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TB persistence is futile, time to end them all

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Inter TB 17th November 2017

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TB treatment

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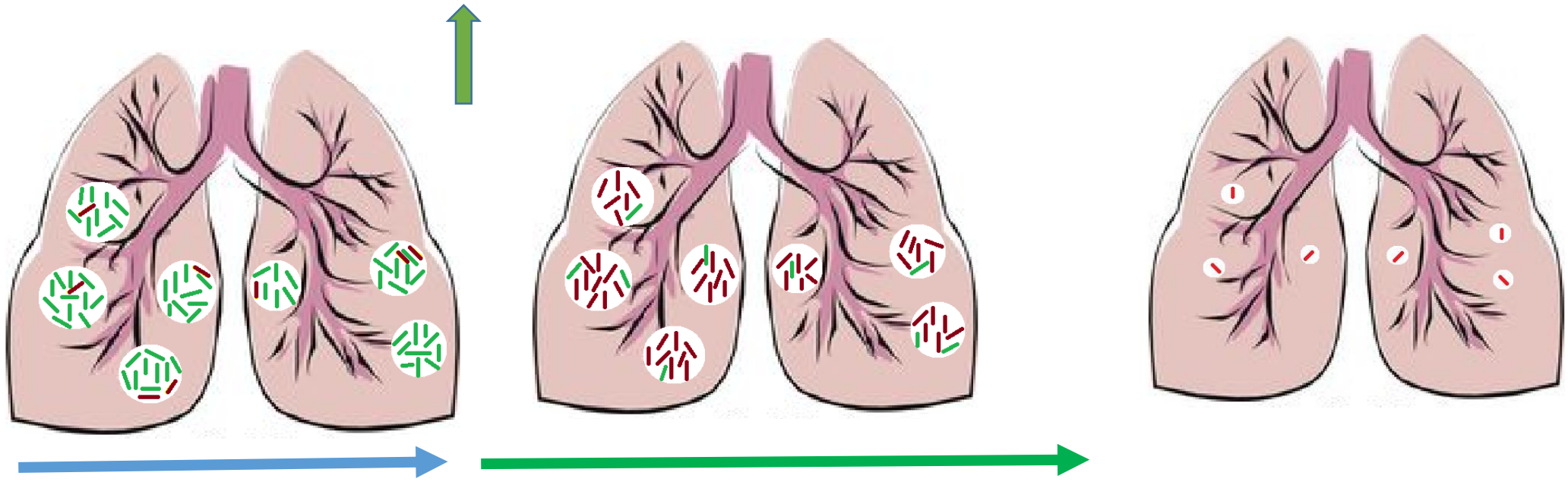
Sputum AFB negative — **Smear -, LJ agar - and MGIT -**



Intensive phase
R/H/Z/E
2 months

Continuation phase
R/H
4 months

5 to 10% relapse

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Shortening current chemotherapy

Kill persistent bacteria

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Persistent *M. tuberculosis*

- Undetectable using microbiological methods
- Fail to show acid fast stains
- Unable to form colonies on agar plates (- LJ agar)
- Unable to multiply in liquid medium (- MGIT)

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Novel drug regimens fail to shorten treatment duration

1. Moxifloxacin → isoniazid or ethambutol
   little or no improvement in patients
2. Rifapentine + Moxifloxacin regimens
   did not shorten the treatment duration
   in patients

Gillespie *et al.* 2014. *N Engl J Med.* Jindani *et al.* 2014. *N Engl J Med*

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Waking up persistent bacteria

Resuscitation promoting factors (RPFs)

- 5 small secreted proteins by *M. tuberculosis*
- Present in the culture supernatant
- Waking up persistent bacteria to start replication
- Stimulating bacterial growth

