Enhancing genetic disease control by selecting for lower host infectivity

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Host genetic variation affects the severity and spread of infectious diseases

<u>Host Susceptibility</u>: "propensity of becoming infected upon contact with pathogens"

- **Genetic selection schemes in livestock aim to reduce susceptibility**
  - Marker assisted selection targeting reduced susceptibility to infectious pancreatic necrosis in Atlantic salmon (Houston et al. 2010)
  - Genetic evaluations for resistance to bovine tuberculosis in UK cattle (Banos et al. 2016)

Infectivity: "the host's ability to transmit infection"

- **Super-spreaders**

  Small fraction of highly infectious individuals, responsible for a disproportionally large number of transmission events

  Pareto principle, 20% of infected individuals are responsible for 80% of new infections

  Measles, SARS, Ebola (humans), *Salmonella* (mice), *E. coli* and bovine tuberculosis (cattle)

- **What if host infectivity was genetically controlled?**

  ⚠ **Infectivity is a social effect, not directly observable**

  - Recent advances in inference and data collection methods enable estimation of infectivity genetic parameters (Anacleto et al. 2015; Wilson paper 462, Anacleto paper 500 Biology-Disease Resistance 3)

  ➢ ***Genetic selection for reduced host infectivity?***

Aim of study

Assess the benefits of including infectivity in genetic selection schemes for reducing the risk and severity of infectious disease outbreaks

Simulation process

Model genetic selection for reduced susceptibility and infectivity

Generate and renew populations

Polygenic genetic variation in infectivity and susceptibility

Individual infectivity and susceptibility phenotypes

$$Log(y_i) = \mu + A_i + e_i$$

$$A_i = (TBV_{si}+TBV_{di})/2+MS_i \quad TBV \sim MVN(0,\mathbf{G})$$

20 non-overlapping generations

Select for reduced susceptibility and infectivity with assumed accuracy and intensity

New trait-means μ due to response to selection on sires (Breeder's equation) and new offspring A_i sampled with new variances after selection (Bulmer effect)

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Simulation process

50 Replications

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Model Epidemiological Impact

Simulate epidemics

Randomly chosen index case within each group, e.g. herd

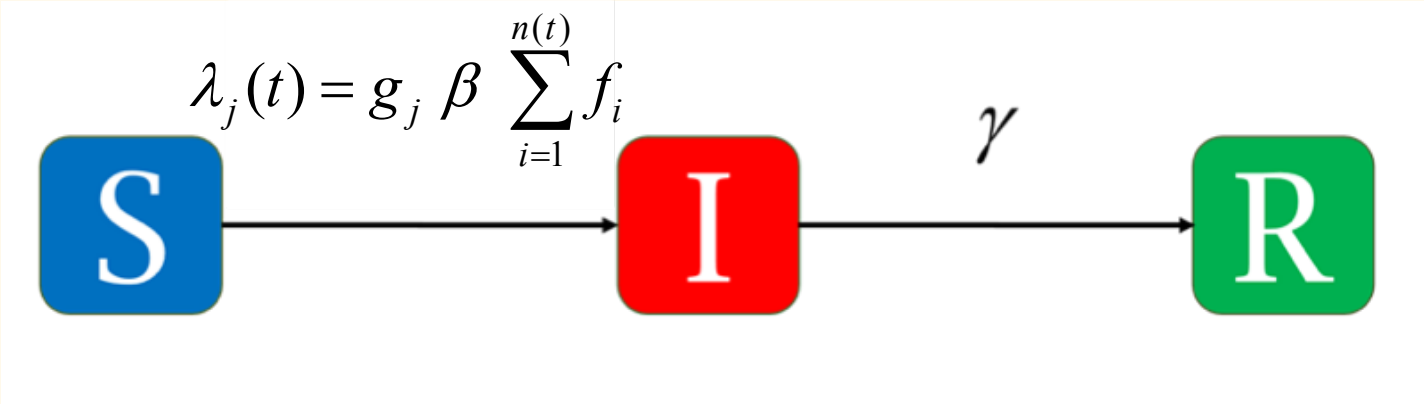
Stochastic SIR model*

Assess Epidemiological Impact of Selection

Link changes in epidemic risk and severity to genetic gain per generation

Genetic epidemiological prediction model

- **Stochastic compartmental SIR (Susceptible - Infectious - Recovered) model**
  - Individual infection and recovery events simulated using the Gillespie direct method (Gillespie 1977)
  - Infection rate $\lambda_j(t)$ of individual j depends on individual susceptibility g_j and on infectivity f of infected individuals in the same group, at time t (Anacleto et al. 2015)



