



# 12<sup>th</sup> Annual Conference IUATLD-NAR

- Dr. Jacques Grosset has no financial relationship with companies who have provided support to this meeting that suggests a personal conflict of interest in relations to the planning for the above captioned CME Event.

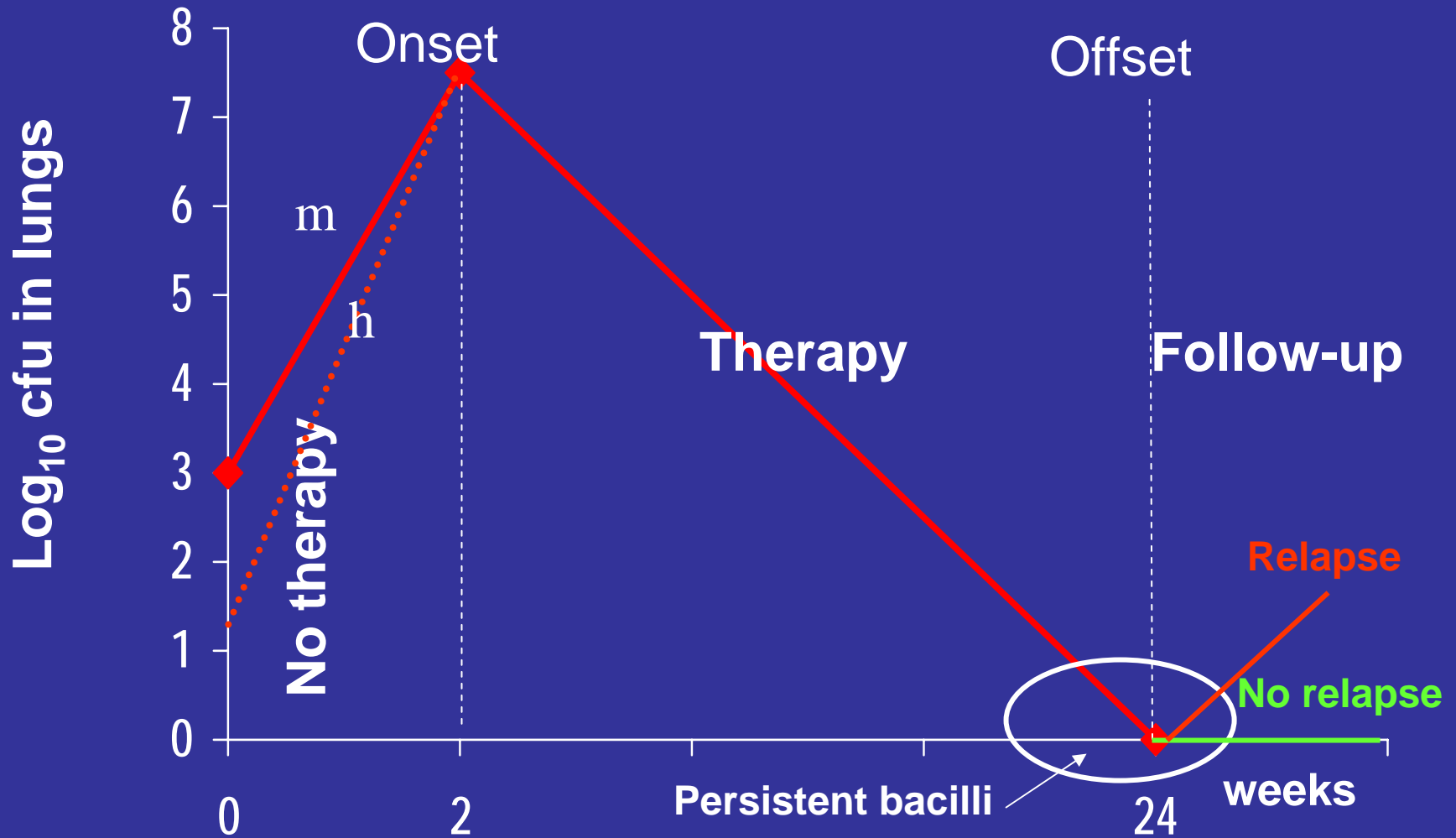
*“Mining the Mouse: Latest  
Insights into TB Chemotherapy.”*

Jacques H. Grosset  
Johns Hopkins University

# Why do we need new drugs?

We need new anti-TB drugs

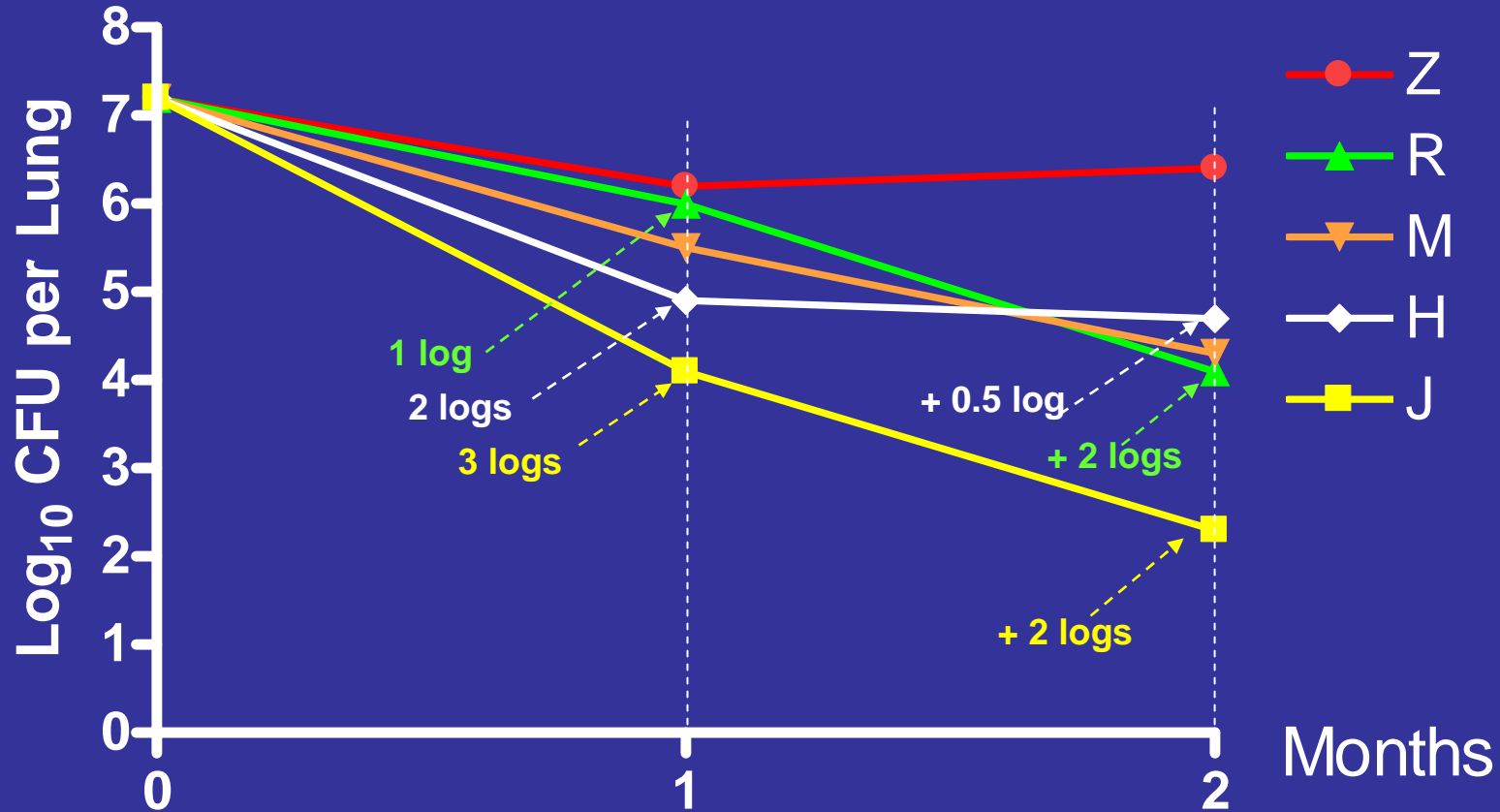
- to shorten the current 6-month duration of treatment
- to treat MDR and XDR TB patients



