ROSLIN

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Large scale transmission experiment reveals substantial genetic variation in both host susceptibility and infectivity affecting disease spread and survival

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UKRI Biotechnology and Biological Sciences Research Council

FISHBOOST
The next level of aquaculture breeding

Reducing pathogen transmission is paramount for planetary health

Image: freepik.com. Design by Mali Welch

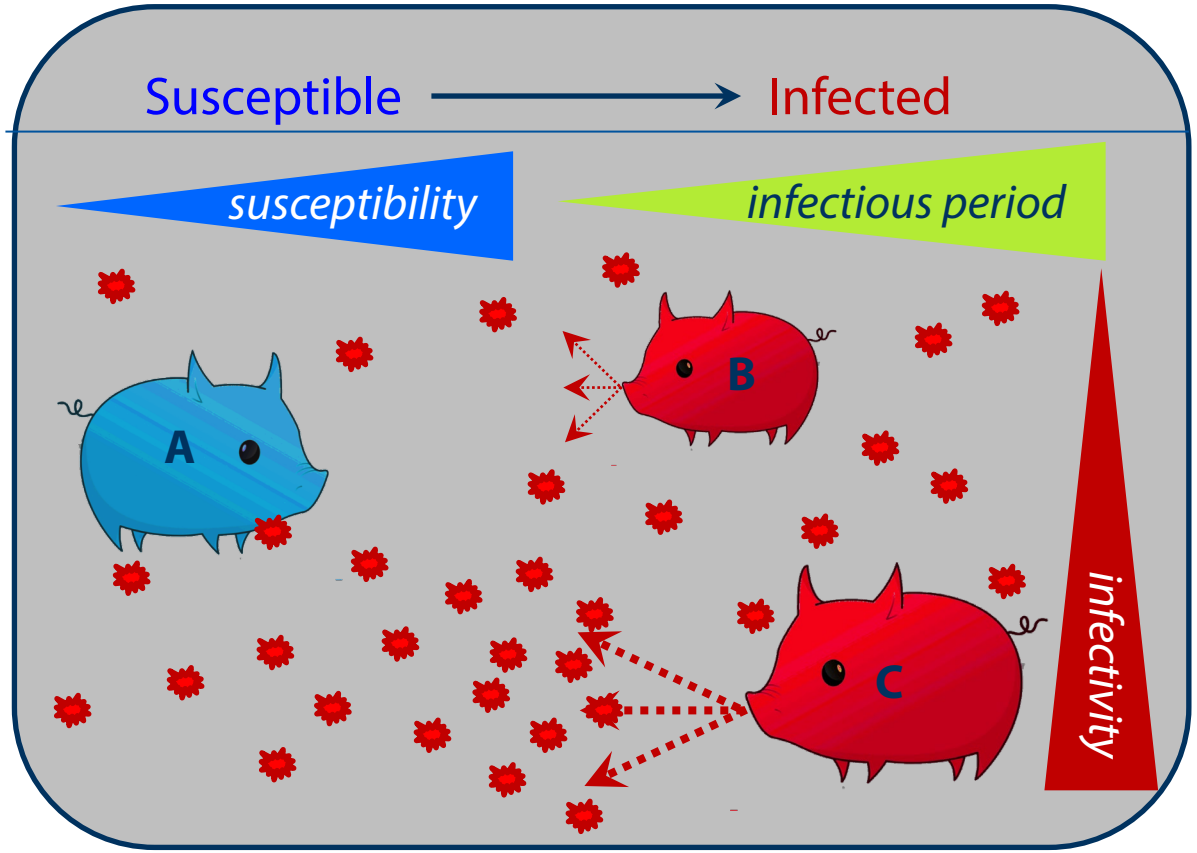
Epidemiological approach:
reduce $R_0 < 1$

Can geneticists help?

How to detect and estimate genetic variation in host ability to transmit infection?

Host traits affecting disease transmission

R_0: expected number of secondary infections caused by 1 infectious individual in a susceptible population over its infectious lifetime



