

# Shortening the Clinical Development of Drugs for Tuberculosis

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# What can we shorten?

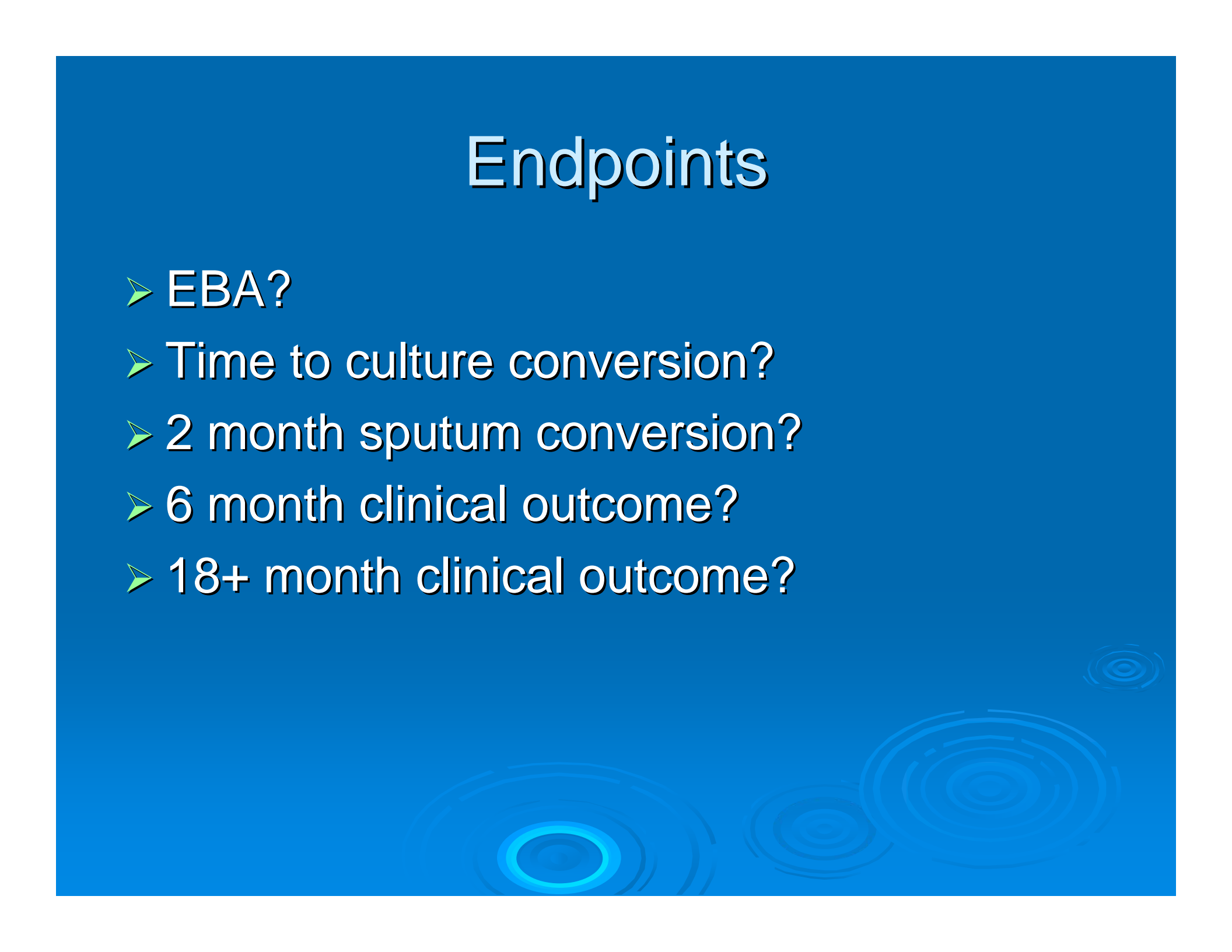
- Drug development program
- Duration of each study



# The major challenges

- Choice of endpoints
  - Clinically meaningful, scientifically robust
- Demonstration of activity within a multi-drug regimen
  - Superiority/non-inferiority

# Endpoints

- EBA?
  - Time to culture conversion?
  - 2 month sputum conversion?
  - 6 month clinical outcome?
  - 18+ month clinical outcome?
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# What can we shorten?

