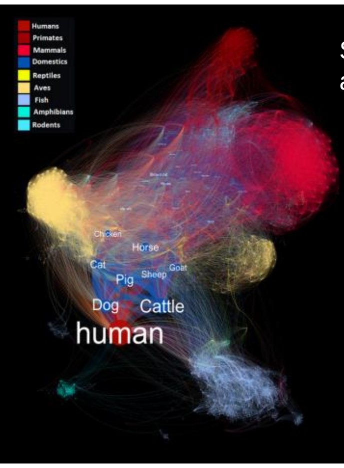
LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

Applications in veterinary epidemiology: spatial transmission and meta-population models

Introduction to Infectious Disease Modelling and its Applications
2018

Shared infections among vertebrates



Wardeh et al. *Scientific Data* 2015

Introduction: similarities & differences

- Approaches used for modelling human diseases are similar to those used for investigating spread of animal diseases.
- Some critical differences:

Epidemiology

- Frequency or density dependence in transmission
- Unit of interest (animal/groups of animals)
- Multiple species
- Susceptibility/infectivity may vary by species
- Life-expectancy may be short (high turnover of population)
- Spatial spread very important
- Experimental infection studies are possible (though rare)

Control

- Culling of animals frequently used
- Spatial policies are common (e.g. ring policies)
- Vaccination issues
  - *Mask infection & disease*
  - *Eradication and disease free status*
  - *Economics*
  - *Turnover of populations*

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Density vs frequency-dependent transmission

Frequency-dependent:
contacts made per unit time is *independent* of population size

- Commonly used assumption for human infectious diseases
- "True mass action"
- Someone living in London does not have 100 times the contacts (pop ~8m) as someone in Wigan (pop ~80,000)

$\lambda = \beta I / N$

(although sometimes $\beta = c/N$)

Density-dependent:
contacts made per unit time is *dependent* on population size

- As population increases, contacts increase
- "Pseudo mass action"
- May be more true for some animal (and plant) disease
- Increase the herd size, increase contacts, and therefore transmission

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Density vs frequency-dependent transmission

- Experimental data on pseudorabies in pigs suggests transmission frequency dependent
  - Adding more pigs does not increase transmission
- But density-dependence is sometimes argued
  - STD in 2-spot ladybirds appears to be density dependent
- Generally more important to distinguish than in human diseases, as population size may fluctuate greatly through time
  - Birthing season, slaughtering (livestock) / Birthing season, winter pressures (wildlife)
  - Populations may be growing/shrinking rapidly from year to year (particularly wildlife)
  - Disease (and/or the intervention) can have a large impact on mortality rates, and therefore the population size

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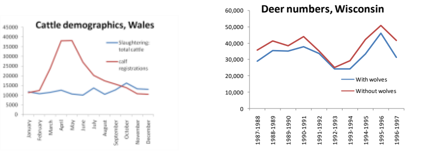
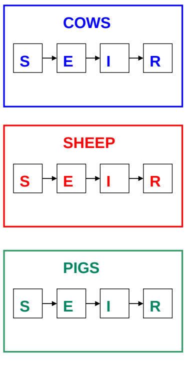


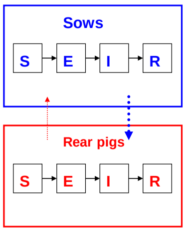
Unit of interest: within-farm models

- In the same way as we do for human infections, we can divide, say a farm population, into SEIR classes
- This may be for a single-species (e.g. chickens for avian influenza) or we may want to stratify the model by species (e.g. cattle, pigs, sheep etc. for FMD)
- Such a model represents the dynamics of infection within a farm – hence termed a "within-farm" model



Within-farm models

- Mixing often not homogenous on a farm
  - On mixed farms different species often separated
  - Animals may be segregated by age
    - E.g. sows and rearing-pigs
- Can reflect heterogeneous mixing
  - Contact between groups not necessarily symmetrical
- Chance effects (stochasticity) may be very important
  - Relatively small # animals on a farm



$$\begin{array}{c|cc} & \text{Sows} & \text{R pigs} \\ \hline \text{Sows} & \beta_1 & \beta_2 \\ \text{R pigs} & 0 & \beta_1 \end{array}$$

