

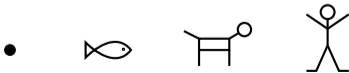
# Antimicrobial drug therapy of infectious diseases

Evolutionary rescue or extinction at multiple scales

Hildegard Uecker

Max Planck Institute for Evolutionary Biology

ESEB Montpellier 2018



# Evolutionary rescue

Can a population escape extinction through adaptive evolution?



## Conservation biology

e.g. adaptation to anthropogenic change



## Medicine

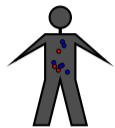
drug resistance: **undesired rescue**

*e.g. antibiotic resistance:*

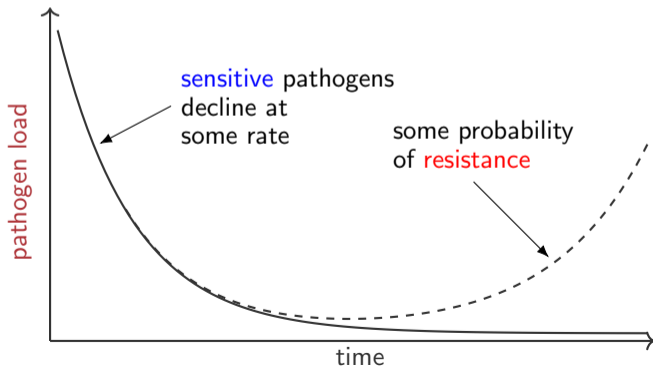
resistant bacteria are responsible for  
25,000 deaths/year in the European Union

WHO, Fact sheet "Antibiotic resistance", October 2015

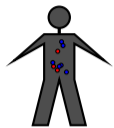
# Drug treatment in the face of resistance



one host



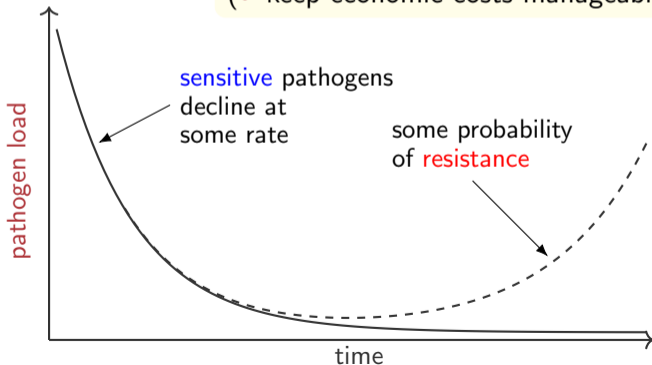
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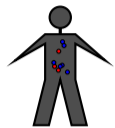
one host

## Goals:

- maximise rate of decline ( $\rightarrow$  rapid recovery/survival)
- minimise probability of resistance evolution
- treatment should not kill the patient
- (• keep economic costs manageable)



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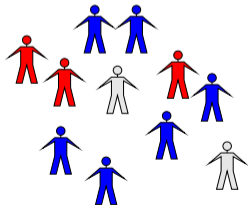


one host

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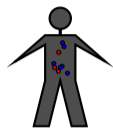
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## Infectious diseases: rescue/extinction at two scales



population

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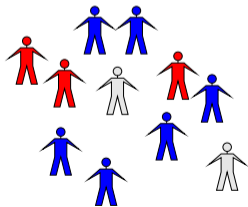


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- minimise probability of resistance evolution
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- (• keep economic costs manageable)

## Infectious diseases: rescue/extinction at two scales



population

## Additional goals:

- minimise the disease prevalence
- minimise the outbreak probability of an epidemic
- minimise transmission of resistance
- (• keep economic costs manageable)

## Big question

**How do we need to treat patients to best achieve these goals?**

Treatment strategies:

- combination therapy
- drug cycling
- treatment coverage
- length of treatment
- drug dose
- ...

