Simplifying TB Treatment

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Inter TB Symposium
September 9, 2019
St George's Medical School, London UK

Disclaimer

Opinions herein are those of the author, and do not reflect an official position of the Centers for Disease Control and Prevention

Prof Mitchison and team at Hammersmith Hospital, London ~1975

Profs Jindani and Mitchison during visit to CDC Atlanta, 2012

What is “simplified TB treatment”?

to make less complicated, clearer, or easier;
to reduce (an equation, fraction, etc) to a simpler form by cancellation of common factors, regrouping of terms in the same variable, etc.

to make something less complicated and therefore easier to understand:

to make simple or simpler: such as
a : to reduce to basic essentials
b : to diminish in scope or complexity : streamline
c : to make more intelligible : clarify

Components of TB treatment:

- Selection of drugs
- Number of drugs
- Dosing of drugs
- Sequence of drugs
- Rhythm of administration
- Ensuring/monitoring efficacy:
  - Bacteriologic
  - Pharmacokinetic
- Monitoring/managing toxicity
- Monitoring/managing acquired resistance
- Monitoring/assuring adherence
- Duration of treatment

What might be Simplified TB Treatment?

- Specific (?simpler) drugs
- Fewer drugs
- Uniform doses
- No sequencing (IP→CP)
- Less frequent administration
- More effective therapies
- Less toxicity
- Less risk of acquired resistance
- Easier ways to assure adherence
- Shorter treatments

Selection of Drugs

- Recommendations have followed the availability and investigation of new drugs
- Initially, streptomycin, PAS, INH became the 18-month standard (mid 1950's)
- Rifamycins reduced duration by 50% (1970's)
- PZA allowed shortening from 9 to 6 months (1990)
- Need for MDR therapy drives choices of new drugs

Selection of Drugs

MDR Trials recently/currently underway:

- STREAM st 1-2 -9MC+Inj→6-9LxCB+-Inj
- Otsuka 213 -Delamanid + OBR
- NeXT -BLzLx+(Eth/PZA/hdINH)
- NIX and ZeNiX -BPaLz
- MDR-END -DLzLxZ
- end TB -9BLzMZ/BLzCLxZ/BLzDLxZ/ DLzCLxZ/DCMZ
- TB PRACTECAL -6BPaMLz/6BPaLzC/6BPaLz
- SIMPLICITB -BPaMZ
- BEAT TB -6BD+Lx/Lz

Number of drugs

- Early trials 1948-52 established need for >1 drug; by mid-1950s the standard had become 3 drugs
- Since MRC trials, SCC has included 4 drugs: SHRZ
- BTA and CDC trials led to EHRZ, and confirmed treatment shortening effect of PZA
- MDR therapy has favored 5 active drugs, in part due to relative weak efficacy of available agents

Dosing of Drugs

- Weight based vs standardized
- Establishment of dosing represented compromises on diverse features (e.g., efficacy, toxicity, cost); not optimized
- Varied by frequency of administration
- Adjustment for renal/hepatic function
- Adjustment for toxicity

Sequence of Drugs

- May be responsive to phasing of TB therapy
  - Early phase arrests replication with rapid killing action
  - Latter phase sterilizes by eliminating persisting bacilli

Sequence of Drugs

- May be responsive to phasing of TB therapy
  - Early phase arrests replication with rapid killing action; may be a maximum
  - Latter phase sterilizes by eliminating persisting bacilli; unclear if can be accelerated
- Special position of PZA, now influenced by synergy with bedaquiline
- Would rapid drug sequencing allow bacilli less time to adapt to each agent's challenge?

Rhythm of administration

- Intermittent regimens thought to be of great programmatic advantage:
  - MRC's thrice weekly;
  - Denver regimen twice weekly;
  - RPT trials seeking once-weekly;
  - Long-acting injectable goal of $\geq$ 30 days

Rifapentine and isoniazid once a week versus rifampicin and isoniazid twice a week for treatment of drug-susceptible pulmonary tuberculosis in HIV-negative patients: a randomised clinical trial

*The Tuberculosis Trials Consortium**

Lancet 2002; **360:** 528–34

Methods We did a randomised, multicentre, open-label trial in the USA and Canada of HIV-negative people with drug-susceptible pulmonary tuberculosis who had completed 2 months of a 6-month treatment regimen. We randomly allocated patients directly observed treatment with either 600 mg rifapentine plus 900 mg isoniazid once a week or 600 mg rifampicin plus 900 mg isoniazid twice a week. Primary outcome was failure/relapse. Analysis was by intention to treat.

