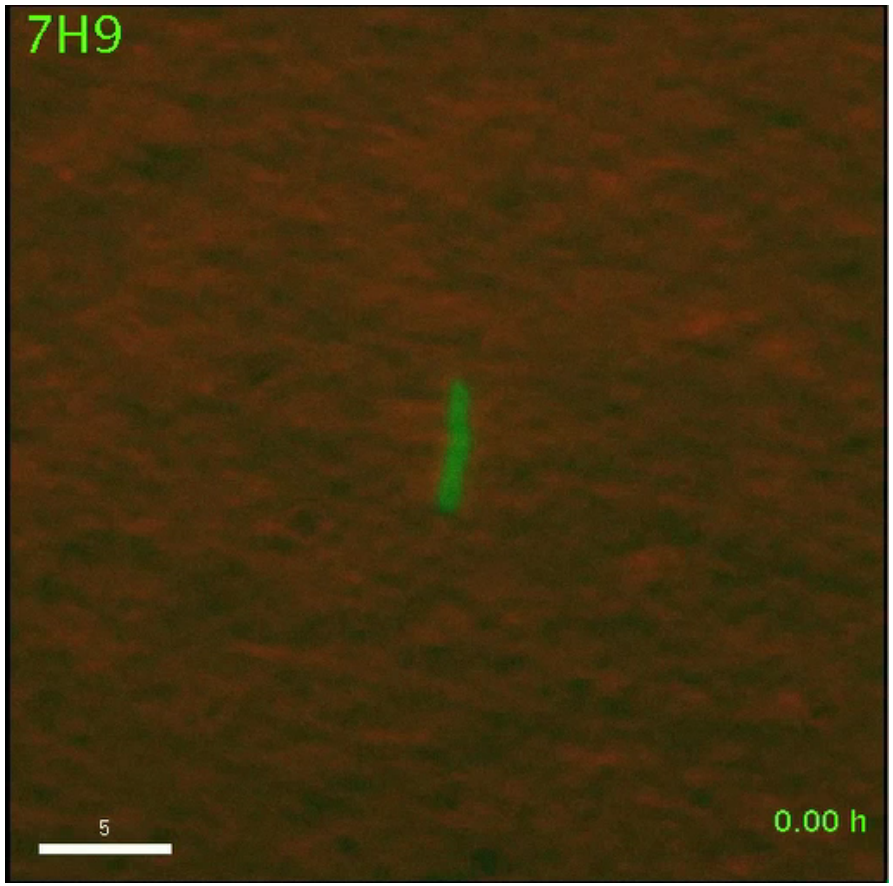
Group	8 wks.		12 wks.		24 wks.	
C						
Isoniazid 8 wks.	3.3×10^3	2.0×10^3	1.1×10^1	0	1.9×10^5	5.2×10^3
Pyrazinamide 4	2.9×10^3	3.4×10^3	0.8×10^1	0	3.2×10^4	0
wks.	2.6×10^3	1.7×10^3	0	0	1.6×10^4	0
					3.7×10^3	0
					1.9×10^3	7.1×10^5
					1.3×10^3	0
					0	0

Antibiotic tolerance

Tolerance mechanisms

- Dormancy regulon in hypoxia : DosR (Voskuil, J Exp Med 2003)
- Biofilms
- Efflux pumps (Adams, Cell, 2011)
- Pulsed KatG (Wakamoto, Science 2013)





Aldridge, Microbiol Spectr 2014

Rifampin and caseum

- Prideaux, Nature Medicine 2015, Sarathy, AAC 2018

Bactericidal activity in caseum

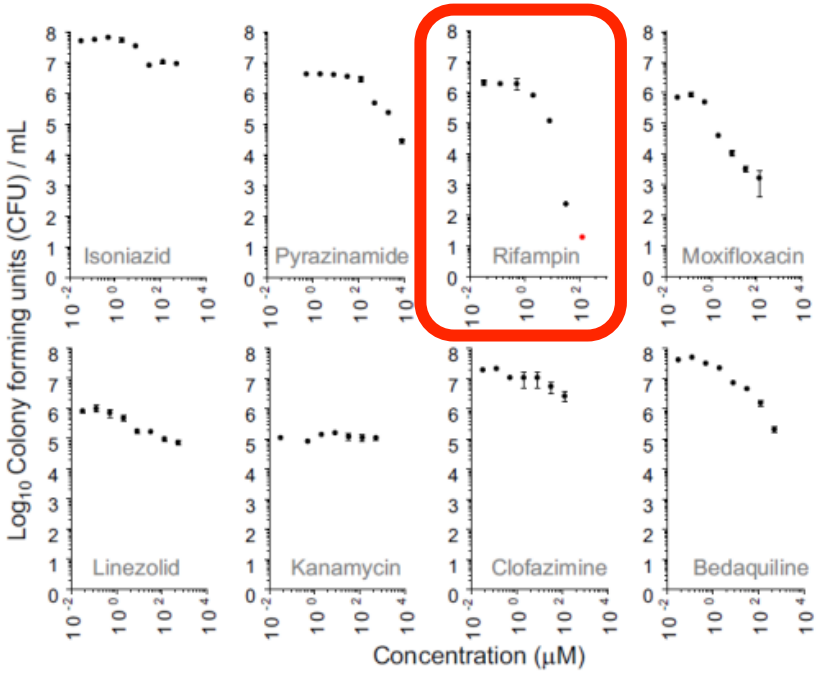
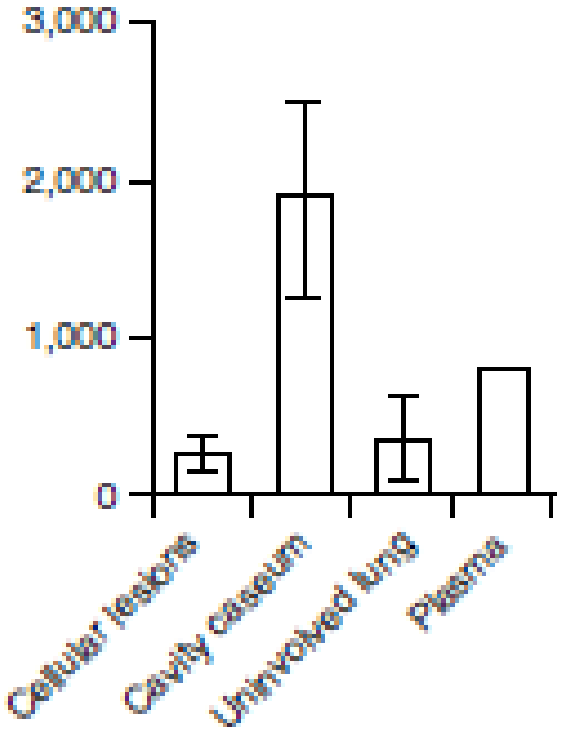


FIG 2 Bactericidal activity of eight standard TB treatment drugs in caseum. Data are expressed as $\log_{10}$ of average CFU per milliliter of homogenized caseum from three replicates. A red dot highlights data points below the limit of detection (LOD [approximately 20 CFU]); i.e., no CFU was recovered from the lowest dilution of caseum homogenate plated. Standard deviations are indicated by error bars.

RIF penetration in pulmonary lesions



Accumulation of RIF in caseum may explain that it reduces treatment duration

Treatment duration shortening thanks to sterilizing drugs

Year	Treatment	Consequence
1948	Streptomycin	1er antiTB drug
1950	Streptomycin+ PAS > Streptomycin	A drug combination prevents drug resistance
60s	Isoniazid + Streptomycin + PAS **18 months**	1st real TB treatment
70s	Isoniazid + **Rifampin** + Ethambutol **9 months**	Lenght of treatment divided by 2
80s	Isoniazid + Rifampin + **Pyrazinamide** **6 months**	« Short » treatment of TB

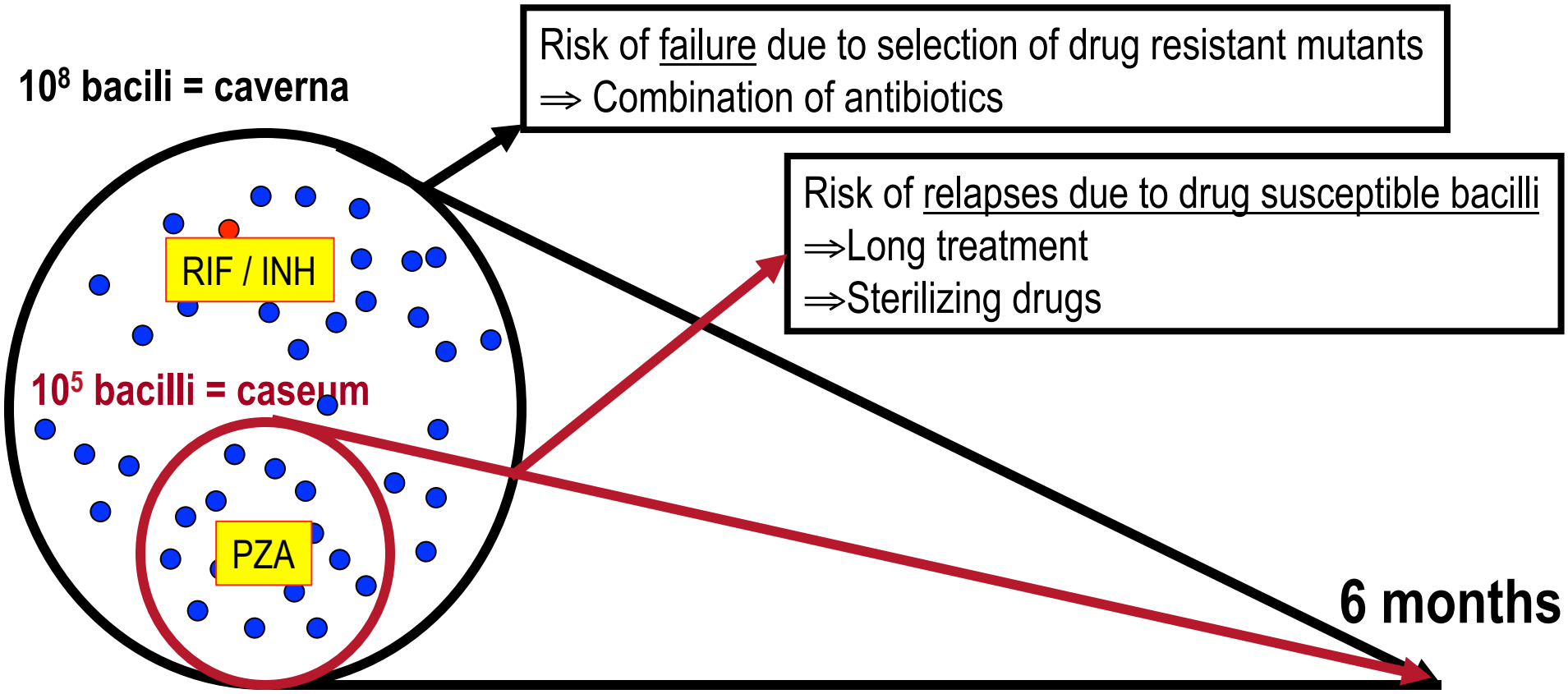
⇒ Treatment duration depends mainly on the use of « sterilizing » drugs (rifampin and pyrazinamide)

2 caracteristics of treatment

- Many antibiotics in order to prevent selection of drug resistant mutants

- Long treatment **in order to prevent relapses with drug susceptible bacilli**

Bacteriological basis of treatment



Treatment

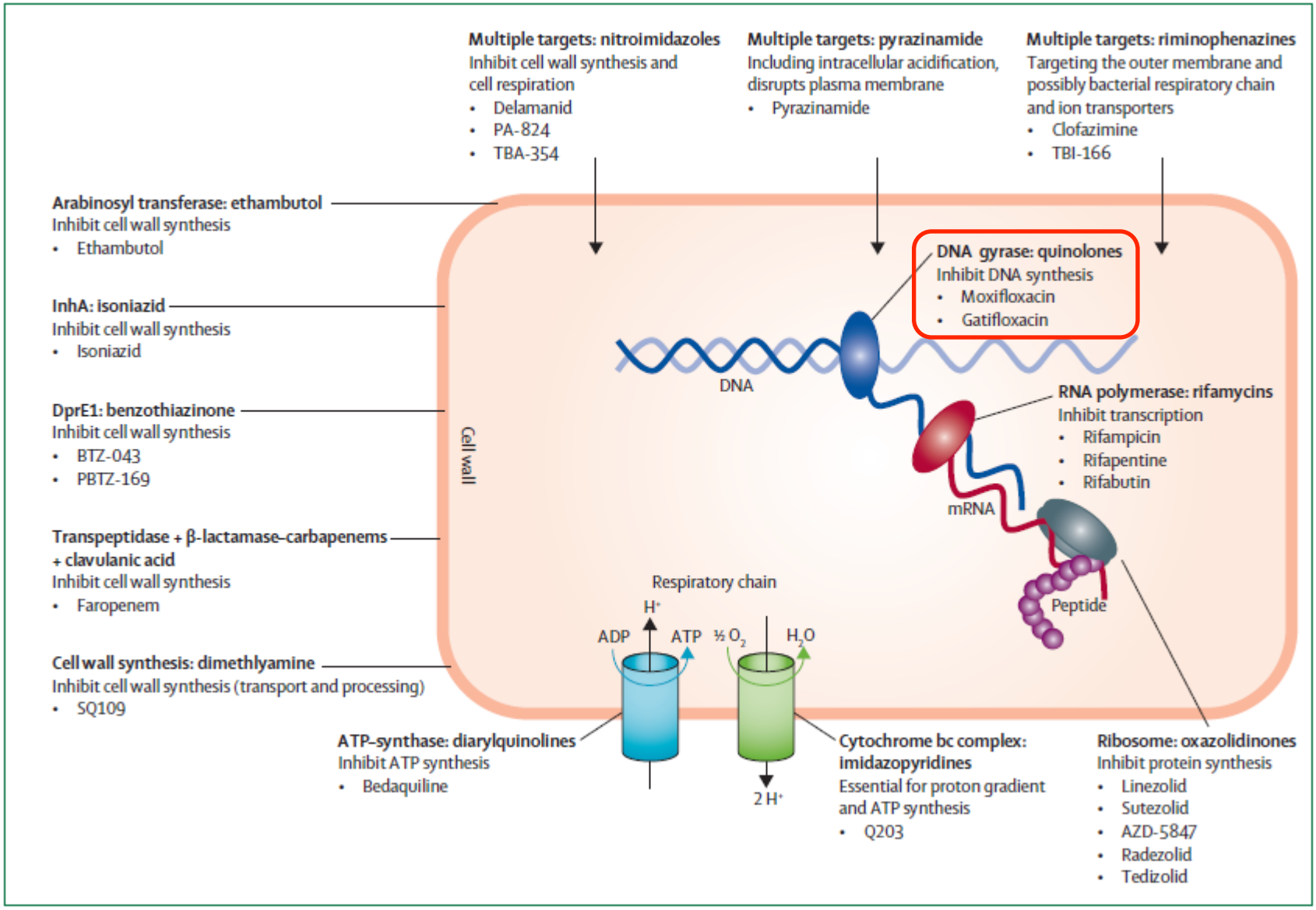
- Isoniazid + rifampin for 6 months plus during the first 2 months
  - pyrazinamide (allowing a 6 months duration)
  - ethambutol (in order to avoid multidrug resistance in case of pre-existing isoniazid resistance)

