

# Speeding up clinical trials for MDR-TB by remembering the lessons of the past

William Burman MD  
Denver Public Health  
Tuberculosis Trials Consortium

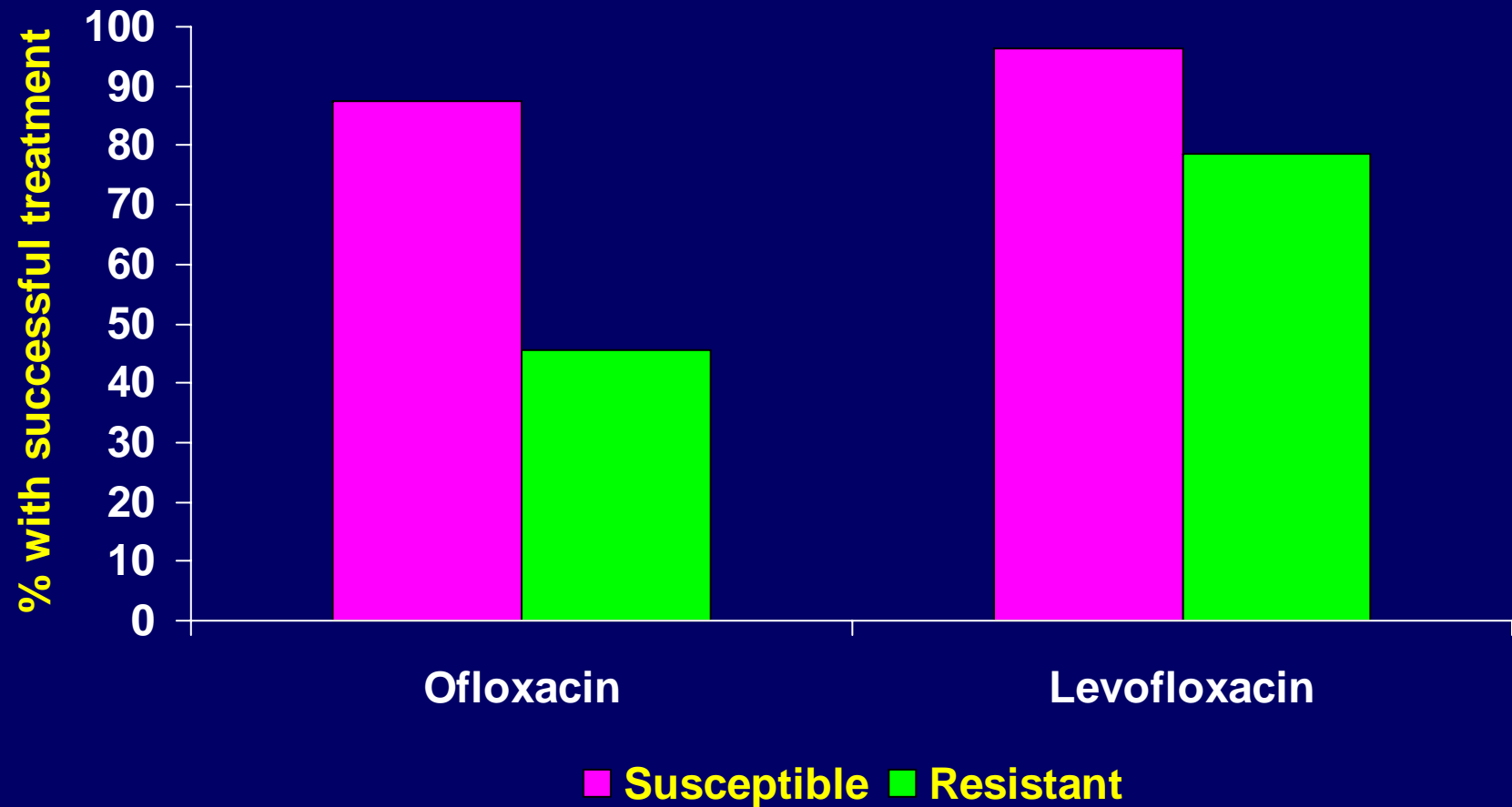
## Do we need clinical trials for MDR-TB?