- Generation time
  - For MTB 12-18 hrs (limits what a drug can be expected to show in a short time)
  - For *E coli* 20-30 minutes
- Bactericidal activity-
  - Does not take long to demonstrate
  - Is not a major factor in trial duration
  - Modern regimens highly effective- may be difficult to demonstrate superiority
- **Sterilizing activity**
  - **The biggest obstacle**
  - **Weak surrogates (2 months sterilization-based on limited data)**
  - **No good marker**
  - **With cure rates at ~95%, we are forced to look at very late outcomes in very large numbers of patients.**

# Choice of endpoints

- We are looking at two distinguishable antimicrobial activities-
  - “bactericidal” (easy to study)
  - “sterilizing” (hard to study)
- Bactericidal
  - 75-80% smear negative after 3 months
  - 95% culture negative after 4 months
  - Are there situations where this endpoint would be sufficient for drug approval?
- Sterilizing
  - Currently recommended endpoint for clinical trials for TB is 12-24 months after completion of therapy\*

	Rifampin	Rifapentine
2 month smear positive	13.2% (7/53)	17.8% (13/73)
2 month culture positive	16.7% (13/78)	23.5% (24/102)
~20 month failure/relapse	5.6% (28/502)	9.2% (46/502)

\*IDSA Clin Infect Dis 1992; 15 (S1): 282

TBTC Lancet 2002;360:528

# Old lessons

## ➤ Streptomycin

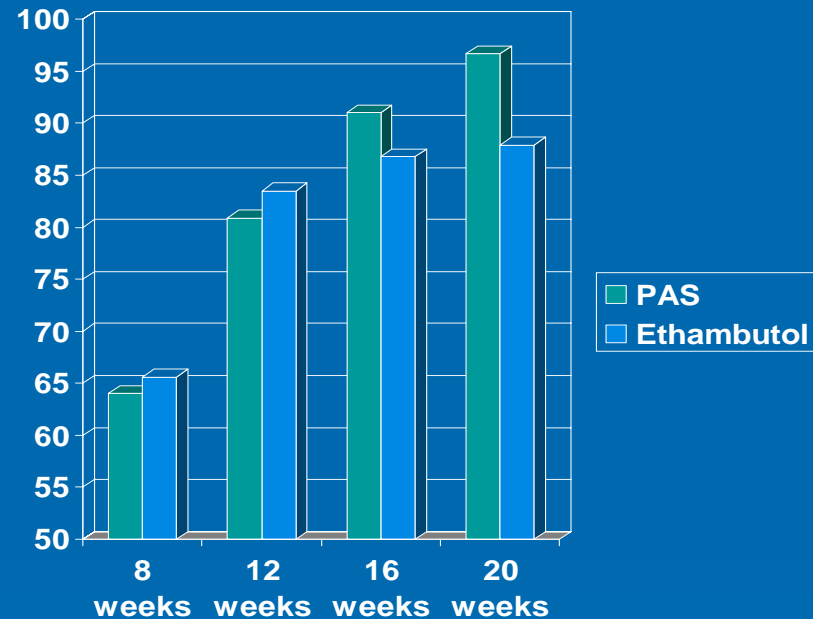
- Short term outcome good
- 5 year follow up – little better than controls

## ➤ EBA-

- INH performs better than Rifampin
- Would lead to gross underestimate of the utility of rifampin

# Is culture conversion at 8 weeks a reliable surrogate?

N=90	N=91
INH	INH
PAS	Ethambutol 6mg/kg



Eight patients in the ethambutol arm reverted from culture negative early in the study, to culture positive at 20 weeks.