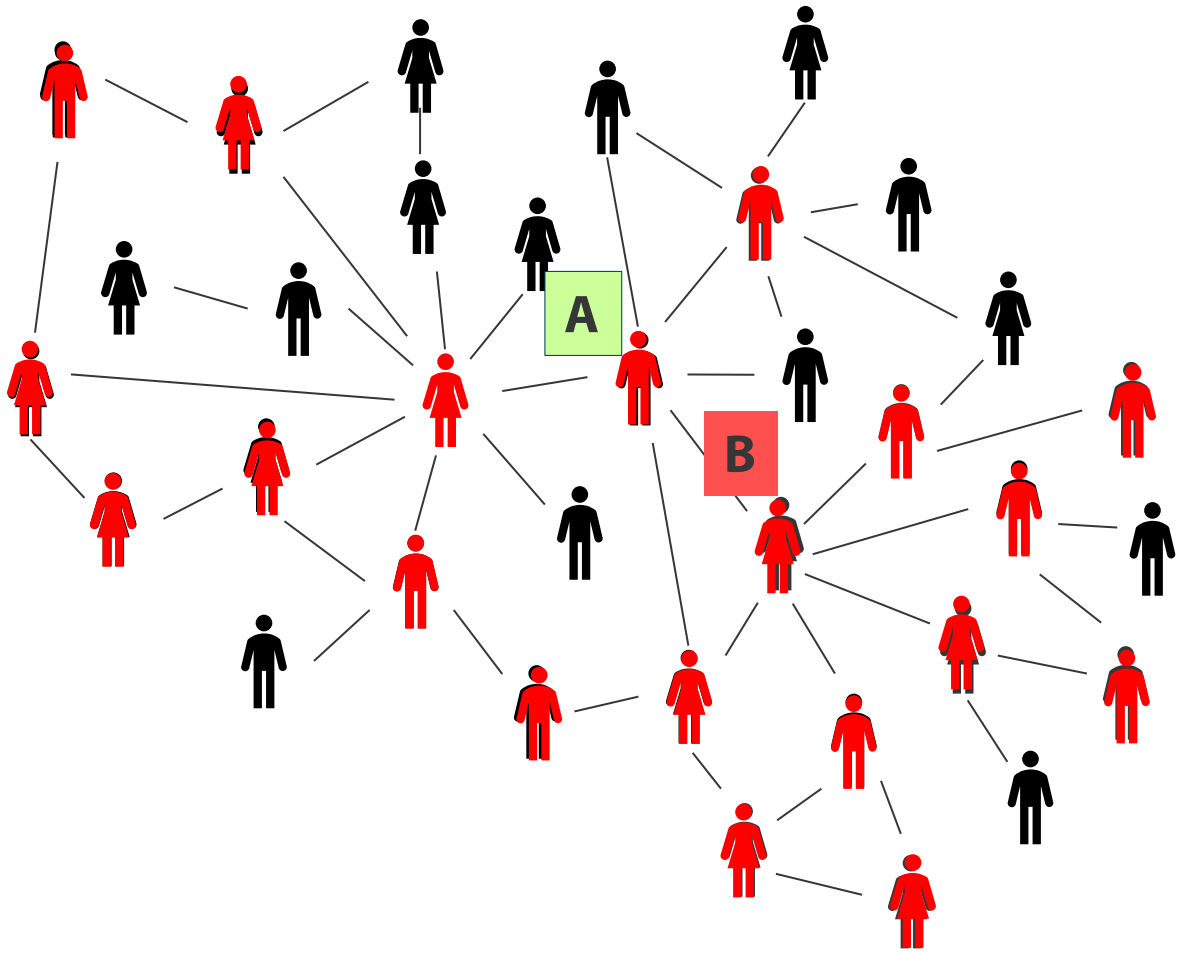
Susceptibility:
Propensity to acquire infection

Infectivity:
Propensity to transmit infection

Duration of infectious period:
- Related to tolerance (propensity to recover / die)

Latent traits; confounded

How to estimate genetic variation susceptibility, infectivity & tolerance



Data:

- Proxies of individuals' infection times
- From many epidemics

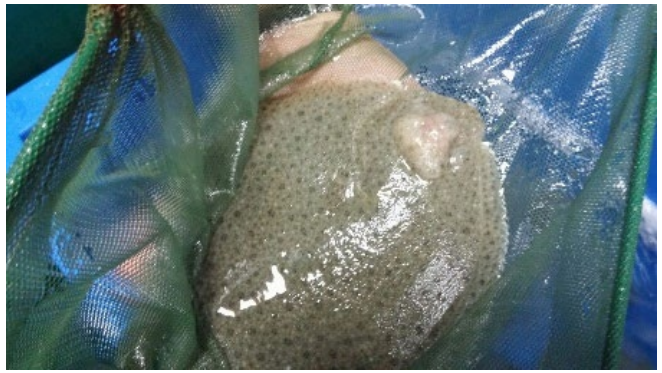
Models that represent infection dynamics

Inference methods that can handle uncertainty

Case study: Scuticocciliatosis in Turbot

Skin infection in turbot caused by protozoan *P. Dicentrarchi*

- Good genetic model:
  - Easy to create many large full / half-sib families
  - Evidence for genetic variation in resistance

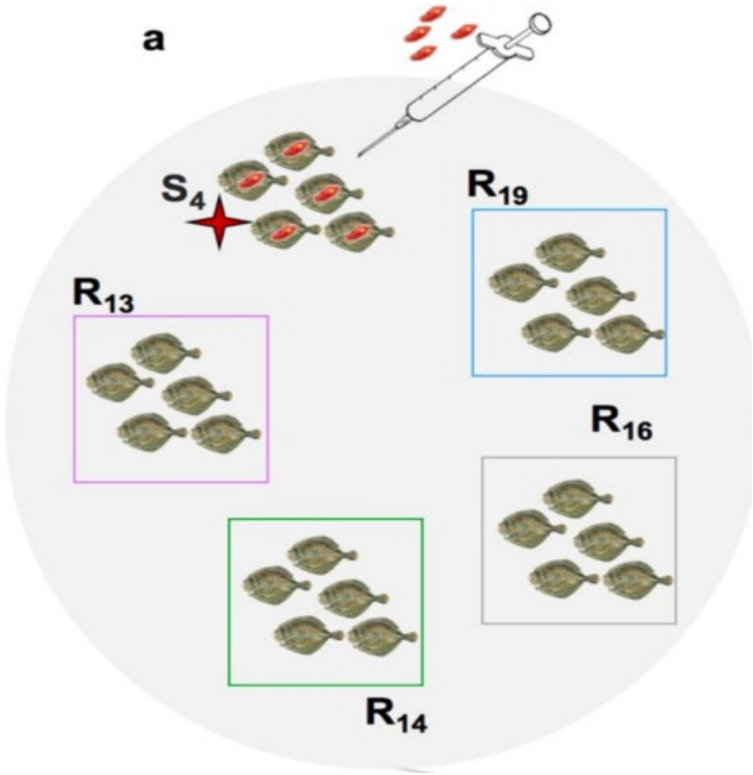


- Good infection model:
  - Possible to generate many independent epidemics with moderate mortality
  - Easy to identify infected fish through visual inspection

Experimental design & data

Experimental design

- 1800 fish (60 full-sib families) distributed into 72 isolated tanks (36 per trial)
- 25 fish/tank
  - Epidemics seeded by 5 **seeder fish** from 1 family
  - 20 susceptible **contact fish** from 4 families
- Family composition in each tank optimised for disentangling susceptibility and infectivity