TB chemotherapy in aerosol-infected mice (m) and in humans (h)

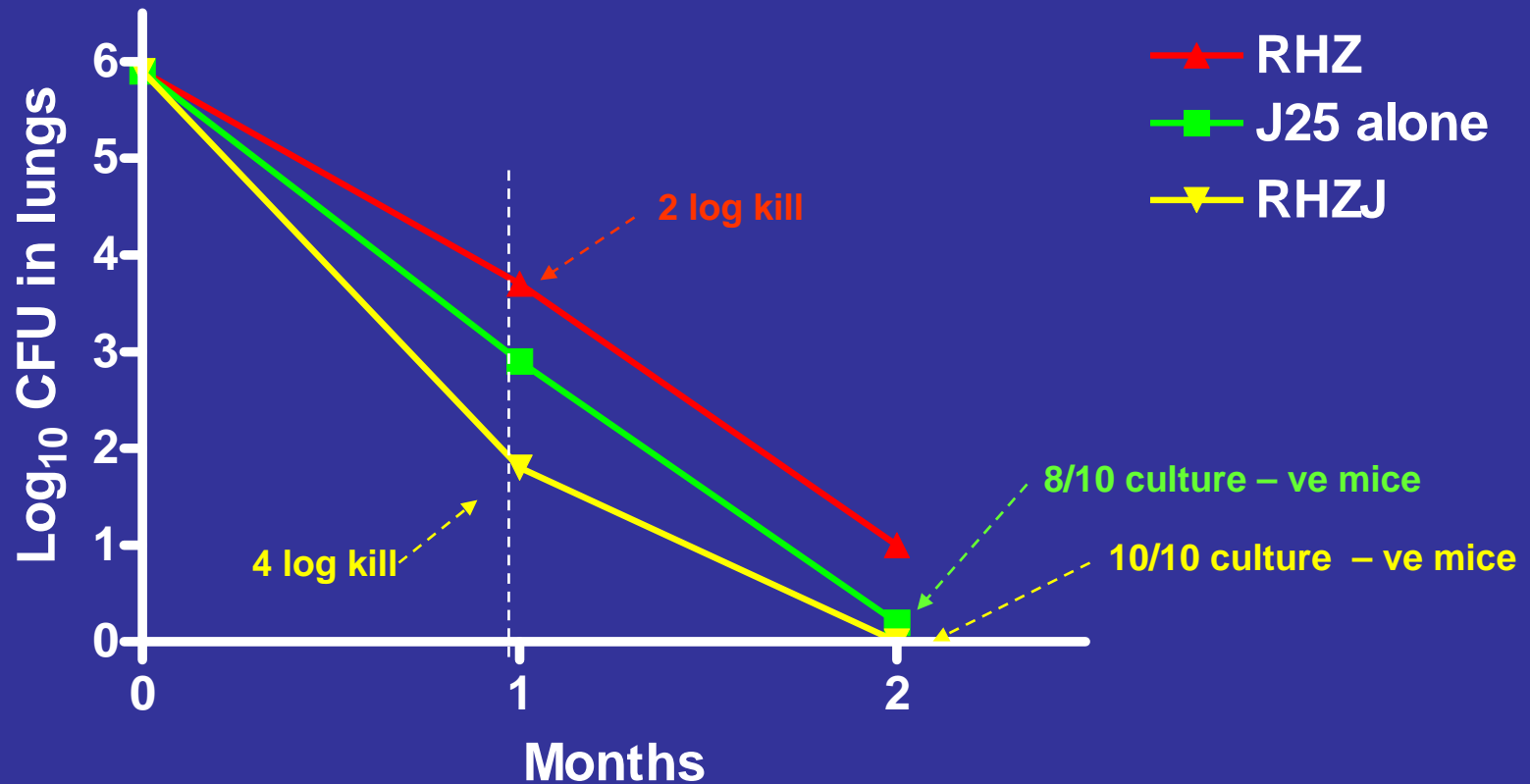
# New drugs in development

- **The diarylquinoline TMC-207 (J)**
- **The nitroimidazole derivatives: PA-824, OPC-67683**
- **Others?**