USPHS Study 22 found 5 factors independently associated with risk of failure/relapse:

- **2-month culture result,**
- **cavitation on CXR,**
- **being underweight,**
- **bilateral disease on CXR, and**
- **non-Hispanic white race.**

Other studies also identified: increased age, alcohol abuse, irregular compliance, male gender, shorter therapy, more intermittent therapy, weaker regimens (e.g., thiacetazone) [in Poland, East Africa, Hong Kong]

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Identification of patients at high risk for treatment failure or relapse with directly observed short-course therapy for pulmonary tuberculosis

A Report from the Tuberculosis Trials Consortium (TBTC)

[A listing of contributors appears at the end of this report]

Running head: Risk factors for relapse after TB treatment

Word count: 2671

Requests for reprints:

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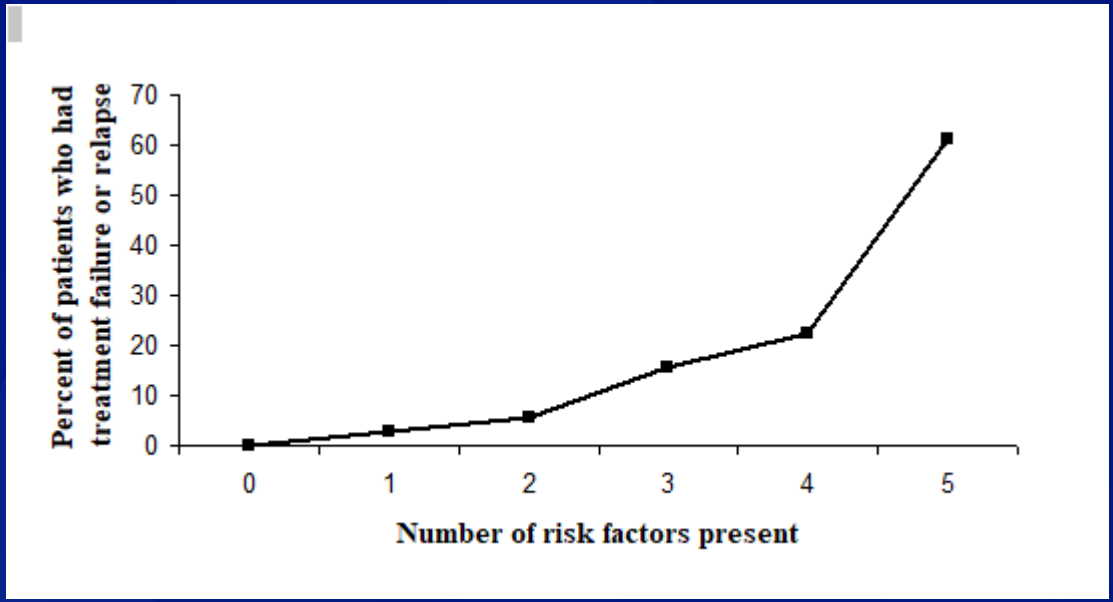
This study was funded by the Centers for Disease Control and Prevention, U.S. Public Health Service. Rifapentine was provided by Hoechst Marion Roussel Inc., Kansas City MO

This study was presented in part at the 38th Annual Conference of the Infectious Diseases Society of America, September 8, 2000, New Orleans, LA

Date of revision: July 31 2001 *22 risk factors paper 7_31.doc*

Key words: tuberculosis, rifampin, rifapentine, isoniazid, multicenter clinical trial, relapse, treatment failure, risk factor analysis, directly observed therapy

Credit to W Burman and USPHS Study 22 Team



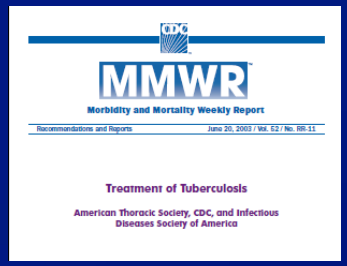
The rate of failure/relapse was 3.5% for patients with 0-2 risk factors, but 21% among patients with 3-5 risk factors.

Risk factor	Sensitivity	Specificity	Pos Pred Value	Neg Pred Value	Nr needed to treat
Cavity	84%	48%	12%	97%	8.6
2m smear +	27%	88%	16%	94%	6.3
2m cult +	53%	83%	21%	95%	4.9
2m sm+cav	25%	91%	19%	94%	5.2
2m cul+cav	46%	87%	25%	95%	4.0

[F/R] Event rates were especially high in patients with multiple risk factors (for example, for patients with both cavitation and positive sputum culture at 2 months, 26.8% in the rifapentine group and 21.8% in the rifampicin group).

