



Should one aim for
genetic improvement of
host **resistance or tolerance**
to infectious disease?

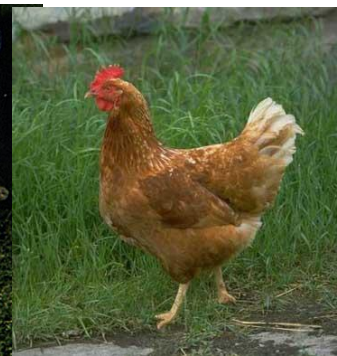
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- **Definitions:** resistance / tolerance / resilience
- **Should** we aim for genetic improvement of host resistance or tolerance?
- **Can** we improve tolerance?
 - Estimating the tolerance phenotype



- **Resilience:** host ability to maintain high performance levels whilst infected
 - **Resistance:** ability to **limit pathogen replication**
 - **Tolerance:** ability to **limit the impact of pathogens** on host performance
- Resistance and tolerance
 - may be antagonistically related
 - have different evolutionary and epidemiological consequences

→ **distinction important**



Improve resistance or tolerance?

Pro resistance:

- Fully resistant animals don't need to be tolerant
- Improving resistance may lead to disease eradication
- Resistant animals may protect non-resistant animals

Pro tolerance:

- More likely to be generic to a range of pathogens
- No risk for pathogen evolution to higher virulence

Pro resistance:

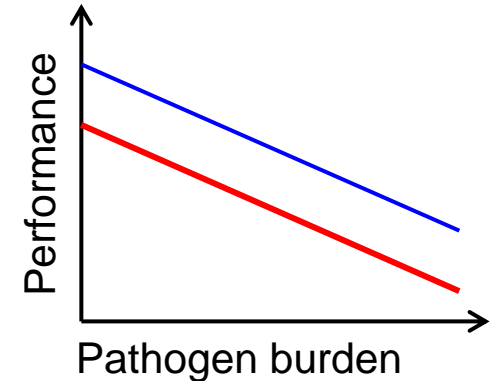
Pro tolerance:

- Improving tolerance should only be considered if
 - all animals are susceptible to some degree
 - disease eradication is unlikely
 - animals are exposed to wide range of pathogens
 - pathogen mutation rate is high
- e.g. Nematode infections, PRRS

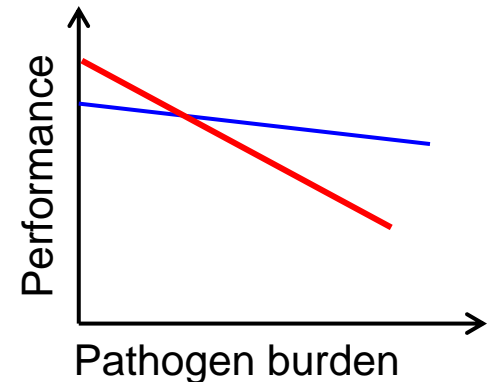
Quantifying resistance & tolerance

- Not directly measurable
- Resistance:
 - inverse pathogen burden
- Tolerance:
 - change of host performance with respect to change in pathogen burden (i.e. slope)
 - Tolerance is a “Reaction-norm”

