The evolution of and challenges in defining the clinical endpoint in tuberculosis (TB) treatment trials with non-inferiority designs

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Outline

- Tuberculosis (TB) Case Studies in the 20th Century
  1. Streptomycin treatment for TB, 1948
  2. Isoniazid treatment for TB, 1953

- TB Case Studies in the 21st Century
  1. Rifapentine FDA submission, 2000
  2. Study C, 2011

- Conclusions

1.

BRITISH MEDICAL JOURNAL

LONDON SATURDAY OCTOBER 30 1948

STREPTOMYCIN TREATMENT OF PULMONARY TUBERCULOSIS

A MEDICAL RESEARCH COUNCIL INVESTIGATION

- Comparison between Streptomycin (S) and Bed Rest (C)
  - Clear reduction in deaths

TABLE II.—*Assessment of Radiological Appearance at Six Months as Compared with Appearance on Admission*

Radiological Assessment	Streptomycin Group		Control Group	
Considerable improvement ..	28	*51%*	4	*8%*
Moderate or slight improvement	10	*18%*	13	*25%*
No material change	2	*4%*	3	*6%*
Moderate or slight deterioration	5	*9%*	12	*23%*
Considerable deterioration ..	6	*11%*	6	*11%*
Deaths	4	*7%*	14	*27%*
Total	55	*100%*	52	*100%*

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- However, multiple endpoints were presented

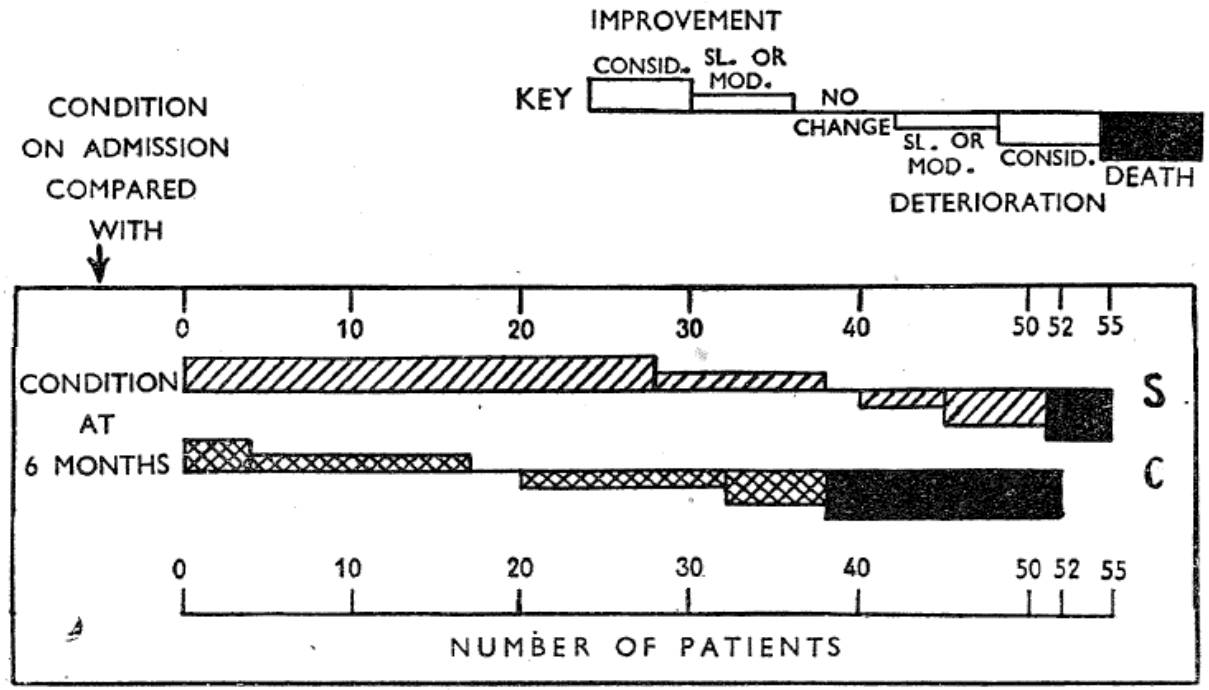
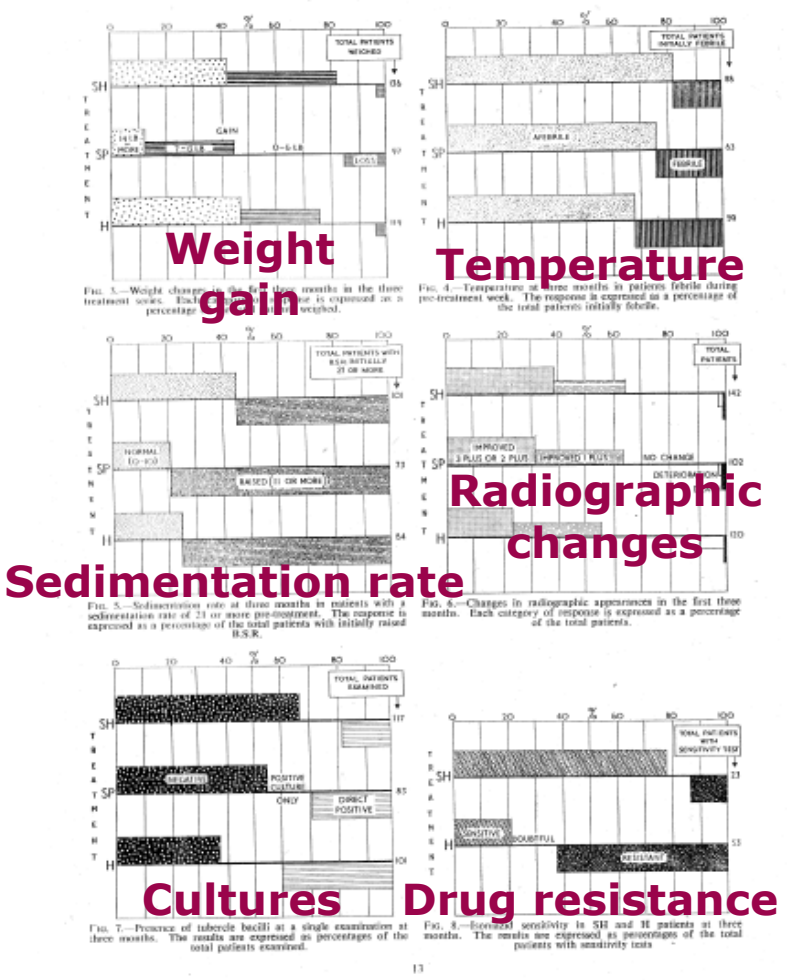


