

The mechanisms of TB drug resistance

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Finnish Lung Health Association

THE AMERICAN REVIEW OF TUBERCULOSIS

OFFICIAL JOURNAL OF AMERICAN TRUDEAU SOCIETY
MEDICAL SECTION OF NATIONAL TUBERCULOSIS ASSOCIATION

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Published Monthly at Mount Royal and Guilford Avenues, Baltimore 2, Maryland by the National Tuberculosis Association • Business Off., 1790 Broadway, New York 19, N.Y.

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PRINTED IN U.S.A.

INH monotherapy

- 6 patients with cavitary tuberculosis
- smears and cultures weekly for 11 weeks

Patients showed increasing

INH resistance

within 4 - 8

weeks

Bacteriological basis of MDR in *M. tuberculosis*

- **I. Natural point mutations**
- **II. Large bacterial populations**
- **III. Selection by use of drugs**

I. Natural point mutations

Occur in all multiplying bacteria at varying rates in different loci

Average mutation rates in genes coding for resistance (prevalence of mutants) to

EMB	10⁻⁵ to -7 CFU*
INH	10⁻⁶ to -8 CFU
SM	10⁻⁶ to -8 CFU
RMP	10⁻⁸ to -10 CFU

*colony forming bacterial cells

Fate of bacilli with natural point mutations in active tuberculosis?

- A spontaneously mutated drug resistant clone
 - is not more virulent
 - does not survive among the 10^6 - 10^{10} susceptible bacilli without interference by drugs
- **"Wild" TB –strain remains sensitive if not interfered by medication**

Bacteriological basis of MDR in *M. tuberculosis*

- I. Natural point mutations
- **II. Large bacterial populations**
- **III. Selection by use of drugs**

Importance of large bacterial populations

- The higher bacterial count the more likely there are naturally occurring R-mutants
- Bacillary load in infected tissues varies by extent of disease:
 - ◆ Silent lymph nodes solitary bacilli
 - ◆ Small lung infiltrates 10^2 - 10^4 bacilli
 - ◆ Lung cavities 10^7 - 10^9 bacilli

Large bacterial populations – a key issue

- No R-mutants in minor infections
- R-mutants always present in smear-positive cavitory TB

Clinical experience:

- 1949 “Resistance develops easily in cavitory TB”
- Prophylactic INH does not induce INH-resistance

Bacteriological basis of MDR in *M. tuberculosis*

- **I. Natural point mutations**
- **II. Large bacterial populations**
- **III. Selection by use of drugs**

