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Tuberculosis treatment and drug development: The value of cohort studies

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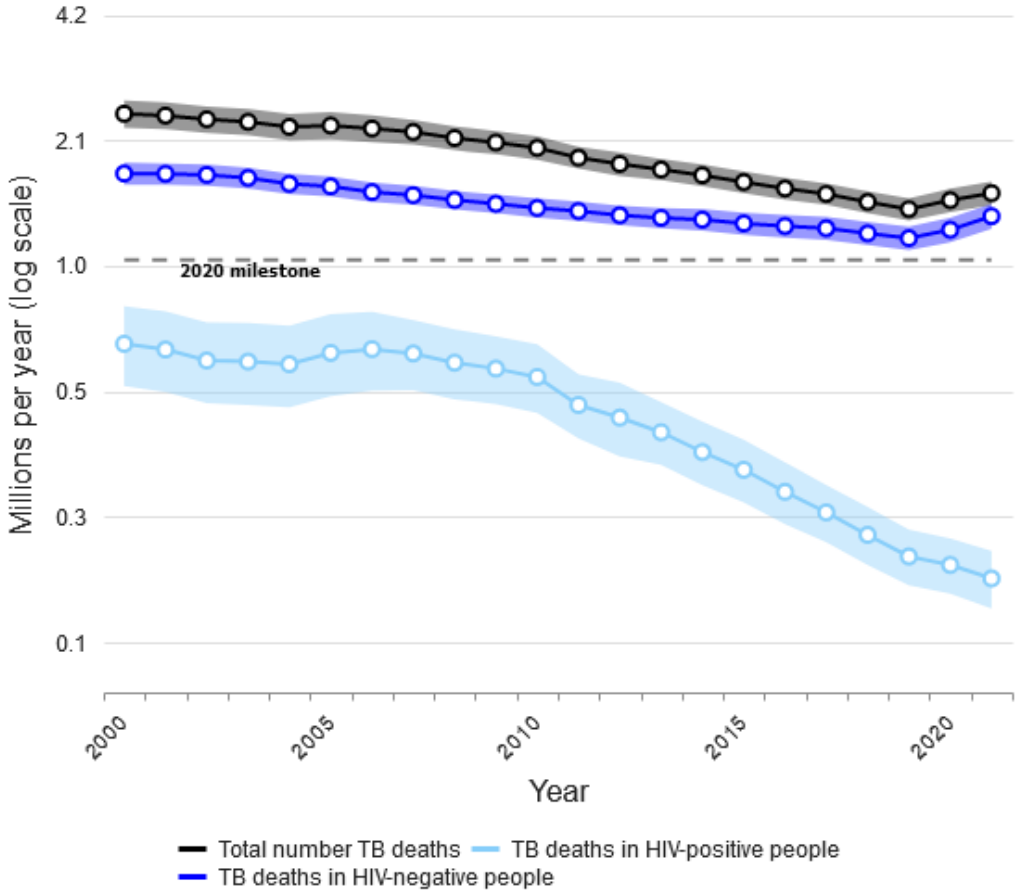
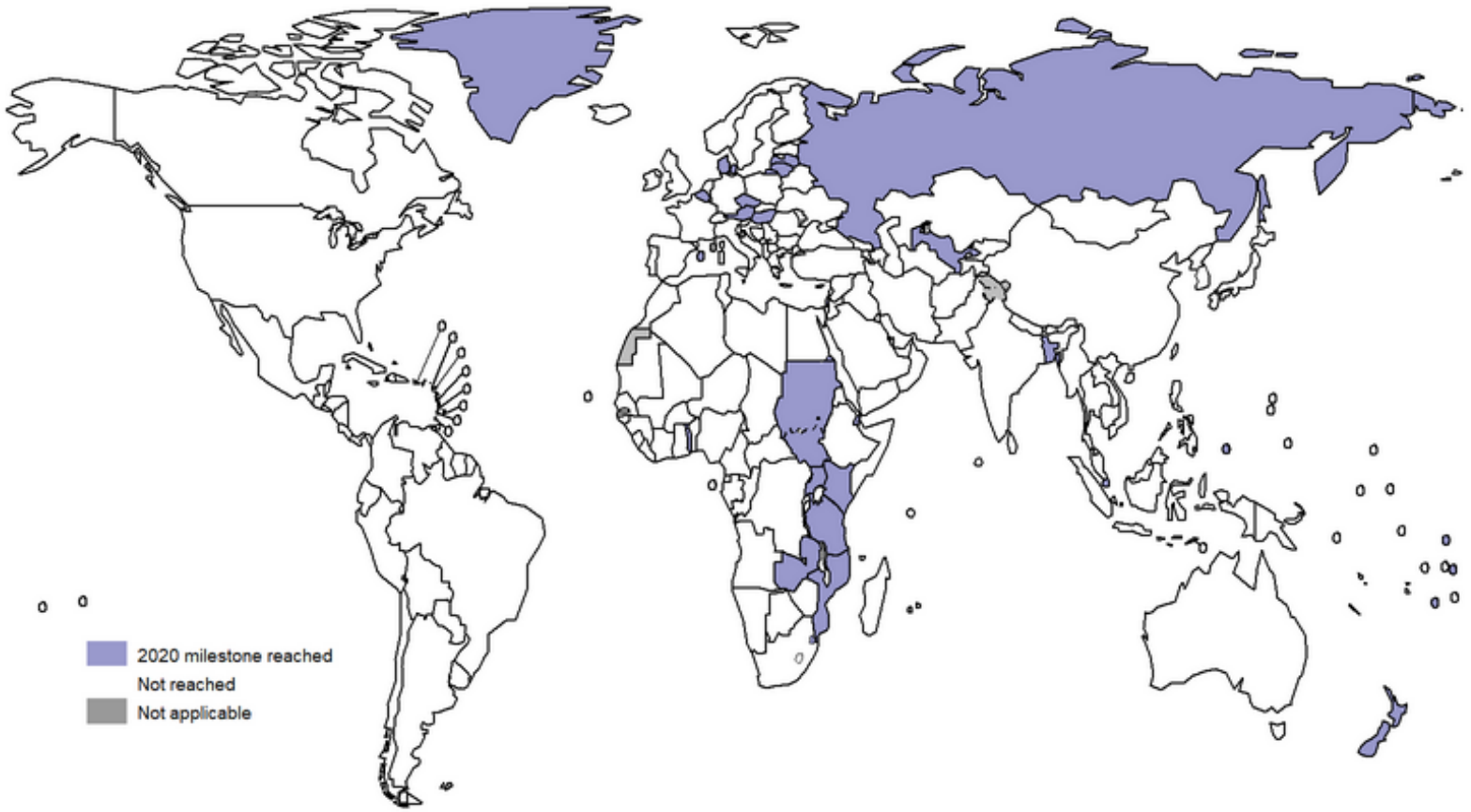
Introduction

