

**From bedside to bench:
Search for shorter TB treatment**

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Why not from the bench to the bedside?

Because

- It is how it began ...for me (cough with blood...)
- It is how I became really interested in TB
- It is how I became deeply interested in the cure of TB

On the road to the sanatorium bed (1)



On the road to the sanatorium bed (2)



Welcome to the sanatorium at St-Hilaire-du-Touvet, France

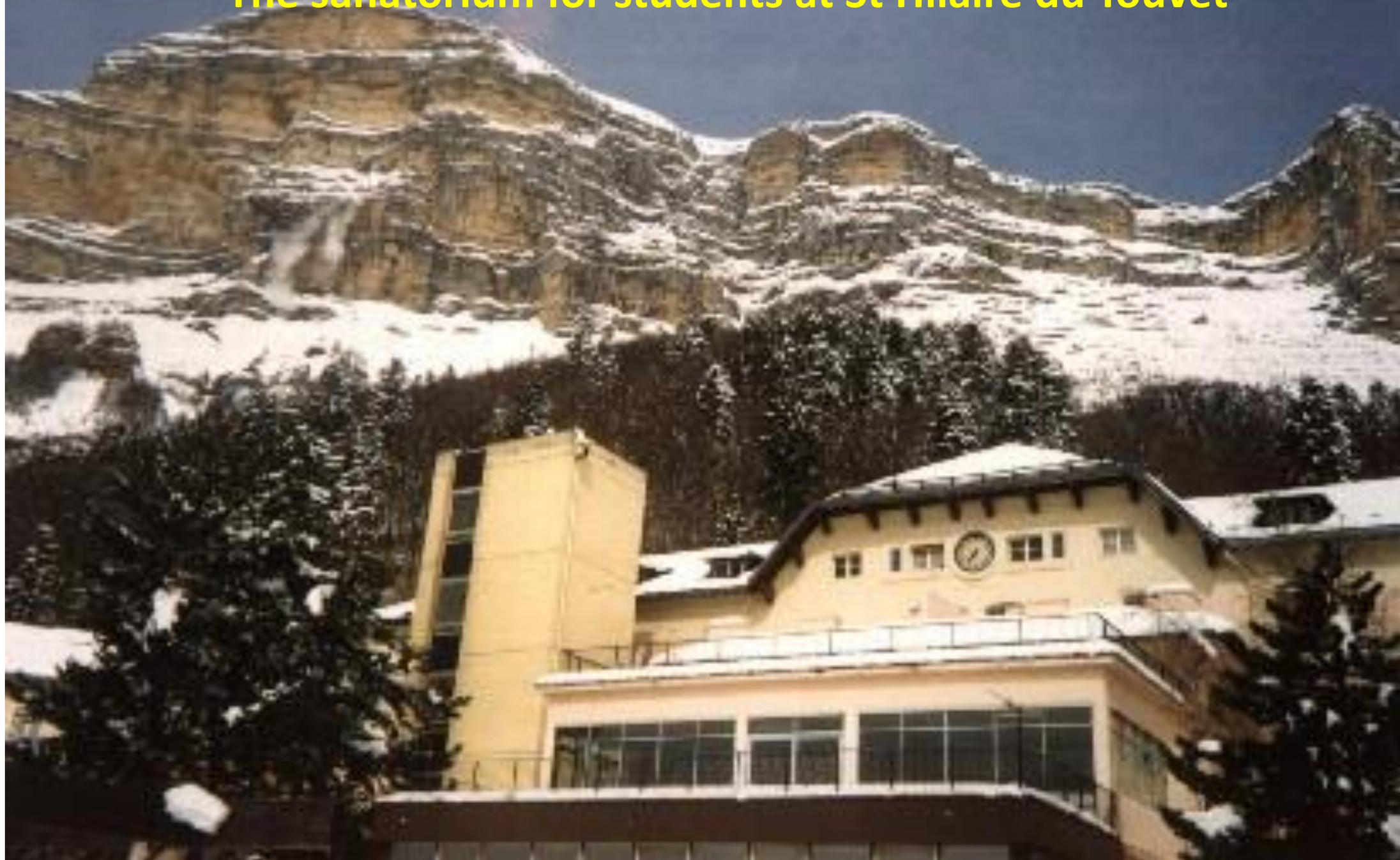
on July 15, 1954

To the patient with pulmonary TB (myself), the medical director said:

You should fully realize, and the sooner the better, that

- Your future is behind you
- If you survive..., you will just be able to work part time!