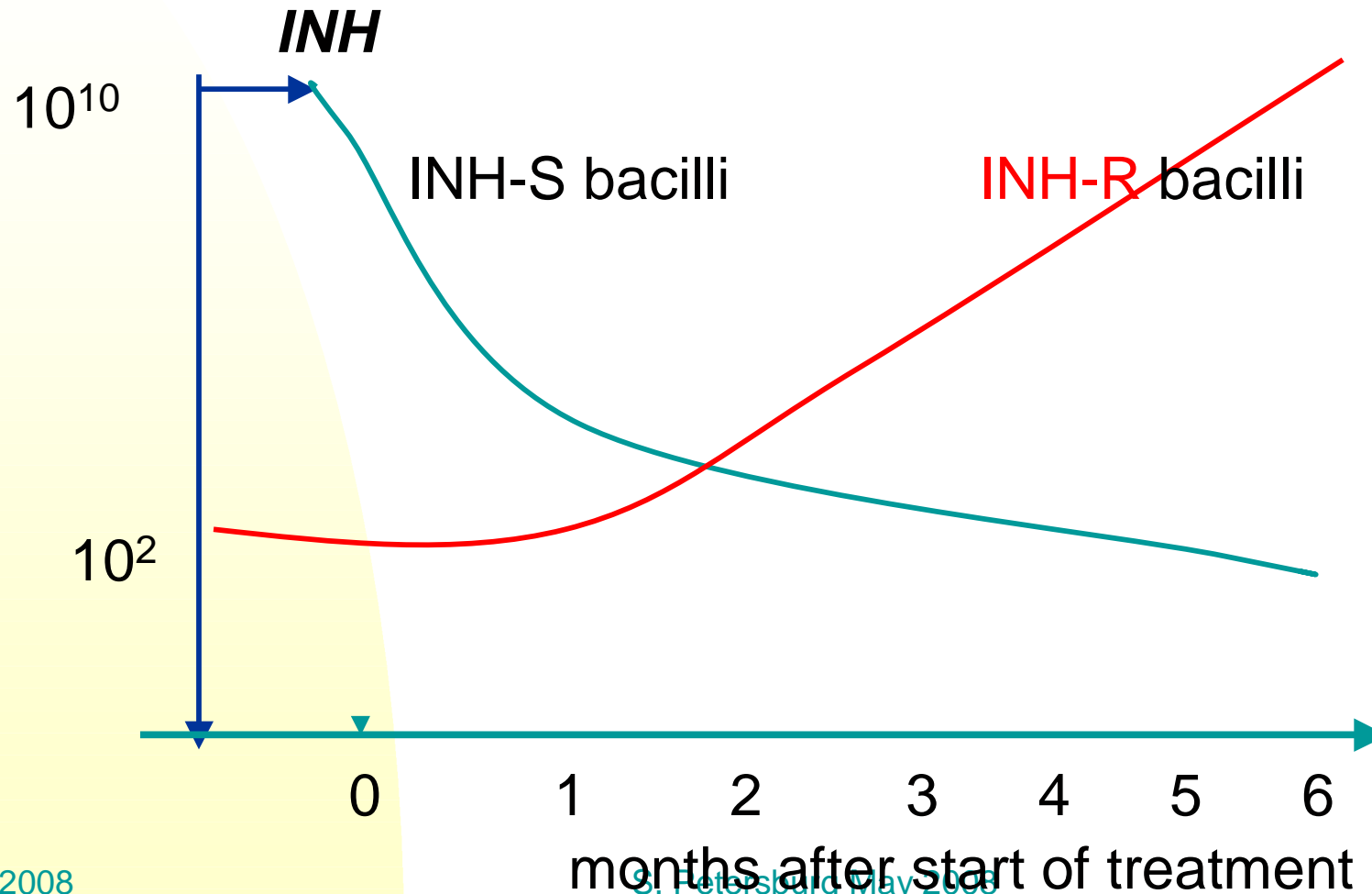
III SELECTION BY DRUGS

The only chance for a resistant clone to overcome susceptible bacteria is via **selective mono-therapy*

- **susceptible bacilli rapidly killed**
- **bacilli rendered resistant by point mutation survive and start to multiply**