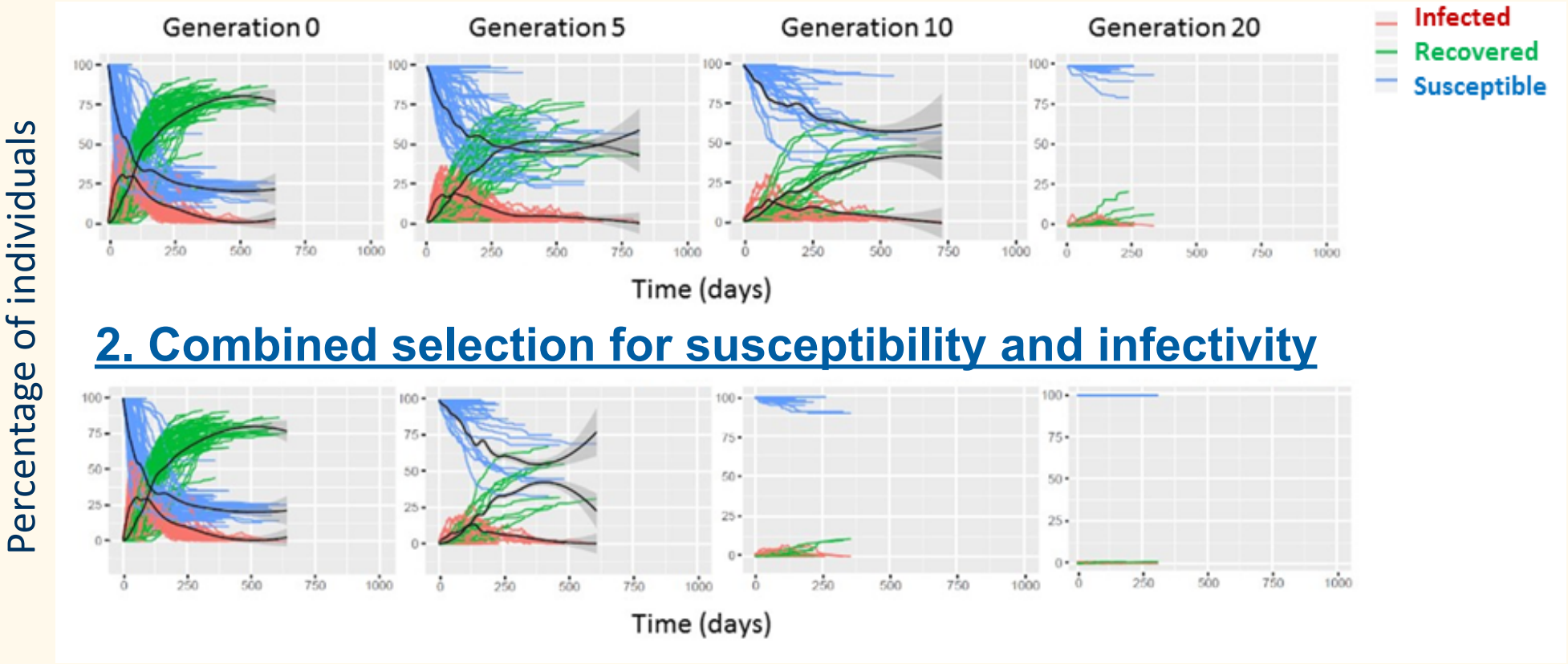
- Susceptible
- Infected
- Recovered

- β average effective contact rate
- γ recovery rate

Results

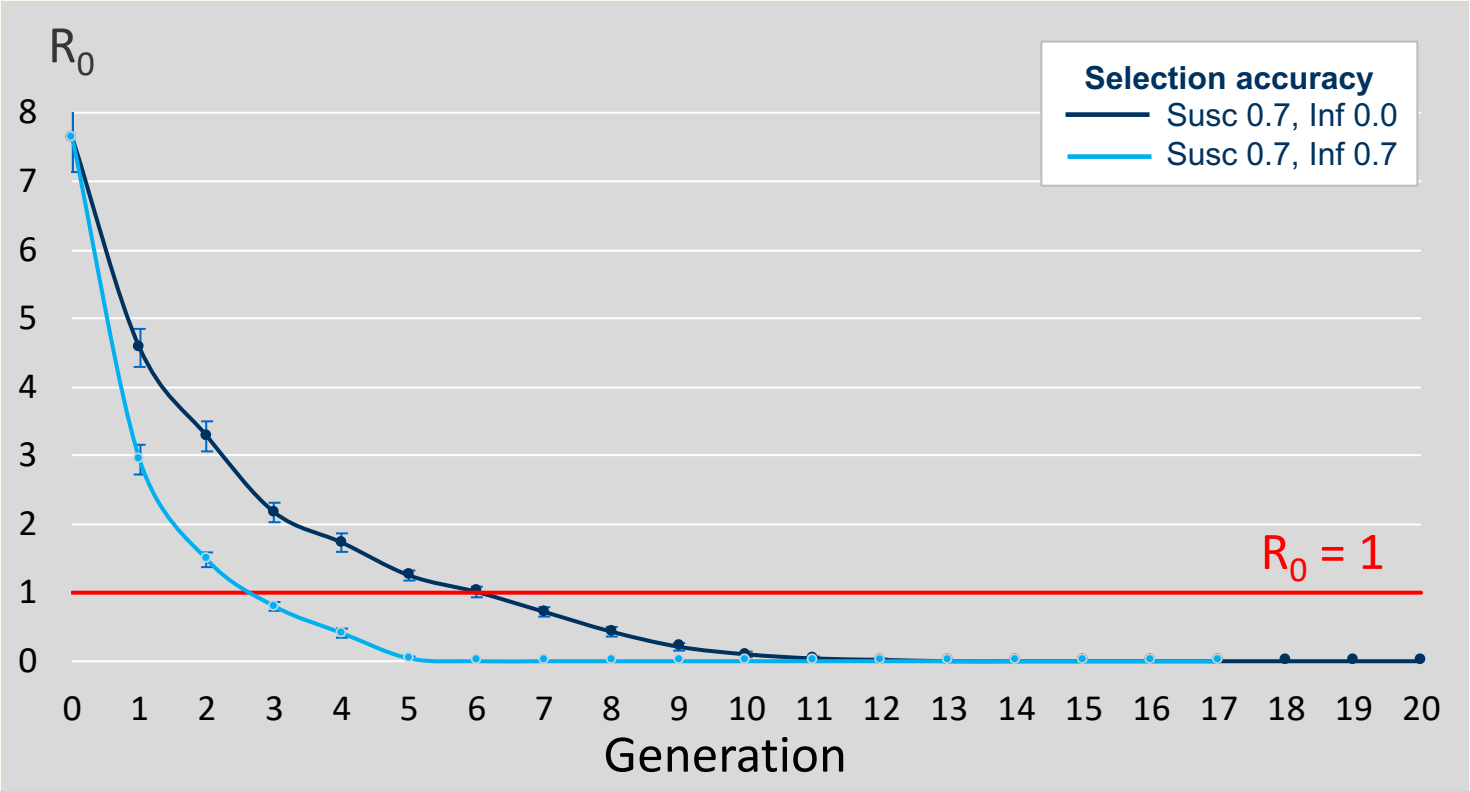
Stronger and quicker reduction in the number and severity of epidemics with combined selection

1. Selection for susceptibility



Combined selection reduces the number of generations required for effectively controlling epidemics

Basic reproductive ratio R_0: "expected number of secondary cases produced by a typical infectious individual in a susceptible population"