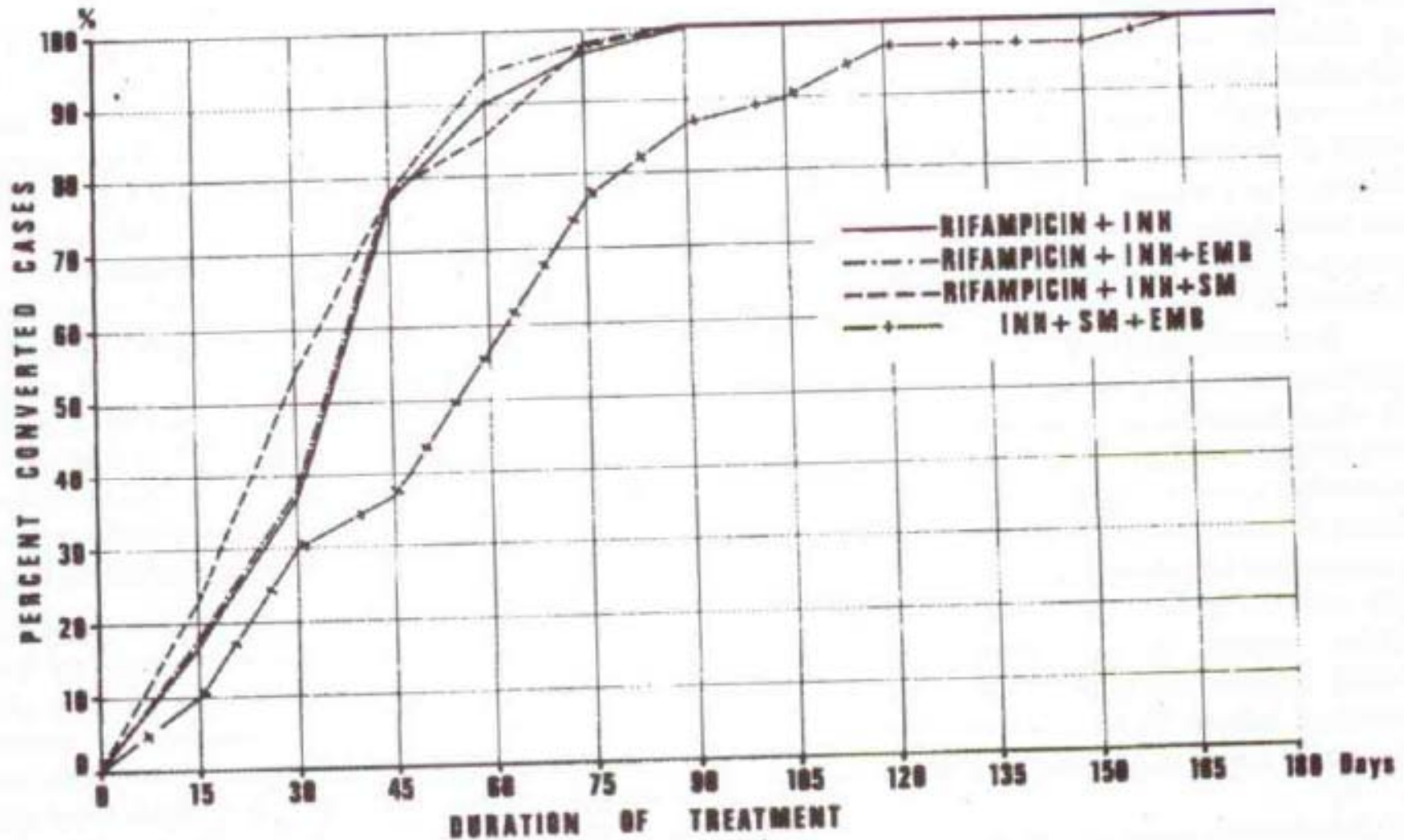
# Is “end of therapy” a reliable surrogate?

