Introduction to Mathematical Models of Infectious Disease in Livestock

Lecture 3: Some model examples

Andrea Doeschl-Wilson

ROSLIN

Purpose of this lecture

- Provide a brief demonstration of existing mathematical models of infectious disease dynamics in livestock
  - Chosen subjectively
  - Not a comprehensive review!
- Get some insight into:
  - How biological concepts and mathematical approaches are incorporated in models
  - How the diverse models contribute to infectious disease research & policy

Overview

Models of within host infection dynamics:

1. *PRRS virus infection in pigs*

   Micro-parasite infection; based on immunological principles

2. *Gastro-intestinal parasite infection in sheep*

   Macro-parasite infection; based on resource allocation theory

Epidemiological models:

3. *Gastro-intestinal parasite infection in sheep*

   Example for using models to inform breeding strategies

4. *Foot and mouth disease*

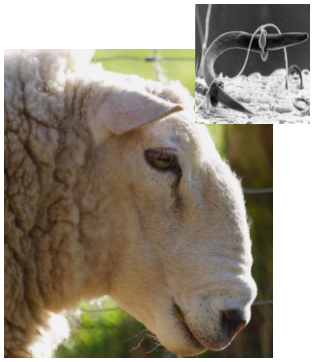
   Example for using models as decision making tool

Mathematical models of infection dynamics

- Distinguish between two broad categories
  (1) Within host models
  – Model interactions between pathogen and host response
  (2) Epidemiological models
  – Model disease spread between hosts / farms
- They require **different knowledge**, use **different data** & answer **different** kind of **questions**
  – But use **similar mathematical tools**
- Both models can be combined into an immuno-epidemiological model

Within-host infection models

- Relatively few models for animal diseases
- 2 contrasting examples to demonstrate diversity in approach and scope:
  1. Modelling PRRS virus infection in pigs
     - Mathematical representation of immune response to micro-parasite infection
  2. Modelling nematode infection in sheep
     - Mathematical representation of resource allocation theory for macro-parasitic infections

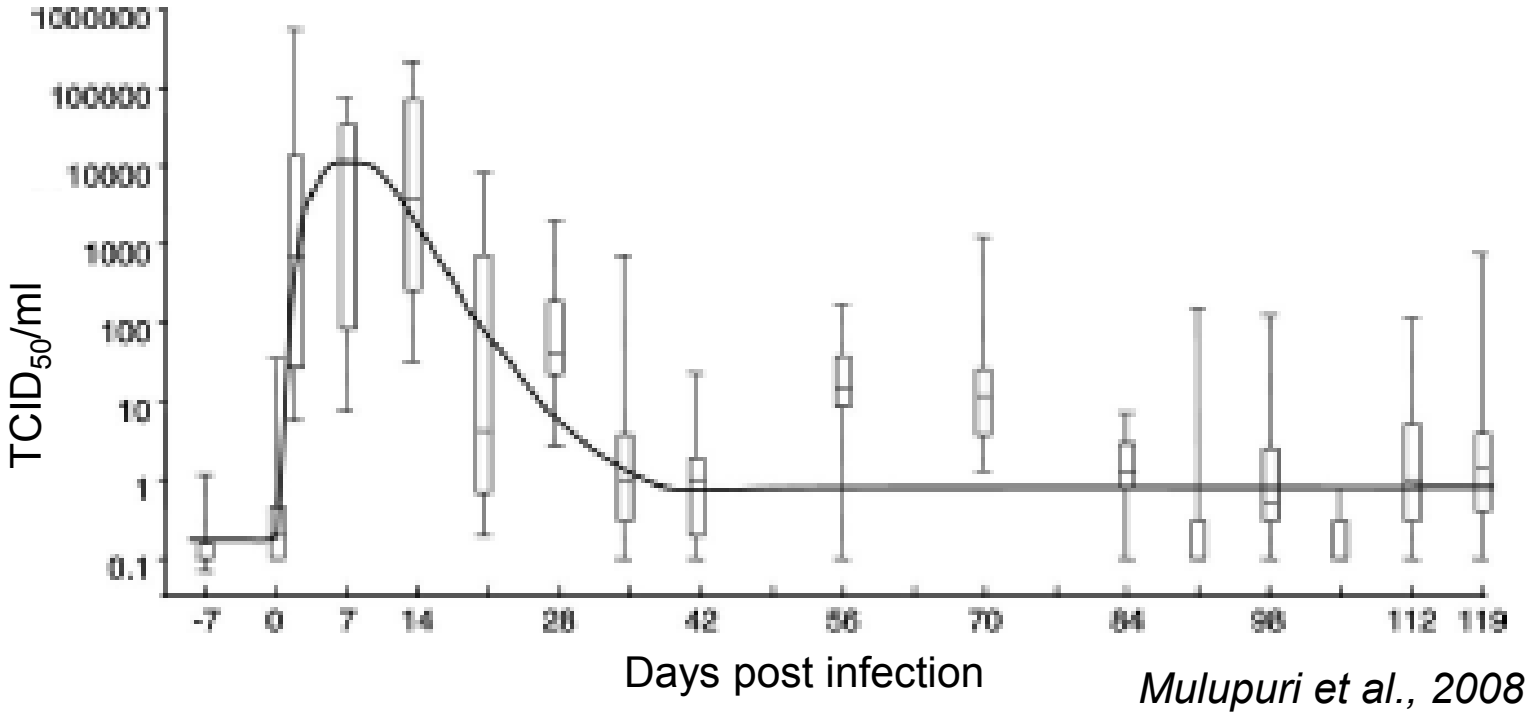


Within-host model of PRRS virus infections in pigs

The Porcine Reproductive and Respiratory Syndrome (PRRS)

- Endemic viral disease worldwide
  - Infectious agent: RNA-virus PRRSV
  - causes dramatic losses to pig industry
- Symptoms:
  - Reproductive failure in mature pigs
  - Respiratory problems, fever, weight loss, death in growing pigs
- Target cells: subpopulation of macrophages in lung and other tissues
- Vast amount of research, but no efficient control measures