CHART II.—Condition on admission compared with condition at two, four, and six months (radiological assessment).

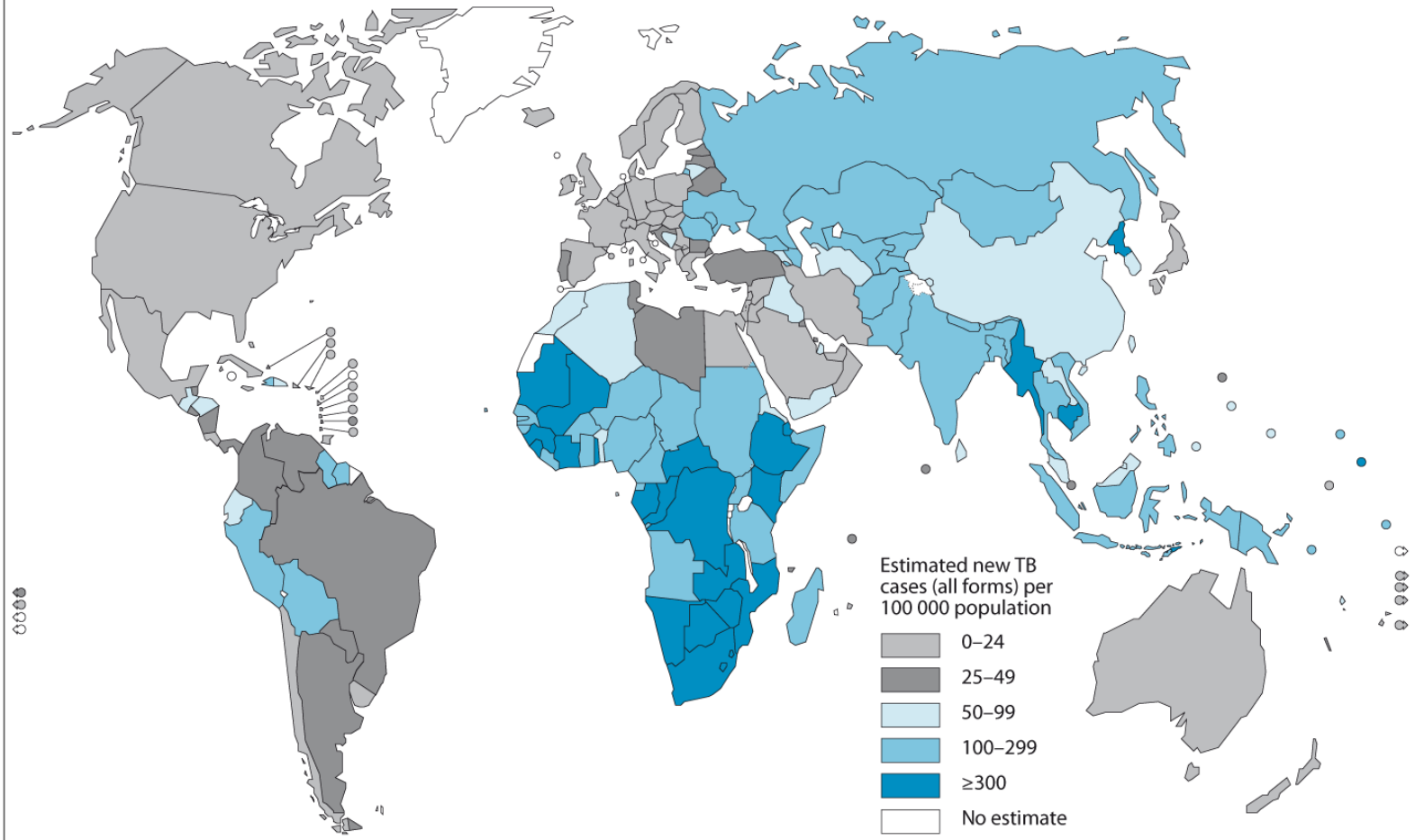
2. Isoniazid in the treatment of pulmonary tuberculosis. (MRC. BMJ,1953)

- Large number of endpoints presented, with no clear '*primary endpoint*'.

- "It is concluded, **judging solely from the results [on 10 endpoints] at three months**, that streptomycin + isoniazid… is clinically the most effective of the treatments studied."
  - (Study conclusions)