The sanatorium for students at St Hilaire du Touvet





SANTO DOMINGO DE LOS RIOS

PROPERTY OFFICE
GENERAL BUILDING







Enjoyment at St-Hilaire-du Touvet

I survived ... in spite or because of

- Total bed rest for 9 months!
- Resistance of my tubercle bacilli to streptomycin and isoniazid (I was a MDR-TB precursor!)
- Pulmonary resection on Jan 21, 1955

My mentor Georges Canetti 1911-1971



Fall of 1955: Why not come and do research with me at the Pasteur Institute to get your revenge?

History of TB antibiotic treatment (1)

- First step in the 1940s.. Prevention of death

The discovery of streptomycin by Schatz, Bugie and Waksman in 1944, at Rutgers, NJ. opened the door to TB treatment with antibiotic:

- Only 7% of streptomycin (2g/day) + bed-rest treated patients died before the end of six months vs 27% of bed-rest only treated patients (BMRC 1948).
- However bacilli of 80% of patients treated with streptomycin became resistant to streptomycin!

- Second step in the 1950s.. Prevention of acquired drug resistance

The discovery of para-amino-salicylic acid or PAS (1946) and isoniazid (1952) was decisive: combining streptomycin with PAS and isoniazid prevented the development of resistance to streptomycin...and isoniazid.

- Third step in the 1960s.. The time needed to obtain stable culture conversion = **The cure of TB**

All conducted clinical trials concluded that 18-24 months of treatment with streptomycin (S), isoniazid (H) and PAS (P), abbreviated 3SHP/15 HP, was curing TB but with ~ 10% relapses (MRC. Tubercle 1962;43:201-267).

The IUAT trial, 1960 (IUAT Bull. 1964 ; 34 : 82-150)

- At the end of the fifties, a majority of TB “experts” were still convinced that once a TB patient, always a TB patient (like a “leper”): you can be “stabilized” but never cured
- A multi-center (Europe, Asia, America, Africa) study was conducted under the auspices of IUAT among 581 sputum-smear positive patients with pulmonary TB to study the efficacy of 18 months daily treatment with 3SHP*/15HP
- The results were unambiguous...

* (S, streptomycin, 1g IM; H, isoniazid, 300mg orally; P, PAS, 10g orally)

Results of the multi-center IUAT trial 1960-61

(IUAT Bull. 1964 ; 34 : 82-150)

Patients	Number	%
Included*	581	100
Received the prescribed treatment	317	54.6**
Did not receive the prescribed treatment	196	33.7
Dead	10	1.8
Lost to follow up	58	9.9
*with organisms fully susceptible to streptomycin, isoniazid, and PAS		
** All cured		

Two crucial findings

1. All of the patients (n= 317) who received the prescribed regimen were cured (not a single failure!)
2. But ... **almost 50% of the patients** did not receive or did not take the prescribed regimen for the full duration, and ... did not perform as well

Conclusion: There is a long way between theory and practice! Implementation (adherence, compliance) in the field is as important as science.

The development of XDR-TB, a man-made phenomenon, could have been predicted in the sixties!

The home and sanatorium study

(W. Fox. Advances in TB Research 1963; 12:28-149)

- Up to 1960, the rule was to treat TB in hospitals or sanatorium.
- At Madras, India, home treatment was tested under the leadership of Wallace Fox:

First, a comparison was conducted in patients of home and sanatorium treatment for a period of 12 months

- Treatment INH+PAS
- Cured at 12 months: 92% (73/81) in sanatorium vs 86% (67/82) at home

Second, a study of relapses in patients in a 4-year period of follow-up:

- 3 (5%) among home treated patients
- 6 (9%) among sanatorium treated patients

Third, the incidence of TB in a 5-year period of follow-up was assessed:

- 6.2% of the 297 family contacts of home treated patients
- 7.1% of 312 family contacts of sanatorium treated patients

Conditions for success of ambulatory treatment of TB

(TCC Madras, Bull. Wld. Hlth. Org 1959 22. 51-144; W. Fox. Advances in TB Research 1963; 12:28-149)