Combined treatments

- Dosings(mg/kg) :
- isoniazid : 5
- rifampin : 10
- ethambutol : 15
- pyrazinamide : 25

- Combined treatments:
  - isoniazid + rifampin + pyrazinamide = RIFATER®
  - isoniazid + rifampin = RIFINAH®
- Albanna, 2013
  - More failures or relapses when using combined treatments RR 1,28 (95% CI 0,99-1,7)
  - No trial shows positive impact of combined treatemnt on treatment observance

Fluoroquinolones



Zumla, 2014

Fluoroquinolones

- Antituberculous activity known since more than 30 years
- Tsukamura, ARRD 1985 : ofloxacin
  - 19 patients, TB treatment failure
  - Decrease of sputum bacillary load
  - Appearance of ofloxacin resistant mutants

  → Demonstration of in vivo activity

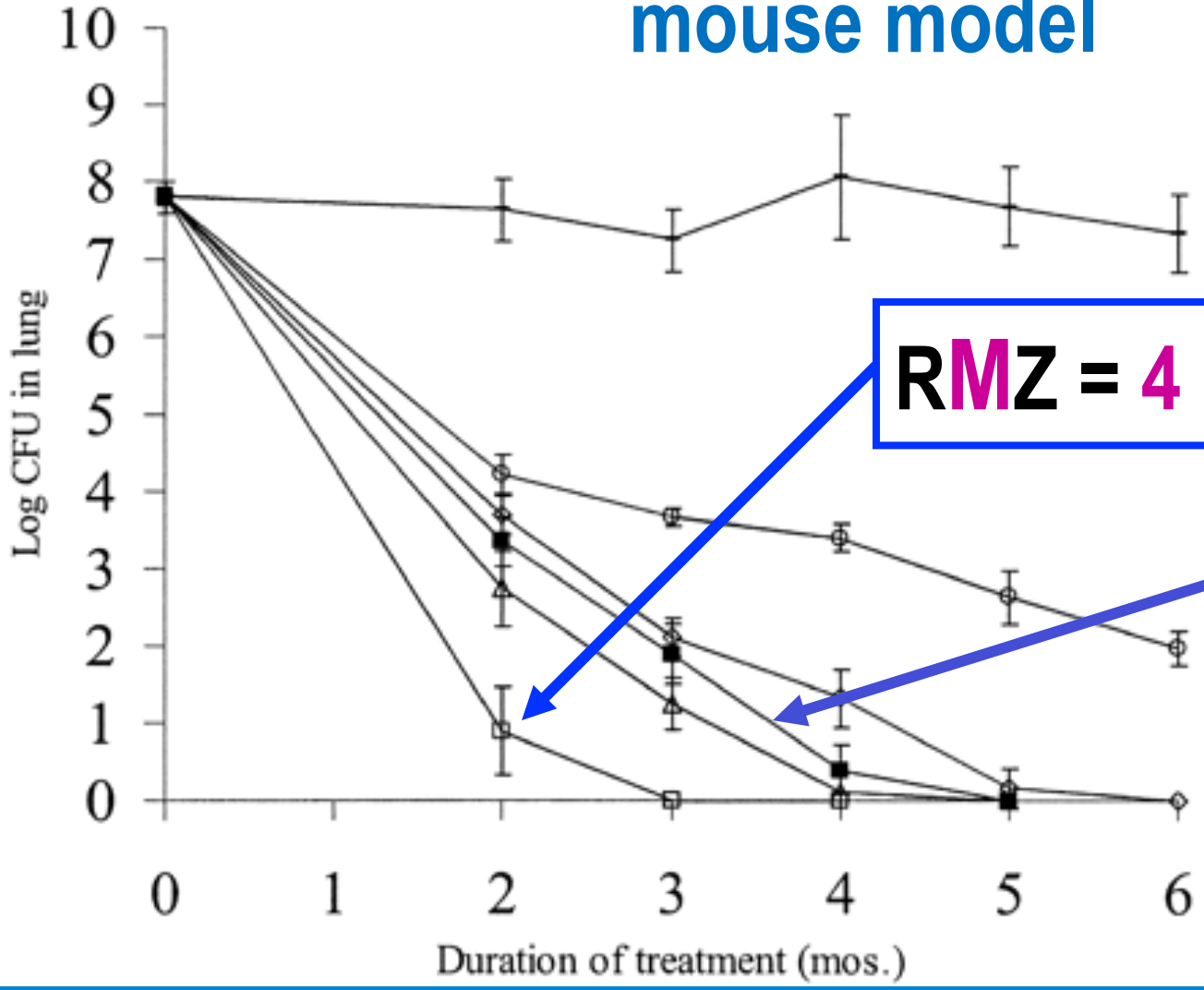
- Moxifloxacin MIC = 0,25 mg/l
  - Peak serum level = 3 mg/l

Fluoroquinolones

FLUOROQUINOLONE	J0	CFU decrease after 4 weeks (spleen)
Ofloxacin 200 mg/kg	7,4	-0,9
Levofloxacin 200 mg/kg	7,4	-2,4
Moxifloxacin 100 mg/kg	6,8	-4,8

- EBA equivalent to that of rifampin but less than that of isoniazid (Gillespie 2003)
- Sterilizing activity in vitro (Mitchison 2003)

Moxifloxacin and drug susceptible TB : mouse model



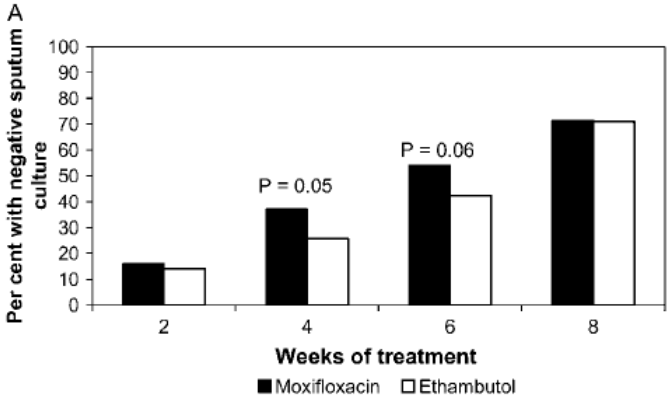
RMZ = 4 mois

RHZ = 6 mois

Nuermberger
AJRCCM 2004

Moxifloxacin may reduce treatment duration

Moxifloxacin : human



Burman, AJRCCM 2006
Culture negativity at 2 months
Isoniazid (H) +rifampin (R) + pyrazinamide (Z) +
ethambutol (E) 3/week
ou
moxifloxacin (M) (5/week)

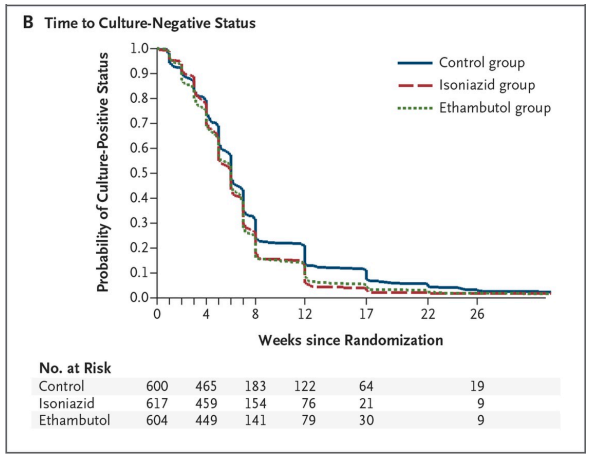
Moxifloxacin increase treatment activity but…
No difference at 2 months

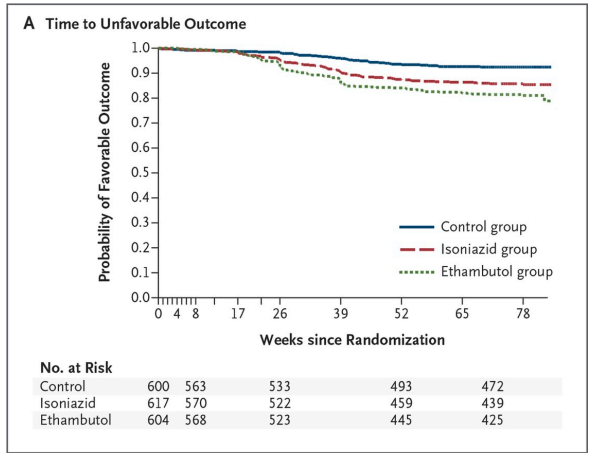
Treatment shortening with fluoroquinolones

- Gillespie, NEJM 2014
- Merle, NEJM 2014
- Jindani, NEJM 2014

- More than 4000 patients
- 4 months moxifloxacin or gatifloxacin based treatment instead of isoniazid or ethambutol

⇒ Less active than standard 6 months treatment

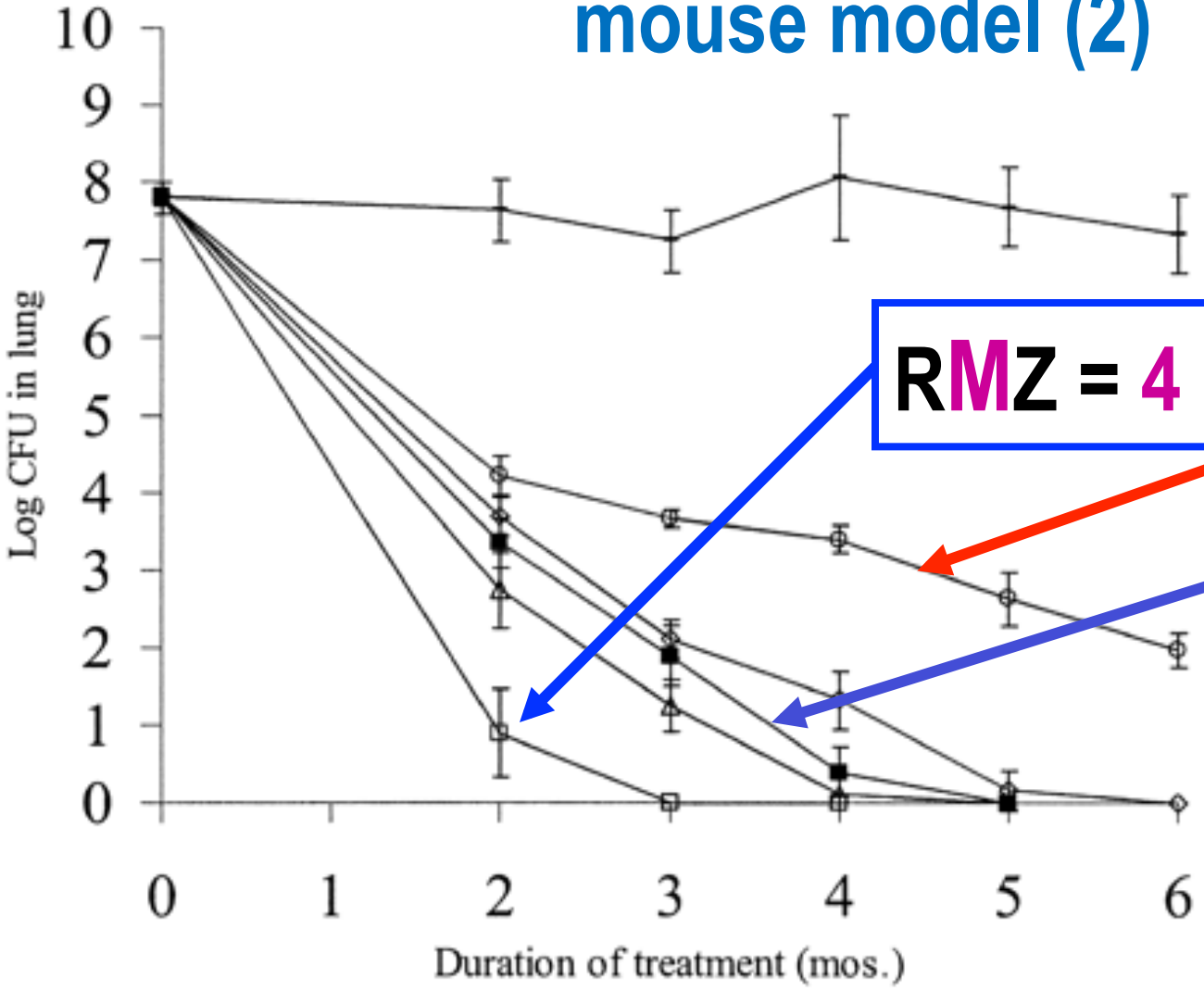




Gillespie SH et al.
N Engl J Med 2014

Despite faster culture negativity, no shortening at 4 months

Moxifloxacin and drug susceptible TB : mouse model (2)



RMZ = 4 mois

MHZ

RHZ = 6 mois

Nuermberger
AJRCCM 2004

Moxifloxacin much less active than rifampin!