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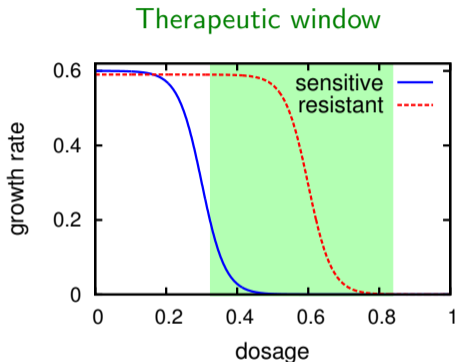
For this talk:

**What is the optimal drug dose?**

*Focus:* Which dose is best at managing resistance?



## What is the current strategy?

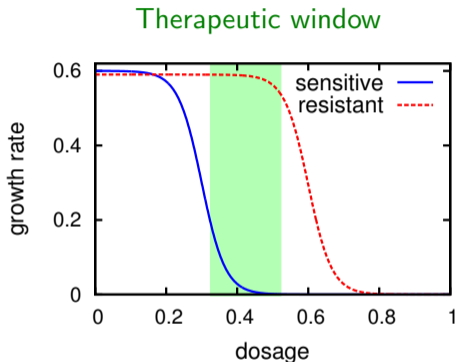


### Use the highest possible dose:

- faster patient recovery
- less chance for de novo mutations
- if high enough: no (single-step) resistance

**In the face of resistance, is this always the best choice?**

## What is the current strategy?



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# Which drug dose minimises the risk of within-host resistance?

## Advantages of a low dose:

- suppression of the resistant strain through competition
- immune response is mounted by the sensitive strain

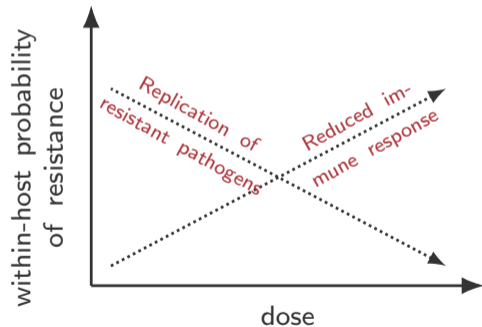


FIGURE ADAPTED FROM KOUYOS ET AL. 2014

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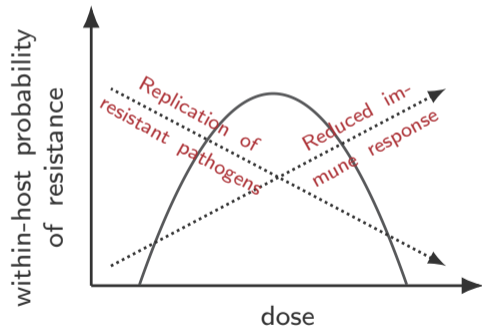


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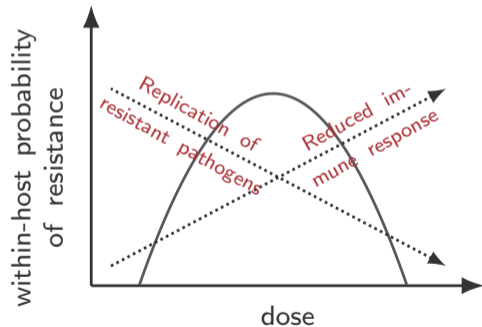
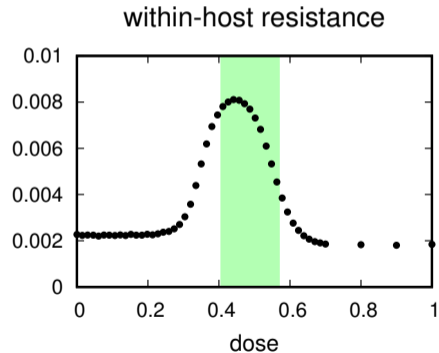