- New drugs are being evaluated in clinical trials among patients with drug-susceptible TB
- MDR-TB is uncommon and is a heterogeneous disease - different patterns of drug resistance and prior drug exposure
- Clinical trials for MDR-TB will be more expensive and take longer than studies of drug-susceptible TB
- Define roles of new drugs in trials of drug-susceptible TB

# Fluoroquinolones and MDR-TB

- Fluoroquinolones have good activity against TB *in vitro* and in the mouse model
- Fluoroquinolones are well-tolerated – good short-term side effect profile, increasing data on the safety of long-term use
- In retrospective cohorts, response to MDR treatment correlates with baseline fluoroquinolone susceptibility

# Association between fluoroquinolone susceptibility and response to MDR-TB treatment



Chest 2003;124:1476-81

# Use of fluoroquinolones for MDR-TB

- Key drug in the treatment of MDR-TB
- Uncertainty about the best fluoroquinolone for MDR-TB treatment
- Uncertainty about optimal treatment duration for fluoroquinolone-based therapy (for susceptible isolates)
- Marked differences in treatment durations
  - 24 months after culture conversion (US guidelines)
  - Average of 14 months (Hong Kong)

## Lesson #1 – What happens in the absence of clinical trials: fluoroquinolones for MDR-TB

- Drugs with *in vitro* activity against TB will be used – with or without clinical trials

## Lesson #1 – What happens in the absence of clinical trials: fluoroquinolones for MDR-TB

- Drugs with *in vitro* activity against TB will be used – with or without clinical trials
- Drugs with promising activity in observational cohorts will be incorporated in standard treatment regimens – and randomized trials will become impossible

## Lesson #1 – What happens in the absence of clinical trials: fluoroquinolones for MDR-TB

- Drugs with *in vitro* activity against TB will be used – with or without clinical trials
- Drugs with promising activity in observational cohorts will be incorporated in standard treatment regimens – and randomized trials will become impossible
- Uncertainty about the effects of using a new class leads to marked differences in treatment duration – limiting expansion of MDR treatment

## Lesson #1 – What happens in the absence of clinical trials: fluoroquinolones for MDR-TB

- Drugs with *in vitro* activity against TB will be used – with or without clinical trials
- Drugs with promising activity in observational cohorts will be incorporated in standard treatment regimens – and randomized trials will become impossible
- Uncertainty about the effects of using a new class leads to marked differences in treatment duration – limiting expansion of MDR treatment
- Lack of rigorous long-term safety data may place patients at risk (e.g., stavudine in Africa)

## How to pick drugs, doses, dosing frequency, and drug combinations to advance to clinical trials

- *In vitro* data – MIC, MBC, synergy studies to evaluate combination therapy
- PK data, PD parameters ( $C_{max}/MIC$ , AUC/MIC, time over MIC)
- Analogies that seem reasonable
- Animal model data

How well do these factors predict efficacy?

## PK / PD parameters of available rifamycins

Parameter	RIF	RPT
C <sub>max</sub> (600 mg)	10	15
MIC	0.15	0.04
C <sub>max</sub> / MIC (600 mg)	67	375
Time over MIC (hrs/week)	16	104

# Results of a large randomized trial of weekly RPT/INH vs. twice-weekly RIF/INH

Event	RIF/INH	RPT/INH
Culture-positive failure	3 (< 1%)	5 (1%)
Culture-positive relapse	22 (4%)	39 (8%)
Failure or relapse	25 (4%)	44 (9%)

Lancet 2002;360:530

## PK / PD parameters of available rifamycins

Parameter	RIF	RPT
C <sub>max</sub> (600 mg)	10	15
MIC	0.15	0.04
C <sub>max</sub> / MIC (600 mg)	67	375
Time over MIC (hrs/week)	16	104
% binding	85%	97%
Unbound C <sub>max</sub> (est.)	1.5	0.45
Unbound C <sub>Max</sub> / MIC	10	11

## PK / PD parameters of available rifamycins

Parameter	RIF	RPT	RBT
C <sub>max</sub> (600 mg, 300 mg)	10	15	0.45
MIC	0.15	0.04	0.06
C <sub>max</sub> / MIC	67	375	7.5
Time over MIC (hrs/week)	16	104	111
% binding	85%	97%	71%
Unbound C <sub>max</sub>	1.5	0.45	0.13
Unbound C <sub>Max</sub> / MIC	10	11	3.5