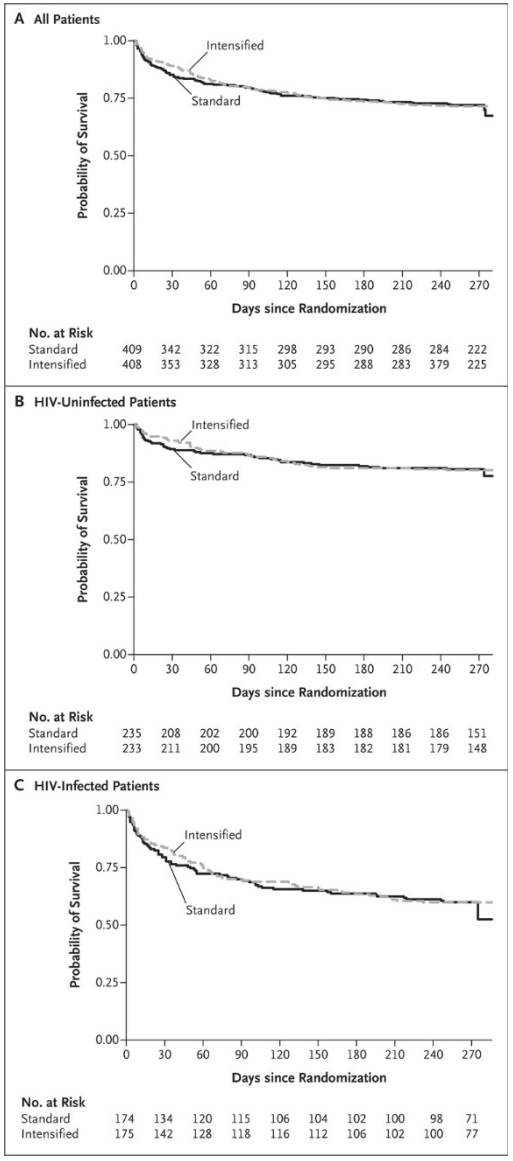
TB meningitis

- Ruslami, Lancet 2013
  - TB meningitis: randomization rifampin 450 mg PO (=10 mg/kg) or 600 mg IV (=13 mg/kg) and ethambutol or moxifloxacin 400 mg or 800 mg
- Heemskerk, N Engl J Med 2016
  - Rifampin 15 mg/kg, levofloxacin 20 mg/kg

	Oral rifampicin 450 mg	Intravenous rifampicin 600 mg	Total
Ethambutol 750 mg	7/12 (58%)	3/10 (30%)	10/22 (45%)
Moxifloxacin 400 mg	6/10 (60%)	2/9 (22%)	8/19 (42%)
Moxifloxacin 800 mg	7/9 (78%)	5/10 (50%)	12/19 (63%)
Total	20/31 (65%)	10/29 (34%)	30/60 (50%)

Data are n/N (%). All patients received standard dose isoniazid, pyrazinamide, and adjunctive corticosteroids.

Table 5: 6 month mortality by rifampicin regimen



Disappointing results for rifampin, higher dosing needed?

Drug resistance

BRITISH MEDICAL JOURNAL

LONDON SATURDAY OCTOBER 30 1948

STREPTOMYCIN TREATMENT OF PULMONARY TUBERCULOSIS

A MEDICAL RESEARCH COUNCIL INVESTIGATION

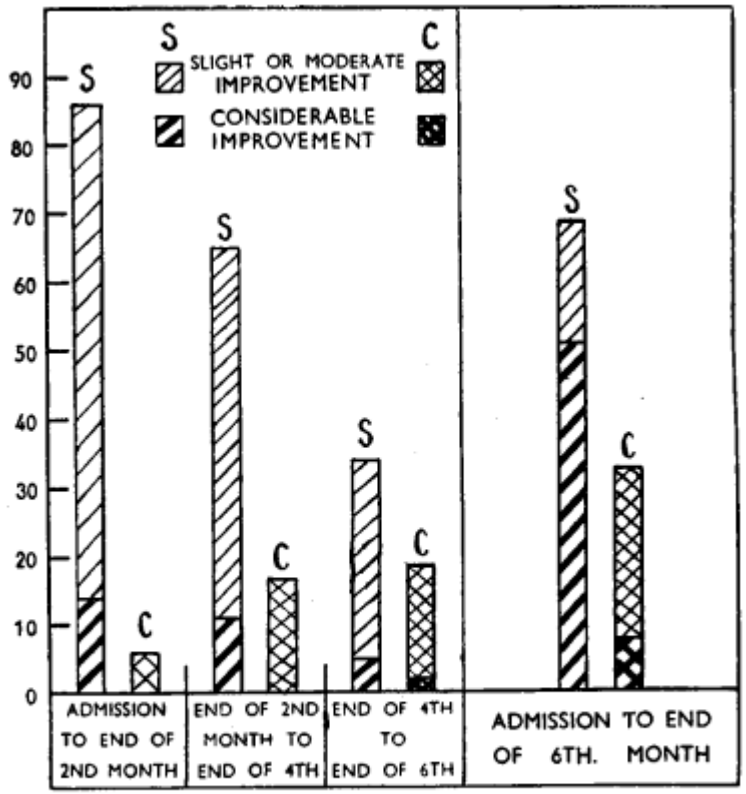
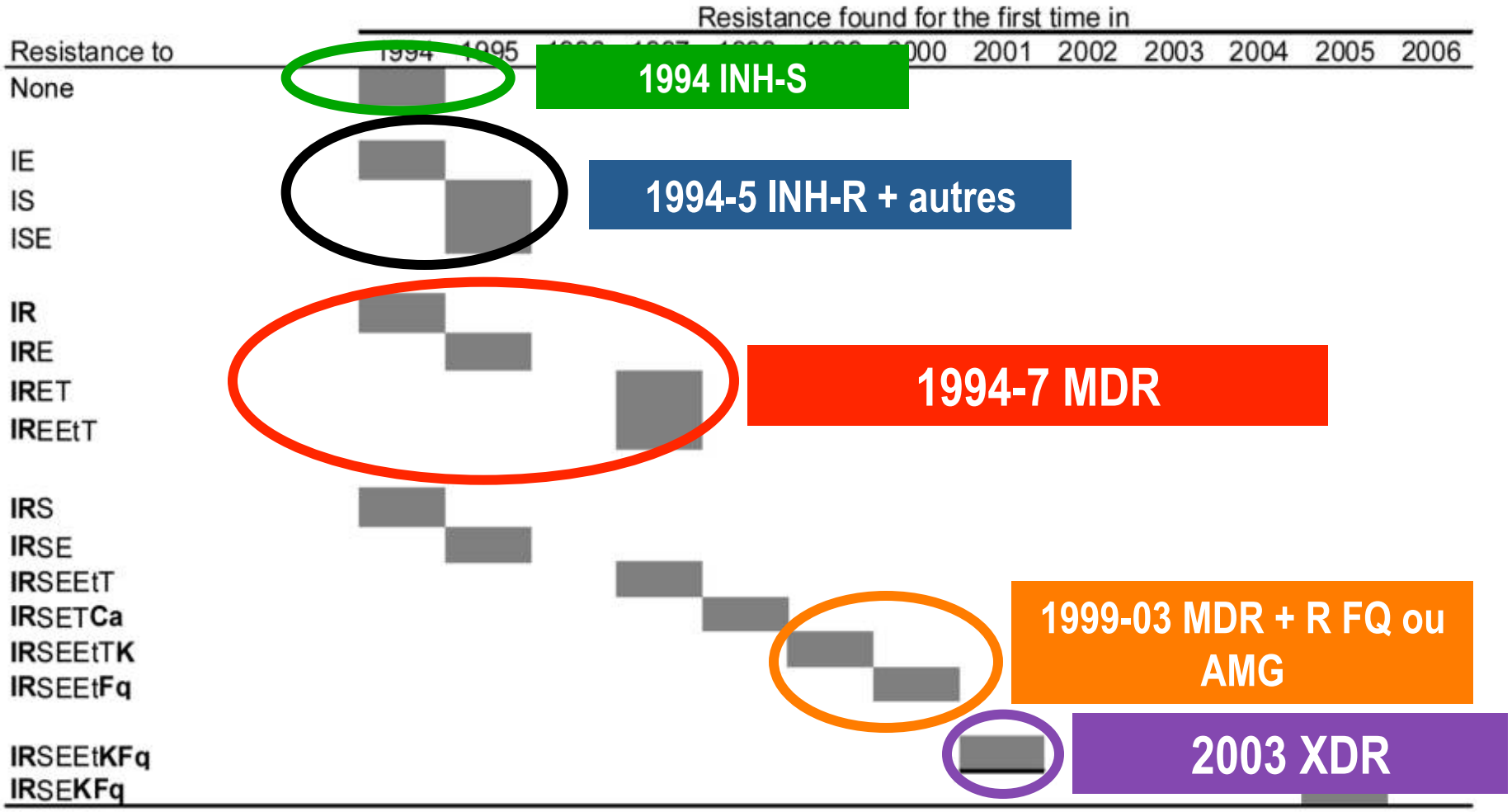


CHART IV.—Percentage of total patients admitted (*not* of survivors at beginning of each period) showing improvement in radiological picture in succeeding two-monthly periods and in six months.

TABLE XIII.—*Presence of Tubercle Bacilli*

Results on Admission	Total	Deaths	Results in Third Month			
			Direct Smear		Smear Negative Culture Positive	Culture Negative
			Strongly Positive	Weakly Positive		
S Cases:						
Smear strongly positive	40	0	16	12	10	2
Smear weakly positive ..	11	0	1	3	1	6
Smear negative, culture positive	3	0	1	0	0	2
C Cases :						
Smear strongly positive	29	5	19	3	1	1
Smear weakly positive ..	17	1	6	8	2	0
Smear negative, culture positive	4	0	1	1	2	0
			Results at End of 6 Months			
S Cases:						
Smear strongly positive	40	4	24	1	7	4
Smear weakly positive ..	11	0	3	3	2	3
Smear negative, culture positive	3	0	1	0	1	1
C Cases:						
Smear strongly positive	29	11	15	2	0	1
Smear weakly positive ..	17	3	4	7	3	0
Smear negative, culture positive	4	0	0	1	2	1

From drug susceptible TB to XDR : F15/ LAM4/KZN strain, South Africa

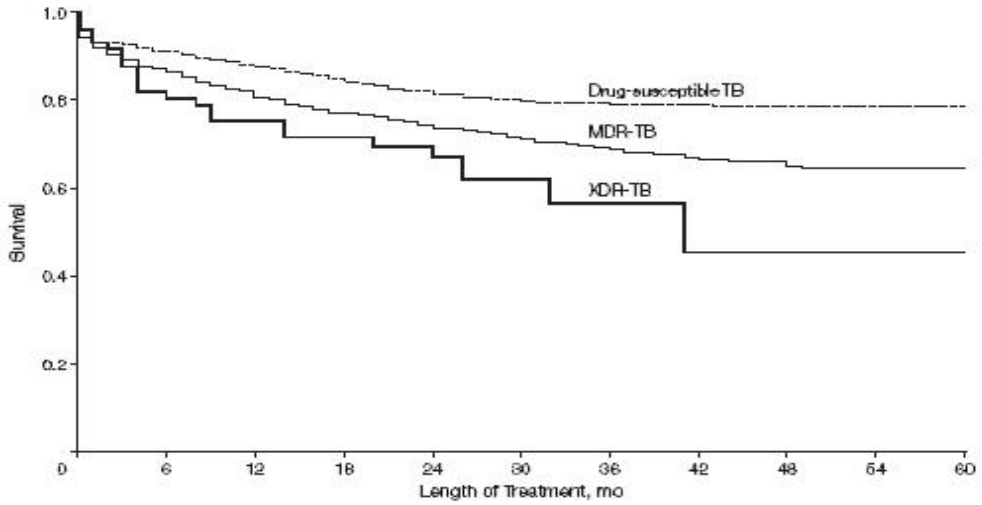


Pillay CID 2007

Definitions

- *Mycobacterium tuberculosis* multi-drug resistance (MDR) defined by simultaenous resistance to at least
  - isoniazid
  - rifampin
- Extensive-drug resistance (XDR) defined by resistance to at least isoniazid and rifampin and
  - fluoroquinolones
  - one of second-line injectables (amikacin, kanamycin, capreomycin)

Prognosis of MDR and XDR cases



DS TB

MDR TB

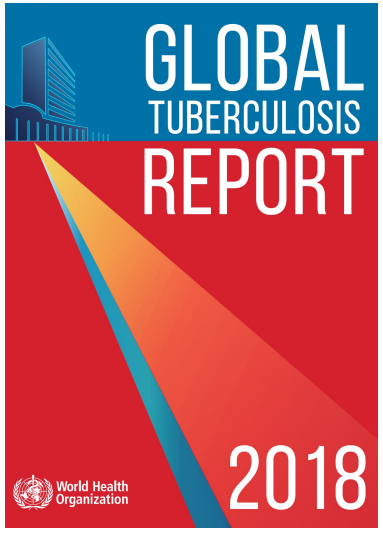
XDR TB

Shah et al., JAMA, 2008

Epidemiology

Tuberculosis epidemiology

- 2 billions with latent infection
- In 2017
  - 10 million new cases
  - 1,6 million death



	TOTAL TB INCIDENCE	
	BEST ESTIMATE	UNCERTAINTY INTERVAL
Angola	359	232–512
Bangladesh	221	161–291
Brazil	44	37–50
Cambodia	326	224–447
Central African Republic	423	274–604
China	63	54–73
Congo	376	239–545
DPR Korea	513	446–584
DR Congo	322	208–460
Ethiopia	164	115–221
India[b]	204	140–281
Indonesia	319	291–348
Kenya	319	195–472
Lesotho	665	430–949
Liberia	308	199–440
Mozambique[c]	551	356–787
Myanmar[c]	358	263–466
Namibia[c]	423	324–535
Nigeria	219	143–311
Pakistan	267	189–357
Papua New Guinea	432	352–521
Philippines	554	311–866
Russian Federation	60	39–85
Sierra Leone	301	193–431
South Africa[c]	567	406–754
Thailand	156	119–199
UR Tanzania	269	127–464
Viet Nam[c]	129	106–155
Zambia	361	234–514
Zimbabwe	221	164–287

Multidrug resistance : world

- Estimation : 450 000 new cases in 2017
  - Primary : 3% of new cases
  - Secondary : 20% of previsouly treated cases
- 10% of MDR cases are XDR

% TB RIF-R among new TB cases	Country
25 to 50	Belarus, Kirghizstan, Russia, Ukraine, Kazakhstan, Moldavia
10 to 25	Uzbekistan, Tajikistan, Egypt, Estonia, Turkmenistan, Azerbaijan, Samoa, Lithuania, Armenia, Bahamas, Bhutan, Georgia

Diagnosis of resistances

A long time ago in a galaxy far, far away….

Revue de Tuberculose et de Pneumologie. T. 27, 1963, n° 2-3 (pp. 217-272).

