ROSLIN

The impact of vaccination & genetic selection on disease transmission in farm animals

Andrea Doeschl-Wilson

Prof. Infectious Disease Genetics & Modelling

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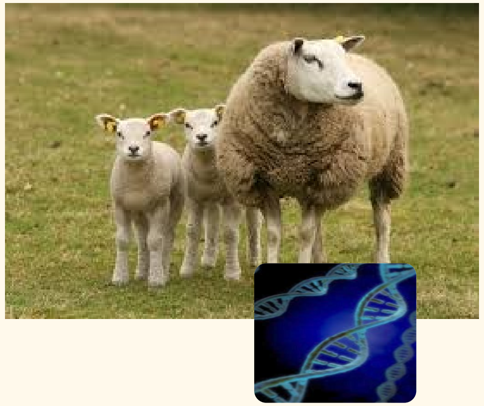
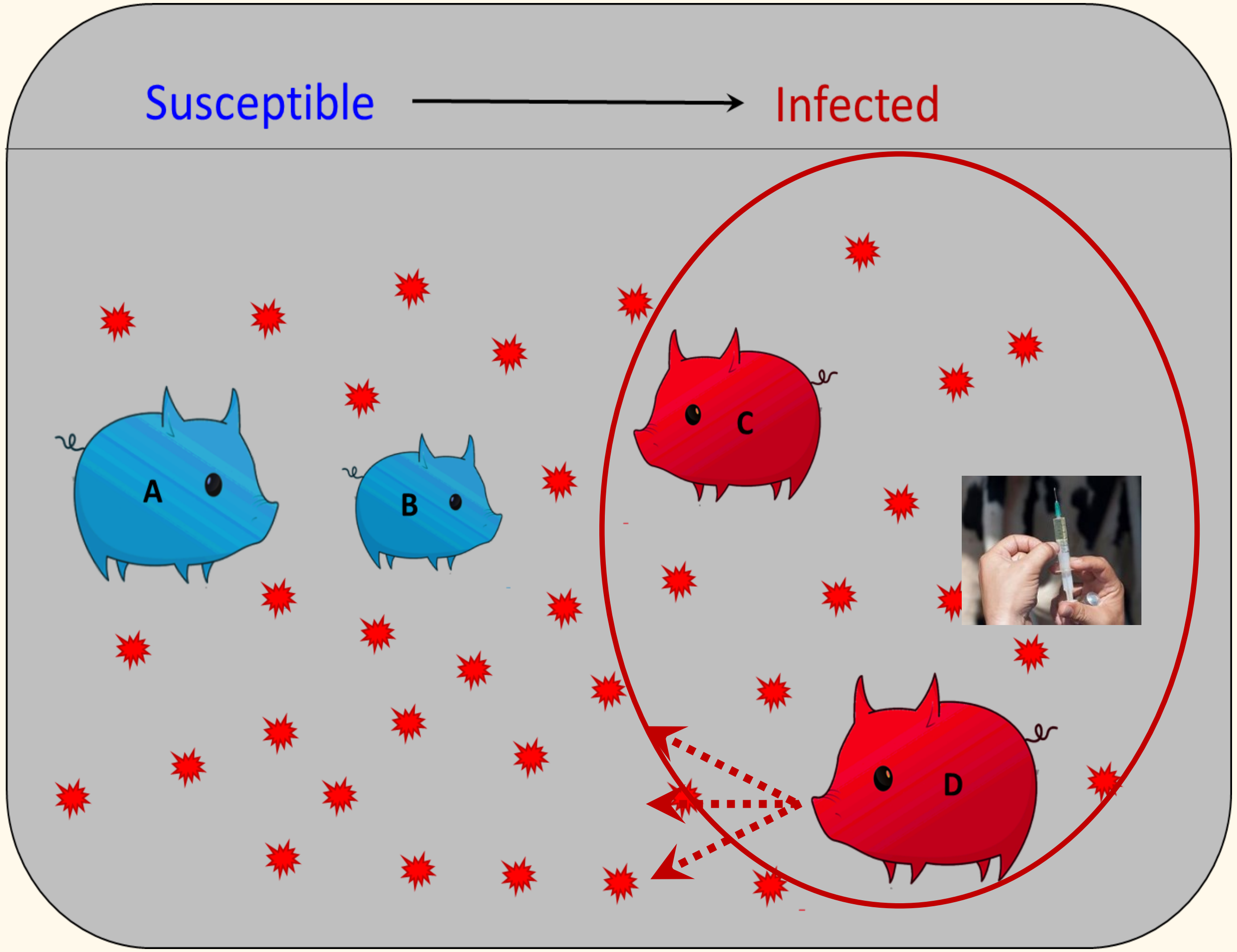
How do host genetics & vaccines
affect infectious disease spread?
... and how to best utilize them?

Outline

1. Status quo: application of vaccination & selective breeding as infectious disease control
   - Do they limit transmission?
2. New insights from experiments & modelling studies
3. Nowcasting & forecasting COVID-19 spread in Scotland



The role of vaccines in reducing disease transmission



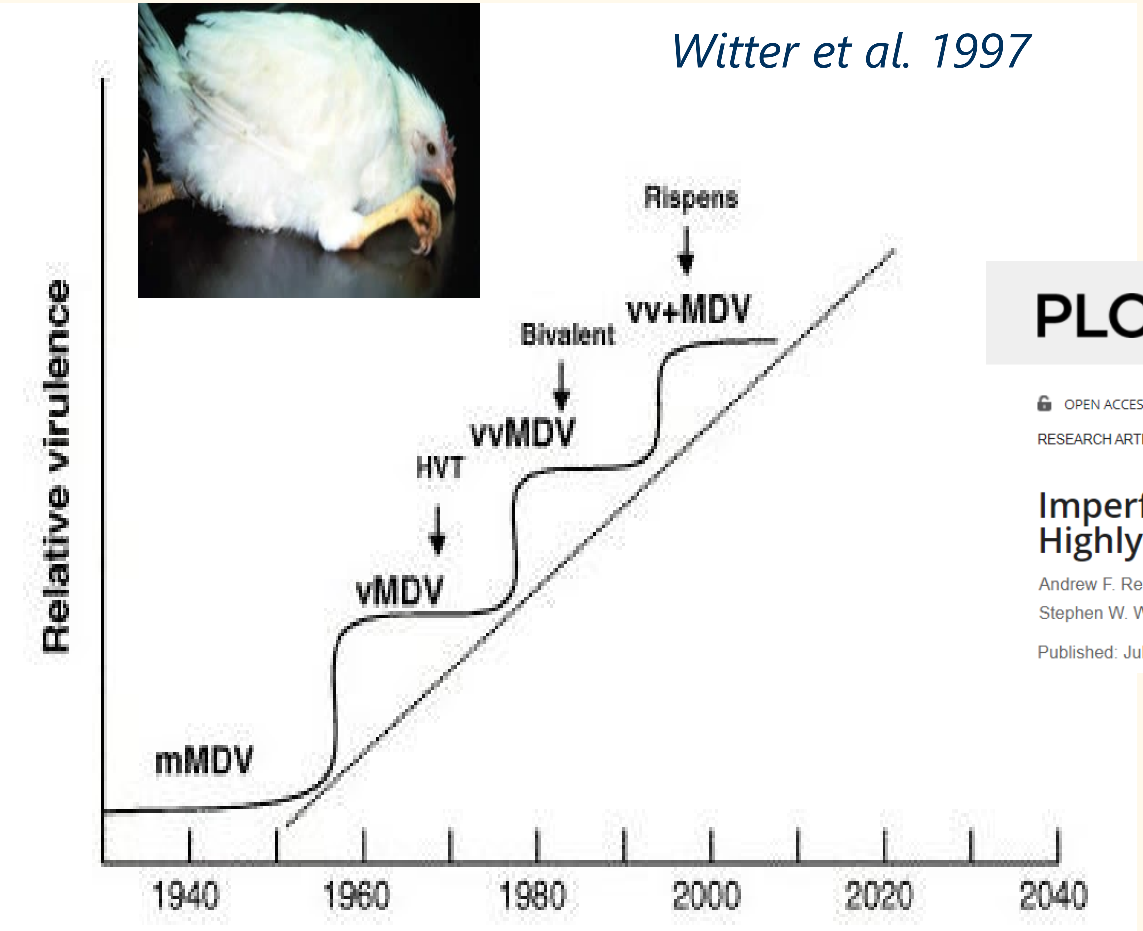
Vaccine efficacy:
The ability of a vaccine to **protect against adverse effects of the infection to the vaccinated individual** (Pastoret, 1997)

- Vaccines do not necessarily protect from becoming infected & transmitting the infection
- Vaccination studies ignore individual variation

Marek's disease vaccines in poultry

- Cancer caused by the Marek's disease virus (MDV)
- Controlled through wide-spread vaccination
- MD vaccines are 'leaky', i.e. they inhibit formation of tumour, but don't block infection & transmission of the MDV

Vaccination may drive virulence evolution



Witter et al. 1997

PLOS BIOLOGY

advanced search

OPEN ACCESS PEER-REVIEWED

RESEARCH ARTICLE

Imperfect Vaccination Can Enhance the Transmission of Highly Virulent Pathogens

Andrew F. Read, Susan J. Baigent, Claire Powers, Lydia B. Kgosana, Luke Blackwell, Lorraine P. Smith, David A. Kennedy, Stephen W. Walkden-Brown, Venugopal K. Nair

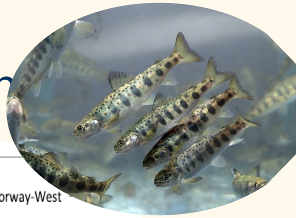
Published: July 27, 2015 • https://doi.org/10.1371/journal.pbio.1002198

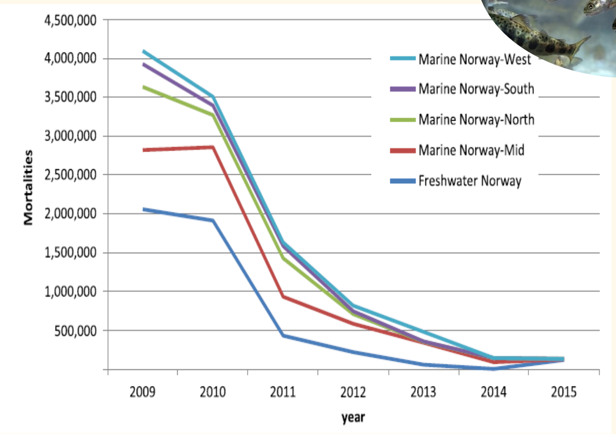
How does vaccination affect MDV transmission?

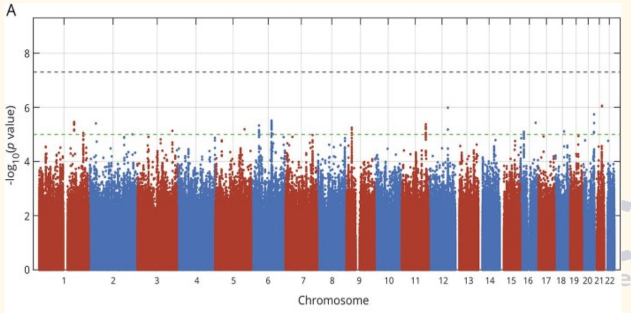
Genetic disease control in farm animals

- Universal evidence for genetic variation in response to infectious pathogens & treatment
- **Genetic selection for disease resistance** advocated as a viable (green) disease control
- Highly successful for some diseases
  - Mostly where host resistance is controlled by a single gene
- But limited applications & success for the majority of 'polygenic' diseases

IPN in Atlantic salmon



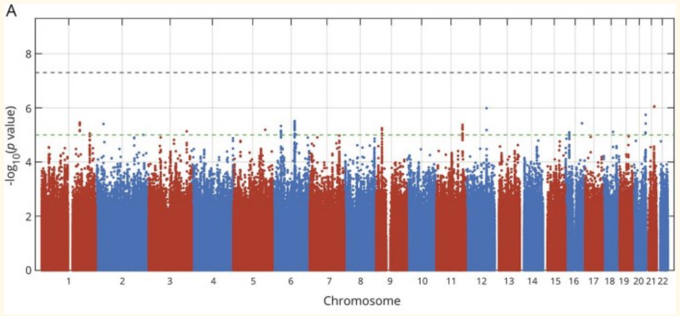




Requirements for genetic selection for disease resistance

1. BIG Data

- genetic / genomic information from 1000s of animals
- Informative disease records for these animals
  - Field disease data are notoriously noisy



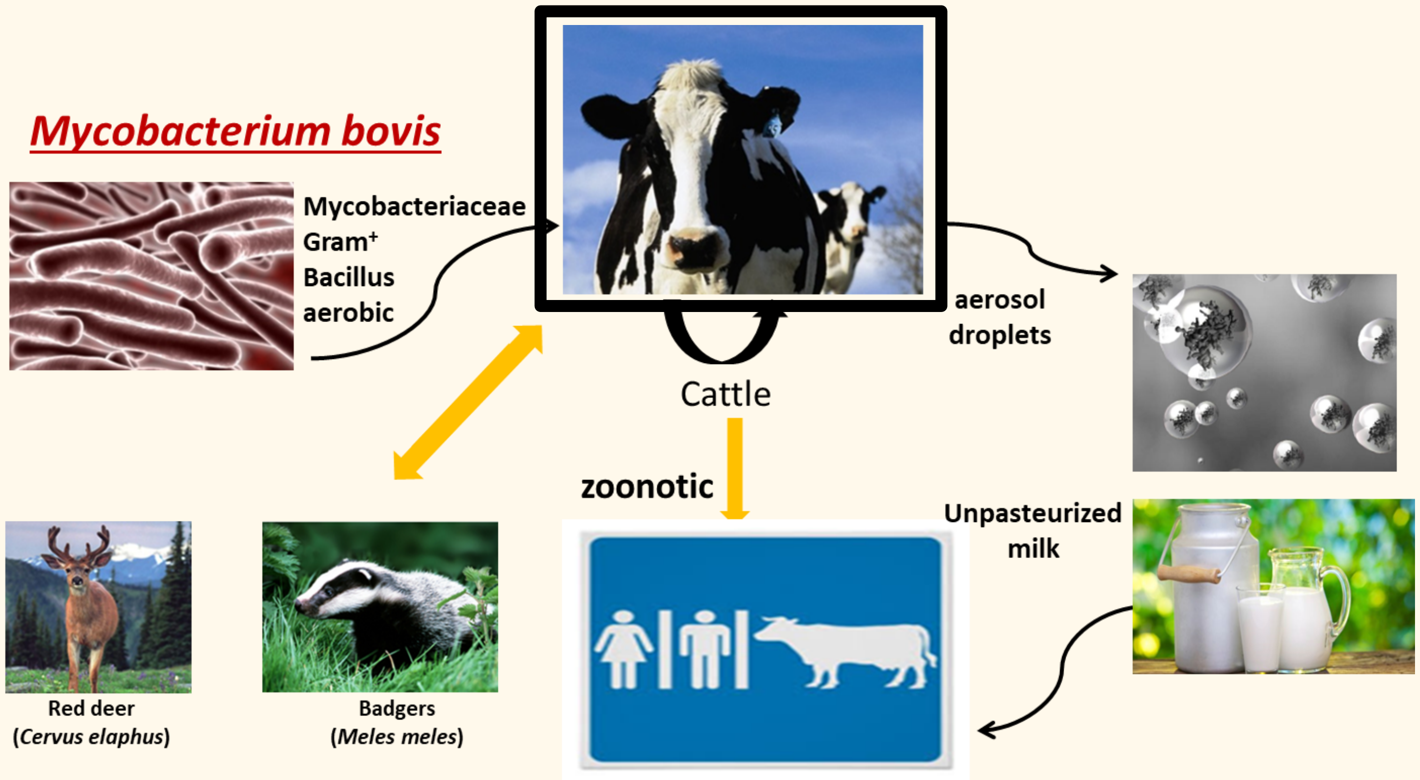
2. Statistical models that can unmask the genetic signal