- **50% selection on susceptibility and infectivity**

Selection on susceptibility required 7 generations to achieve R_0<1

Combined selection required 3 generations

R_0 > 1
epidemic will spread
R_0 < 1
epidemic will die out

N = 10 000 offspring, 200 sires, 50 dams/sire

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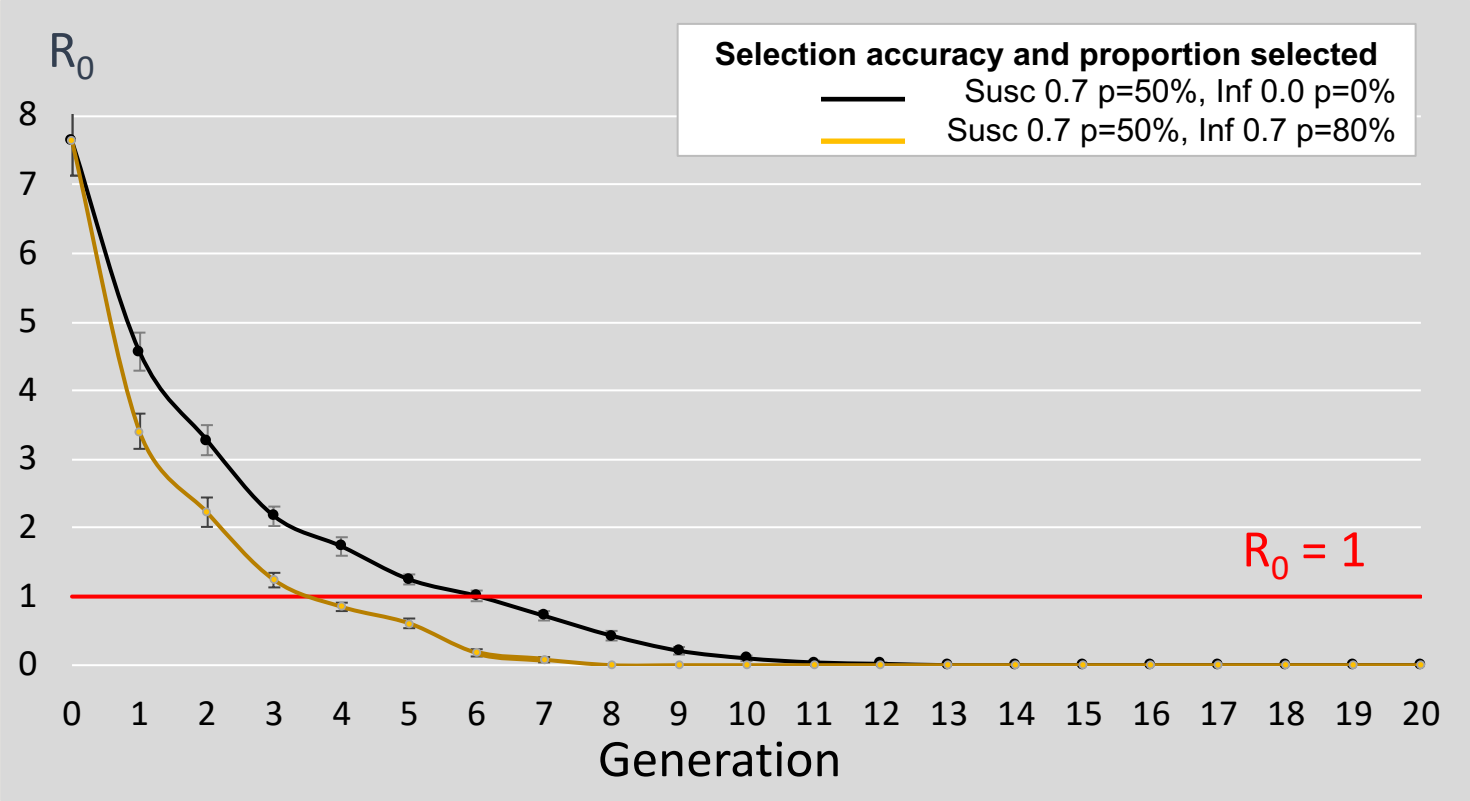
Removing designated super-spreaders is more efficient than selection on susceptibility alone