Estimated TB incidence rates, by country, 2009



The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

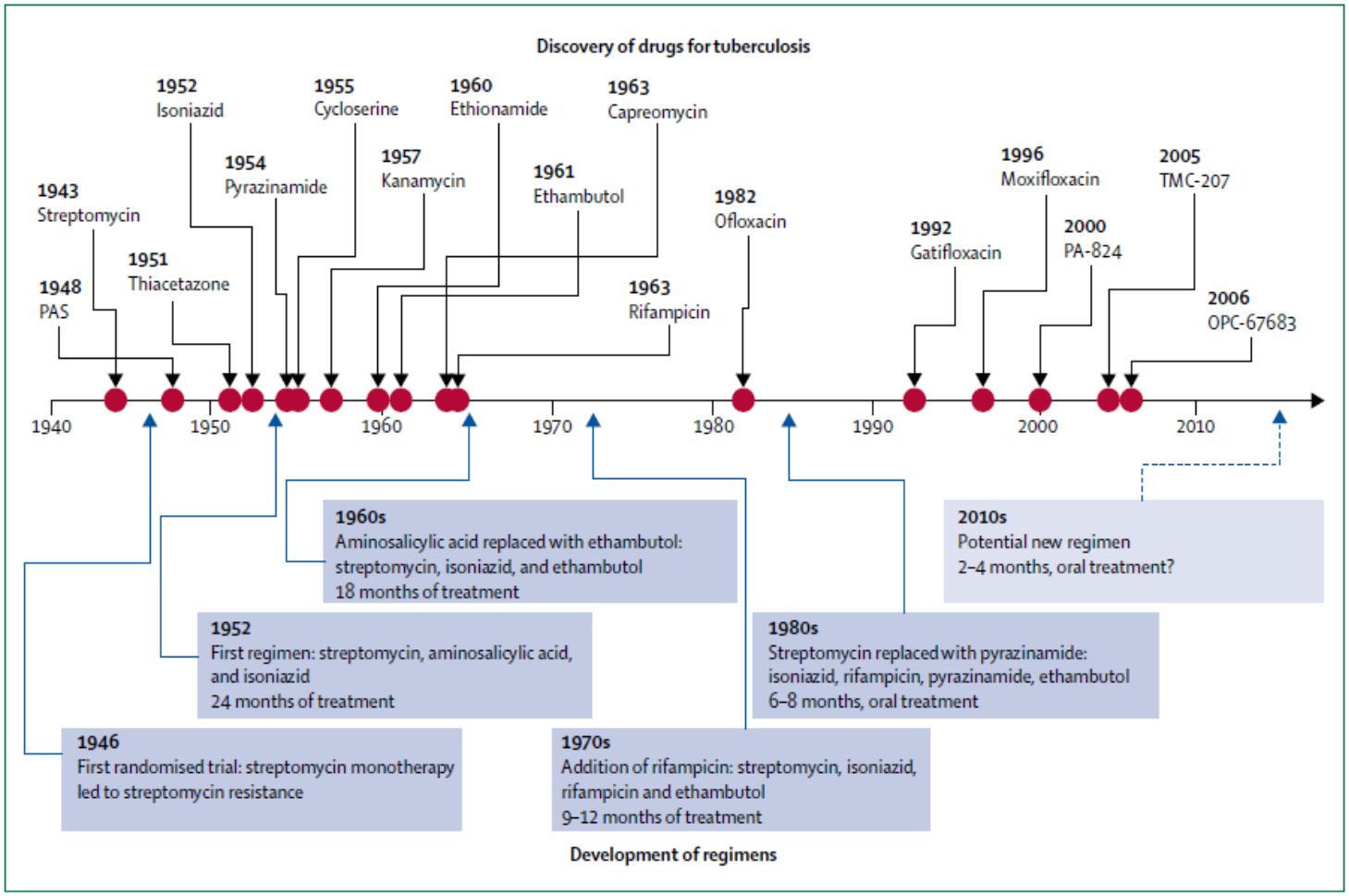
Source: *Global Tuberculosis Control 2010.* WHO, 2010.

World Health Organization

Tuberculosis in the 21st Century

- Consistent **cure rate of 90-95% or more in clinical trials** of standard 6-month regimen in multiple settings
- Symptoms usually stop within 2-3 months
  - Not all patients complete treatment resulting in **much lower rates of cure in clinical practice**
- **Can new drugs shorten and simplify treatment?**
  - Trials therefore have non-inferiority design
- ICH E9 (1998) recommends: "There should generally be **only one primary variable**."

Historic TB Drug Development



Ma Z, Lienhardt C, McIlleron H, Nunn AJ, Wang X. Lancet, 2010

Possible outcomes of patients in a TB trial

	Treatment Outcome after 18 months follow-up	% of total	Suggested classification (MITT)
True clinical endpoints (~70%)	Long-term cure	63%	Favourable
	End of treatment failure	1%	Unfavourable
	Relapse	5%	Unfavourable
	TB death	1%	Unfavourable
Endpoint missing (~30%)	Default during treatment	7%	Unfavourable
	Exogenous reinfection	2%	Excluded
	Non-TB death	2%	Excluded
	Lost to follow-up: Cured	15%	Excluded
	Lost to follow-up: Unknown?	4%	Unfavourable

1. Rifapentine Submission to the FDA, 2000

	1. Lost to follow-up as **favourable**	2. Lost to follow-up **excluded**	3. Lost to follow-up as **relapse**
Relapse Rate in **Rifapentine arm**	**12%** (29/248)	**17%** (29/171)	**43%** (106/248)
Relapse rate in **Control arm**	**7%** (15/226)	**9%** (15/160)	**36%** (81/226)
Absolute difference in rate	**5.1%** (-0.5%, 10.6%)	**7.6%** (-0.2%, 15.4%)	**6.7%** (-2.3%, 16.1%)
Width of 95% CI	11.1%	15.6%	18.4%

Results as presented in the statistical review.