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DAY AND READ 2016

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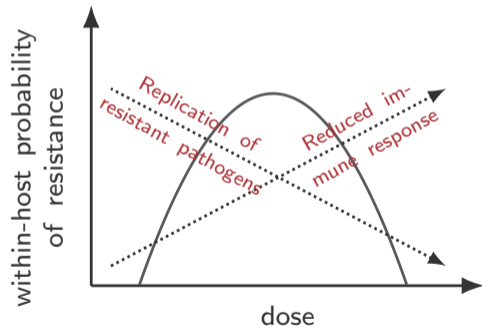
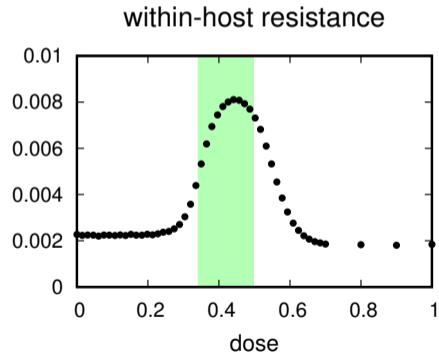


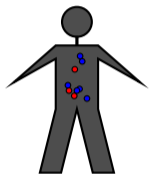
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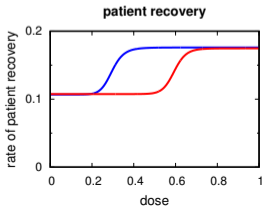
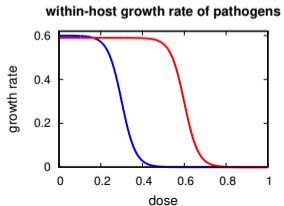
# From the individual host to the population

one host



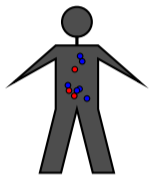
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resistant

The drug dose affects pathogen replication.



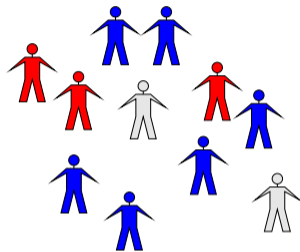
# From the individual host to the population – trade-offs?

one host

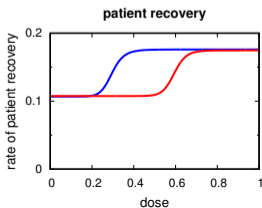
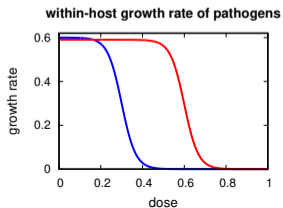


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resistant

population



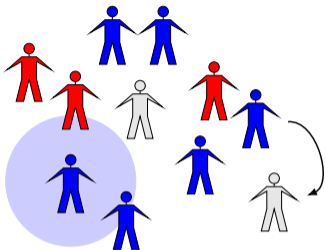
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consequences for the  
disease dynamics in  
the population



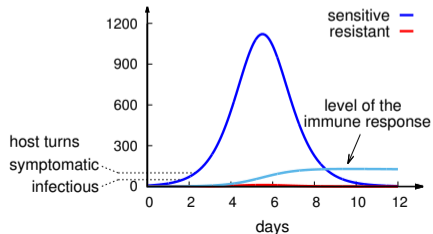
# How do we consider both scales?



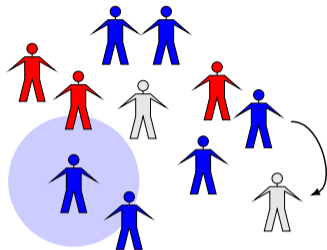
random transmission  
between hosts:  $\beta SI$   
(single strain  
is transmitted)

life-long immunity

## Sketch: within-host dynamics



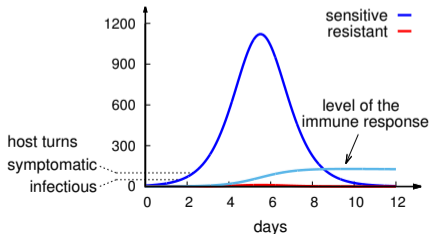
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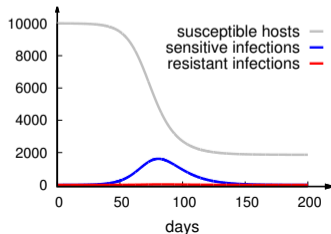
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### Sketch: within-host dynamics