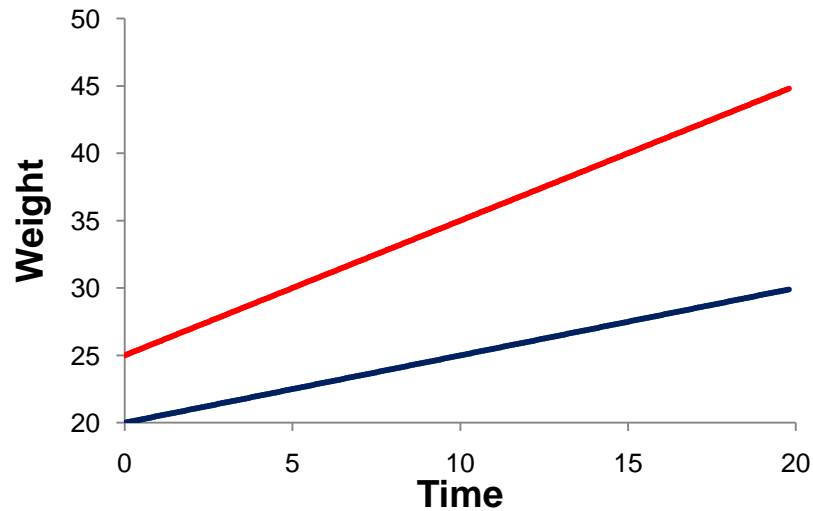
Same tolerance



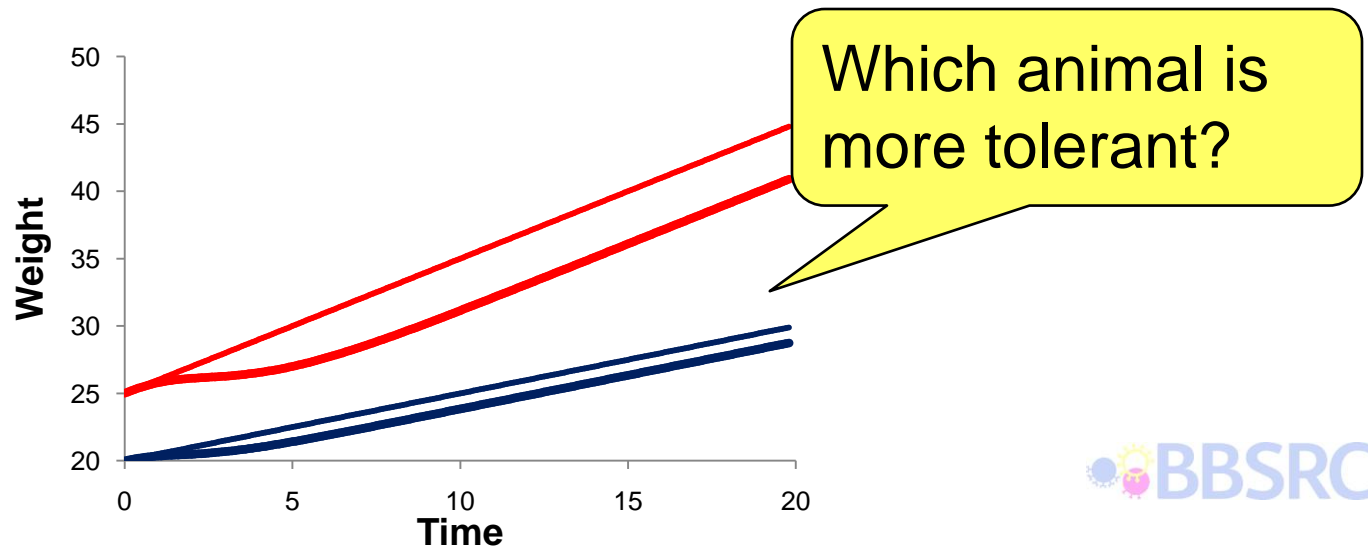
Different tolerance



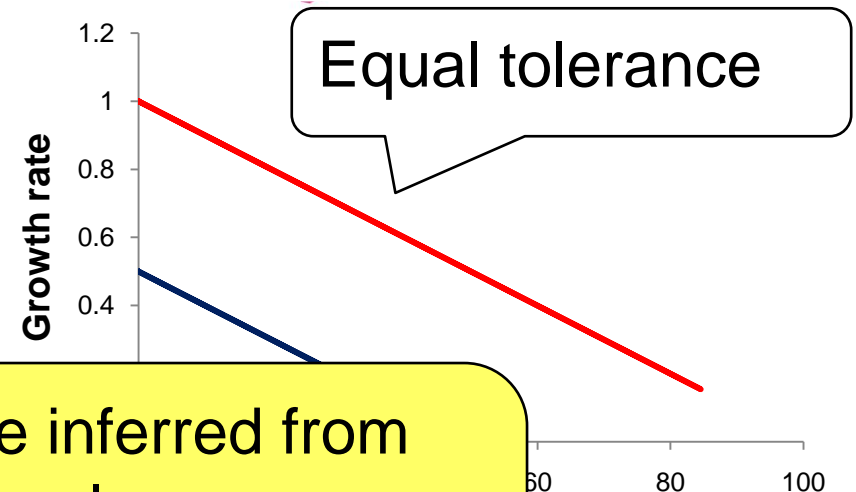
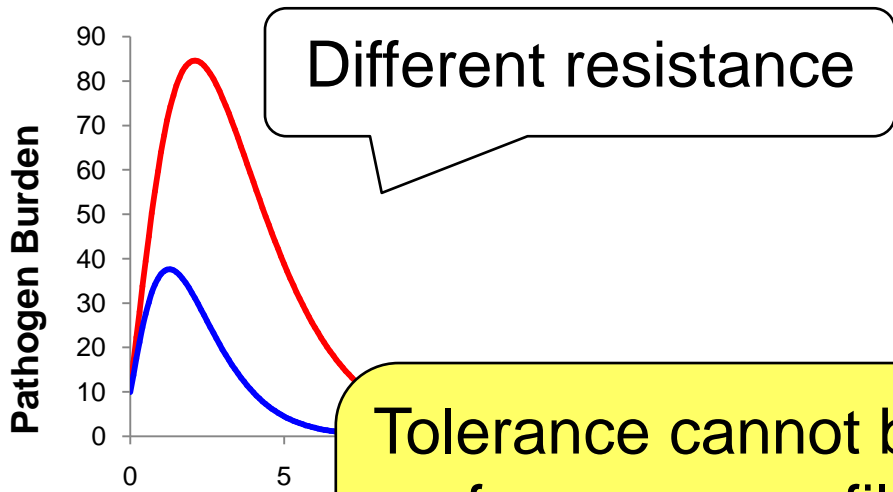
Specifying pathogen burden is crucial



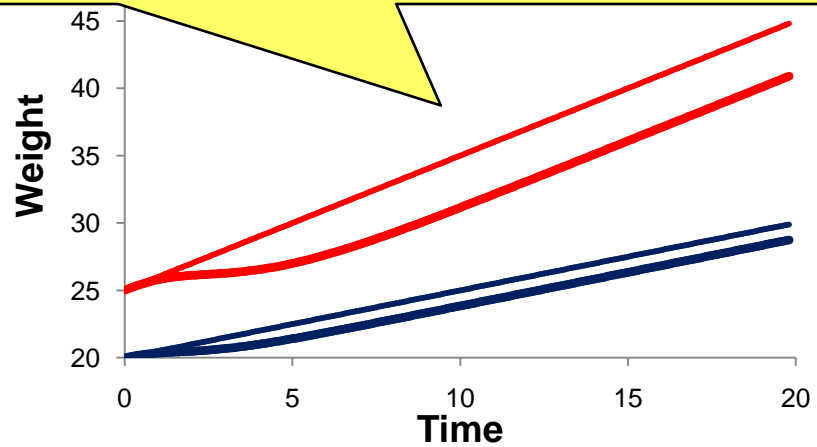
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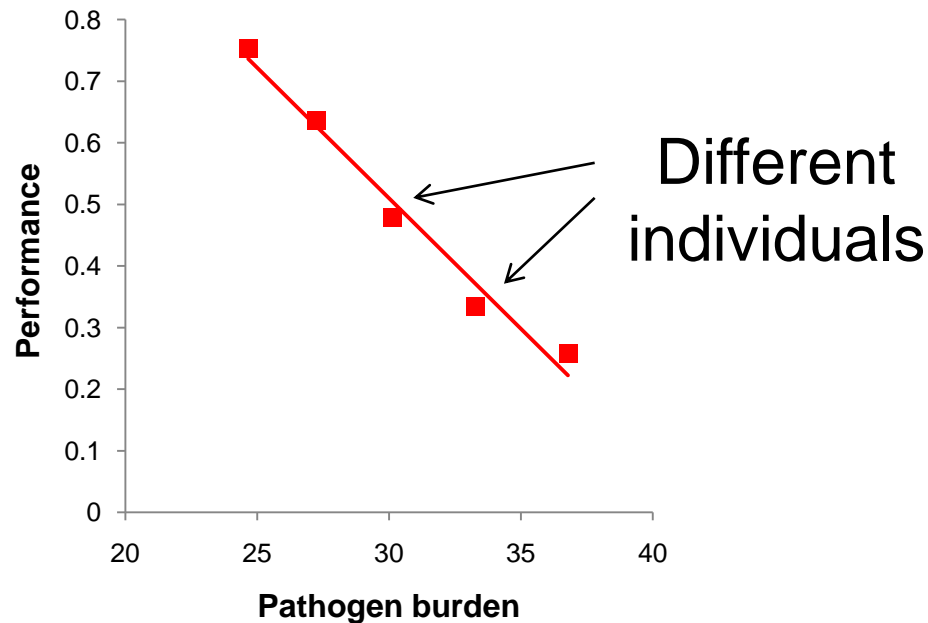