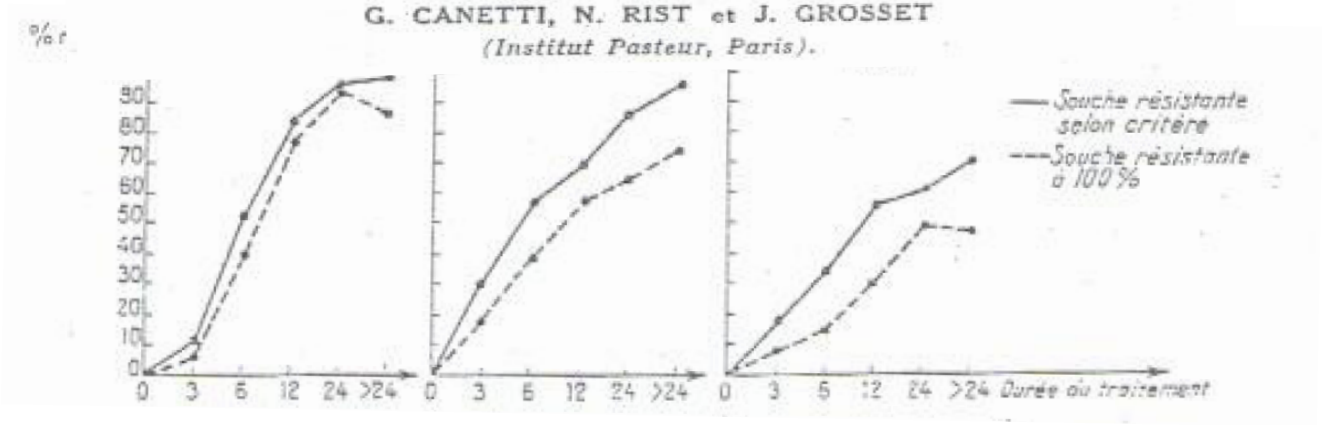
MESURE DE LA SENSIBILITÉ DU BACILLE TUBERCULEUX AUX DROGUES ANTIBACILLAIRES PAR LA MÉTHODE DES PROPORTIONS.

MÉTHODOLOGIE, CRITÈRES DE RÉSISTANCE, RÉSULTATS, INTERPRÉTATION

par

G. CANETTI, N. RIST et J. GROSSET

(Institut Pasteur, Paris).

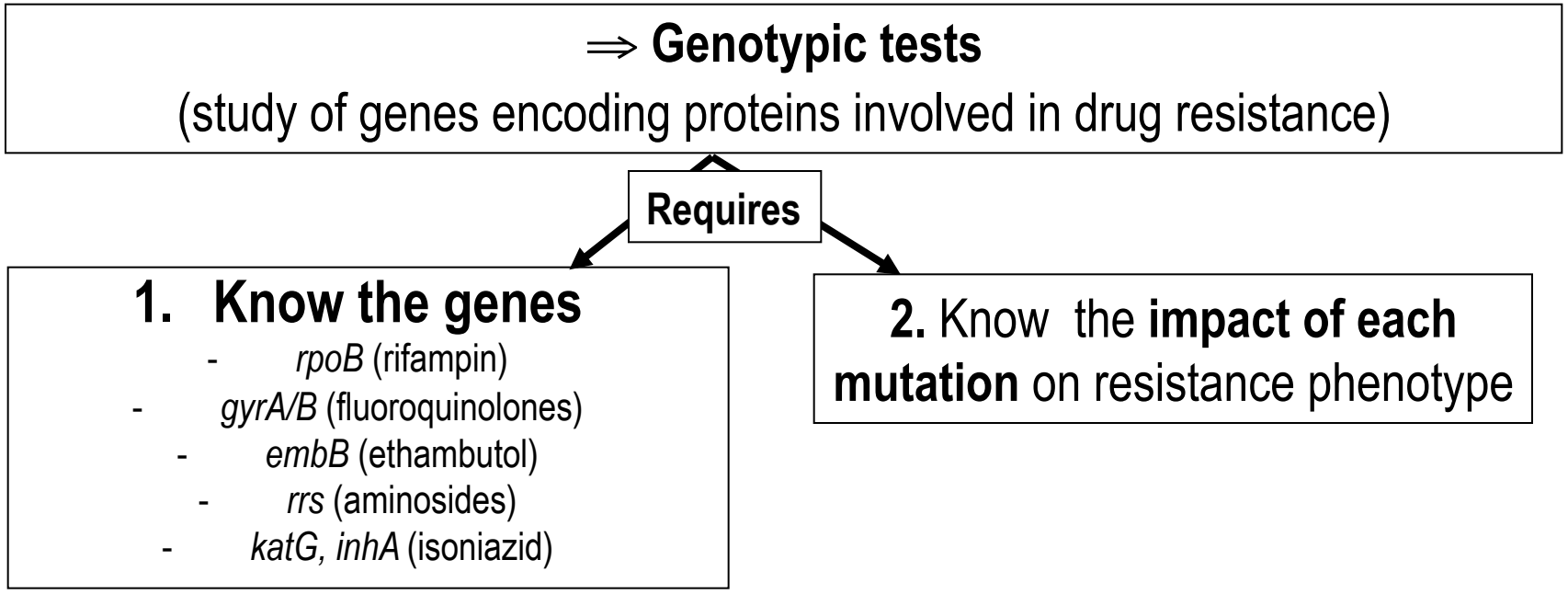


Proportion method : reference method for phenotypic diagnosis of resistance

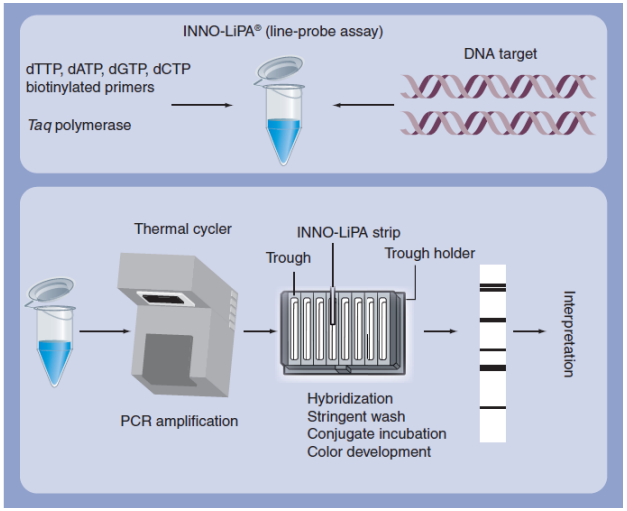
One critical concentration

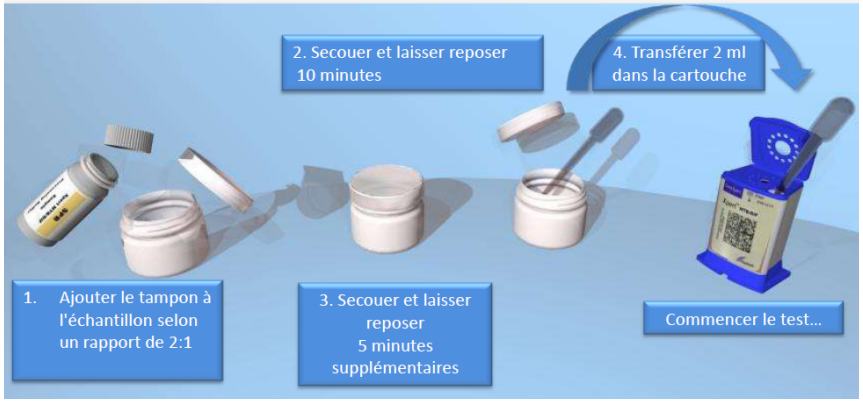
Long, due to slow growth of *M. tuberculosis*

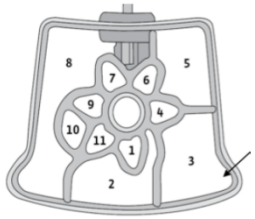
Genotypic diagnosis of resistance

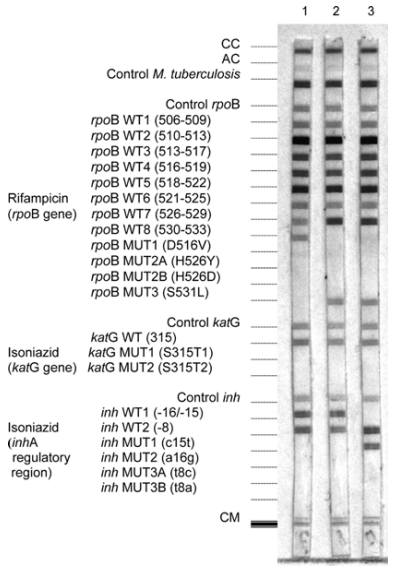


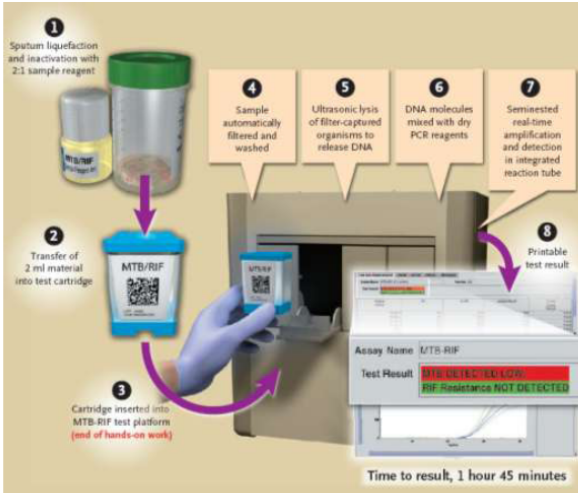
MTBDR, Xpert MTB/RIF











Sensitivity, specificity of commercial tests

		sensitivity	specificity	Performances
Rifampin	MTBDR*plus*	98%	99%	Excellente
	Xpert MTB/RIF	94%	98%	
Isoniazid	MTBDR*plus*	84%	99%	Good
Fluoroquinolones	MTBDR*sl*	87% (95%V2)	97%	Good
Amikacin		83%	99%	Good
Kanamycin		44% (91% V2)	98%	Poor
Capreomycin		82%	95%	Good
Ethambutol		68%	80%	Poor

Theron, 2014; Steingart 2013 ; Feng 2013 ; Ling 2008; Brossier 2016

Performances

- Excellent for rifampin→recommandation in France for each new TB case
- Good for isoniazid, fluoroquinolones, amikacin, capreomycin
- Poor for kanamycin and ethambutol (better with MTBDR*sl* V2)

Whole genome sequencing

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Prediction of Susceptibility to First-Line Tuberculosis Drugs by DNA Sequencing

The CRyPTIC Consortium and the 100,000 Genomes Project

- 10 000 *M. tuberculosis* genomes
- WGS performances for susceptibility and resistance detection :

	Isoniazid	Rifampin	Ethambutol	Pyrazinamide
Resistance detection	97%	98%	95%	91%
Susceptibility detection	99%	99%	94%	97%

Very goog prediction for 1st line drugs

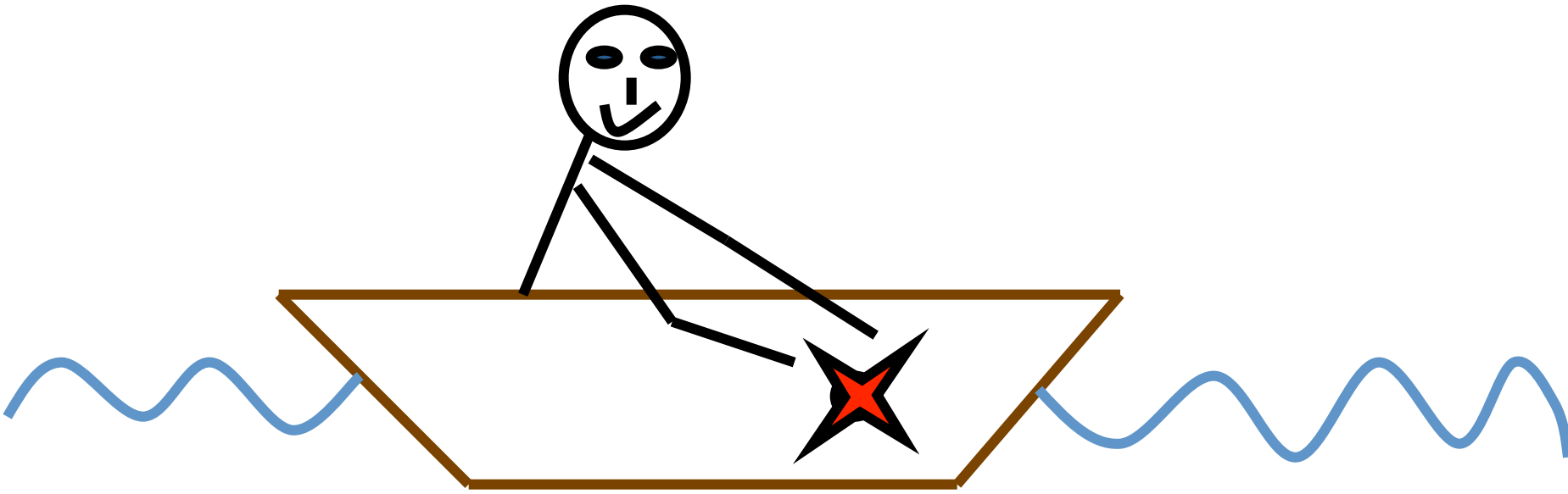
TREATMENT

When the ship is sinking…

You can take off the water
= treat MDR and XDR

But you'd better…

Plug the hole =
prevent MDR and XDR



Plug the hole
= to prevent resistance

1. Prevention of primary resistance

   = prevention of community transmission

   = prevention of hospital transmission

XDR TB: South Africa, early 2000s

- 53 XDR
- 100% HIV+
- Mortality 98%

- 2/3 hospital acquired

Gandhi Lancet, 2006

A case born in France

- Man 34 years old
  - Schizophrenia
  - ankylosing spondylitis, Pitié-Salpêtrière hospital:
    - TST 10 mm : RIFINAH) 3 months in 2008
    - adalimumab (HUMIRA®) from 2008 to 2011 then again from August 2012
- June 2014 : fever, cough, asthenia, etc
- Disseminated TB : lung, liever, spleen testicles

- *katG* : S315T
- *rpoB* : S531L
- *rrs :* A1401G
- *gyrA* : D94G
- DST: XDR strain susceptible pyrazinamide, linezolide, PAS and cycloserine
- MIRU-VNTR : 1 identical strain among all strains in France since 2006

- Man 38 years,
  IV drug abuse, HIV+, HCV+
  Georgian arrived in France in november 2013 after 2 years treatment of TB

- Hospitalized at Pitié-Salpêtrière !