- 80% selection for infectivity and 50% selection for susceptibility



N = 10 000 offspring, 200 sires, 50 dams/sire

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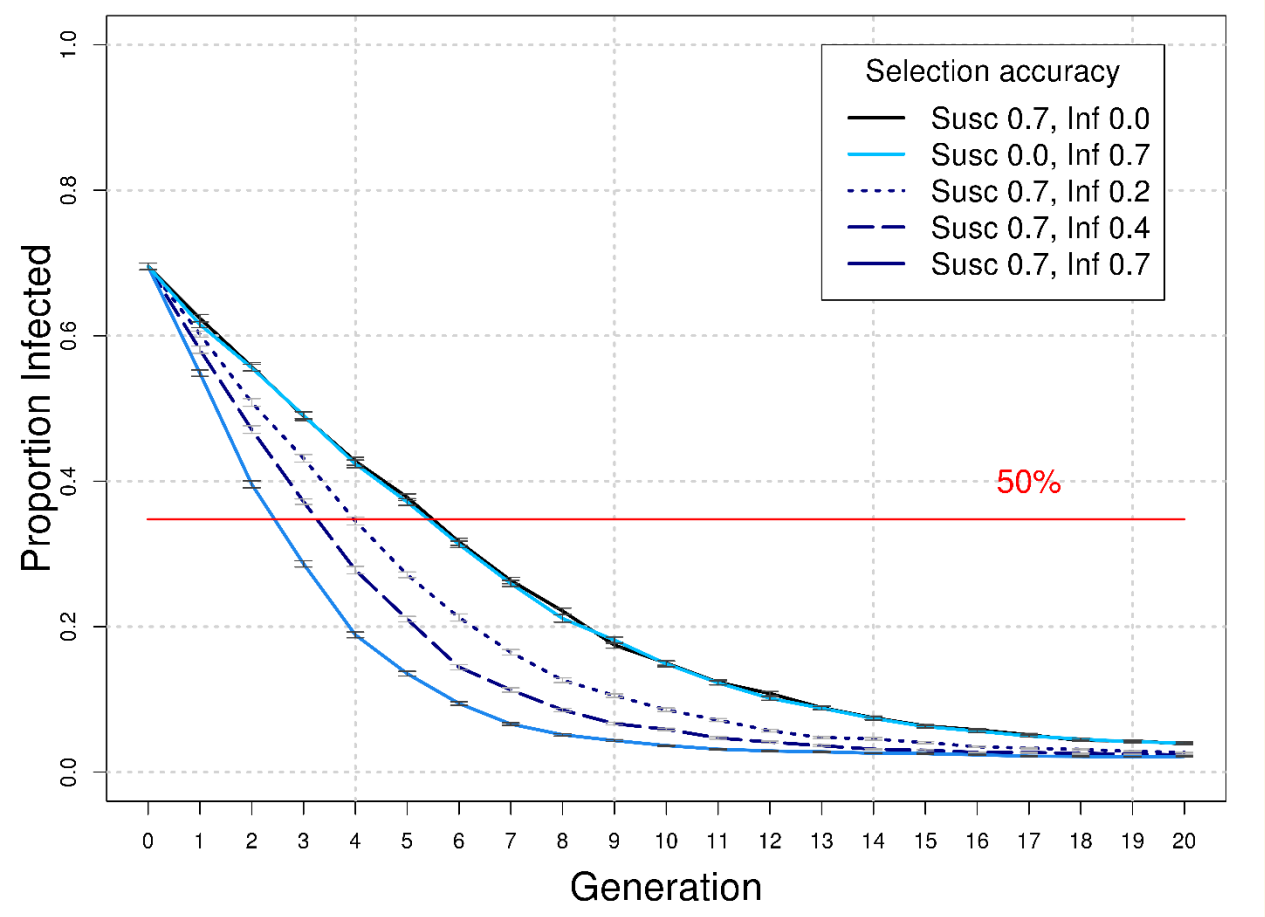
Combined selection requires fewer generations for reducing epidemic severity by 50%