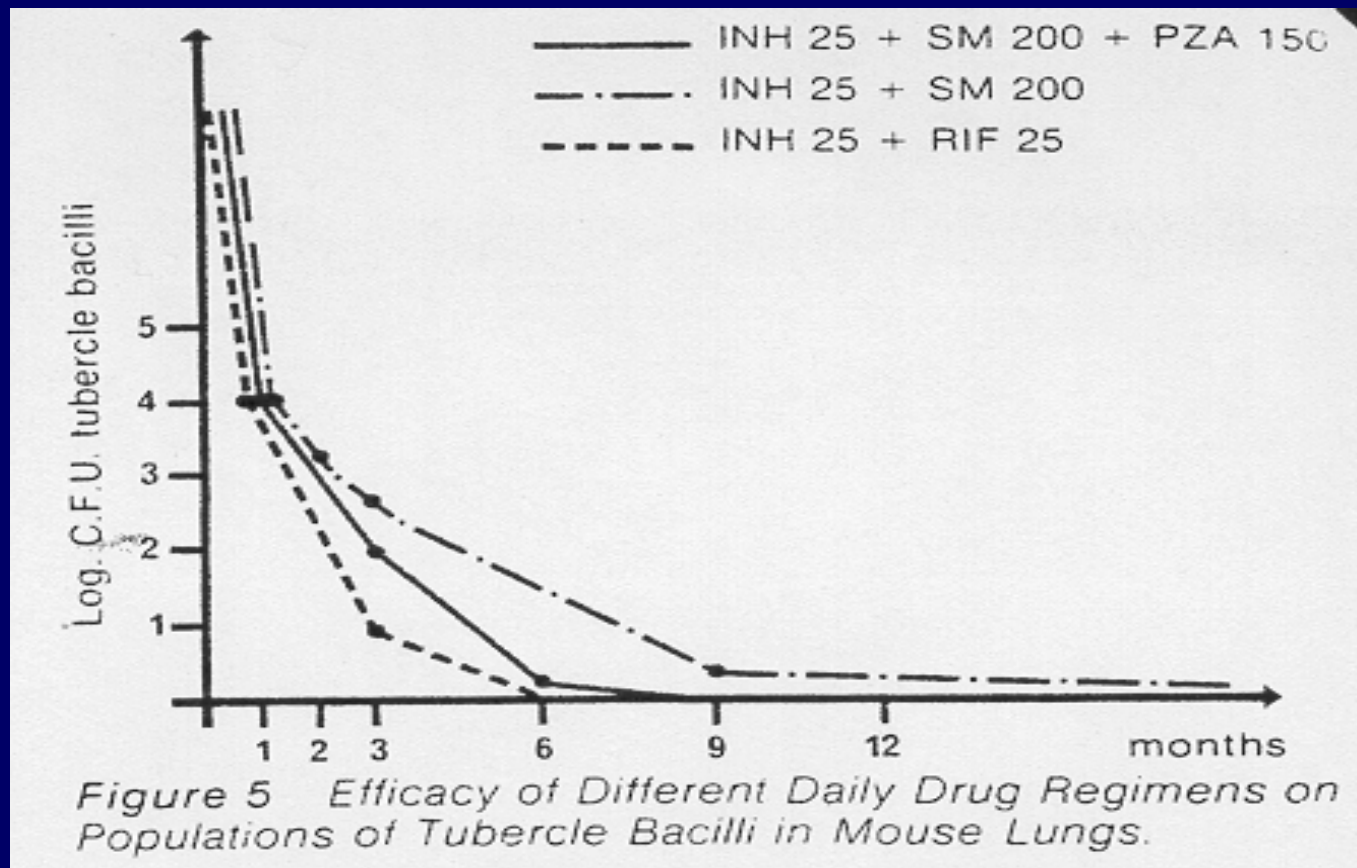
## Words of wisdom from early in the chemotherapy era

---

“The protean character of the infectious process thus causes bacilli and drugs to come into contact in areas differing markedly in their physicochemical characteristics... As drugs are selected on the basis of their ability to function in the normal physiological environment, they are often ineffective within the lesions, where conditions are profoundly different from the physiological.” **R. Dubos**