Unit of interest: between-farm models

- Often more interested in spread between farms
- Control efforts often targeted at the farm
  - Want to control spread between farms
  - Once one animal infected all animals are slaughtered
- For diseases that spread rapidly within farms (such as FMD, or AI), may be plausible to ignore within-farm dynamics & treat farms as unit of interest.
- So farms are either susceptible, infectious (E), infected (I) or recovered (R).
  - The recovered state typically tracks premises in which all animals have been slaughtered
- If a premise is re-stocked, then we may additionally want to consider recovered premises moving back to susceptible
  - SIRS structure (often with very short period of immunity)

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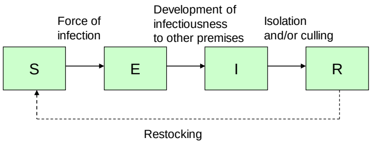
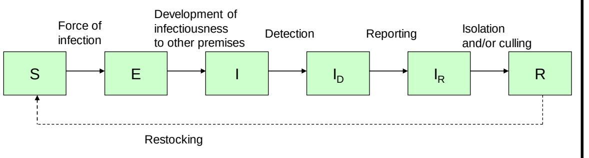
Between-farm model structures



Between-farm model structures



- Frequently would incorporate detection and reported status of the farm into the model

Parameters

- As for human infections, there are 3 basic parameters:
  - force of infection acting on susceptibles
  - duration of the latent period
  - duration of the infectious period
- However, parameters now relate to premises (farms) rather than individual animals
- This complicates duration of latent and infectious period as can depend on:
  - the within-farm dynamics
  - the number of animals and different species at the premise
  - detection times
- Note: infectious period on an uncontrolled farm will be longer than individual animals' infectious period

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Susceptibility and infectivity

- Additional parameters often included to allow for variation in susceptibility to infection, and onward infectivity of infection
- E.g. could depend on number of animals at a premise
- Let *i* denote the size of the infected farm and *j* the size of the susceptible farm, then the force of infection from *i* to *j* would be given by

infectivity

$$foi(i,j) = \beta_i \alpha_j$$

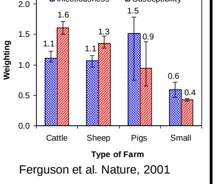
susceptibility

- Then summing over all different sizes of farms *i*, the equations for loss of susceptible farms of size *j* would be

$$\frac{dS_j}{dt} = -\alpha_j S_j \sum_i \beta_i \frac{I_i}{N_i}$$

Susceptibility & infectivity: e.g. FMD

- Ferguson model:
  - Infectiousness and susceptibility of a farm allowed vary by the size of the farm and the species kept at the farm
  - Cattle farms were most susceptible
  - Pig farms were more infectious than other species
  - Small farms (<100 animals) were least susceptible & infectious



Ferguson et al. Nature, 2001

- Keeling model
  - Susceptibility and infectiousness function of number of animals of different species (L) on each farm
  - Species-specific parameters estimated by fitting model to data

Inf rate for farm j

$= \text{Suscept}^j * \Sigma_i \text{ Infectivity}^i * K(d_{ij})$

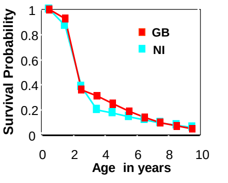
$= \Sigma_L S_L N_L^j * \Sigma_i \Sigma_L T_L N_L^i * K(d_{ij})$

Survival of animals

- Survival can be important in interpreting disease statistics
- The lifespan of animals reared for food (e.g. cows, lambs, chickens, pigs) is generally much shorter than their natural lifespan
- This can impact on the epidemiology in two ways:
  - Short survival results in fast turnover of animals. In absence of restrictions, can result in replenishment of the susceptible pool, further fuelling an epidemic
  - Survival may be shorter than incubation period, so disease could go undetected in many animals
- Short survival also affects potential controls – animals which only live for a short time more easily replaced, hence it may be easier to implement controls that include slaughtering