### Sketch: between-host dynamics



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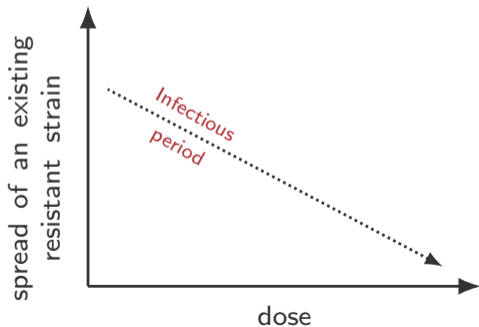
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**Two factors:** *appearance + spread of resistance*

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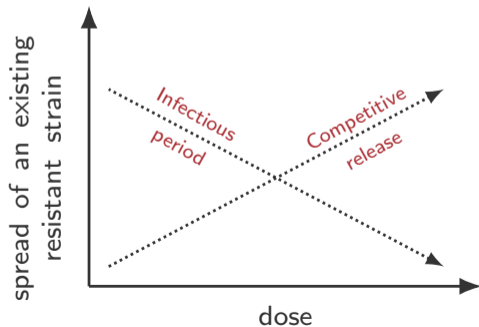
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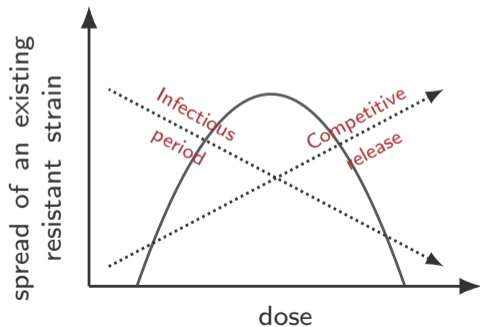
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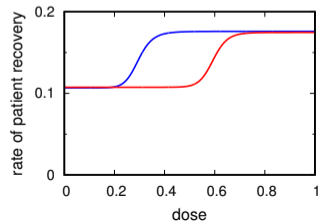
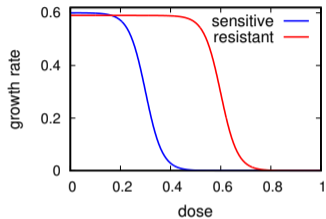
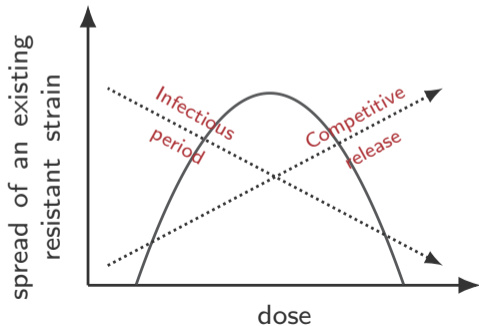
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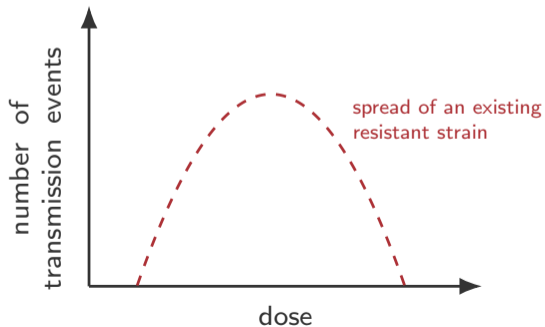
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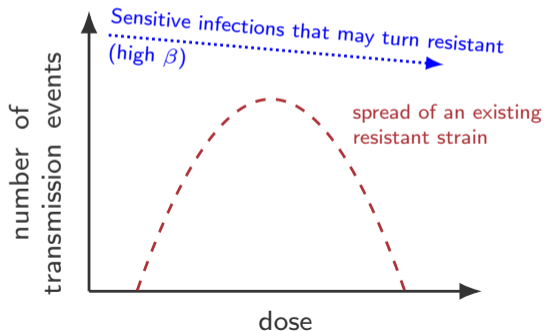




