



FMD 2001: Using Statistics and Mathematics for Outbreak Control and Eradication

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Introduction



The disease

Start of the epidemic and initial spread

Key distributions and spatial spread

Transmission model

Early predictions of the impact of control measures.

Analysing heterogeneities in transmission risk

Implementation and efficiency of culling.

‘What if’ scenario analysis

Conclusions

Foot and mouth disease



Highly infectious *aphthovirus*, infecting cloven-hoofed mammals.

Causes characteristic lesions around mouth and feet.

High mortality in young, but most adult animals recover.

Sheep



Lesions

Pig



FMD case handling



Statutory process applies:

1. **Farm infected.**

Animals show few signs for several days, while infection spreads between livestock. Rate of spread depends on species, stocking density etc.

2. **Infection reported.**

Farmer/vet/patrol reports suspicious clinical signs. Delay to detection depends on husbandry practices, species etc. Form A notice imposed once infection reported. Form C follows after visit of vet. Farms in area placed under movement restriction.

3. **Infection confirmed.**

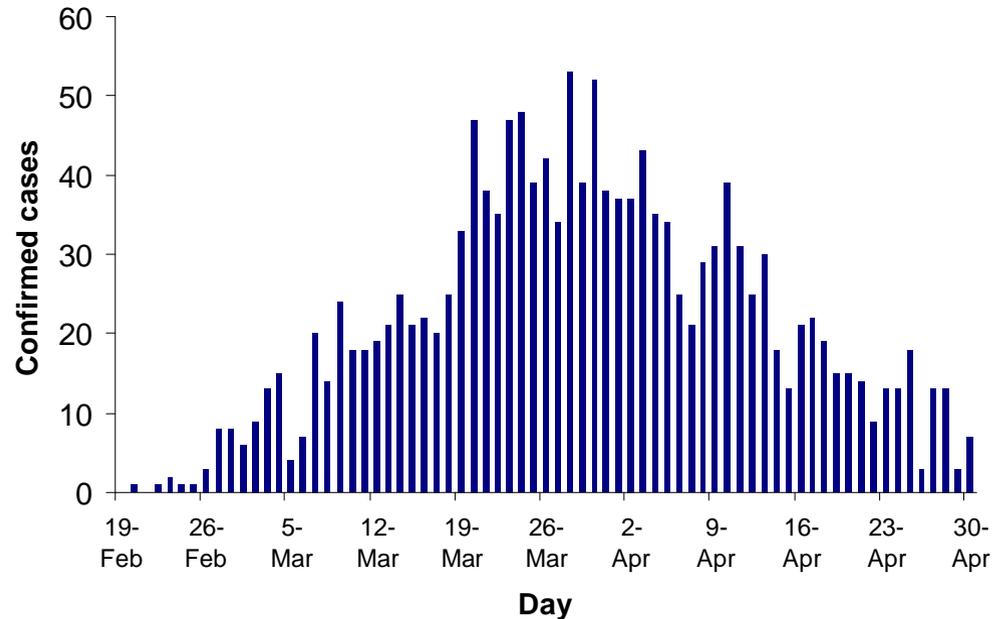
At start of epidemic, confirmation often only followed lab tests, but more often confirmed on basis of clinical signs. On confirmation, Form D imposed, and 10km infected area round farm declared.

4. **Livestock slaughtered.**

Slaughter and disposal on farm to avoid infection risk. Disinfection process follows.



Early temporal pattern



Rapid spread in following 2 weeks via animals movements and markets before infection detected.

Movement ban on all livestock imposed on 23rd February.

Intensity and range of spread reduced following movement ban.

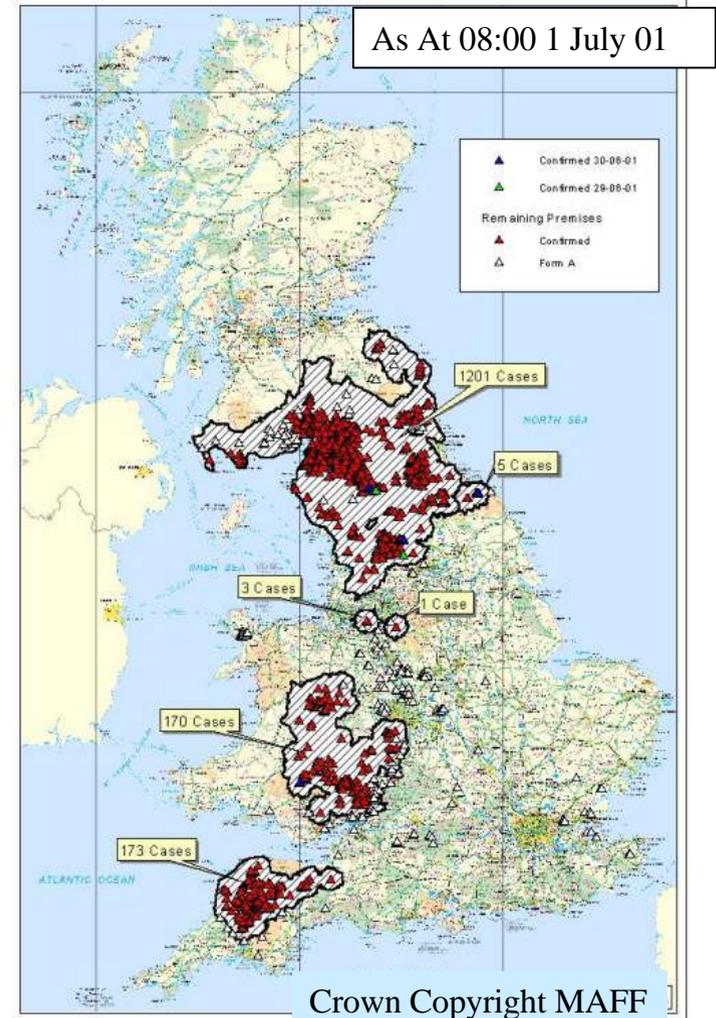
FMD infection on ~1500 farms reported by 1/5/01, ~2050 by 1/10/01

Spatial distribution



First identified infection in Northumberland pig farm in early February.

Rapid spread in following 2 weeks via animals movements and markets before infection detected.



Choice of models



Key aim was to inform policymakers of potential future scale of epidemic, and of the potential impact and efficiency of control options.

Analysis had to be performed as rapidly and reliably as possible, on the basis of incomplete data.

Two modelling options:

1. Deterministic model – non-explicitly spatial, but capable of modelling neighbourhood based control – to give insight into national or regional temporal dynamics of epidemic and predict impact of control policies.
2. Explicitly spatial micro-simulation – gives more realistic description of true pattern of spatial spread and extinction dynamics, but much more complex to construct and fit to data.

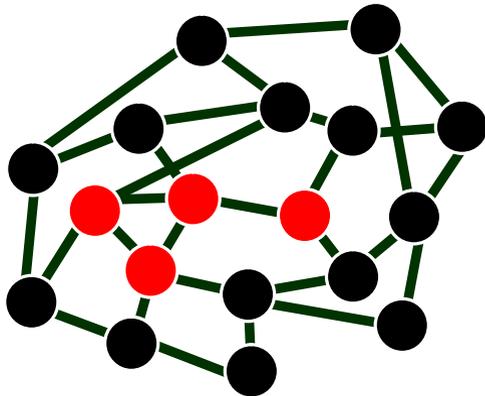
Given timescale (~1 week), we chose 1.

Some criticism re lack of inclusion of species/farm size in model – but made judgement that global dynamics and impact of non-farm-type specific control policies could be estimated with simpler framework - a lesson learnt from past history of modelling (measles, HIV...).

Modelling disease transmission (1)



Used quasi-spatial approach – modelled transmission between farms as occurring on a *contact network*:



The network reflects geographic proximity plus contact patterns.