- **Does not respect respiratory isolation**

Invesigation inside hopsital

Fig 1.a. Autochton patient's history

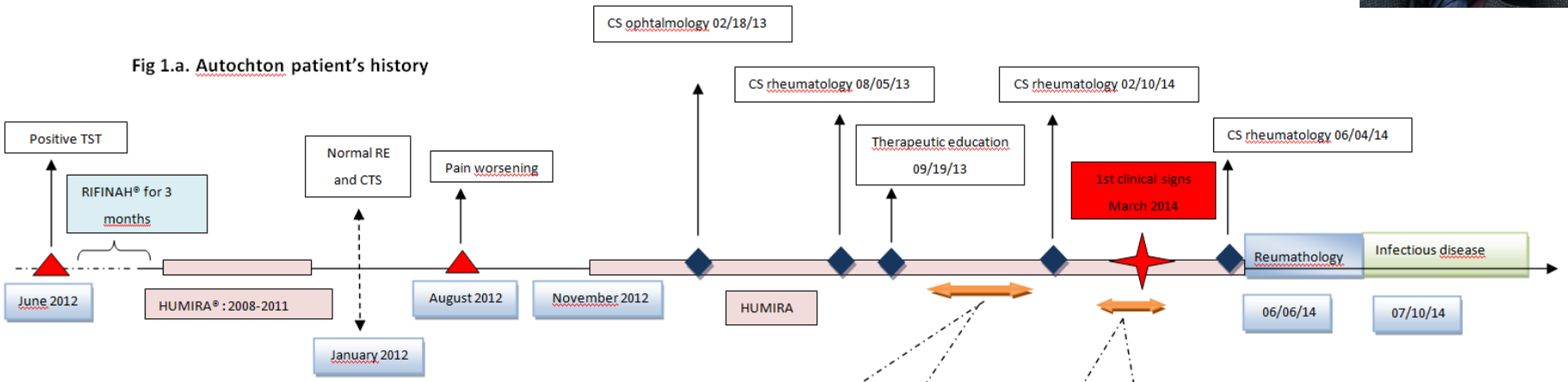
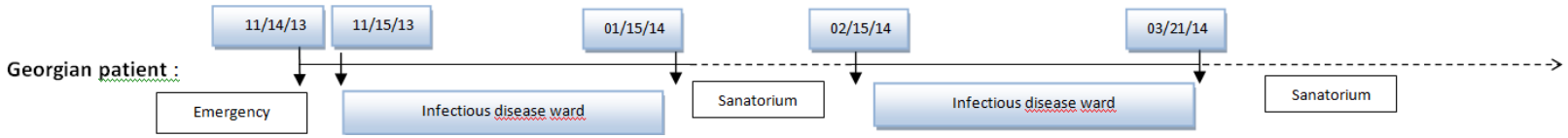
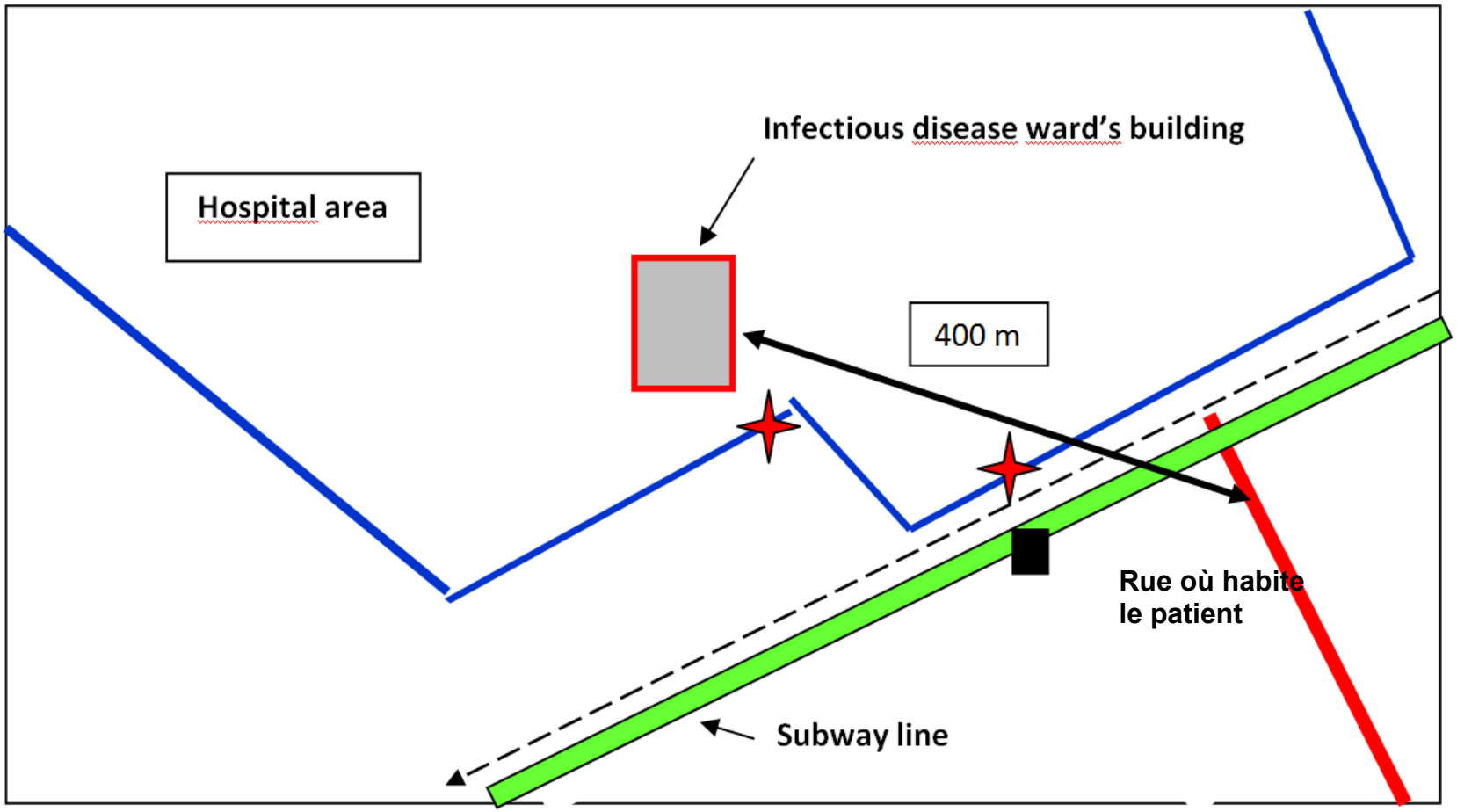


Fig 1.b. Comparison of hospitalization histories



No hospitalization at the same moment

Invesigation outside hopsital



Secondary case lives 400 m from hospital

Plug the hole = PREVENTION
= to avoid creating resistance

2. Prevention of secondary resistance

   = Avoid selection of drug resistant mutants

How to avoid creating resistance

-To add one molecule to a failing regimen

-No detection of pre-existing resistance

-Wrong choice of treatment regimen

-No to take into account compliance problems

-Preventive treatment of TB diseases

Mahmoudi, JAMA 1993

In case of despair…

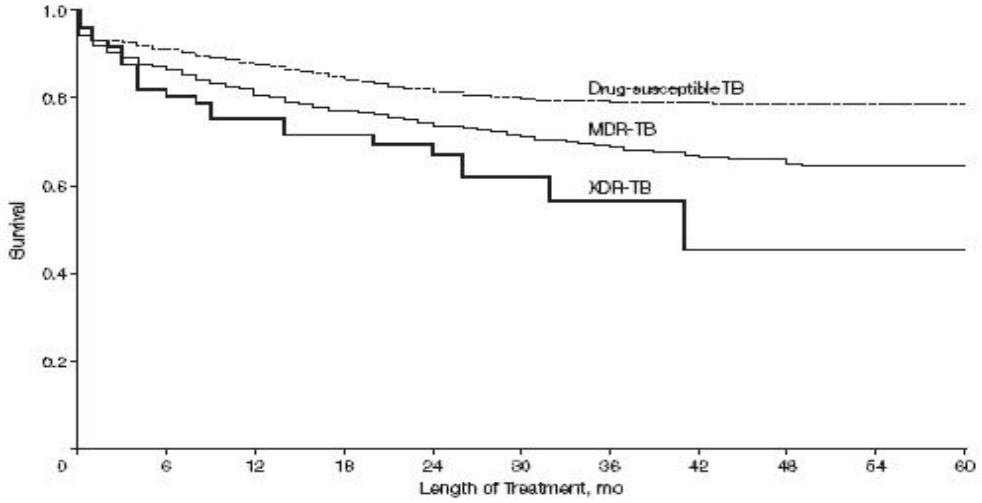
- XDR-TB: entering the post-antibiotic era?

  Raviglione Int J Tuberc Lung Dis 2006

- Drug resistant tuberculosis: back to sanatoria, surgery and cod-liver oil?

  Murray Eur Respir J. 1995

Prognosis of MDR and XDR cases

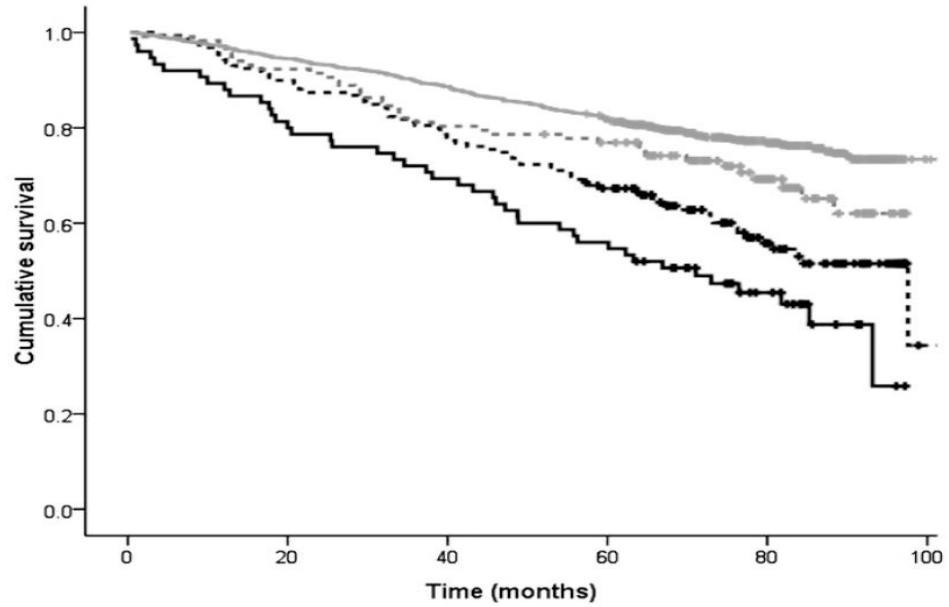


DS TB

MDR TB

XDR TB

Shah et al., JAMA, 2008



MDR TB

MDR TB + aminoglycosides

MDR TB + **FQ R**

XDR TB

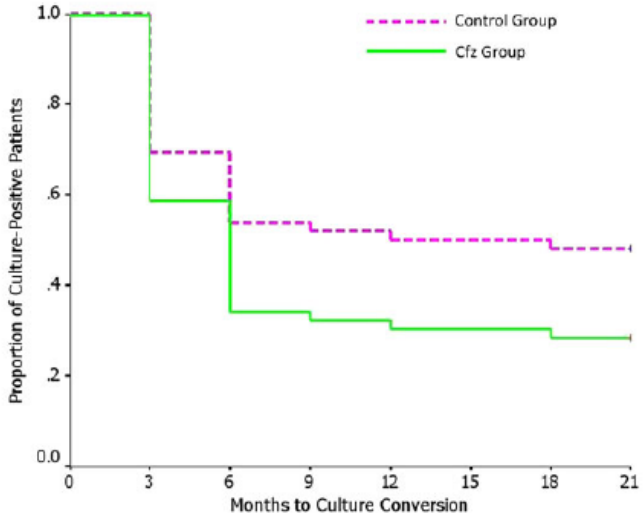
Kim et al., AJRCCM, 2010

Clofazimine

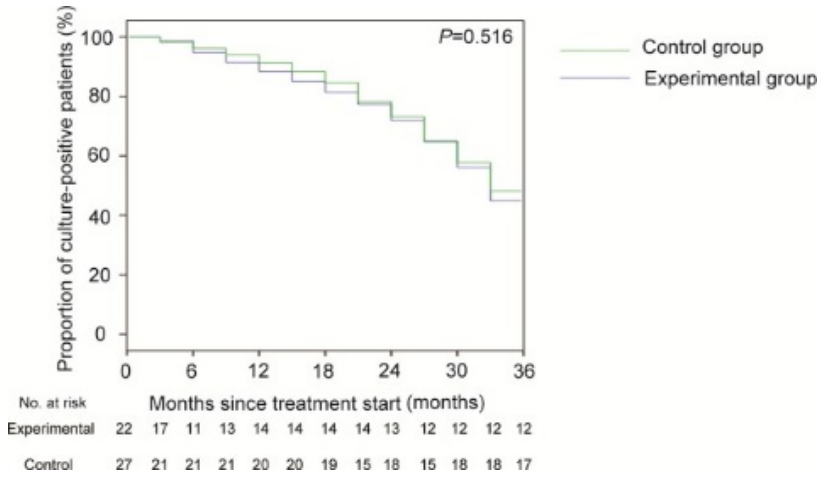
MIC = 0,06 to 2 mg/l
Plateau serum level 0,24 mg/l after 1 month at 50 mg/j

Diacon, AJRCCM 2015
No EBA after 2 weeks

Tang, CID 2015, Randomized trial MDR TB



Wang, AAC 2018, Randomized trial XDR TB

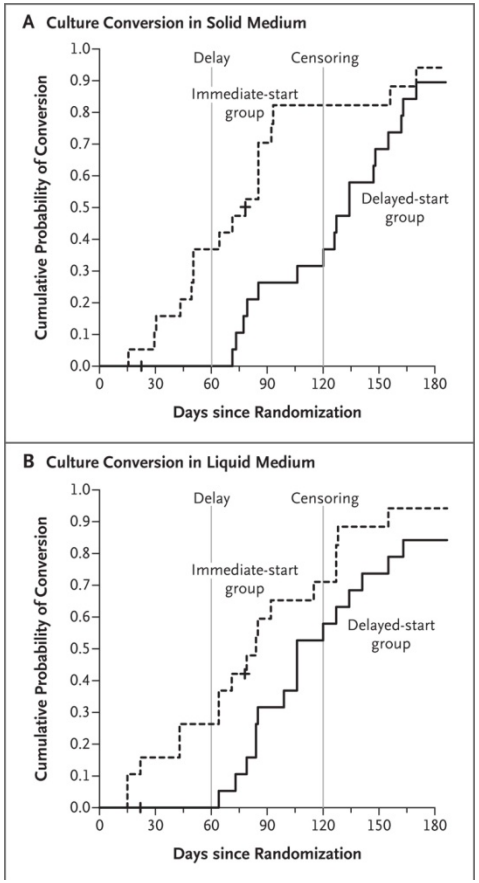


CFZ
has no EBA
increases sterilizing activity in MDR TB but not XDR TB??