- Selection on susceptibility required 6 generations to reduce epidemic severity by 50% in groups where epidemics occurred
- Combined selection required 3 generations

- Even with **lower accuracy** for infectivity, combined selection conferred significant reduction of epidemic severity
- **Genetic variance** is a driving parameter

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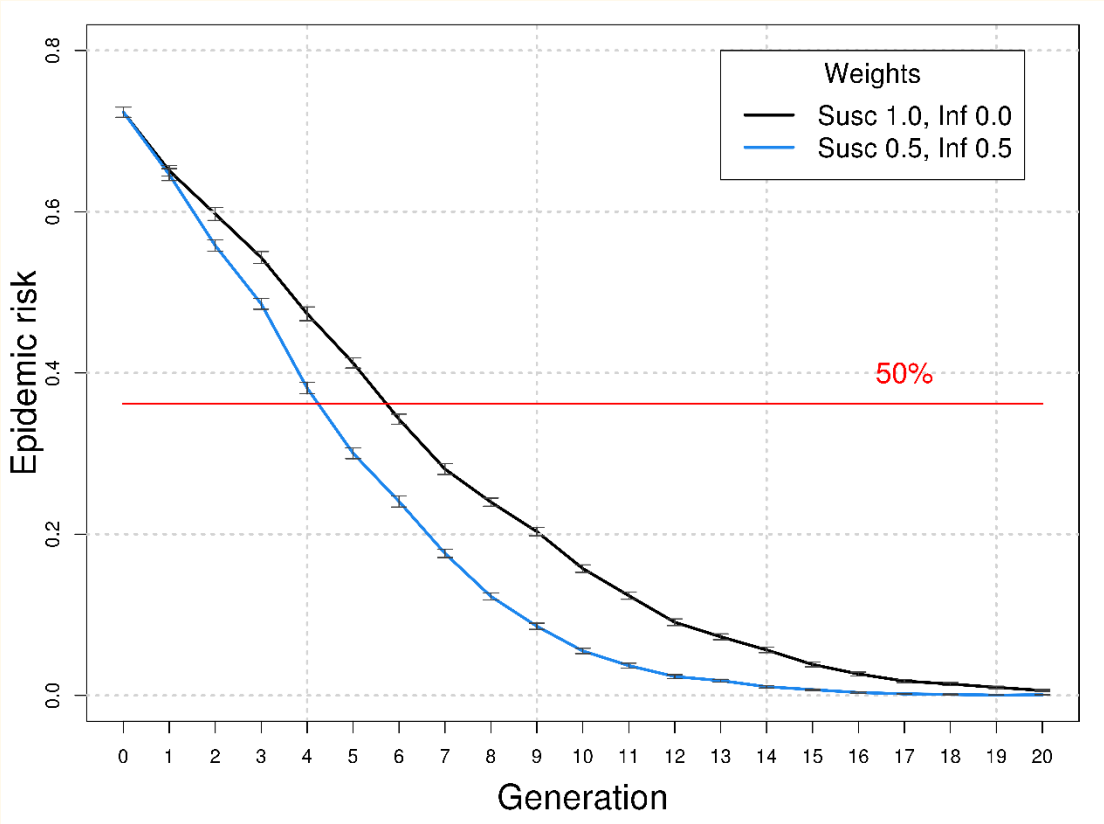
Favourable genetic correlation between susceptibility and infectivity reduces the benefits of adding infectivity