Model can be mapped onto geographic space using contact kernel and farm location data.

Transmission can only occur along links.

Neighbourhood size in this model is just the number of farms connected to any index farm – so effective neighbourhood sizes and neighbourhood based culling can be incorporated in the model quite easily.

Modelling disease transmission (2)



Dynamical equations derived describing temporal evolution of the numbers of connected pairs of different types (e.g. S-I) = *pair-correlation model*.

[Altmann 95, Keeling 99, Ferguson 2000]

More accurate representation of localized disease transmission than mass-action model.

Less accurate than spatial micro-simulation – but much less computationally intensive.

Deterministic model used for computational simplicity to allow parameter estimation, so model less appropriate for examining disease extinction.

Multiple sequential infection states (each with exponentially distributed transit time) used to accurately capture key delay distributions.

Modelling disease transmission (3)



Equations somewhat tedious, even for simplified form of model:

$$d[S]/dt = -(\tau + \mu + \omega)[SI] - p\beta[S][I]/N$$

$$d[E]/dt = p\beta[S][I]/N + \tau[SI] - \nu[E] - \mu[EI]$$

$$d[I]/dt = \nu[E] - s[I] - \mu[II]$$

$$d[SS]/dt = -2(\tau + \mu + \omega)[SSI] - 2p\beta[SS][I]/N$$

$$d[SE]/dt = \tau([SSI] - [ISE]) - \mu([SEI] + [ISE]) - \omega[ISE] + p\beta([SS] - [SE])[I]/N$$

$$d[SI]/dt = \nu[SE] - (\tau + \mu + \omega)([ISI] + [SI]) - p\beta[SI][I]/N$$

$$d[EE]/dt = \tau[ISE] - 2\mu[EEI] - 2\nu[EE] + 2p\beta[SE][I]/N$$

$$d[EI]/dt = \nu[EE] - \mu([EI] + [IEI]) - (\nu + \sigma)[EI] + p\beta[SI][I]/N$$

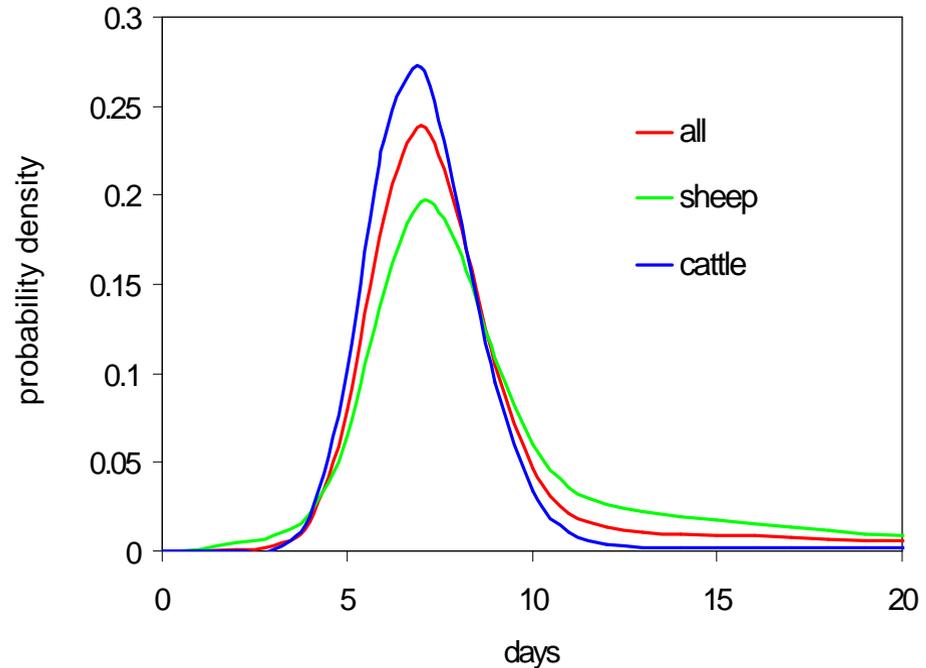
$$d[II]/dt = 2\nu[EI] - 2\sigma[II] - 2\mu([II] + [III]).$$



Infection-report distribution

The delays between infection, report, confirmation and slaughter are key, since animals are infectious from 2-3 days after infection to 10+ days after.

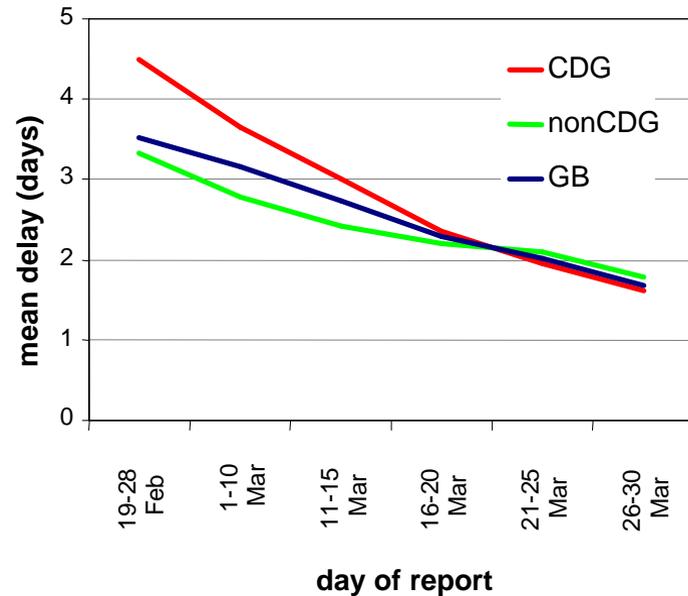
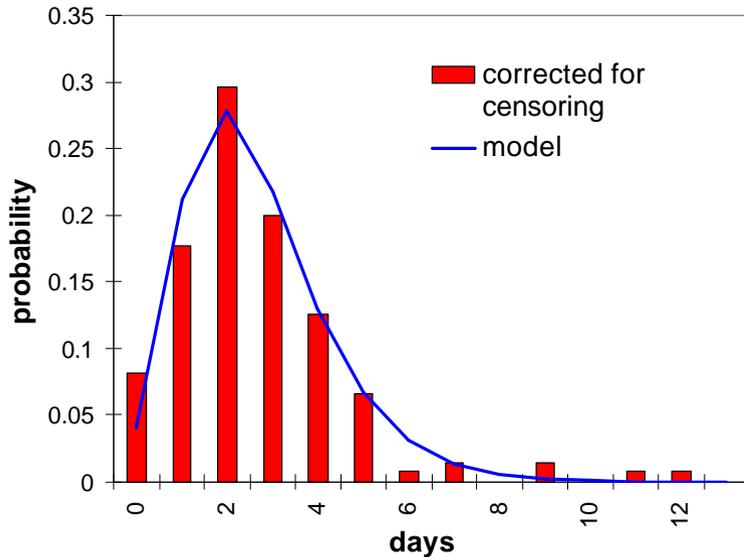
Infection-report distribution for 24 Feb to 5 Mar (by initially infected species) demonstrates the increased delay in sheep – due at least in part to the difficulty in detecting clinical signs, and perhaps less surveillance as well.