- Identifying genetically resistant animals with high accuracy is difficult

3. Genetic-epidemiological prediction models

- To predict impact of genetic selection on future disease prevalence

Example bovine Tuberculosis



Huge bTB eradication efforts world-wide

- **One of the most persistent animal health problems**
  - Endemic in many countries
  - Huge financial losses

- **An important public human health concern**
  - » zoonotic transmission
  - » 10-15% of human TB cases caused by bTB in developing world

Failed attempts to eradicate bTB in UK cattle

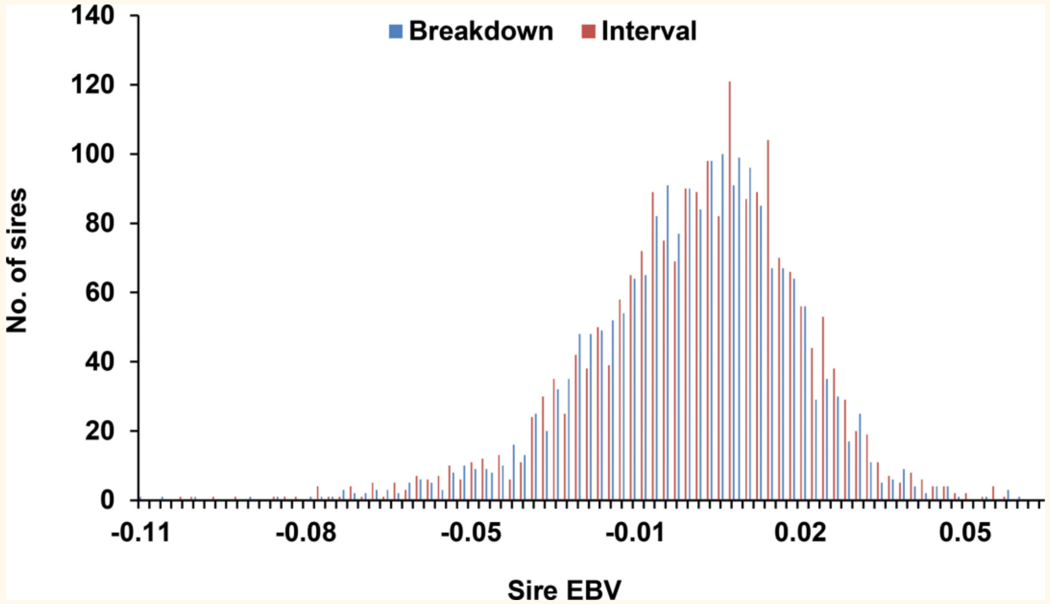
- **No safe vaccine**
- **Stringent routine herd testing & culling of infected cattle + movement restrictions until herd is declared bTB free**
  - Very labour intense and expensive
  - But strategy not sufficient for eradicating the disease
- **Badger culling**
  - Only short term benefits

Genetic bTB control

Huge dataset for genetic analyses:
- Genetic data available from routine genetic evaluations (>1 Mio cattle)
- Disease phenotypes from test & cull regime (~500,000 cows, >10,000 bTB positive herds)

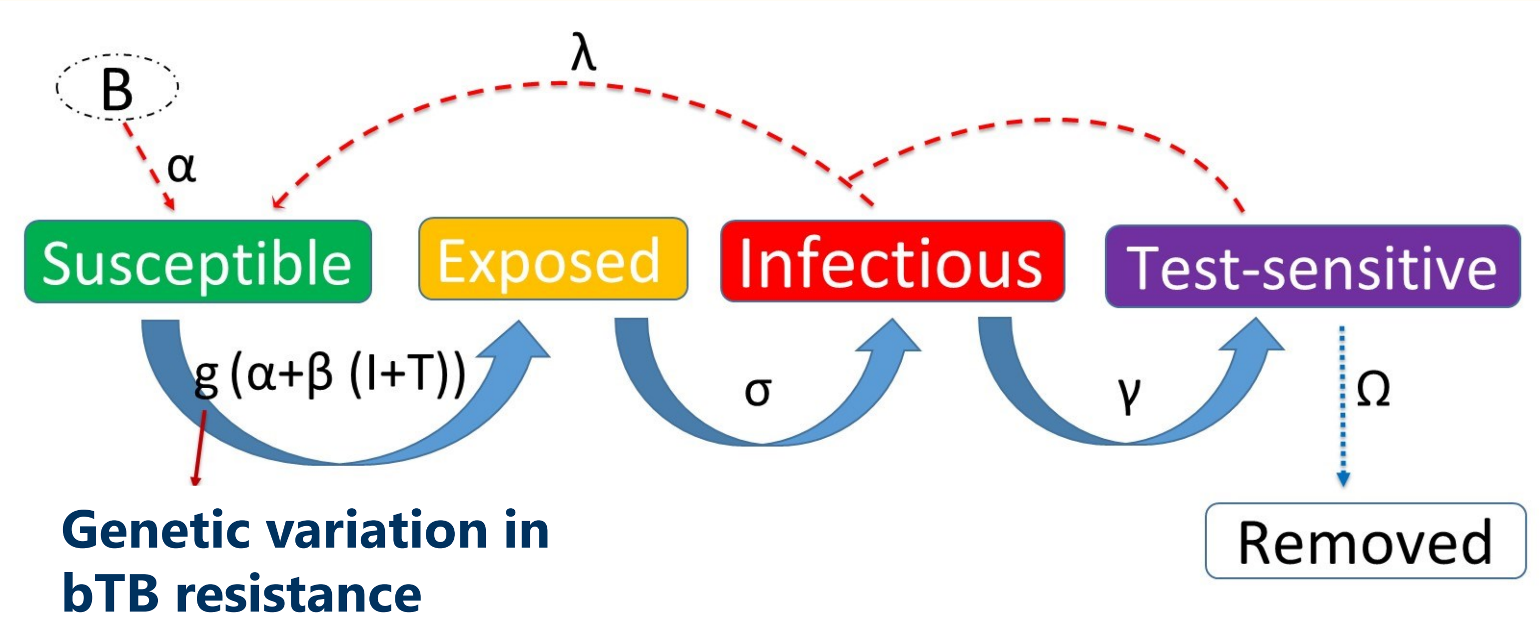
Strong evidence for genetic variation in bTB resistance
- Heritability: 0.08-0.23; polygenic resistance
- Prediction accuracy: 72%

2016: Launch of TB Advantage selection index:
- Voluntary selection of bulls with high genetic bTB resistance
- But epidemiological benefits unknown



Banos et al. J Dairy Sci 2017

Genetic-epidemiological model for bTB



- Model bTB transmission dynamics within each exposed herd
- Use UK national bTB & genetic studies to inform model parameters
- Simulate genetic selection & current bTB control measures

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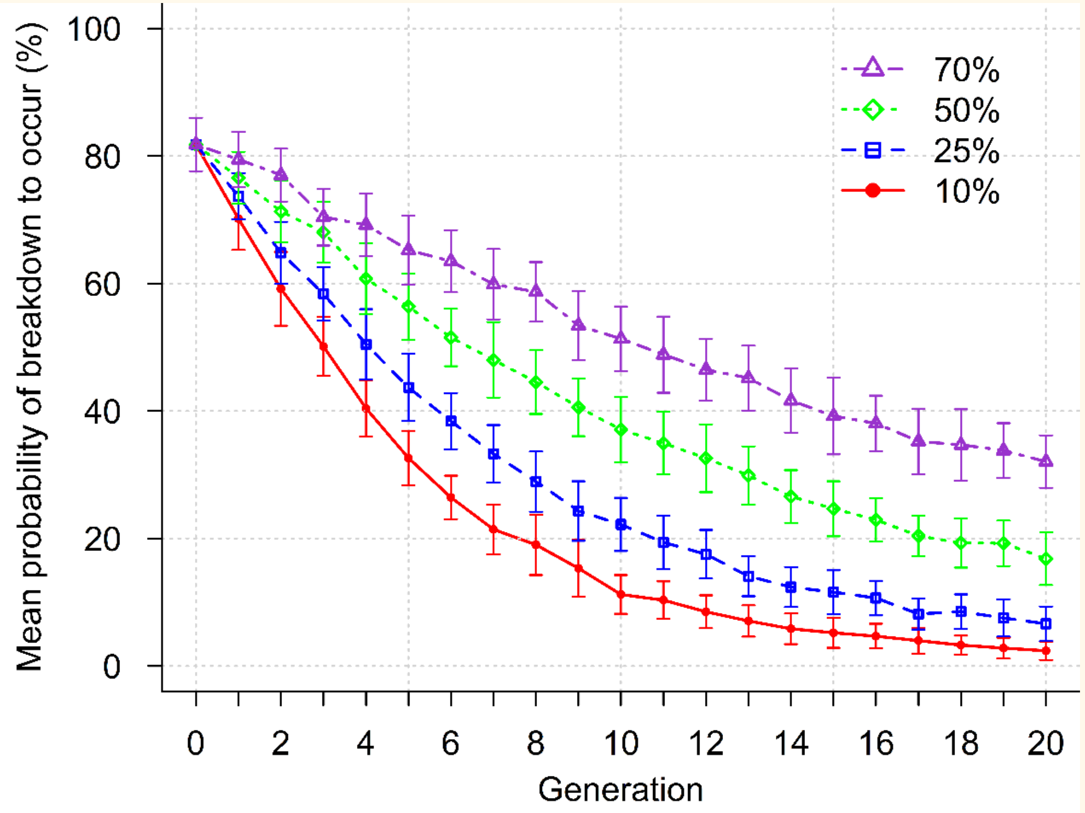
Kethusigele et al., Front. Vet. Sci. 2018

Impact of genetic selection on reducing bTB prevalence: beneficial but slow



Risk of bTB breakdown in a herd

- Before selection = 81.8%
- Reduced by half after 4-15 generations of selection

Genetic selection for bTB resistance helps to reduce bTB incidence, but not sufficiently effective to eradicate bTB

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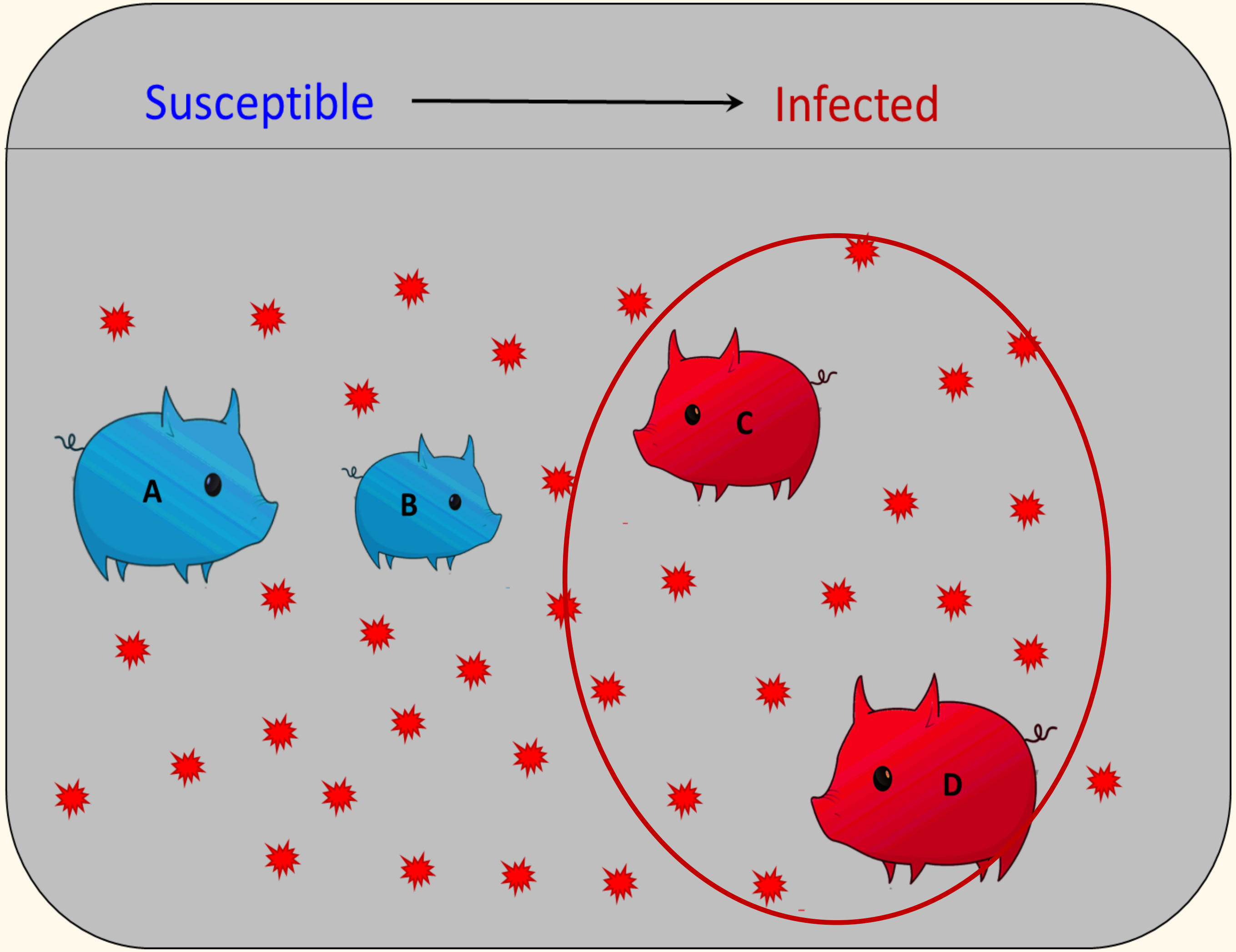
Kethusegile R. et al, Front. Vet Sci. 2018.