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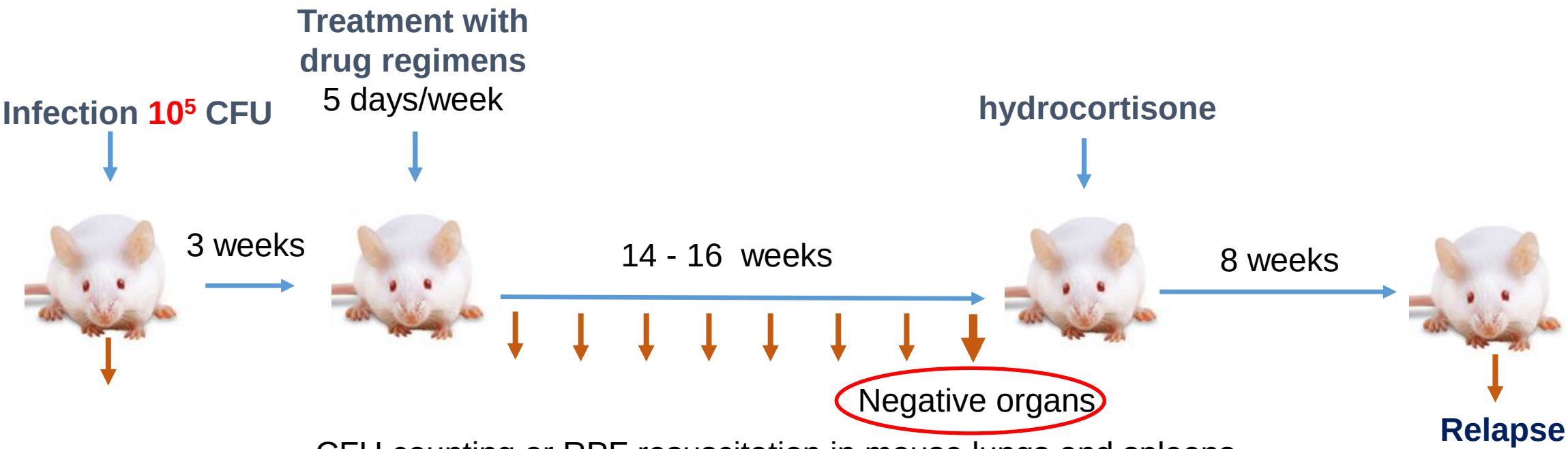
We hypothesised

1. We may be able to predict disease relapse by measuring RPF-dependent bacilli
2. We may be able to shorten the treatment duration and reduce disease relapse if we eliminate RPF-dependent persisters

Using Cornell mouse model as a testbed, we evaluated the therapeutic efficacies of drug regimens against RPF-dependent persisters

