

# **Opportunities and Challenges for an M(X)DR Clinical Development Program**

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# Outline

- What we know about treatment of MDR and XDR and how we learned it
- Potential endpoints for MDR clinical trials
- Controlling for other predictors of these endpoints
- MDR trial designs for licensure
- MDR trial designs to optimize treatment effectiveness

# What we know about treatment of MDR and XDR and how we learned it

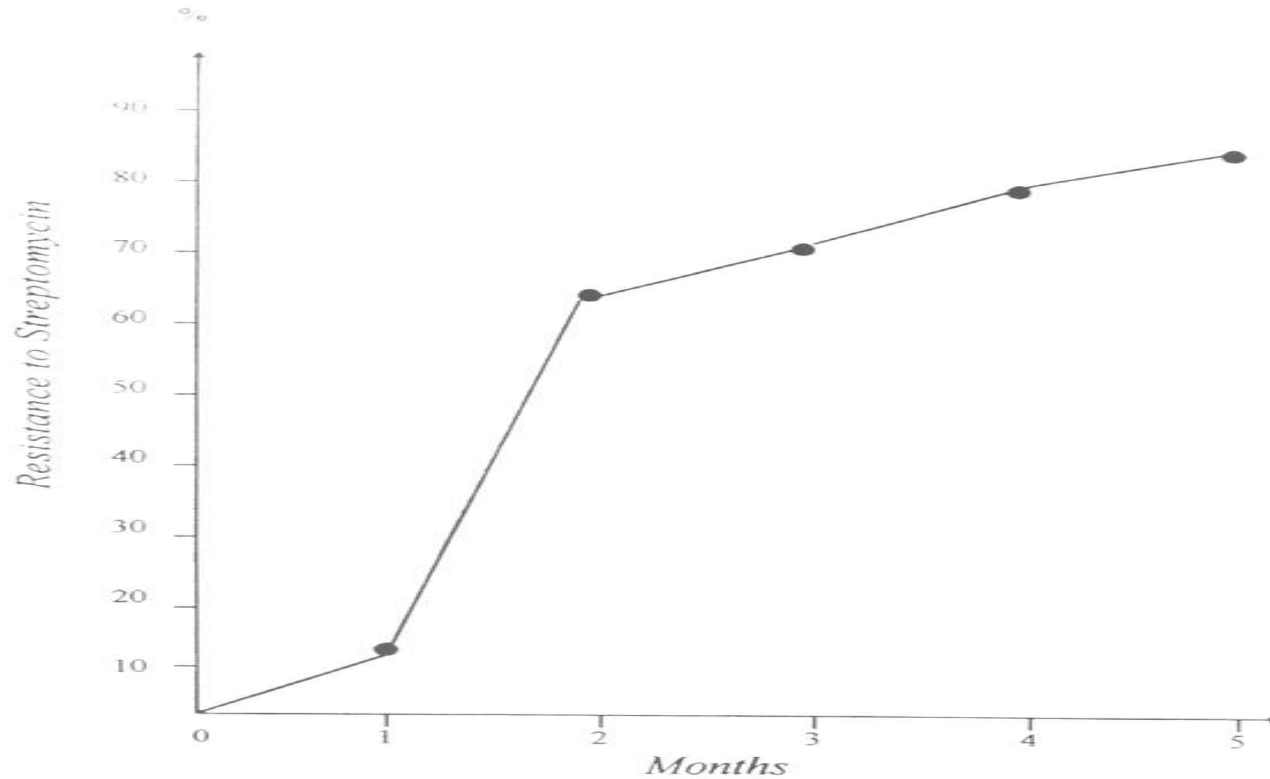


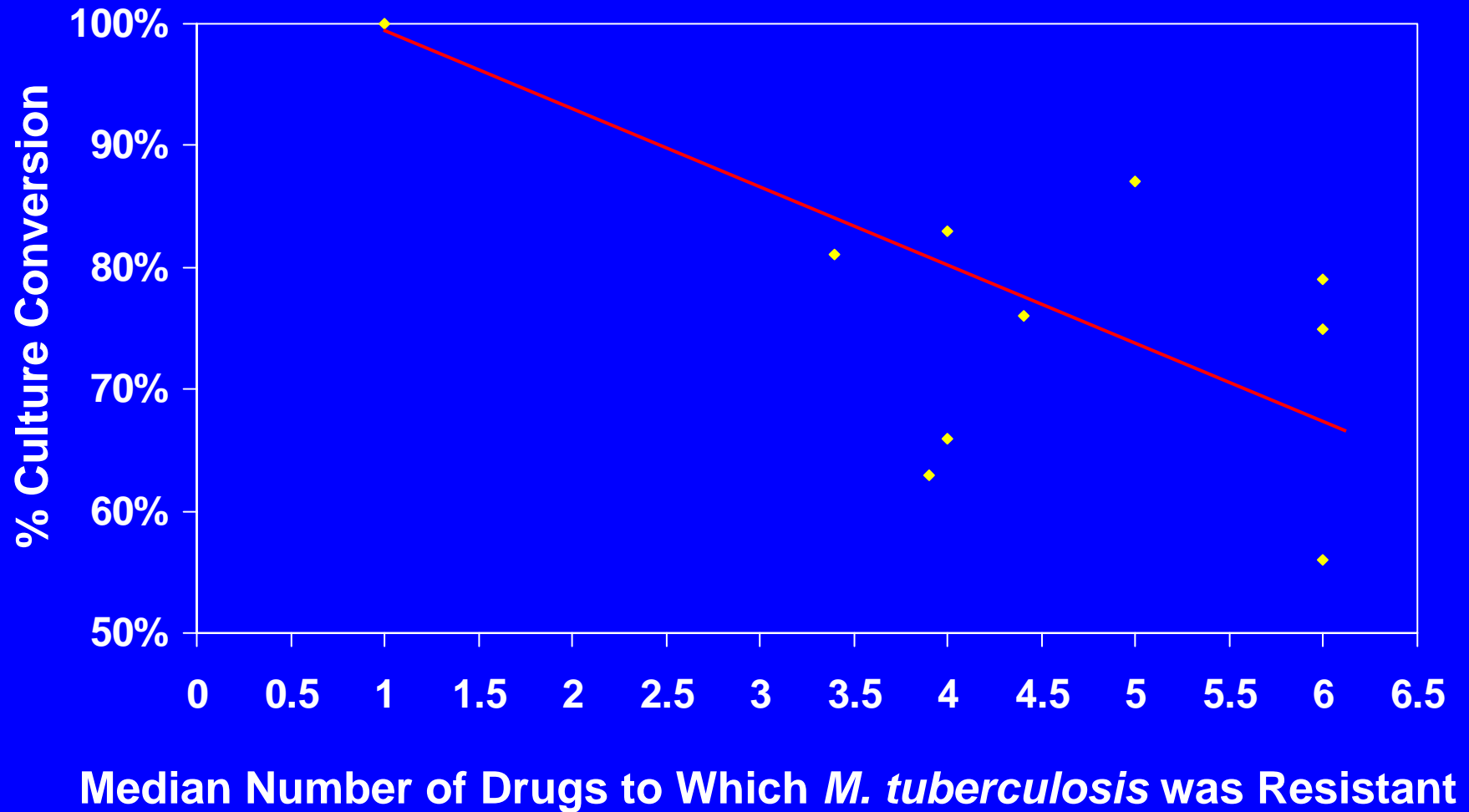
Fig. 1 - Streptomycin investigation 1948. (BMRC).  
Cumulative percentage of resistant strains isolated during treatment from 42 cases.