TABLE 11. Percentage of culture-positive relapse* by continuation phase regimen, radiographic status, and 2-month sputum culture: USPHS Study 22

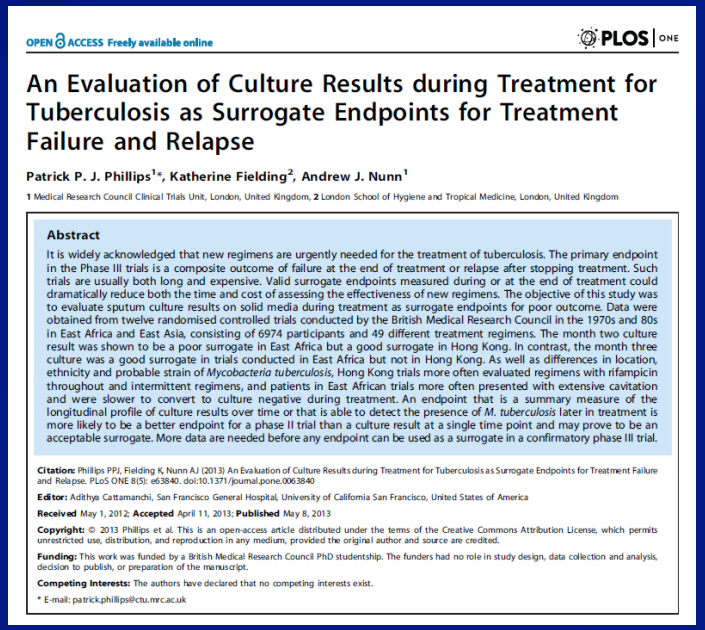
Continuation phase, INH–RIF twice weekly†			Continuation phase, INH–RPT once weekly†		
	Culture-positive at 2 months			Culture-positive at 2 months	
Cavity	Yes	No	Cavity	Yes	No
Yes	20.8 (48)‡	4.7 (150)	Yes	22.2 (72)	9.1 (154)
No	5.9 (17)	1.7 (181)	No	11.8 (17)	1.9 (162)



- **Assuring/Monitoring efficacy:**
  - **Bacteriologic**
  - **Pharmacokinetic**

- Most available bacteriologic measures not adequate

- PK monitoring remains poorly accessible



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PLOS ONE

An Evaluation of Culture Results during Treatment for Tuberculosis as Surrogate Endpoints for Treatment Failure and Relapse

Patrick P. J. Phillips[1]*, Katherine Fielding[2], Andrew J. Nunn[1]

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Abstract

It is widely acknowledged that new regimens are urgently needed for the treatment of tuberculosis. The primary endpoint in the Phase III trials is a composite outcome of failure at the end of treatment or relapse after stopping treatment. Such trials are usually both long and expensive. Valid surrogate endpoints measured during or at the end of treatment could dramatically reduce both the time and cost of assessing the effectiveness of new regimens. The objective of this study was to evaluate sputum culture results on solid media during treatment as surrogate endpoints for poor outcome. Data were obtained from twelve randomised controlled trials conducted by the British Medical Research Council in the 1970s and 80s in East Africa and East Asia, consisting of 6974 participants and 49 different treatment regimens. The month two culture result was shown to be a poor surrogate in East Africa but a good surrogate in Hong Kong. In contrast, the month three culture was a good surrogate in trials conducted in East Africa but not in Hong Kong. As well as differences in location, ethnicity and probable strain of *Mycobacteria tuberculosis*, Hong Kong trials more often evaluated regimens with rifampicin throughout and intermittent regimens, and patients in East African trials more often presented with extensive cavitation and were slower to convert to culture negative during treatment. An endpoint that is a summary measure of the longitudinal profile of culture results over time or that is able to detect the presence of *M. tuberculosis* later in treatment is more likely to be a better endpoint for a phase II trial than a culture result at a single time point and may prove to be an acceptable surrogate. More data are needed before any endpoint can be used as a surrogate in a confirmatory phase III trial.