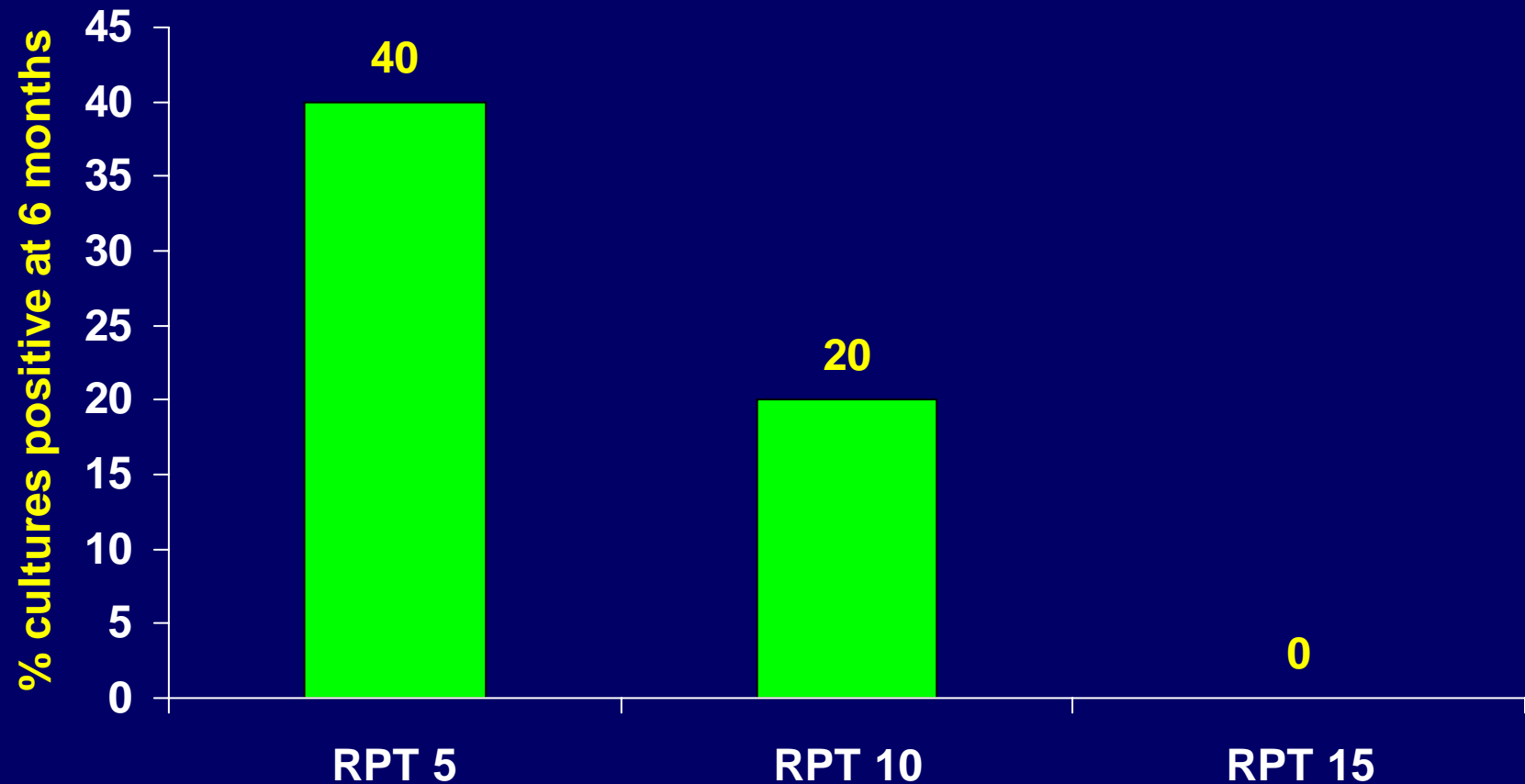
*Am Rev Tuberc* 1954;70:398

# Multidrug regimens in mouse model of TB