Tolerance cannot be inferred from performance profiles alone - need measure of (within host) pathogen burden



Tolerance has only been estimated for groups

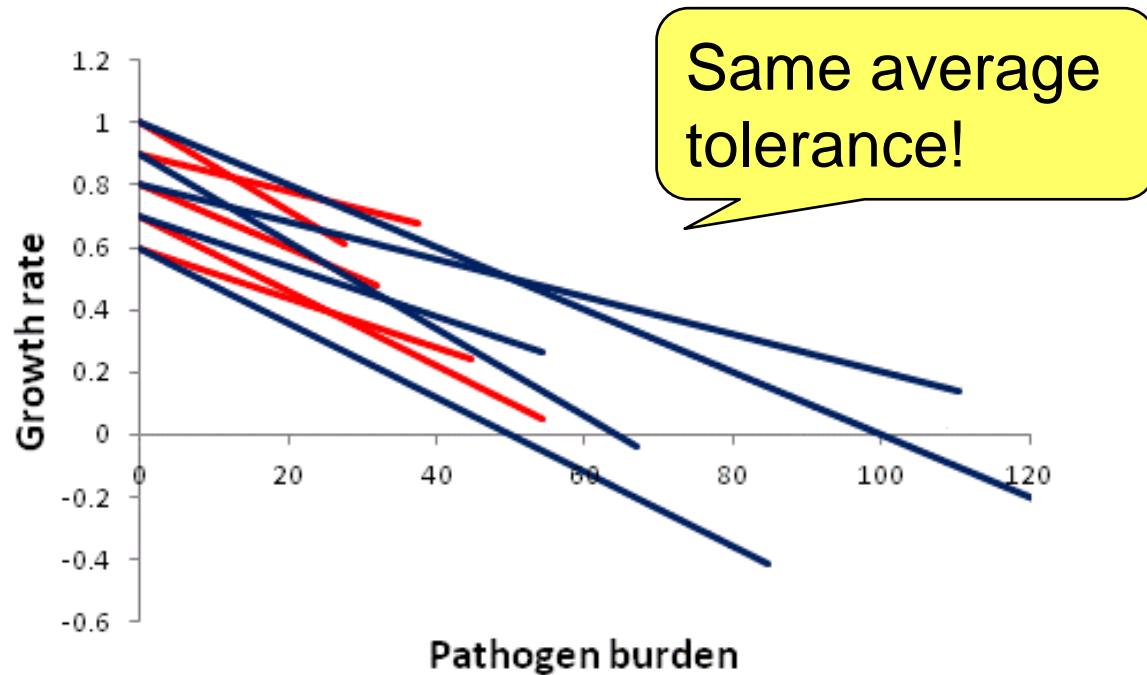
- Estimation of a tolerance slope requires variation in pathogen burden
- An individual cannot have simultaneously different values of within host pathogen burden
- Tolerance has only been estimated for groups of individuals (regression, ANCOVA)



Within group variation affects group tolerance

3 sources of individual variation:

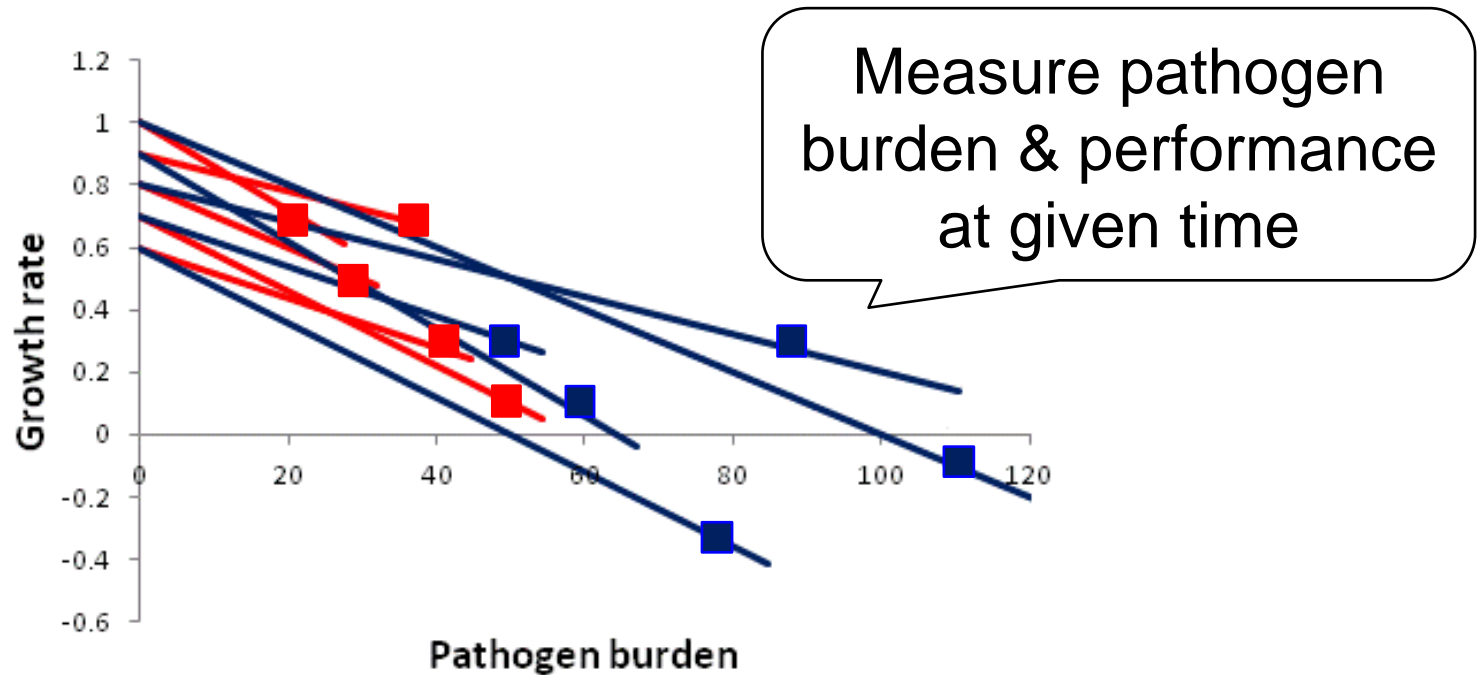
- Resistance (x-value)
- Tolerance (slope)
- Performance in pathogen - free environment (Intercept)