Report-slaughter delay distribution



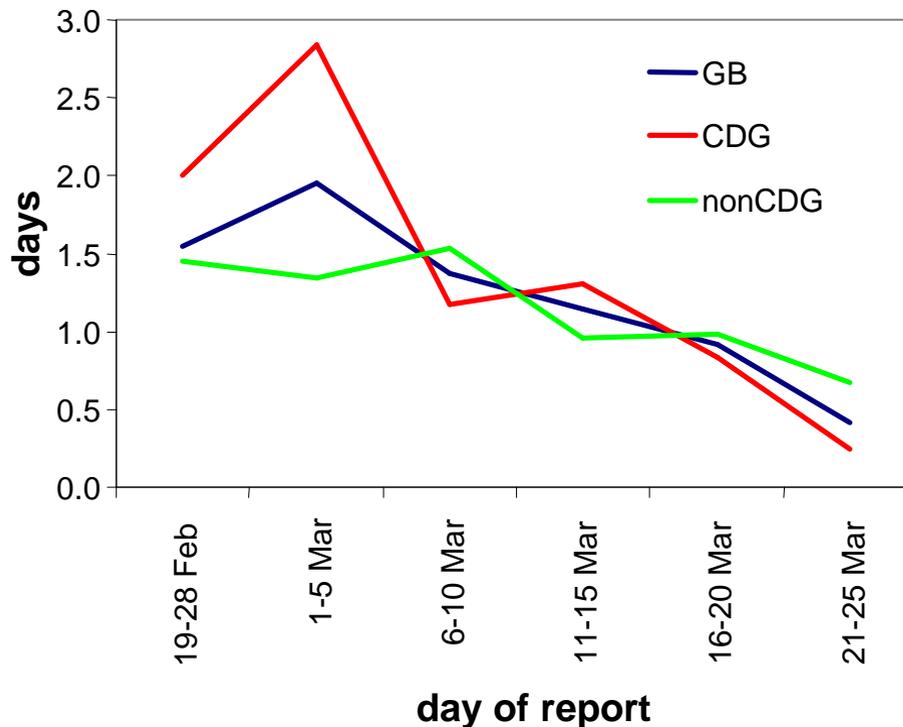
The potentially avoidable risks of transmission after infection has been reported but before the farm has been slaughtered are cause for concern, but these delays are decreasing.





Report-confirmation distribution

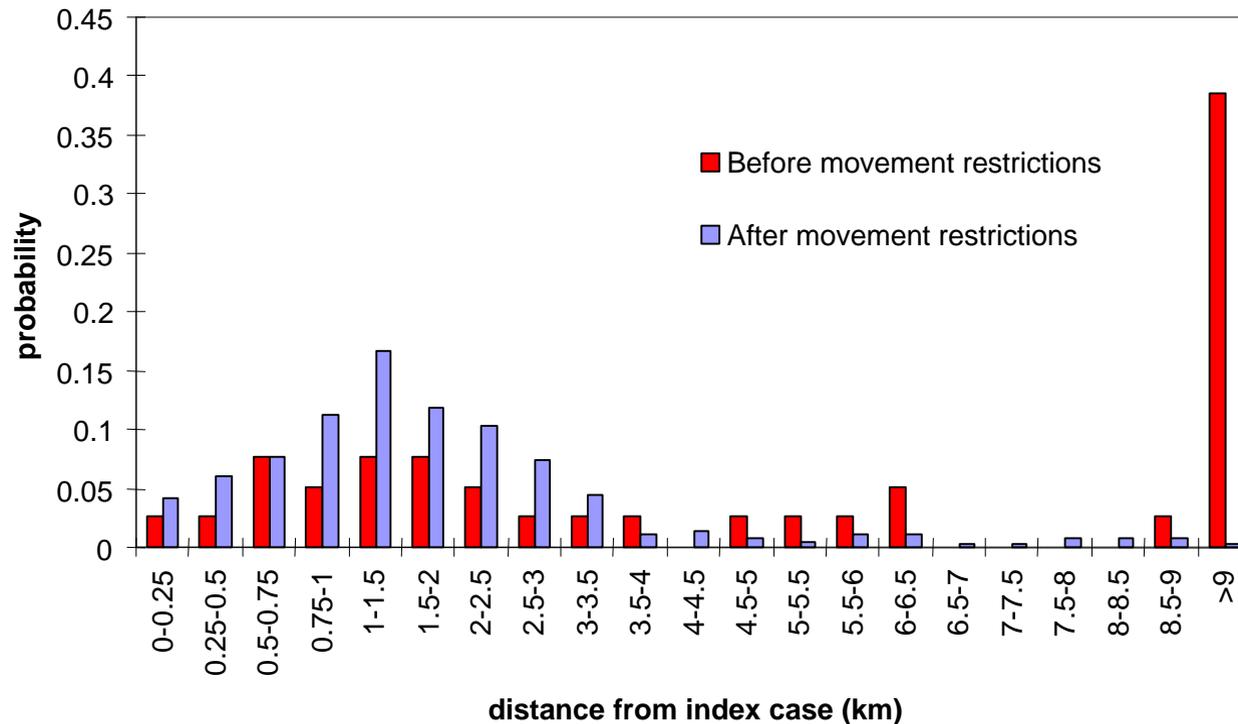
The delay between report of infection and confirmation of disease was initially important because inclusion in the database was condition on confirmed disease. After adoption of slaughter on suspicion, delay became negligible.



Distance between infectious contacts



Movement restrictions dramatically reduced long-range infectious contacts.
Data collected by MAFF via dangerous contact/movement tracing.

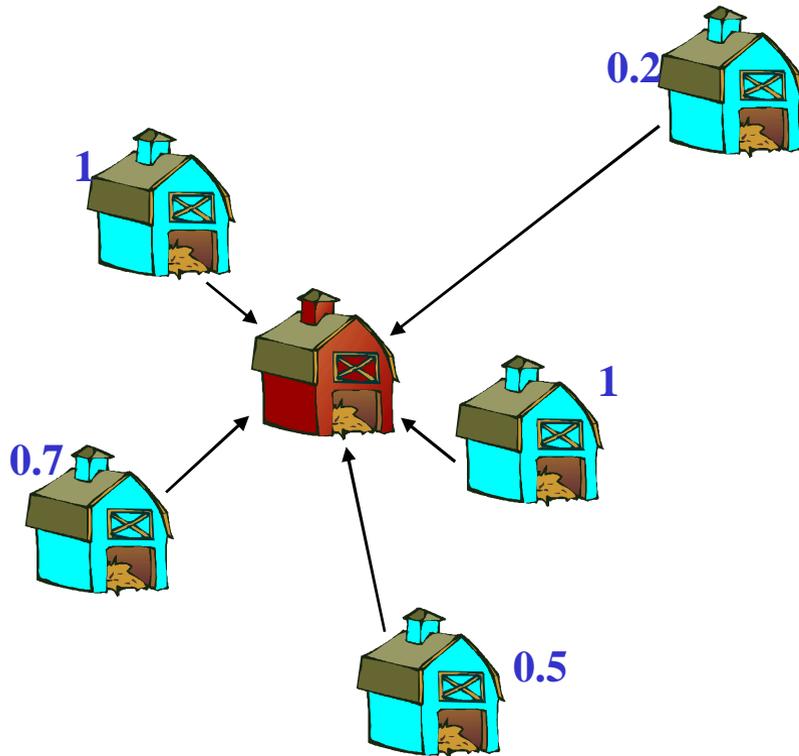


Effective Neighbourhood Size



If transmission risk were only posed by nearest neighbours, it would simply be a matter of counting.

