

Ultra-potent Regimens with Rifapentine Yield Stable Cure by 3-months in a Murine Model of TB

Ian Rosenthal

Center for Tuberculosis Research
Johns Hopkins University

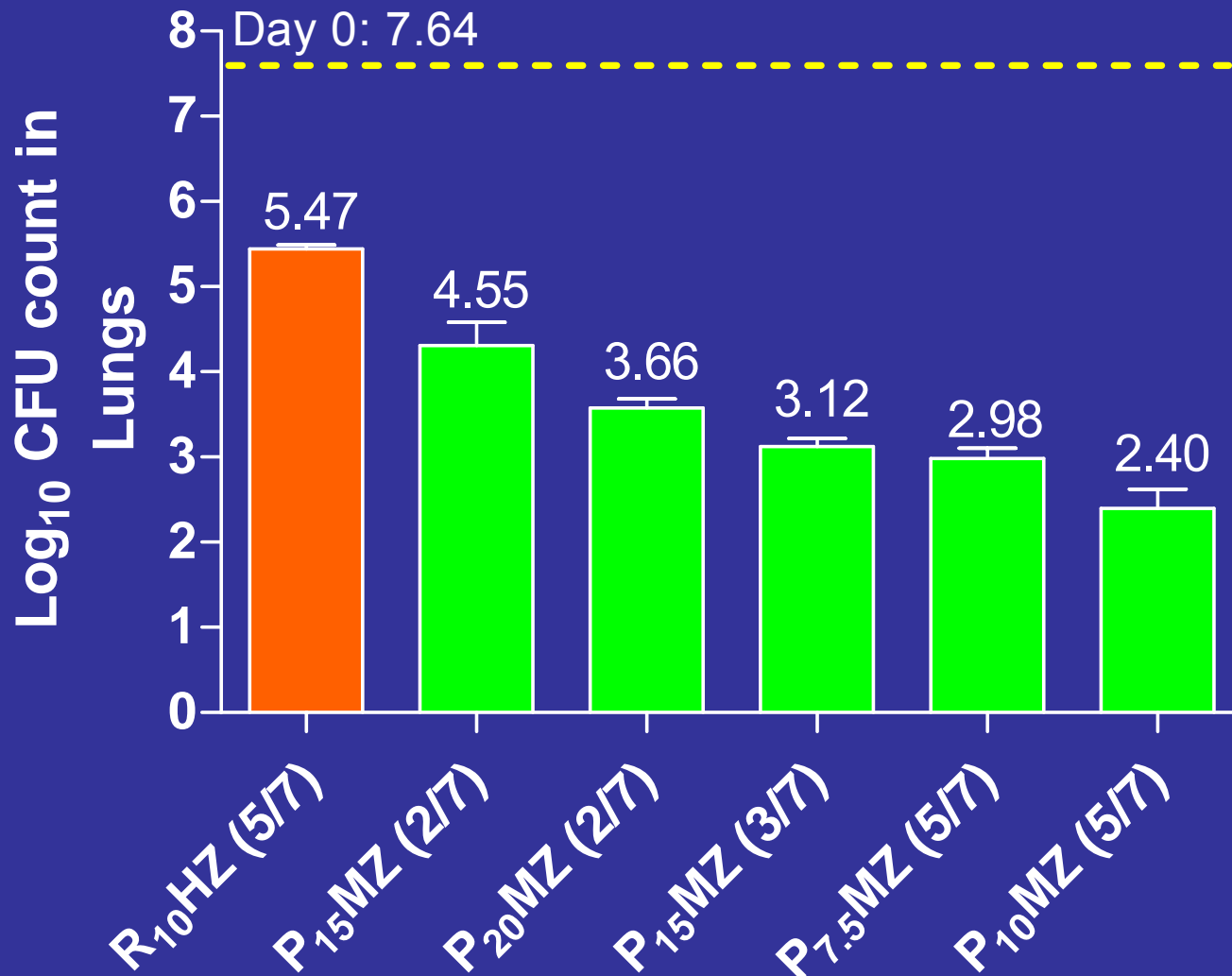
Rationale

- A new “ultra-short-course” regimen capable of curing TB in ≤ 3 months should significantly improve control efforts
- Because the prospects of new drugs in development remain uncertain, we must examine whether existing drugs could be used better