N=286	N=283
INH	INH
PZA	PZA
Ethambutol	Ethambutol
Rifapentine	Rifampin



*Priftin label PDR 2001*

# Rifampin trial



# Conclusions on early endpoints

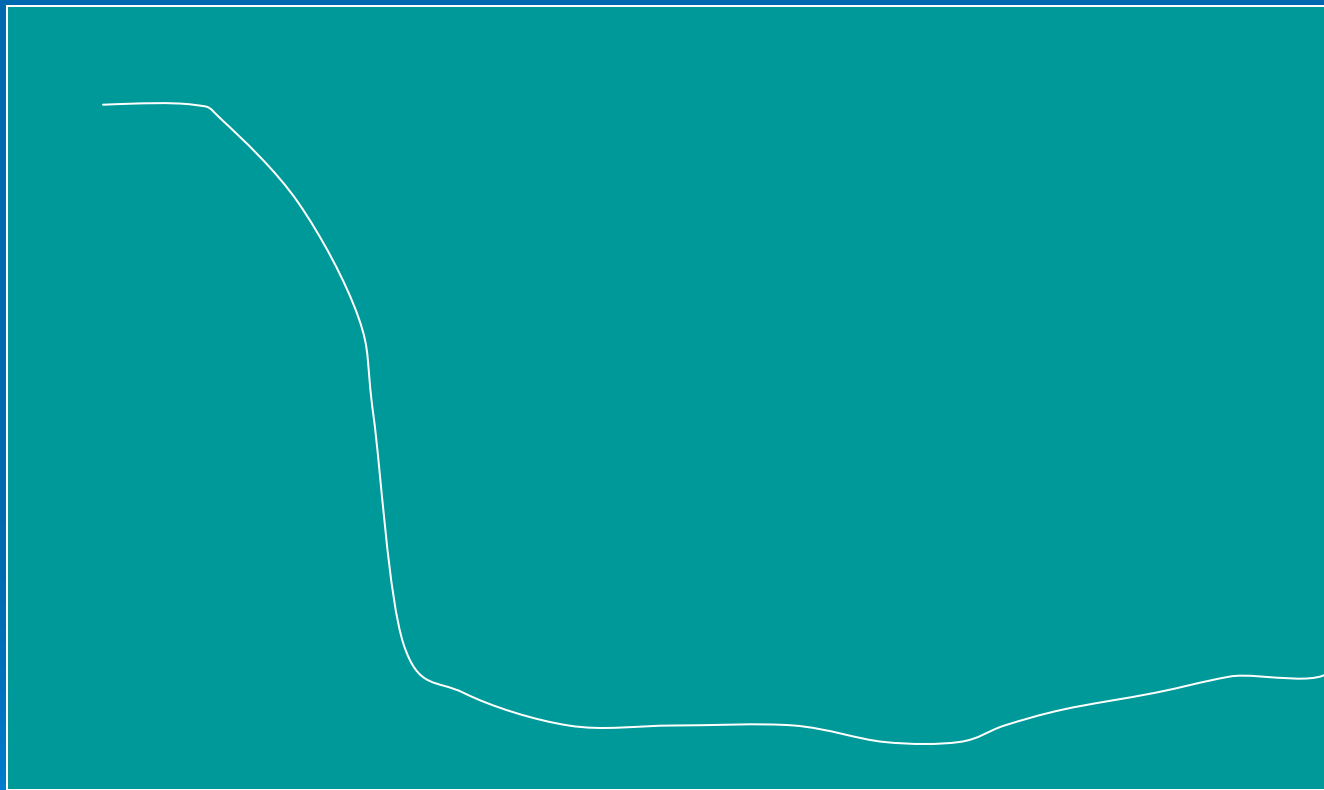
- When the effect size is huge, early endpoints might be helpful
- When the effect size is marginal, early endpoints seem unreliable

# Demonstration of activity within a multi-drug regimen

- Statistical superiority is best
- Non-inferiority,
  - almost impossible to defend the NI margin given multiple drugs and an unclear effect size for each