Data (per fish)

- Time of onset of symptoms and death (censored)
- Weight at start of trial, Infection status at start & end
- RAD-seq data (17,690 SNPs) of 1400 fish, imputed to >1.2 Mio SNPs using WGS data of parents

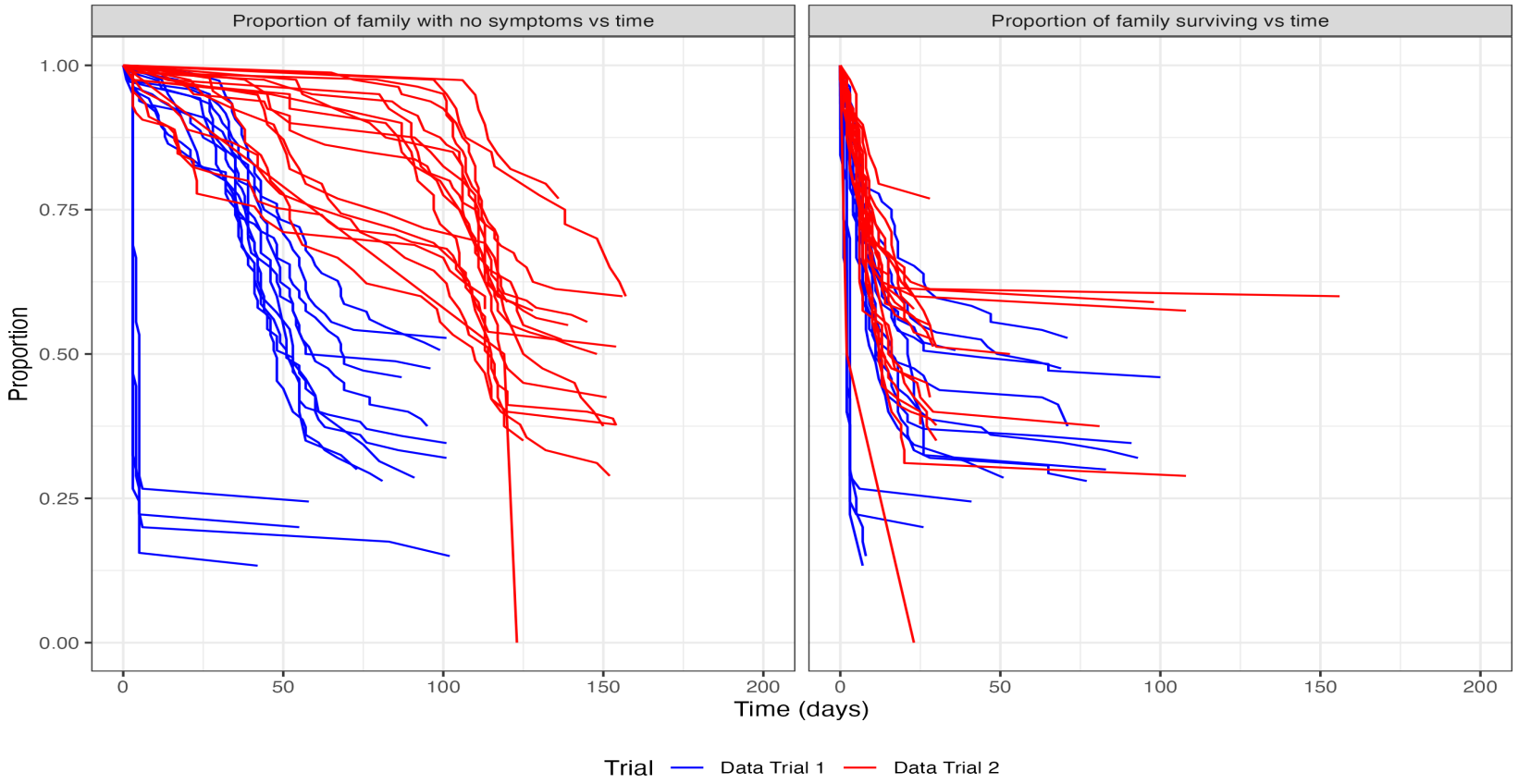
Anacleto et al. , Sci Rep. 2019; Saura et al., Front. Gene. 2019.