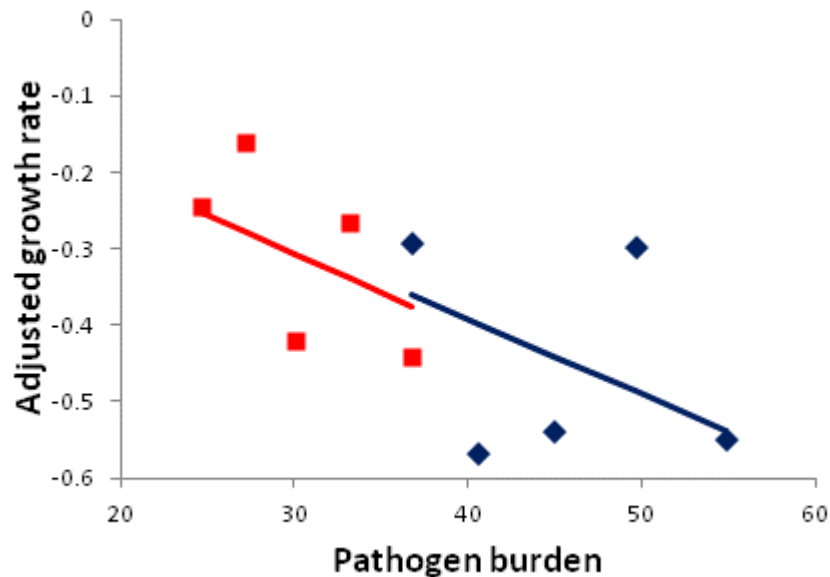
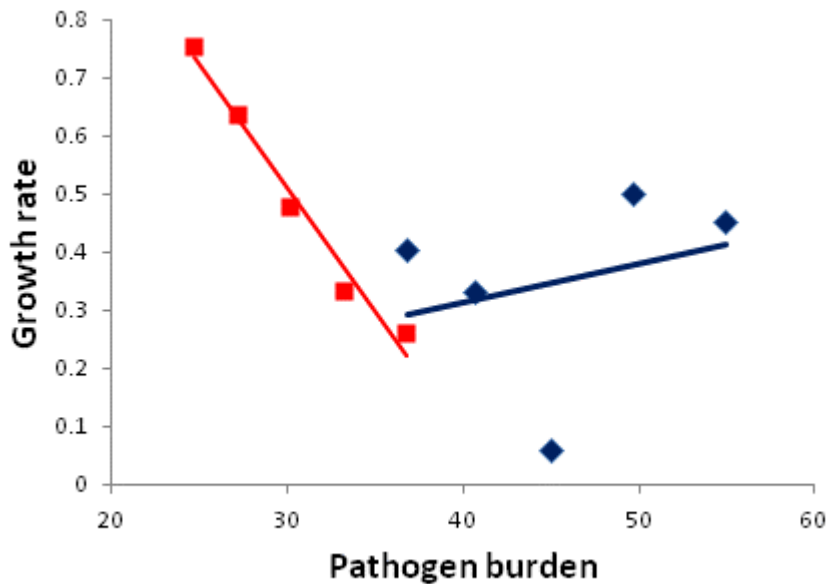
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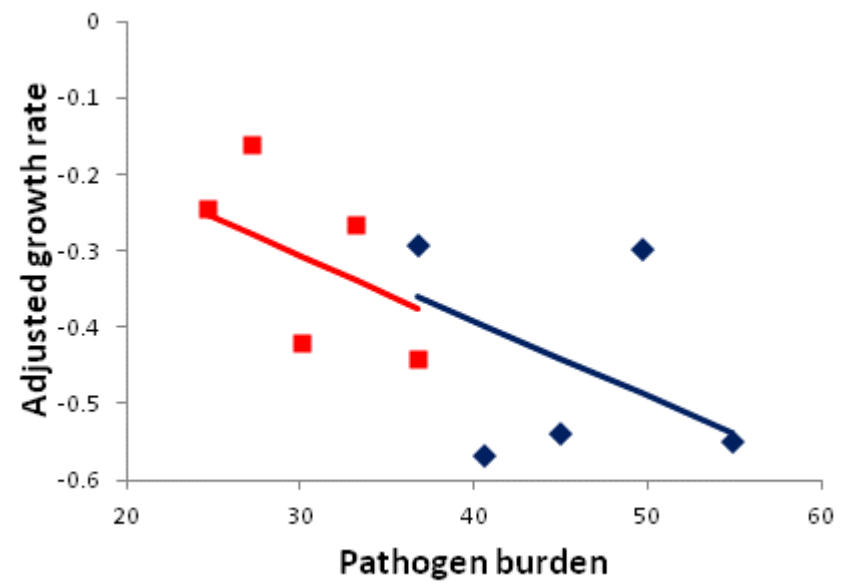
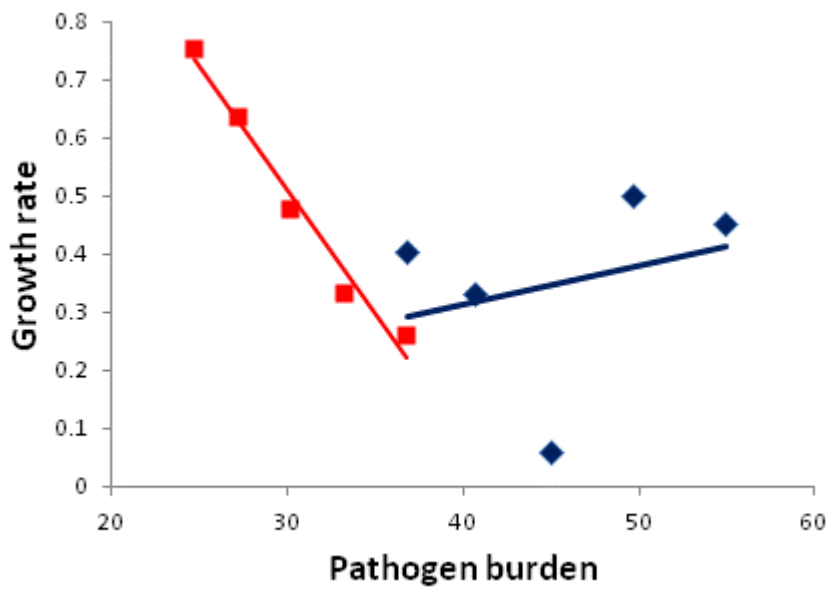
- Resistance (x-value)
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Accounting for individual variation in vigour



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It is essential to account for individual variation in performance in pathogen free environment