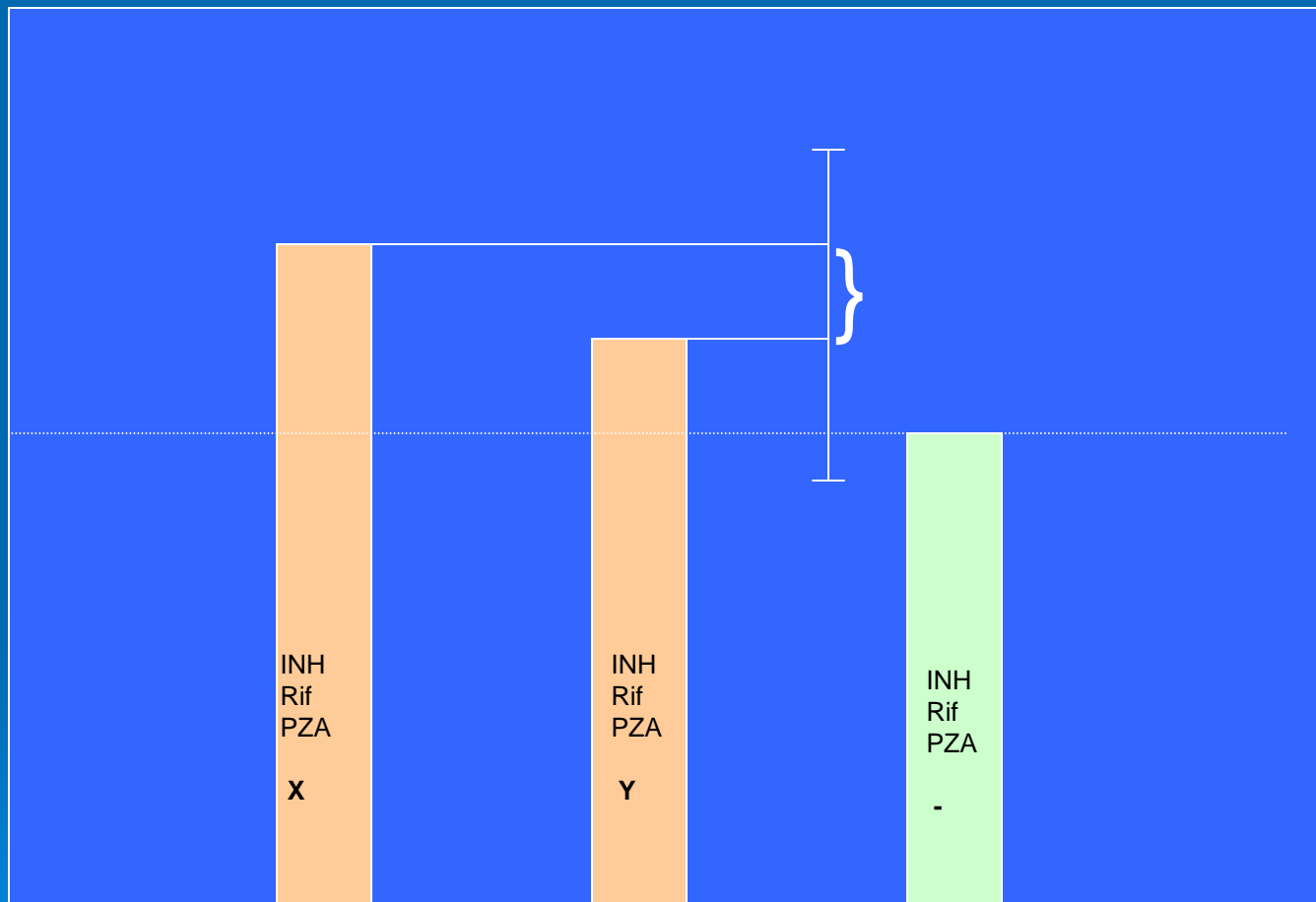
# Pattern of relapses

Percent  
culture  
positive



months

# Non-inferiority in multi-drug regimens



# Evaluation of efficacy is clouded by combination regimens


- With success rates of  $>95\%$ , the contribution of individual drugs may be impossible to see.
- Replacement of the most active components would be the most convincing demonstration of drug effect

# Interim claims

- Are there situations where drug efficacy may be more apparent early on?
  - Early reduction in infectiousness-  
“transmission blocking”
  - MDR TB where the obscuring effect of other effective drugs is reduced
  - Shortening the regimen-(unlikely to be able to rely on earlier endpoints)
  - A robust surrogate for sterilization

- Shortening the duration of follow up in drug sensitive TB is challenging
- Salvage therapy for MDR TB may allow an earlier endpoint since
  - Any response is better than no response even if durability is limited
  - Reduction of infectiousness may have significant public health implications

# Shortening drug development programs

- Finding a model with large effect size to allow reduction in the number of subjects
  - Rapid recruitment- institutionalized procedures for TB treatment where new drugs can rapidly be investigated
  - Consideration of multi-armed studies to economize on controls
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# Shortening Drug development programs

- Multi-pronged concurrent approach
  - High grade MDR study-salvage
  - Lower grade MDR- superiority
  - Drug sensitive population- replacement of component with large effect size
  - Treatment shortening
  - Prophylaxis
- Endpoints:
  - “Transmission blocking”
  - Reduction of resistance
  - Time to...culture conversion, clinical resolution, durable cure



# Challenging areas in the design of phase 3 studies

TB working group



# Regulatory setting

- We are not at the point where drug approval can be based on microbiology and animal studies alone.
- Final approval relies on adequate and well-controlled studies


# Development of TB drugs

- Efficacy - demonstration of clinical efficacy that satisfies clinical and statistical requirements
- Safety-many existing models of prolonged treatment in combination


# Structure of comparative trials

- Where can we demonstrate superiority?
  - XDR
  - MDR
- Where can we demonstrate non-inferiority?
  - Do we know enough of the effect size of quinolones to allow use as comparators in non-inferiority studies?
  - Which components of conventional therapy can be replaced with a new drug to convincingly demonstrate efficacy (1, 2 or more drugs)?

# Points for discussion

- Explore possibilities for salvage therapy protocols for XDR-TB patients
  - Compassionate use of new drugs under development versus use of existing drugs
  - Trial assessing new drugs in HIV + patients
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# More points for discussion

- 1) Are there sufficient data available to estimate an effect size for Quinolones in MDR TB?
  - 2) If the effect size of Quinolones is large and likely to obscure the effect of a new drug, can non-inferiority studies be statistically justified using a quinolone as the comparator?
  - 3) What clinical parameters may be important in stratifying the analysis of patients in an MDR TB trial?
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# More points for discussion

- 4) Rather than putting all our eggs in one basket, are there multipronged approaches that should be used in MDR TB trials- different populations, different endpoints etc?
- 5) Are there ways to prove that a new agent is effective in preventing the development of resistance while on treatment?
- 6) How do we move from MDR TB to drug sensitive TB?
- 7) Is there a role for inhalation therapy?