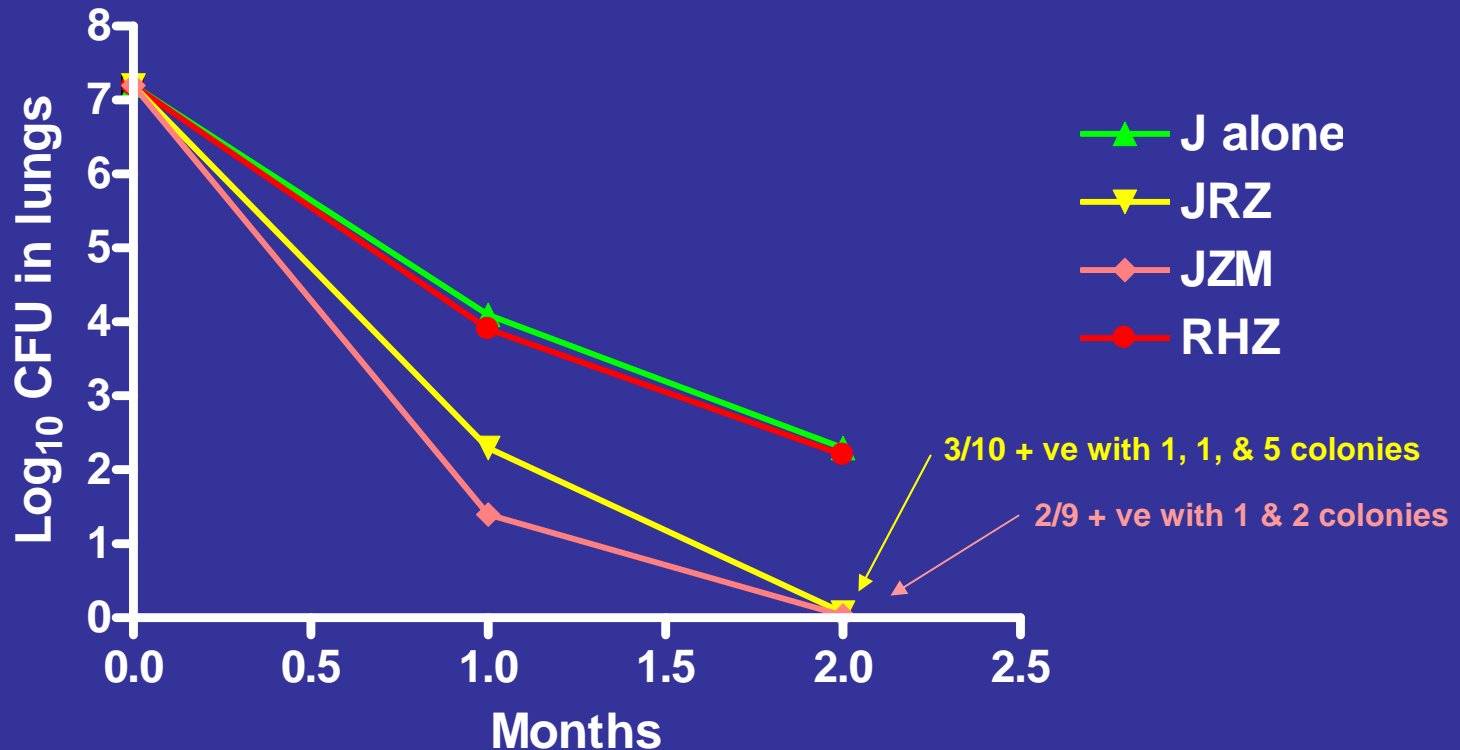
Comparative bactericidal activity of TMC-207 ( $J_{25\text{mg/kg}}$ ), rifampin ( $R_{10}$ ), isoniazid ( $H_{25}$ ), moxifloxacin ( $M_{100}$ ), and pyrazinamide ( $Z_{150}$ ) in the mouse model of TB  
 (From Ibrahim et al., AAC 2007:51:1011-1015)

## Bactericidal activity of "J" alone or in combination with RHZ



From Lounis et al., AAC 2006; 50:3543-47

## Bactericidal activity of J combinations in the mouse model of TB

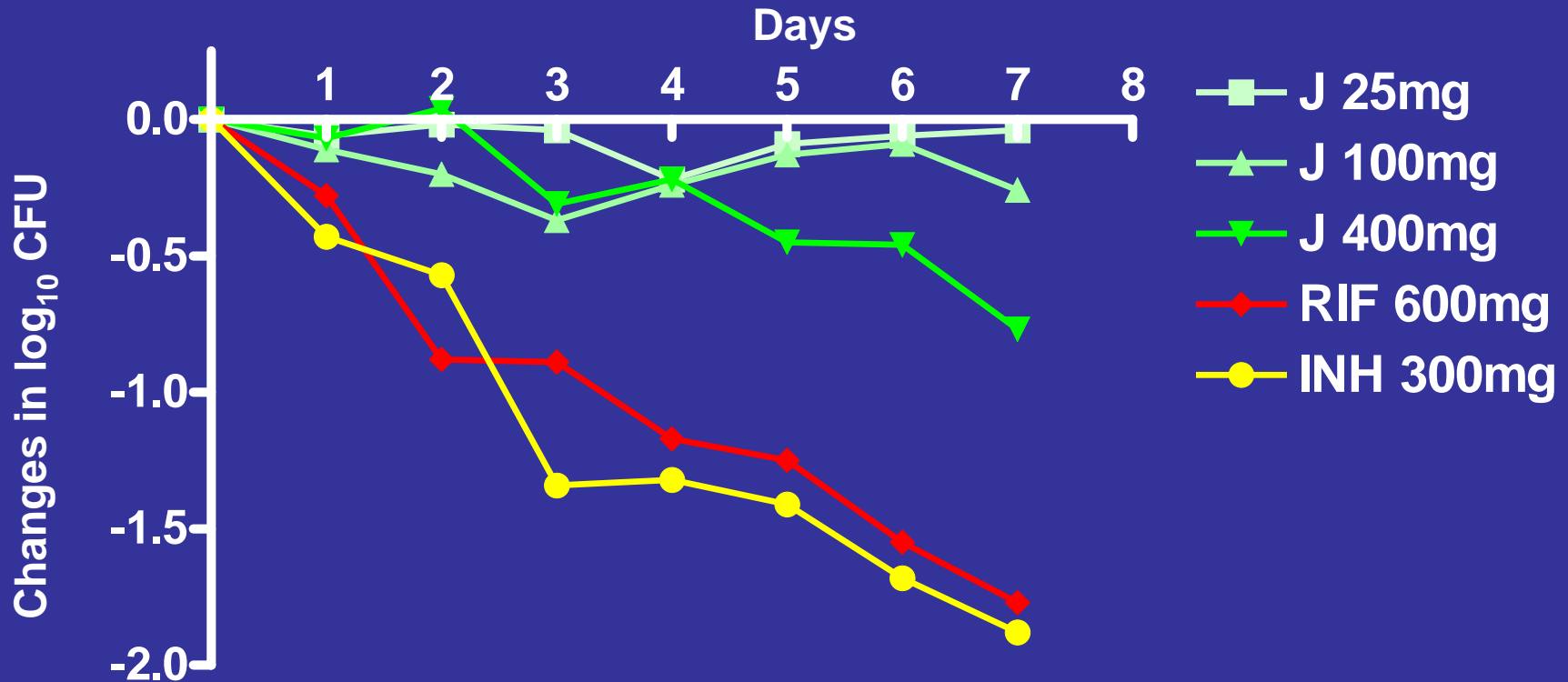


J, diarylquinoline 25mg/kg; R, rifampin 10mg/kg; Z, pyrazinamide 150mg/kg;  
H, isoniazid 25mg/kg