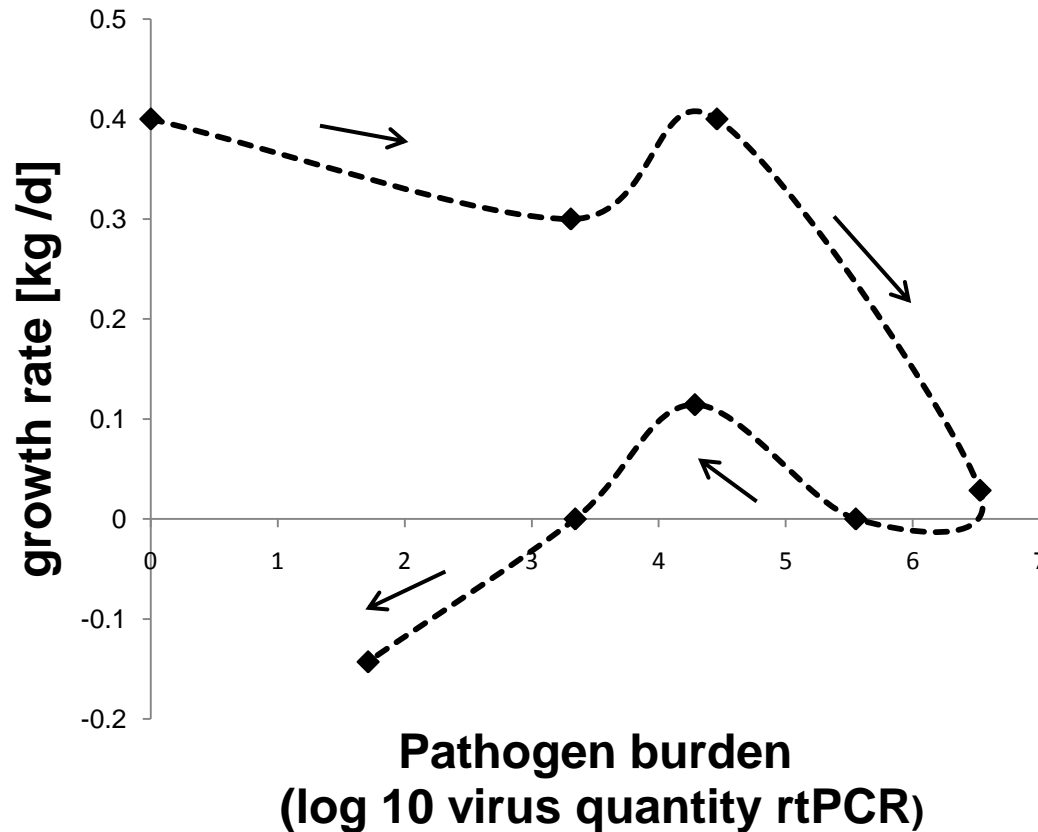
Summary – group tolerance

- Estimating **group** tolerance requires
 - measurements of **individual** performance & within host pathogen burden
 - estimates of **individual** performance in pathogen free environment
- Costly for limited genetic gain