Cattle Survival and its impact on BSE

- Most cattle slaughtered for consumption between 2–2.5 years of age
- Mean incubation period for BSE in cattle is 5 years
- Mean age at infection was approximately 6 months



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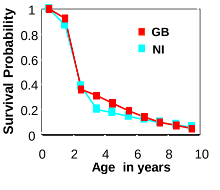
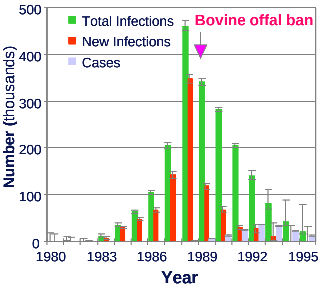


Most infected cattle slaughtered before onset with clinical signs

The impact of survival on estimates of numbers of infected animals



1996 estimates:

763,000 infected before Jan '89
140,000 infected after Jan '89
903,000 infected total

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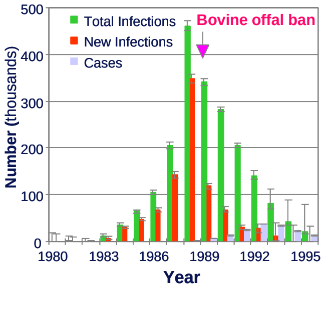

1996 estimates:

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140,000 infected after Jan '89
903,000 infected total

Updated estimates (based on case data to October 2002, screening data and including differential survivorship):

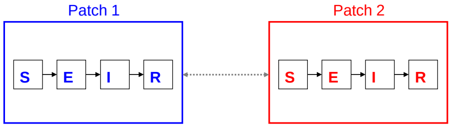
~ 4 million infected & ~3.3 million entered the human food supply

Spatial Spread

- Farms or premises generally clustered in local areas (e.g. very few in London!)
- Spread of infections often occurs through contact processes (e.g. people and vehicles going from one premise to another) and may also be airborne (e.g. FMD).
- Contacts more likely to occur in close geographical proximity
- Control measures are often spatial
  - E.g. culling of CP, ring vaccination
- Thus models are typically spatially explicit

Meta-population (patch) models

- One of the simplest ways to model spatial spread is using a “meta-population” model
- Split the population into areas (e.g. squares) based on geography
- Assume mixing within area is homogenous
- A lower rate of contact between areas



Analogy with mixing patterns

- The model then behaves much like the mixing models you have seen earlier
- Interaction between the two neighbourhoods can be specified by a simple mixing matrix,
  - *m* is the relative strength of mixing between farms in two different areas compared to two within an area

$$\begin{array}{ccc} & N & S \\ N & 1 & m \\ S & m & 1 \end{array}$$

- So the number of new infections e.g. in population N is:

$$\underbrace{\text{beta} * S_N * I_N/N_N}_{\text{Infection rate from infected farms in N to other in N}} + \underbrace{\text{beta} * S_N * m * I_S/N_S}_{\text{Infection rate from infected farms in S to those in N}}$$

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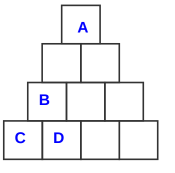
Contiguous neighbourhoods

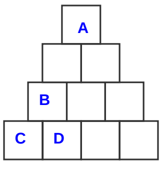
- This concept can be easily extended to incorporate many more neighbourhoods
- To model spatial transmission, infection between neighbourhoods only occurs if they are “contiguous” ie. next to each other in space
  - Or transmission much more likely if neighbourhoods are contiguous



Example: B, C, and D are contiguous neighbourhoods but A is not contiguous to either B, C or D