Kriaridou, Optimizing genotype imputation…, PhD thesis, 2024

Infection and survival profiles per family

Time to onset of symptoms

Time from symptoms to death



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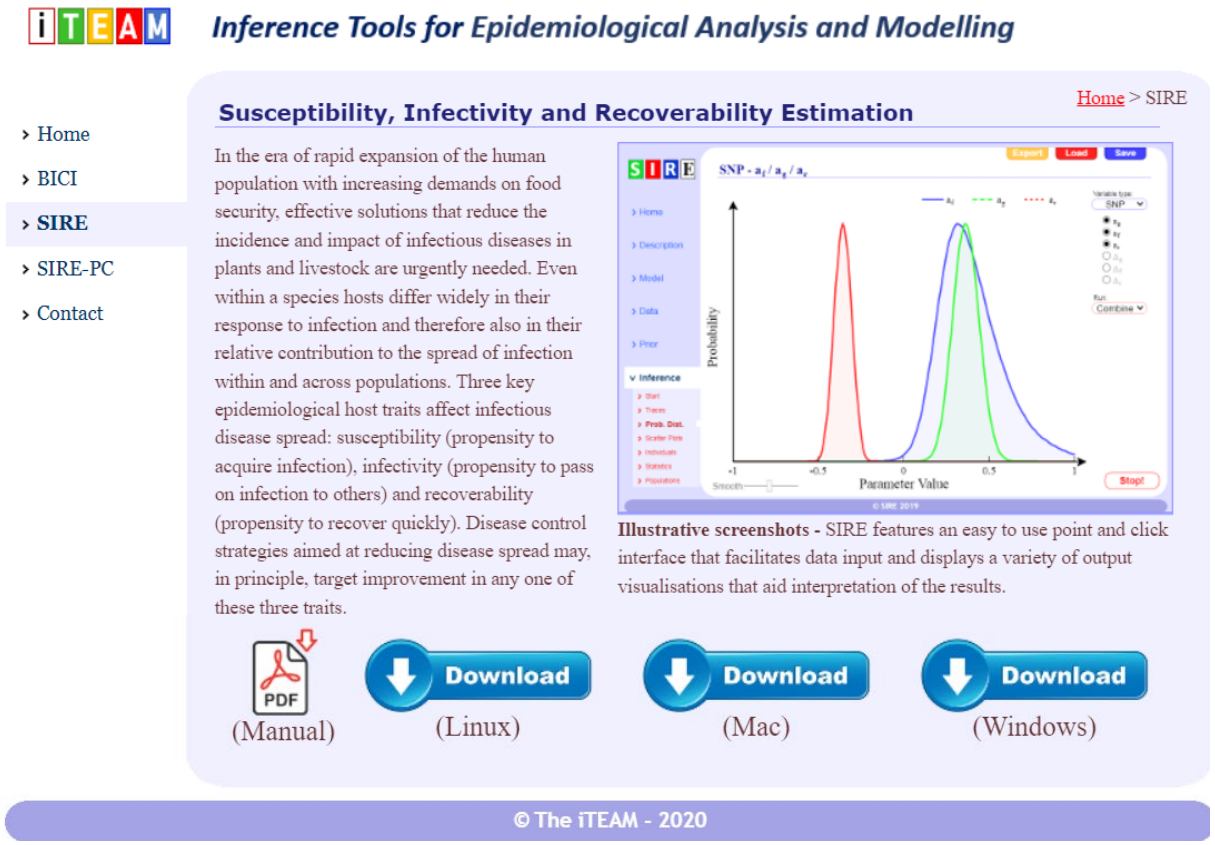
Inferring genetic parameters & SNP effects for susceptibility, infectivity & tolerance: SIRE software



SIRE: Susceptibility-**I**nfectivity-**R**ecoverability **E**stimation

- Bayesian (MCMC based) inference

[1] https://github.com/theITEAM/SIRE1.0

[2] https://github.com/theITEAM/SIRE2.0

[1]Pooley et al., PloS Comp. Biol. 2020;
[2]Pooley et al., under review 2024

Genetic model for the 3 epidemiological host traits

Susceptibility $\mathbf{g} = \mathbf{X}\boldsymbol{b}_g + \boldsymbol{a}_g + \boldsymbol{\varepsilon}_g$

Infectivity $\mathbf{f} = \mathbf{X}\boldsymbol{b}_f + \boldsymbol{a}_f + \boldsymbol{\varepsilon}_f$

Tolerance $\mathbf{r} = \mathbf{X}\boldsymbol{b}_r + \boldsymbol{a}_r + \boldsymbol{\varepsilon}_r$

Fixed effects:
Mode of infection (injection or contact), trial, weight at start

$$\begin{pmatrix} a_g \\ a_f \\ a_r \end{pmatrix} \sim \mathrm{MVN}\left(0, \mathbf{A} \otimes \mathbf{\Omega}\right)$$

H-matrix constructed from sequence & pedigree data

$$\begin{pmatrix} \varepsilon_g \\ \varepsilon_f \\ \varepsilon_r \end{pmatrix} \sim \mathrm{MVN}(0, \mathbf{I} \otimes \mathbf{\Psi})$$

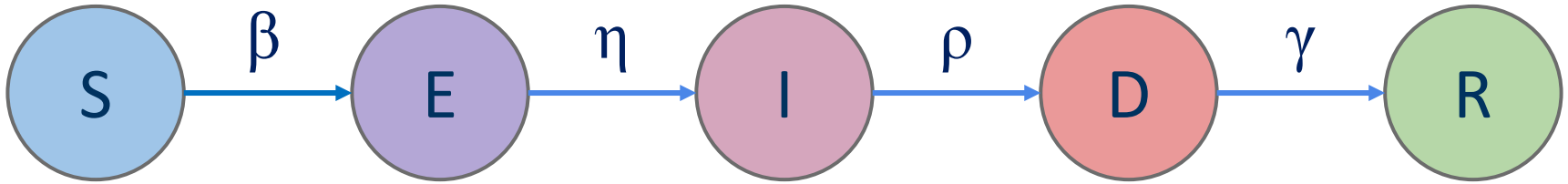
$$\mathbf{\Omega} = \begin{pmatrix} \Omega_{gg} & \Omega_{gf} & \Omega_{gr} \\ \Omega_{gf} & \Omega_{ff} & \Omega_{fr} \\ \Omega_{gr} & \Omega_{fr} & \Omega_{rr} \end{pmatrix}$$

Genetic covariances

$$\mathbf{\Psi} = \begin{pmatrix} \Psi_{gg} & \Psi_{gf} & \Psi_{gr} \\ \Psi_{gf} & \Psi_{ff} & \Psi_{fr} \\ \Psi_{gr} & \Psi_{fr} & \Psi_{rr} \end{pmatrix}$$

Environmental covariances

Epidemiological model



Susceptible (Not yet infected)