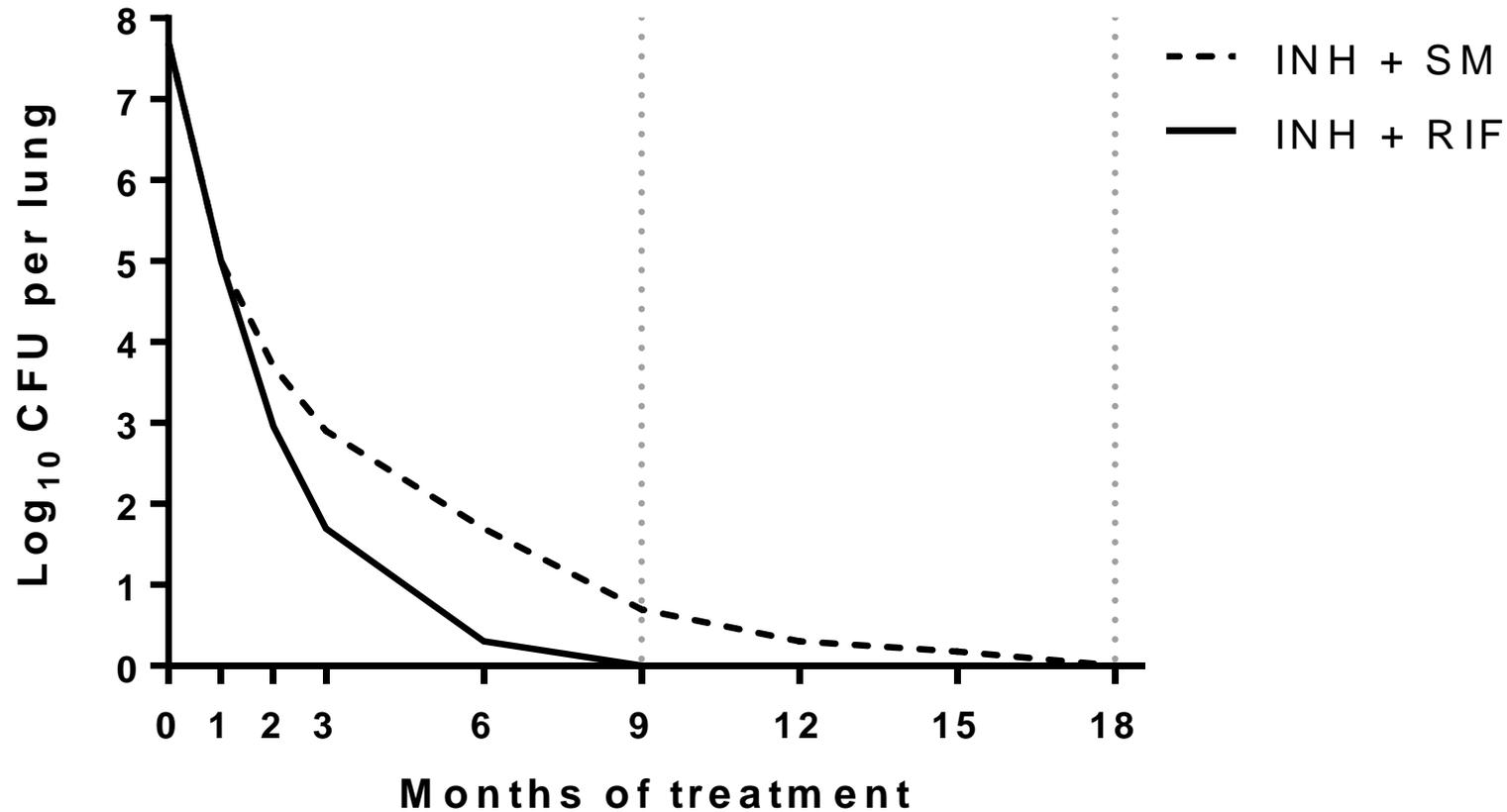
- Adequate supply of drugs
- Enough staff to supervise the patients
- Efficient appointment system
- Adequate transport for ill patients with reserved beds in hospital
- Organized system for surprise visits and check of drug stock
- A capable laboratory

Unfortunately, the explicit conditions set forth by W. Fox for the success of ambulatory treatment, i.e. **the rigorous organization and supervision of antibiotic intake**, was then and is still now so overlooked that the percentage of patients who do not take the prescribed treatment may exceed 50%.

History of TB antibiotic treatment (2)

- **First step**, in the 1940s.. Prevention of death
- **Second step**, in the 195s.. Prevention of acquired drug resistance
- **Third step**, in the 1960's.. The time needed to obtain stable culture conversion = **The cure of TB in 18 months** (a miracle compared to death of 50% of patients!)
- **Fourth step**, in the 1970s.. The cure of TB in 9 months

The discovery and introduction of rifampin in 1967 was the cornerstone of shortening the course of TB treatment. Patients were cured in 9 months!