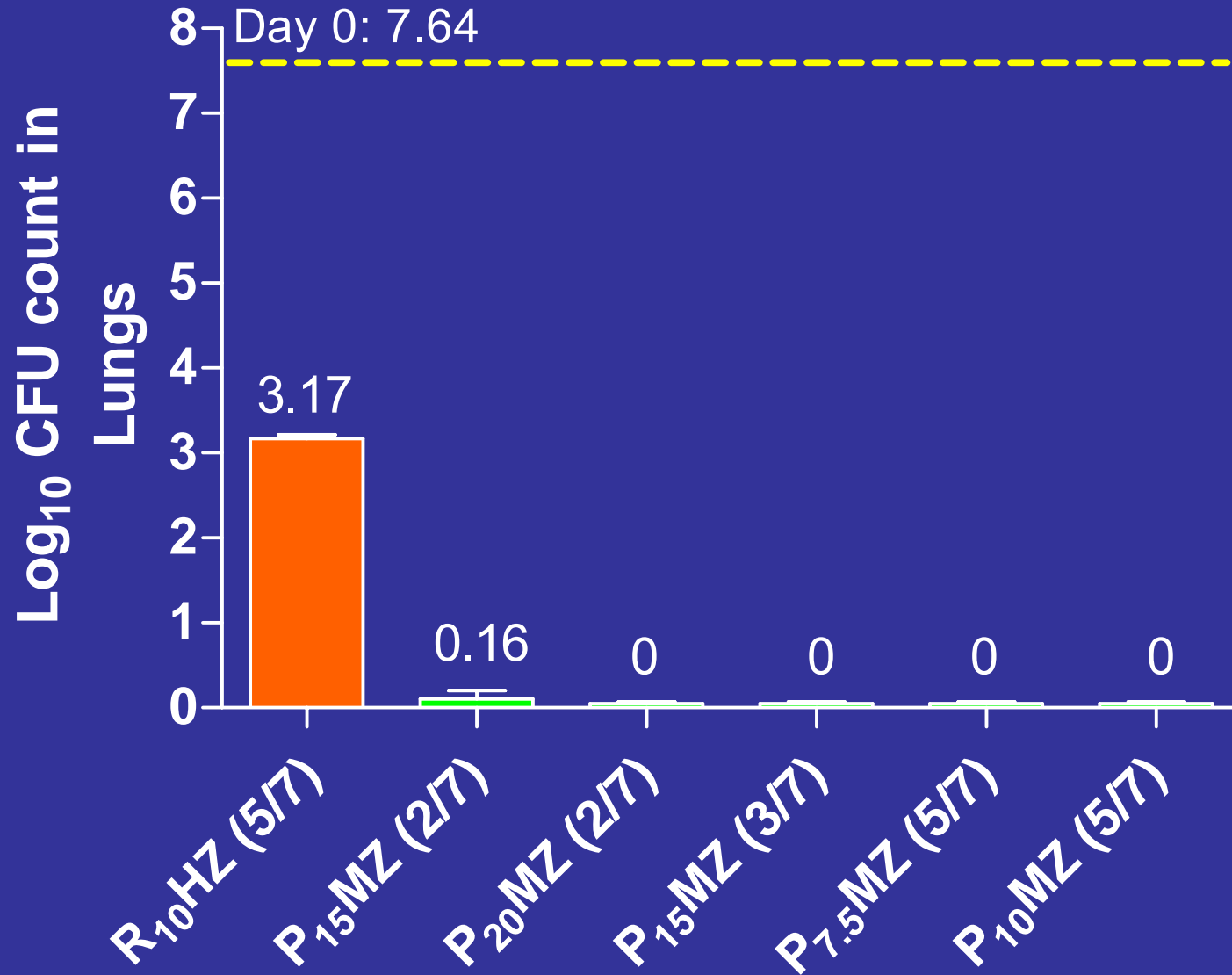
Background

- Rifampin (R) is the most important sterilizing drug in the modern short-course regimen
- Rifapentine (P) has a superior PK/PD profile but was developed solely for use in once-weekly continuation phase regimens
- P may be safely administered more frequently and at higher doses than 600 mg once a week
- We explored whether the increased rifamycin exposure resulting from substituting P for R in more frequently dosed regimens would result in improved sterilizing activity