Daily (5/7) oral treatment; 10 mice per time point

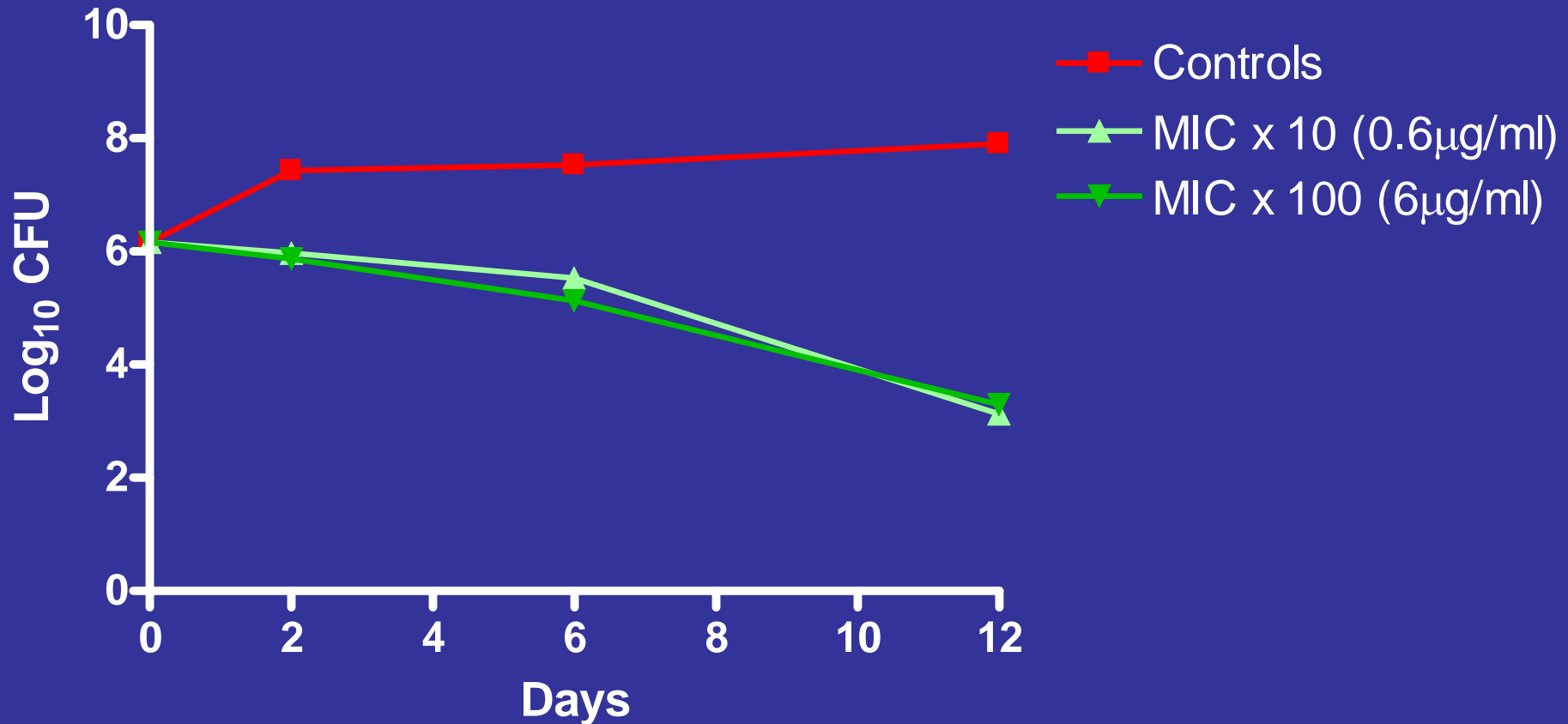
(From Ibrahim et al., AAC 2007; 51:1011-1015)

# Early Bactericidal Activity of Diarylquinoline



(From TB Alliance, Open Forum, London, Dec 12-13, 2006)

# In vitro bactericidal activity of Diarylquinoline (“J”)



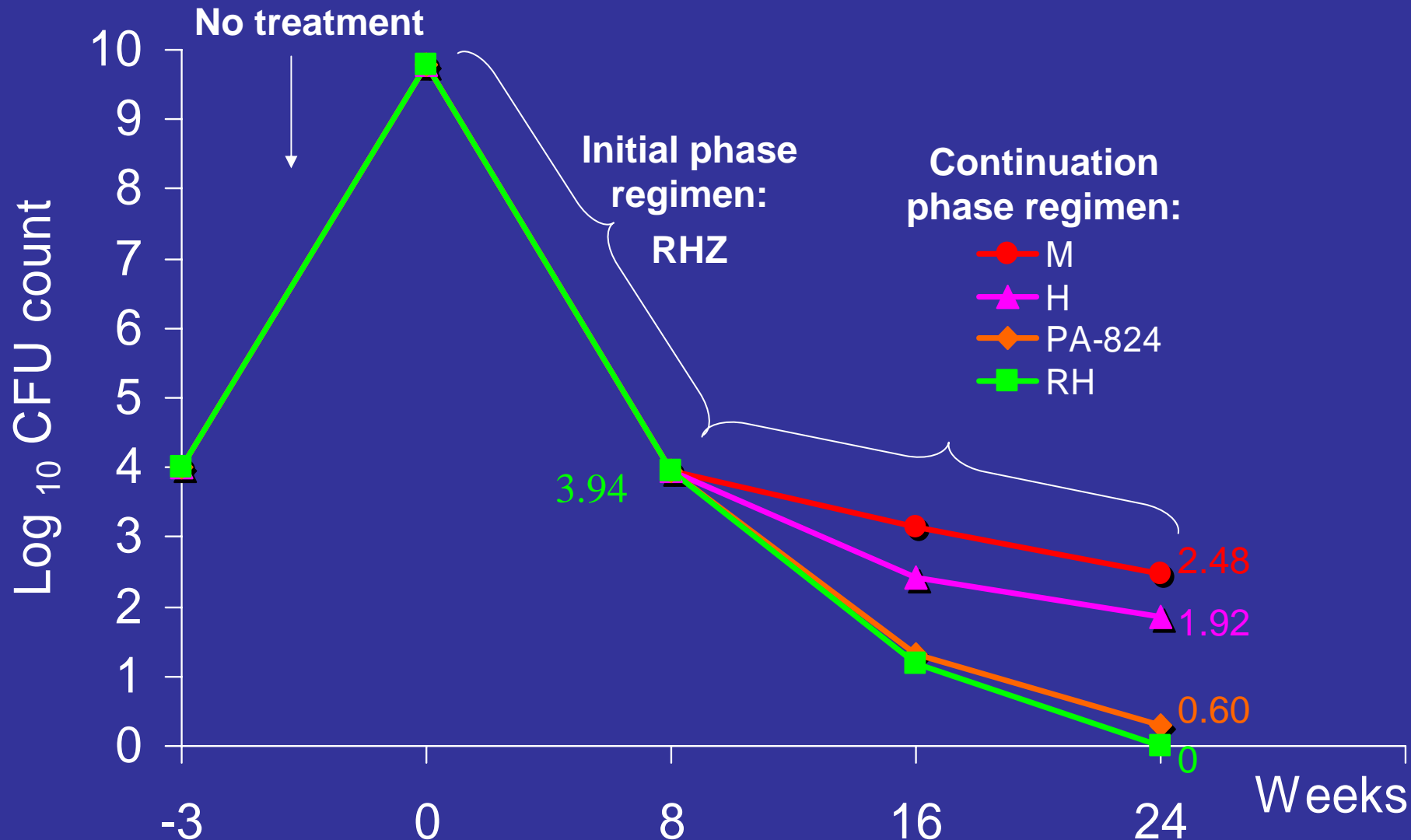
(From Andries et al., Science 2005;307: 223-227)

