When can field trials contribute practically to understanding of efficacy (and when do they not?)

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Alternatives to field trials

- Modelling transmission studies
- Experimental transmission studies

What are the advantages and limitations of these approaches? Should there be stipulations?

Are there times that field efficacy data are essential?

Impact of vaccination

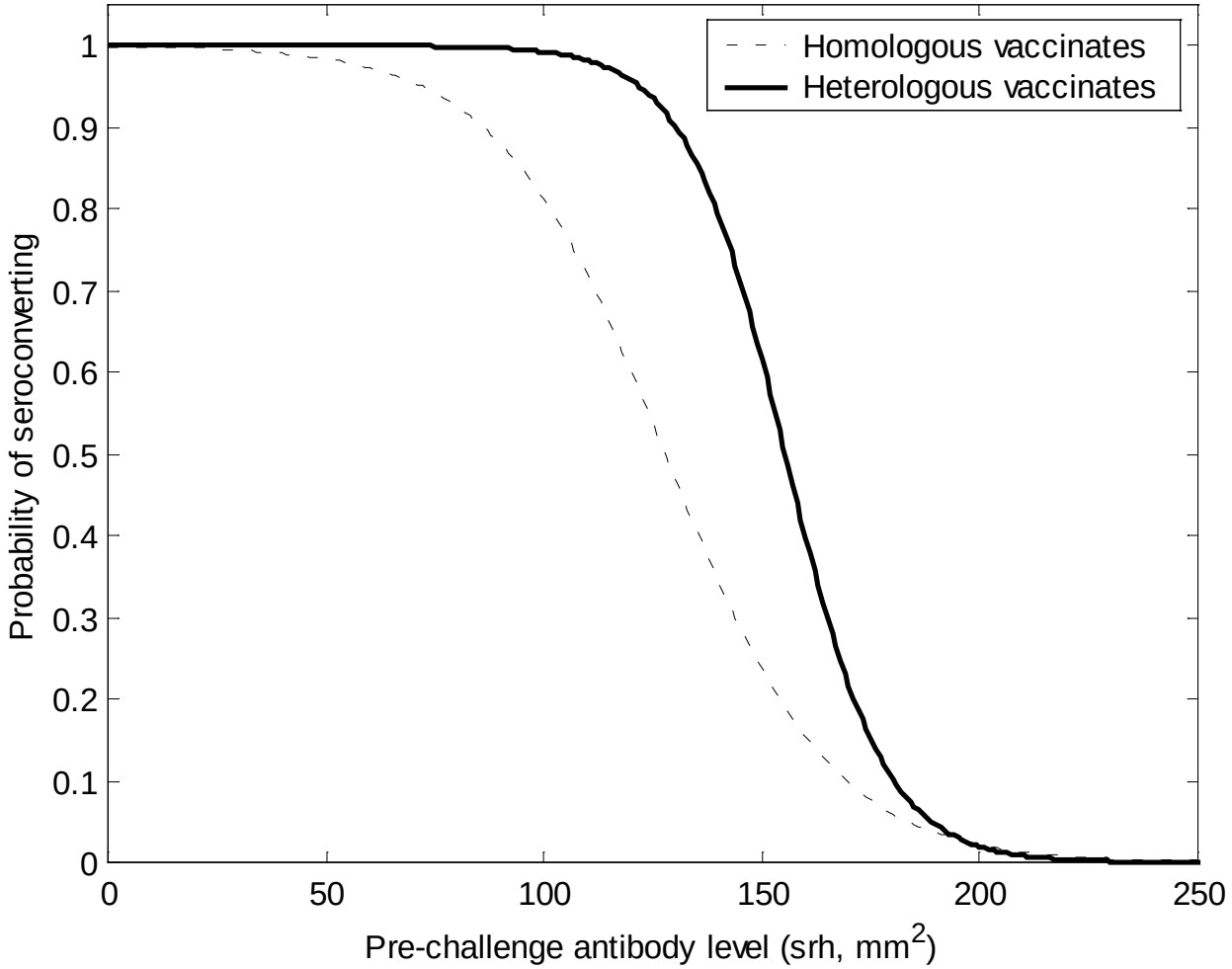
- Vaccines should obviously prevent disease in vaccinated individuals

- One of the largest impacts of vaccination is through indirect protection that comes about through reduced transmission.
  - Many experimental / dossier studies fail to consider transmission at the population level
  - Unstructured pharmacovigilance data cannot be used to assess transmission
    - Measuring transmission (and reductions) is highly complex