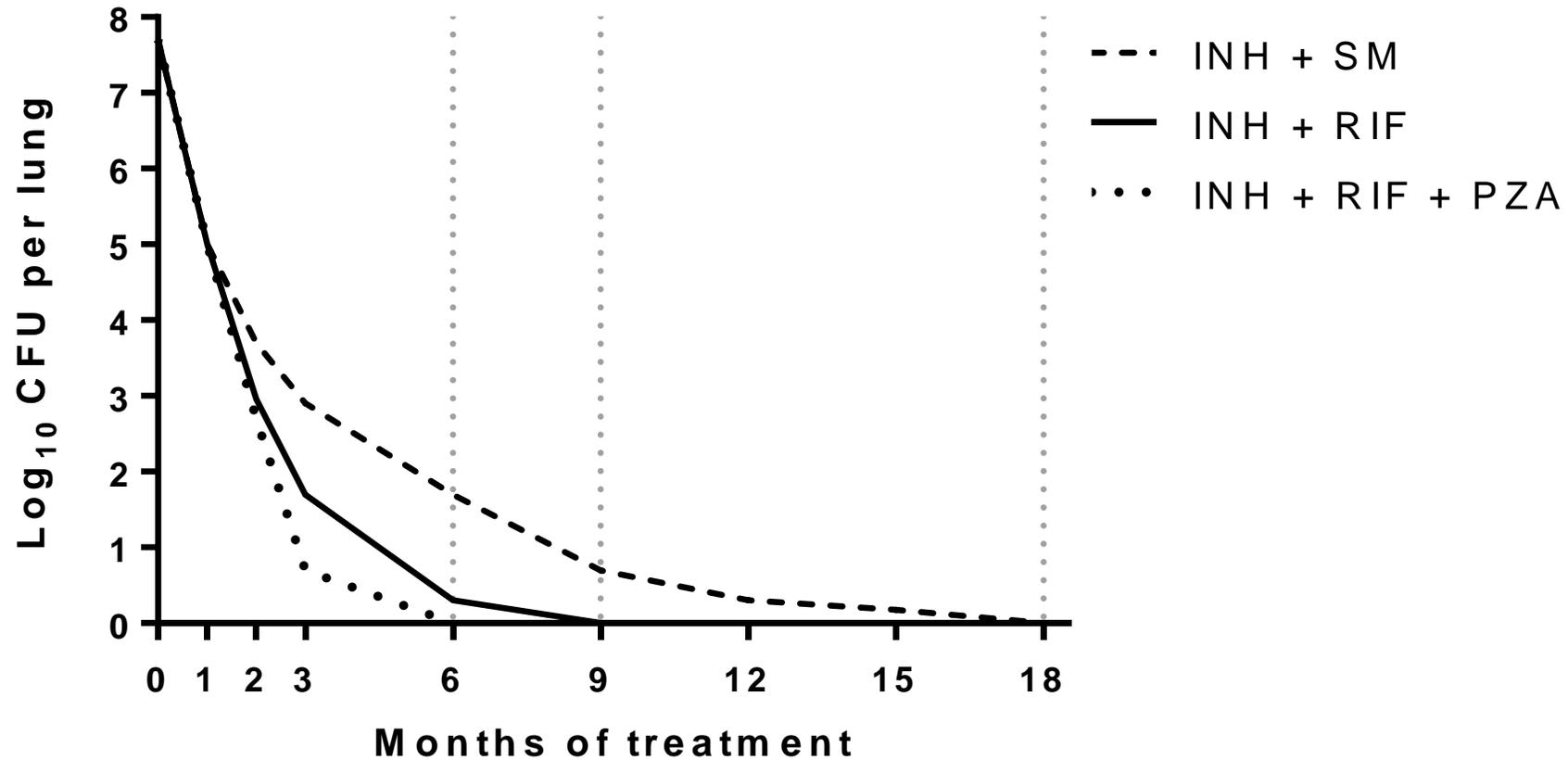
Comparative bactericidal activity of isoniazid (INH) + streptomycin (SM) + PAS, and INH+ rifampin (RIF) in mice (and in humans)

History of TB antibiotic treatment (3)

- **First step**, in the 1940s.. Prevention of death
- **Second step**, in the 1950s.. Prevention of acquired drug resistance
- **Third step**, in the 1960s.. The time needed to obtain stable culture conversion = **The cure of TB in 18 months** (a miracle compared to death in 50% of patients!)
- **Fourth step**, in the 1970s.. The cure of TB in 9 months

The discovery and introduction of rifampin (RIF) in 1967 was the cornerstone of shortening the course of TB treatment: Patients were cured in 9 months!