Towards more effective genetic disease control



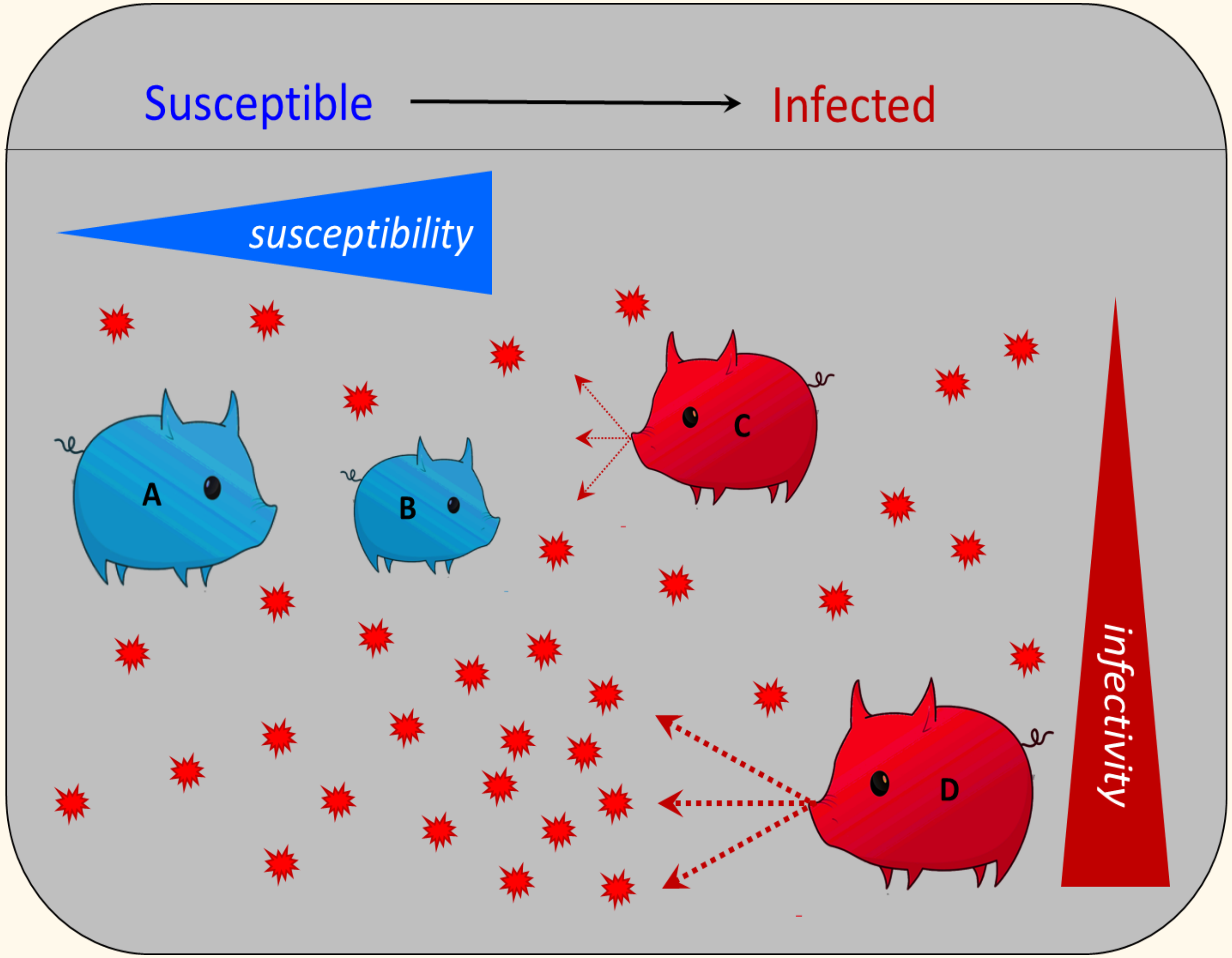
Adapted from Doeschl-Wilson et al., Animal 2021

Current focus on improving individuals' disease resistance:

- Resistance to infection, given exposure
- **Resistance to adverse side effects of infection, given infection**

Genetic effects on transmission usually ignored

Change focus on reducing transmission



Adapted from Doeschl-Wilson et al., under review in Animal

Focus on reducing transmission

- **Susceptibility** = propensity of a susceptible individual to become infected, given exposure
- **Infectivity** = propensity of an individual to transmit the infection to a susceptible individual (of average susceptibility), given infection

Much evidence for individual variation in infectivity

Superspreader: individual, responsible for a disproportional amount of transmissions

COVID-19: 'Superspreader' Santa blamed for coronavirus outbreak at Belgian care home

Veterinary Medicine and Science
Open Access

REVIEW | Open Access

Characterization of potential superspreader farms for bovine tuberculosis: A review

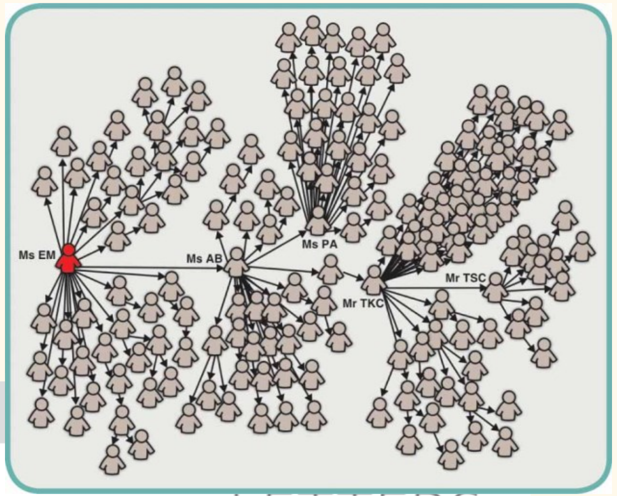
Helen R. Fielding, Trevelyan J. McKinley, Richard J. Delahay, Matthew J. Silk, Robbie A. McDonald

Vol 438|17 November 2005|doi:10.1038/nature04153

LETTERS

Superspreading and the effect of individual variation on disease emergence

J. O. Lloyd-Smith[1,2], S. J. Schreiber[3], P. E. Kopp[4] & W. M. Getz[1]



Is infectivity genetically controlled?

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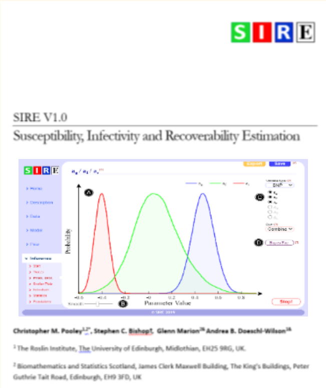
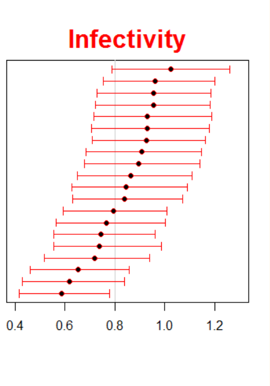
Infectivity questions

1. If there was genetic variation in infectivity, can we detect it?
   – What type of data / models are required?
2. How big is the genetic variation in infectivity?
   – And how is it correlated with resistance?
3. Can we substantially reduce disease transmission by selection for low infectivity?

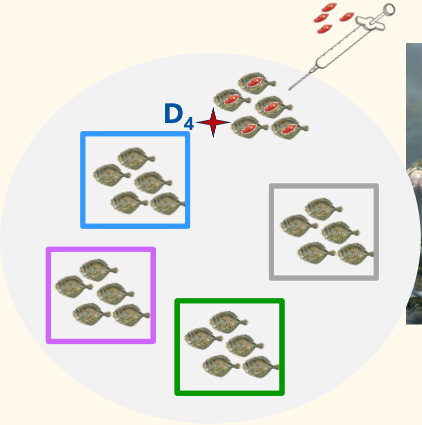
Approach

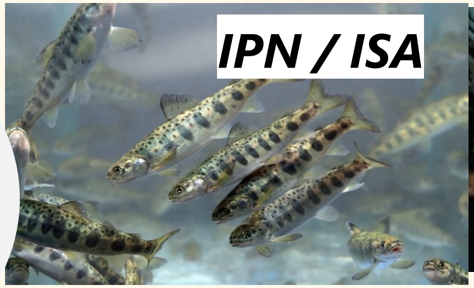
1. Develop methodology
   & validate on simulated data





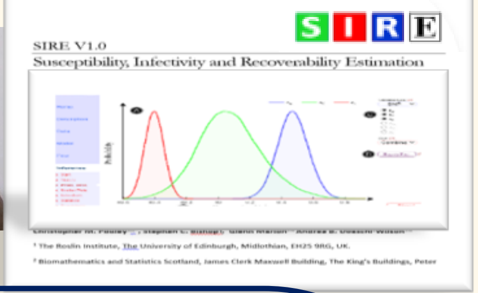
2. Design & conduct disease
   transmission experiments





3. Apply to field data

Methodology

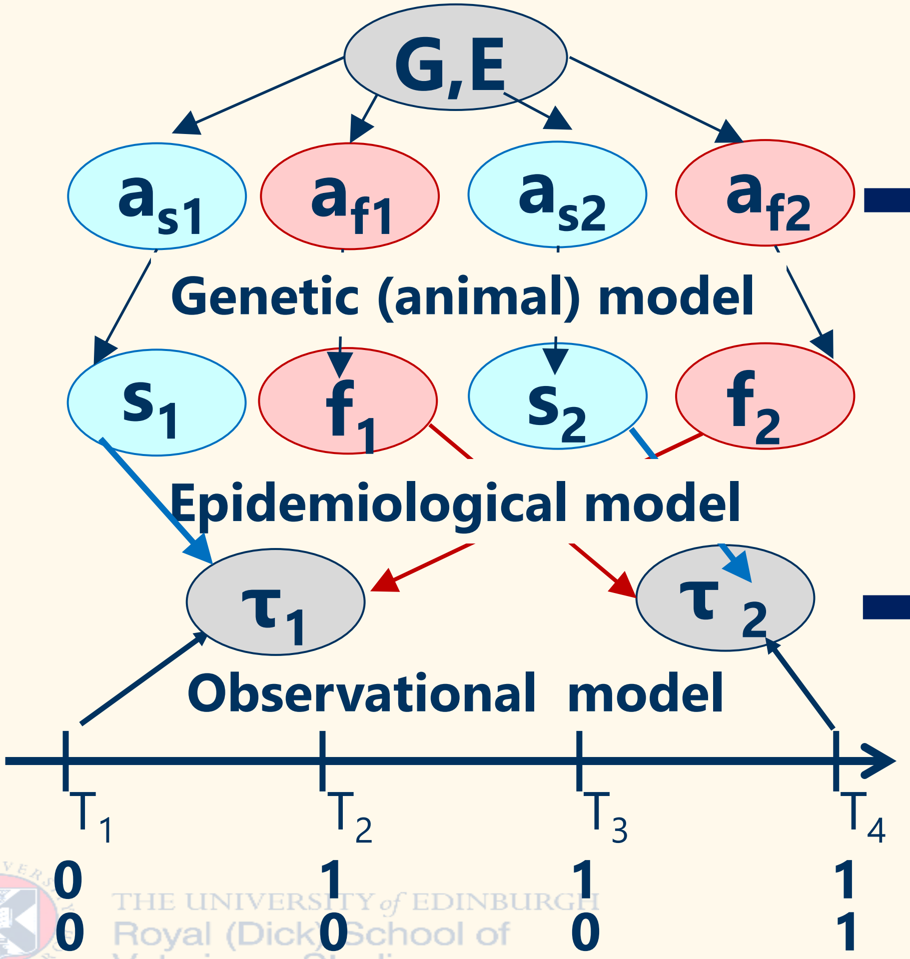


Input data → Bayesian Inference → Estimates / Predictions

Pedigree / genomic data

Fixed effects, e.g. vaccination status

Repeated measures of individuals' infection status



Genetic risk estimates for Susceptibility & Infectivity & Cov_G

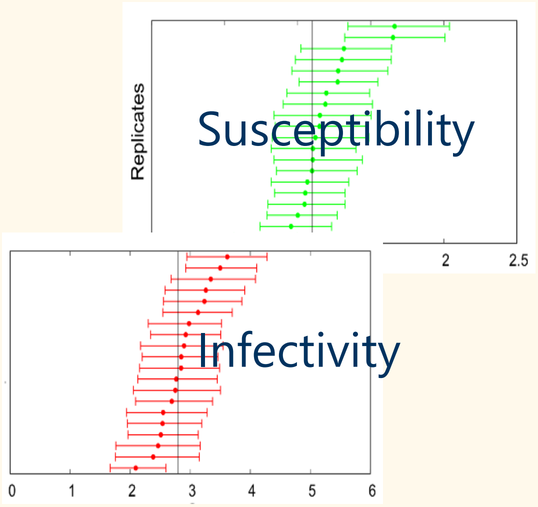
Effects of fixed effects on Susceptibility & Infectivity

True infection times & duration of infectious period

Anacleto et al. Genetics 2015
Pooley et al. Plos Comp. Biol 2020

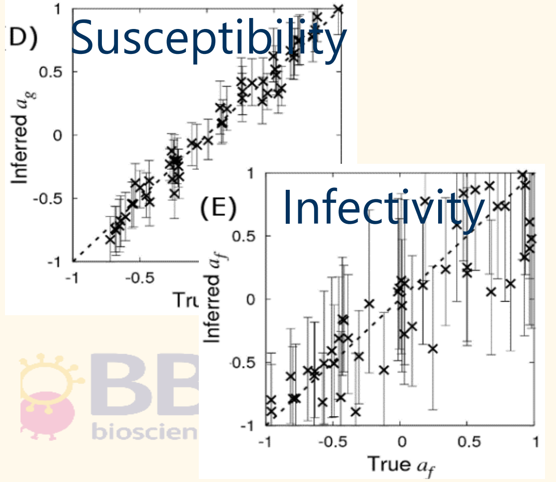
Key findings to date

Genetic Variance



- It is possible to get accurate, unbiased estimates for genetic infectivity (& other traits) given appropriate data
  - Model can identify genetic super-spreaders, if they exist
- Estimating infectivity requires 'specific' sampling design
  - several independent epidemics with genetically related animals (e.g. herds)
  - Temporal information of individual's infection / survival status
- Robust estimates even for noisy / incomplete data

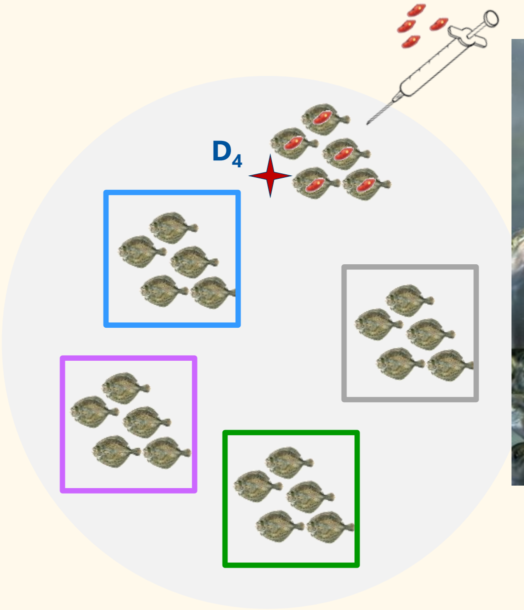
SNP effects



Anacleto et al. Genetics 2015; Pooley et al. Plos Comp. Biol. 2020

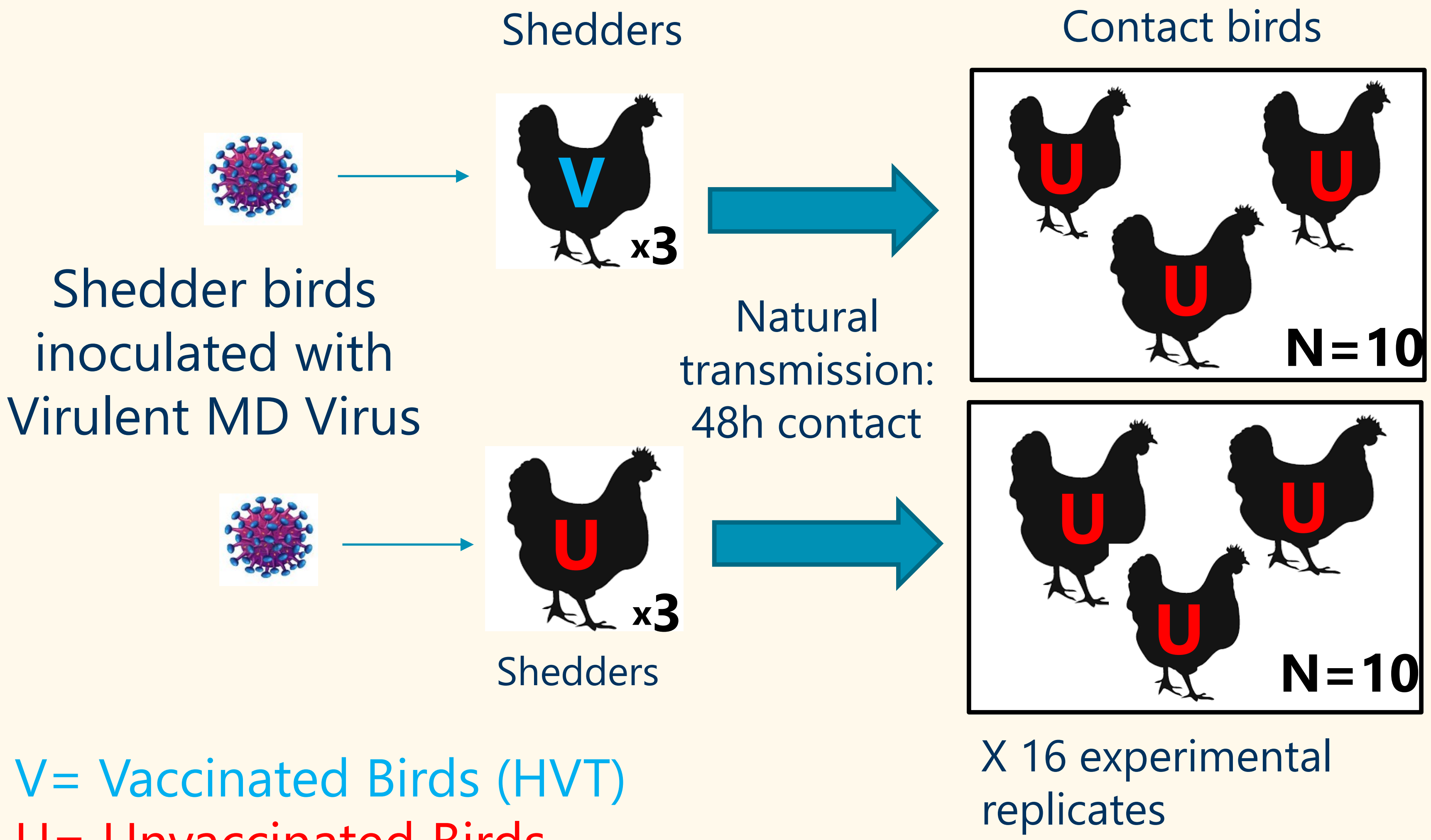
Insights from transmission experiments

Marek's disease



IPN / ISA

Marek’s disease transmission experiments



Measures:

- Virus load in blood & feather follicles at different time points
- Presence of tumour 8 weeks post contact
- Mortality

V= Vaccinated Birds (HVT)

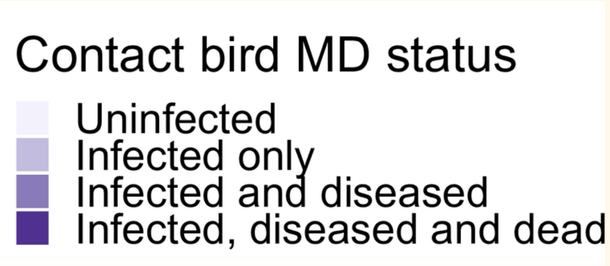
U= Unvaccinated Birds (sham vaccine)

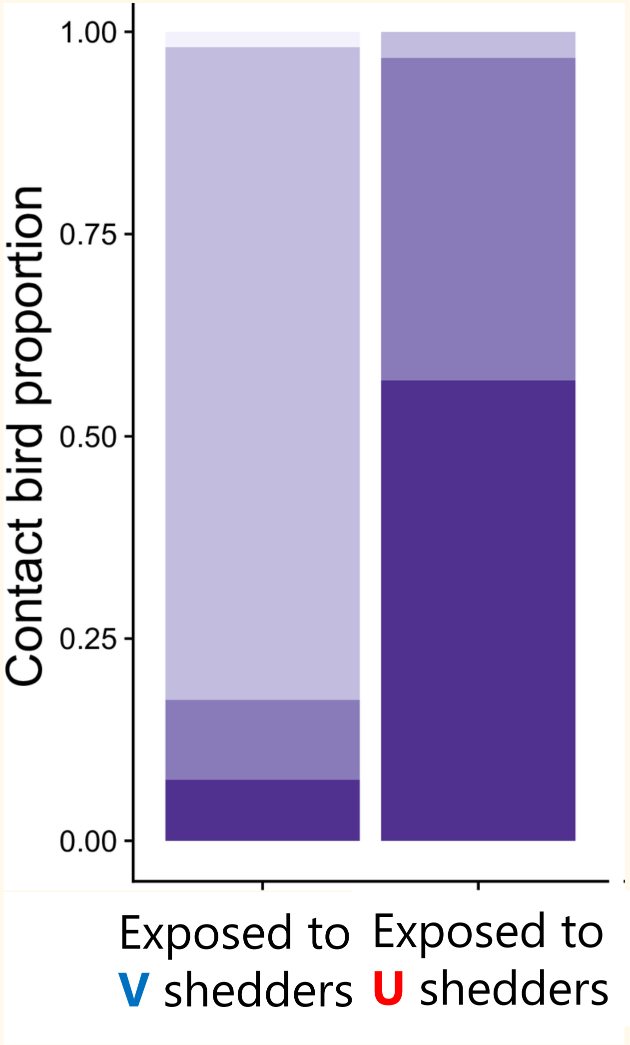
Dunn, Cheng et al., USDA ADOL

Surprising indirect effects of vaccination

Vaccine effects on vaccinated shedder birds:
- Vaccinated shedder birds did not develop MD when infected with MDV
- Vaccinated shedder birds still shed the virus when infected

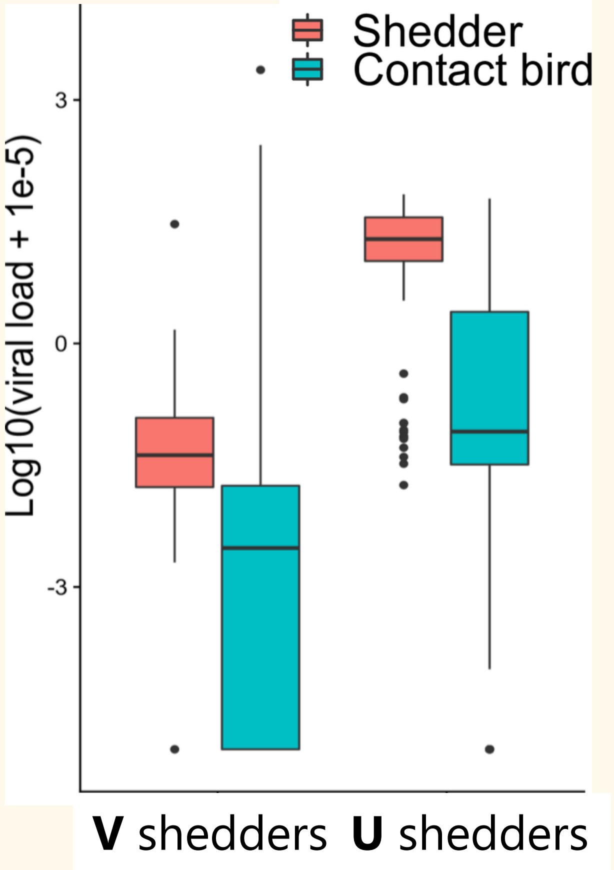
Vaccine effects on non-vaccinated contact birds:
- Almost all contact birds became infected
- BUT: contact birds exposed to infected vaccinated shedders were less likely to develop MD and die



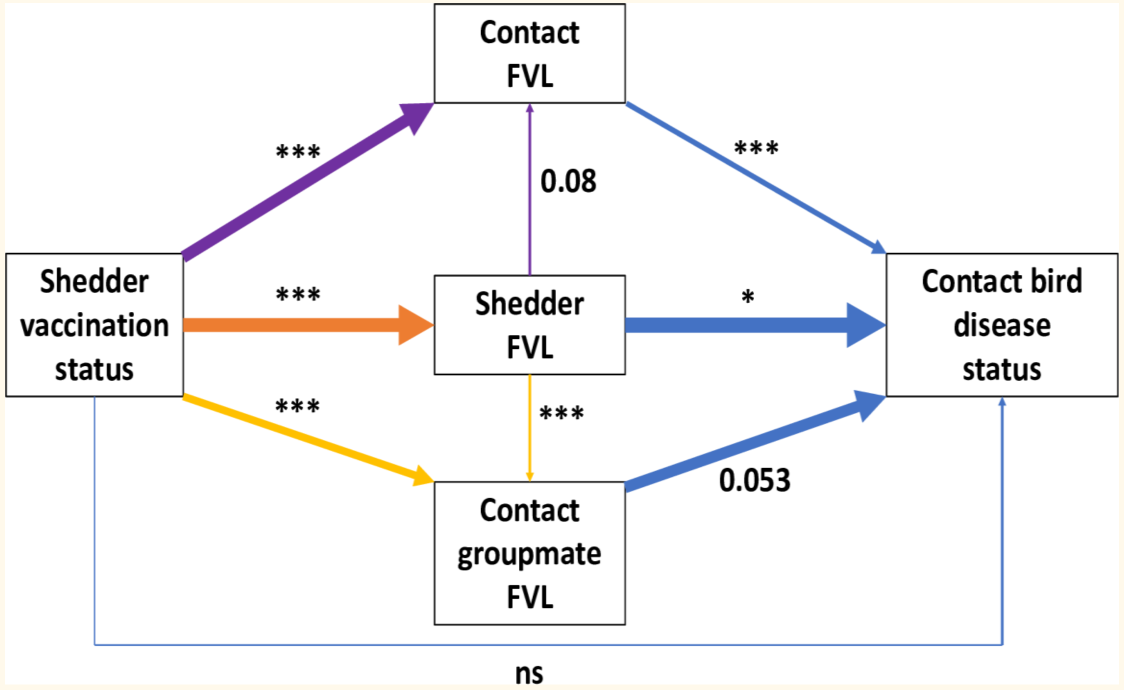


Bailey et al., PloS Biol. 2019

Virus transmission from vaccinated birds causes dose-dependent reduction in virus virulence



Path analysis:

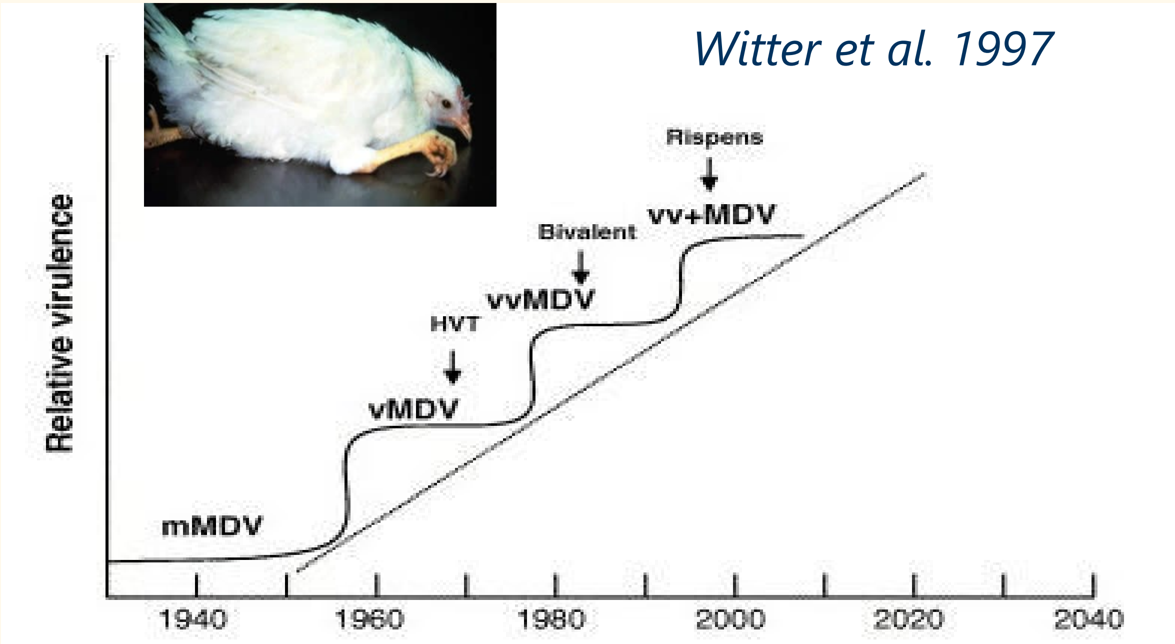


Similar trends for comparing transmission patterns between birds with high / low genetic resistance to MD

- Although effects were less pronounced than vaccine effects

Bailey et al., PloS Biol. 2019

What are the implications on onwards transmission and virulence evolution?



Under current investigation

POST-DOC OPPORTUNITY!!

Does this have implications for other diseases?

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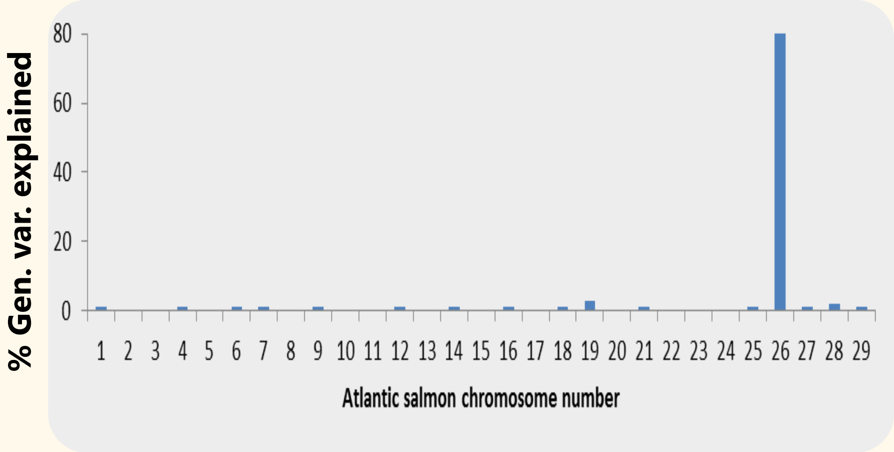
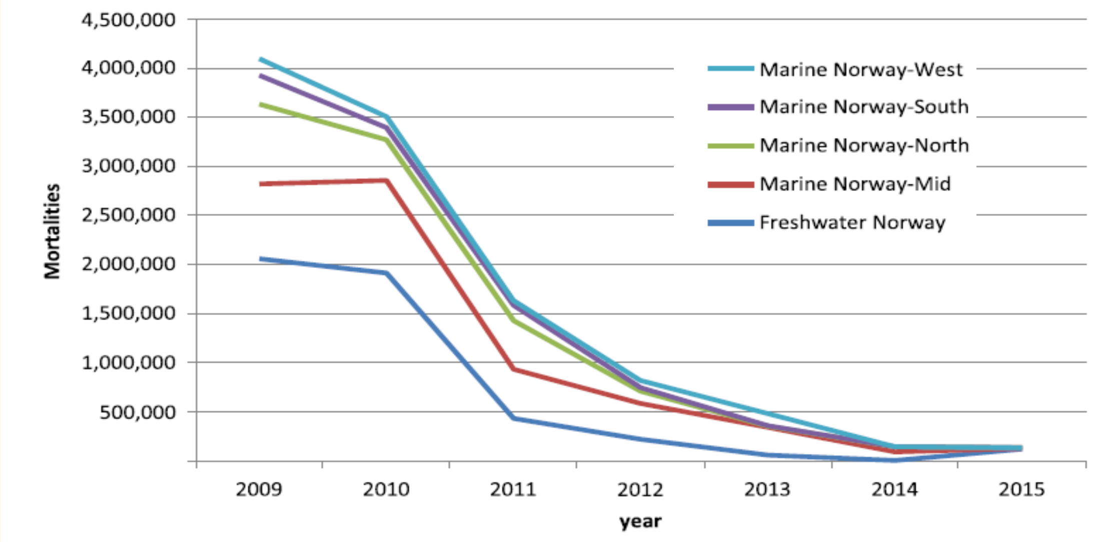
‘The IPN lucky case’ (Atlantic salmon)