***If two effective drugs are used no point-mutated clone survives**

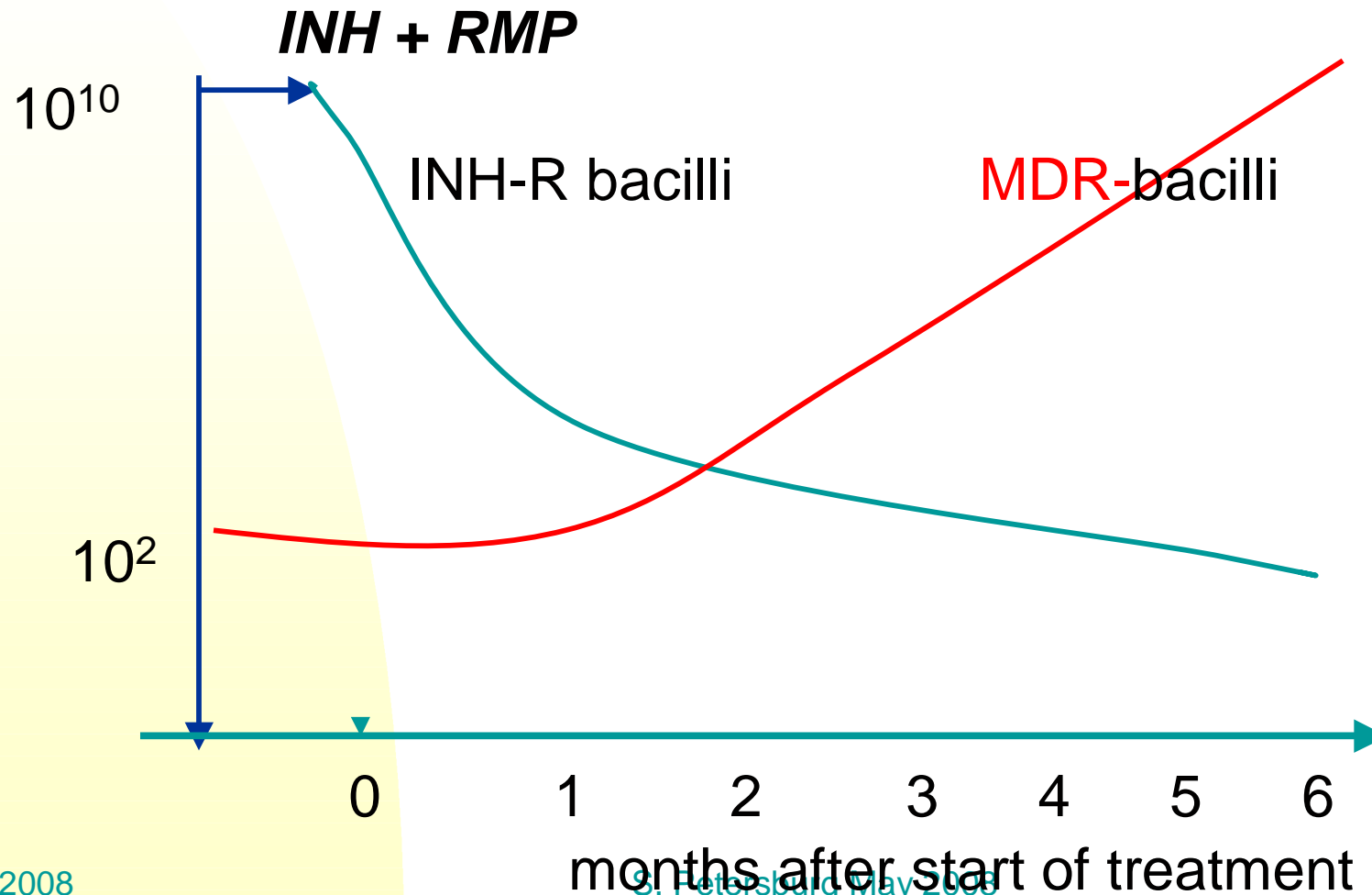
S-bacilli are replaced by R-bacilli (modified from Michison 1968)



How about multi-resistance ?

- In a bacterial replication, point mutations to two drugs do not occur simultaneously (10^{15})
- Multi-resistance develops step by step
- *Example. Therapy of a patient with INH-R tuberculosis using only INH and RMP leads to MDR-TB because of RMP-monotherapy*

STEP-2: INH-R bacilli are replaced by **MDR**-bacilli



Can a resistant strain turn susceptible ?

- Can the thousands to millions of replicating R-bacteria in infectious tissue simultaneously experience the same point mutation that would render them susceptible ?

No

Drug resistant TB is a man-made disease

Adding one drug at a time allows a step-wise development of resistance to the drug added

Prevent further development of drug resistance by always **ADDING 2 OR MORE DRUGS TO WHICH THE STRAIN IS SUSCEPTIBLE**

Conclusions

- 1. Reading errors of DNA code lead to point mutations at low frequency.
- 2. High bacterial loads always harbour R-mutants
- 3. R-bacilli don't survive without help of man:
- If no drug exposure **NO DRUG RESISTANT STRAINS**
- 4. Development of MDR is based solely on uncontrolled use of anti-TB drugs
 - ◆ either patient or doctor induced