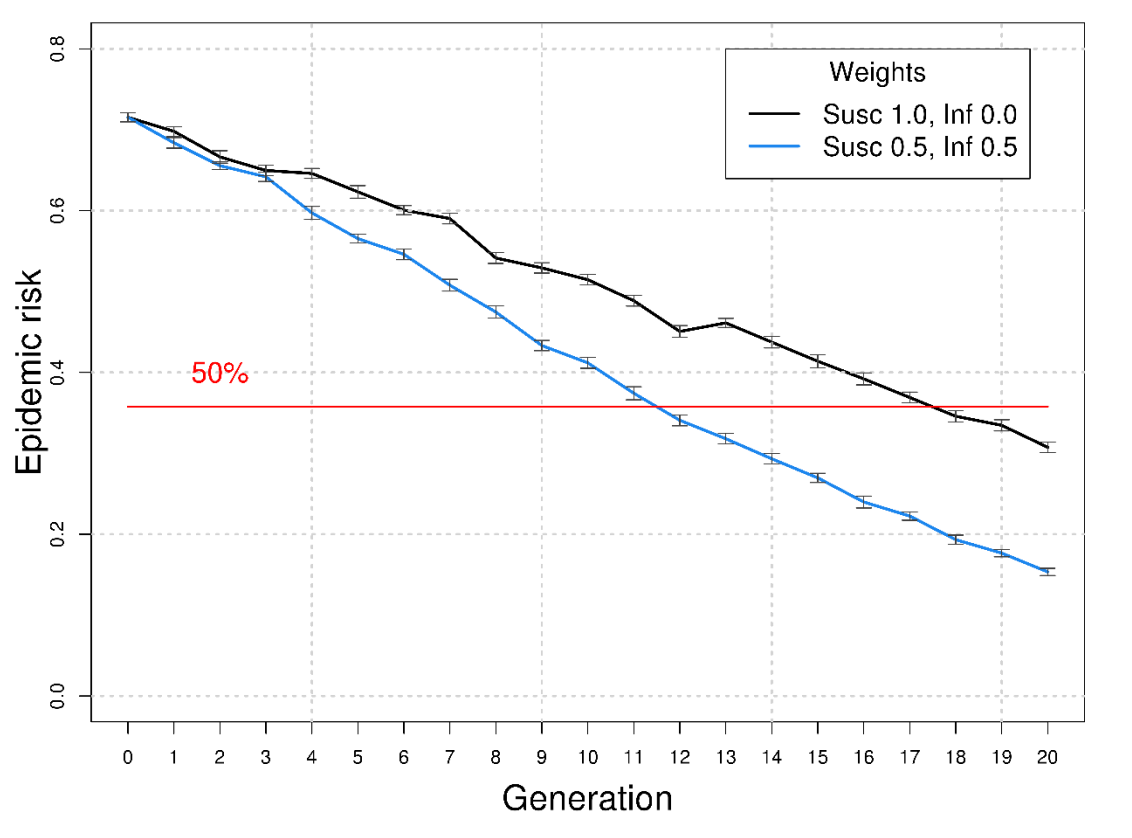
Favourable genetic correlation of 0.5



- Combined selection with equal weights for both traits, was only one generation faster than selection on susceptibility alone in reducing epidemic risk by 50%

Unfavourable genetic correlation makes inclusion of infectivity more pertinent

Unfavourable genetic correlation of -0.5



- Reducing epidemic risk by 50% was substantially delayed due to indirect correlated responses
- Combined selection alleviated the delay

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Application to bovine tuberculosis (bTB)

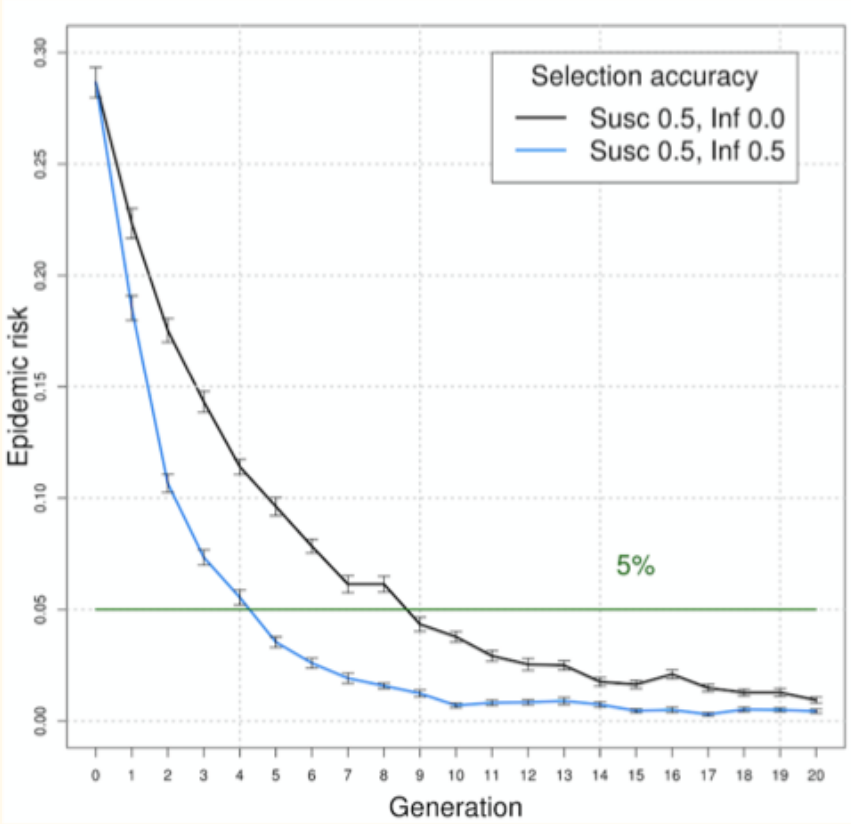
Susceptible → Latent → Infectious → Test-sensitive ⇢ 60 days testing and removal with Sensitivity 60%