- **Fifth step**, in the 1980s.. The cure of TB in 6 months
 - The anti-tuberculosis activity of pyrazinamide (PZA) was literally rediscovered in 1972 by the East Africa and British Medical Research Councils [Lancet1972;i:1079-1085].
 - PZA and RIF have similar potential for shortening the duration of treatment (Tubercle 1975;56:81-96)
 - Combining RIF and PZA resulted in the cure of patients in 6 months (Br.J.Dis.Chest1984;78:330-336)



Comparative bactericidal activity of INH+SM, INH+RIF, or INH+RIF+PZA in mice (and in humans)

The triumph of medicine: The 6-month short-course treatment for tuberculosis

In forty years (1940-1980), an infectious disease that was lethal in 50% of the cases was cured by only six months of treatment with oral antibiotics:

Rifampin, isoniazid, pyrazinamide, and ethambutol
for 2 months

+

Rifampin and isoniazid for 4 months

The failure of medicine: TB remains one of the world's biggest killers⁰

Forms of TB	Number of cases	Deaths
All*	9.6 million (1.2 HIV+)	1.5 million 400,000 HIV+
MDR-TB**	480,000 (3.5% of the total TB)	210,000
XDR-TB***	43,200 (9.6% of the MDR-TB)	?

⁰ In the 22 high-burden countries that collectively account for 80% of TB cases

* with 86% success rate of treatment (for drug-susceptible, WHO 2013)

** with 48% success rate of treatment

*** with 33% success rate of treatment

What should be done?

The facts

- Each year out of the 9 million new TB cases with drug-susceptible bacilli
 - more than 1,000,000 patients die of TB (1/3 with TB and HIV)
 - treatment fails in 1,260,000 patients
- Each year, 480,000 patients acquire MDR-TB

The priorities:

- (i) Stop the hemorrhage of deaths and treatment failures by organizing the “cure” of every new TB patients (The End TB Strategy, WHO)
- (ii) Focus more on preventing MDR-TB than on treating MDR-TB (Frieden et al., 1995)

The end TB strategy (WHO)

Pillars and Components

1. Integrated, patient-centered care and prevention

- Diagnosis of all patients and infected contacts
- Cure of all patients and infected contacts. “Cure” is not synonymous with “treat”: it means make the treatment available to all in need and have them swallow their medicines from initiation to completion of treatment, i.e., DOT as standard of care (Frieden et al. NEJM 1995)

2. Bold policies and supportive systems

- Adequate resources for diagnosis, treatment and prevention.
- Universal health coverage policy

3. Intensified research and innovation

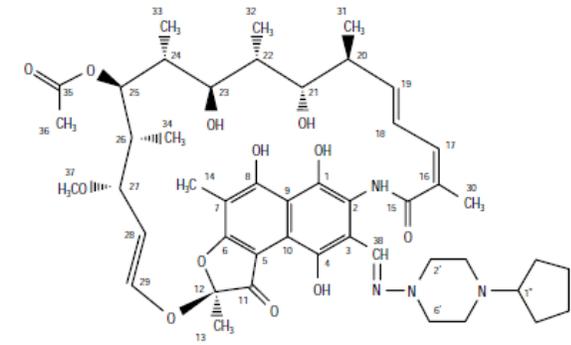
Discovery of new tools (drug, vaccine), interventions and strategies

Personal remark: nothing of the above strategy is new; it is just a reminder of the basic rules that allowed North America and Western Europe to control TB for the past 50 years /since the Sixties!

Current bench research

- Though the 6-month drug regimen is a wonderful achievement it implies a lot of requirements on the patients and TB control network
- Develop **much shorter TB drug regimens**, for example of 3 months duration, would be very beneficial.
- For that 3 drugs only are potentially available: rifapentine, moxifloxacin and clofazimine.