Atypical & highly diverse virus load profile



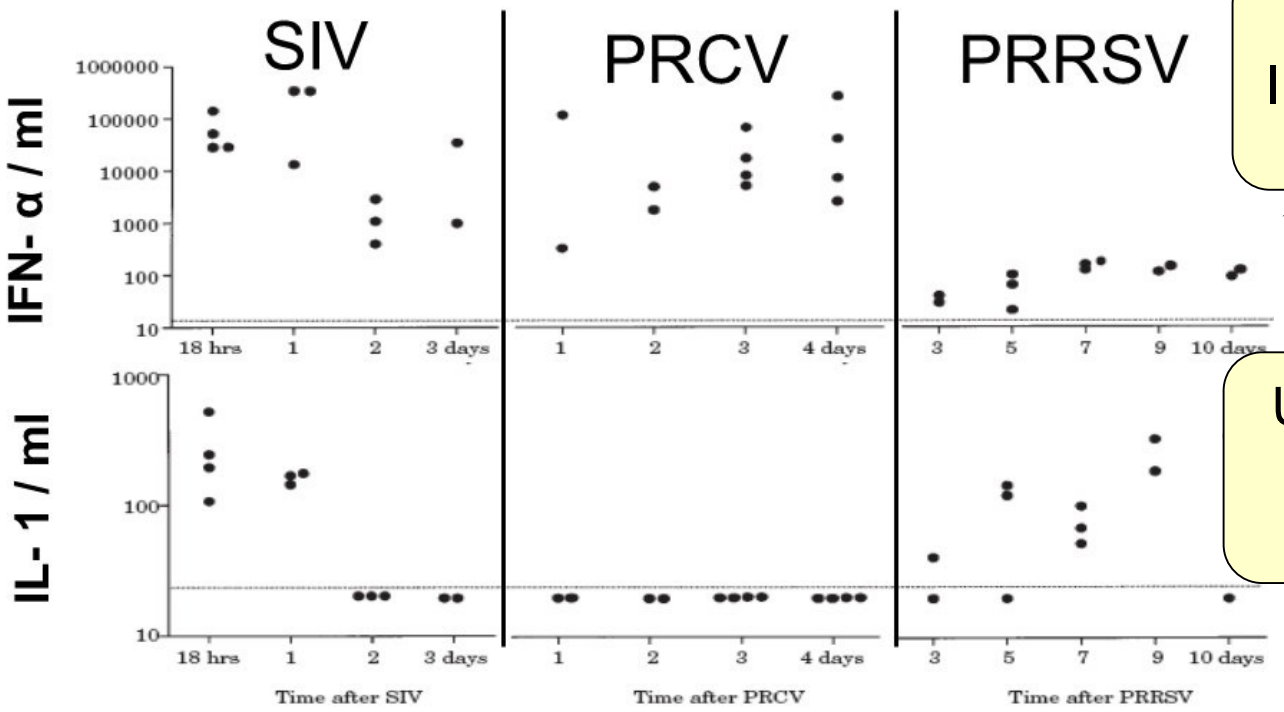
Mulupuri et al., 2008

- peak levels at 7-14 days post infection
- acute phase lasts approx. 4 weeks
- long-term persistence at low levels
- large variation between hosts

} Atypical profile for virus infections!

Weak innate immune response

- Lack of typical cytokine expressions
- Virus seems to manipulate innate response to its favour