# Clinical Trials for INH-monoresistant TB before the availability of RIF

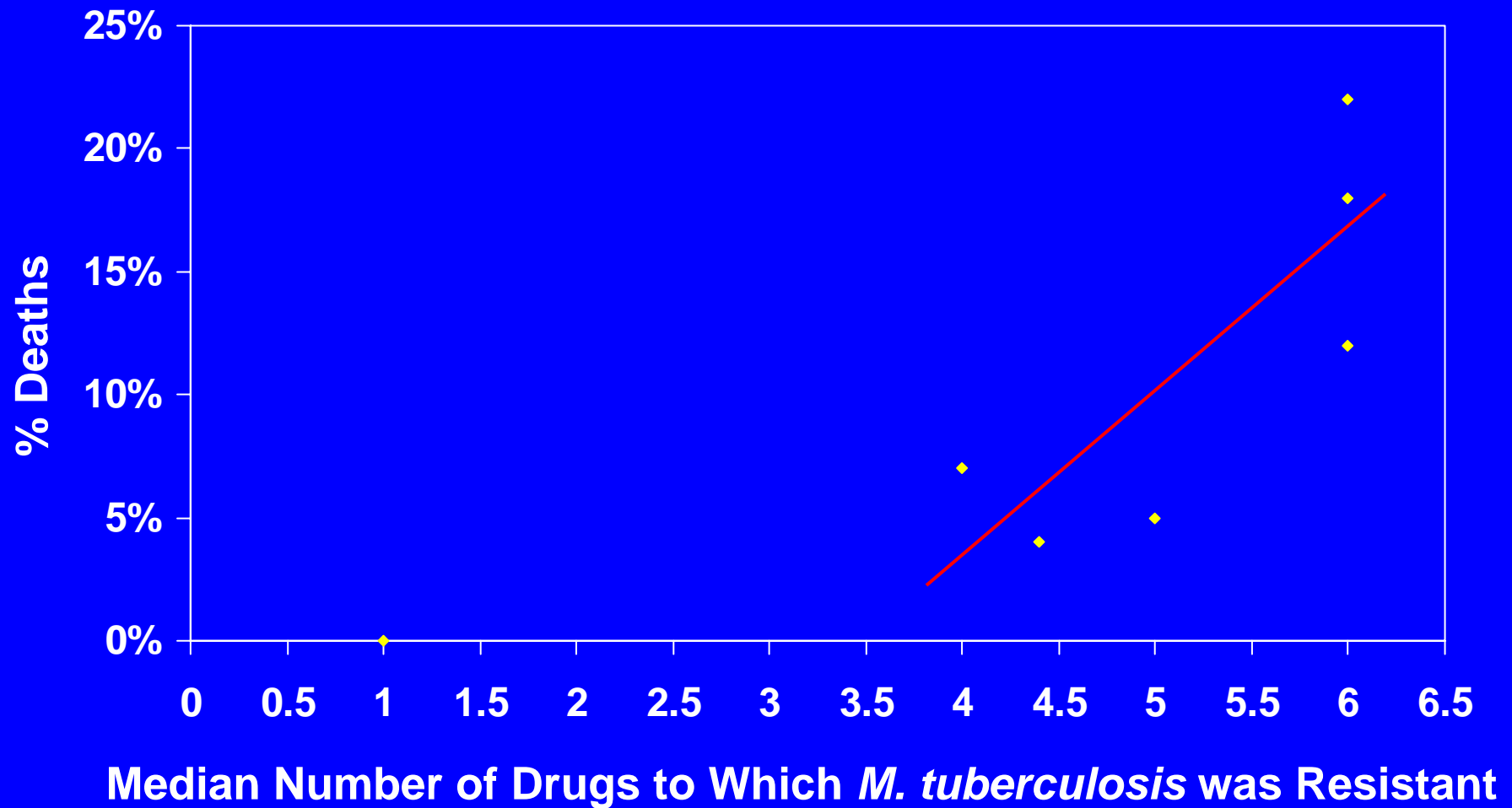
<u>Regimen</u>	<u>Duration</u>	<u>Culture conversion at end of course</u>
SM+PZA	6 months	58%
SM+PZA	12 months	90%
SM+PZA	18 months	94%
SM+PZA+PAS	12 months	94%

Tubercle 50;81, 51;359, 52;191

# Culture Conversion of Patients with DR-TB



# Survival of Patients with DR-TB



# Current Recommendations for Treatment of MDR-TB

<u>Resistance Pattern</u>	<u>Regimen</u>	<u>Duration</u>
HR+3 <sup>rd</sup> drug	4 drugs*	18-24 months
HR+3 <sup>rd</sup> ,4 <sup>th</sup> drugs	5 drugs*	Conversion+24months
HR+3 <sup>rd</sup> ,4 <sup>th</sup> ,5 <sup>th</sup> drugs	5 drugs*	Conversion+24months

\*to which isolate is susceptible

Adapted from NEJM 1993;329:788

# BMRC Streptomycin Trial -1947

	<u>Death (%)</u>	<u>Culture Negative (%)</u>	<u>Radiographic Improvement (%)</u>
<u>3 Months</u>			
SM	0/55 (0)	10/55 (18)	--
No SM	6/52 (12)	1/52 (2)	--
	p=0.01	p<0.01	
<u>6 Months</u>			
SM	4/55 (7)	8/55 (15)	28/55 (51)
No SM	14/52 (27)	2/52 (4)	4/52 (7)
	p=0.007	p=0.05	p<0.0001