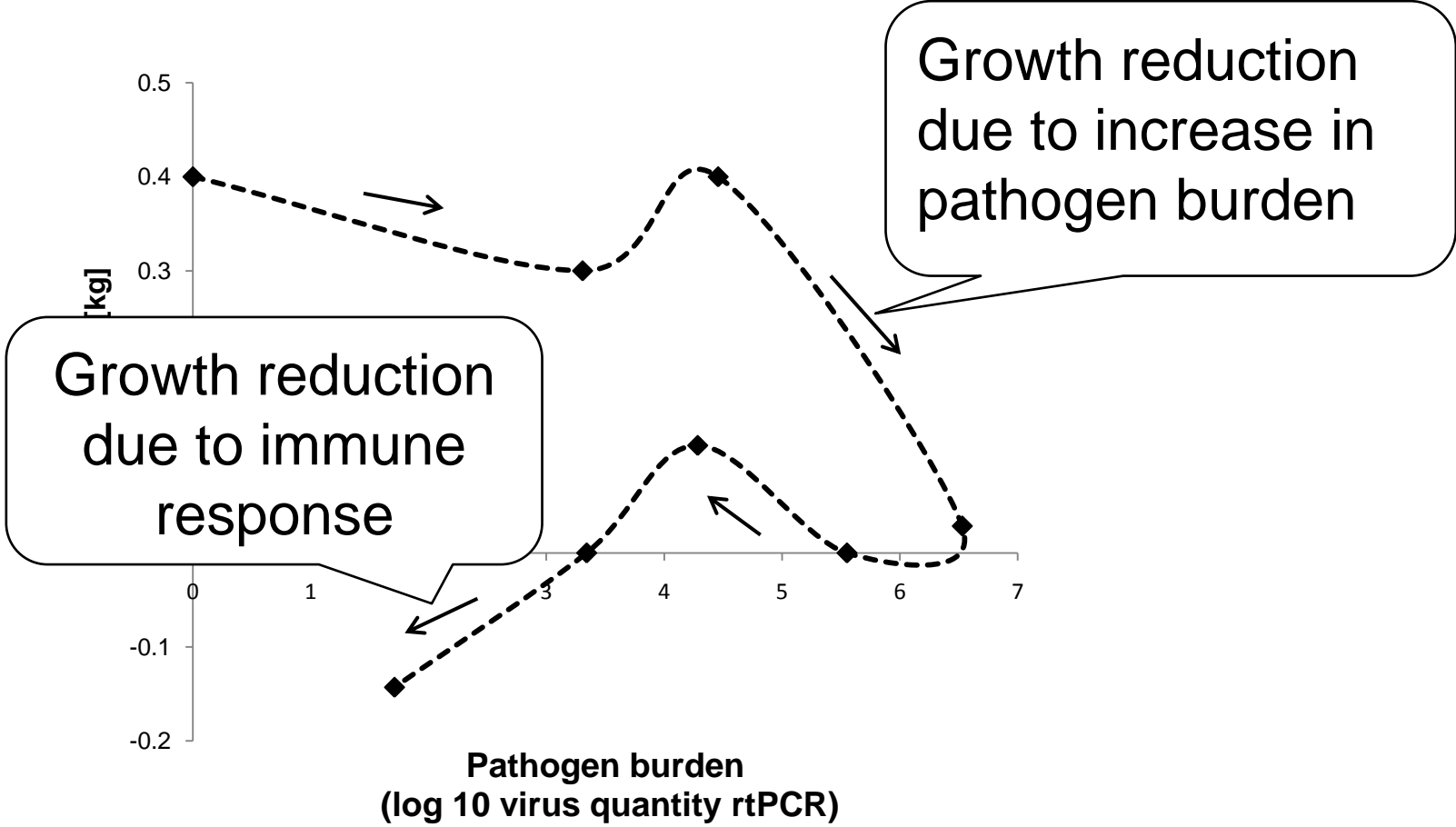
From groups to individuals

Individual pathogen burden – performance trajectories

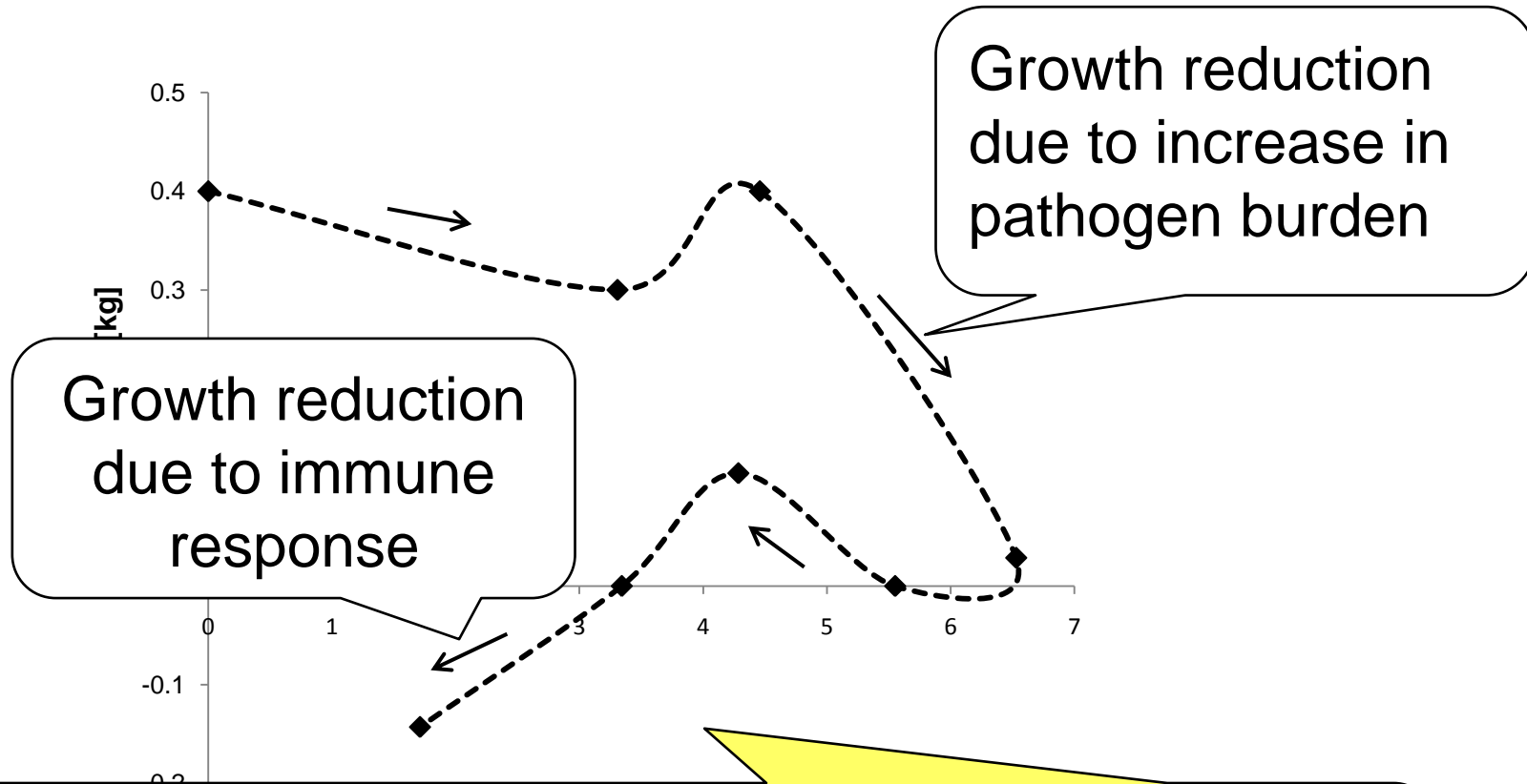


Data are courtesy of PRRS HOST Genetic Consortium

From groups to individuals



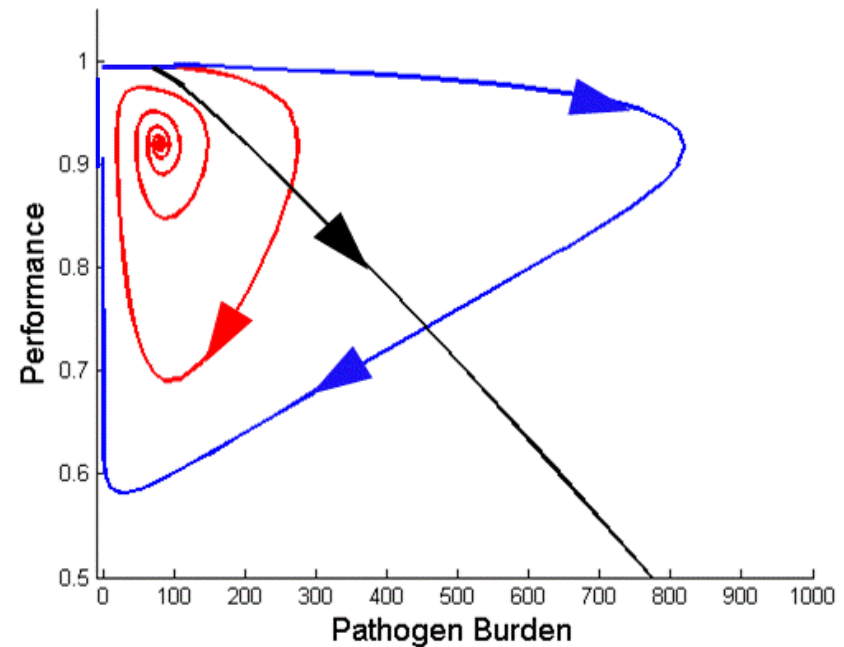
From groups to individuals



Trajectories describe dynamic interaction between host resistance and tolerance over time

- Trajectories are commonly used to study behaviour of dynamical systems

$$\begin{aligned}\frac{dS}{dt} &= \mu P - \rho S I \\ \frac{dI}{dt} &= \lambda + \kappa I \frac{S}{S + \phi} - \delta I \\ \frac{dP}{dt} &= P_0 \left(1 - \tau \frac{dI}{dt}\right)\end{aligned}$$