- Tuberculosis (TB) is a curable disease
- It kills approx. 4,300 people daily
- TB epidemiology and determinants differs locally
- High mortality (82%) in Africa and S-E Asia



Source: Global TB Report, 2022

Introduction



Only 25 countries that had reached reduction of TB mortality per End TB strategy in 2021

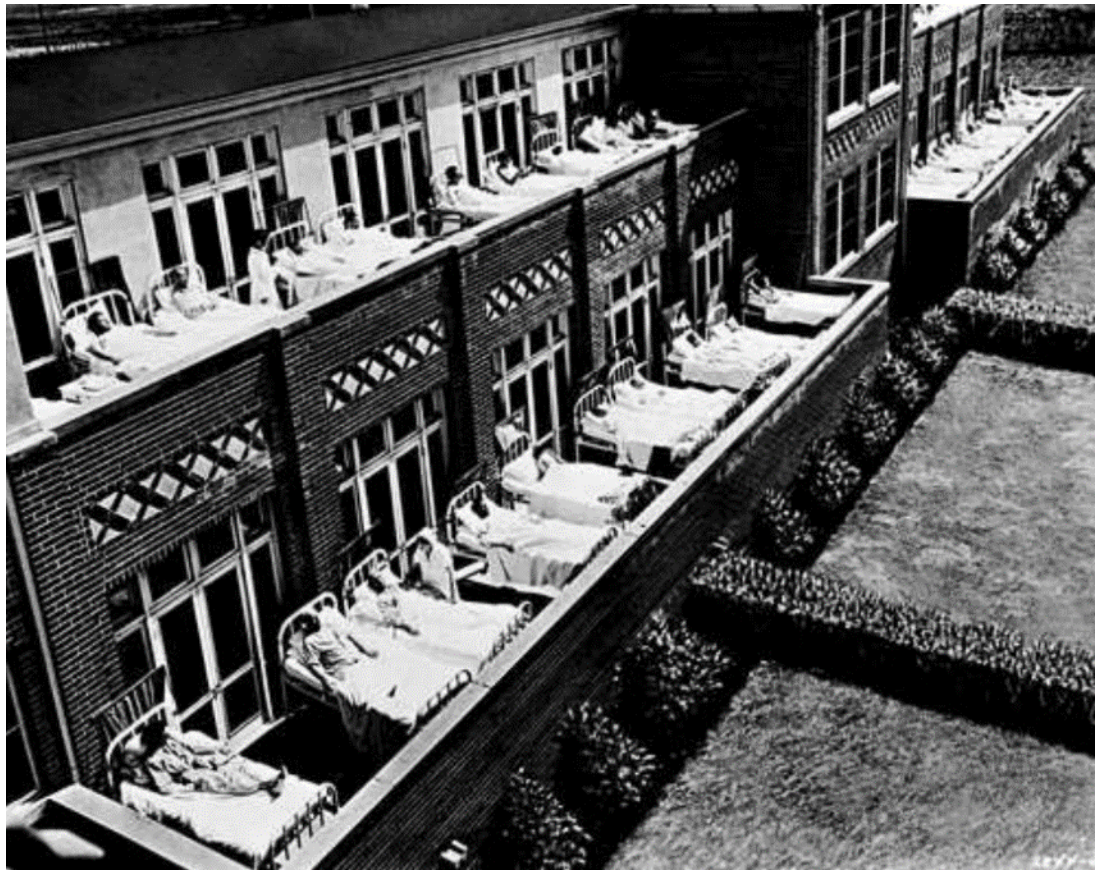
Source: Global TB Report, 2022

The ideal therapy

1. Short duration of treatment
2. Target drug resistant strains
3. Reduced daily pill burden
4. Reduced dosing frequency
5. Less drug-drug interactions

History of TB treatment

- Discovery of *Mycobacterium tuberculosis* in 1882
- Sanatorium movement
- Body and lung were rested
- Highlighted the impact of TB on patients
- Called for a public health action



Cure Chairs at the Jewish National Sanatorium in Denver, c. 1930

Discovery of Streptomycin (SM)

- SM discovered in 1945
- Used as monotherapy
- Cured 44% of pts with TB meningitis
- Resistance to SM developed quickly

TABLE 1. RESULTS OF BRITISH MEDICAL RESEARCH COUNCIL STREPTOMYCIN TRIAL

Regimen	No. of Patients	Deaths	X-ray Improvement (%)	Culture Negative	
				3 mo	6 mo
SM	54	4	69	10*	8
Control	50	14	33	1	2

