Aggressive or moderate drug therapy for infectious diseases?

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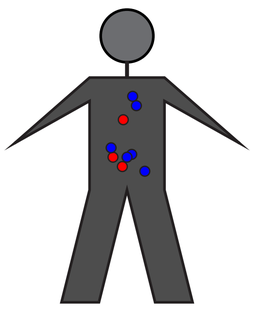
Infectious diseases: Resistance dynamics at two levels

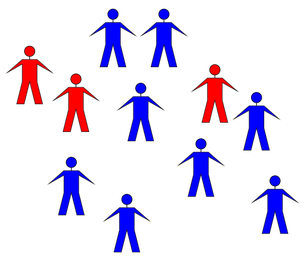
within-host

Resistance can evolve within any one patient during treatment.



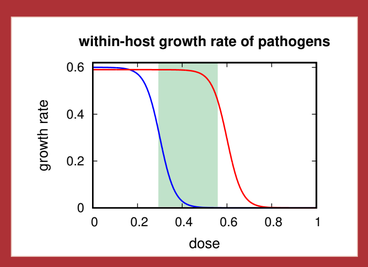
sensitive
resistant

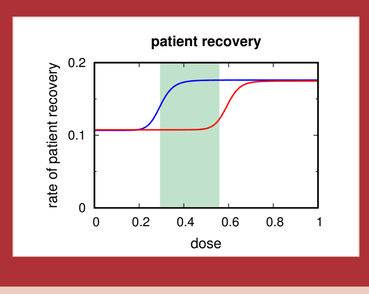
between-host



Resistant pathogen can get transmitted in the community.

The drug dose affects pathogen replication.





consequences for the disease dynamics in the population

Therapeutic window between the minimally effective and the maximally tolerable dose

The drug dose may be modulated to influence the evolutionary dynamics at both scales. This may be exploited to manage resistance.

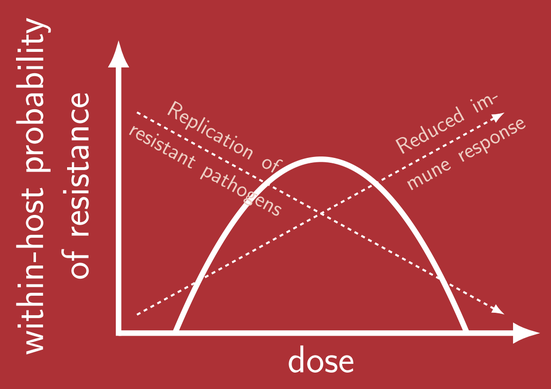
Are there trade-offs between the individual and the population levels?

Within-host evolution of resistance[3,4]

Opposing forces:

low doses: high abundance of sensitive pathogens triggers strong immune response
high doses: drug substantially reduces growth even of the resistant strain

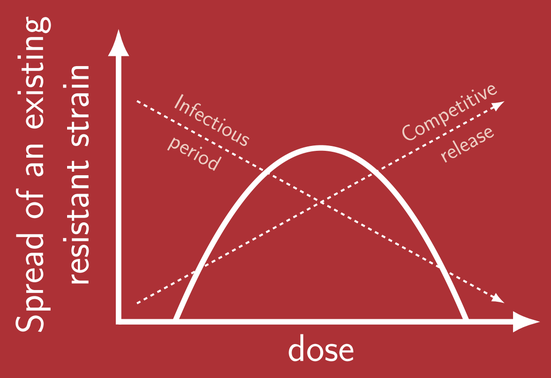
Figure adapted from [4]



Spread of an existing resistant strain

Opposing forces:

low doses: strong competition with the sensitive strain for susceptible hosts
high doses: short period of infectiousness even for the resistant strain

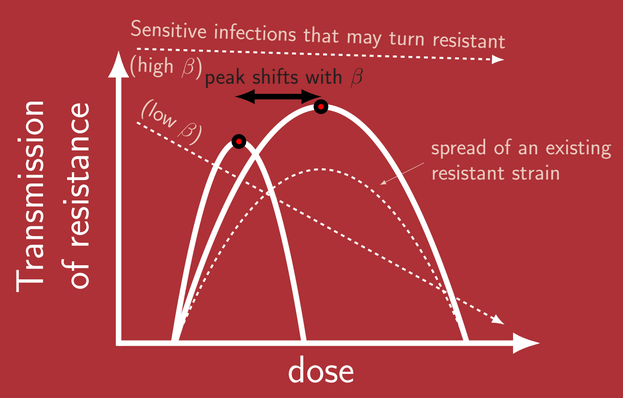


Transmission of the resistant strain

Two factors:

- spread of the resistant strain once emerged
- *de novo* development of resistance across all patients ($\sim$ number of sensitive infections)

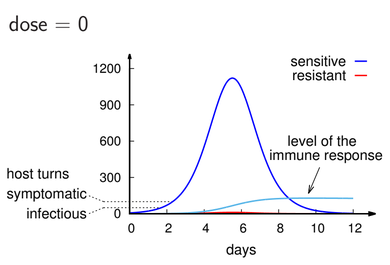
$\Rightarrow$ peak shifts with the transmission coefficient β ($\sim R_0$)