However, since risks are posed by farms at various distances, they are weighted as a function of distance, according to the contact kernel:



Effective neighbourhood size, in units of nearest neighbour farms, was estimated as

$$n = \frac{\int_0^{\infty} g(r) dr}{\int_0^R g(r) dr}$$

where R is given by the solution of

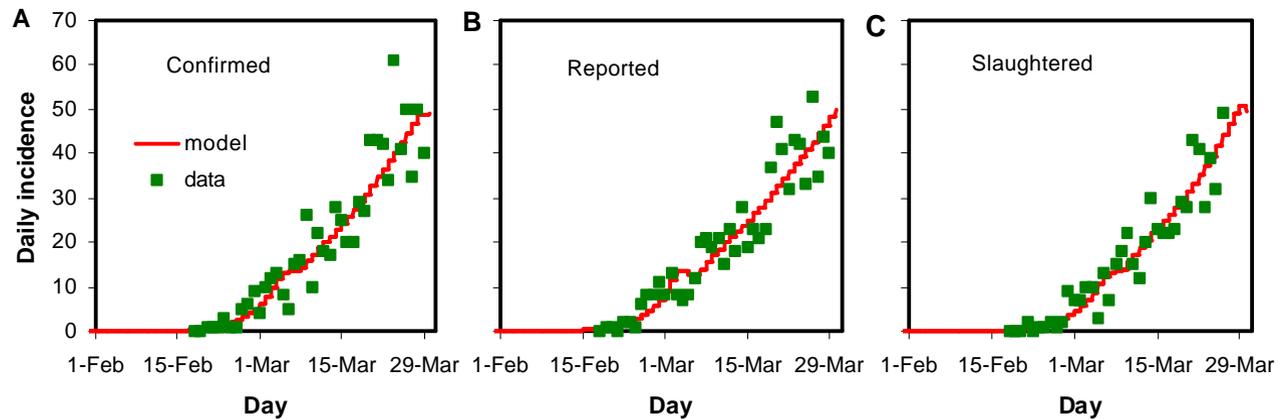
$$\int_0^R k(r) dr = 1$$

where $g(r)$ is the spatial kernel and $k(r)$ is the radial density of farms

Fit of model to growth phase of epidemic



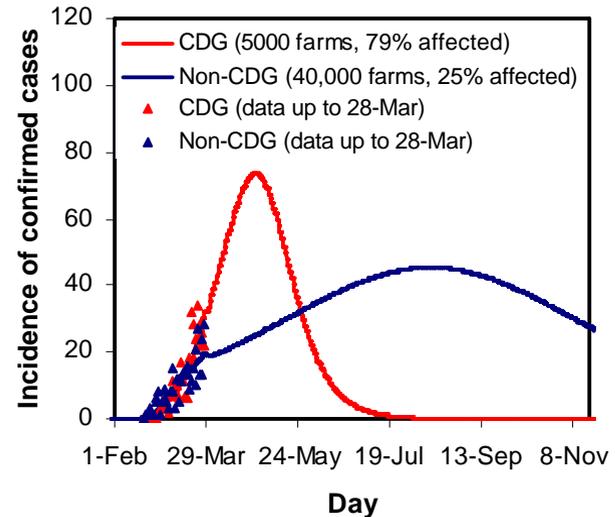
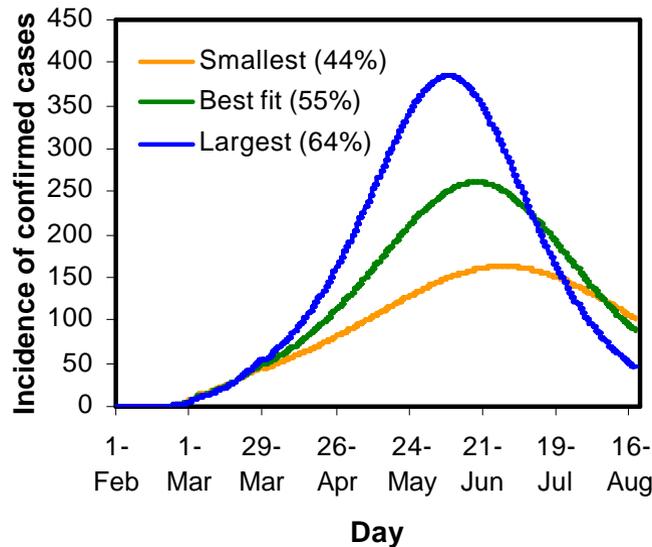
Good fit to data, given over-dispersion.



Model fitted to all three time-series simultaneously using ML methods and non-linear optimisation.

Note: very little non-infected premise (IP) culling had taken place by 29-Mar.

Early predictions if nothing had changed from 27-March



Not allowing for regional variation gives larger epidemic than when heterogeneity allowed for by fitting to different regions.

Predictions assume farm has constant infectiousness from 3.5 days after infection.

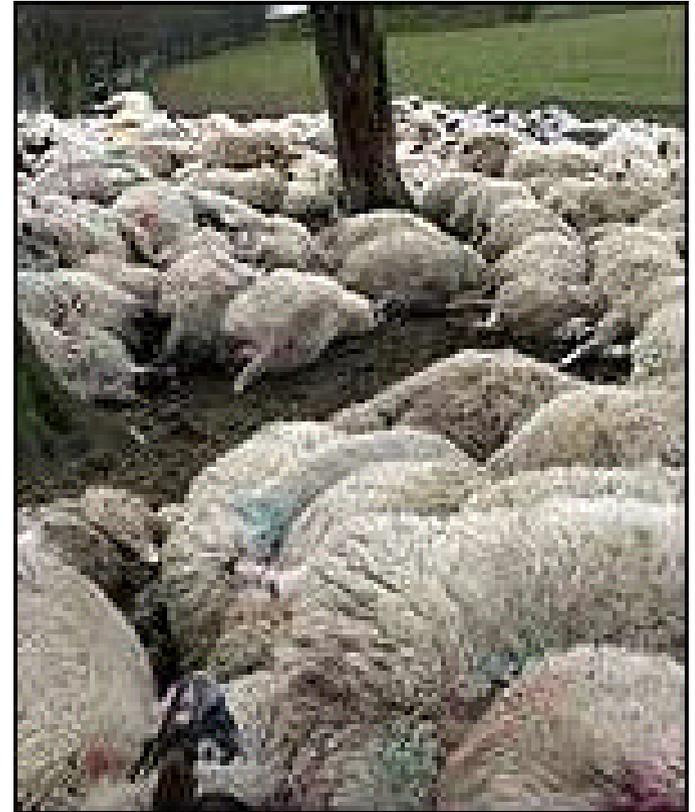
Control measures: culling



Explored effect of two types of culling:

- Faster slaughter of farms on which infection reported
- Ring-culling = slaughter of farms within certain distance of infected farm.

(Contiguous farm culling a form of ring culling where only farms neighbouring an infected premise are culled.)

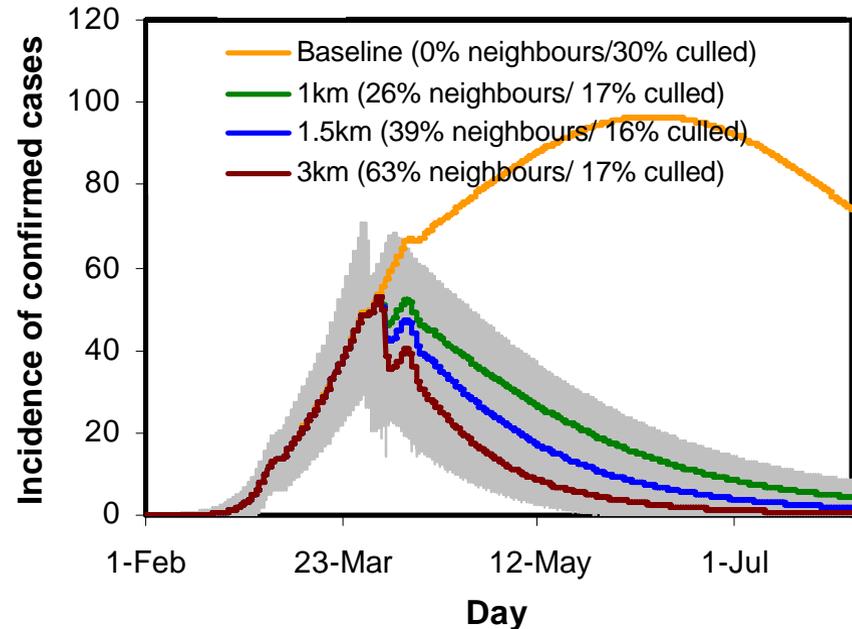


Effects of culling



1st key early prediction: IP culling not enough.