1. Rifapentine (P)

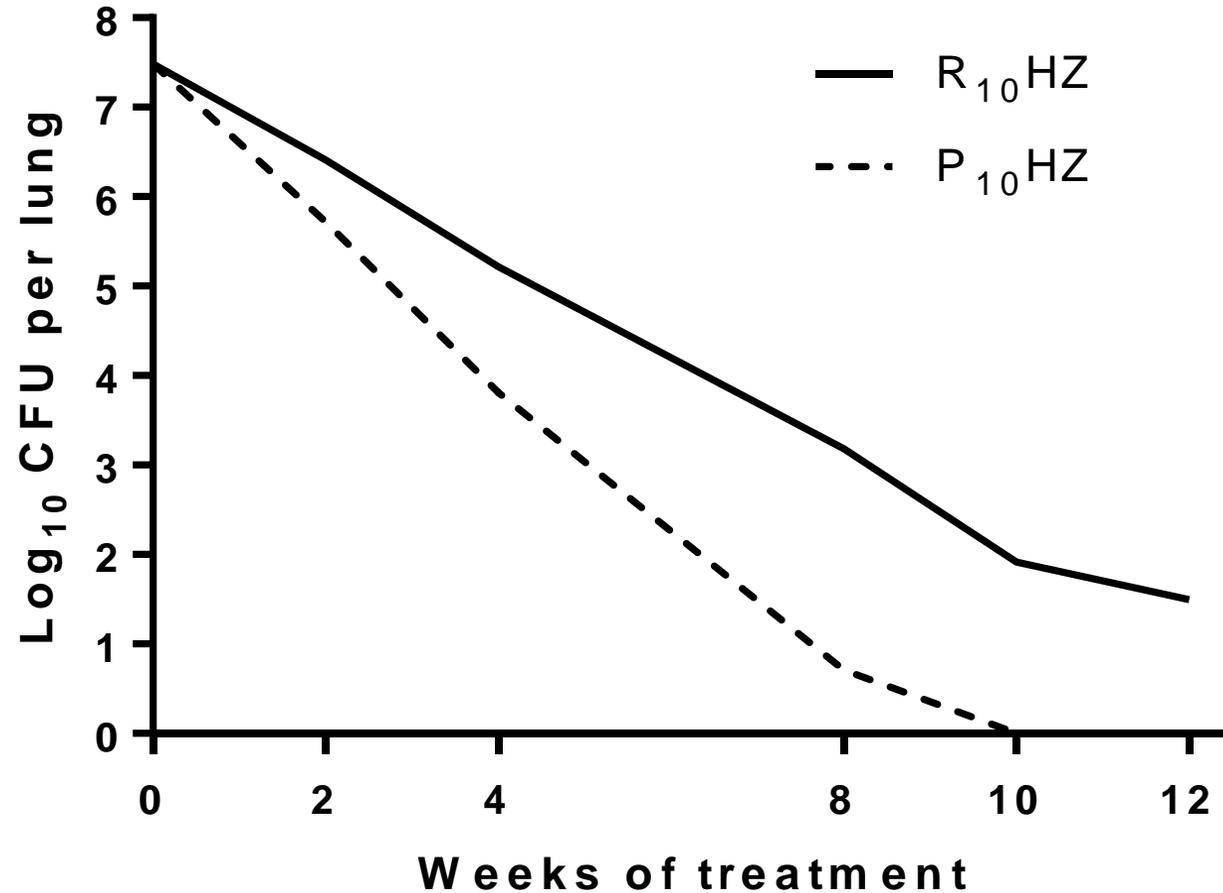


- Rifapentine (P) is a long-lived rifamycin derivative
- Rifapentine offers potential for improved activity because of its superior PK/PD profile:

Drug	Half life (h)	MIC ₉₀ (µg/ml)	C _{max} /MIC*
Rifampin (10 mg/kg)	2.46	0.25	60
Rifapentine (10 mg/kg)	15.9	0.12	100

*Optimal C_{max} / MIC₉₀ : >10

Bactericidal activity of R₁₀HZ & P₁₀HZ



Conclusion:

Negative cultures are obtained much more rapidly (10 weeks) with P₁₀HZ than with weeks with R₁₀HZ.

The current TBTC clinical trial with rifapentine

Regimens

2HP₁₂₀₀ZE/2HP₁₂₀₀

2HP₁₂₀₀ZM/2HP₁₂₀₀

2HR₁₀ZE/2HR₁₀

Duration

4 months

4 months

6 months

Endpoints

- Time to culture conversion
- Relapse rate

2. Moxifloxacin

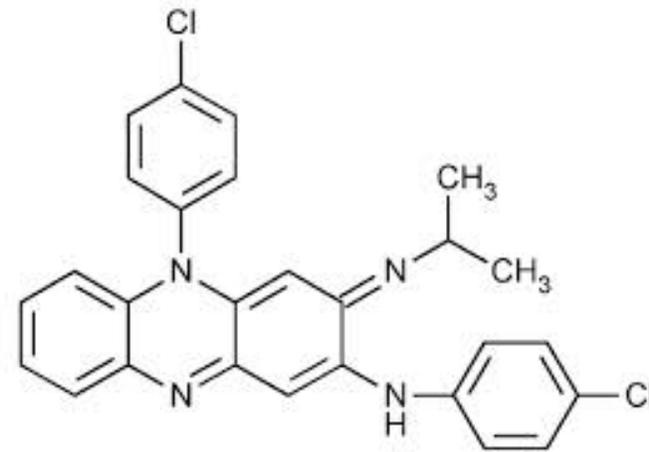
- Fluoroquinolone
- MIC range 0.125-0.5 µg/ml
- Concentration dependent activity
- Half life in humans, 10-12h
- Inhibits DNA gyrase
- As active antimicrobial as isoniazid