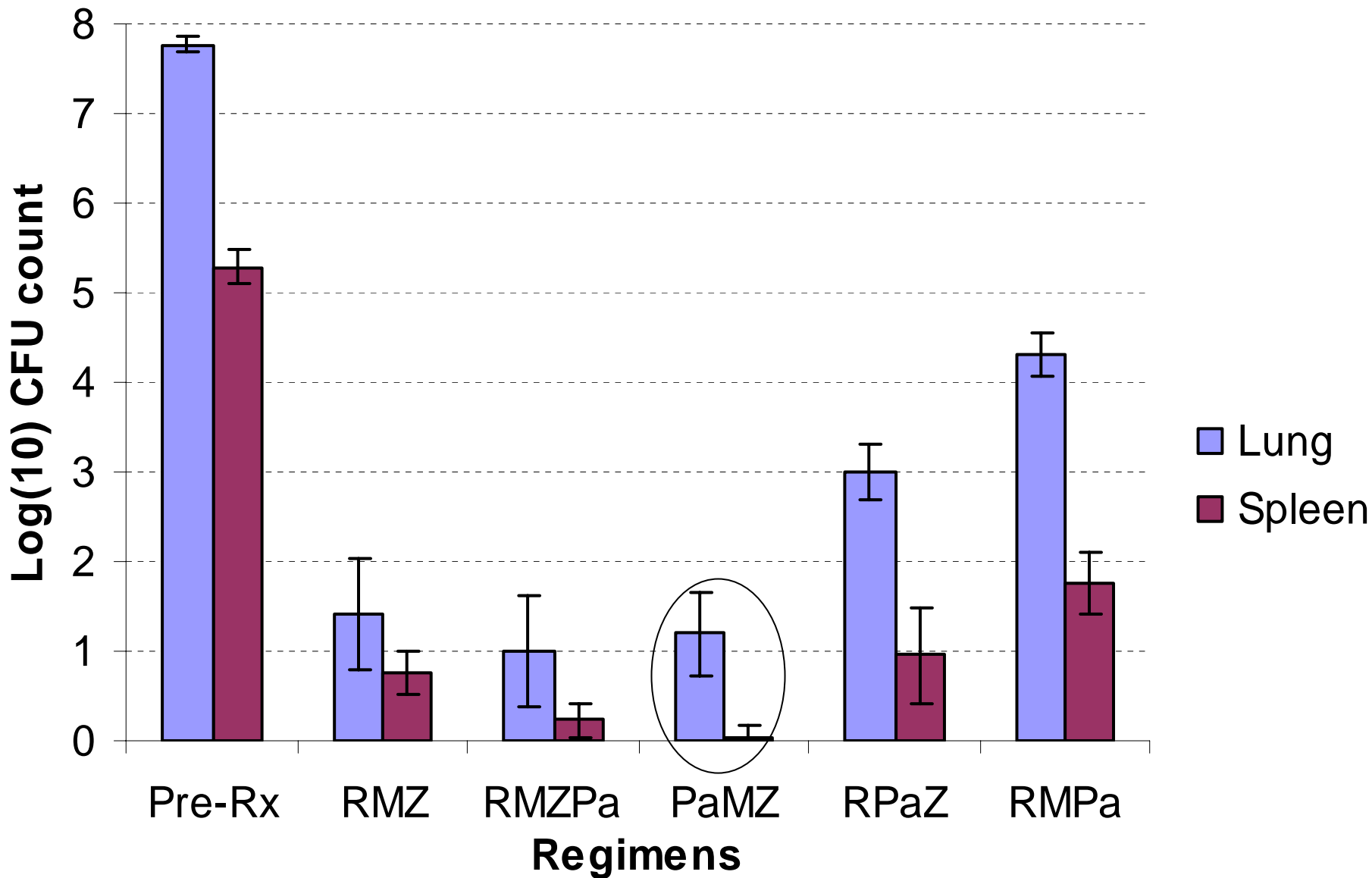
# Current conclusions about the “J” compound

- J is very active in the test tube
- J is very active in the mouse model
- J has time-dependent activity, thus demonstrates its full potency in the test tube and in humans (EBA) only after days of exposure
- J is still a promising anti-tuberculosis drug and is currently in Phase II testing for MDR-TB

# The nitroimidazole derivatives

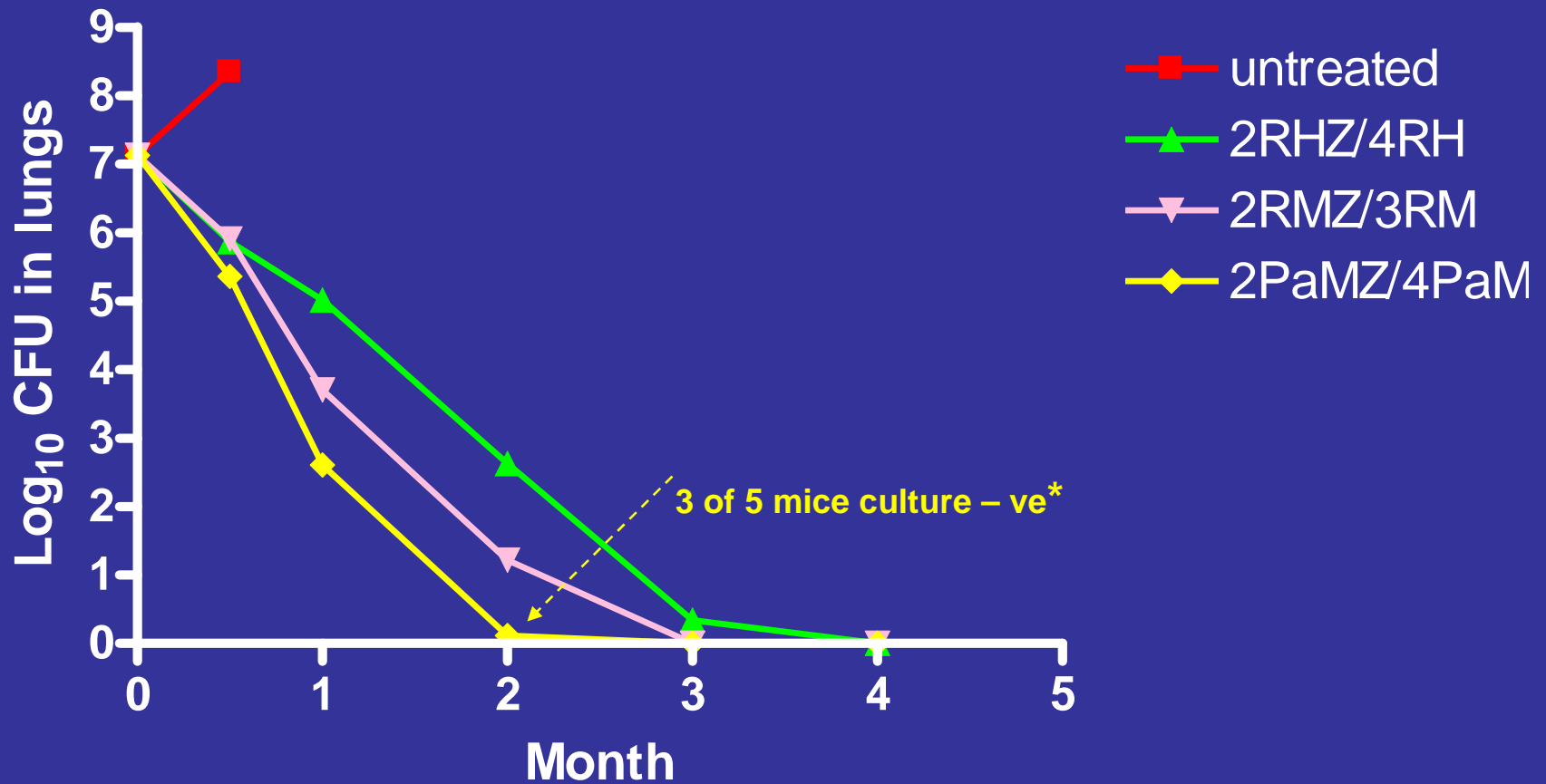
# CFU counts in the lungs of mice treated with PA-824 in the continuation phase