# BMRC Isoniazid Trial - 1952

Regimen	Number (%) of negative cultures at 3 months
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INH	37/101 (37)
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SM+PAS	46/83 (55)
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INH+SM	78/117 (67)
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# BMRC – Optimal Duration of TB therapy with INH+PAS

Duration	Relapse rate
6 months	62%
12 months	19%
24+ months	4%

# Evolution of Endpoints Over 50 years of TB Clinical Trials

- Identify effective drugs
  - **endpoints:** death, clinical/radiologic improvement
- Prevent emergence of drug resistance
  - **endpoint:** bacteriologic conversion
- Achieve cure
  - **endpoints:** bacteriologic conversion, relapse
- Shorten duration of therapy
  - **endpoint:** relapse

# Controlling for Other Predictors of Outcome in Clinical Trials

- Restriction/Stratification
- Matching
- Randomization
- Multivariate analysis

# Predictors of outcome in treatment of MDR-TB – retrospective studies

- Age
- Sex
- BMI
- No. Previous Drugs Received
- No. Drugs Resistant
- Previous Treatment
- Extent of Disease
- Quinolone use
- Surgery
- HIV Infection

# Most efficient strategies to control for confounding in MDR Clinical Trials

## Restriction/Stratification

- No. Previous Drugs Received
- No. Drugs Resistant
- Previous Treatment
- Extent of Disease
- HIV infection

## Randomization/Multivariate analysis

- Age
- Sex
- BMI
- Background Regimen
- Surgery

# Randomization to Control for the Effect of Background Regimen in Clinical Trials

## Enfuvirtide trial for drug-resistant HIV

- *Study population:* previously heavily antiretroviral treated patients, HIV not completely suppressed
- *Design:* Randomize to best available antiretroviral regimen, plus/minus new drug
- *Outcome:* HIV titer in serum

NEJM 348;22:2175-95

# Enfuvirtide - Efficacy at Week 24

Variable	Enfuvirtide Group	Control Group	Difference between groups or Odds Ratio (95% CI)	P Value
Mean change from baseline*	-1.696	-0.764	0.933 (0.594-1.271)	<0.001
<50 copies (%)	19.6	7.3	3.30 (1.70-6.39)	<0.001
<400 copies (%)	31.7	16.4	3.17 (1.96-5.13)	<0.001
Percent >1 log reduction	51.8	29.1	2.64 (1.77-3.95)	<0.001
Mean increase in CD4+ cell count	76.2	32.1	44.1 (22.5-65.8)	<0.001

\*plasma HIV-1 RNA level, log<sub>10</sub> copies/ml.

NEJM 2003;348:2181

# Trial Designs for Licensure of New Antituberculous Agents

## Goals:

- Demonstrate clinical effectiveness
- Demonstrate acceptable toxicity
- Minimize time and resources

# Proposal 1: Trial to Decrease Death Rate in XDR-TB

- Study population: previously treated patients
- Design: Randomize to best available regimen, plus new drug or placebo, stratify by HIV status
- Outcome: death/clinical deterioration
- Advantages: Small sample size, brief follow-up
- Disadvantages: can only be done until a new drug is shown to be effective; subsequent trials must include new drug

# Proposal 2: Trial to Increase Culture Conversion in MDR-TB

- Study population: previously treated patients, smear positive
- Design: Stratify by cavitory status, randomize to best available regimen, plus new drug or placebo
- Outcome: Bacteriologic conversion
- Advantages: Could examine conversion at two months, allowing rapid assessment
- Disadvantages: Will licensing agencies accept this surrogate endpoint?

# Trial Designs to Optimize MDR-TB Treatment Efficacy

## Goals:

- Achieve high rate of cure
- Minimize duration of therapy
- Minimize toxicity
- Develop intermittent regimens
- Determine if HIV-infected patients require different regimen/duration

# Conclusions

- A systematic series of clinical trials over 50 years defined (and continues to define) optimal treatment for drug susceptible TB
- Trial endpoints evolved as regimens improved
- The goals of MDR-TB clinical trials will evolve over time: reduce deaths; improve culture conversion rates; improve cure rates; decrease relapse rates; shorten regimens

# Conclusions

- As one goal is achieved, the next will need to be addressed until we have optimally shortened regimens that achieve less than 5% failures/relapses
- As additional new drugs become available for treatment of MDR-TB, this process will need to be refined to determine the simplest and most effective regimens