- Infectious **P**ancreatic **N**ecrosis Virus
- Causes high **mortality** at freshwater stage and at sea
- Single QTL explains most genetic variation in **mortality**
- Breeding for disease resistance has drastically reduced mortality rates



Houston et al. (2008) Genetics & (2010) Heredity. Moen et al. (2009) BMC Genomics

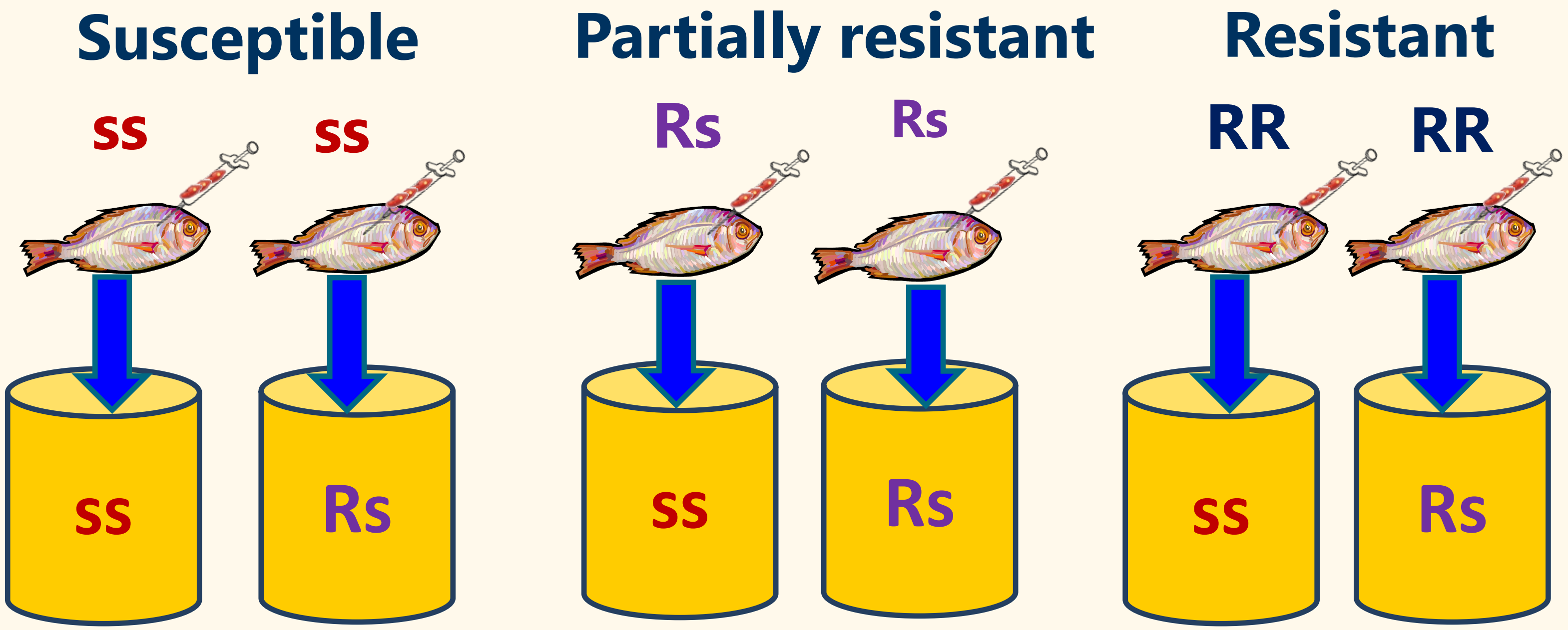


Norris (2017) Marine Genomics

IPN transmission experiment

Infected shedders (n = 8)

Uninfected Cohabitants (n = 40)



Record time to death in cohabitant and shedder fish

Estimate genotype effects on (cohabitant) susceptibility & (shedder) infectivity

Statistical models for epidemiological parameter estimates

Estimate β_k and γ_k for each shedder – cohabitant genotype combination k:

1. **Bayesian algorithm (MCMC) to infer infection times from mortality data**

$$S \xrightarrow{\beta_k} I \xrightarrow{\gamma_k} R$$

2. **Generalized linear mixed models to estimate β_k and γ_k**

Number of cases $C_k(t)$ at day t: $C_k(t) \sim \text{binomial}(S_k(t), p_k)$

Probability of infection: $$p_k = 1 - e^{-\frac{\beta_k I}{N}}$$

GLM: $$\log(-\log(1 - p_k) = \boldsymbol{X}_{\boldsymbol{k}}^{\boldsymbol{T}}\,\boldsymbol{b} + \log({}^{I_k}/_{N}) \qquad \boldsymbol{b} = \log(\boldsymbol{\beta})$$

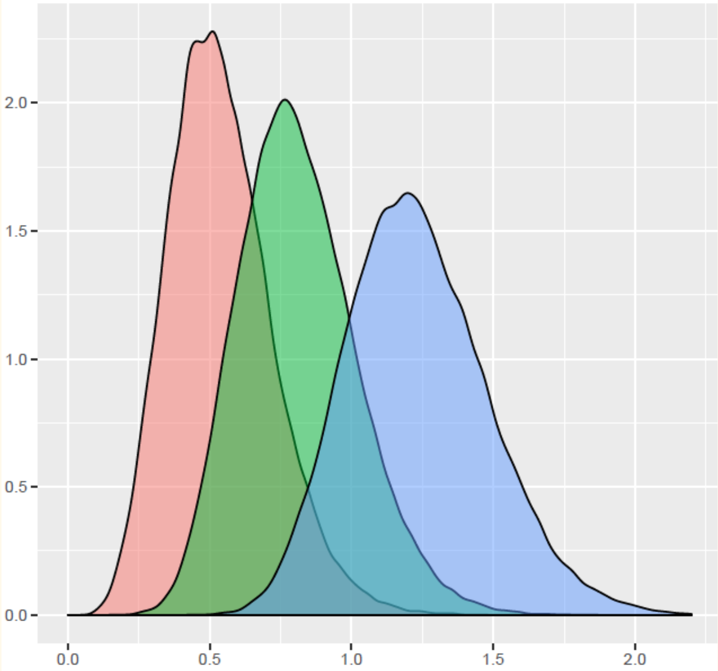
Doeschl-Wilson et al., Proc. WCGALP 2018

R-allele reduces both susceptibility & infectivity

Shedder

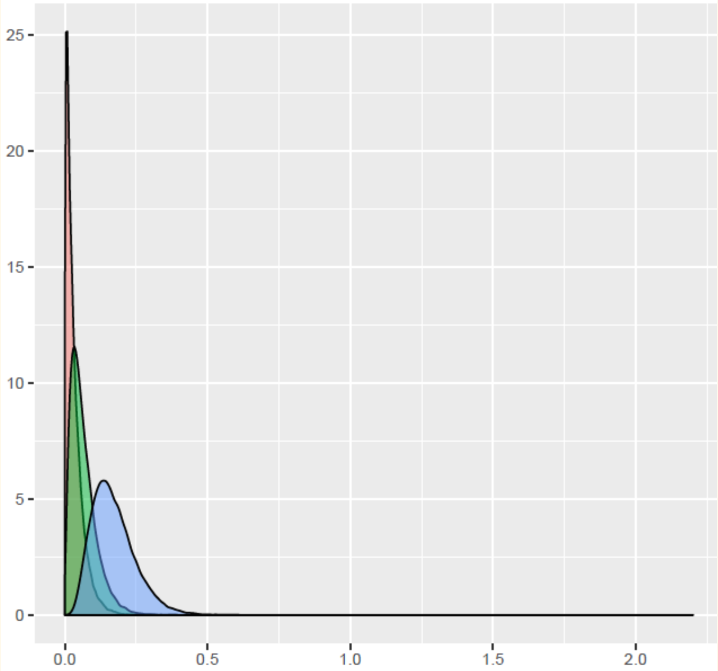
- RR
- Rs
- ss

ss cohabitants



Relative risk of infection

Rs cohabitants



Relative risk of infection

- ss cohabitants were >10 times more susceptible to infection than Rs cohabitants
- ss shedders were at least 2x more infectious than RR shedders

Doeschl-Wilson et al., Proc. WCGALP 2018

ISA virus infections (Atlantic salmon)

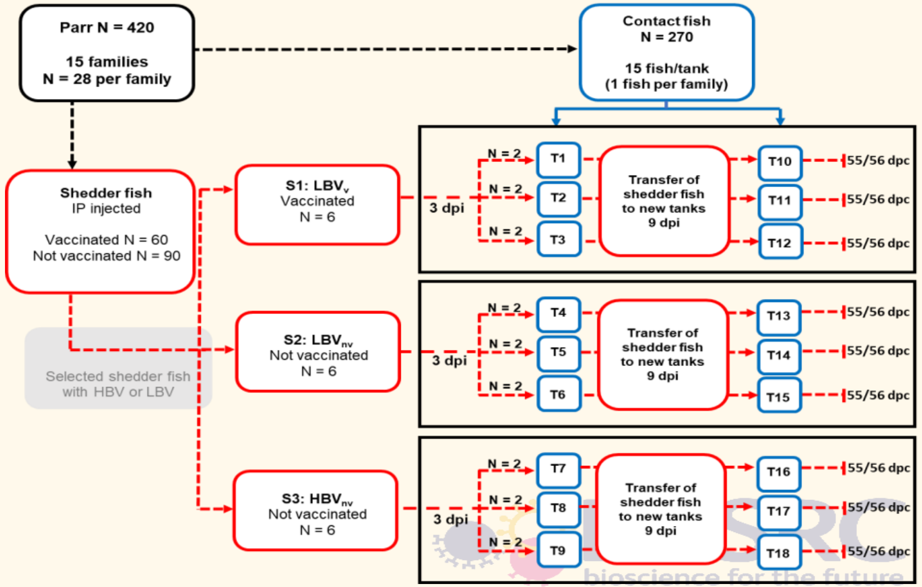
Benchmark Genetics Norway

Nofima

- Infectious **S**almon **A**nemia Virus
- Listed as notifiable disease → control disease spread
- Mostly controlled by vaccines with limited effectiveness
- Genetic selection for ISA resistance (EBV for survival given exposure) ongoing

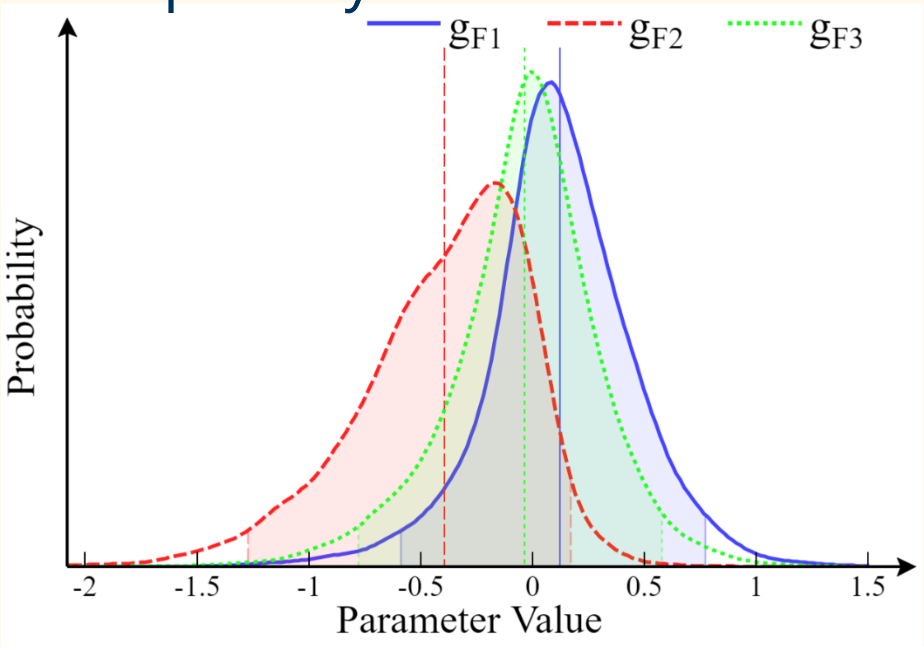
Does selection for ISA resistance reduce ISAV transmission?

→ Transmission experiment to assess effect of genetic selection & vaccination on ISAV transmission

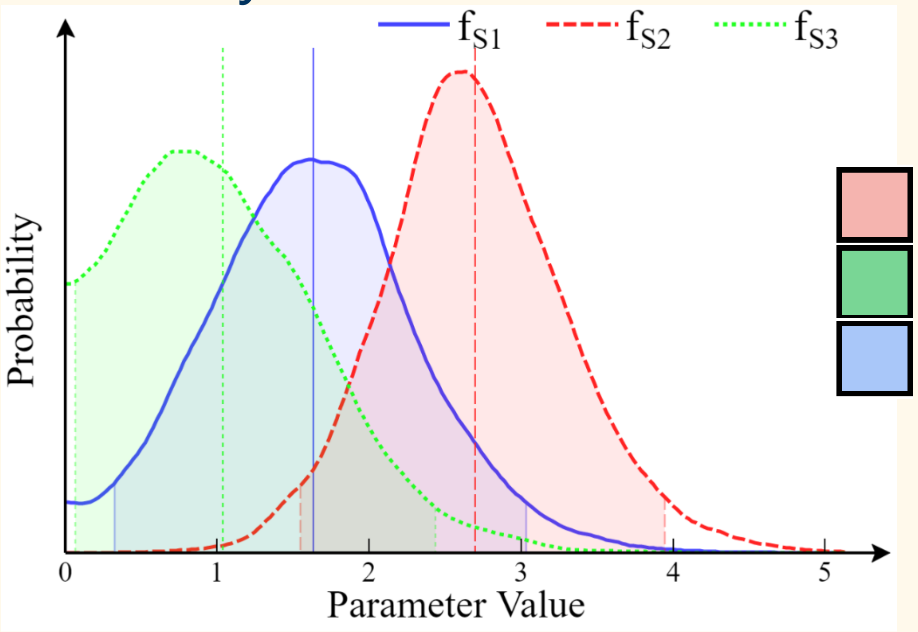


Selection for ISA resistance reduces infectivity, but not susceptibility

Susceptibility



Infectivity



Low resistance EBV
High resistance EBV
Low resistance EBV + Vaccinated

- ‘Resistance’ EBV has larger effects on infectivity than susceptibility
- Genetic effects on infectivity larger than vaccine effects