**CFU counts after 2 months of treatment**

## Lung CFU counts in mice treated with Pa without RIF and INH



\* Very similar to the results obtained with JMZ!

# Relapse rate after stopping treatment with Pa + MXF + PZA

Drug Regimen	Relapse rate 3 months after stopping treatment at		
	4th mo.	5th mo.	6th mo.
2RHZ/4RH	10/20	0/20	0/20
2RMZ/3RM	1/20	0/20	ND
2PaMZ/4PaM	0/20*	0/20	0/20

\*p<0.01 versus 2RHZ/4RH

# Current conclusions for PA-824

- PA-824 at 100mg/kg is highly active against persisters in the mouse model of TB
- In combination with moxifloxacin and pyrazinamide, it offers a regimen more active than 2RHZ/4RH but without R and H
- PA-824 is currently in Phase II testing
- **Caveat:** will human doses provide similar activity as the 100mg/kg murine doses?

# The nitro-imidazo-oxazole OPC-67683

Data from Matsumoto et al., (PLoS Med 2006) indicate that:

- MIC: 0.012  $\mu\text{g/ml}$  ( $\sim 20$  times lower than Pa) and  $C_{\text{max}}$  of 0.3  $\mu\text{g/ml}$  and  $t_{1/2}$  of 5.9h in mice treated with 3 mg/kg
- At a daily dose of 2.5 mg/kg, OPC is as active as PA-824 at 40-100mg/kg

**Conclusion:** OPC-67683 may be more potent in humans than PA-824 and is in Phase II testing for MDR-TB

# Other new drugs ?

- The truth is that several new drugs are in early state of development
- But solid data are currently available for none of them

# The drug development process

The estimated likelihood of introducing a successful anti-TB drug by 2010 is <5%; for 2 successful anti-TB drugs, the likelihood is <1%

Thus, despite the great optimism over the new drug candidates, it is unlikely a truly novel regimen will enter Phase II/III in the near future

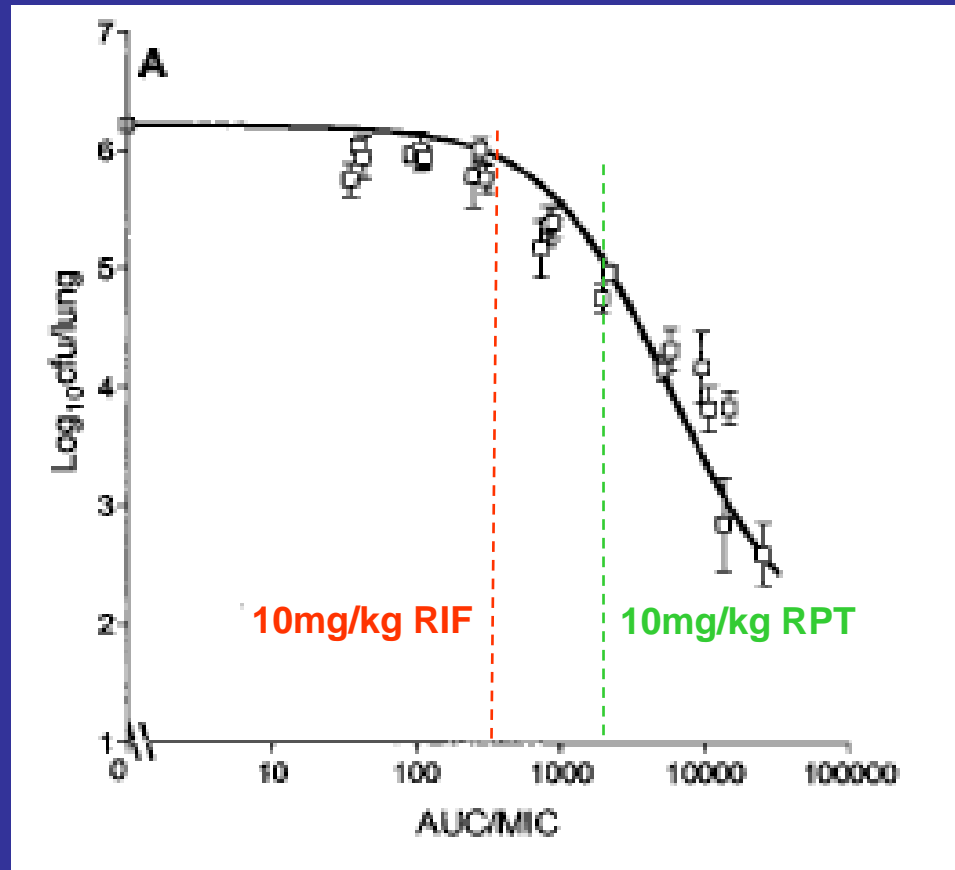
Therefore, it is essential that existing drugs be used in ways that maximize their potential contribution

# How to maximize the potential contribution of existing drugs?

Among all existing drugs, only rifamycins (rifampin, rifapentine) offer potential for improved activity because of their characteristics:

<b>Drug</b>	<b>Half life (h)</b>	<b>MIC<sub>90</sub> (µg/ml)</b>	<b>C<sub>max</sub>/MIC<sub>90</sub></b>	<b>AUC<sub>24</sub>/MIC<sub>90</sub></b>
<b>Rifampicin (10mg/kg)</b>	<b>2.46</b>	<b>0.25</b>	<b>58.44</b>	<b>471</b>
<b>Rifapentine (10 mg/kg)</b>	<b>15.9</b>	<b>0.12</b>	<b>98</b>	<b>2658</b>

# Relation between AUC/MIC of rifamycins and $\log_{10}$ CFU per lung when the total dose was given as one, three or six equally divided doses over 144h (6days)

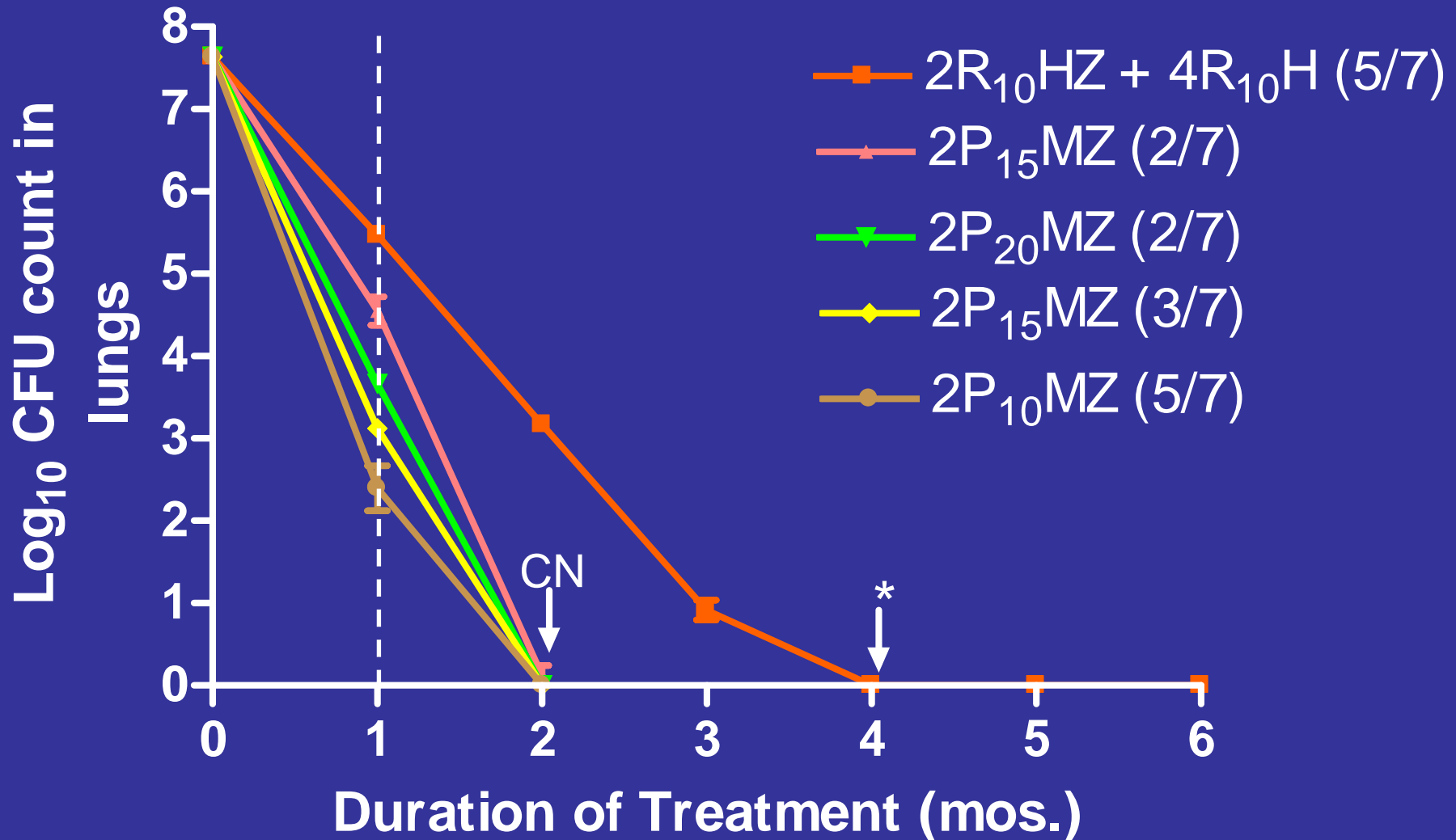


Will increased rifamycin exposure permit a decrease in treatment duration?

Options for increasing rifamycin exposure

- increase the dose of rifapentine (P)
- increase frequency of rifapentine (P) administration