Reducing slaughter times reduces scale of epidemic, but fails to bring $R_0 < 1$. ($R_0 = 1.1$).

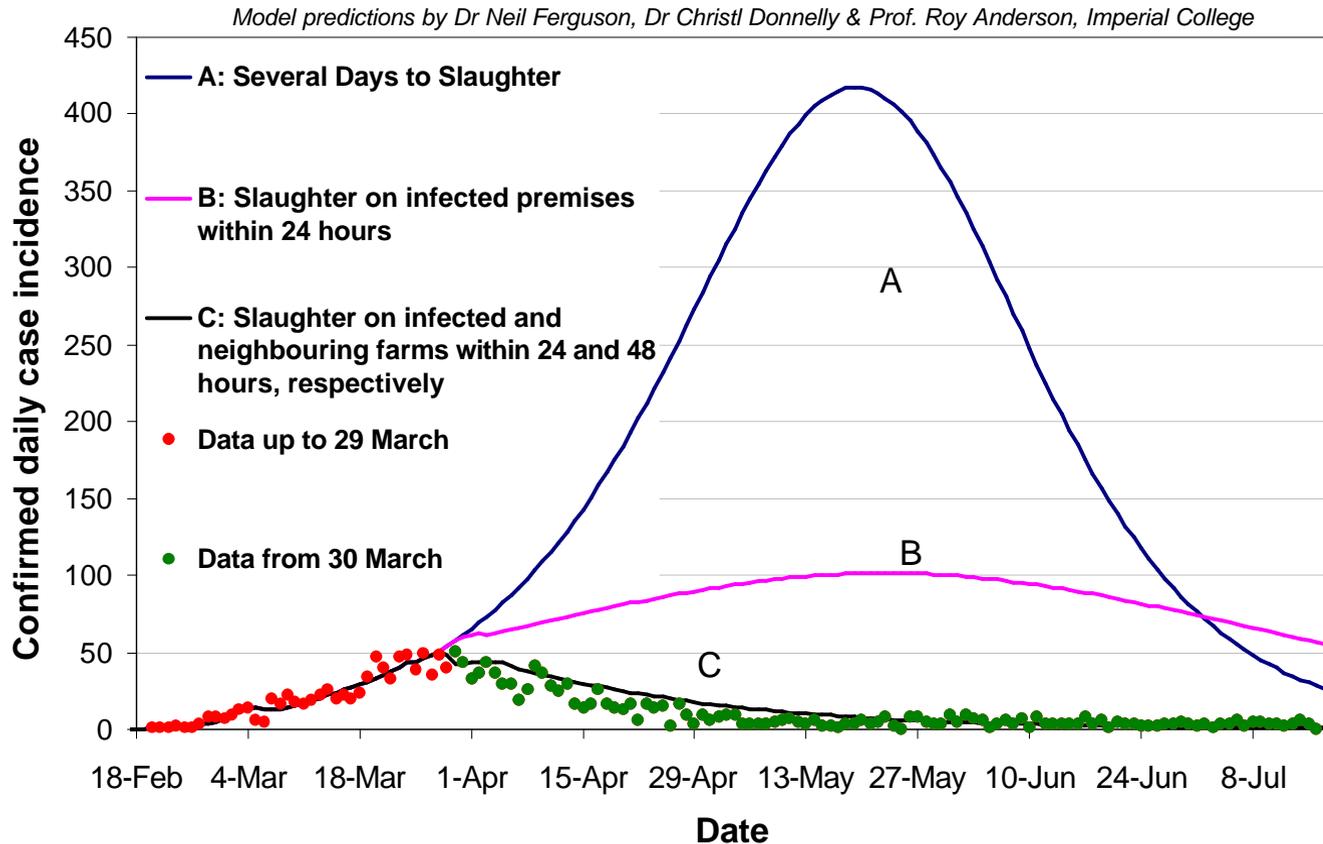


2nd key early prediction: ring-culling able to rapidly control the epidemic.

- by reducing the effective reproduction number, R – via elimination of most at-risk possible infected and susceptible contacts.

Culling of ‘healthy animals’ not without purpose – generates ‘firewall’ between infection focus and uninfected farms further out.

Predictions as released by OST



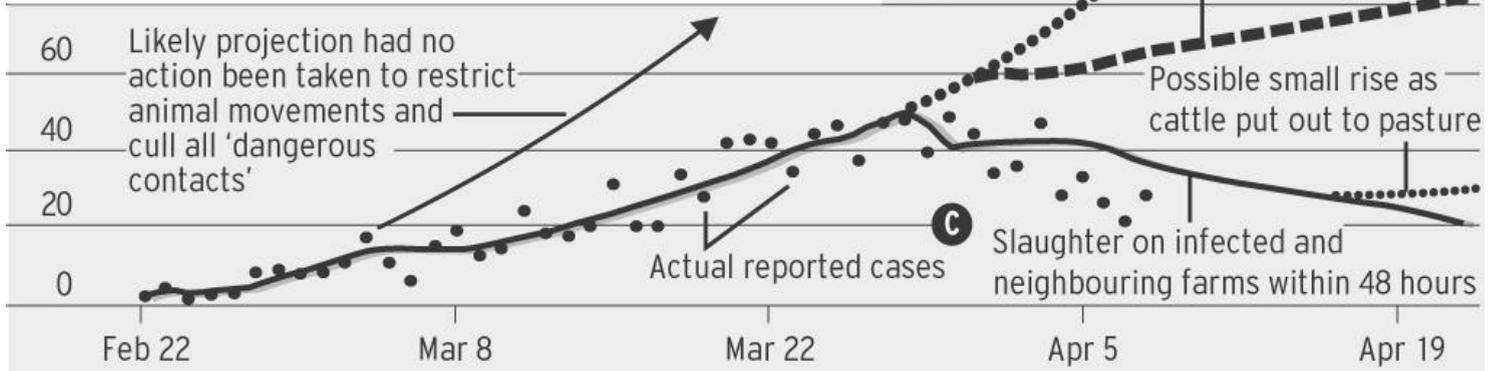
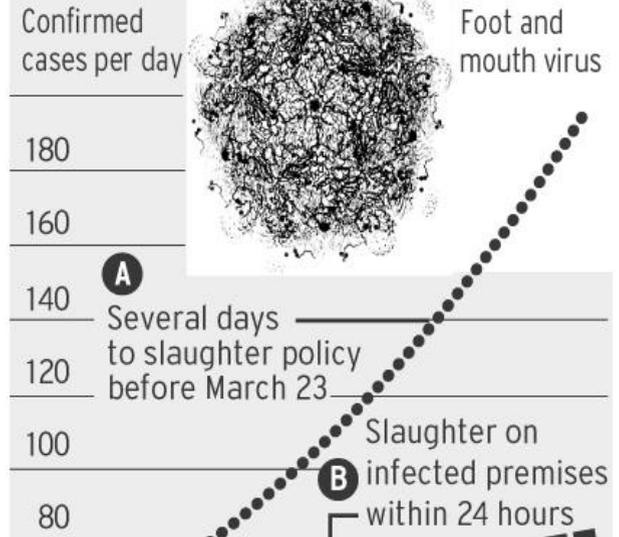
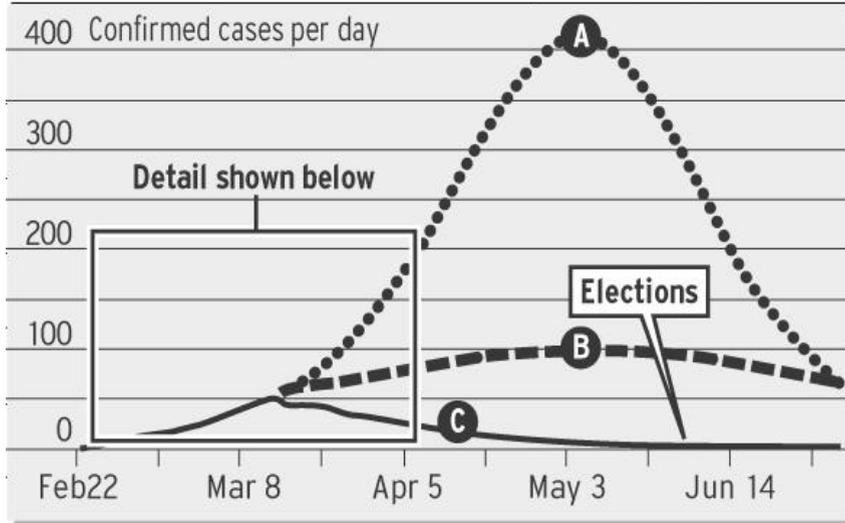
Predictions as made using data up to 29-March.