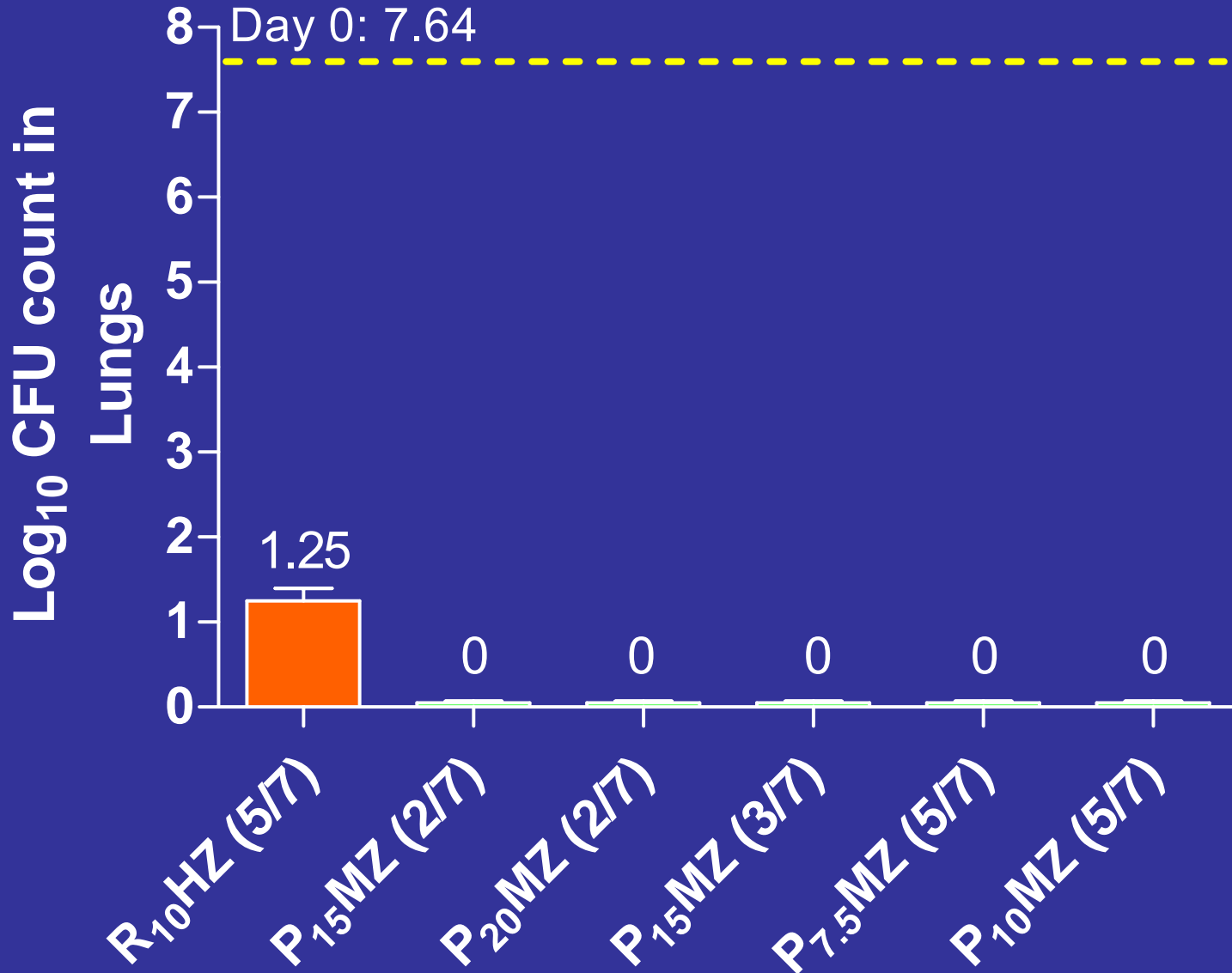
Lung CFU counts after 1 Month of Treatment