# Time to Culture Negativity



CN: Culture negative, \*: 1/5 mice culture positive with 1 CFU/Lung

# Conclusions

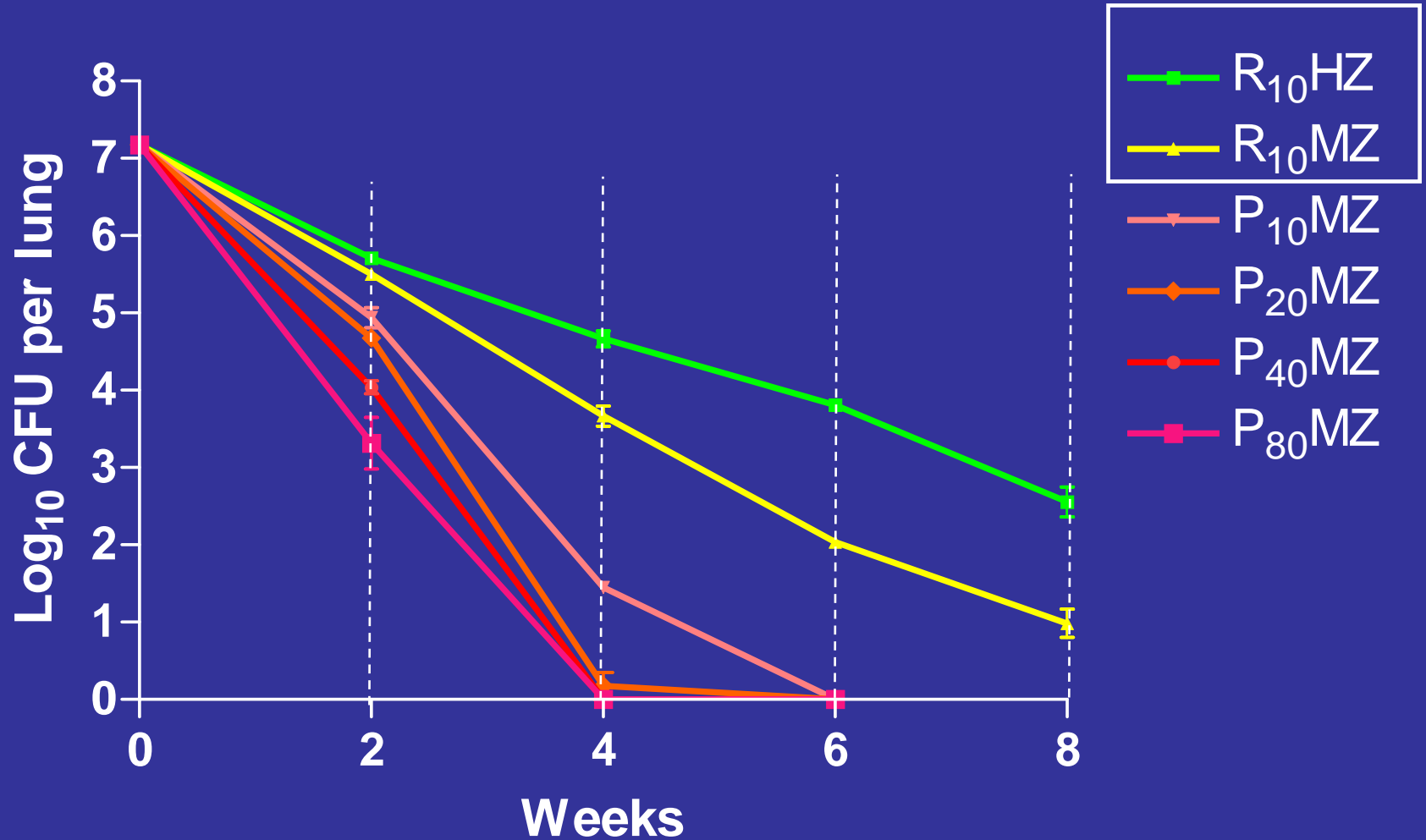
1. Regimens based on the PMZ combination are dramatically more potent than the standard 6-month RHZ regimen
2. Activity correlates with the extent of rifapentine exposure
3. Just 3 months of treatment with daily  $P_{10}$ MZ or thrice-weekly  $P_{15}$ MZ resulted in stable cure of all mice

Is it conceivable to cure TB  
in weeks rather than in months?

**A proof of principle**

# Bactericidal Activity for P + M<sub>100</sub>Z<sub>150</sub>

Controls

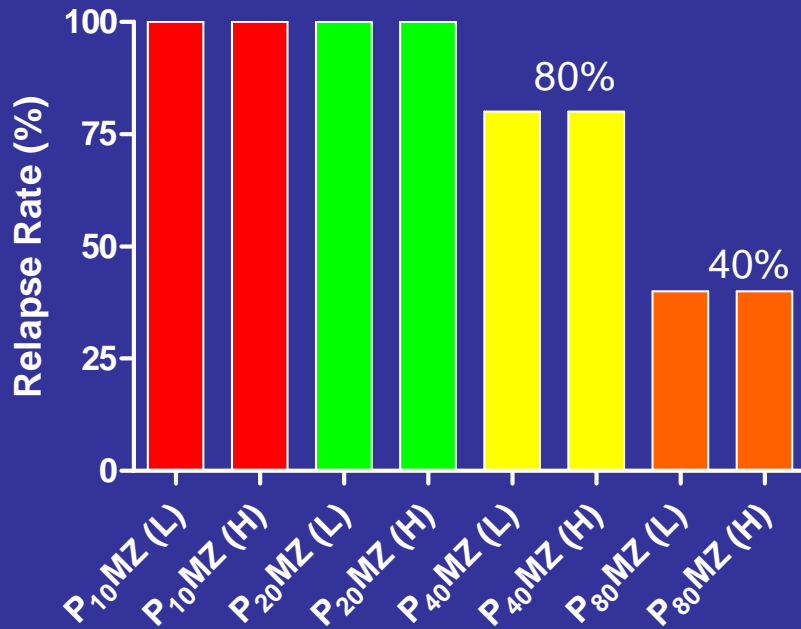


n = 5

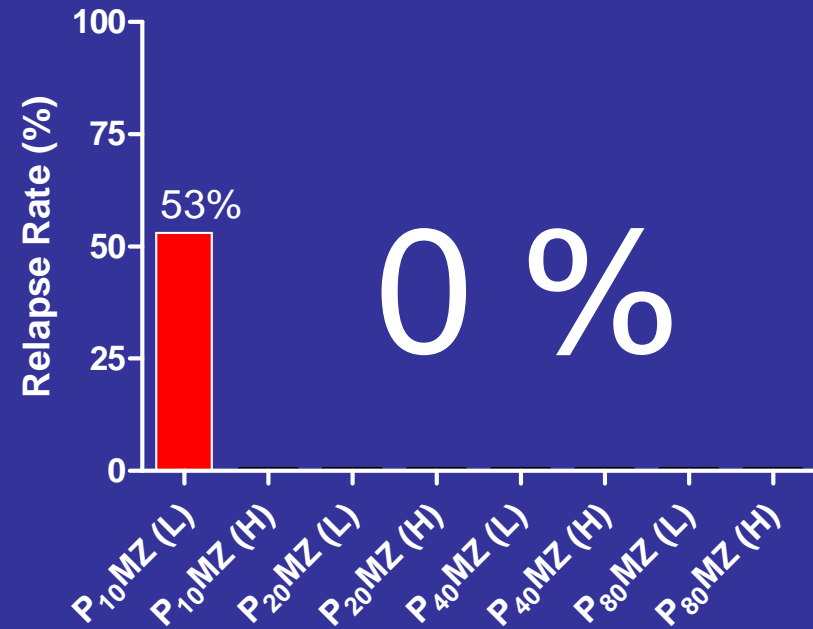
H; isoniazid, Z; pyrazinamide, M; moxifloxacin, R; rifampin, P; rifapentine

# Relapse Rates after 4 and 8 weeks treatment

4 weeks



8 weeks



L; Low dose (M<sub>100</sub>Z<sub>150</sub>), H; High Dose (M<sub>400</sub>Z<sub>600</sub>)

n = 15

# Overall conclusions

- With rational use of available drugs (rifapentine, moxifloxacin, and pyrazinamide) at reasonable doses, the treatment of TB can likely be shortened without reducing efficacy
- *M. tuberculosis* does not present an insurmountable biological barrier to antimicrobial therapy
- TB may be cured in weeks rather than months if adequate antimicrobial agents are developed!

# Support and Acknowledgments

- NIH-NIAID (Contract # N01-AI-4007)
- Global Alliance against Tuberculosis (GATB)
- JHU-UFRJ Study Team:

Eric Nuermberger

Ian Rosenthal

Ming Zhang

Kathy Williams

Sandeep Tyagi

Deepak Almeida

Tianyu Zhang

Rokeya Tasneen