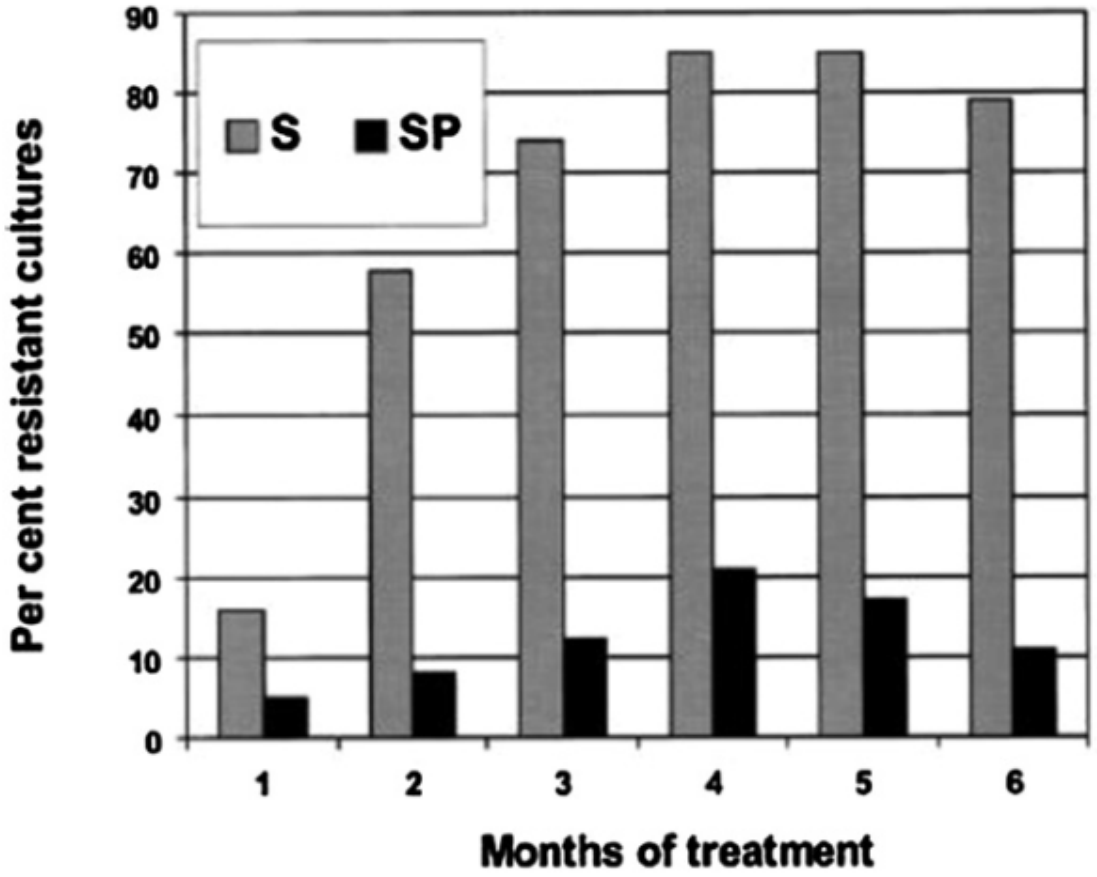
Definition of abbreviation: SM = streptomycin.

Corwin Hinshaw

Wiliam Feldman

Discovery of PAS and the era of combination therapy

- Para-aminosalisylic acid (PAS) treated a moribund patient in 1944
- PAS alone had limited efficacy
- PAS had significant side effects
- However PAS + SM as combination therapy → less resistant strains
- New treatment axiom → Never treat active TB with a single agent