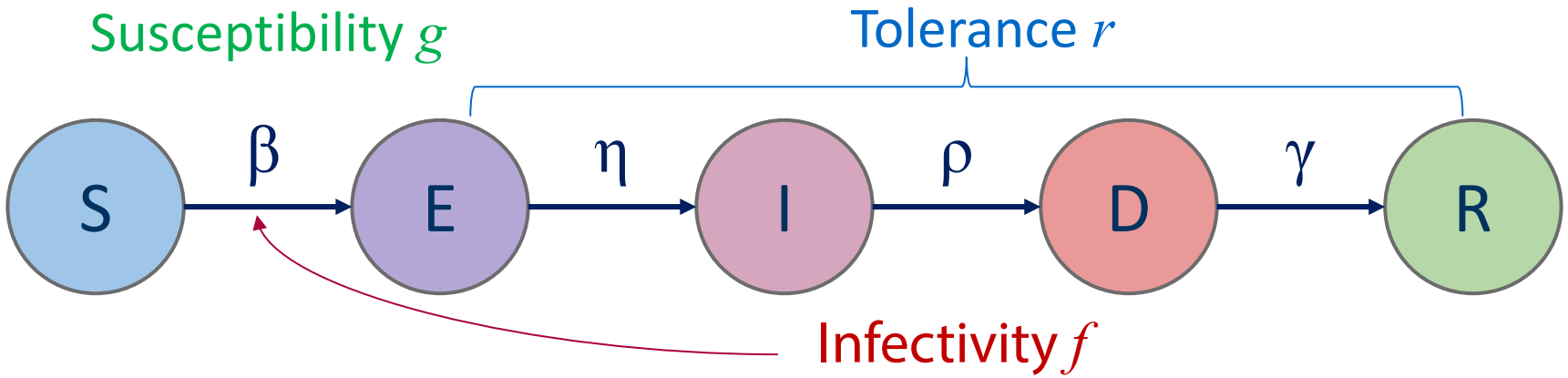
Exposed (Not yet infectious)

Infectious (Asymptomatic)

Detectable (Symptomatic)

Removed (Dead)

Epidemiological model: link to traits of interest



Individual's infection rate: (S → E)

$$\lambda_i(t) = \beta_{group}\, e^{g_i} \sum_{j(t)} e^{f_j}$$

Random tank effect

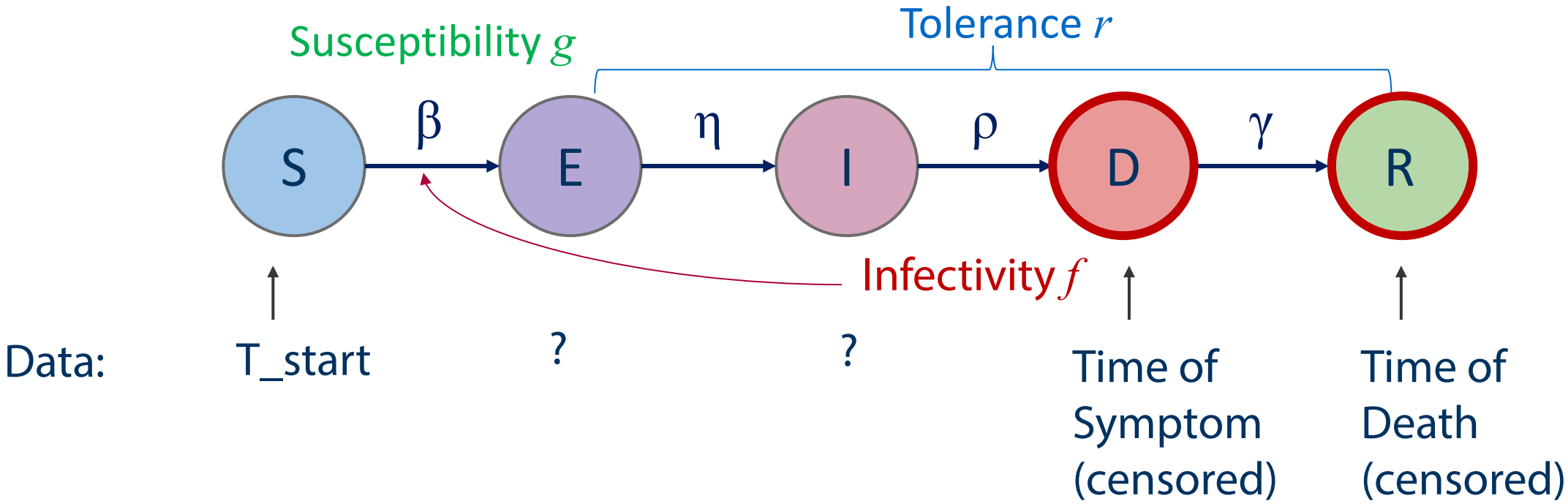
Infectious individual at time t

Individual's transition rates

$$\eta_i = e^{r_i}\,\eta,\quad \rho_i = e^{r_i}\,\rho,\quad \gamma_i = e^{r_i}\,\gamma$$

- **Complex, dynamic model, non-linear in susceptibility and infectivity**
- **Not easily implemented as GLMM**

Epidemiological model – link to data

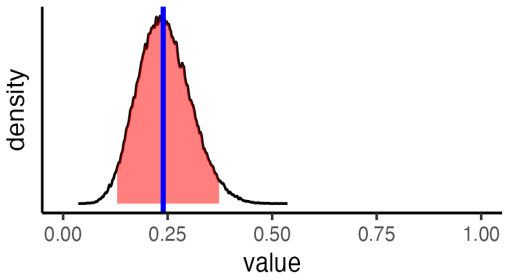


- **Moderately informative disease data**
- **Inference method needs to handle large degree of uncertainty**

Susceptibility, infectivity and tolerance are heritable

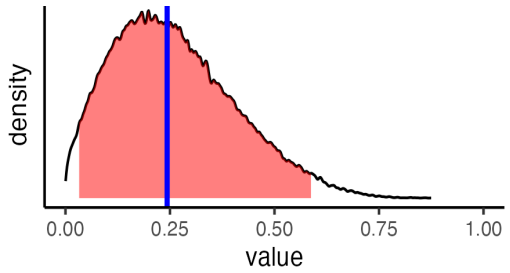
Susceptibility

h^2: 0.24 (0.13,0.37)