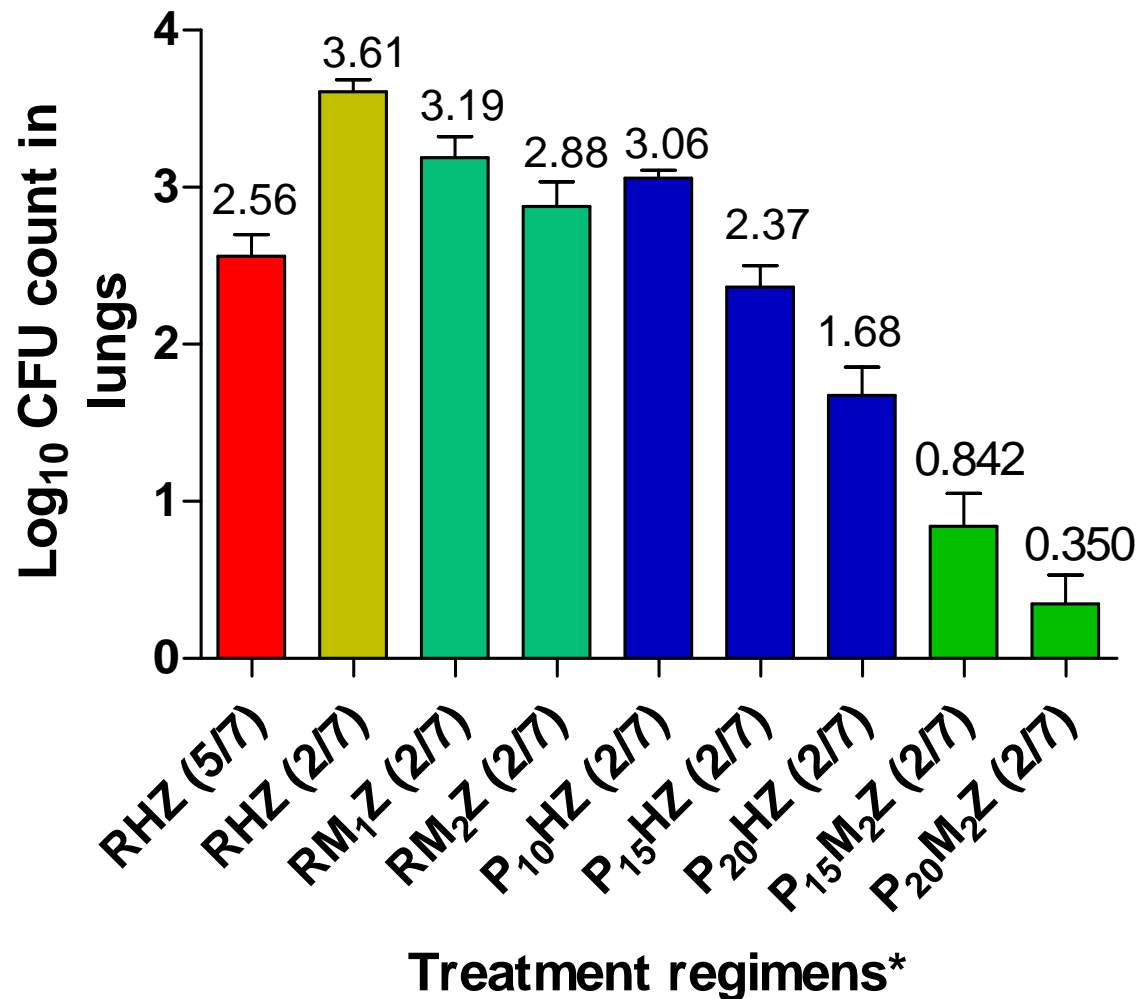


*Tubercle* 1978;59:287-97

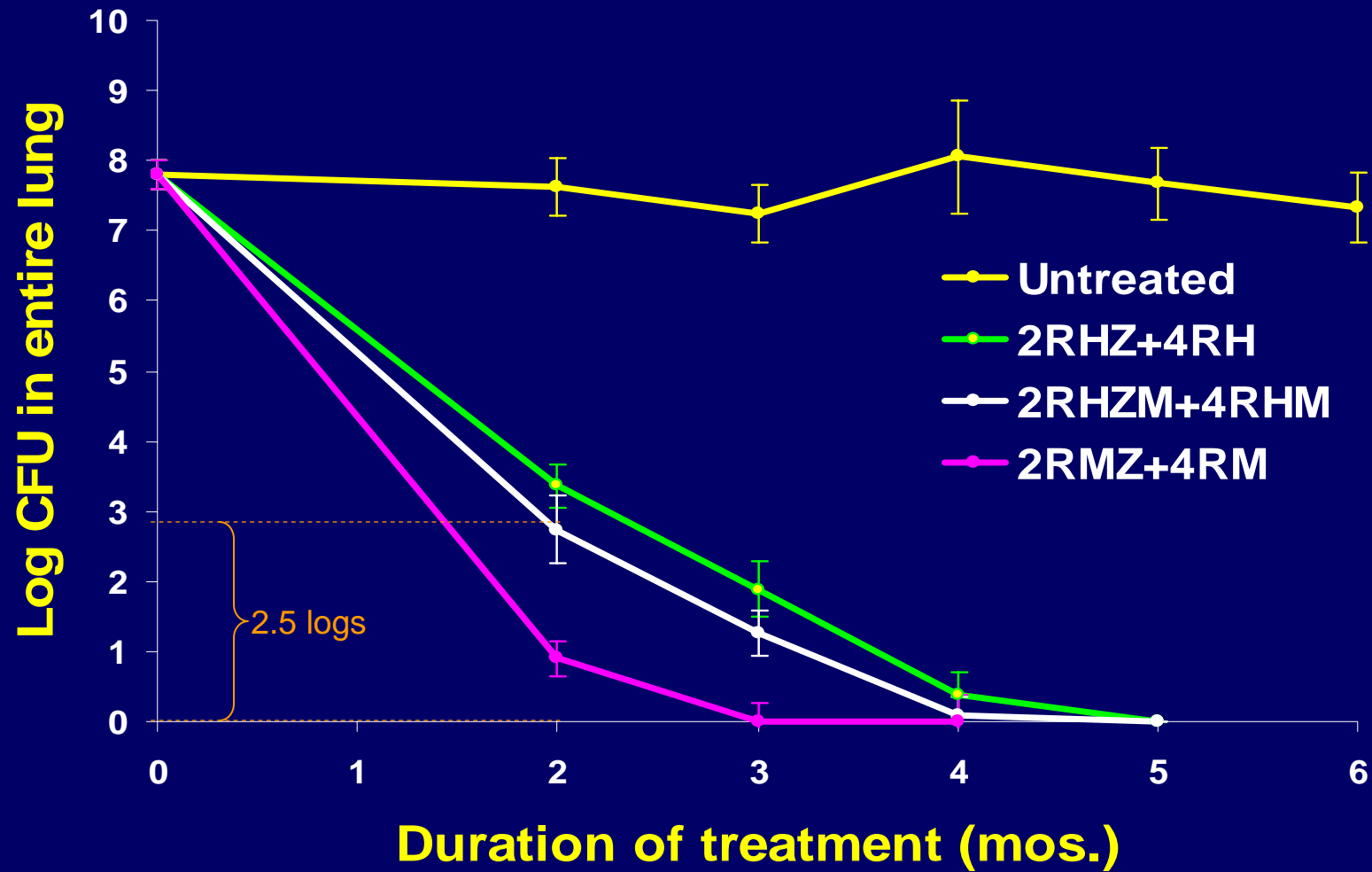
# Effect of rifapentine dose on the activity of once-weekly RPT/INH/PZA in continuation phase (mouse model)