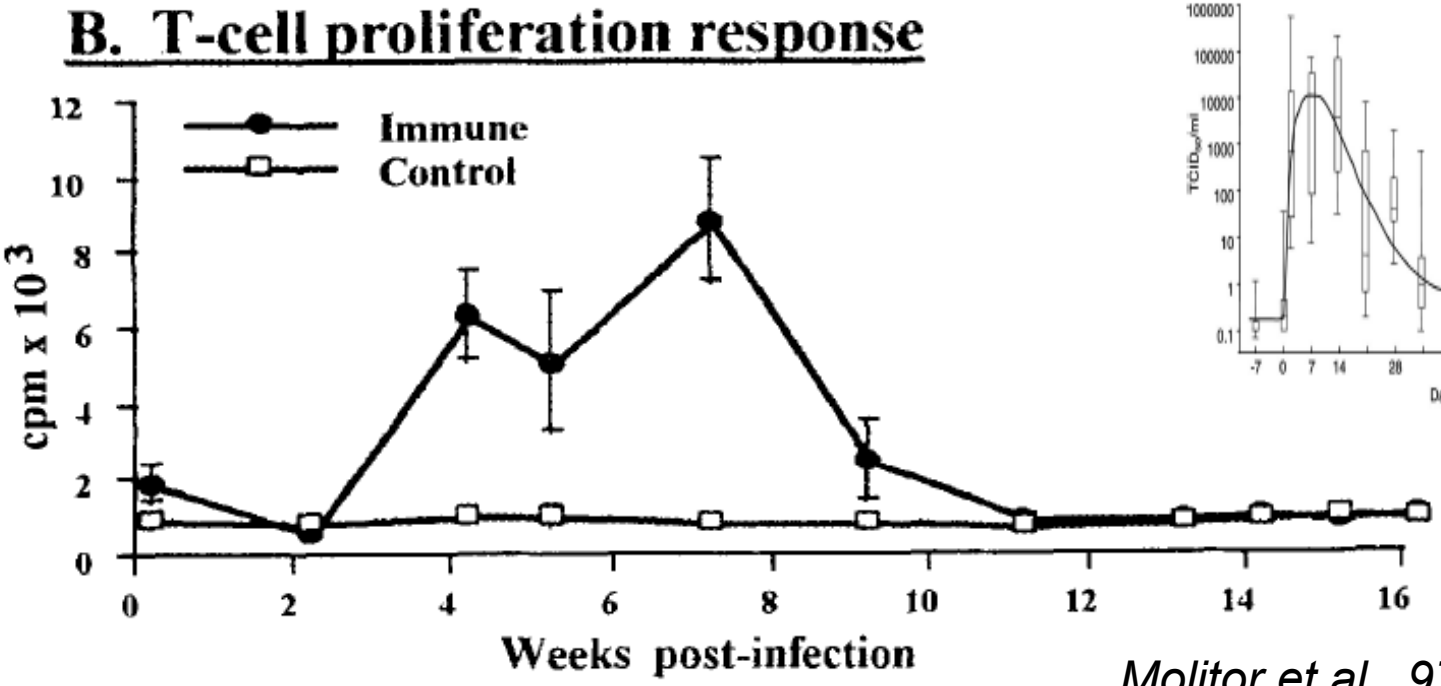


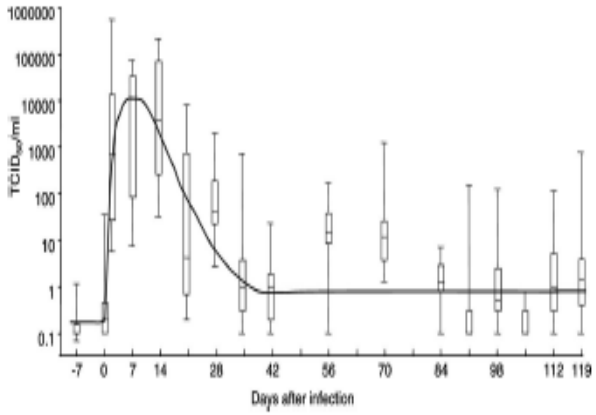
Down-regulation of IFN-α facilitates virus replication

Up-regulation of IL-1 stimulates influx of new target cells

Van Reeth et al., 1999

Weak & delayed adaptive response



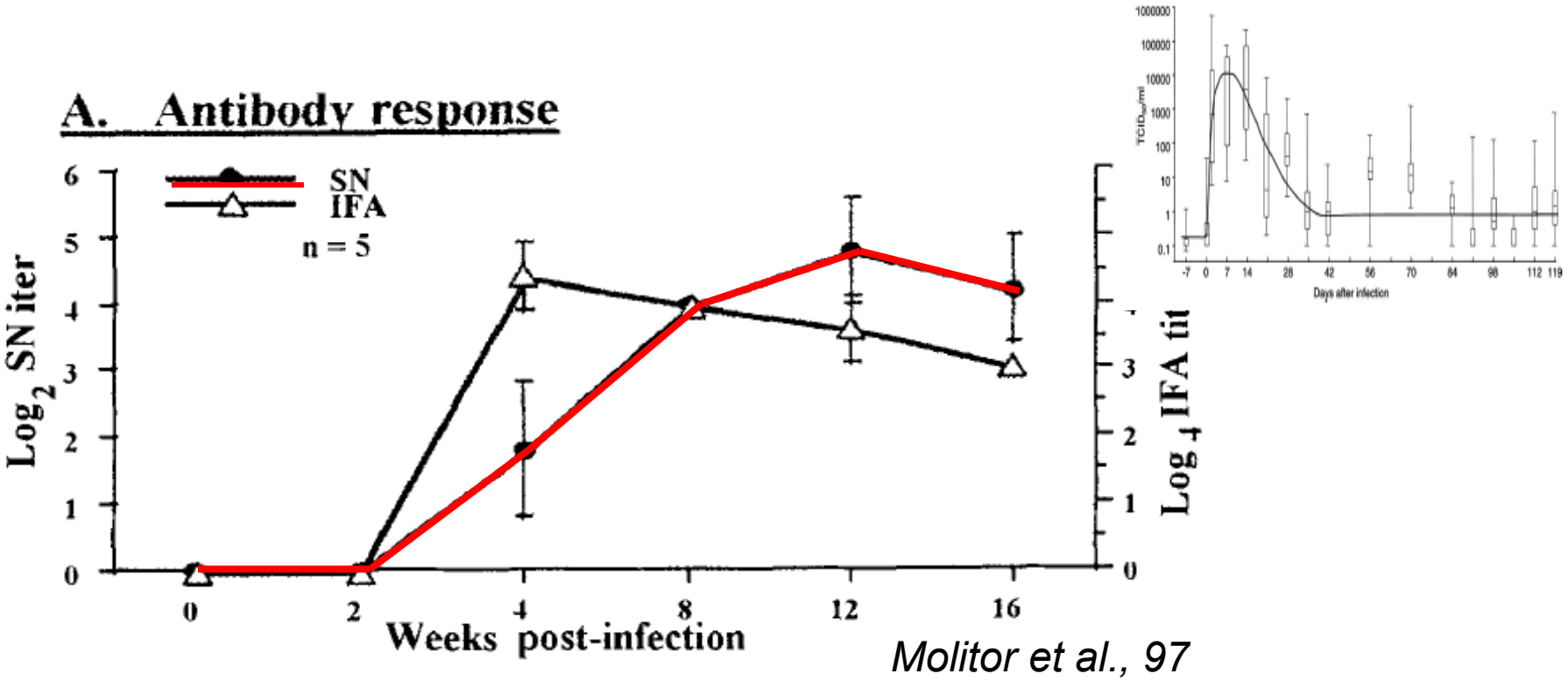


Molitor et al., 97

- T cell response delayed & weak
- Out of synch with virus load
- Large variation between hosts

What role do T cells play in clearing the infection?

Atypical neutralizing antibody response



Molitor et al., 97

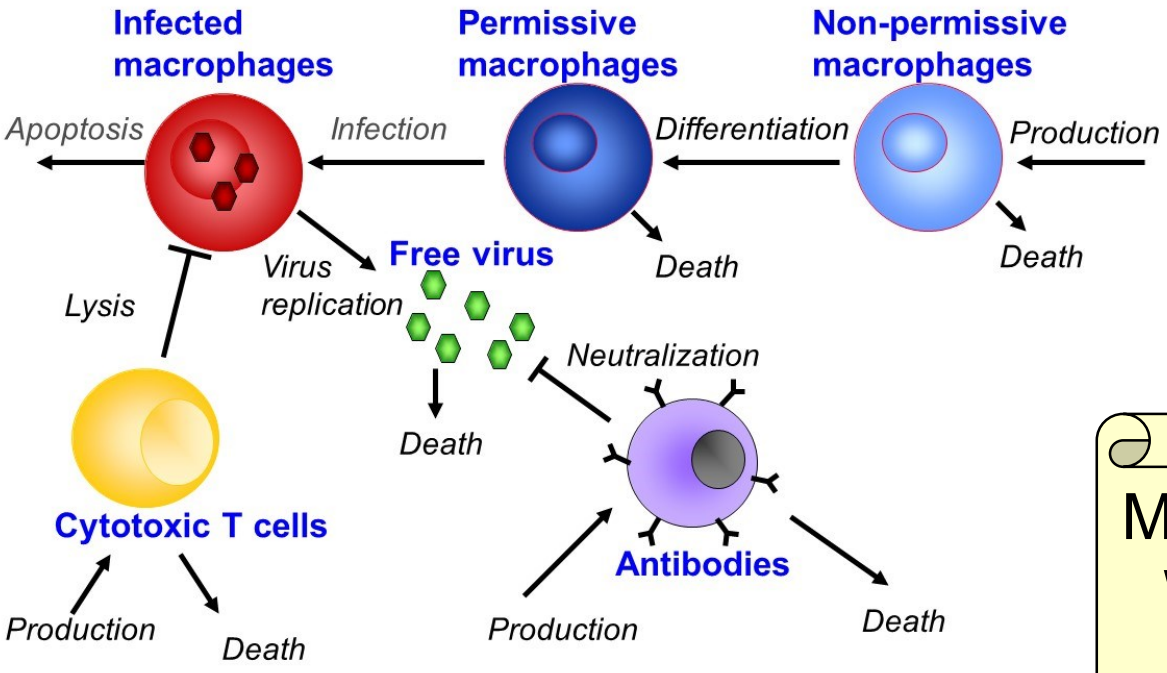
- Neutralizing antibodies appear late
- Antibody levels remain high
- Large variation between hosts