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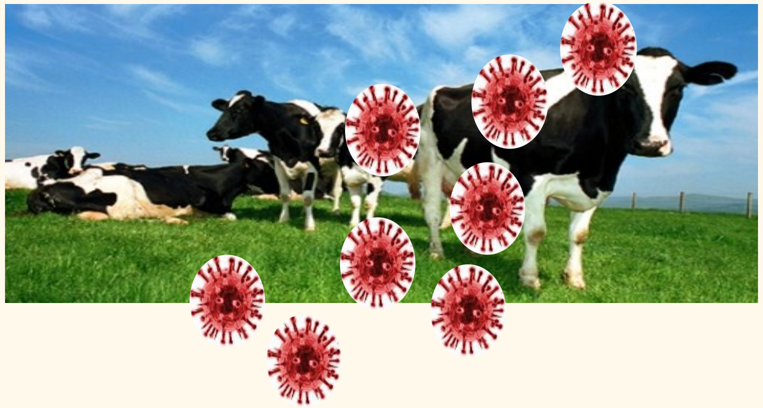
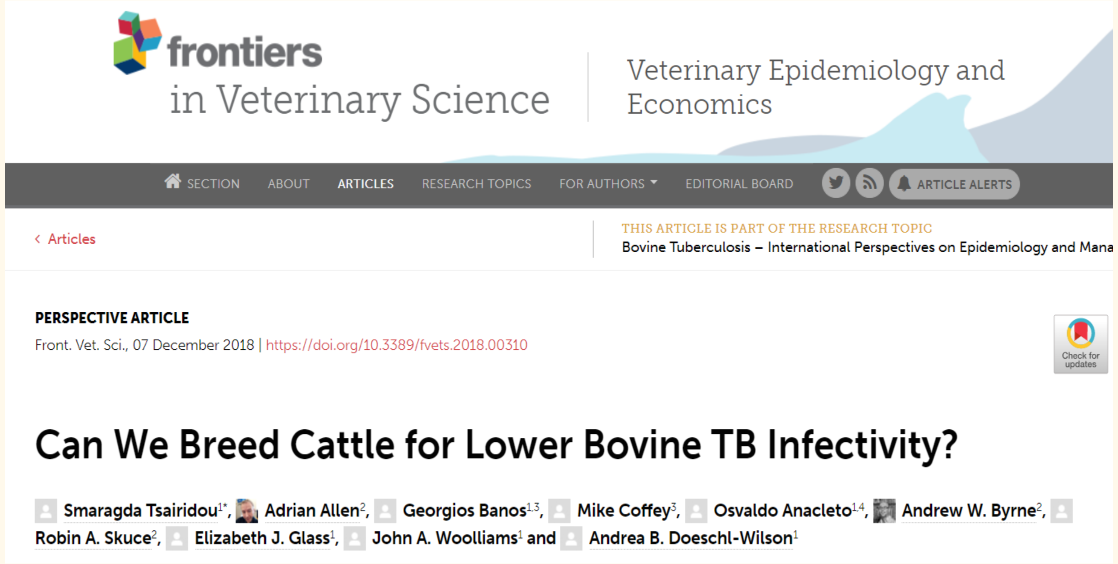
Chase-Topping et al., Aquaculture 2021

Application to field data: Bovine Tuberculosis



Proof of concept:

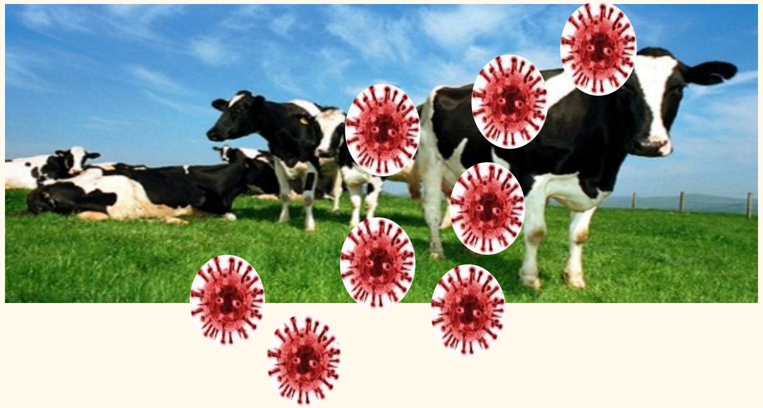
- **Empirical evidence for genetic variation in infectivity**



- Experimental evidence for high variation in shedding rates
- Evidence for presence of bTB superspreaders from field data
- Preliminary estimates from quantitative genetic analyses indicate similarly high heritability for infectivity as for resistance

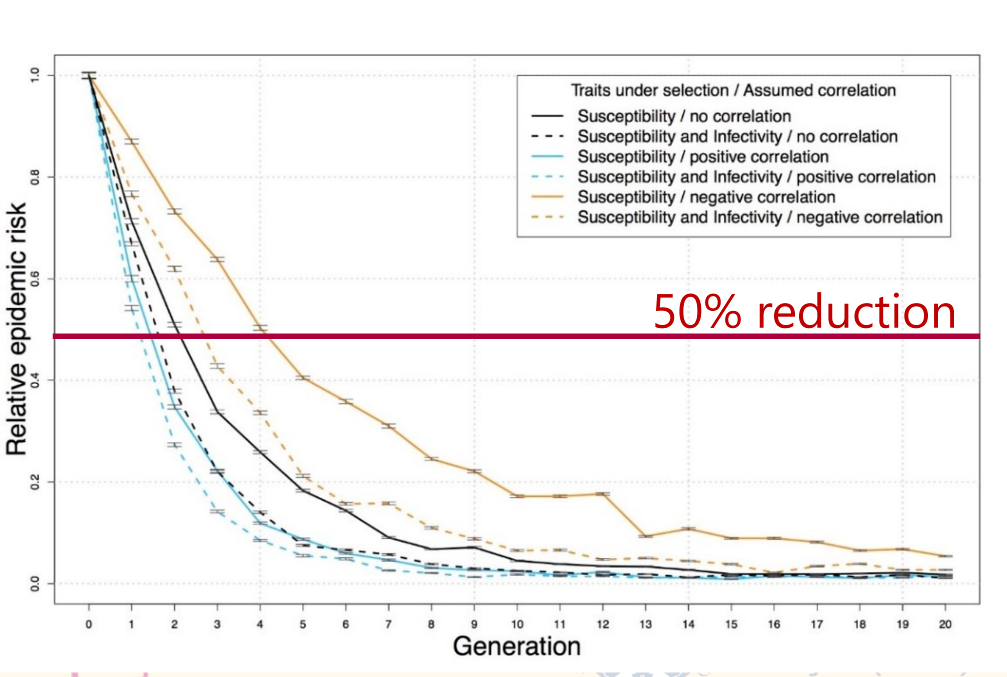
Tsairidou et al., Front. Vet Sci 2008

Application to field data: Bovine Tuberculosis



Proof of concept:

- **Genetic-epidemiological model confirms potential benefits from incorporating infectivity into genetic selection**



- Adding infectivity into the selection index could double the rate of reduction in bTB risk
- Project on adapting SIRE software to bTB currently ongoing

Tsairidou et al., Front. Vet Sci 2008

Take-home messages from animal models

- Vaccination and host genetics potentially play an important role in reducing pathogen transmission
- But their actual effects on transmission are rarely known & difficult to directly measure
- Novel Bayesian Inference tools can estimate vaccine and genetic effects for transmission traits from temporal individual-based epidemiological data
- Genetic-epidemiological prediction models can predict the outcome of combined control strategies

Data-driven now-casting & fore-casting of COVID-19 spread in Scotland

BioSS

Contributing to

THE UNIVERSITY of EDINBURGH | Data-Driven Innovation

Scottish COVID-19 Response Consortium

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A typical day in a politician's life

What movement restrictions?

When to open / close schools & universities?

Who to vaccinate first?

What travel restrictions?

How many hospital beds to reserve?

What test & quarantine rules?

Interventions need to be:

- Timely and targeted
- Based on data-informed models

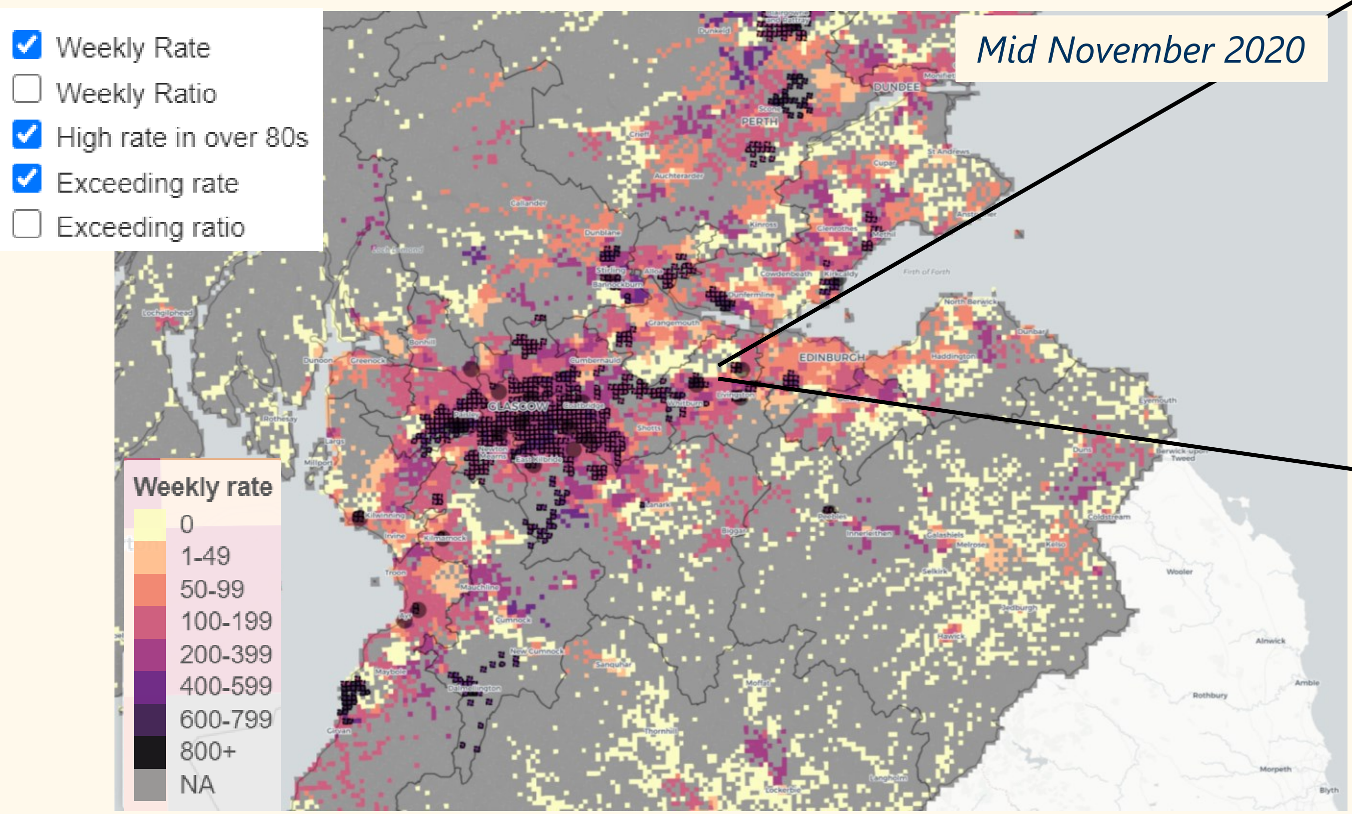
Public Health Scotland

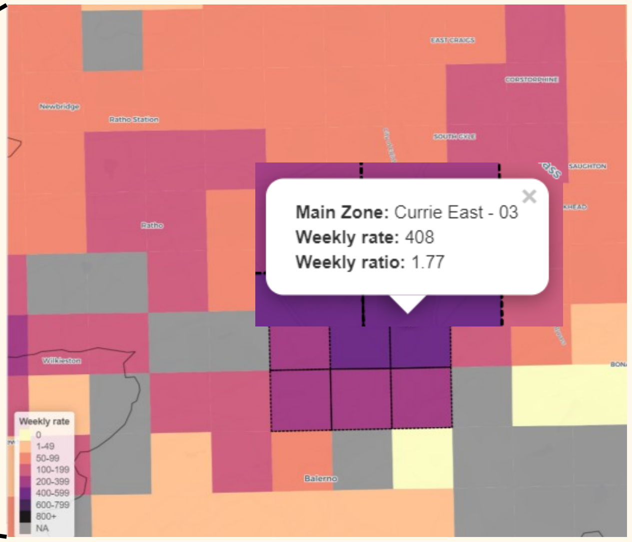
eDRIS: electronic Data Research & Innovation Service
COVID-19 data for research

BBSRC

Covid-19 dashboard for Scotland

Weekly COVID-19 cases per 100,000





- Rapid identification of weekly COVID-19 hotspots
- Accompanied with statistics for specific areas & age category

https://theiteam.shinyapps.io/COVID19Scotland_TrackandModel/

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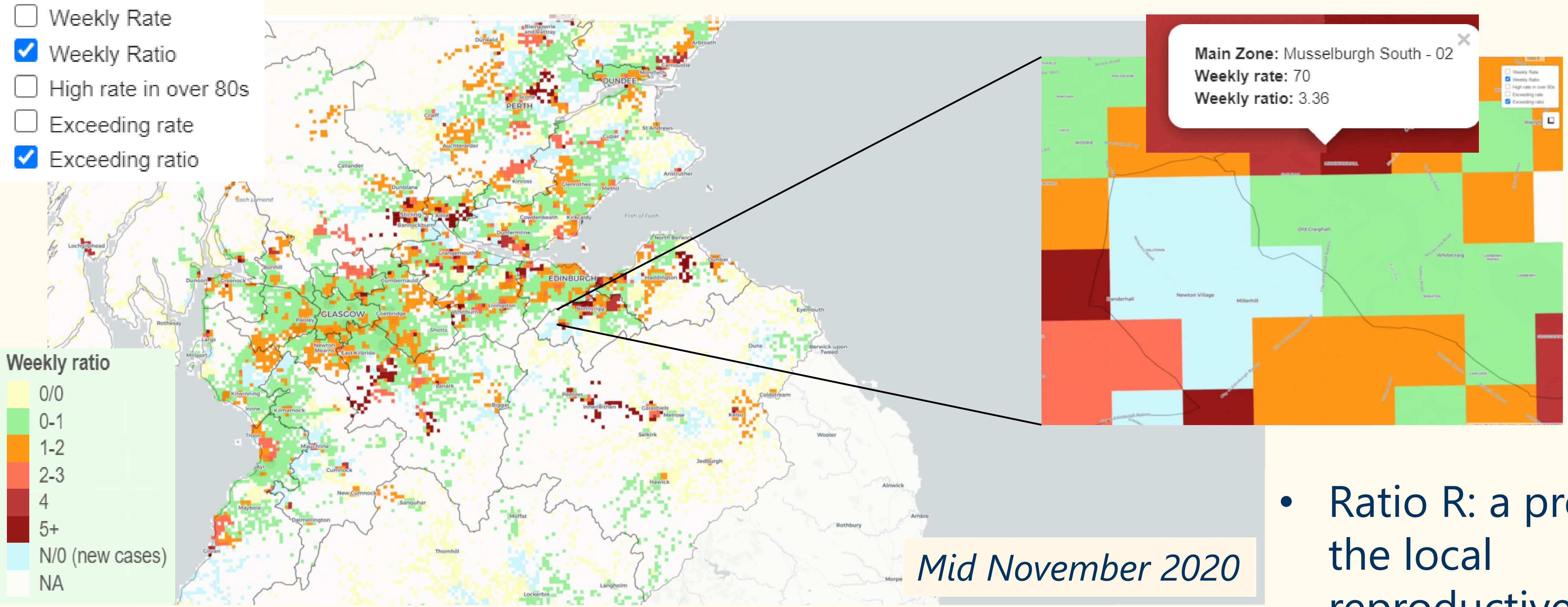
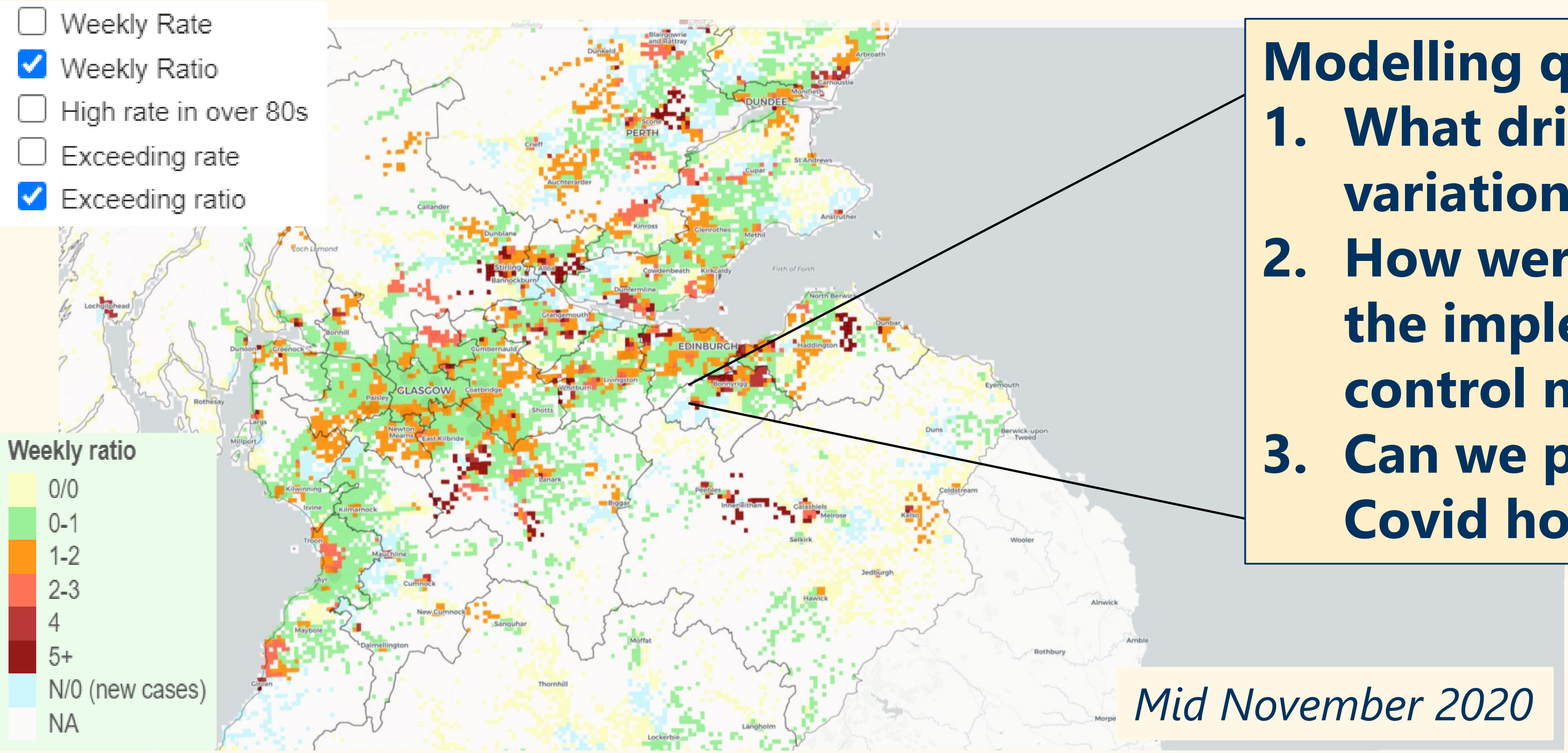
Weekly changes in COVID-19 cases