Individual trajectories are fully specified by system parameters

Aim: Generate specific types of trajectories

1. Categorize observed trajectories into distinct types (Schneider 2011)
2. Find a suitable mathematical dynamic model that reproduces the data trajectories types
3. Use dynamical systems theory to determine which parameter values correspond to specific trajectory types
4. Use Bayesian inference to estimate model parameter values from data
5. Use genetics / genomics to determine host genetic influence on trajectories
6. Modify trajectories by selecting for parameters

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- Genetic improvement of tolerance is desirable (in some cases)
- Tolerance can only be estimated at a group level
 - But stringent data requirements
- Individual pathogen burden – performance trajectories may provide a new solution for improving host response to infectious challenge

Acknowledgements

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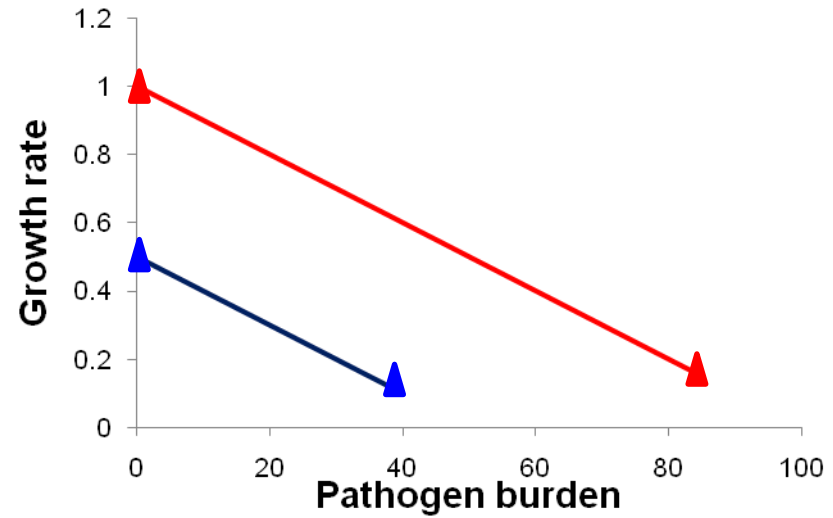
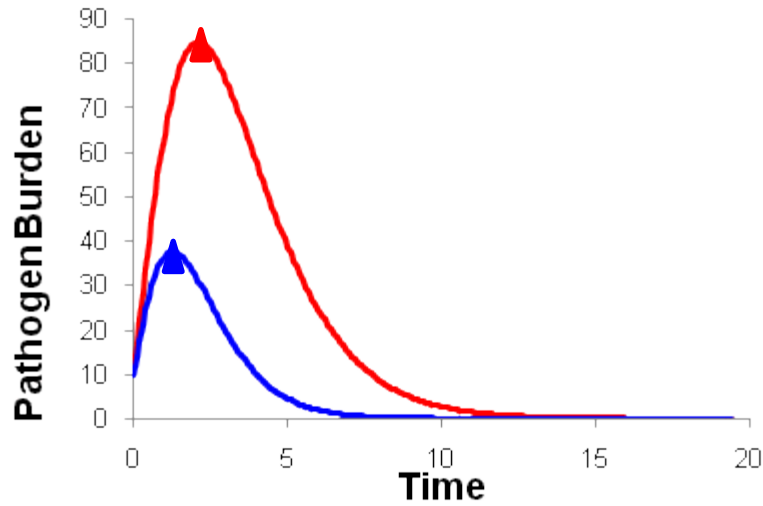
BBSRC Institute Strategic Programme grant

For more on this topic see:

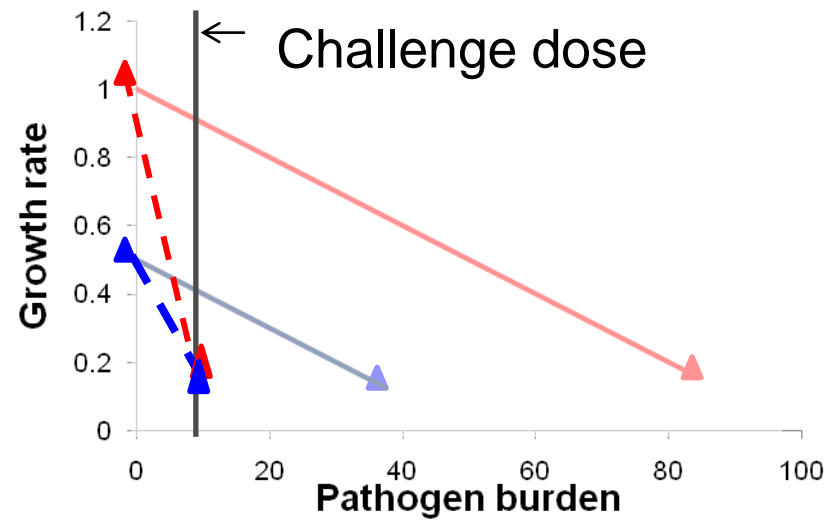
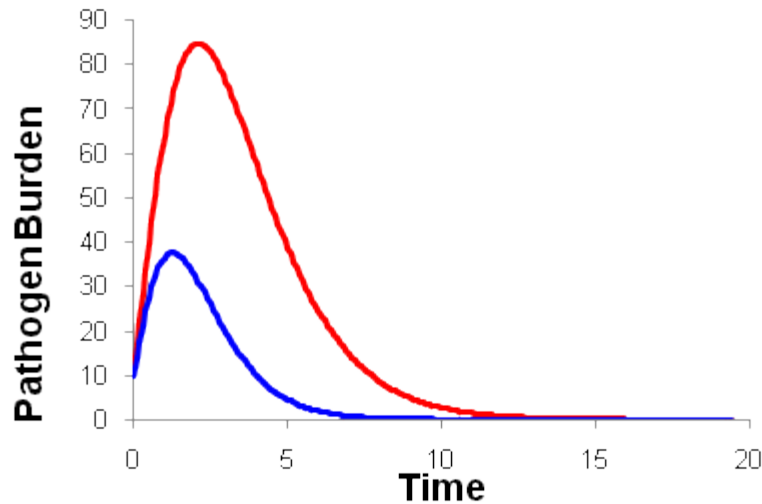
“Should we aim for genetic improvement of host resistance or tolerance to infectious disease”

Special research topic in *Frontiers in Livestock Genomics*,
to appear Nov / Dec 2012