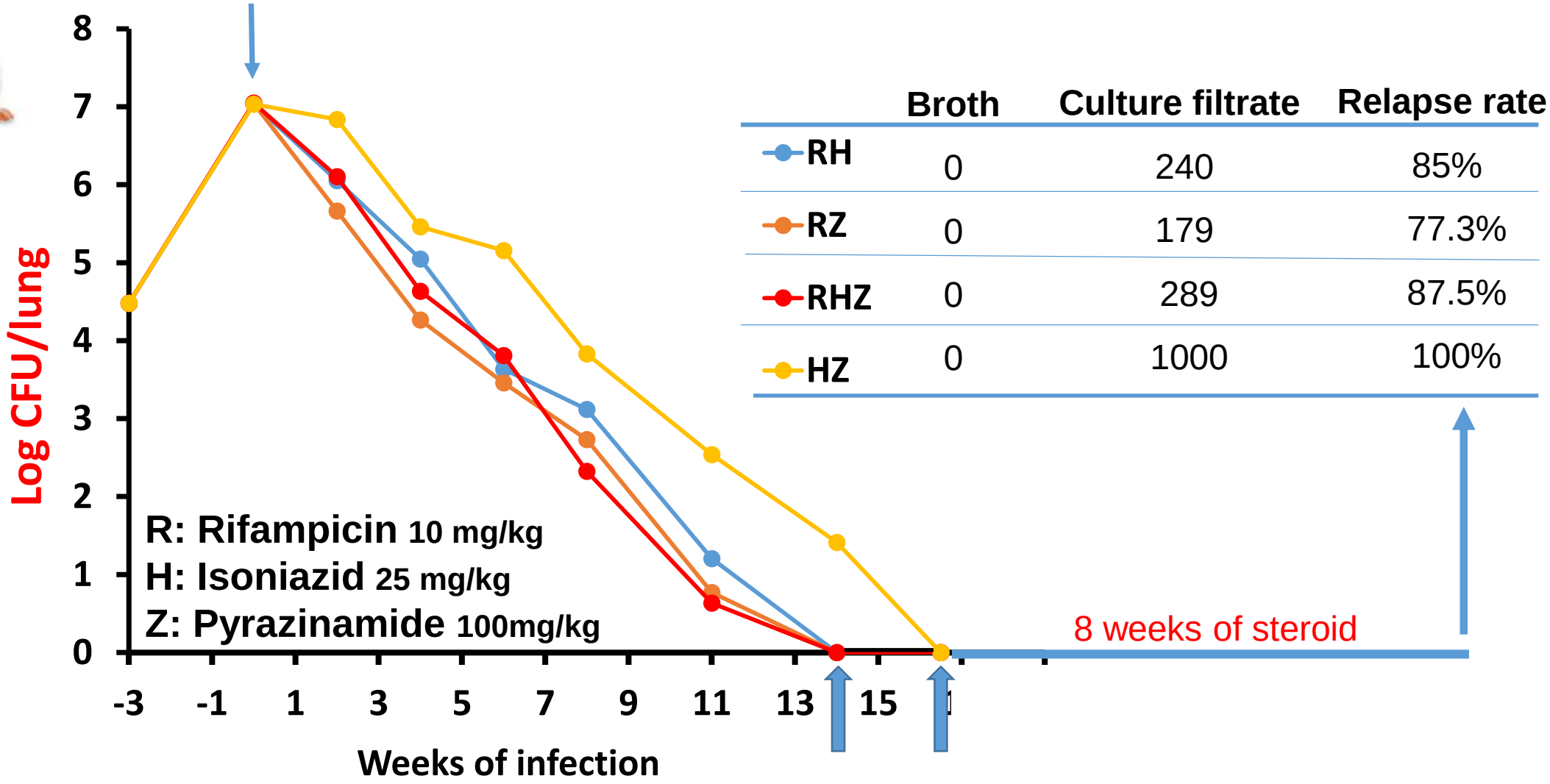
Cornell mouse TB model



1. **To evaluate efficacy of drug regimens**
2. **To measure relapse rates**
3. **To detect and quantify RPF-dependent persisters**

McCune et al 1956 J Exp Med

Standard regimens fail to remove RPF-dependent persisters



	Broth	Culture filtrate	Relapse rate
RH	0	240	85%
RZ	0	179	77.3%
RHZ	0	289	87.5%
HZ	0	1000	100%

Hu *et al*. 2016 Antimicrobial Agents and Chemotherapy

Moxifloxacin regimens fail to remove RPF-dependent persisters

	Persisters	Persisters in negative organ	Relapse rate
RHZE	347	2010	90%
RHZM	368	3300	95%
RMZE	228	1116	59%

	RHZE	RHZM	RMZE
Organ positive	19	20	13
Organ negative	2	1	9
Total mice	21	21	22

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High dose rifampicin regimens speed up kill of MTB in mice