Case Study 1: Equine influenza vaccination

- Equine influenza vaccines need to be adequately potent against homologous virus
  - But continuous antigen drift also interferes
    - even if not linear
- When do vaccines need to be updated with new strains?
  - Experimental investigation in ponies
  - Comparison of in date with out of date vaccination
  - Carefully parameterised models demonstrate that impact is far larger than expected from experimental data

Difference 1: Seroconversion depends on antibody level and homology of viruses



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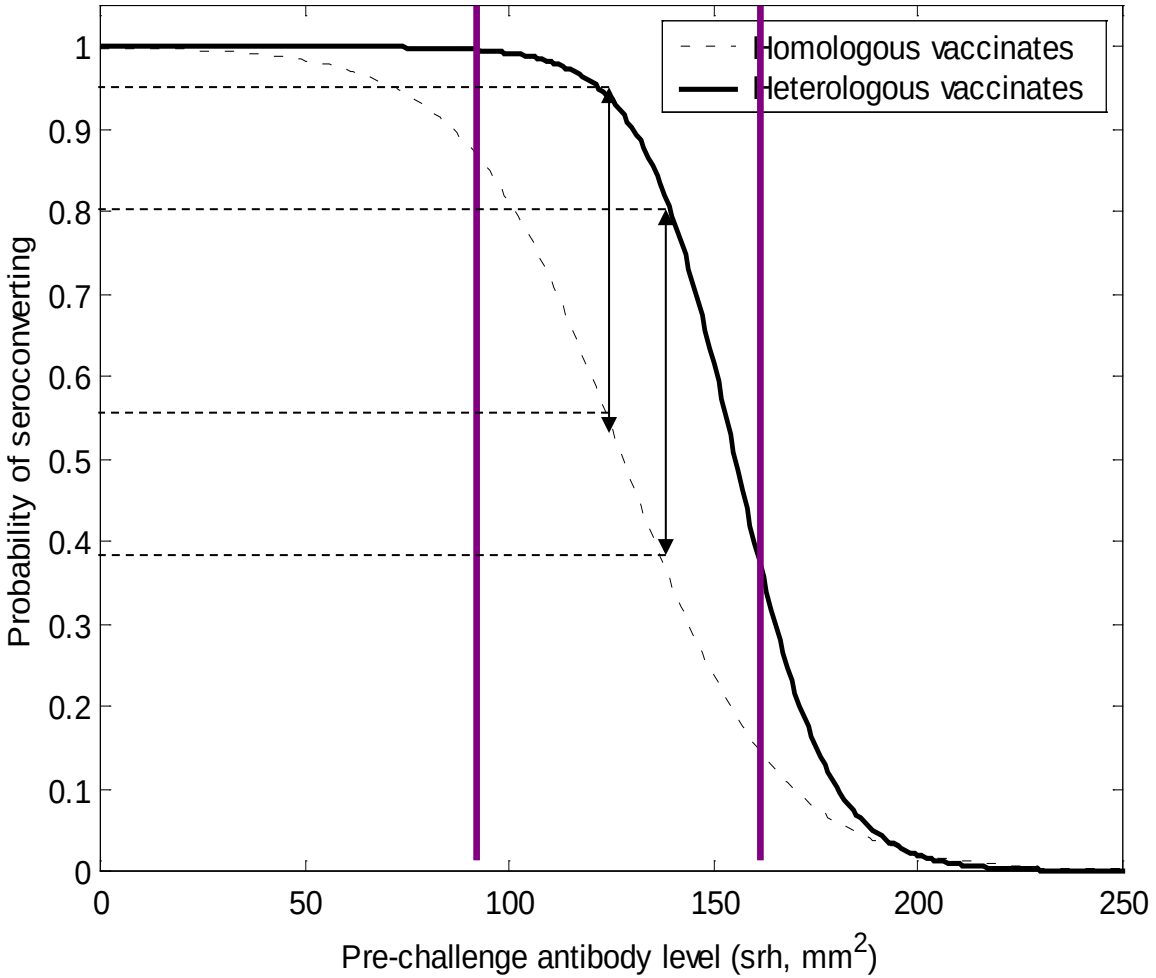