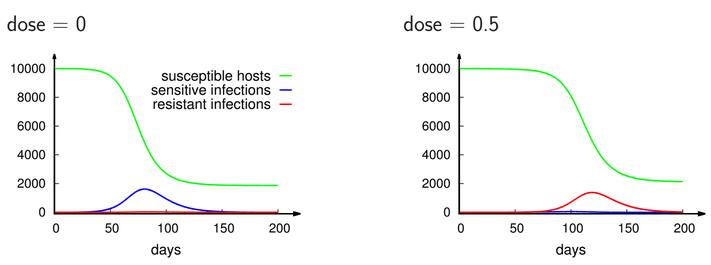
The dose that minimizes the within-host probability of resistance within the therapeutic window may maximize transmission of the resistant strain in the community.

Quantitative model

Sketch of the within-host dynamics[3]

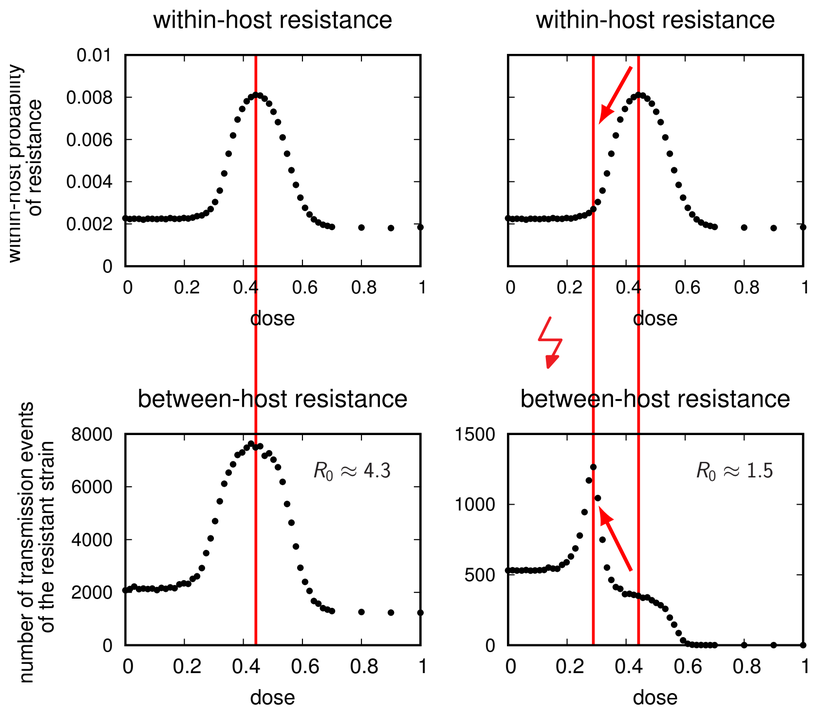


Sketch of the between-host dynamics



acute self-limiting infection (life-long immunity), random transmission between hosts (single strain is transmitted)

Analysis



Other optimality criteria

Outbreak probability

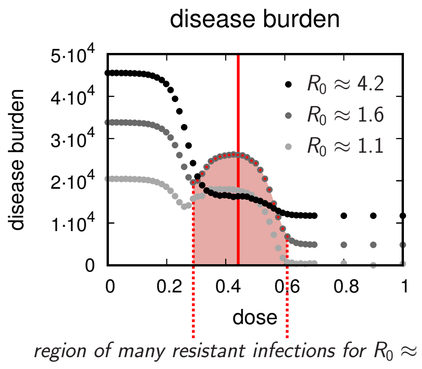
If initially a single individual is infected, there are two possible outcomes: (1) early extinction of the epidemic after few infection events (2) a large outbreak with many infected hosts.

A higher dose leads to a lower outbreak probability.
The effect is particularly strong for low R_0.

Disease burden

= *total number of days that members of the population suffer from symptoms* (here: conditioned on the occurrence of a large outbreak)

Competition with the sensitive strain for susceptible hosts hampers spread of resistance. With increasing dose, competitive release allows its spread, unless R_0 is large. For very high doses, both strains are equally affected by the drug.



region of many resistant infections for $R_0 \approx 1.6$

Discussion

Summary, Limitations & Conclusion

The best dose choice depends on whether the main goal is to rapidly increase individual patients' health, to reduce morbidity at the population level (burden), to limit the outbreak probability, or to reduce resistance emergence at the individual or the population levels. What is more, there can be trade-offs between achieving treatment goals at the within-host and between-host levels.

Limitations of the model:
no mortality; no immuno-compromised patients; no danger of under- or overdosing for individual patients; ...

Conclusion:
Deciding on a drug dose based on within-host considerations alone may be insufficient for resistance and disease management.

Literature:

[1] Sciré et al., submitted
[2] Levin at al., Trends Microbiol. 2017
[3] Day & Read, PLOS Comput. Biol. 2016
[4] Kouyos et al., Proc. Royal Soc. B 2014
[5] Read et al., PNAS 2011

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