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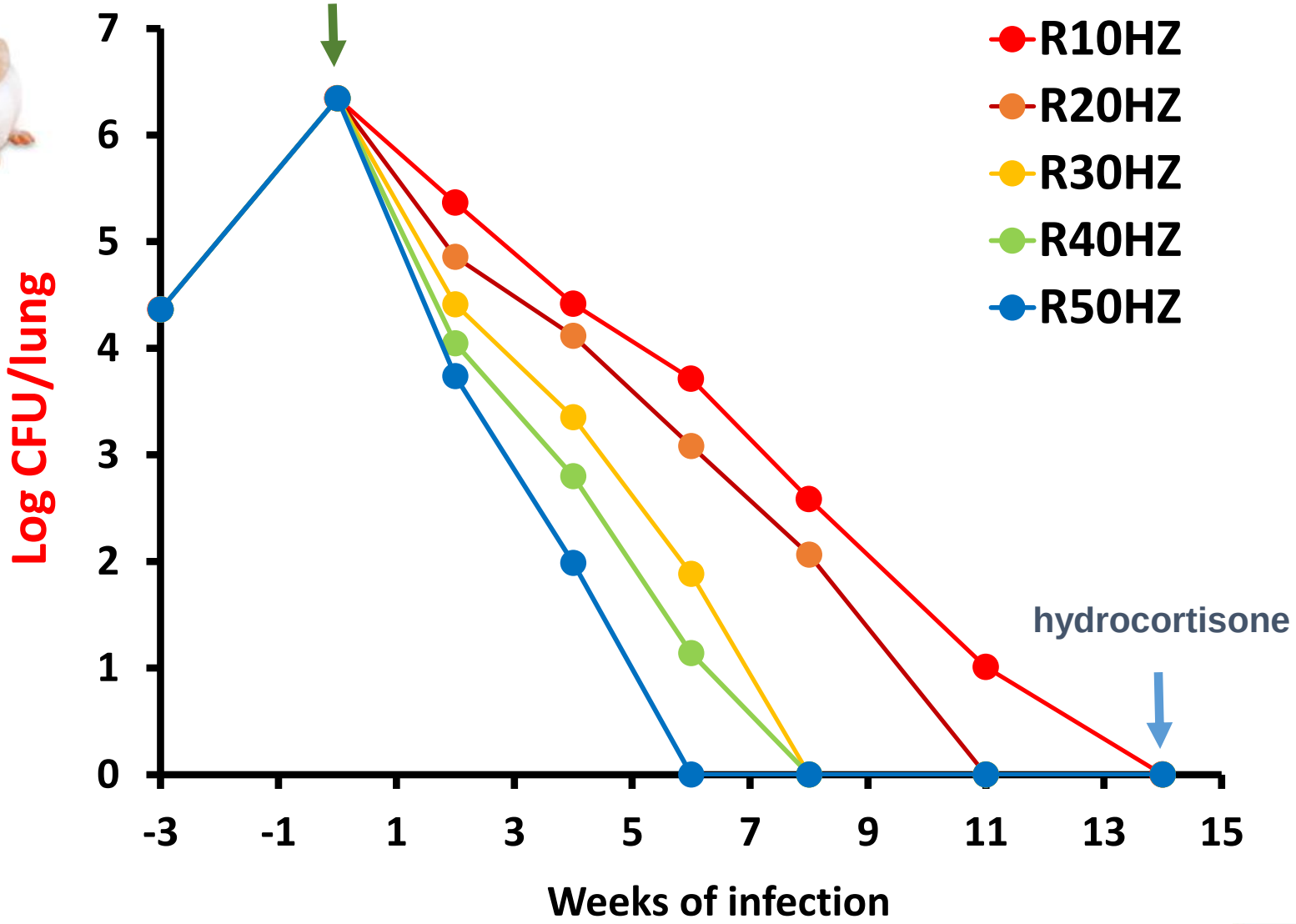

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High dose rifampicin regimens killed persistent Mtb

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		MPN counts (CF)				
Organs	**Weeks of treatment**	**R10HZ**	**R20HZ**	**R30HZ**	**R40HZ**	**R50HZ**
Lung	**6**	-	-	-	-	1
	8	-	-	9	0	0
	11	-	90	0	0	0
	14	245	20	0	0	0