- Ratio R: a proxy for the local reproductive ratio

https://theiteam.shinyapps.io/COVID19Scotland_TrackandModel/

Weekly changes in COVID-19 cases



Mid November 2020

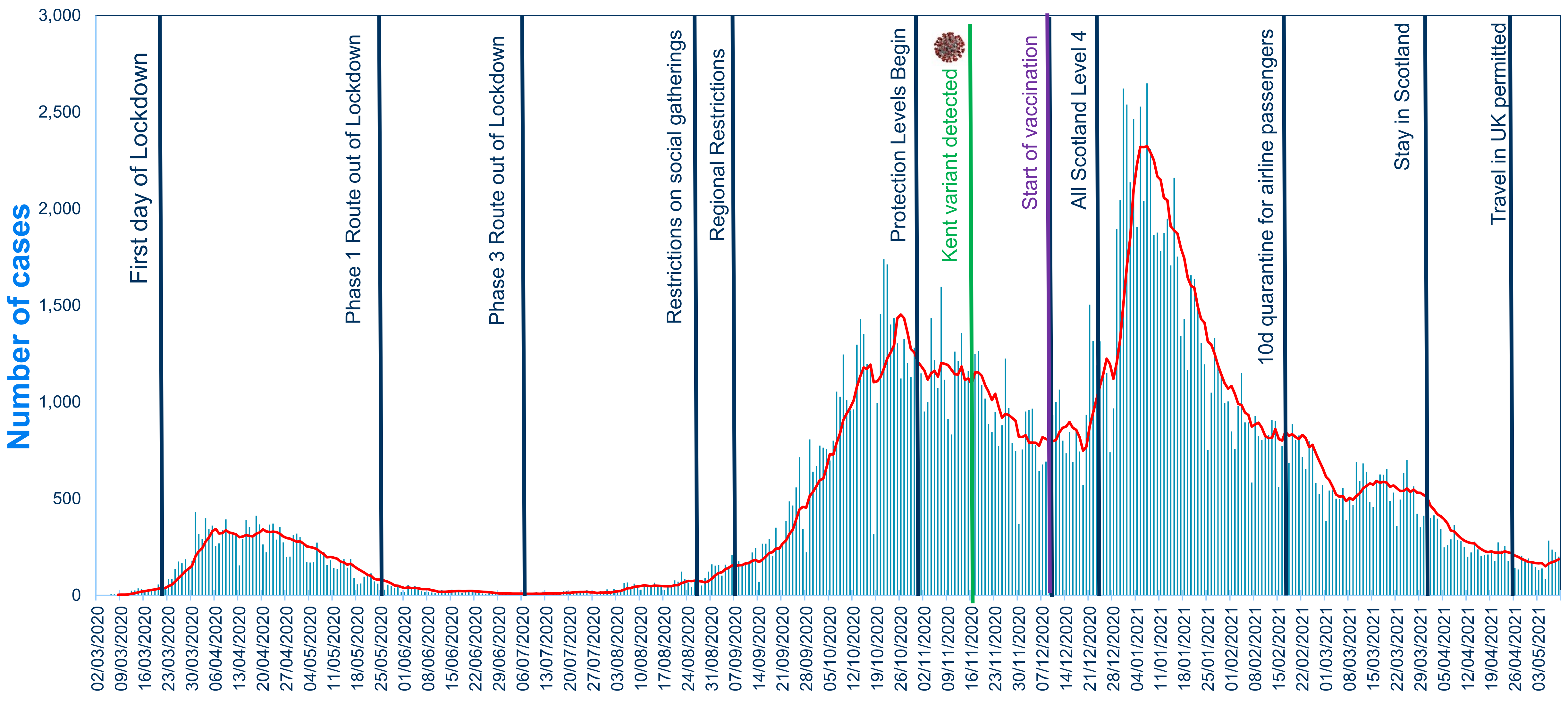
Modelling questions:

1. **What drives the spatial variation in these patterns?**
2. **How were these affected by the implemented Covid-19 control measure?**
3. **Can we predict the next Covid hotspot?**

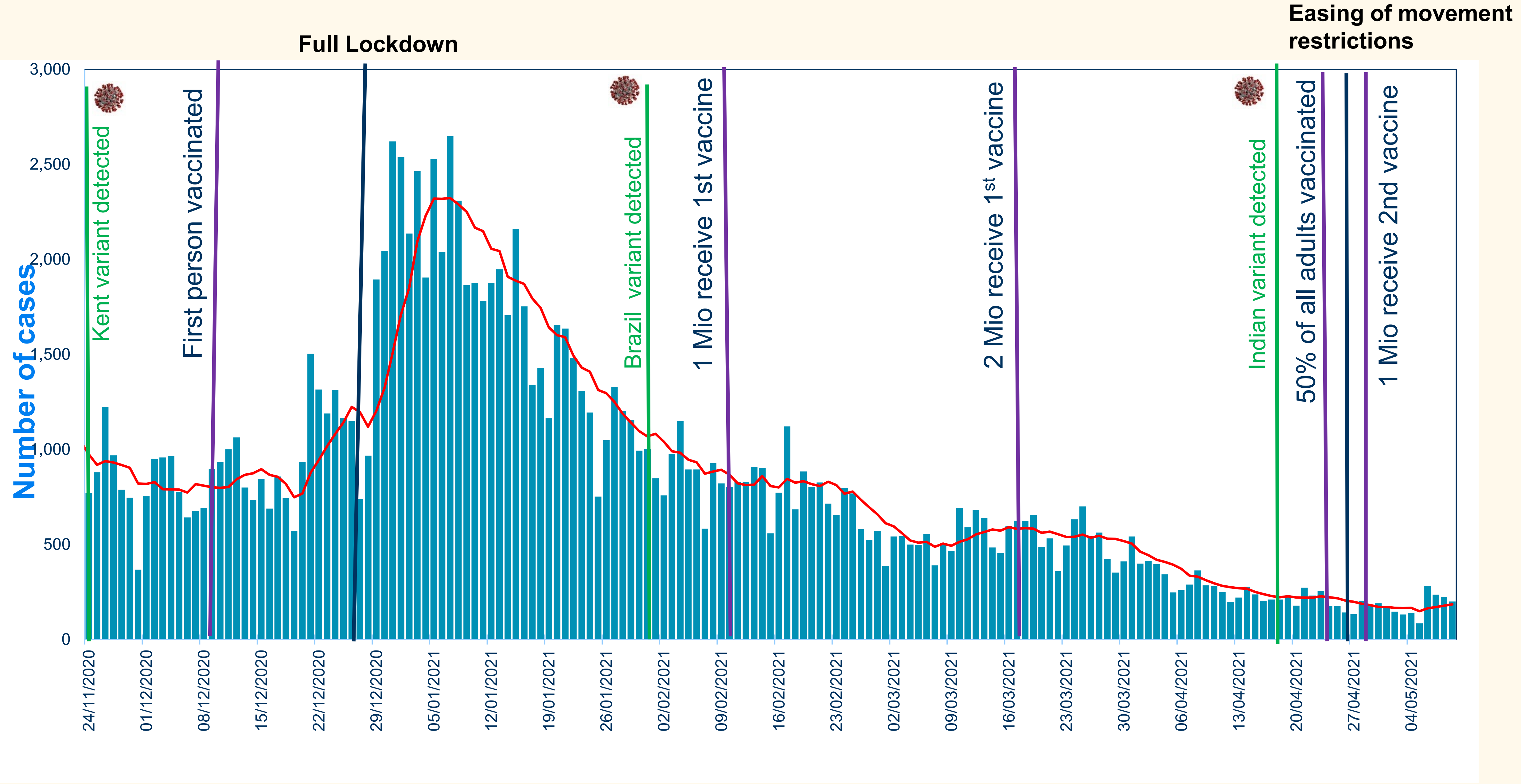
- Ratio R: a proxy for the local reproductive ratio

https://theiteam.shinyapps.io/COVID19Scotland_TrackandModel/

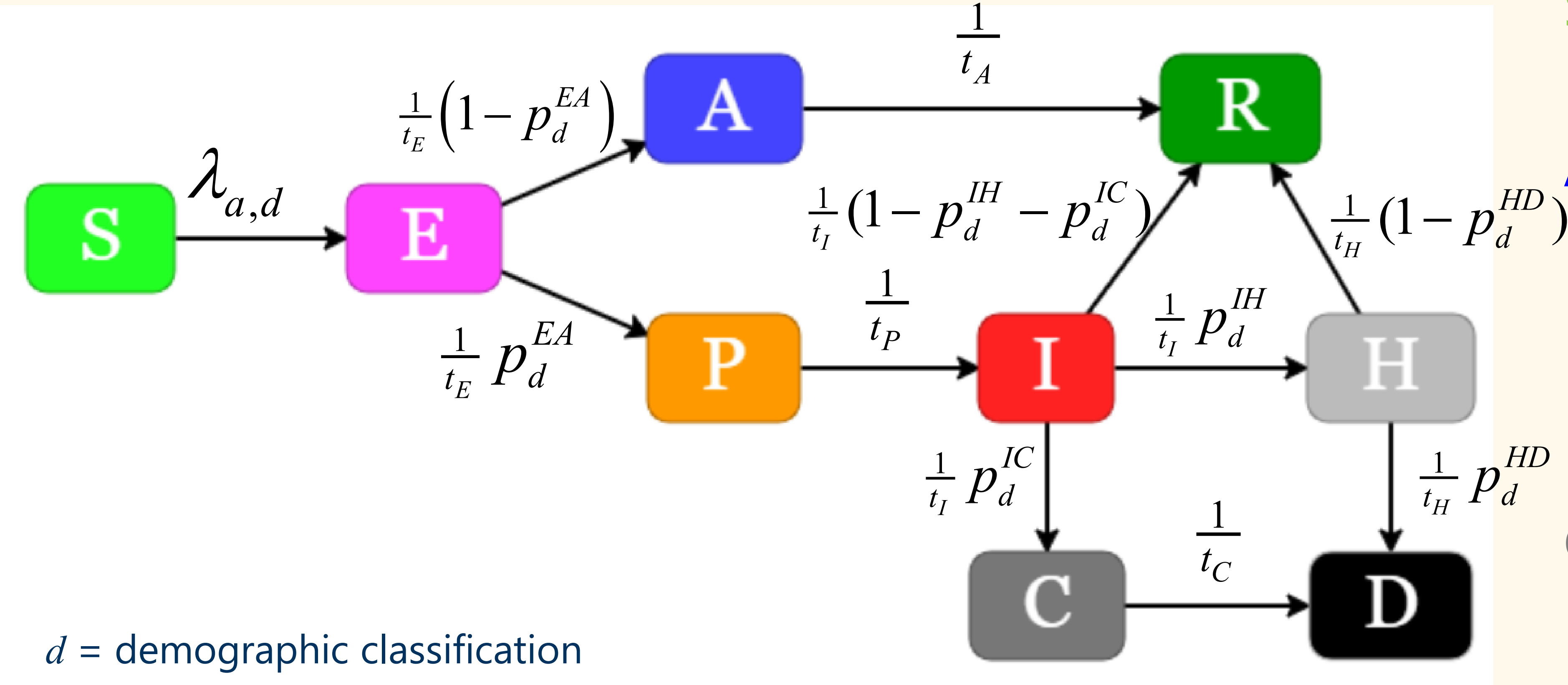
Scottish COVID-19 trends & event timeline



Vaccination timeline - Scotland



A COVID-19 epidemiological model



S: Susceptible
E: Exposed
A: Asymptomatic
P: Pre-symptomatic
I: Symptomatic
R: Recovered
H: Hospitalised
C: Critically ill
D: Dead

- Quality of predictions depends on accuracy of model parameter estimates
- Accurate parameter estimates requires good data

Adaptation of inference methods developed for livestock epidemics to humans

- Account for various sources of heterogeneity
  - Spatial heterogeneity (e.g households, regions, counties…)
  - Individual heterogeneity (age, sex, genetics)
  - Heterogeneous contact structure
  - Temporal heterogeneity due to implementation of local / national control measures & SARS-Cov2 strains
- Include a variety of data (cases, hospital admissions, deaths, demographic, …)