Lung CFU counts after 2 Months of Treatment



Lung CFU counts after 3 Months of Treatment



Relapse Rates after Treatment

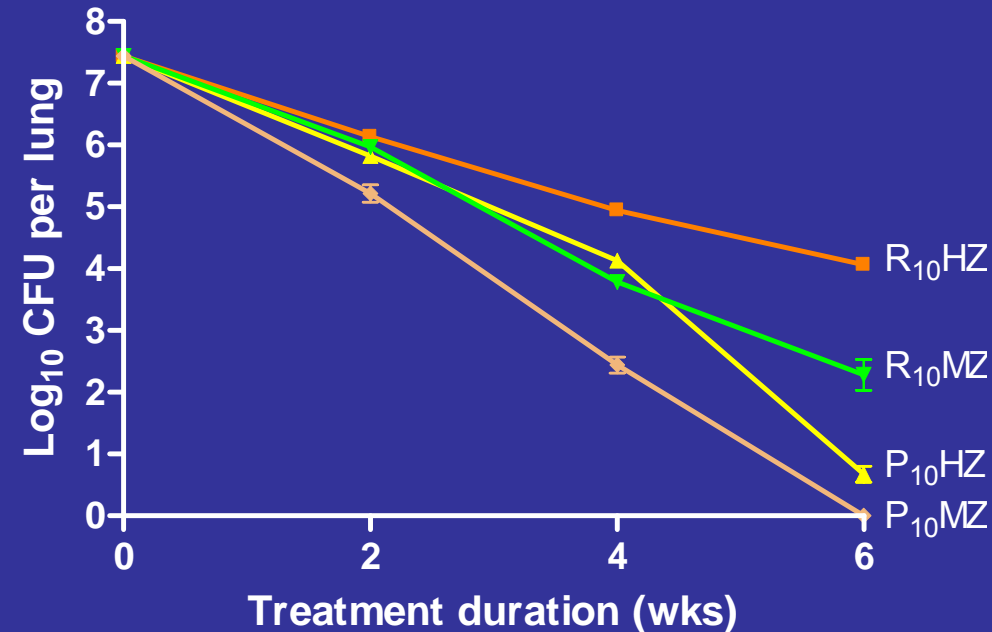
Regimen	After 2-mo.	After 3-mo.	After 4-mo.	After 6-mo.
RHZ (5/7)	C+	C+	90%	0%
P ₁₅ MZ (2/7)	—	10%	0%	—
P ₂₀ MZ (2/7)	95%	20%	—	—
P ₁₅ MZ (3/7)	95%	0%	—	—
P _{7.5} MZ (5/7)	60%	5%	—	—
P ₁₀ MZ (5/7)	35%	0%	—	—