But to what extent was policy C really implemented? - difficult to answer at the time, due to long delays in collation of culling statistics.

Telegraph – April 2001



Foot and mouth: scientific predictions



Later analyses (up to July 16th)



Wanted to understand the very rapid decline in April, and the later extended tail to the epidemic.

Were there changes in culling policy timing, rigour or efficiency that contributed to tail?

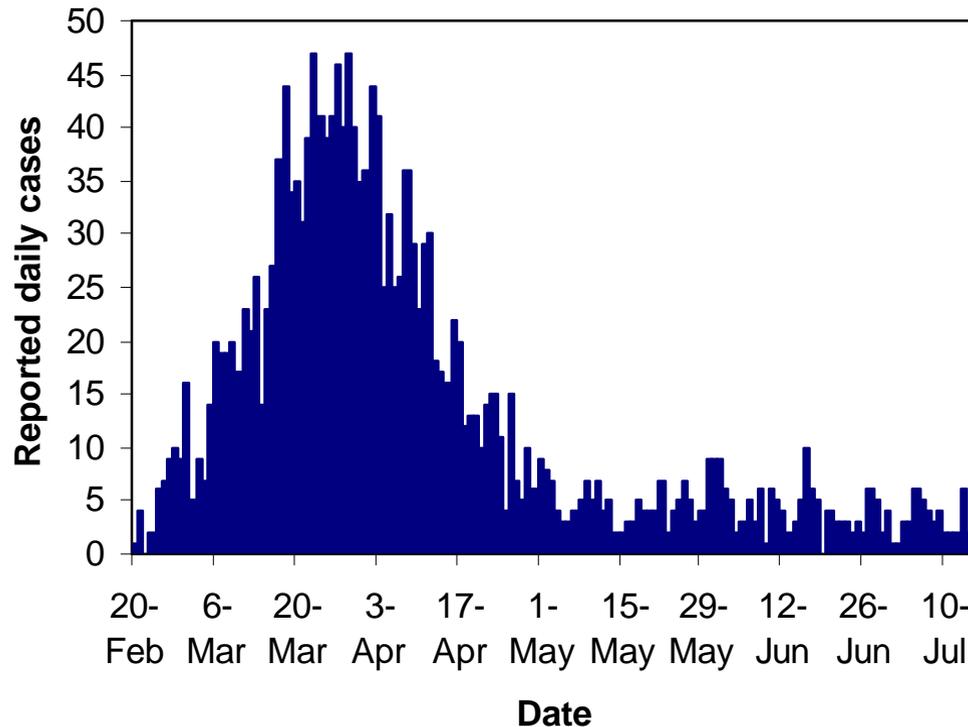
Were there other temporal changes in transmission potential attributable to other policies (biosecurity/movement controls)?

What were the impact of farm level heterogeneities (species mix, farm size etc.) on transmission risk?

Could we better characterise spatial spread and geographic variation in intrinsic transmission risk?

Analyses largely complementary to microsimulation studies.

Later pattern of epidemic



FMD infection on ~1500 farms reported by 1/5/01, ~2050 by 1/10/01

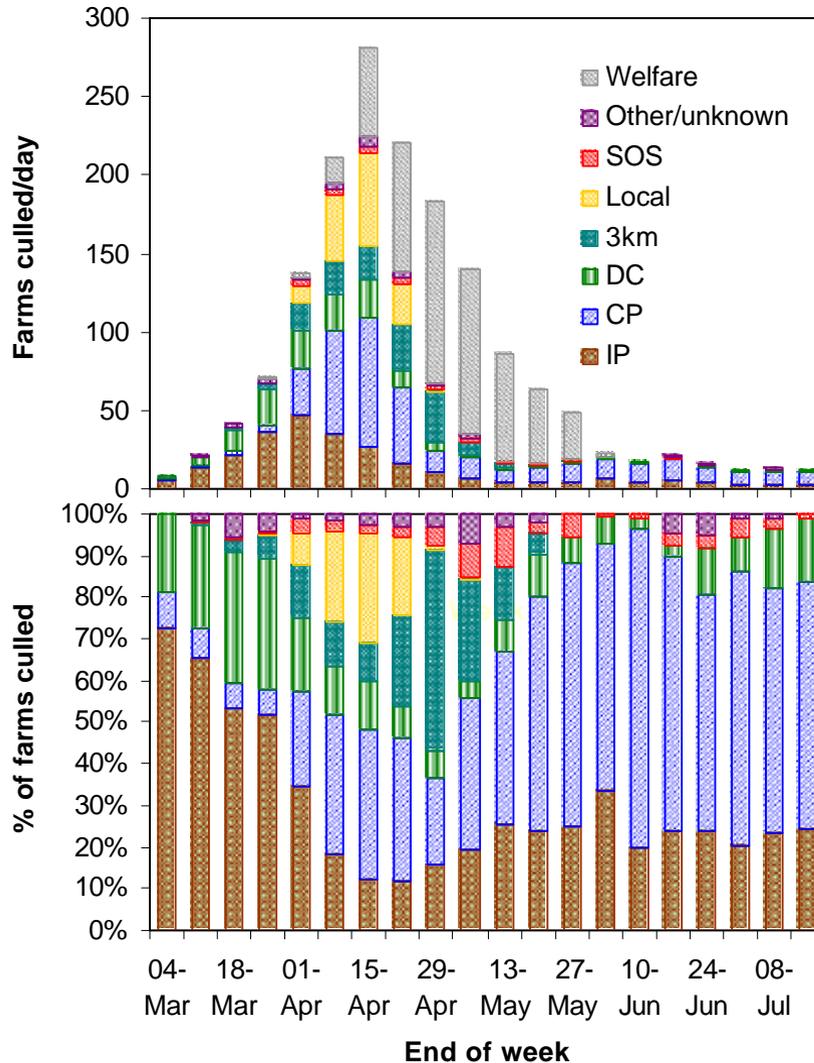
2,400,000 animals slaughtered by 1/5/01

3,900,000 animals slaughtered by 1/10/01

Strikingly long tail (out to end of September) after initial peak of epidemic.

Suggestive of frequency dependent control and/or wave-like spatial spread.

Temporal changes in culling



Multiple policies in place at peak of epidemic.