Citation: Phillips PPJ, Fielding K, Nunn AJ (2013) An Evaluation of Culture Results during Treatment for Tuberculosis as Surrogate Endpoints for Treatment Failure and Relapse. PLoS ONE 8(5): e63840. doi:10.1371/journal.pone.0063840

Editor: Adithya Cattamanchi, San Francisco General Hospital, University of California San Francisco, United States of America

Received May 1, 2012; **Accepted** April 11, 2013; **Published** May 8, 2013

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Funding: This work was funded by a British Medical Research Council PhD studentship. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

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Monitoring for toxicity

- Hepatotoxicity persists as a problem with INH; most trials using INH in low resource settings include liver deaths
- Hepatotoxicity challenges some novel agents (e.g., pretomanid) and increases need for monitoring
- QT effect of multiple agents poorly understood; simple means to monitor are not validated; cause of sudden death is difficult to assess in most trials

Monitoring for Acquired Drug Resistance

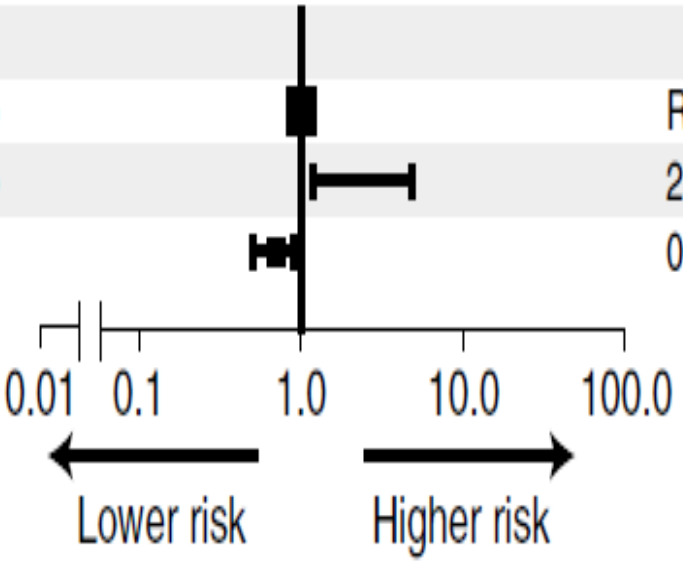
- Uncertain contributions of multiple quantitative processes (bacillary load, rate of replication, relative types of drug exposures, degree of immunologic impairment)
- Ability to assess RR with Xpert, soon to be supplemented with IR
- Very limited ability to monitor novel agents, with consequent risk of loss of utility

Monitoring for/assuring adherence

- Non-completion of therapy is perhaps the most severe problem confronting TB control
- It is NOT a new problem
- Our sophistication in addressing this is poor, despite better understanding of its importance