Linezolide

Culture negativity

Lee M N Engl J Med 2012

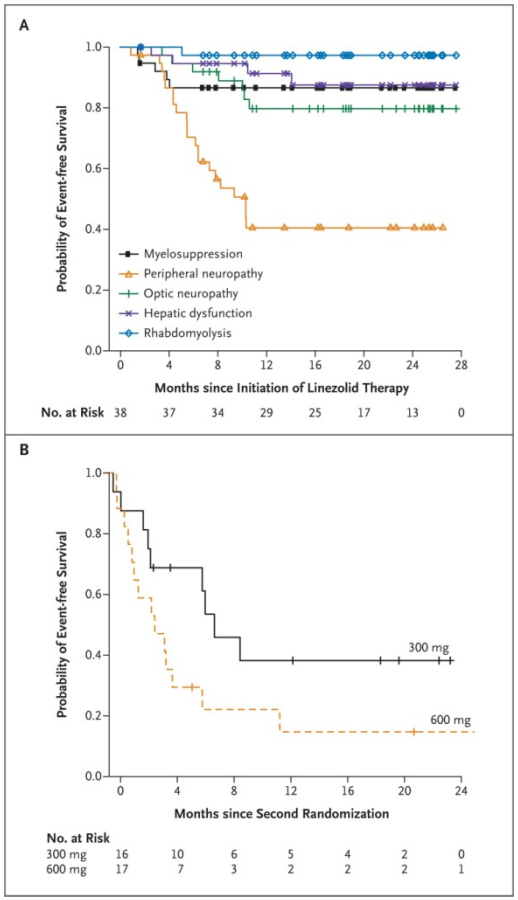


Oxazolidinone
MIC 0,5 mg/l
Peak serum level = 10 à 20 mg/L

Lee, 2012

- RCT
- 41 cases XDR TB, failure
- Adds linezolide 600 mg/day immediatly or after 2 months

Survival probability without toxicity

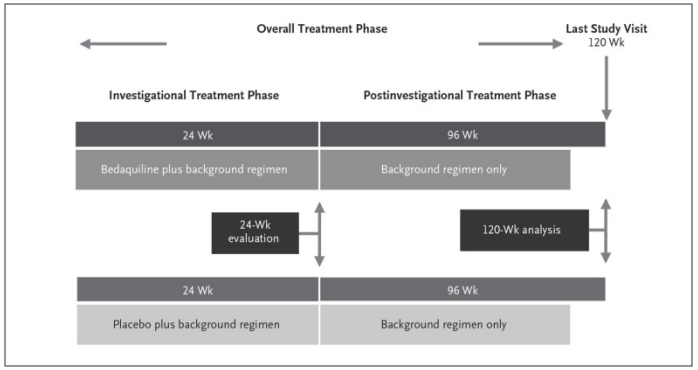


Linezolide increases culture negativity after 2 months if added to XDR TB regimen

Toxicity warning

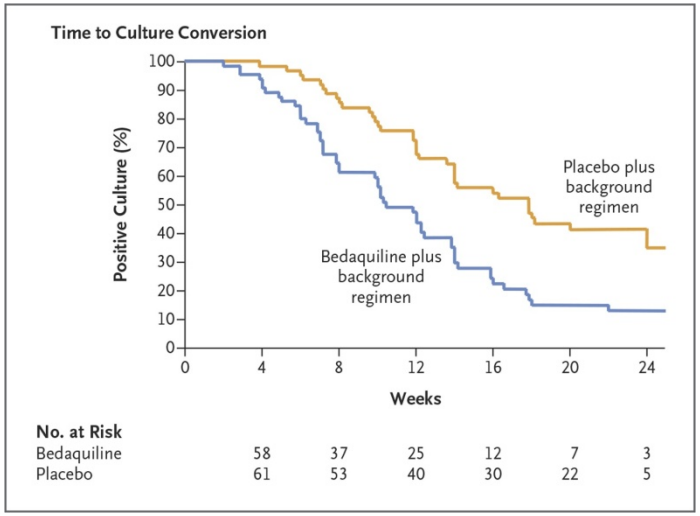
Bedaquiline

Diacon AH N Engl J Med 2014

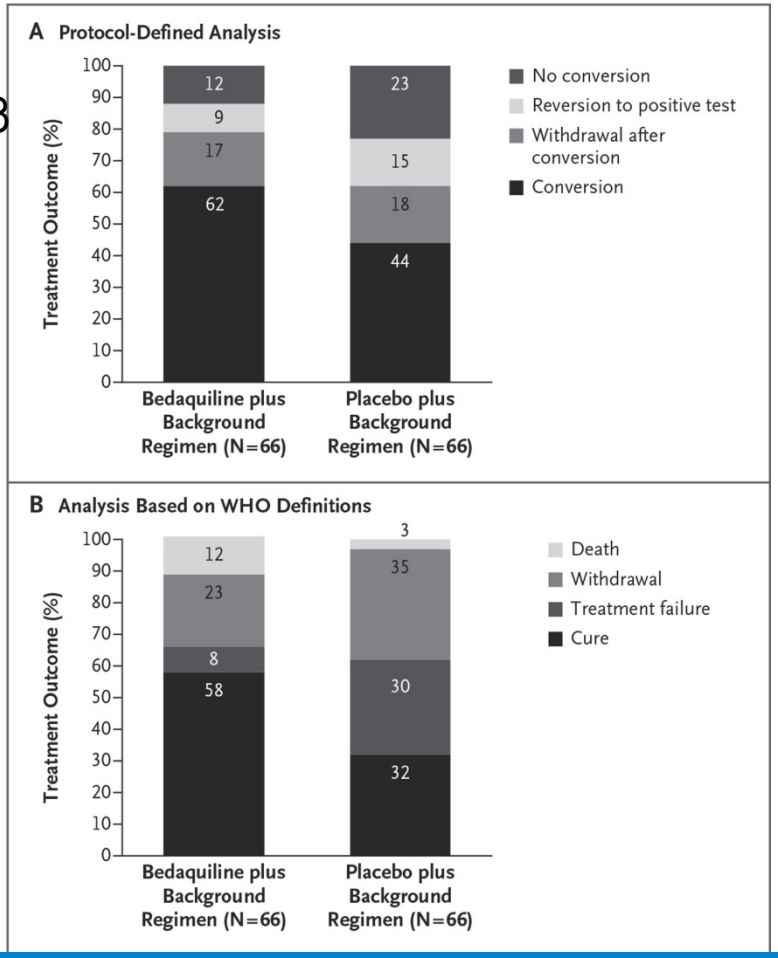


MIC = 0,01 mg/L

Peak serum level = 2 to 3 mg/L



2 years outcome



BDQ improves treatment outcome when added to background MDR regimen

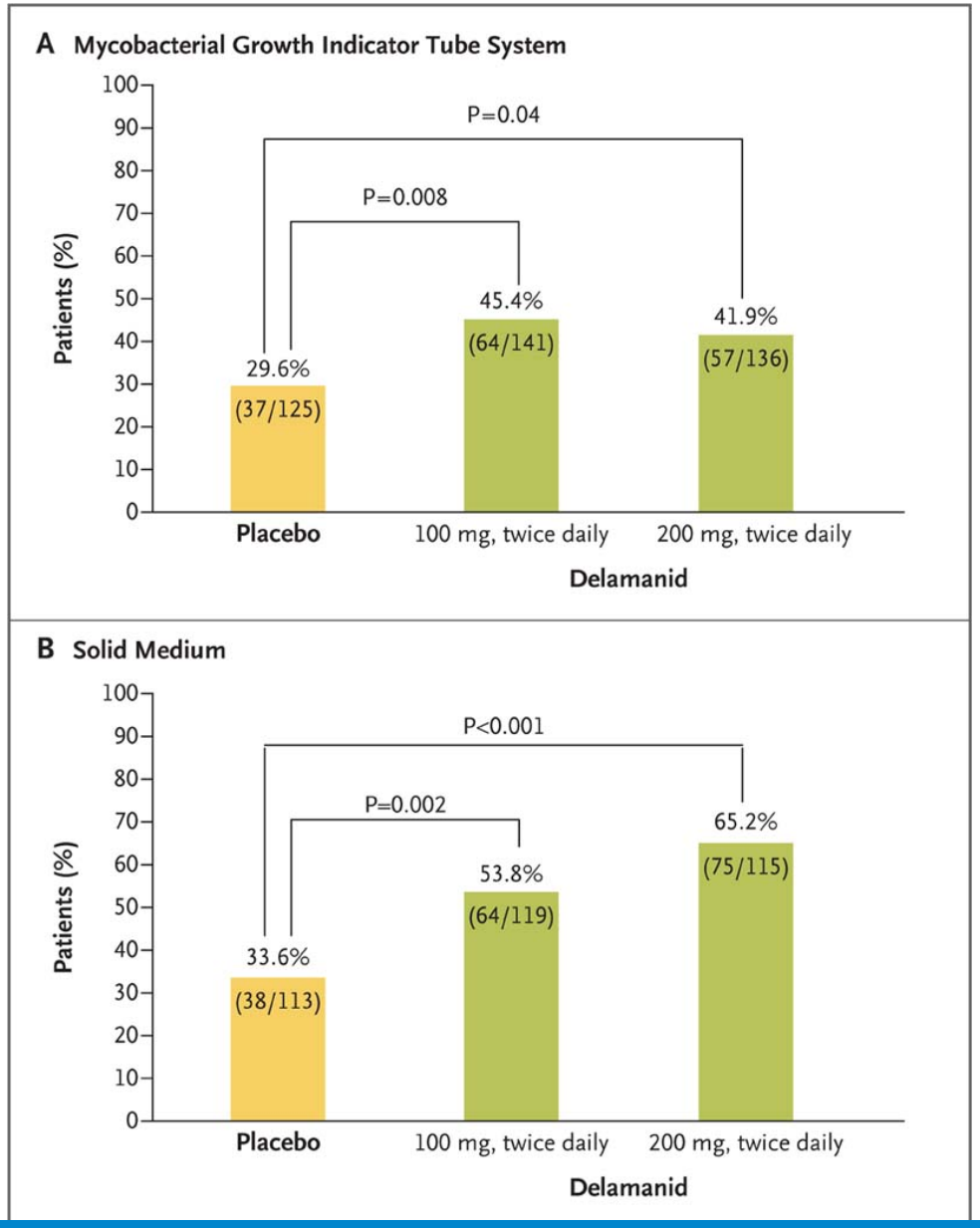
Mortality warning

Delamanid

Gler N Engl J Med 2012

MIC = 0,006 mg/L
Pieak serum level = 0,5 mg/L

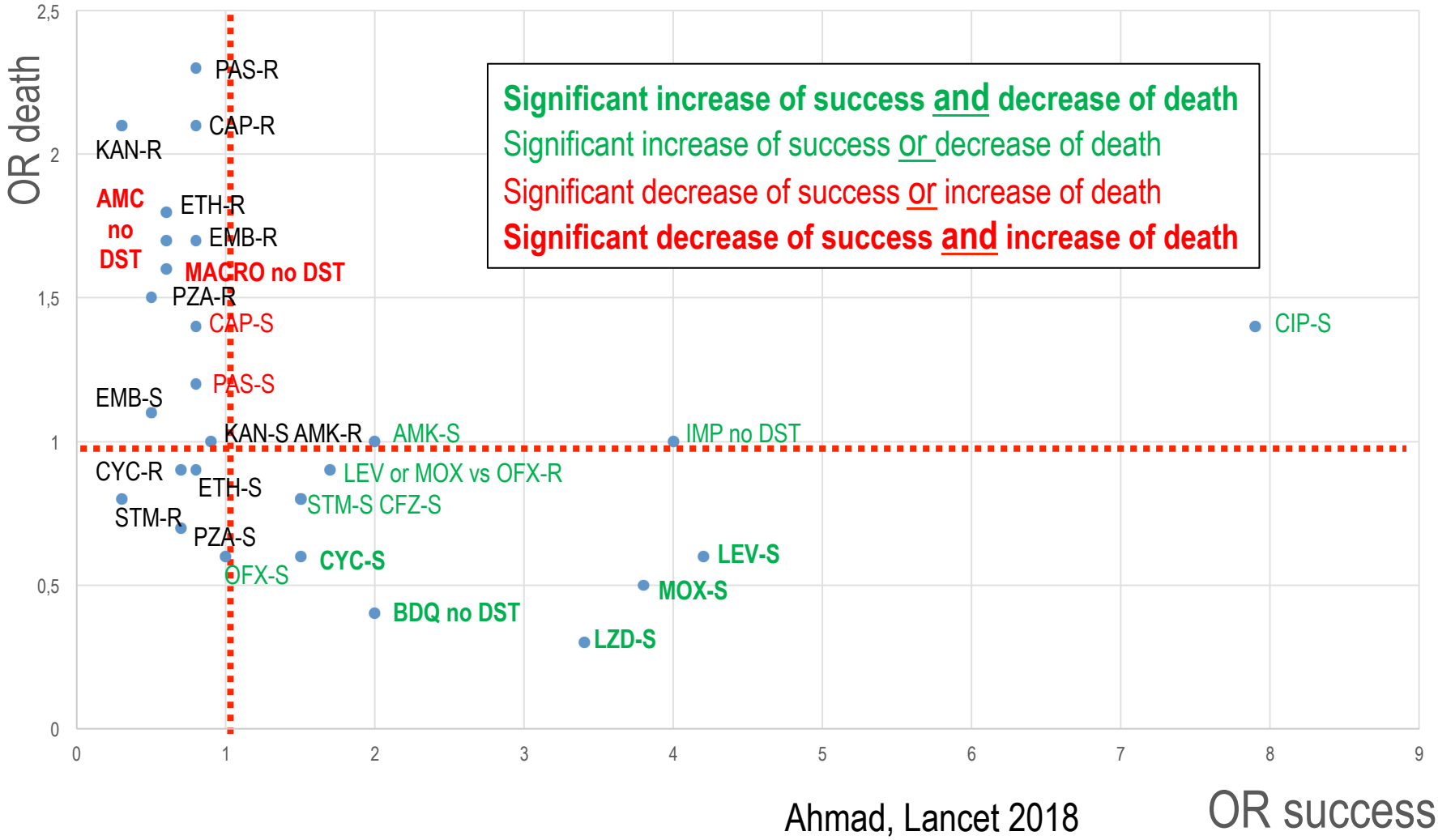
Proportion of patients culture negative at 2 months



Delamanid increase culture negativity at 2 months when added to background MDR regimen