Classical Bayesian inference approaches

SIMULATION-BASED PROPOSAL

- Initial particle state (θ_i, ξ_i)
- Sample $\theta_p \sim K(\theta_p | \theta_i)$
- Simulate ξ_p from model using θ_p
- Calculate error function $\mathrm{EF}(\xi_p)$
- If $\mathrm{EF}\ (\xi_p) > \mathrm{EF}_{\mathrm{cut}}$ reject else

accept with prob. $\dfrac{K(\theta_i|\theta_p)}{K(\theta_p|\theta_i)} \dfrac{\pi(\theta_p)}{\pi(\theta_i)}$

Examples:

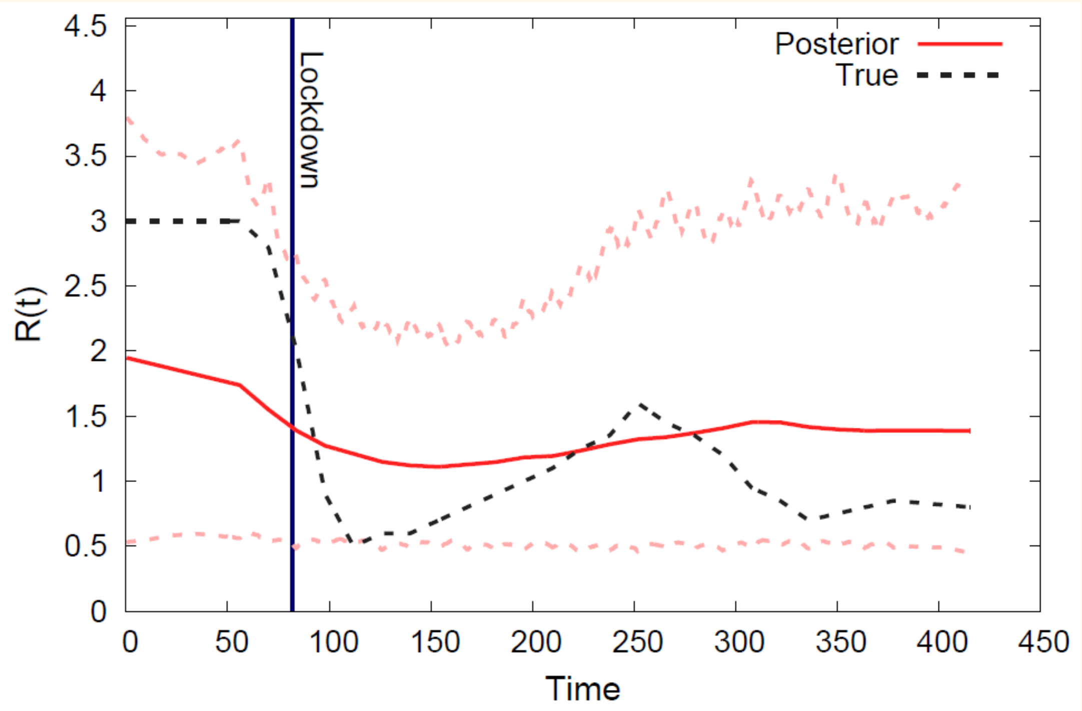
- ABC
- ABC-Sequential Monte-Carlo
- Particle MCMC

Classical Bayesian inference approaches

SIMULATION-BASED PROPOSAL

- Initial particle state (θ_i, ξ_i)
- Sample $\theta_p \sim K(\theta_p|\theta_i)$
- Simulate ξ_p from model using θ_p
- Calculate error function EF(ξ_p)
- If EF (ξ_p) > EF$_{cut}$ reject else accept with prob. $\frac{K(\theta_i|\theta_p)}{K(\theta_p|\theta_i)} \frac{\pi(\theta_p)}{\pi(\theta_i)}$

Poor Inference



Model-Based Proposals

SIMULATION-BASED PROPOSAL

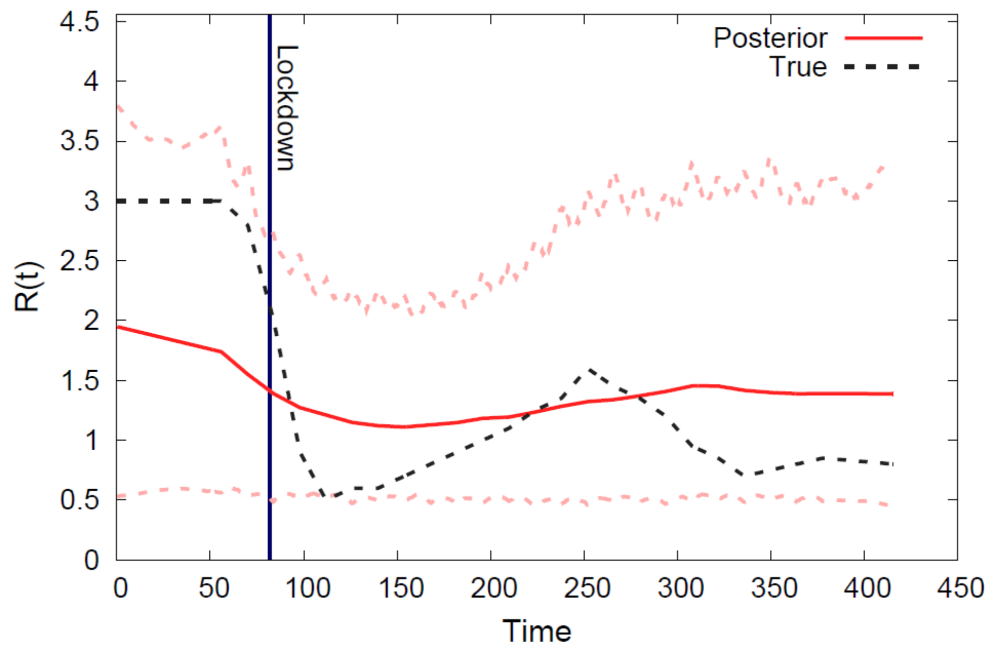
- Initial particle state (θ_i, ξ_i)
- Sample $\theta_p \sim K(\theta_p|\theta_i)$
- Simulate ξ_p from model using θ_p
- Calculate error function EF(ξ_p)
- If EF (ξ_p) > EF$_{\text{cut}}$ reject else accept with prob. $\frac{K(\theta_i|\theta_p)}{K(\theta_p|\theta_i)}\frac{\pi(\theta_p)}{\pi(\theta_i)}$

MODEL-BASED PROPOSAL

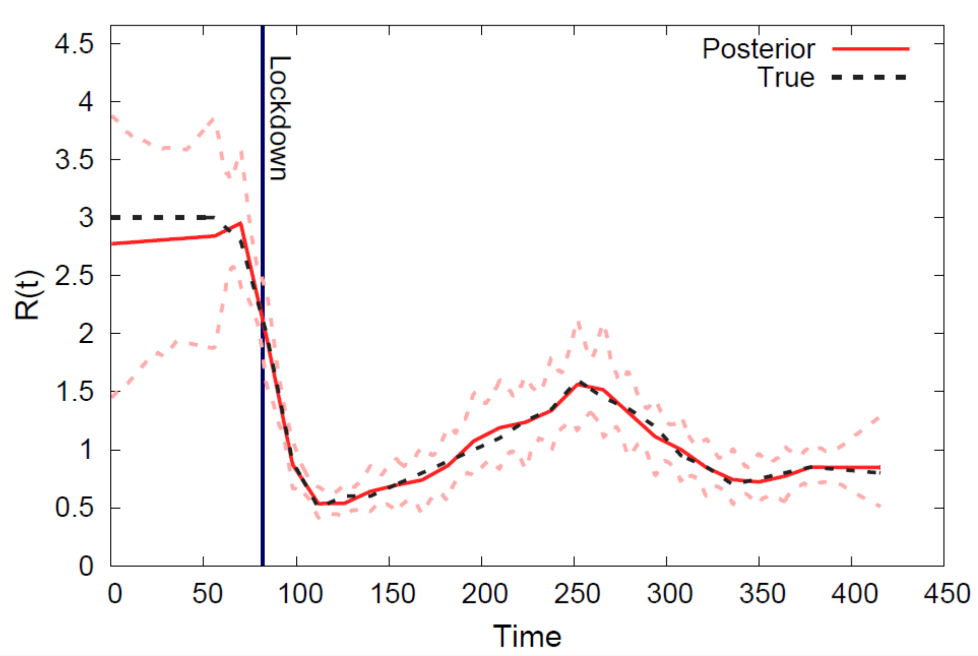
- Initial particle state (θ_i, ξ_i)
- Sample $\theta_p \sim K(\theta_p|\theta_i)$
- Adjust ξ_p based on the change from θ_i to θ_p
- Calculate error function EF(ξ_p)
- If EF (ξ_p) > EF$_{\text{cut}}$ reject else accept with prob. $\frac{K(\theta_i|\theta_p)}{K(\theta_p|\theta_i)}\frac{\pi(\theta_p)}{\pi(\theta_i)}$

Simulation based vs model based proposals

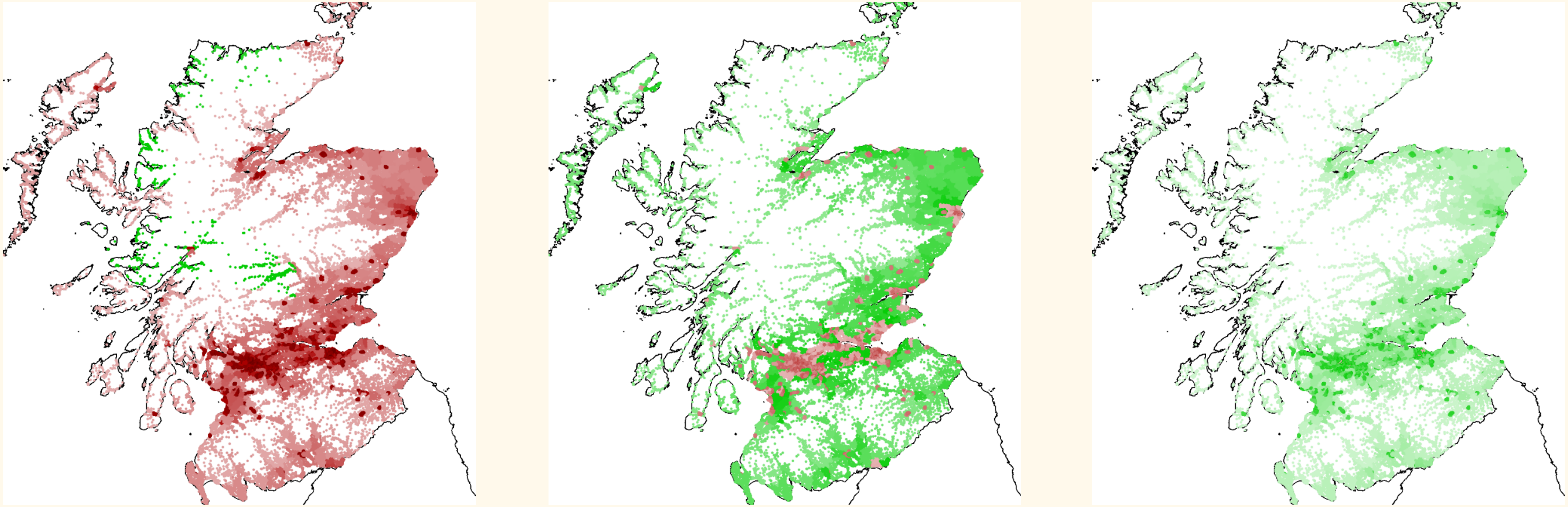
Simulation based approaches



Model based proposals



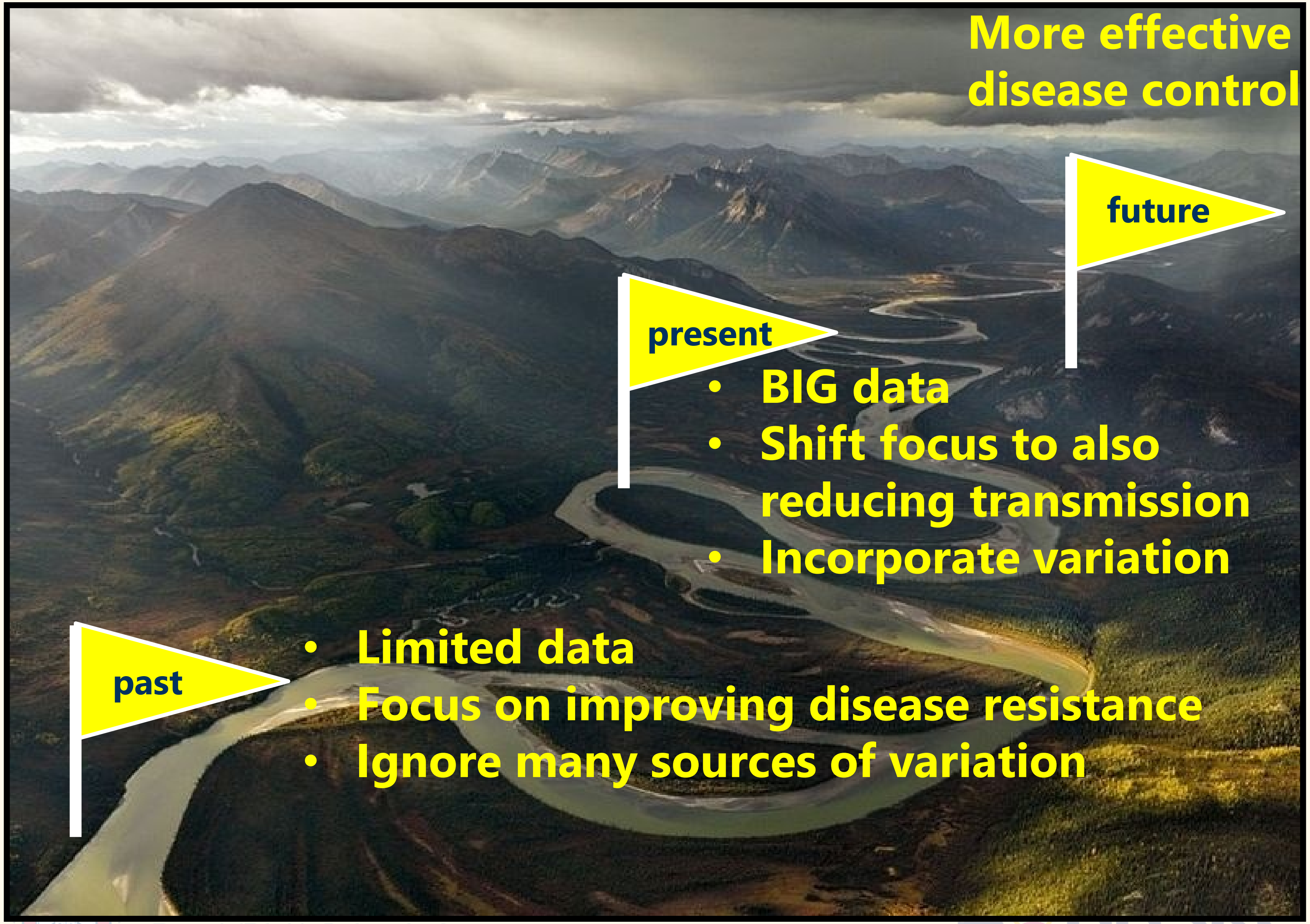
Infer reproductive ratio & other epidemiological parameters for different regions in Scotland over time



Before 1st lockdown (March 2020)   August 2020   May 2021

ROSLIN   THE UNIVERSITY of EDINBURGH Royal (Dick) School of Veterinary Studies   BBSRC bioscience for the future

Conclusions & visions for disease control



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We are recruiting a post-doc in phylodynamic modelling