Impact of adherence under 6/7 dosing strategy

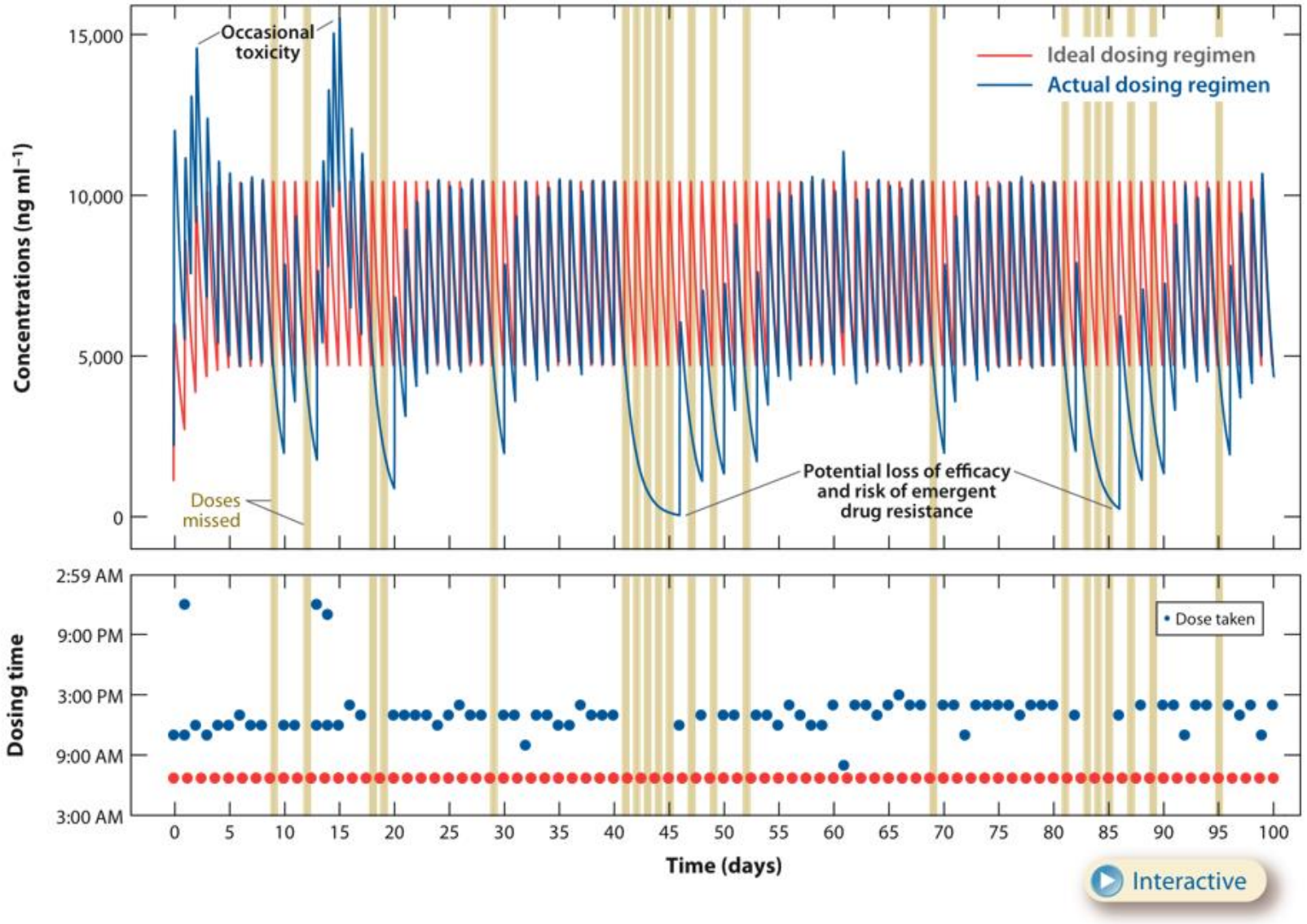
Variable	Number of unfavorable outcomes/ number of study participants (%)	HR (95% CI)
Total doses		
144 (6 doses per week)	50/533 (9)	Reference
112–143 (on average 5 doses per week)	13/65 (20)	2.4 (1.2–4.8)
Treatment duration (per week)	c	0.7 (0.5–0.9)



ARTICLES
https://doi.org/10.1038/s41591-018-0224-2
nature medicine
OPEN
Corrected: Publisher Correction

A patient-level pooled analysis of treatment-shortening regimens for drug-susceptible pulmonary tuberculosis

Marjorie Z. Imperial[1,11], Payam Nahid[1,11], Patrick P. J. Phillips[1], Geraint R. Davies[2], Katherine Fielding[3], Debra Hanna[4,5], David Hermann[5], Robert S. Wallis[6], John L. Johnson[7,8], Christian Lienhardt[9,10] and Rada M. Savic[1*]



From Blaschke et al, Ann Rev Pharm Tox 2012

Duration of treatment

- Developments have paralleled selection of drugs:
  - -- 18 mo H+PAS+Strep
  - -- 9 mo HR(E)
  - -- 6 mo HRS or HRSZ/HR
  - -- 6 mo HREZ/HR

- Driven by roles of key drug(s)

A Nested Case–Control Study on Treatment-related Risk Factors for Early Relapse of Tuberculosis

Kwok C. Chang, Chi C. Leung, Wing W. Yew, Suzanne C. Ho, and Cheuk M. Tam

AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE VOL 170 2004

In the Treatment of Tuberculosis, You Get What You Pay for…

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PLoS MEDICINE

Effect of Duration and Intermittency of Rifampin on Tuberculosis Treatment Outcomes: A Systematic Review and Meta-Analysis

Dick Menzies[1]*, Andrea Benedetti[1], Anita Paydar[1], Ian Martin[1], Sarah Royce[2], Madhukar Pai[1], Andrew Vernon[3], Christian Lienhardt[4], William Burman[5]

Table 7. Stratified estimates of relapse in RCT in new cases.

Factor	Studies (*M*)	Events/Participants (*M*)	Pooled Event Rate (Across All Trials)
Overall			
Duration of rifampin			
Rifampin 1–2 mo	70	367/3,349	**16.0**
Rifampin 3–5 mo	42	185/2,389	**7.1**
Rifampin 6–7 mo	171	364/8,639	**3.8**
Rifampin 8+ mo	18	14/1,181	1.0

Table 9. Adjusted incidence rate ratios of failure, relapse, and acquired drug resistance (from negative binomial regression).