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1. Rifapentine Submission to the FDA, 2000

- The FDA approved rifapentine, but the statistical reviewer noted the following caution:

  - *"It might be in the patients' best interest to add a statement to the proposed label cautioning that relapse rates could actually be much higher than they appear due to the fact that* ***we don't know what happened to almost a third of the patients who converted****."*

2. Study C: The comparison of a 4-drug fixed-dose combination (FDC) with separate drugs

- The first non-inferiority trial in TB comparing a combination formulation (FDC) with separate tablets (Lienhardt et al, 2011, JAMA).

- Three primary analyses conducted:
  1. **Per-protocol**: Inadequate treatment = Excluded
  2. **Modified ITT 1**:

     Change of treatment for any reason = Unfavourable
  3. **Modified ITT 2** (post-hoc):

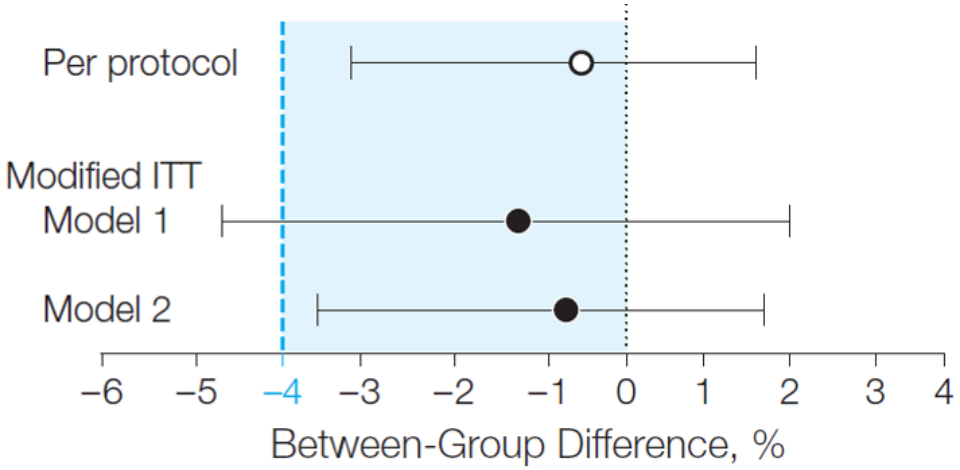
     Change of treatment for non-therapeutic reason = Classify according to long-term endpoint

- Margin of non-inferiority, **δ=4%**

2. Study C: Results

	FDC group		Control group		Difference (90% CI)
	N	Favourable	N	Favourable	
Per Protocol Analysis	591	555 (93.9%)	579	548 (94.6%)	-0.7% (**-3.0%**, 1.5%)
Modified ITT 1	684	570 (83.3%)	664	563 (84.8%)	-1.5% (**-4.7%**, 1.8%)
Modified ITT 2	658	591 (89.8%)	647	589 (91.0%)	-1.2% (**-3.9%**, 1.5%)

- Non-inferiority was formally demonstrated in only **2 of the 3 analyses.**



2. Study C: Conclusions

- Final agreed wording:
  - "…a 4-drug FDC regimen for treatment of tuberculosis satisfied pre-specified noninferiority criteria in 2 of 3 analyses."
  - "**Although the results do not demonstrate full noninferiority**… using the strict definition applied in this trial, **use of FDCs is preferred** because of potential advantages associated with the administration of FDCs compared with separate-drug formulations."

- Many national tuberculosis programmes already used FDCs.
  - **Public health importance, clear message needed**

Conclusions I

- A composite endpoint is **usually used to improve power**
  - The multiplicity of outcomes to TB treatment **makes a composite endpoint necessary**.

- In non-inferiority trials misclassification of endpoints:
  - Results in a loss in power
  - Is not conservative (could bias towards the alternative)!

Conclusions II

- Informative censoring → Biased PP analysis
- Poor adherence to treatment → Biased ITT analysis
  - **No uniformly conservative analysis**

- ***Both* PP and ITT analyses are important** and should be broadly consistent (as generally recommended, e.g. FDA draft guidance on non-inferiority trials)

- **Further sensitivity analyses are particularly important**

Practical Implications

1. Quality of trial conduct ***particularly*** important
   - Quick response to missed visits to improve retention
   - Verification and validation of data quality
   - Robust, objective endpoint
     - Expert clinical team to give real-time advice to avoid premature re-treatment.

2. A single *primary analysis* of a single *primary endpoint* is too simplistic in non-inferiority trials for TB treatments.
   - ITT, PP and further (secondary) sensitivity analyses are necessary

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