What role do neutral. antibodies play in clearing the virus?

Questions addressed by the mathematical model

- What causes the observed diversity in PRRS viraemia profiles?
- Which biological processes are responsible for viral clearance?
  - What role does the adaptive immune response play?

Modelling approach: A mechanistic model of virus and immune system dynamics



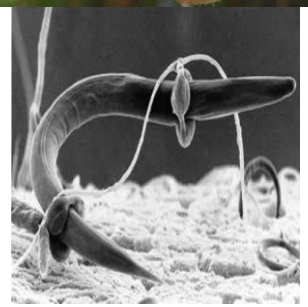
Note: Difference in host resistance can be represented by difference in immune parameters

More on this in Wednesday lecture & tutorial!

Within-host model of gastro-intestinal parasite infections in sheep

Gastro-intestinal parasite infections in sheep

- Endemic; major problem for sheep production: slow growth -> economic loss
- Conventional control strategies no longer work (anthelmintic resistance)
- Strong evidence for large influence of diet & host genetics on parasite burden
- Breeding for resistance a possible solution?
- But not clear if breeding for resistance would indeed lead to faster growth:
  - Estimates of genetic correlation between parasite burden & growth in field studies range between -0.8 to 0.4



Model objectives:

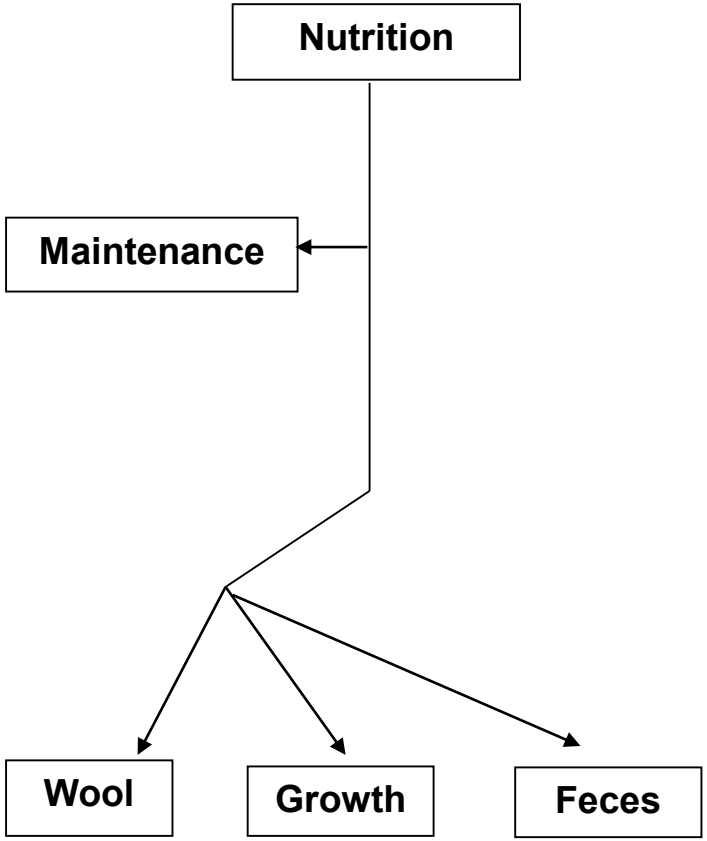
- To investigate what causes the conflicting estimates from field studies

  Hypotheses: Field estimates depend on

  - Parasite challenge
  - Breed
  - Nutritional environment
  - Timing of measurements