Conclusions from recent moxifloxacin trials

- Moxi improved culture conversion at 2 months
- 2-month culture conversion surrogate marker was not confirmed to predict 2-month treatment shortening
- Fluoroquinolones are active against *M. tuberculosis*, but do not appear to add sterilizing activity
- The combination of moxi and rifapentine appears to have excellent activity and may contribute to TB treatment shortening

3. Clofazimine (CFZ)

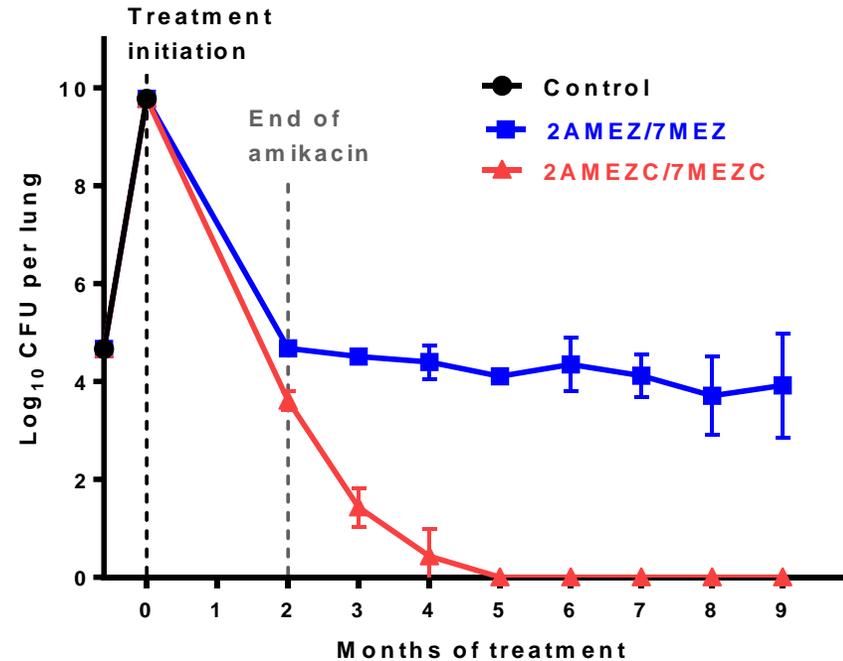
- Fat-soluble, phenazine-based dye
- Developed in 1950s by Vincent Barry as TB drug
- Used in combination therapy for leprosy



CFZ for TB treatment

- Highly active against *M. tuberculosis in vitro* and in mice
- Associated with tissue accumulation, red discoloration, very long half-life
- Initial formulation had poor absorption when orally administered
- Lacked sensation compared to streptomycin-isoniazid-*para*-amino-salicylic acid
- Used for MDR-TB as a Group 5 drug: not recommended because its contribution to the efficacy of multidrug regimens is unclear