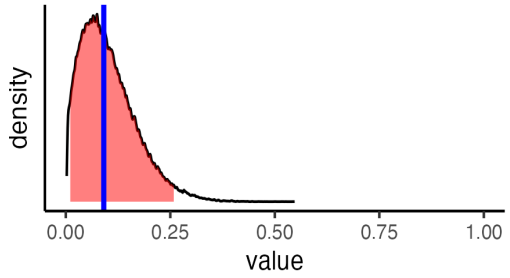
Infectivity

h^2: 0.24 (0.03,0.59)



Tolerance

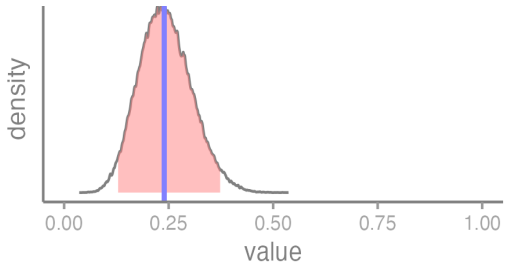
h^2: 0.09 (0.01,0.26)

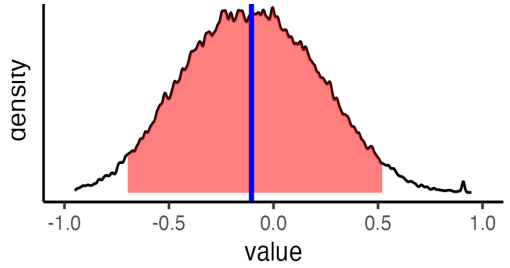


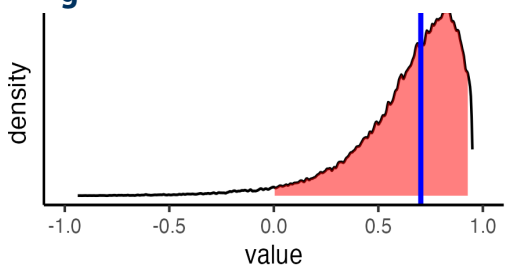
- Moderate h^2 for susceptibility & infectivity
- Low h^2 for tolerance

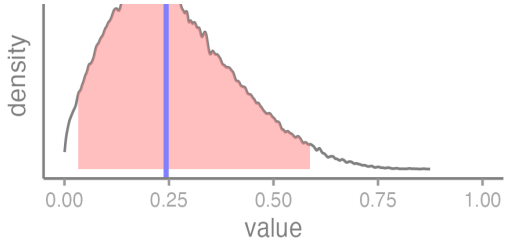
Indication for unfavourable genetic correlations

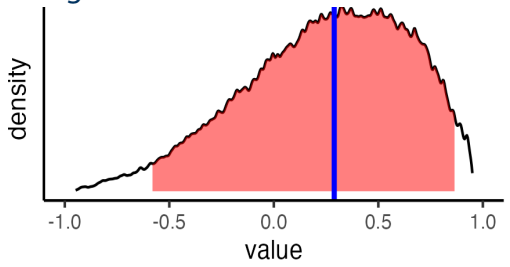
	Susceptibility	Infectivity	Tolerance
Susceptibility	h^2: 0.24 (0.13,0.37)	r_g: -0.11 (-0.70, 0.52)	**r_g: 0.70 (0.004, 0.93)**
Infectivity		h^2: 0.24 (0.03,0.59)	r_g: 0.29 (-0.58, 0.26)
Tolerance			h^2: 0.09 (0.01,0.26)