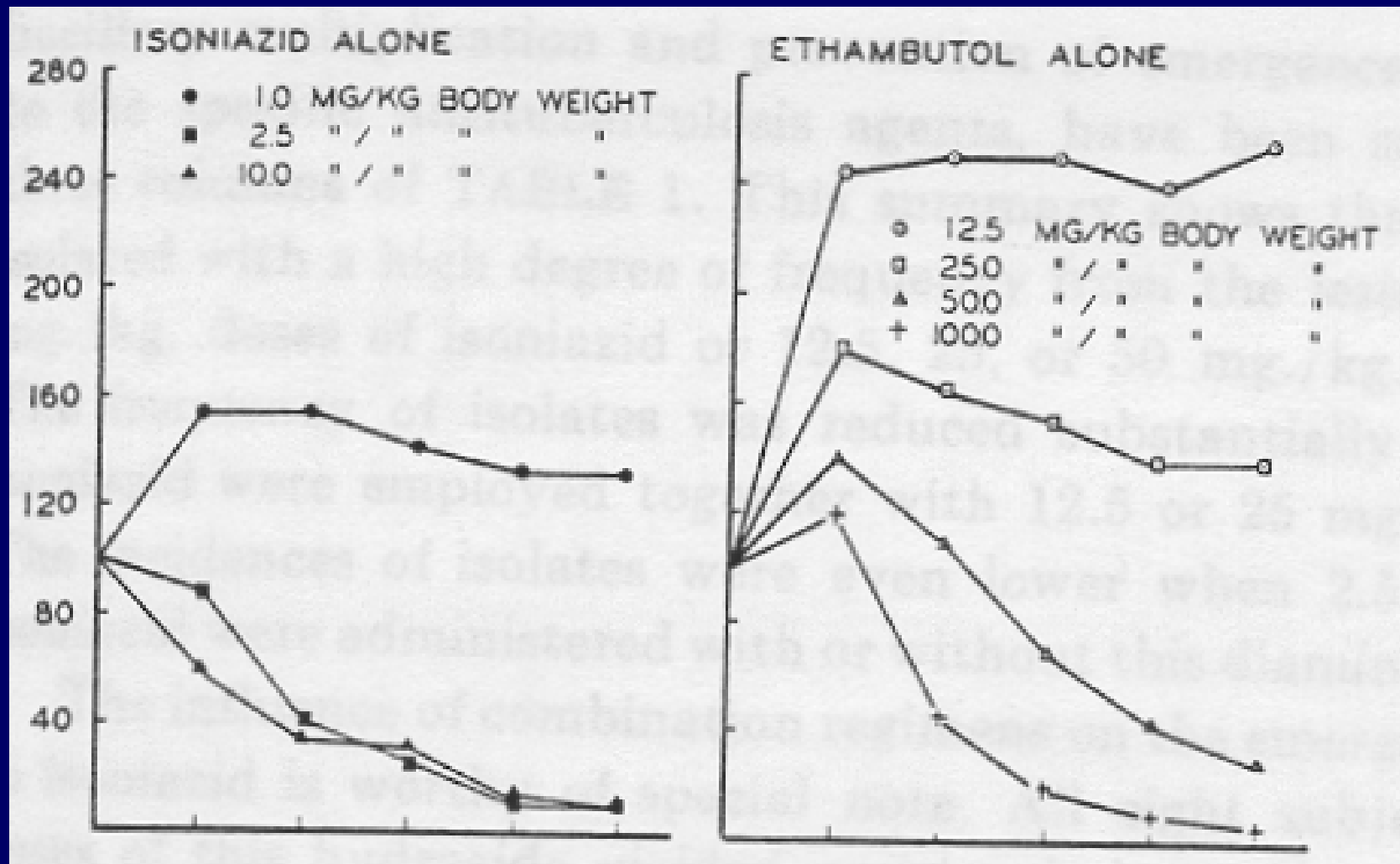
# Lung CFU Counts after 2 Months Treatment from Rosenthal, Grosset et al.



# Activity of moxifloxacin in combination therapy in a mouse model of TB



# Activity of INH and ethambutol in monkeys



## Conclusions – animal models of TB treatment

- With careful attention to mirroring human PK, the mouse model is predictive of results in human TB treatment
  - Two phases of INH activity – rapid, then very slow killing
  - Sterilizing effects of rifampin, PZA
  - Duration of treatment necessary with different multidrug regimens
  - Effect of dosing frequency

# Value of preclinical measures for predicting clinical efficacy

- Preclinical markers
  - Classic *in vitro* assays of very limited value, new techniques of uncertain value
  - Carefully performed mouse studies correlate with results of clinical trials

## Lesson #2 – Speed up clinical trials by taking the time to do full evaluation of prospective regimens in the mouse model

- Lessons of rifapentine
  - Inadequate evaluation prior to Phase 3 clinical trials led to use of a sub-optimal dose
  - Suboptimal activity in initial Phase 3 clinical trials led to near-abandonment of a promising drug
- Lessons of moxifloxacin
  - Need to evaluate drug activity in context of different companion drugs

## Lessons from the history of TB

- We will need clinical trials of new drugs for MDR-TB treatment to promote the development of efficient, effective regimens that allow program expansion
- These clinical trials should be guided by extensive testing of dose, dosing frequency, and drug combinations in animal models that mimic human PK