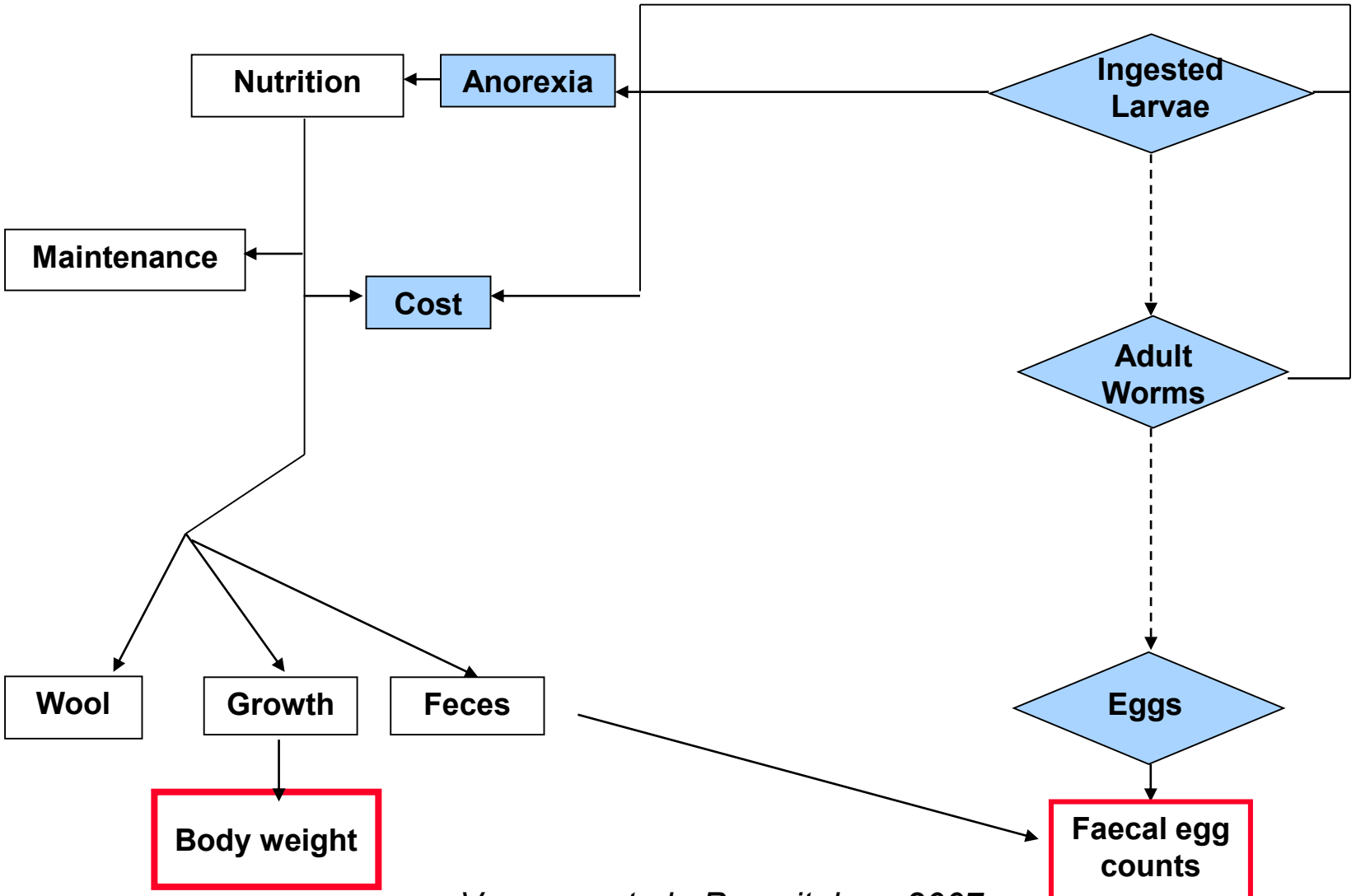
- Ultimately: to determine if / under what conditions selective breeding is a viable alternative to drug administration

Base model: Nutrient allocation in healthy animal



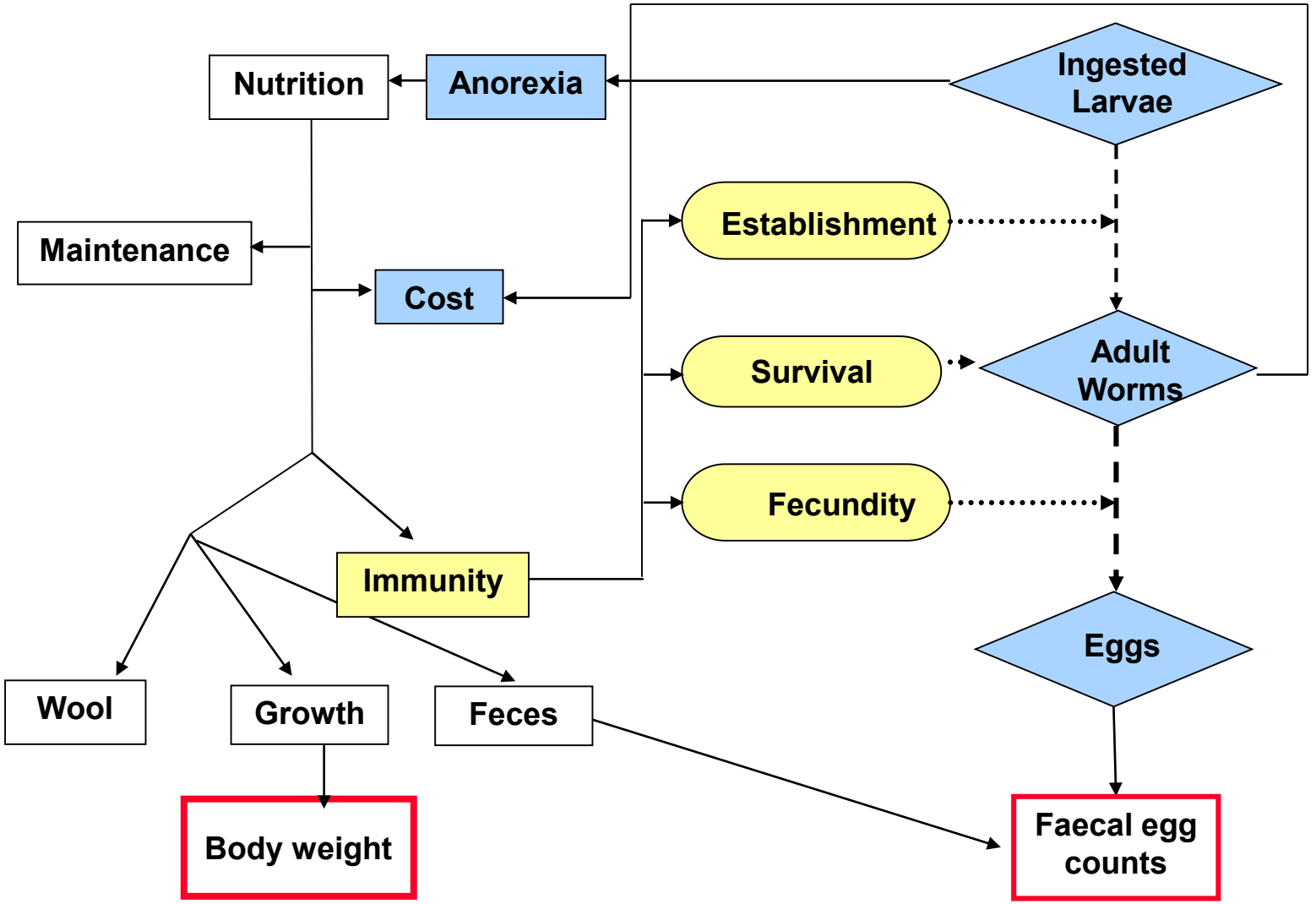
Vagenas et al., Parasitology 2007

Influence of parasite on nutrient allocation and performance



Vagenas et al., Parasitology 2007

Influence of host immune response



Mathematical representation

Hybrid mechanistic model of nutrient allocation:

- Mass balance equations for nutrient flow
- Parameterization based on empirical estimates for energy and protein costs associated with diverse biological processes
  - Assume production and health traits change proportional to nutrients allocated to these
- Within host-dynamics represented by large system of non-linear equations (discrete time step, deterministic)
- Expand to a population model: Host genetic variation represented by normal distributions in key model parameters (e.g. rate of parasite establishment) (stochastic)

Vagenas et al., Int. J. Paras. 2008; Doeschl-Wilson et al., GSE 2008

Simulation experiment

Simulate growth and immune response for a population of lambs

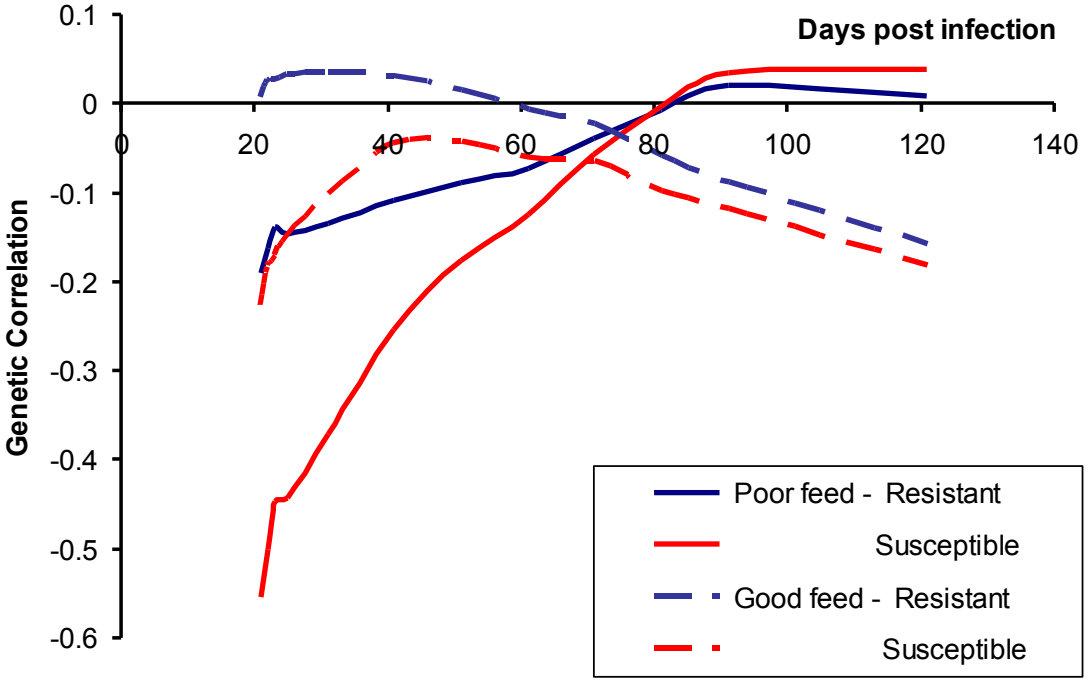
Immune challenge: Trickle infection with 3000 nematode larvae

Simulate 2 x 2 factorial experiment:

- 2 breeds for resistance (different population means for immune parameters): Susceptible / Resistant breed
- 2 diets (ad libitum access): Good / poor quality grass

Impact of host genetics & diet on genetic correlations

Genetic correlations between body weight and faecal egg counts (log)



Doeschl-Wilson et al., GSE 2008

Summary of model findings

Model can explain ambiguous field study estimates:

- Traits and relationships change drastically over time
  - Repeated measurements required
- Strong breed x diet interactions
  - Trends are consistent with field observations
  - Model provides insight of underlying mechanisms
- Strong positive correlations between growth and health could only be obtained if growth and resistance mechanisms are controlled by common genes
- Genetic selection for disease resistance is most beneficial for susceptible breeds in poor quality diet

Doeschl-Wilson et al., GSE 2008

Extension to epidemiological models

- Both models produce predictions for pathogen burden (viral load or faecal egg counts) over time
- They thus lends themselves to expansion to immuno-epidemiological models