Background force of infection e.g. wildlife, neighbouring herds

$$\lambda_j(t) = \alpha + g_j \, \beta \sum_{i=1}^{I(t)+T(t)} f_i$$

- ❑ Infectious bacterial disease with devastating consequences worldwide
- ❑ UK TB eradication strategy: **systematic testing** of herds to identify and remove infected cattle

- ❖ **Combined selection for reduced bTB susceptibility and infectivity required fewer generations to reduce bTB breakdown risk to 5%**
  - Model calibrated with data from UK genetic evaluations (Banos et al. 2016; Raphaka et al. Phd thesis 2018)
- ❖ Early identification and removal of cattle with high genetic infectivity can help eliminate a major risk factor for herds exposed to bTB and a source of infection for wildlife



Conclusions - Implications

Genetic selection considering both susceptibility and infectivity can reduce disease risk and prevalence more efficiently

- Estimating infectivity is a challenge – requires sophisticated methods and data designs
  - But it can substantially benefit genetic disease control strategies
- Infectivity – new opportunities for disease control
  - Removing super-spreaders
- Awareness of genetic variation in infectivity when genetic correlations are unfavourable can be crucial

Thank you for listening

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Mike Coffey

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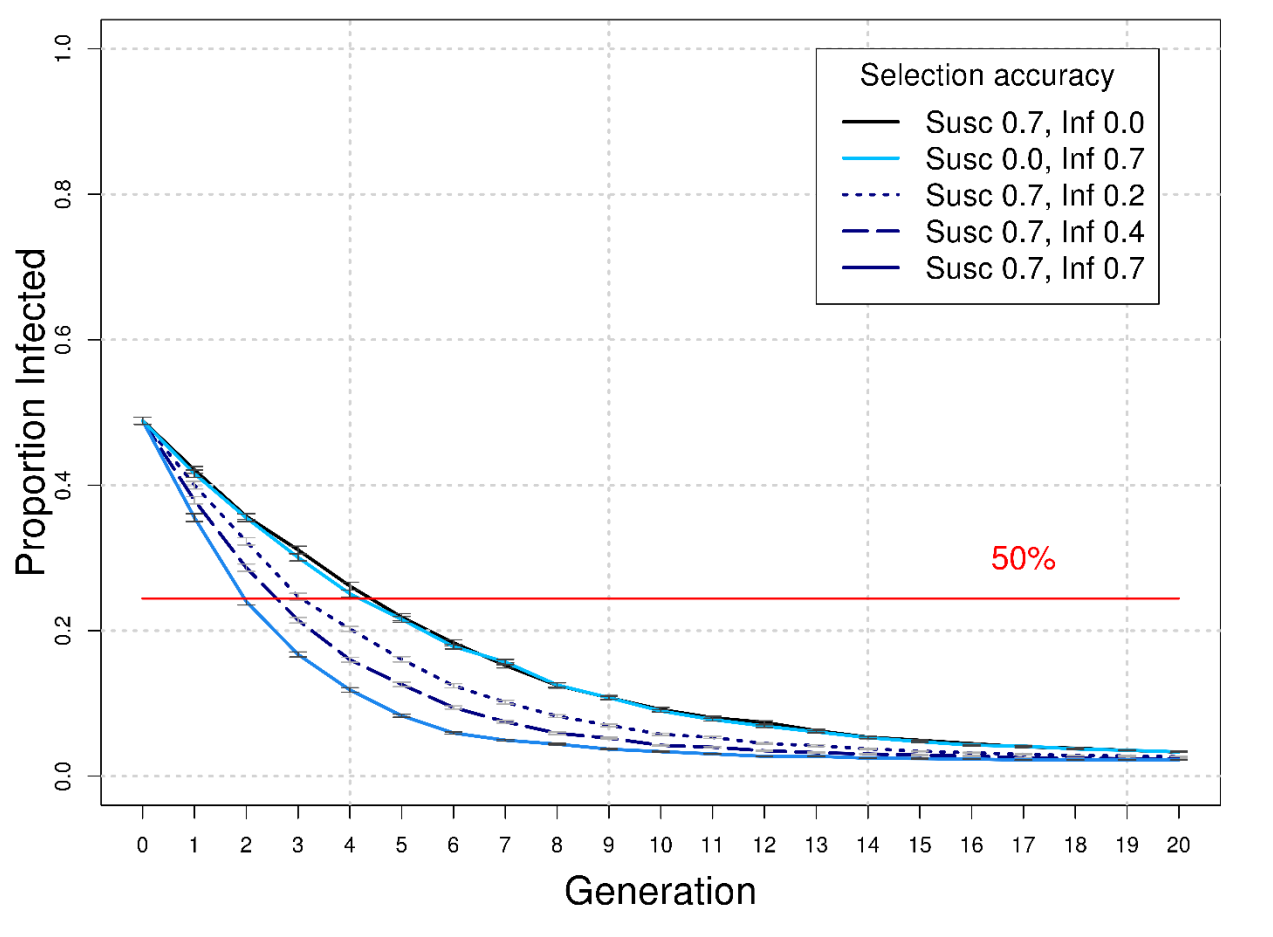
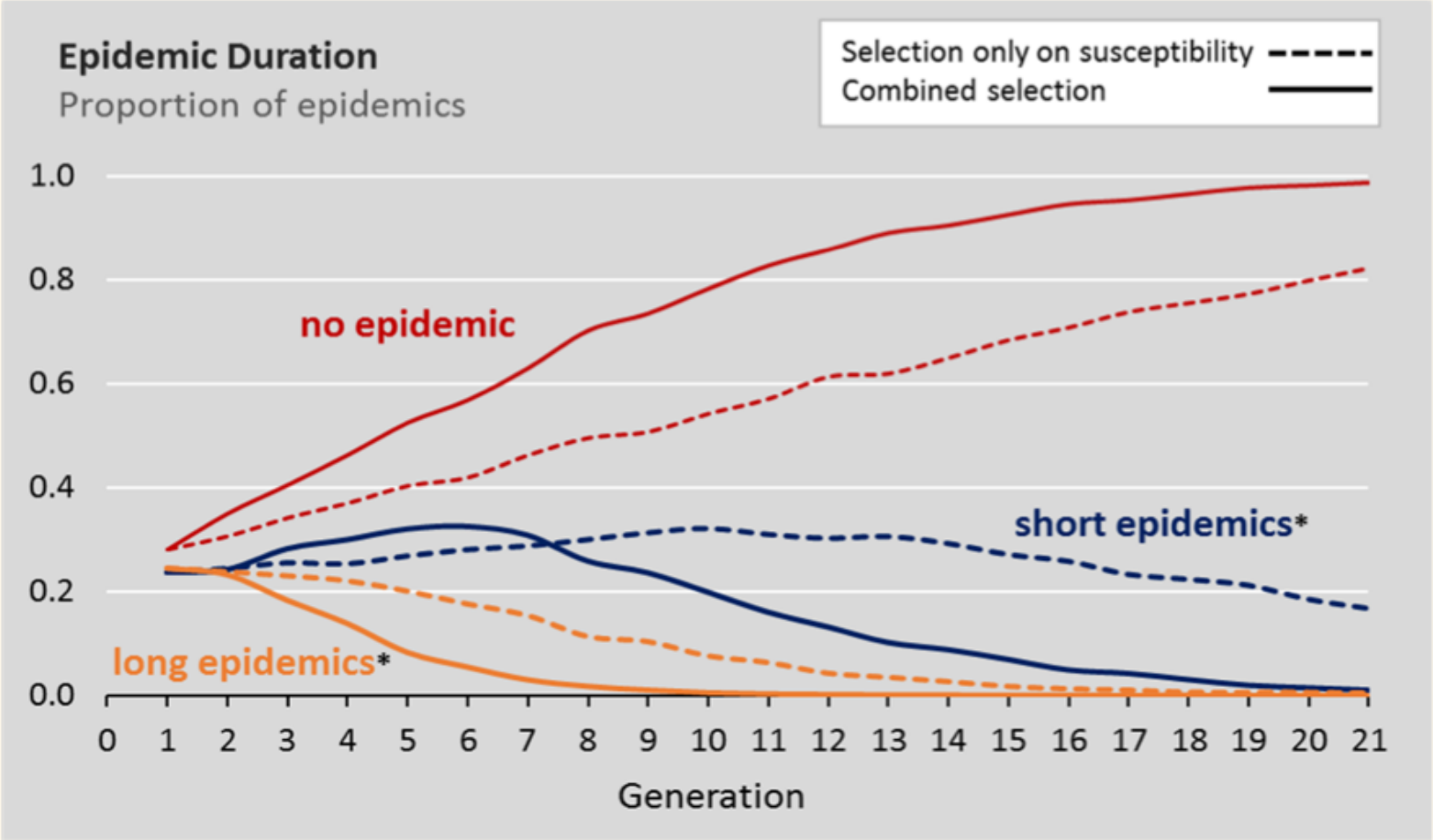
Supplementary



- Differences between combined selection and selection only on susceptibility in reducing epidemic severity, were less pronounced when the assumed genetic variances were lower (σ_A^2=0.2)

Supplementary
Impact of selection on epidemic duration



* Where long and short epidemics were defined as epidemics whose duration was in the upper and bottom tertile in the base population

- After 5 generations of combined selection <10% of epidemics were **long epidemics**, while 10 generations of selection on susceptibility alone were required for the same outcome
- After 12 generations of combined selection there were no long epidemics