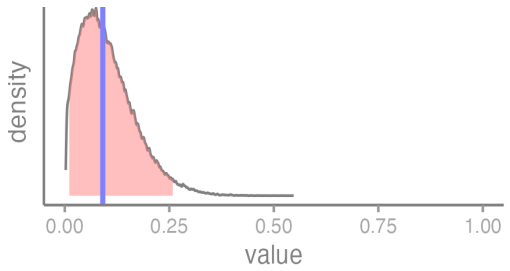






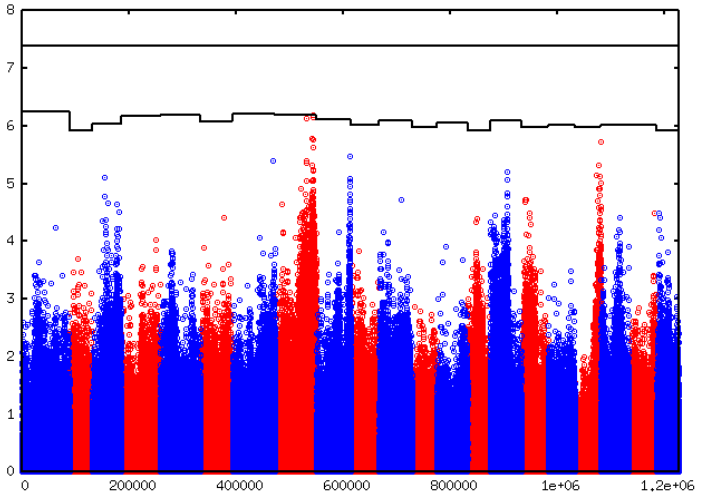




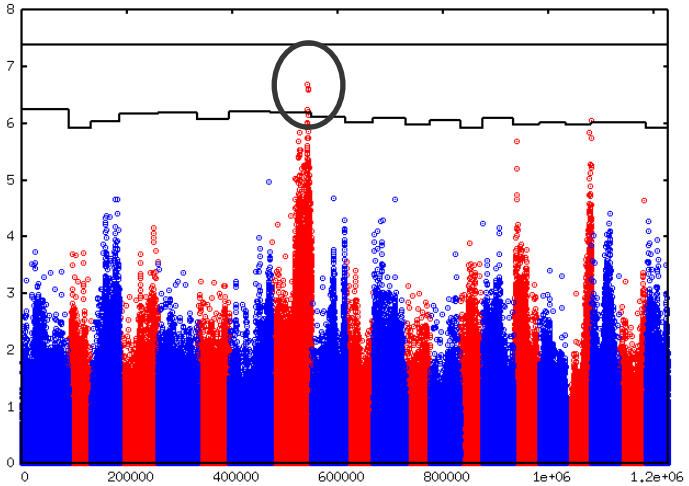


Genetic architecture

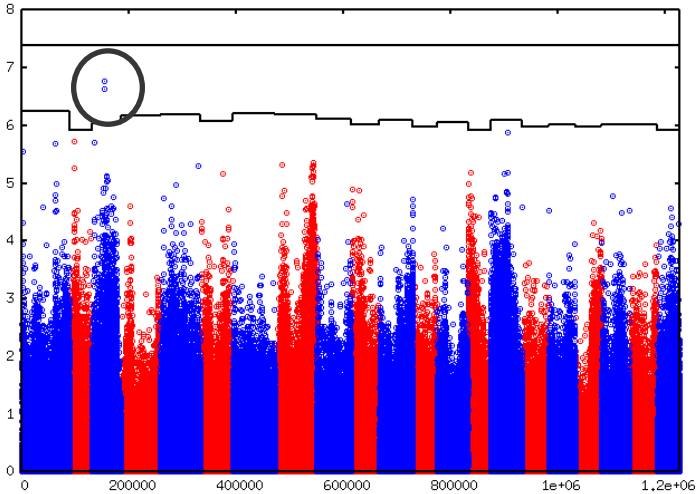
Susceptibility



Tolerance

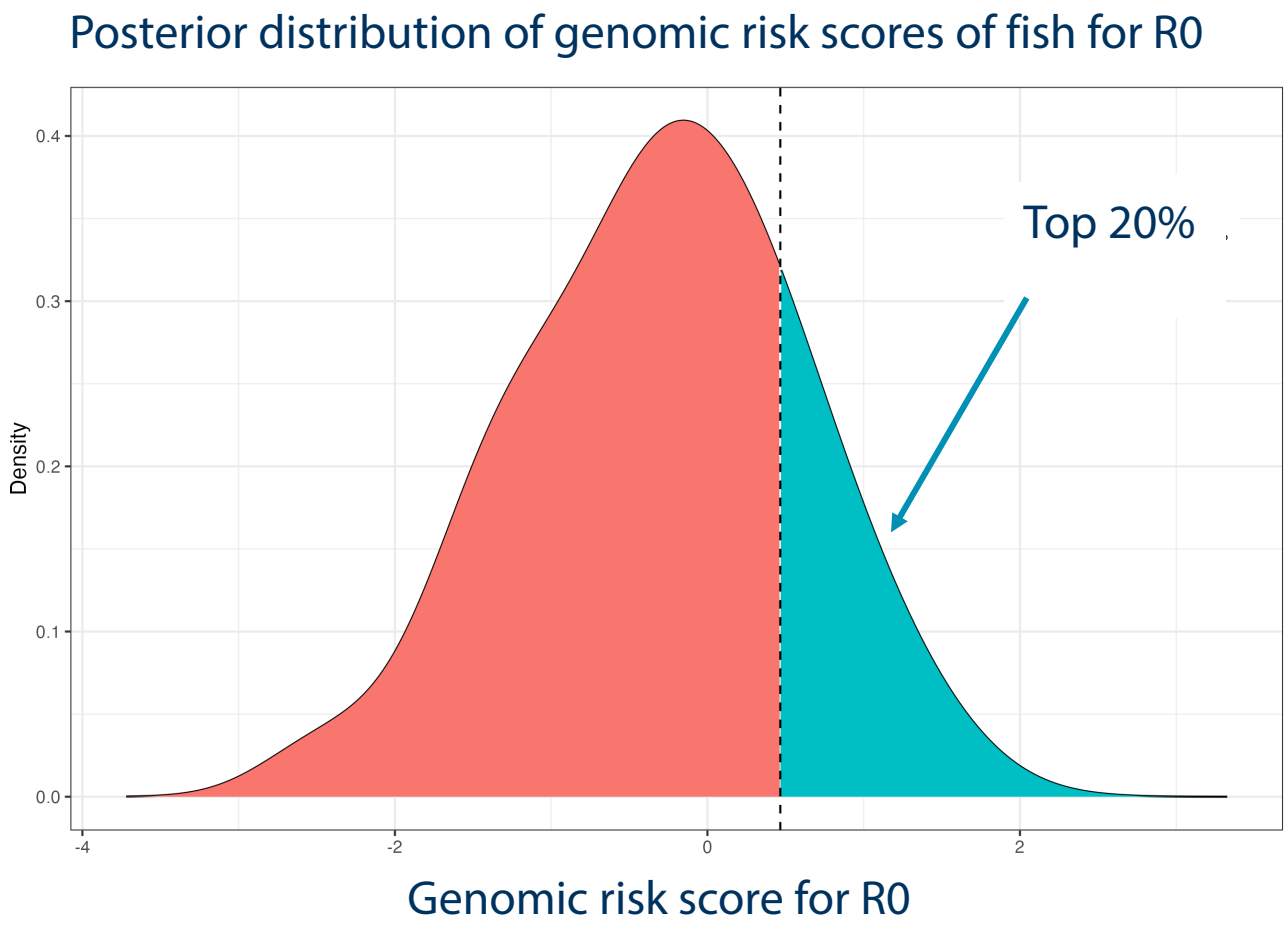


Infectivity



- Polygenic genetic architecture
- Some suggestive variants
  - At different genomic regions