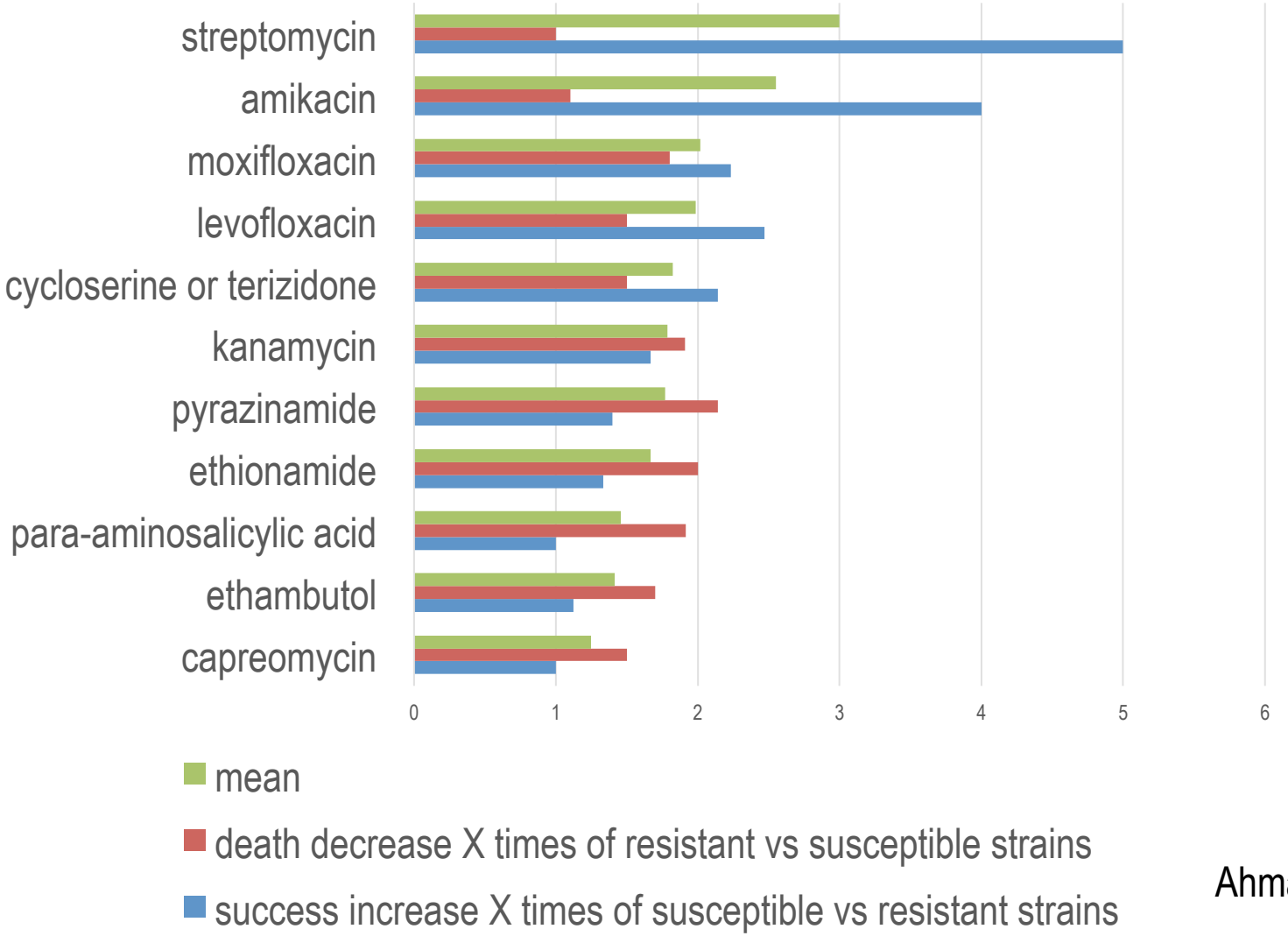
Impact of antibiotic use on treatment success or death of MDR TB depending on *in vitro* DST

Individual patient data meta-analysis of 12 030 patients from 25 countries



Ahmad, Lancet 2018

Impact of *in vitro* susceptibility/resistance on treatment success and mortality



Ahmad, Lancet 2018

Impact of antibiotic use on treatment success or death of XDR TB depending on *in vitro* DST

	Drug given (events/total)	Drug not given (events/total)	Propensity score matched multivariate regression			
			Pairs (n)	Adjusted OR (95% CI)	I^2	Adjusted RD (95% CI)
Injectables						
Amikacin*						
Success	62/69	384/551	68	2·5 (0·9–6·6)	NC	0·09 (–0·04 to 0·22)
Death	15/84	395/946	83	0·4 (0·2–0·8)	NC	–0·16 (–0·30 to –0·03)
Kanamycin†						
Success	52/74	394/546	73	0·9 (0·5–1·9)	15·1%	–0·01 (–0·16 to 0·14)
Death	19/93	391/937	93	0·9 (0·5–1·9)	40·5%	–0·01 (–0·13 to 0·10)
Capreomycin (all patients)						
Success	217/338	229/282	332	0·5 (0·4–0·7)	3·7%	–0·14 (–0·20 to –0·07)
Death	354/692	56/338	675	3·4 (2·7–4·3)	NC	0·25 (0·20 to 0·30)
Capreomycin (sensitive patients only)						
Success	72/91	229/282	91	0·8 (0·4–1·7)	6·0%	–0·04 (–0·16 to 0·08)
Death	25/116	56/338	115	3·8 (1·6–8·9)	NC	0·16 (0·07 to 0·25)
Other drugs						
Levofloxacin or moxifloxacin‡						
Success	279/360	119/182	359	1·2 (0·8–1·6)	7·7%	0·01 (–0·05 to 0·06)
Death	122/482	253/435	482	0·6 (0·4–0·8)	NC	–0·07 (–0·12 to –0·02)
Linezolid						
Success	255/281	221/392	280	6·6 (4·1–10·6)	7·3%	0·31 (0·24 to 0·38)
Death	33/314	418/810	314	0·2 (0·1–0·3)	7·5%	–0·29 (–0·36 to –0·23)
Clofazimine						
Success	141/173	335/500	173	1·5 (0·9–2·6)	NC	0·04 (–0·04 to 0·13)
Death	43/216	408/908	216	0·4 (0·2–0·6)	19·7%	–0·18 (–0·27 to –0·10)
Bedaquiline						
Success	126/145	350/528	139	2·5 (1·3–4·8)	NC	0·12 (0·03 to 0·21)
Death	18/163	433/961	155	0·5 (0·2–0·9)	NC	–0·09 (–0·17 to –0·02)

The analyses were done for all patients with extensively drug-resistant tuberculosis, and all patients who received each drug were compared with all patients who did not receive that drug. Patients who switched injectable drugs were excluded, as were patients who switched fluoroquinolones. OR=adjusted odds ratio. RD=adjusted risk difference. NC=not calculated. *Of the 84 patients that received amikacin, 39 were susceptible. †Of the 93 patients who received kanamycin, 12 were susceptible. ‡All of these patients were resistant to ofloxacin; only 175 had drug susceptibility testing results to later generation fluoroquinolones, and all of them were resistant.

Table 4: **Association of selected drugs used in extensively drug-resistant tuberculosis with success and death**

Ahmad, Lancet 2018

Impact of number of antibiotics used on treatment success of MDR TB

5 drugs initial phase

4 drugs continuation phase

	Success/total	Death/total	Propensity score matched multivariate regression			
			Pairs (n)	Adjusted OR (95% CI)	I^2	Adjusted RD (95% CI)
Initial phase						
Success vs failure or relapse						
0–2 drugs	1428/1742	NA	..	1 (ref)	..	..
3 drugs	1659/1891	NA	1891	1·8 (1·5–2·1)	0·2%	0·08 (0·06 to 0·10)
4 drugs	1996/2243	NA	2243	2·0 (1·8–2·4)	0·1%	0·09 (0·07 to 0·10)
5 drugs	1152/1262	NA	1262	2·6 (2·1–3·2)	0·1%	0·12 (0·10 to 0·14)
>6* drugs	587/642	NA	642	2·7 (2·0–3·6)	0·1%	0·14 (0·10 to 0·17)†
Died vs success, failure, or relapse (≥6)						
0–2 drugs	NA	524/2266	..	1 (ref)	..	..
3 drugs	NA	333/2224	2223	0·6 (0·6–0·7)	17·0%	−0·06 (−0·08 to −0·05)
4 drugs	NA	423/2666	2666	0·7 (0·6–0·8)	17·5%	−0·04 (−0·06 to −0·03)
5 drugs	NA	141/1403	1403	0·4 (0·3–0·5)†	13·1%	−0·14 (−0·16 to −0·12)†
>6* drugs	NA	66/708	708	0·4 (0·3–0·5)†	11·9%	−0·19 (−0·22 to −0·15)†
Continuation phase						
Success vs failure or relapse						
0–1 drugs	1264/1528	NA	..	1 (ref)	..	..
2 drugs	1591/1807	NA	1807	1·6 (1·4–1·9)	NC	0·06 (0·04 to 0·08)
3 drugs	1934/2177	NA	2177	1·7 (1·5–2·0)	NC	0·05 (0·03 to 0·07)
4 drugs	1017/1097	NA	1097	2·8 (2·2–3·5)†	NC	0·13 (0·11 to 0·15)†
>5 drugs	422/476	NA	476	1·7 (1·3–2·3)	NC	0·13 (0·09 to 0·16)†
Died vs success, failure, or relapse (≥5)						
0–1 drugs	NA	336/1864	..	1 (ref)	..	..
2 drugs	NA	280/2087	2087	0·7 (0·6–0·8)	6·0%	−0·04 (−0·06 to −0·02)
3 drugs	NA	366/2543	2543	0·8 (0·7–0·9)	6·1%	−0·02 (−0·04 to 0·00)
4 drugs	NA	114/1211	1211	0·5 (0·4–0·6)†	4·3%	−0·10 (−0·12 to −0·08)†
>5 drugs	NA	53/529	529	0·5 (0·4–0·7)†	3·9%	−0·12 (−0·15 to −0·08)†

Results were adjusted as described in Methods. We excluded 2763 patients from the initial phase analyses (1938 patients were lost to follow-up, 825 patients were missing information about initial phase drugs) and 3796 patients from the continuation phase analyses (1938 patients were lost to follow-up, 1858 patients were missing information about continuation phase drugs). OR=adjusted odds ratio. RD=adjusted risk difference. NA=not applicable. NC=not calculated. *40 patients received seven drugs. †Significantly better outcomes than another interval, in turn significantly better than reference group.

Table 5: Association of number of possibly effective drugs with success or death

Ahmad, Lancet 2018

Impact of duration of treatment on treatment success of MDR TB

6-8 months initial phase

18-20 months total duration

	Success (n)	Total (N)	Propensity score matched multivariate regression			
			Pairs (n)	Adjusted OR (95% CI)	I^2	Adjusted RD (95% CI)
Duration of initial phase (months)*						
0·5–5·0	1169	1432	..	1 (ref)	..	..
5·01–6·0	1381	1529	1529	1·7 (1·4–2·1)	NC	0·06 (0·04 to 0·08)
6·01–8·0	1602	1696	1695	3·2 (2·5–4·0)	NC	0·09 (0·07 to 0·10)
8·01–12·0	1346	1522	1519	1·4 (1·2–1·7)	NC	0·05 (0·03 to 0·06)
12·01–25·3	557	679	677	0·8 (0·7–1·0)	NC	−0·04 (−0·07 to −0·01)
Interval from culture conversion to end of initial phase (months)†						
0–1·0	239	251	..	1 (ref)	..	..
1·01–3·0	668	695	694	1·5 (1·0–2·3)	NC	0·02 (0·00 to 0·03)
3·01–5·0	878	917	906	1·4 (1·0–2·0)	NC	0·02 (0·00 to 0·03)
5·01–7·0	1158	1179	1179	3·3 (2·1–5·2)	NC	0·04 (0·03 to 0·05)
7·01–15·0	1025	1080	1079	1·1 (0·8–1·5)	NC	0·01 (−0·01 to 0·02)
Total duration of treatment (months)‡						
6·0–11·9	119	176	174	0·6 (0·4–0·8)	42·2%	−0·10 (−0·17 to −0·03)
12·0–16·0	250	297	..	1 (ref)	..	..
16·01–18·0	1343	1482	1482	1·8 (1·5–2·4)	11·6%	0·20 (0·18 to 0·22)
18·01–20·0	1219	1264	1264	7·5 (5·5–10·1)	10·6%	0·23 (0·22 to 0·24)
20·01–22·0	995	1091	1091	2·9 (2·3–3·6)	11·1%	0·19 (0·17 to 0·20)
22·01–24·0	1609	1911	1911	1·5 (1·3–1·7)	13·7%	0·14 (0·12 to 0·17)
24·01–36·9	1391	1611	1608	1·8 (1·5–2·0)	17·7%	0·16 (0·14 to 0·18)
Interval from sputum culture conversion to end of treatment (months)§						
0·1–12·0	360	396	394	0·5 (0·4–0·7)	NC	−0·04 (−0·07 to −0·01)
12·01–15·0	565	593	..	1 (ref)	..	..
15·01–18·0	1206	1235	1223	2·1 (1·4–3·1)	NC	0·02 (0·01 to 0·04)
18·01–21·0	1122	1158	1154	1·6 (1·1–2·3)	NC	0·02 (0·00 to 0·03)
21·01–24·0	858	893	889	1·2 (0·9–1·8)	NC	0·01 (−0·01 to 0·02)
24·01–69	386	416	413	0·7 (0·4–1·0)	NC	−0·02 (−0·05 to 0·00)

All duration analyses were restricted to the patients with treatment success or failure or relapse; the 3667 patients who died or were lost were excluded. Patients who were included or excluded in each analysis are detailed in the footnotes. OR=adjusted odds ratio. RD=adjusted risk difference. NC=not calculated. *6858 patients were included and 1505 patients were excluded (n=1323 not reported; n=182 initial phase > 25·3 months [>2 SDs from the mean]). †4122 patients included and 4241 excluded (n=3777 time to culture conversion or initial phase duration was not reported; n=390 conversion occurred after end of initial phase; n=74 sputum conversion occurred after 14·3 months [>2 SD]). ‡7832 patients included and 531 patients excluded (n=248 missing information; n=203 total duration <6 months; n=80 total duration >36·9 months [>2 SD]). §4691 patients included and 3672 excluded (n=3413 information about time to conversion or total duration missing; n=259 total duration <6 months, >36·9 months [>2 SD], or culture conversion was more than 14·3 months).

Table 6: Association of treatment duration with treatment success

Ahmad, Lancet 2018

Available antituberculous drugs : WHO list

- **Group A**: Medicines to be prioritised: levofloxacin/moxifloxacin, bedaquiline and linezolid
- **Group B**: Medicines to be added next: clofazimine, cycloserine/terizidone
- **Group C**: Medicines to be included to complete the regimens and when agents from Groups A and B cannot be used: ethambutol, delamanid[iii], pyrazinamide, imipenem-cilastatin, meropenem, amikacin (streptomycin), ethionamide/prothionamide, *p*-aminosalicylic acid;

Medicines no longer recommended are kanamycin and capreomycin, given increased risk of treatment failure and relapse associated with their use in longer MDR-TB regimens. Use of amikacin did not show a similar association, although the same safety concerns as for the other injectables apply. Amoxicillin-clavulanic acid is only to be used to accompany the carbapenems.