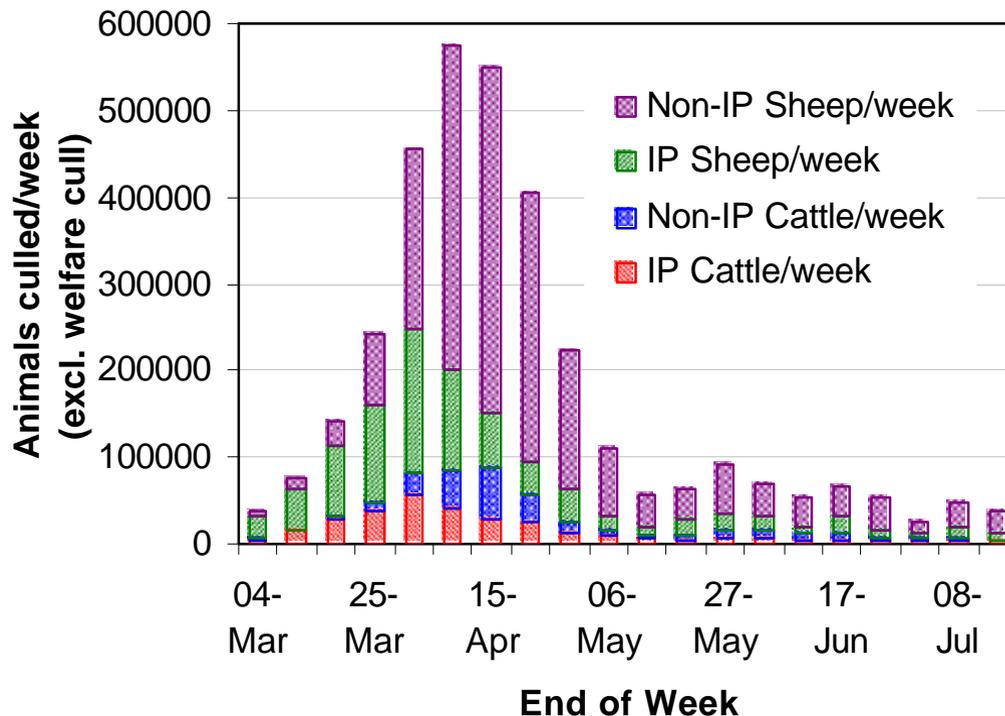
DC, CP, 3km and local policies aimed at controlling disease. Welfare cull for animal welfare reasons.

Ratio of non-IP to IP culling gives some information, but not highly predictive of impact as spatial locality of culled farms to recent IPs key.



Culling: species bias

Sheep were particularly targeted by DEFRA policies of 3km and local cull, and later relaxation of CP cull to allow veterinary discretion in culling cattle. Economic factors also probably played a role in determining farmer acquiescence to policy implementation.





Risk factor analysis: spatial hazard model

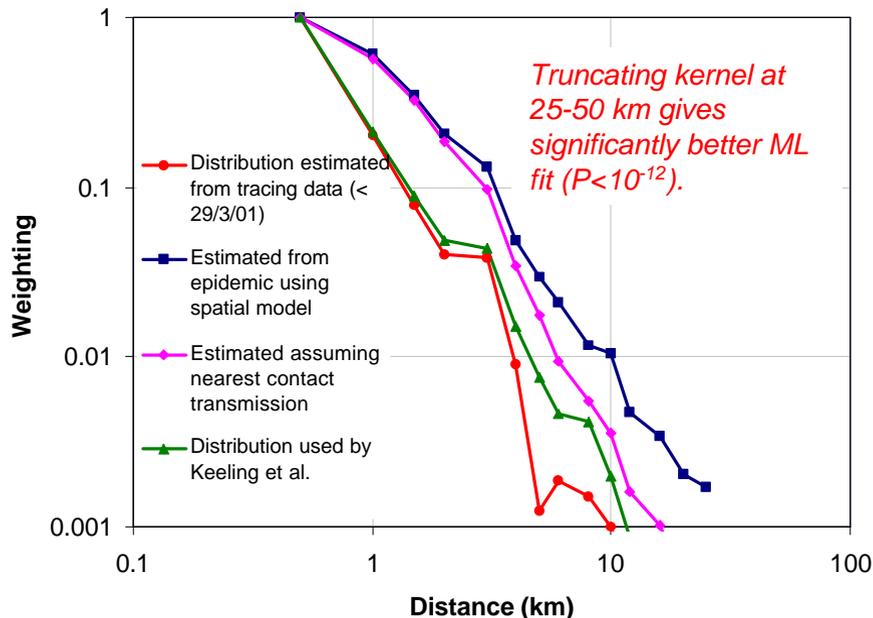
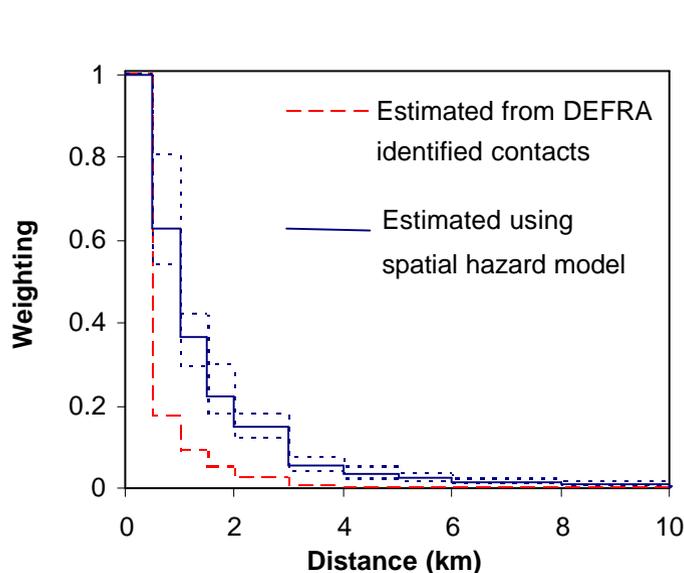
- Rigorous statistical analysis of an epidemic requires the fitting of a transmission model incorporating relevant heterogeneities to the detailed spatio-temporal pattern of observed cases at the farm-level.
- Optimally would use Maximum-Likelihood (ML) methods for doing this, but very computationally intensive.
- We therefore used a combination of methods, involving both ML techniques, but also fitting to marginal distributions of observed ‘infecting’ and ‘to be infected’ farm pairs.
- Published results makes 1st order approximation that epidemic fully observed (no hidden infection with recognition of infection on pre-emptively culled farms).



Spatial kernel estimates

Original kernel was estimated from DEFRA contact tracing.

New estimates from observed pattern of cases give rather wider kernel (more risk at longer distances), with longer median transmission distance



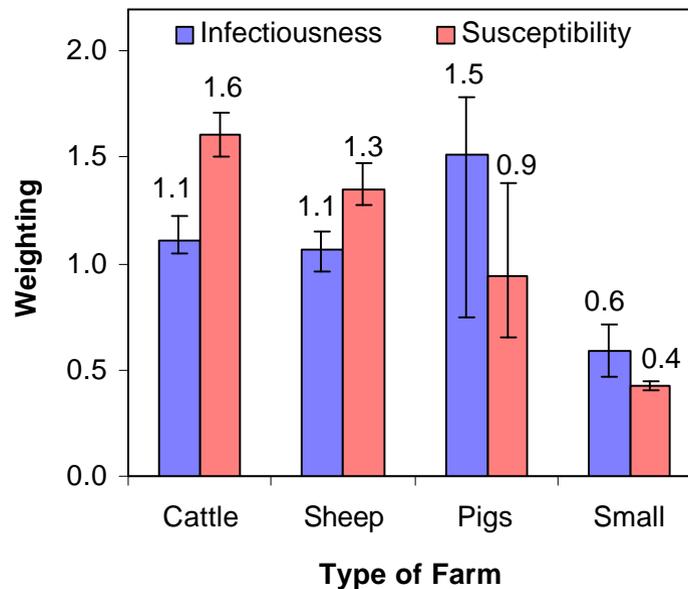
Preliminary results from additional work incorporating 1 generation of hidden infection indicates impact on parameter estimates marginal (slight reduction in width of spatial kernel).

Species type and number of animals



Published results crudely stratify farms by majority species (weighting sheep by 1/3 due to higher stocking numbers), and estimate susceptibility and infectiousness assuming contacts are random between all farms.