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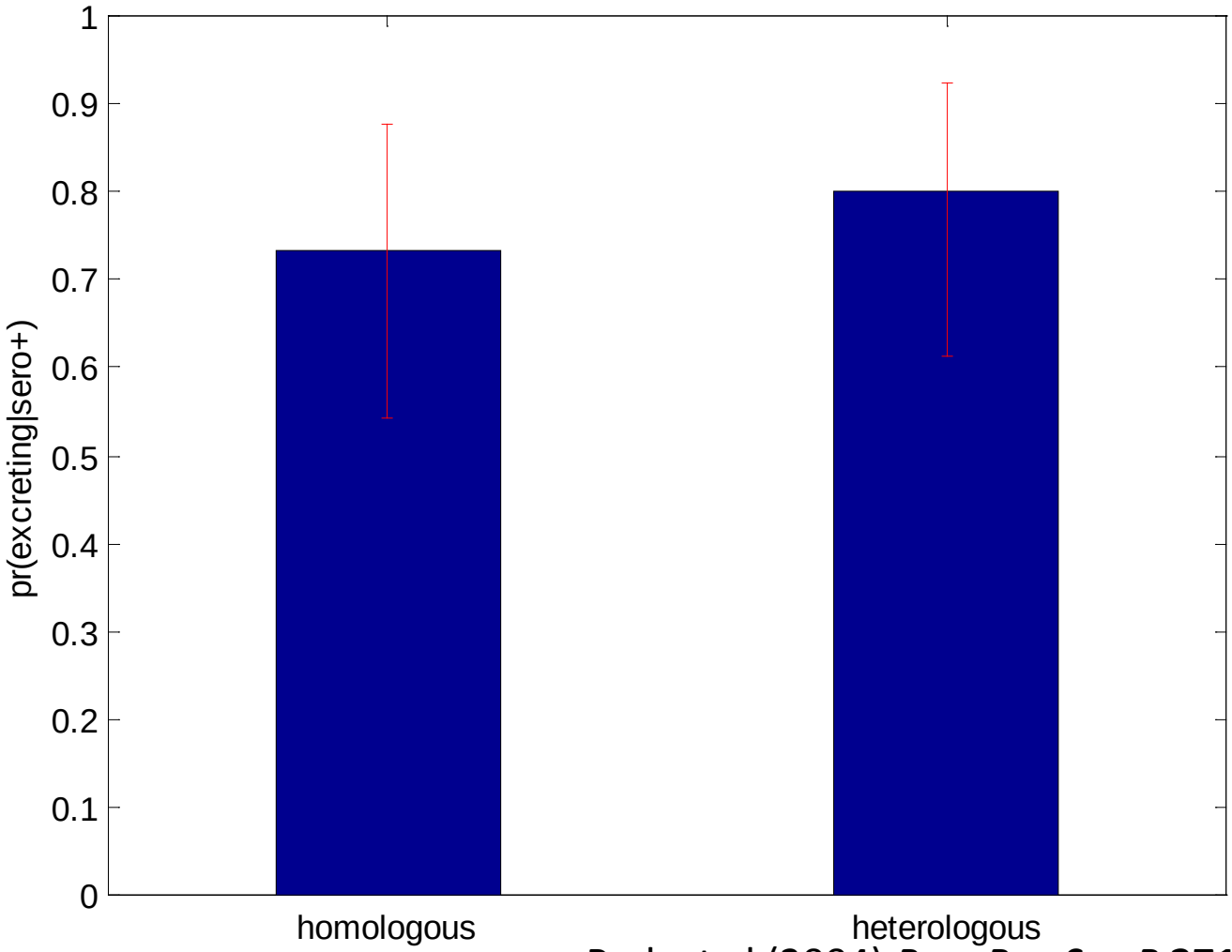
Difference 2:
Not all seroconverters excrete virus