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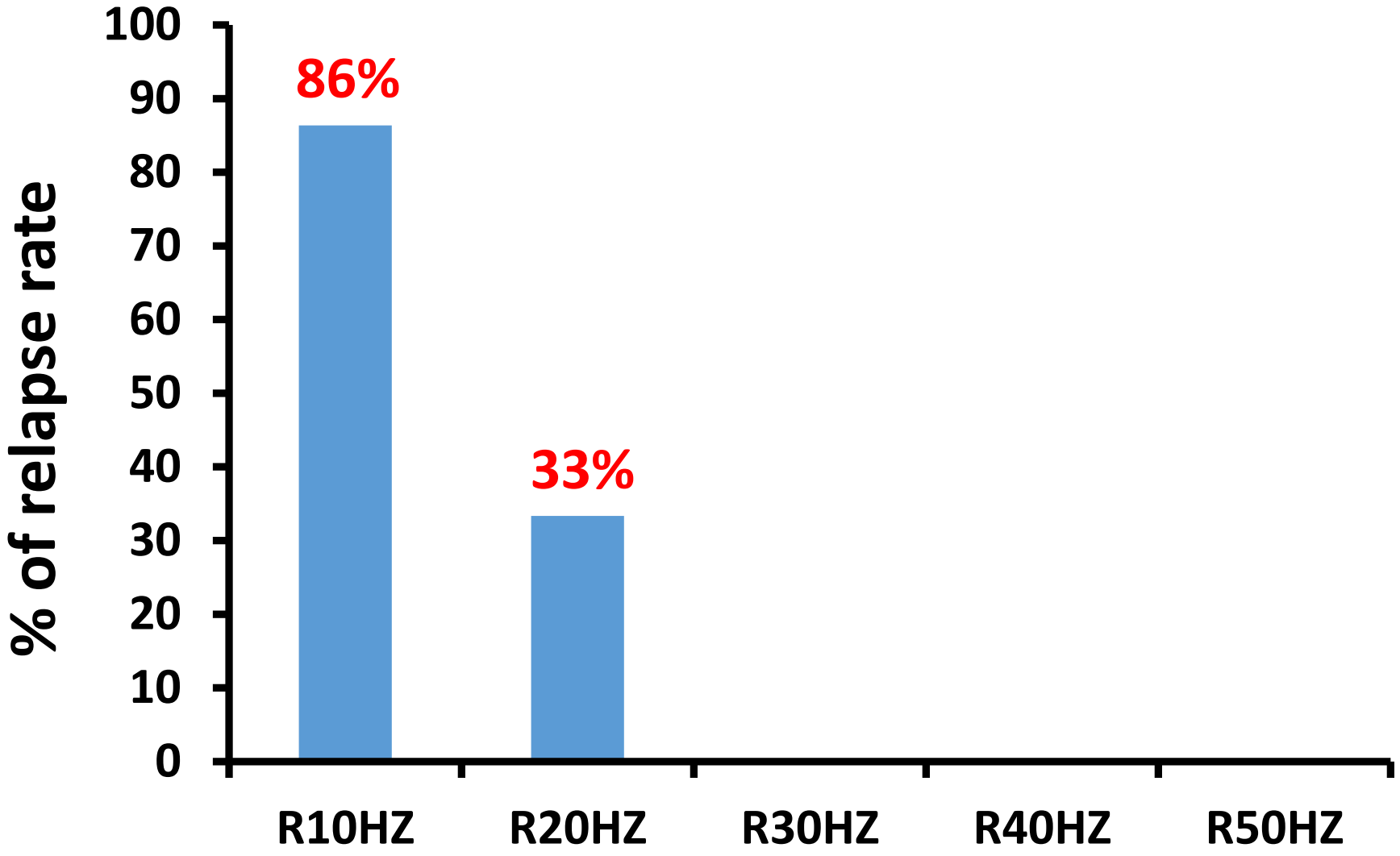
Relapse rates



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Summary and Conclusion

1. RPF-dependent persisters determine disease relapse
2. Standard TB regimens failed to removed RPF-dependent persisters in mice
3. Moxifloxacin replacement regimens failed to remove persistent Mtb in mice
4. Using high dose rifampicin: shorten treatment duration and reduced relapses
5. We can predict disease relapse by determining RPF-dependent persisters
6. It is essential to measure persistent bacteria in clinical studies to evaluate the efficacy of tuberculosis treatment, focusing on relapse

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