(C+) All mice tested at treatment completion were culture positive

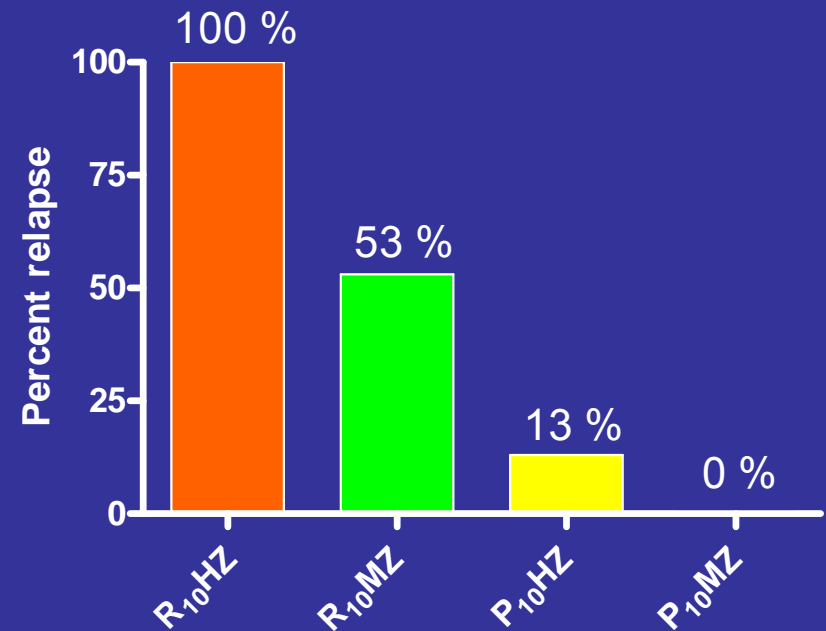
n = 20

Individual Contributions of Rifapentine and Moxifloxacin

Bactericidal Activity

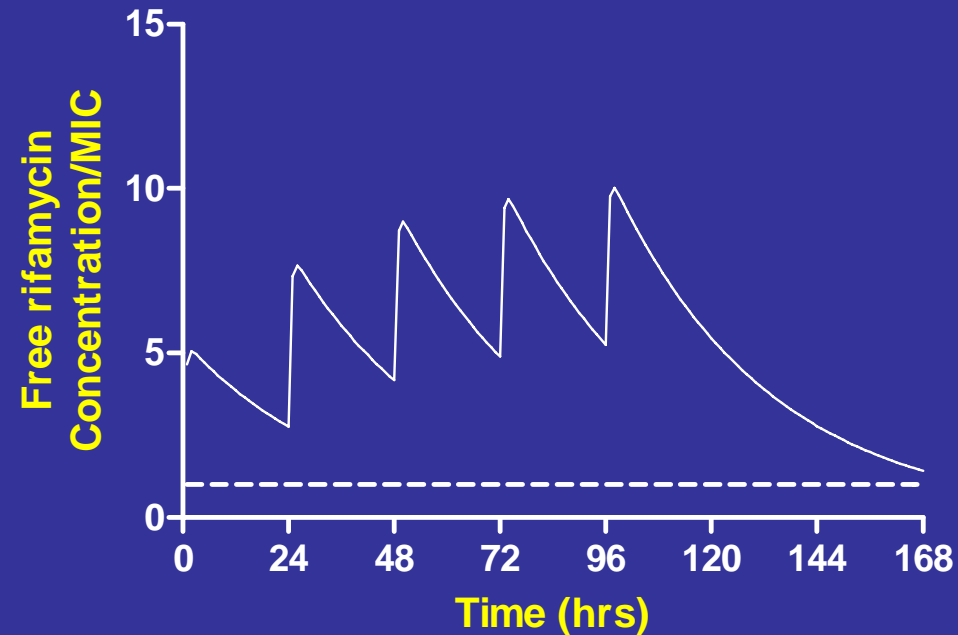


Relapse rates after 10 wks Tx

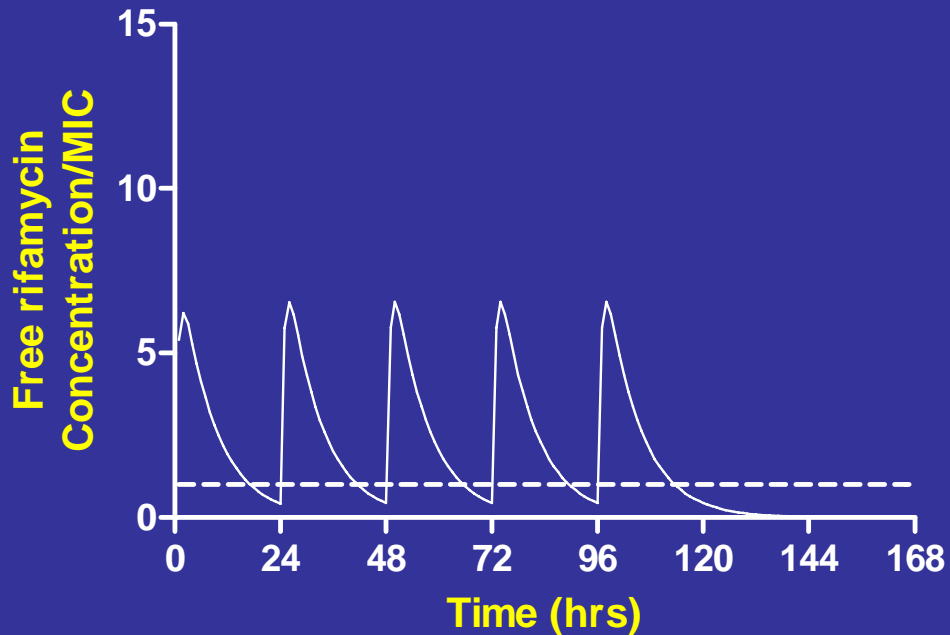


Pharmacodynamics of daily rifapentine and rifampin in mice

Rifapentine (10mg/kg)



Rifampin (10mg/kg)



Rifapentine provides greater rifamycin exposure than does rifampin at the same given dose

Conclusions

- P-based regimens are much more potent than the standard 6-month RHZ regimen
 - Daily P₁₀MZ cured 65% of mice in 8 wks & all mice in 10 wks
 - Daily P₁₀HZ cured 87% of mice in 10 wks
 - P₁₅MZ (3/7) cured 5% of mice in 8 wks & all mice in 12 wks
- The superiority of the P-based regimens comes from the increased rifamycin exposure
- P should no longer be viewed solely as a rifamycin for once-weekly administration

Support and Acknowledgements

NIH-NIAID (Contract # N01-AI-4007)

Ming Zhang

Kathy Williams

Sandeep Tyagi

Chuck Peloquin

William Bishai

Dick Chaisson

Eric Nuermberger

Jacques Grosset