Factor	Failure IRR (95% CI)	Relapse IRR (95% CI)	Acquired Drug Resistance[a] IRR (95% CI)
Duration of rifampin[b]			
1–2 mo	**5.8 (2.9 to 11.0)**	**3.6 (2.5 to 5.3)**	**4.6 (2.0 to 0.4)**
3–4 mo	1.3 (0.6 to 3.0)	**2.6 (1.6 to 4.0)**	1.2 (0.4 to 3.1)
5–7 mo	1.0 (reference)	1.0 (reference)	1.0 (reference)
8+ mo	2.0 (0.8 to 4.9)	**0.4 (0.2 to 0.7)**	2.1 (0.8 to 5.3)
Overall significance (*p* value)[c]	(<0.0001)	(<0.0001)	(<0.002)
Isoniazid resistant	**10.9 (5.9 to 20)**	**1.8 (1.2 to 2.6)**	**5.1 (2.3 to 11.0)**
Schedule of drug administration[b]			
Daily throughout	1.0 (reference)	1.0 (reference)	1.0 (reference)
Daily then thrice weekly	0.7 (0.2 to 2.1)	1.0 (0.6 to 1.5)	0.7 (0.2 to 2.6)
Daily then twice weekly	0.9 (0.5 to 1.6)	0.8 (0.5 to 1.2)	0.5 (0.3 to 1.2)
Thrice weekly throughout	0.7 (0.3 to 1.4)	1.2 (0.8 to 1.6)	**2.4 (1.05 to 5.5)**

Conclusion

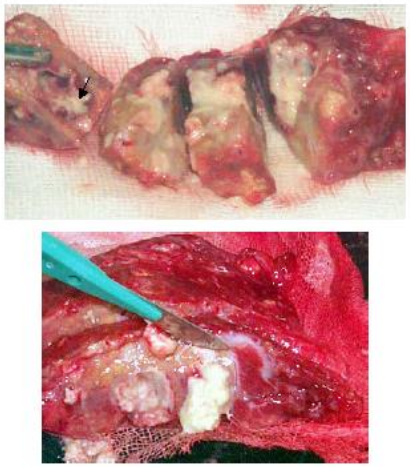
This review provides evidence against continued use of regimens that utilize rifampin for the first 2 mo only, as they are significantly and substantially inferior to regimens that use rifampin for at least 6 mo. This review also has identified an important need for adequately powered clinical trials that address dosing schedules, management of isoniazid mono-resistance, and the optimal duration of treatment to prevent relapse.

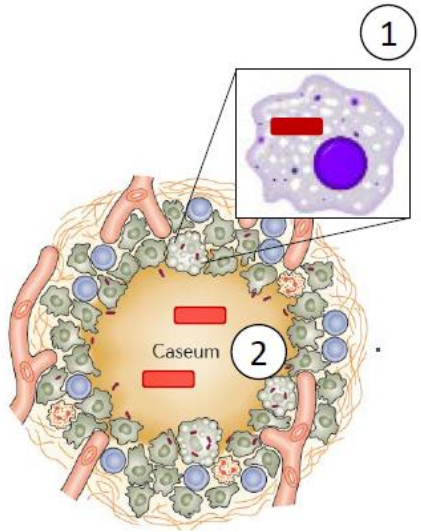
Duration of treatment-2

- May be limited by issues related to tissue architecture, lesion repair, and drug penetration

HYPOTHESIS

If TB drugs reach all bacterial populations at sufficient concentration in lesions, cure rates will increase and treatment duration will decrease





Two populations:

1. Intracellular in macrophages
2. Mostly extracellular in caseum

Slide from Prof Veronique Dartois

Duration of treatment-3

Year	Regimen (14 wk)	CFU at EOT	CF dep at EOT	Relapse after 2 mo of HC (lung or spleen)
2018	R10HZ	Negative	Positive	86%
2018	R30HZ R40HZ	Negative	Negative	0%
2019	R10HZE	Negative	Positive	90%
2019	R10HZB	Negative	Negative	0%

Liu et al, JAC 2018 and Hu et al, JAC 2019

…to get to
Smarter
~~Simplified~~ TB Treatment

- Increase engagement with laboratory scientists
- Increase use of animal models
- Increase emphasis on phase 2
- Increase use of quantitative data
- Increase collaboration among trial groups
- Develop more accessible program platforms for trials

The End

Thank You for your Attention

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