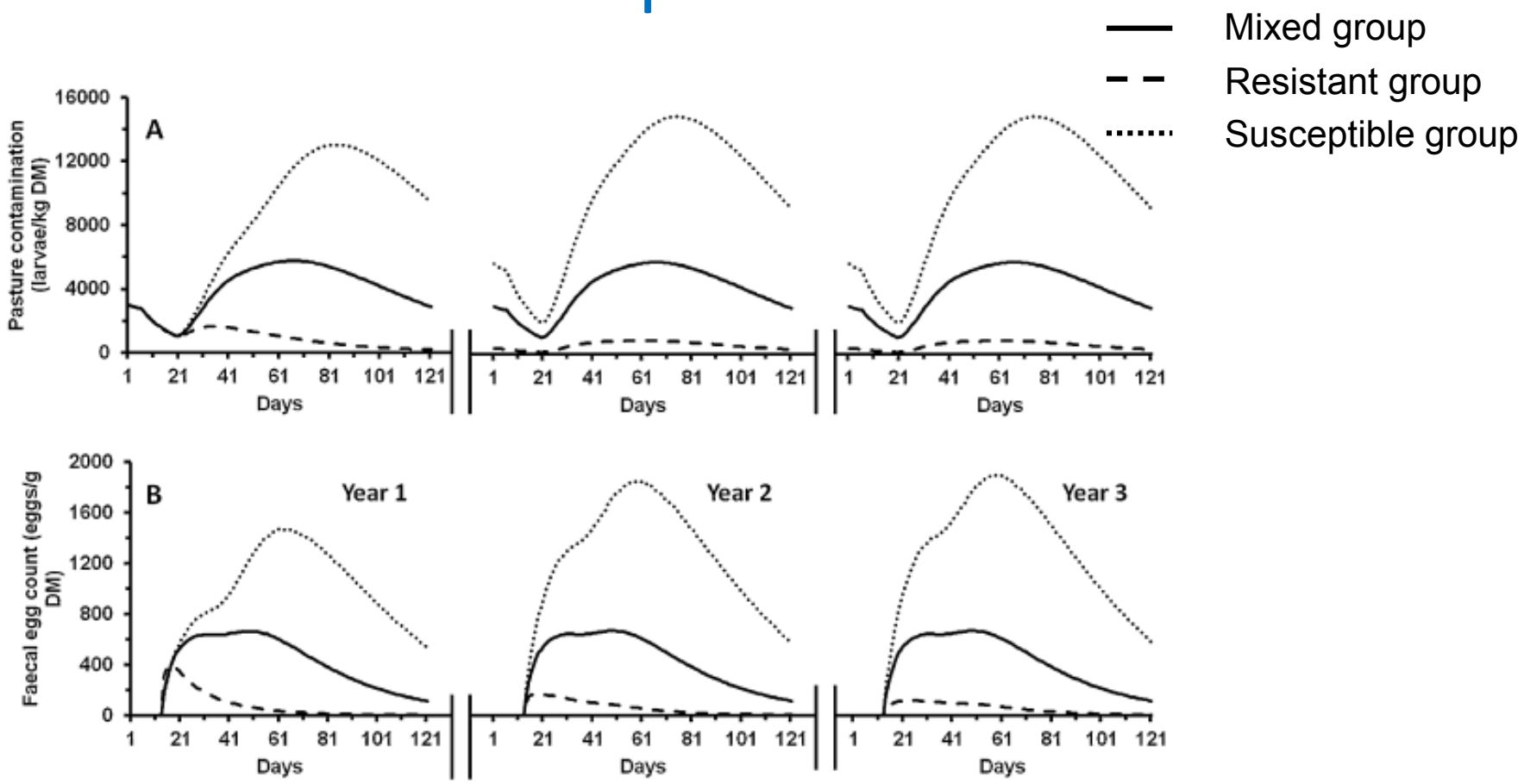
Epidemiological model of gastro-intestinal parasite infections in sheep

Epidemiological model for gastro-intestinal parasitism (GIP) in sheep

- Extension of the within-host GIP model by a 'pasture module'
  - Define pasture characteristics (size, volume of grass available, initial contamination)
  - Calculate pasture contamination over time: based on parasite eggs excreted (FEC) by infected lambs, natural parasite life-cycle on grass & removal of larvae by grazing
- Aim: to explore epidemiological consequences of resistance and grazing management

Laurenson et al., Vet Parasitol. 2012. 189:238-49

Model predictions



Model predicts that biggest benefit of anthelmintics treatment and grazing is to be expected for susceptible sheep

→ Promotes targeted selective treatment

Laurenson et al., 2012.

Model application: Predicting response to selection

- Classical quantitative genetics formula for calculating response to selection ignores epidemics
- **Positive epidemiological feedback:**

  Select for reduced faecal egg counts (FEC):

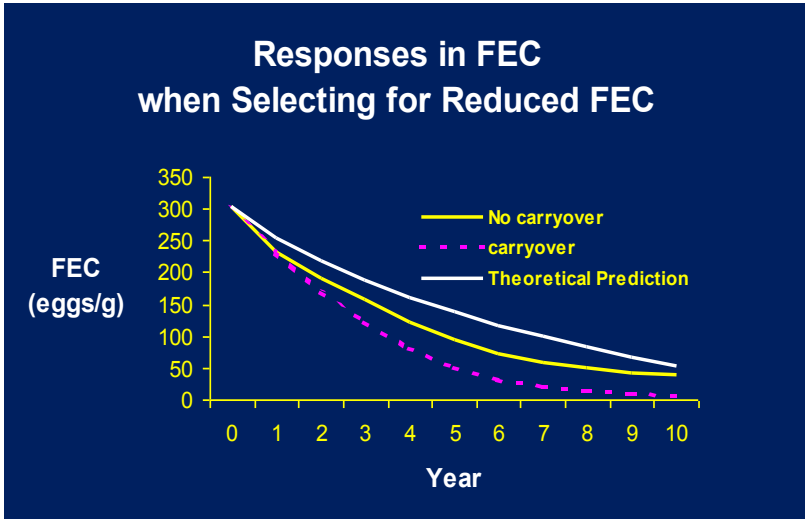
  => decrease pasture larval contamination

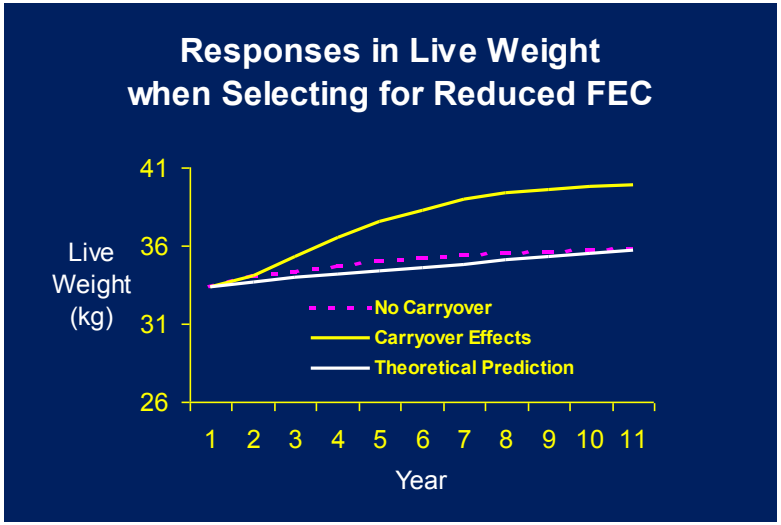
  => decrease larval challenge for others

  *=> **lower FEC in ALL sheep at same pasture***

  => greater productivity in ALL sheep
- Resistant sheep protect all sheep

Model application: Predicting Response to Selection





- Theoretical prediction: based on quantitative genetics theory (ignores epidemics)
- No carryover: include epidemic, but ignore long-term benefits
- Carryover: include epidemic & long-term benefits

Bishop & Stear 1997

Epidemiological models as decision making tools

Foot & Mouth Disease (FMD)