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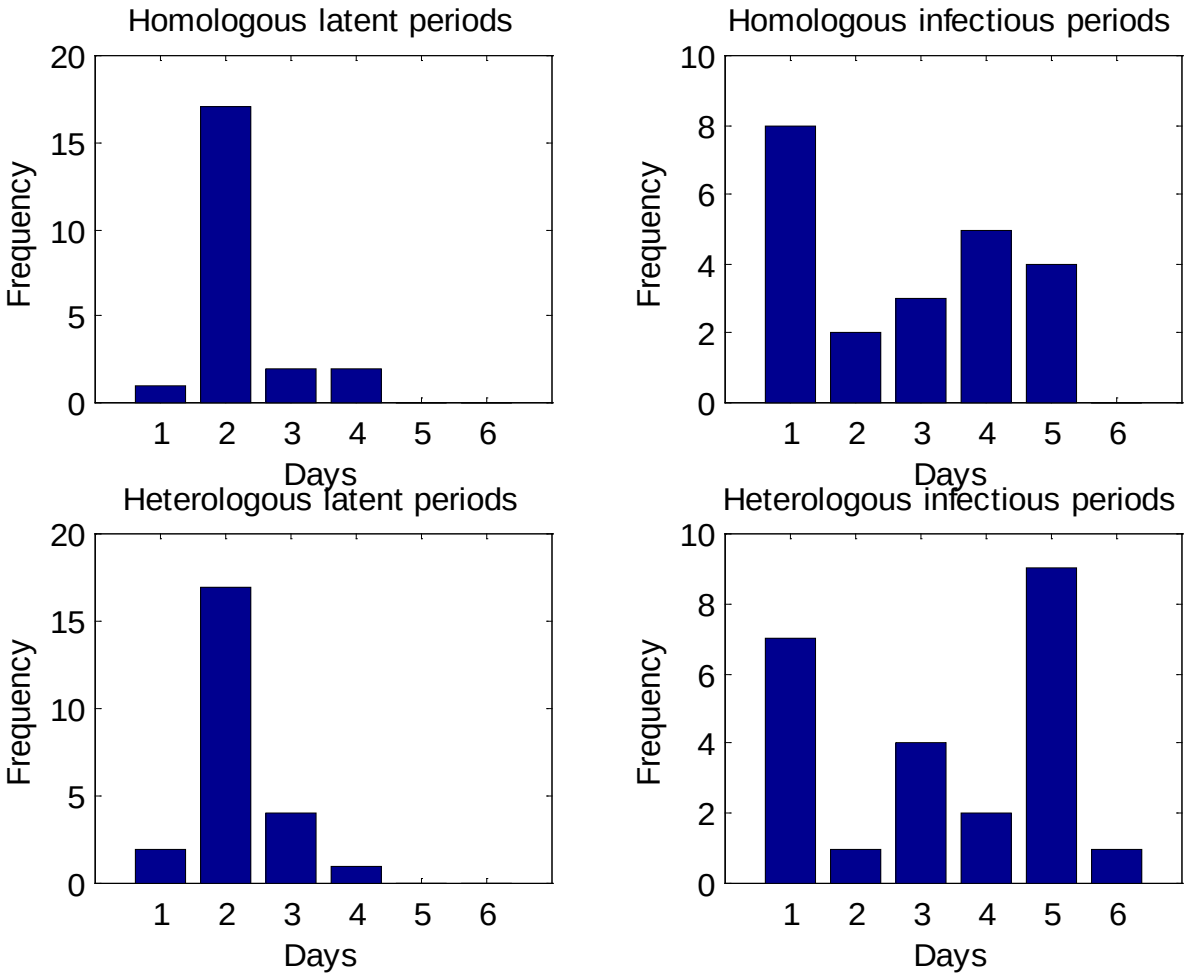
Difference 3: Latent/infectious periods