Within-host vs environmental pathogen burden

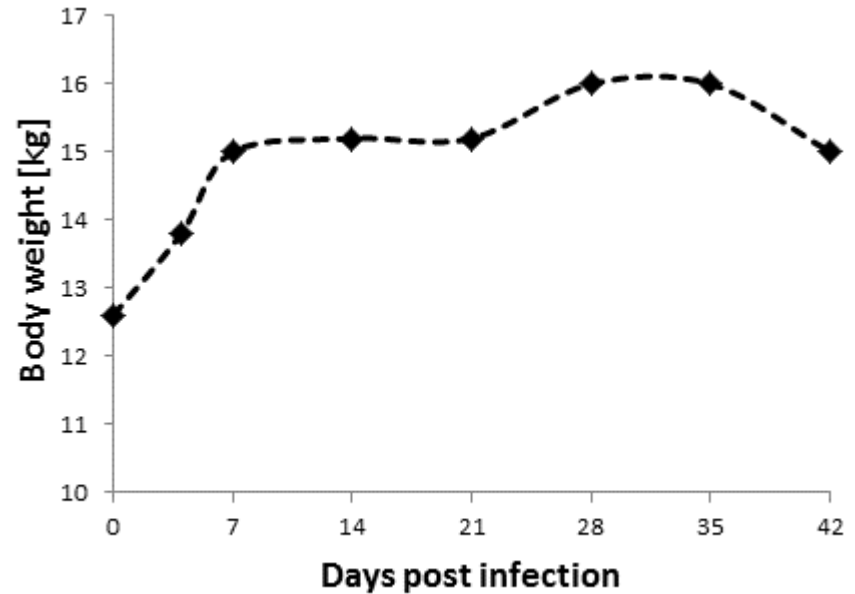
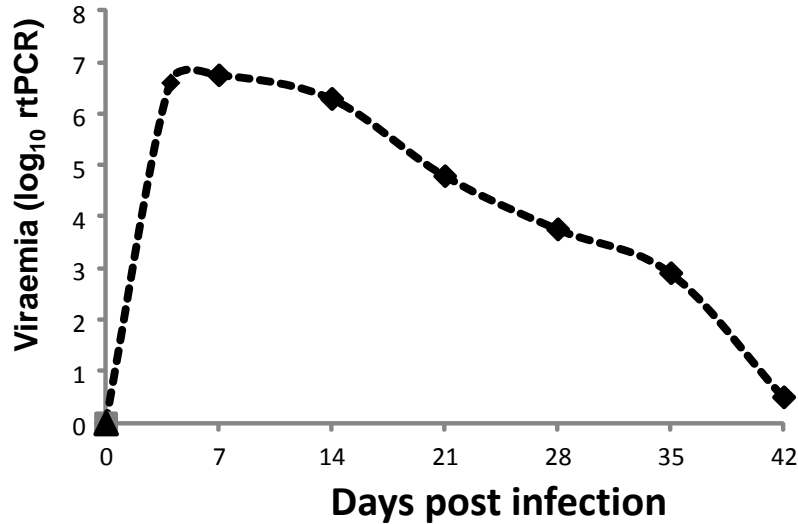


Within-host vs environmental pathogen burden



Estimation of tolerance requires a measure of within host pathogen burden rather than environmental pathogen burden

From groups to individuals

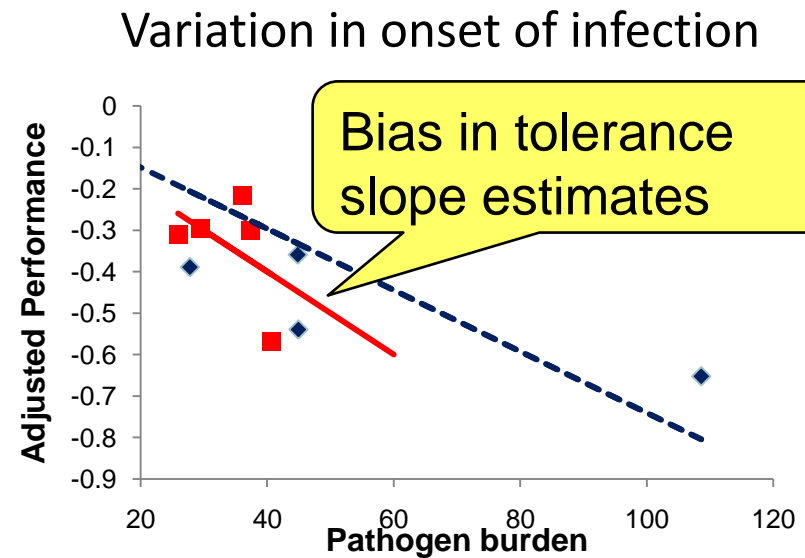
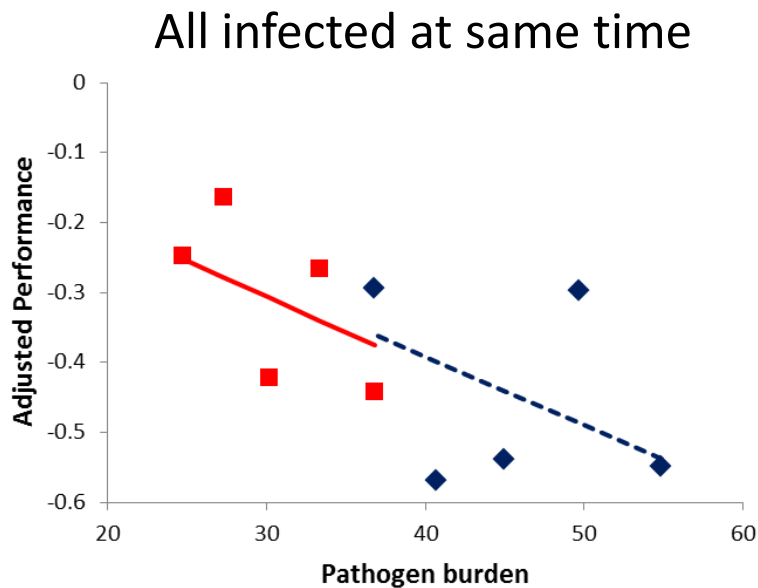


If repeated measurements of pathogen burden and performance are available:

- Many issues associated with field data (see e.g. Bishop et al., *Frontiers in Livestock Genomics* 2012)
- Individuals are likely to become infected at different times
- Time of onset of infection usually unknown

Estimating tolerance from field data

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Estimating tolerance from field data

- Individuals are likely to become infected at different times
- Time of onset

Obtaining unbiased group tolerance estimates from field data is extremely challenging