CFZ activity in a second-line regimen in a mouse model of MDR-TB

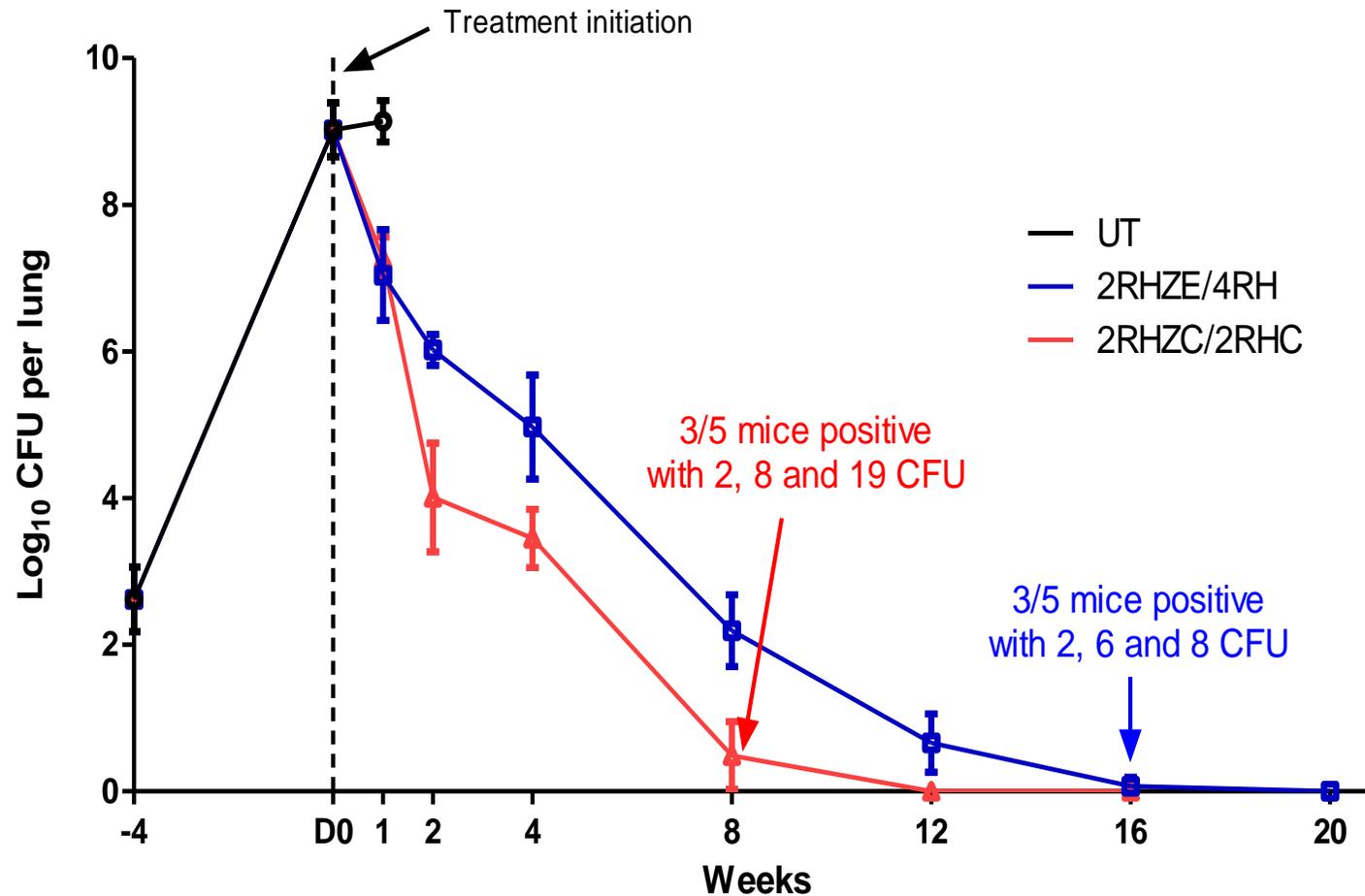


CFZ-containing regimen relapse-free cure: 93% after 8 or 9 months of treatment

BALB/c mice infected by aerosol with an isoniazid-resistant strain of *M. tuberculosis*. A: amikacin 100 mg/kg; M: moxifloxacin, 100 mg/kg; E: ethambutol, 100 mg/kg; Z: pyrazinamide, 150 mg/kg; C: clofazimine, 25mg/kg. All drugs were administered by oral gavage, except for amikacin, which was administered by subcutaneous injection.

Grosset *et al.*, *Am J Resp Crit Care Med* 2013; 188: 608-612.

Decline of lung CFU counts in mice treated with the first-line regimen with or without clofazimine



The proposed clinical trial with clofazimine

- Drug regimens:
 - Control: 2 months of RHZE / 4 months of RH
 - Test 1: 2 months of RHZE + C50mg / 1 month of RH+C50mg followed by 3 months of RH to complete the usual 6-month treatment
 - Test 2: 2 months of RHZE + C100mg / 1 month of RH+C100mg followed by 3 months of RH to complete the usual 6-month treatment
- Target sample size: 41 participants per arm
- Endpoints:
 - Culture conversion at week 12 and
 - Comparison of culture conversion at week 8,
- Length of participant follow-up: 24 weeks

Conclusion from the bedside to the bench

- The only benefit of having gone from the bed to the bench is the motivation
- A huge amount of research work has been done but it is the easiest that has been done, the most difficult remains to come.
- Implementation in the field is more problematic than pure science in the lab.
- Please don't believe in dogma, in short-cuts, in easy-going
- All together and only all together we will control TB

Thank you