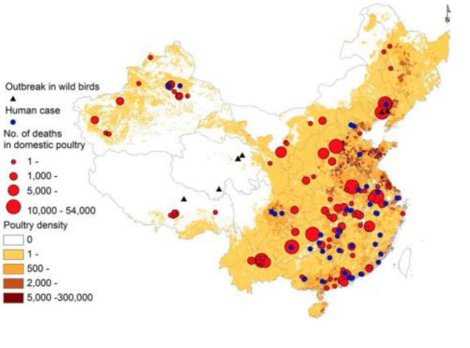
Contiguous neighbourhoods

- Can define a **contact matrix** between patches
- E.g.
  - Assume no farms in the empty patches
  - Contact within patches = β_1
  - Contact between contiguous patches = β_2
  - No contact between non-contiguous patches



$$\begin{array}{cc} & \begin{array}{cccc} A & B & C & D \end{array} \\ \begin{array}{c} A \\ B \\ C \\ D \end{array} & \begin{pmatrix} \beta_1 & 0 & 0 & 0 \\ 0 & \beta_1 & \beta_2 & \beta_2 \\ 0 & \beta_2 & \beta_1 & \beta_2 \\ 0 & \beta_2 & \beta_2 & \beta_1 \end{pmatrix} \end{array}$$

H5N1 in China



Li et al. *Int. J. Environ. Res. Public Health* 2015

Spatial kernel

- May want a more general function that allows the probability of transmission to decay naturally as the distance between 2 premises increases
- This is termed a “spatial kernel”

- Suppose *d* is the distance between two neighbourhoods and *f(d)* is the spatial kernel
- The new infections in neighbourhood B from A which is distance x away is:

  $f(x)*beta*S_B*I_A/N_A$

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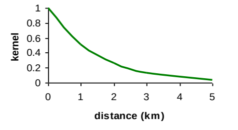
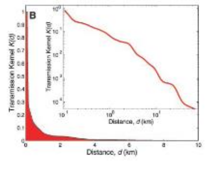
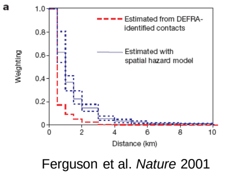


Estimating spatial kernel: FMD 2001

- Two potential ways of incorporating a spatial kernel:
  - Use contact tracing data directly
    - E.g. Keeling et al. 2001
  - Estimate the spatial kernel in the model
    - specify functional form (e.g. exponential decay)
    - Fit model to data, to get best-fit parameter estimates
    - E.g. Ferguson et al. 2001

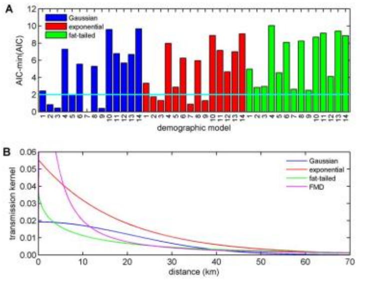


Keeling et al. *Science* 2001



Ferguson et al. *Nature* 2001

Estimating spatial kernel: Bluetongue virus



Szmaragd et al. PLoS One 2009

Interventions

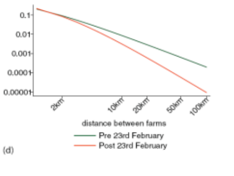
- Wider range of interventions is possible:
  - Culling of infected premises
  - Culling of animals near to infected premises
  - Movement restrictions
  - Reducing time to detection
  - Vaccination

Success will also depend on:

- compliance (may be economically driven)
- logistical constraints (e.g. vaccine stocks, numbers of veterinary officers, disposal of slaughtered animals)

Movement restrictions

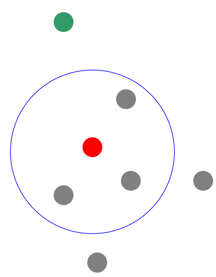
- Movement restrictions reduce the contact pattern
- In a simple model this could simply be through
  - A reduction in the transmission parameter β
  - A change in the mixing matrix
- Restrictions may be placed for a short-period nationally but more likely to be localised
- For a spatial model, efficacy of local restrictions placed around an infected premise will depend on the spatial kernel