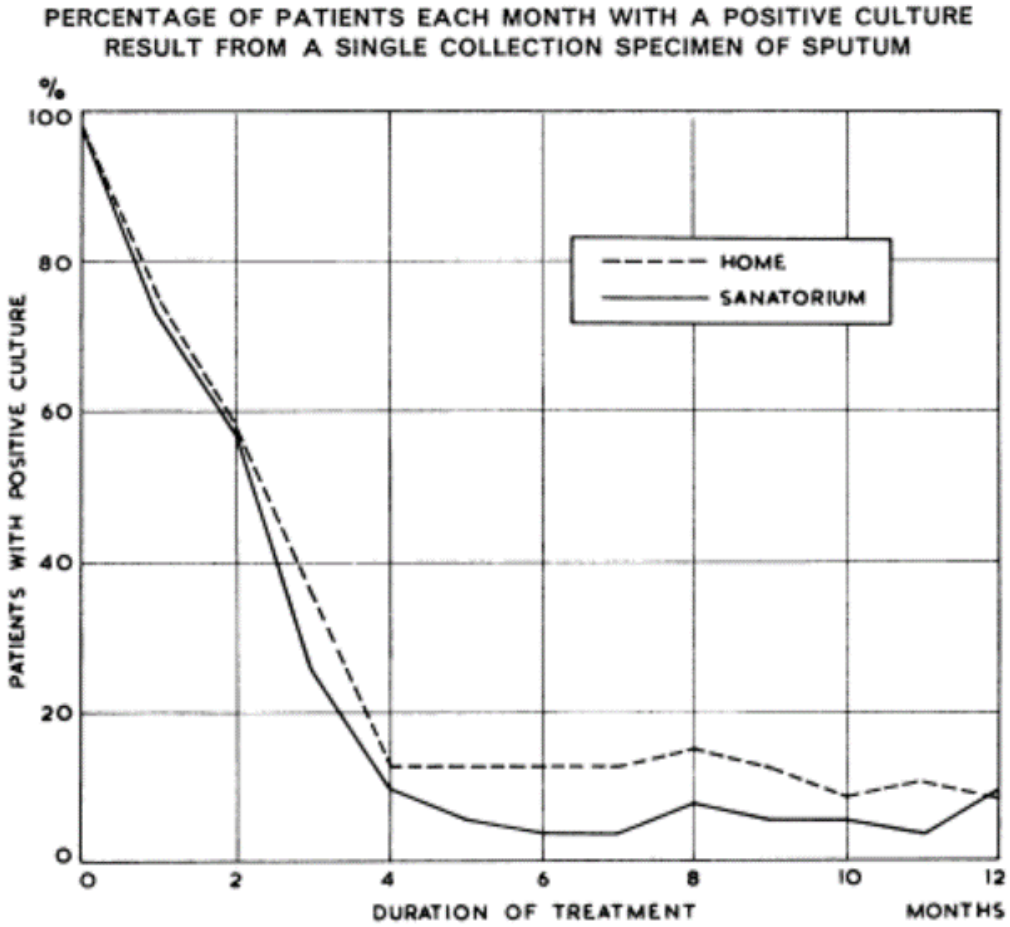
Source: BMJ, 1952

Discovery of Isoniazid (INH)

- INH was first synthesized in 1912
- Anti-TB activity later discovered in the 1950s
- INH was extremely cheap as compared to PAS or SM
- Triple therapy: SM, PAS & INH assured cure by 90-95%, no DR strains created
- Treatment lasted for 18 to 24 months including 6 months of SM injections!

The end of TB sanatoriums

- Monumental change in care occurred in 1956 from Madras, India
- Care could be given at home (INH & PAS)
- No difference in clinical outcome
- No increased risk of infection among household contacts



Source: Bull World Health Organ. 1959

Short course chemotherapy: MRC regimen

- TB treatment trials in East Africa
- Shortened therapy 6 vs., 18 months
- Fewer relapses in Rifampicin and Pyrazinamide containing regimen
- Major development in TB treatment

Clinical Trial > Lancet. 1974 Aug 3;2(7875):237-40.

Controlled clinical trial of four short-course (6-month) regimens of chemotherapy for treatment of pulmonary tuberculosis. Third report. East African-British Medical Research Councils

Regimen*	No. of Patients	Culture Neg. at 2 mo (%)	Relapse (*No.*)	Relapse (%)
SHR	152	69	4	3
SHZ	153	31	13	8
SHT	104	28	23	22
SH	112	8	33	29

Definition of abbreviations: H = isoniazid; Neg. = negative; R = rifampin; S = streptomycin; Z = pyrazinamide.

Short course chemotherapy: “Styblo” regimen

- The cure rate with MRC regimen was low in Tanzania approx. 50%
- Solution → hospitalization for 2 months with SM + INH + RMP + PZA then 6 months of INH + Thiacetazone
- DOT introduced
- This had a 90% effective treatment rate
- Later during AIDS epidemic, ethambutol was introduced to replace SM and Thiacetazone → RHZE (now)

› J Hist Med Allied Sci. 2019 Jul 1;74(3):316-343. doi: 10.1093/jhmas/jrz029.

Treatment on Trial: Tanzania's National Tuberculosis Program, the International Union against Tuberculosis and Lung Disease, and the Road to DOTS, 1977–1991

Tuberculosis Cohort Study – TB DAR

Research platform by prospective collection of clinical data and biological specimens in sputum-smear positive TB cases (≈350 per year), and controls from TB contact households.

Collection of clinical data and biological specimen:

- Clinical data, chest X-ray scans, geocodes of homes
- *M. tuberculosis* isolates
- Blood samples (plasma, serum), (*stimulated samples for immunological analyses, Quantiferon*)
- Dried blood spots
- Sputum, urine, stool samples, (*naso-pharyngeal swabs*)
- Intestinal helminth status
- Whole blood for human DNA

Current status

- Over 2’100 TB cases and 1’300 controls
- Supported multiple sub studies at Temeke, Ifakara
- A platform for external collaborators to embed sub studies
- Supports MSc and PhD thesis among Tanzanians and Swiss
- Sub-clinical TB with over 3,300 TB cases and 10,000 household participants enrolled in next 2-3 years

Conclusion

- We have made significant strides over the last 60 years with TB treatment and control
- These gains are now hampered by;
    - Low case detection in many countries
    - Emergence of DR strains
    - Slow discovery of novel therapeutics and vaccine for TB control
- Continued investments in evaluation of cohorts of TB patients could offer more insight and solutions

Many thanks for your attention!