Antimicrobial drug therapy of infectious diseases

Evolutionary rescue or extinction at multiple scales

Hildegard Uecker
Max Planck Institute for Evolutionary Biology

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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

Drug treatment in the face of resistance

Goals:
• maximise rate of decline (→ rapid recovery/survival)
• minimise probability of resistance evolution
• treatment should not kill the patient (→ keep economic costs manageable)

Sensitive pathogens decline at some rate

Some probability of resistance

Infectious diseases: rescue/extinction at two scales

Additional goals:
• minimise the disease prevalence
• minimise the outbreak probability of an epidemic
• minimise transmission of resistance (→ keep economic costs manageable)
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[Graph showing pathogen load over time with a dashed line indicating the probability of resistance]
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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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Treatment strategies:

- combination therapy
- drug cycling
- treatment coverage
- length of treatment
- drug dose
  
For this talk:

**What is the optimal drug dose?**

*Focus:* Which dose is best at managing resistance?
What is the current strategy?

**Therapeutic window**

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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Therapeutic window

growth rate

dosage

sensitive resistant

0 0.2 0.4 0.6 0.8 1

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growth rate
dosage
sensitive
resistant
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

![Graph showing the relationship between dose and within-host probability of resistance](image)

*Figure adapted from Kouyos et al. 2014*
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**Day and Read 2016**
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Day and Read 2016
From the individual host to the population

one host

sensitive resistant

The drug dose affects pathogen replication.
From the individual host to the population – trade-offs?

The drug dose affects pathogen replication.

consequences for the disease dynamics in the population
How do we consider both scales?

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

Sketch: within-host dynamics

life-long immunity

Sketch: between-host dynamics

susceptible hosts
sensitive infections
resistant infections

level of the immune response
host turns
symptomatic
infectious

days

sensitive resistant
How do we consider both scales?

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Sketch: within-host dynamics

Sketch: between-host dynamics

life-long immunity

[Graphs showing within-host and between-host dynamics with various data points and annotations]
Does the same dose minimise resistance at both scales?

**Measure:** number of transmission events of the resistant strain

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

- **Sensitive infections that may turn resistant**
  - (high $\beta$)
  - (low $\beta$)

**Spread of an existing resistant strain**

- **Number of transmission events**
- **Dose**
Does the same dose minimise resistance at both scales?

**Measure:** number of transmission events of the resistant strain

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

[Graph showing the relationship between dose and within-host resistance and between-host resistance.]
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What about the other treatment goals?

![Graphs showing recovery rates, outbreak probability, and disease burden vs dose with different treatment goals shown.](image)

Trade-offs between different treatment goals.
And now?

Which criterion should be used?

difficult & context-dependent, e.g.

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

Scire et al. (biorxiv)
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Max Planck Institute for Evolutionary Biology

web.evolbio.mpg.de/stochdyn
uecker@evolbio.mpg.de

Thank you for your attention.

Photo credit:

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