Ster and Ferguson *PLoS One* 2008

Slaughtering

- Slaughter of animals is commonly used to “damp out” an outbreak
- Three possibilities
  - Slaughter of animals at infected premises
    - almost always undertaken
  - “Ring-culling” – slaughter of animals on neighbouring premises or within a certain distance
    - used “successfully” in the FMD outbreak in 2001
    - Diameter of ring must be greater than spatial diffusion of infection
  - Slaughter of premises outside of spatial ring who have had recent contact with premise “dangerous contacts”
    - will help to damp down outbreaks with less spatial transmission



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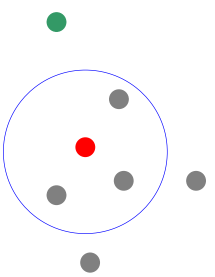

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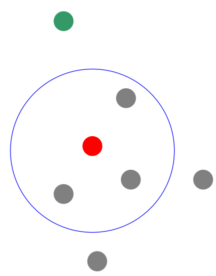

Time to slaughter

- Time to slaughter is an important factor determining the success of slaughter-based controls
- For infected premises, recall for an SEIR model

  $R_0 =$ beta * average duration of infectious period

  $=$ beta * average time taken to cull

  So reducing the time taken to cull directly reduces the reproductive number
- Similar arguments apply to ring-culling and culling of dangerous contacts

Vaccination Strategies

- Vaccination can be used in two ways:
  - Prior to outbreak: to reduce impact of outbreak or protect valuable animals
  - Reactive: To control an outbreak
- Reactive vaccination may be spatial:
  - Ring vaccination – vaccinate in a spatial ring around infectious premises
- Relative effectiveness will depend on the characteristics of the vaccine:
  - Reduction in susceptibility
  - Reduction in infectiousness
  - Change in latent and/or infectious period
  - Degree of protection
  - Type of vaccine (all/nothing or partial protection)
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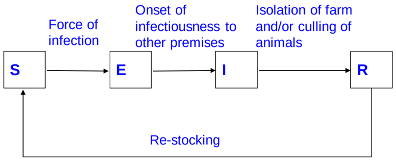
Incorporation of vaccination in models



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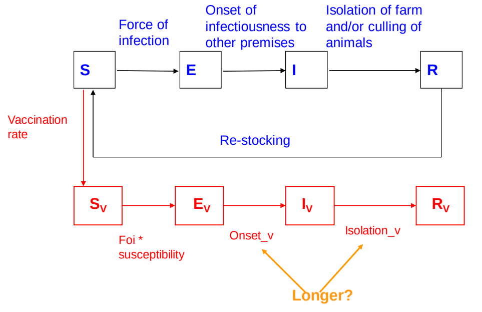

FOI = $\beta*I+\beta*\alpha*I_v$ where α is reduction in infectiousness from vaccination

Summary

- Models for veterinary diseases can be at both within-farm and between-farm level:
  - Within-farm are similar to models for human diseases
  - Greater heterogeneity if multiple species, housing etc.
  - Between-farm models more applicable to understand control as this is the unit at which control measures are aimed
  - Parameterisation of between-farm models is more difficult and dependent on external factors (e.g. time to slaughter)
- Four additional factors are important:
  - Fluctuating population size (and therefore assumptions about transmission)
  - Survival of animals
  - Slaughtering as a potential control option
  - Spatial transmission
- Spatial models:
  - Meta-population structure
  - Spatial kernel needs to be specified
  - Allows consideration of spatial controls
- Control policies are different to human diseases:
  - Culling of infected premises and ring culling

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  - Fluctuating population size (and therefore assumptions about transmission)
  - Survival of animals
  - Slaughtering as a potential control option
  - Spatial transmission
- Spatial models:
  - Meta-population structure
  - Spatial kernel needs to be specified
  - Allows consideration of spatial controls
- Control policies are different to human diseases:
  - Culling of infected premises and ring culling