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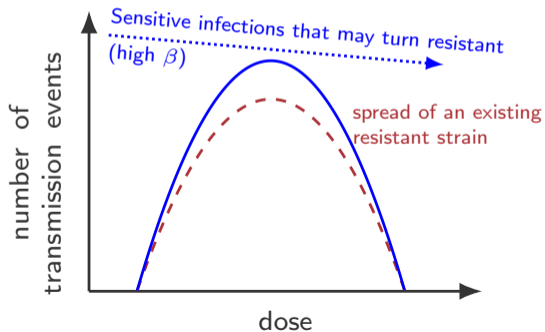
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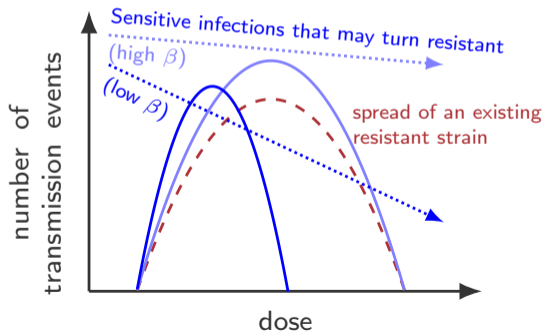
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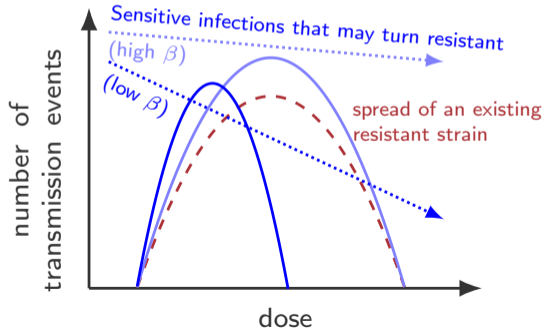
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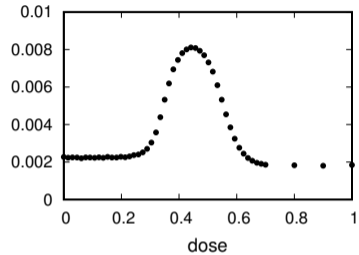
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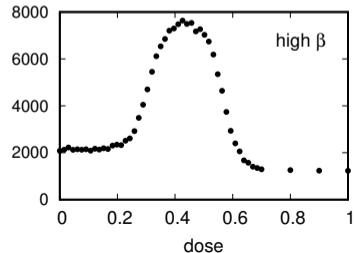
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within-host resistance