[ii] Longer MDR-TB regimens usually last 18-20 months and may be standardized or individualized. These regimens are usually designed to include at least five medicines considered to be effective.

[iii] The position of delamanid will be re-assessed once individual patient data from Otsuka trial 213 has been reviewed; these data were not available for the evidence assessment outlined above.

First phase 8 months
Then without injectable for total duration 20 months

Available antituberculous drugs : WHO list

GROUP	MEDICINE	Abbreviation
Group A: Include all three medicines (unless they cannot be used)	Levofloxacin OR Moxifloxacin	Lfx Mfx
	Bedaquiline[1,4]	Bdq
	Linezolid[2]	Lzd
Group B: Add both medicines (unless they cannot be used)	Clofazimine	Cfz
	Cycloserine OR Terizidone	Cs Trd
Group C: Add to complete the regimen and when medicines from Groups A and B cannot be used	Ethambutol	E
	Delamanid[3,4]	Dlm
	Pyrazinamide[5]	Z
	Imipenem-cilastatin OR Meropenem[6]	Ipm-Cln Mpm
	Amikacin (OR Streptomycin)[7]	Am (S)
	Ethionamide OR Prothionamide	Eto Pto
	p-aminosalicylic acid	PAS

1. Evidence on the safety and effectiveness of Bdq beyond 6 months was insufficient for review; extended Bdq use in individual patients will need to follow 'off-label' use best practices.
2. Optimal duration of use of Lzd is not established. Use for at least 6 months was shown to be highly effective, although toxicity may limit its use.

First phase 8 months
Then without injectable for total duration 20 months

CHOOSING THE MDR-TB TREATMENT REGIMEN IN PATIENTS WITH CONFIRMED RIFAMPICIN-RESISTANT OR MDR-TB

CRITERIA: Do any of the following apply ?

- ✓ Confirmed resistance or suspected ineffectiveness to a medicine in the shorter MDR-TB regimen (except isoniazid resistance)
- ✓ Exposure to ≥1 second-line medicines in the shorter MDR-TB regimen for >1 month
- ✓ Intolerance to ≥1 medicines in the shorter MDR-TB regimen or risk of toxicity (e.g. drug-drug interactions)
- ✓ Pregnancy
- ✓ Extrapulmonary disease
- ✓ At least one medicine in the shorter MDR-TB regimen not available in the programme

NO

Shorter MDR-TB regimen

Intensive phase
Duration: 4-6 months
Composition: 4 second-line drugs

Continuation phase
Duration: 5 months
Composition: 2 second-line drugs

Supported by selected first-line TB drugs

FAILING REGIMEN, DRUG INTOLERANCE, RETURN AFTER INTERRUPTION >2 MONTHS, EMERGENCE OF ANY EXCLUSION CRITERION

YES

Individualised ("conventional") MDR/RR-TB regimens

Intensive phase
Duration: Up to 8 months
Composition: 4 or more second-line drugs

Continuation phase
Duration: 12 months or more
Composition: 3 or more second-line drugs

Supported by selected first-line TB drugs

REGIMEN COMPOSITION

4-6 Km-Mfx-Pto-Cfz-Z-$H_{high\text{-}dose}$-E / 5 Mfx-Cfz-Z-E

Km=Kanamycin; Mfx=Moxifloxacin; Pto=Prothionamide;
Cfz=Clofazimine; Z=Pyrazinamide;
$H_{high\text{-}dose}$= high-dose Isoniazid; E=Ethambutol

Short-course regimen : DST restriction

- Lange, AJRCCM 2016

Table 1. Eligibility for the World Health Organization Short-Course Treatment Regimen for Patients with Multidrug-Resistant Tuberculosis from Europe with Comprehensive Results of First- and Second-Line Antituberculosis Drug Susceptibility Testing

		Full DST*		*Mycobacterium tuberculosis* Drug Resistance from Patients with MDR-TB with Full DST														Eligibility for the MDR-TB Short-Course Regimen	
				H		R		SLID		FQ		Pto/Eto		E		Z			
Cohort	N	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Austria (Vienna), 2003–2012	80	80	100	80	100	80	100	33	41.3	20	25	38	47.5	51	63.8	50	62.5	8	10
France (Bligny), 2006–2014	177	114	64.4	114	100	114	100	34	29.8	36	31.6	81	71.1	74	64.9	67	58.8	7	6.1
Germany (Borstel), 2002–2016	75	70	93.3	70	100	70	100	16	22.9	19	27.1	40	57.1	56	80	51	72.9	6	8.6
Portugal (national), 2001–2015	428	200	46.7	200	100	200	100	101	50.5	96	48	166	83	103	51.5	149	74.5	9	4.5
TBnet (16 countries)	380	148	39.0	148	100	148	100	41	27.7	31	21.0	69	46.6	80	54.1	92	62.2	18	12.2
Total	1,140	612	53.7	612	100	612	100	225	36.8	202	33	394	64.4	364	59.5	409	66.8	48	7.8

Is short-course regimen applicable worldwide?

Resistance to new drugs?

- Pang, AAC 2017
- China, XDR strains

Antimicrobial agent	No. of strains with MIC (mg/liter) of:											Breakpoint MIC for resistance (mg/liter)	No. (%) of resistant strains
	≤0.031	0.063	0.125	0.25	0.5	1	2	4	8	16	32		
MFX	0	0	2	1	5	13	27	29	10	3	0	0.5	82 (91.1)
[illegible]													
LZD	0	0	6	35	40	4	0	1	1	2	1	1.0	5 (5.6)
CLO	0	13	28	34	7	3	4	1	0	0	0	1.0	5 (5.6)
BDQ	81	2	3	1	3	0	0	0	0	0	0	0.25	3 (3.3)
DMD	86	0	0	0	1	0	0	0	0	0	3	0.125	4 (4.4)

Resistance to new drugs already described

Bedaquiline resistance in France

Veziris, ERJ 2017

TABLE 1 Characteristics of the four bedaquiline-resistant *Mycobacterium tuberculosis* strains

	Previous treatments	*M. tuberculosis* strain				
		Lineage	BDQ MIC mg·L^{-1}	*atpE*	*rv0678*	MIRU-VNTR
H37Rv			0.03	WT	WT	
Patient 1	None	Delhi/CAS	0.5	WT	del gg 18-19	242 235 442 244 425 173 344 742
Patient 2	INH, RFB, EMB, PZA, CAP, MXF, LNZ and TER	S	0.5	WT	WT[#]	233 353 212 434 215 133 336 A22
Patient 3	BDQ combined with PZA, ETH, CAP, CYC, PAS and AMC, but only PAS susceptible on DST	Beijing	0.25	WT	ins g140	244 233 352 644 425 153 353 823
Patient 4	INH, RIF, EMB, PZA, SM then KAN, MXF, ETH, CYC and PAS	Beijing	0.015	WT	WT	244 233 352 644 425 173 353 623
	BDQ combined with EMB, PZA, AMK, ETH, LNZ, PAS, CFZ, PAS and IMP/AMC, but only PAS and AMK susceptible on DST		0.25	WT	M139T[¶]	244 233 352 644 425 173 353 623

2% BDQ-R among MDR in France in 2014-2015 :

1/2 = secondary resistance

1/2 = primary resistance = selection par another molecule?

MDR TB : ongoing trials

	Phase	Study population	Study groups	Notes
Otsuka Trial 213 (NCT01424670)	3	511, HIV- adults (aged ≥18 years)	2 months delamanid (100 mg twice daily) and 4 months delaminid (200 mg daily) plus OBR *vs* 6 months placebo plus OBR	Opened September 2011, completed June, 2016, preliminary findings presented at IUATLD October, 2017, confirm efficacy with less toxicity, results mid-2018; Otsuka
STREAM Stage 1 (ISRCTN78372190)	3	424, HIV– and HIV + adults (aged ≥ 18 years)	4 months daily moxifloxacin, clofazimine, pyrazinamide, ethambutol, isoniazid (high dose), kanamycin (daily for 3 months, then 3 times per week), prothionamide, and 5 months of moxifloxacin, clofazimine, pyrazinamide, ethambutol daily	Opened 2012, closed to accrual June, 2015, preliminary findings presented at IUATLD October, 2017, results mid-2018; IUATLD, BRMC, USAID
NC-005 (NCT02193776)	2b	60, HIV- adults (aged ≥18 years)	Serial sputum culture counts: 8 weeks bedaquiline (200 mg daily), pretomanid (200 mg daily), moxifloxacin, pyrazinamide, single arm study with long follow-up	Opened November, 2014, preliminary findings presented at CROI, 2017, results mid-2018; TB Alliance
OPTI-Q (NCT01918397)	2	100, HIV– and HIV + adults (aged ≥18 years)	6 months levofloxacin (14, 17, or 20 mg/kg/d) plus OBR *vs* 6 months levofloxacin (11 mg/kg/d) plus OBR	Opened January, 2015, results mid-2018; South Africa, Peru; NIAID, Boston University, CDC TBTC
NC-006 STAND (NCT02342886)	3	13 (of original target of 300), HIV– and HIV+ children (aged ≥14 years)	6 months pretomanid (200 mg), moxifloxacin, pyrazinamide daily, single arm study	Opened February, 2015, paused October, 2016–May, 2017, accrual not resumed, results March, 2018; TB Alliance
NiX-TB (NCT02333799)	3	109 (of original target of 300), HIV– and HIV + adults (aged ≥18 years)	6 months bedaquiline (200 mg daily for 2 weeks then 200 mg three times weekly), pretomanid (200 mg daily), linezolid (600 mg twice daily), single arm study	Opened March, 2015, preliminary findings presented at CROI, 2017, accrual closed November, 2017, with opening of NC-007 XeNiX trial; TB Alliance
NExT-5001 (NCT02454205)	2/3	300, HIV– and HIV + adults (aged ≥18 years)	6–9 months bedaquiline, linezolid, levofloxacin, pyrazinamide, and either high-dose isoniazid or ethionamide or terizidone daily (all oral) *vs* 6–8 months kanamycin, moxifloxacin, pyrazinamide, ethionamide, terizidone daily, and 16–18 months moxifloxacin	Opened October, 2015, results January, 2019; University of Cape Town
MDR-END (NCT02619994)	2	238, HIV– and HIV + adults (aged ≥18 years)	9 or 12 months delamanid, levofloxacin (750 or 1000 mg), linezolid (600 mg daily for 2 months, 300 mg daily thereafter) *vs* local regimen	Opened January, 2016, results December, 2019; Korea
STREAM Stage 2 (NCT02409290)	3	1155, HIV– and HIV + adults (aged ≥18 years)	9 months moxifloxacin, clofazimine, ethambutol, pyrazinamide daily, with initial 2 months isoniazid, kanamycin, prothionamide daily, or 9 months bedaquiline, clofazimine, ethambutol, levofloxacin, pyrazinamide daily, with initial 2 months isoniazid (high dose), prothionamide daily (all oral), or 6 months bedaquiline, clofazimine, levofloxacin, pyrazinamide daily, with initial 2 months isoniazid (high dose) and kanamycin *vs* 20–24 month local regimen	Opened April, 2016, results April, 2021; IUATLD, BMRC, USAID, TB Alliance
Janssen C211 (NCT02354014)	2	60, HIV- adults (aged ≥18 years)	Pharmacokinetics, safety, dose-range 6 months bedaquiline (daily for 2 weeks, then 3 times a week) plus OBR, single arm study	Opened May, 2016, results March 2021; India, Philippines, Russia, South Africa; Janssen
ACTG A5343 DELIBERATE (NCT02583048)	2	84, HIV– and HIV + adults (aged ≥18 years)	Pharmacokinetics, QTC 6 months bedaquiline daily plus OBR, or 6 months delamanid daily plus OBR, or 6 months bedaquiline and delamanid daily plus OBR	Opened August, 2016, results 2019; ACTG
endTB (NCT02754765)	3	750, HIV– and HIV + adults (aged ≥18 years)	9 months bedaquiline, linezolid, moxifloxacin, pyrazinamide daily, or 9 months of bedaquiline, linezolid, clofazimine, levofloxacin, pyrazinamide daily, or 9 months of bedaquiline, linezolid, delamanid, levofloxacin, pyrazinamide daily, or 9 months of delamanid, linezolid, clofazimine, levofloxacin, pyrazinamide daily, or 9 months of delamanid, clofazimine, moxifloxacin, pyrazinamide daily *vs* local regimen	Opened December, 2016, results September, 2020; Georgia, Kazakhstan, Kyrgyzstan, Lesotho, Peru; MSF, Partners in Health
TB-PRACTECAL (NCT02589782)	2/3	630, HIV– and HIV + adults (aged ≥18 years)	6 months bedaquiline, pretomanid, moxifloxacin, linezolid daily, or 6 months bedaquiline, pretomanid, linezolid, clofazimine daily, or 6 months bedaquiline, pretomanid, linezolid daily (all oral) *vs* local regimen	Opened January, 2017, results March, 2021; Belarus, South Africa, Uzbekistan; MSF
IMPAACT P1108 (NCT03141060)	2	72, HIV– and HIV + children (aged <18 years)	Pharmacokinetics, safety, dose-range 6 months bedaquiline (daily for 2 weeks, then 3 times a week) plus OBR, single arm study	Opened June, 2017, results June, 2020; Haiti, India, South Africa; IMPAACT
NC-007 ZeNiX (NCT03086486)	3	180, HIV- and HIV+ adults and children (aged ≥14 years)	2 or 6 months linezolid (600 or 1200 mg daily, double-blinded), bedaquiline (200 mg daily for 2 weeks, then 100 mg daily), and pretomanid (200 mg daily)	Opened November, 2017, results January, 2021
IMPAACT 2005 (NCT03141060)	1/2	48, HIV– and HIV + children (aged <18 years)	Pharmacokinetics, safety 6 months delamanid (100 mg twice daily) plus OBR, single arm study	Opened January, 2018, results April, 2021; Botswana, India, South Africa, Tanzania; IMPAACT
ACTG A5356	2a	240, HIV– and HIV + adults (aged ≥18 years)	6 months delamanid (100 mg twice daily), linezolid (300 or 600 mg daily or 1200 mg every other day) plus OBR (oral) *vs* 6 months delamanid (100 mg twice daily) plus OBR (injectable)	Opens August, 2018; ACTG
NC-008 SimpliciTB (NCT03338621)	3	150, HIV– and HIV + adults (aged ≥18 years)	6 months bedaquiline, pretomanid, moxifloxacin, pyrazinamide daily, single arm study	Opens August, 2018, results March 2022; TB Alliance

Tiberi, Lancet ID, 2018

What we do in France