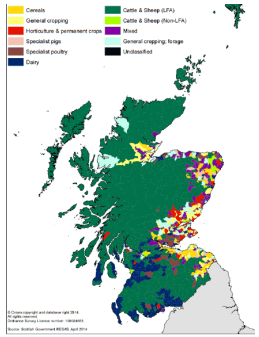
- 2001 FMD crisis in UK:
  - Led to the killing of over 10 million sheep & cattle
  - Cost US$16bn
- Problem: Rapid transmission between wide range of livestock species
- Infection is rarely fatal, but causes severe reduction in growth rate and in milk production (dairy cattle)
- Strong economic impact: export ban of milk and meat, and movement restrictions in affected farms

Epidemiological models & Policy decisions

- Several control options available:
  - Culling, vaccination (with resulting export ban), prolonged movement & export restrictions …
- Main policy aim: achieve disease-free status asap
- Trade-off: minimize time vs minimize disturbance
  - Difficult to achieve optimal balance without a quantitative predictive framework
- "Scientific policy approach": Appointment of Prof. Roy Anderson, leading epidemiological modeler

➢ 3 epidemiological models for FMD were developed to inform policy decisions

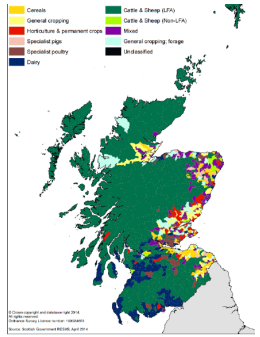
Model 1: InterSpread



- Large, complex, very flexible stochastic simulation model
  - Predicts spread of infection between farms influenced by many mechanisms
  - Most accurate representation of reality (amongst the 3 models)
- Accurate spatial representation
  - seeded with known location of all farms and their number / types of livestock
- Difficult to parameterize, very slow simulation times
  - Requires ‘expert opinion’ or guess for parameter values
  - Difficult to validate
  - Restricted exploration possible

Morris et al., 2001; Keeling 2005

Model 2: Cambridge-Edinburgh model



- Stochastic simulation model
- Takes spatial structure of farms into account
  - same initialization as InterSpread
- Less explicit representation of temporal aspects
- More simple, transparent transmission mechanisms
  - Fewer parameters, easier parameterization
  - Still slow simulation times → restricted exploration

Keeling et al., 2001; Keeling 2005

Model 3: Imperial model

- Deterministic model
  - Only possible to predict average outcomes, not outcomes with low probabilities
- Simplistic representation of the spatial structure
  - Cannot distinguish between high / low risk areas
- Easy to parameterize, fast simulation times
  - Allowed for extensive exploration of a variety of scenarios (delay in reporting, diverse vaccination / culling strategies)

Whilesmith et al. 2003; Keeling 2005

Model predictions

- Models focused on different aspects, depending on the model type:
  - InterSpread: Identify high risk areas by comparing short-term model predictions with observed nr of cases
  - Cambridge-Edinburgh: vaccination / culling strategies
  - Imperial: compare a wide range of control options
- Models overlapped in their main predictions:
  - **Successful control of FMD requires rigorous application of culling (or vaccination) on a wide scale**

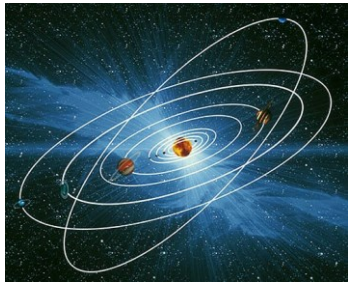
Stakeholder Reactions

- Policy makers: application of stringent culling
  - UK reverted to FMD free status within a few months
- Farmers & Veterinarians:

Resolving the conflict (Keeling 2005): The issue of scale

- Optimum approach & control strategy depends on the scale:
- Individual farm level / local scale:
  - Veterinary judgement is most accurate / suitable
  - Less stringent control measure is optimal

- National level / global scale:
  - Mathematical model best suited to weigh pros & cons
  - More stringent control measure is optimal



Lessons learnt

- Epidemiological models can help decision making when faced with complex problems
- There is not one best model: Different modelling approaches can provide different insights
- Epidemic models can cause friction between modellers / veterinarians / farmers
- All epidemic models over-simplify and lack crucial aspects:
  - Failure to represent within-farm dynamics
  - Failure to capture individual, spatial or temporal heterogeneity
  - Failure to include economic aspects …

Summary

- Mathematical models have proved useful for:
  - Providing explanations for conflicting experimental or field observations
  - Predicting outcome of infection / control strategies
- But the application of mathematical models to livestock diseases is still in its infancy
  - Lack of appropriate data for model parameterization& validation
  - Lack of base models to build upon & inference techniques

Further reading

- Doeschl-Wilson, A. B. "The role of mathematical models of host–pathogen interactions for livestock health and production–a review." *animal* 5.06 (2011): 895-910.
- Doeschl-Wilson, Andrea B., et al. "Unravelling the relationship between animal growth and immune response during micro-parasitic infections." *PLoS One* 4.10 (2009): e7508.
- Bishop, S. C., and M. J. Stear. "Modelling responses to selection for resistance to gastro-intestinal parasites in sheep." *Animal Science* 64.03 (1997): 469-478.
- Vagenas, D., S. C. Bishop, and I. Kyriazakis. "A model to account for the consequences of host nutrition on the outcome of gastrointestinal parasitism in sheep: logic and concepts." *Parasitology* 134.09 (2007): 1263-1277.
- Doeschl-Wilson, et al. "Exploring the assumptions underlying genetic variation in host nematode resistance." *Genet. Sel. Evol* 40 (2008): 241-264. Laurenson et al. “Exploration of the epidemiological consequences of resistance to gastro-intestinal parasitism and grazing management of sheep through a mathematical model."*Veterinary parasitology* 189.2 (2012): 238-249.
- Wilesmith, J. W., et al. "Spatio-temporal epidemiology of foot-and-mouth disease in two counties of Great Britain in 2001." *Preventive veterinary medicine* 61.3 (2003): 157-170.
- Keeling, Matt J. "Models of foot-and-mouth disease." *Proceedings of the Royal Society of London B: Biological Sciences* 272.1569 (2005): 1195-1202
- Keeling, Matt J., et al. "Dynamics of the 2001 UK foot and mouth epidemic: stochastic dispersal in a heterogeneous landscape." *Science* 294.5543 (2001): 813-817.