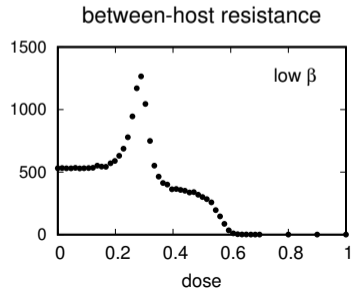
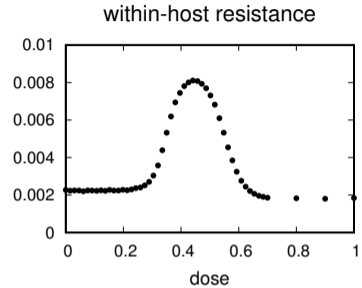
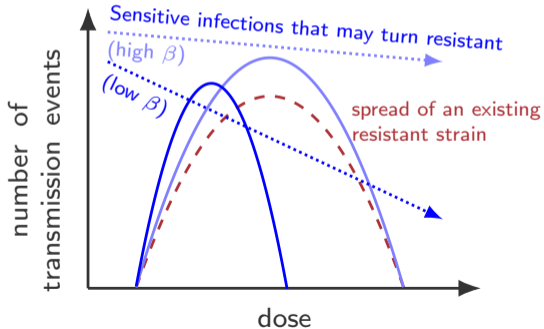
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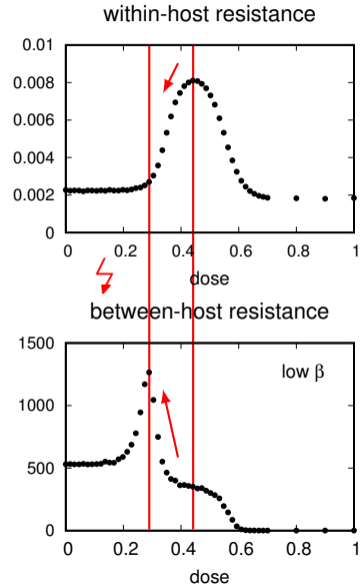
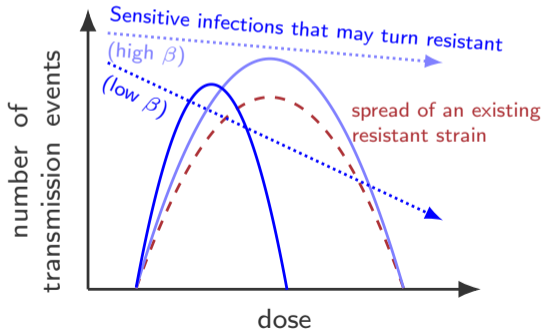
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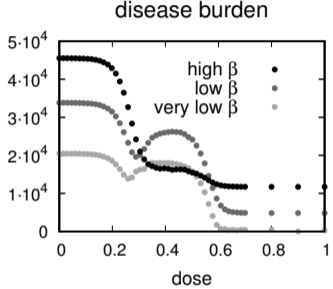
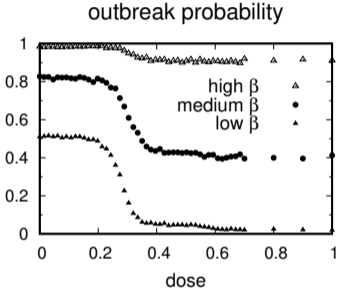
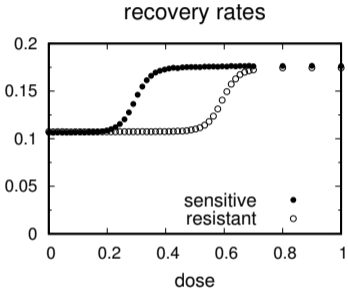
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# What about the other treatment goals?



Trade-offs between different treatment goals.

# And now?

## Which criterion should be used?

difficult & context-dependent, e.g.

- are all individuals immuno-competent?
- is the disease lethal?
- are there other drugs available?



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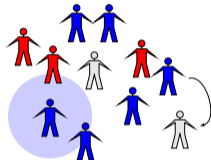
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## How can we resolve the conflicts?

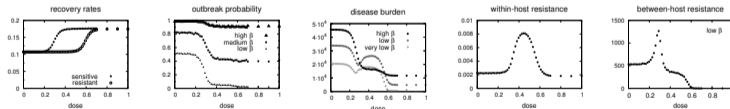
- not possible by modulating nothing but the dose
- additional parameters need to be changed (e.g. isolation of symptomatic cases? combination therapy?)

# Conclusion

- The evolutionary dynamics of pathogens and selection for resistance are determined by both within-patient and epidemiological dynamics.



- Different criteria may suggest different dosing strategies.



- There may be conflicts between the individual and the population levels.

## Acknowledgements:

Jérémie Sciré

Nathanaël Hozé

Sebastian Bonhoeffer

funding: ERC, SNF

THANK YOU FOR YOUR  
ATTENTION.

PhD position available

within the Research group

*Stochastic Evolutionary Dynamics*

("The Rescue Team")

Max Planck Institute for Evolutionary Biology

[web.evolbio.mpg.de/stochdyn](http://web.evolbio.mpg.de/stochdyn)

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Salmonella: *Rocky Mountain Laboratories, NIAID, NIH*