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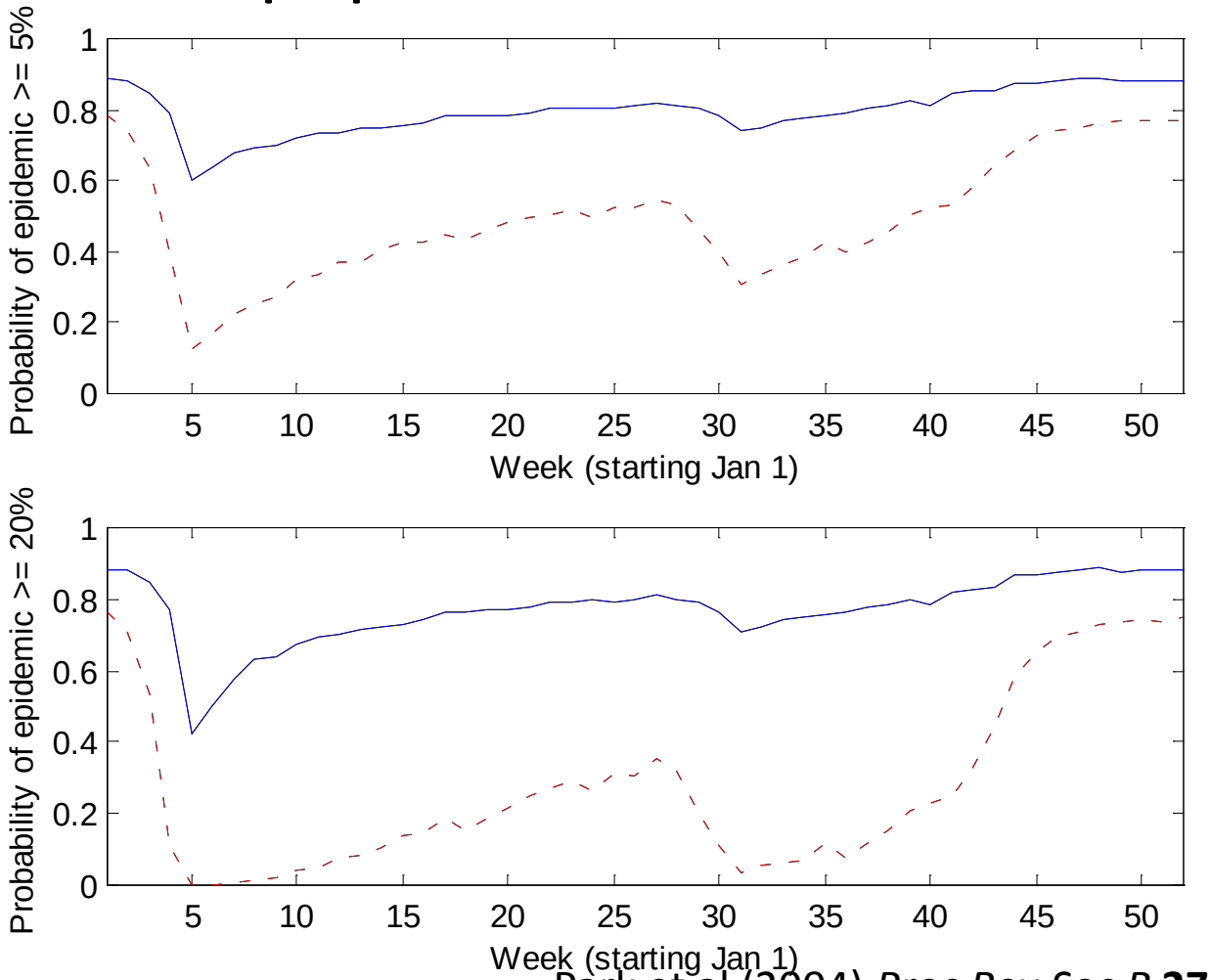
Impact:
Heterology significantly increases modelled risk in populations of racehorses



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Bovine TB vaccination

- An aspiration for GB government policy
- Requires a change in EU law
  - Invited ESPA opinion states need for field trials that show reduced transmission
- Field trials would require vaccination to be a supplement to current measures
  - Positive animals are removed on detection which reduces low transmission to very slow
- We used carefully parameterised within herd transmission models to consider the necessary scale of trials

Conlan, Vordermeier, de Jong & Wood *submitted*

Necessary field trial scale

- Removal of test-positive animals from herds obscures benefits of vaccination
  - severely limits potential to discern impact of vaccination on transmission
- 100 herds required to demonstrate impact of vaccination at animal level
  - But farmers and policy makers need information on farm scale impact as controls operate at level of farm
- >1000 herds required to demonstrate impact at herd level

Conlan, Vordermeier, de Jong & Wood *submitted*

Alternative experimental transmission studies

- Experimental transmission studies
  - Use 50:50 mix of infected seeder animals and sentinel animals
  - Consider joint final size probability distributions
- Very sensitive to assumed / estimated R0 in cattle and herd size effects
- For effect size: 75% and power: 80%, R0 1.5
  - required in-contact time 1-6 years depending on the transmission scenario, with a group size of 52 animals
  - For 50% effect size, group size 128 & duration 1-5yrs

Conclusions

- Modelling can provide greater understanding of meaning of experimental data than simple statistical analysis of data from vaccine trials
  - Massive non-linearities in transmission make impacts of interventions very unpredictable
- Pharmacovigilance data will fail to demonstrate full impact of interventions in many cases
- Field trials can be massively inefficient and costly
  - Can fail to estimate transmission changes
  - Can fail to answer question of interest because of scale
  - Should in many cases be replaced by more efficient experimental design