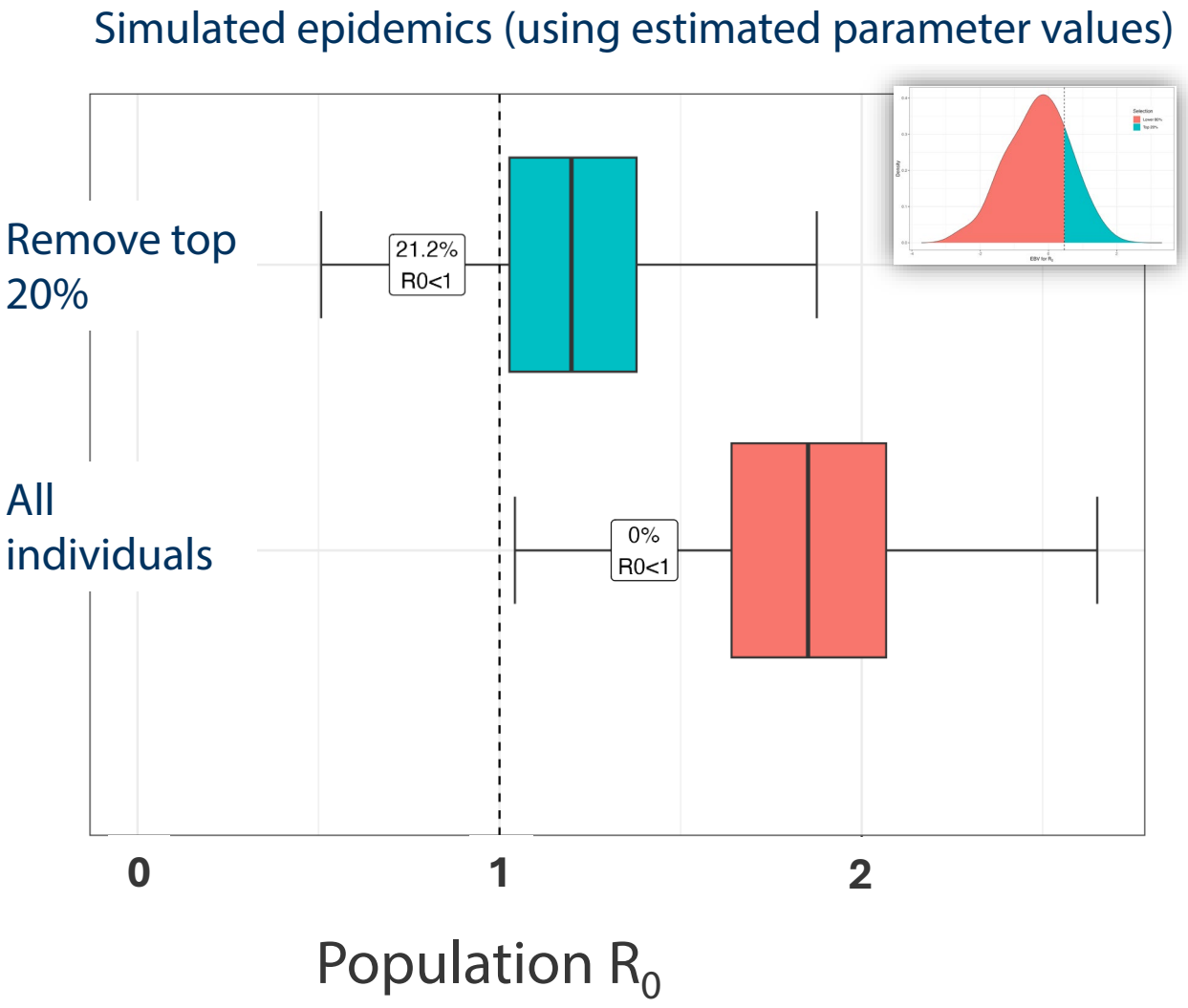
Genetic control of disease transmission



- Aim: Reduce expected R0 <1:
- We can calculate an individual's genomic risk score for R_0 (Bijma et al., 2022):

$$G_{R0,i} = G_{sus,i} + G_{inf,i} + G_{tol,I}$$

Genetic control of disease transmission



Early identification of high risk individuals can substantially reduce the risk and severity of disease outbreaks

Conclusions & Implications

1. **We have the tools** to estimate genetic parameters & SNP effects for the epidemiological host traits from imperfect epidemic data

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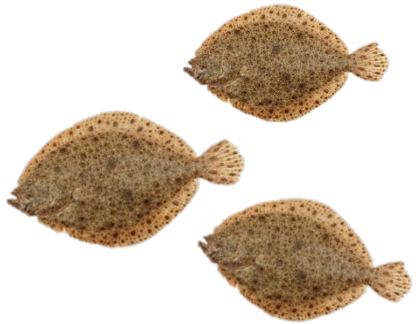
2. **First empirical evidence for substantial exploitable genetic variation in infectivity**, in addition to susceptibility & tolerance

- Potentially antagonistic genetic correlations between traits
- Polygenic architecture, but some suggestive variants



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1. **We have the tools** to estimate genetic parameters & SNP effects for the epidemiological host traits from imperfect epidemic data
2. **First empirical evidence for substantial exploitable genetic variation in infectivity**, in addition to susceptibility & tolerance

   - Potentially antagonistic genetic correlations between traits
   - Polygenic architecture, but some suggestive variants
3. **Further applications** ongoing … and **welcome**!

Acknowledgements

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FISHBOOST
The next level of aquaculture breeding

SEVENTH FRAMEWORK PROGRAMME

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Infection and survival profiles per family

Time to onset of symptoms

Time from symptoms to death