Shows trend for ‘cattle’ farms to be more susceptible than ‘sheep’, and ‘pigs’, while farms with < 100 animals have much lower risk.

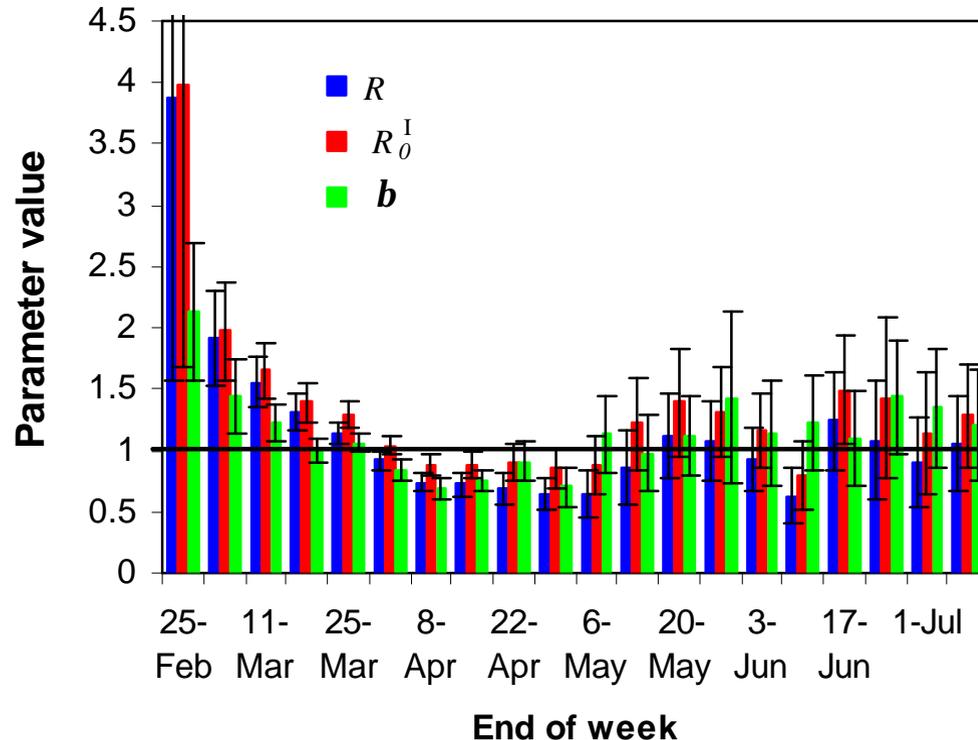


Finer stratification on the basis of farm size indicates risk saturates as number of animals becomes very large (>~800).

Recent work indicates mixing heterogeneity (sheep farms more likely to contact other sheep farms) explains the higher risk experienced by ‘mixed’ sheep and cattle farms [Keeling et al], and explains more regional variability.



Temporal changes in transmission potential

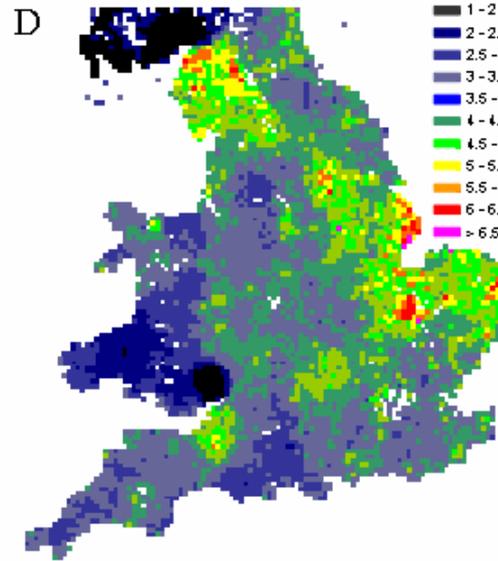
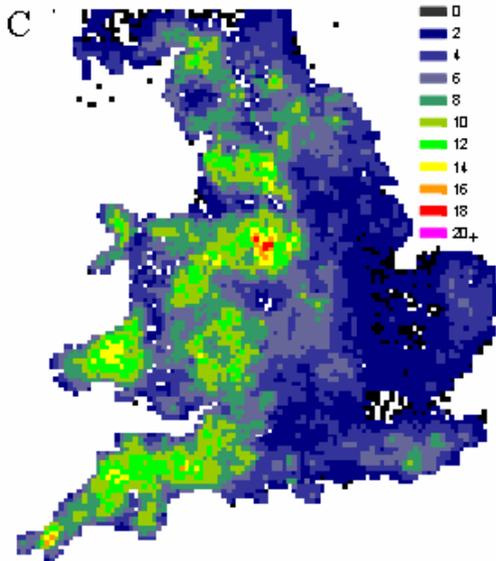
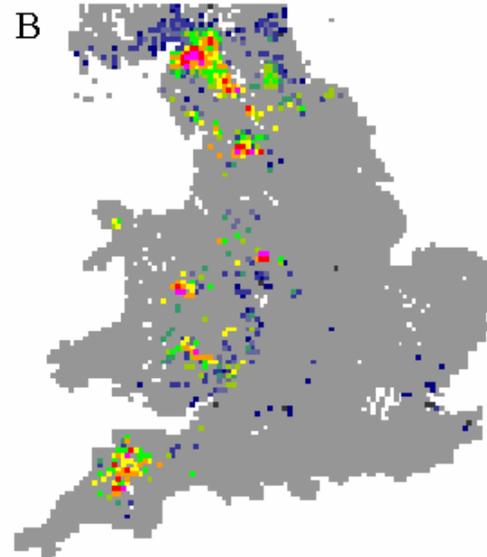
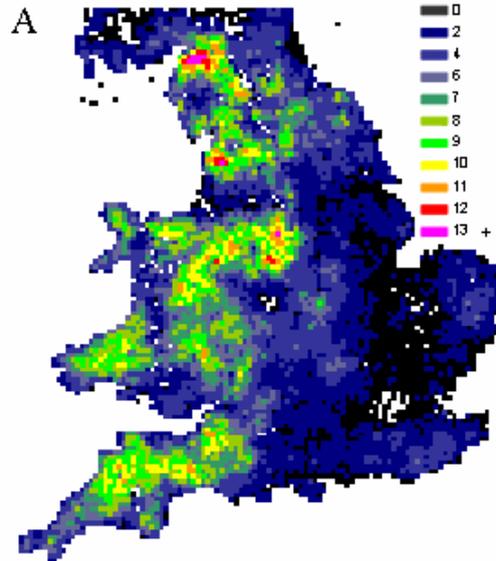


Similar to Woolhouse analysis, but integrated within spatial hazard model, and not assuming nearest contact analysis.

Variability in R values only partly explained by IP and non-IP culling variability and local host density variability, since estimated b values also show significant deviation ($P < 10^{-10}$) from being constant, even after 23rd Feb.

Suggests significant spatio-temporal variability in other control measures (biosecurity/movement controls), eg. in Yorkshire in early May.

Risk maps and farm fragmentation



Hazard model parameter estimates allow generation of risk map predicting areas of highest transmission risk.

The estimated number of discontinuous land fragments in a farm is strongly correlated with risk, and explains as much regional variation as farm-type.

Since we (effectively) only fit to areas where cases were seen, this method predicts some areas where few or no cases were seen might still be at risk if an outbreak started.

Want to read more?



April 2001

Ferguson NM, Donnelly CA and Anderson RM. The foot-and-mouth epidemic in Great Britain: Pattern of spread and impact of interventions. *Science*, 292, 1155-1160, 2001.

October 2001

Ferguson NM, Donnelly CA and Anderson RM. The determinants of transmission intensity and the impact of control policies on the foot and mouth disease (FMD) epidemic in Great Britain. *Nature* 413, 542-548, 2001.

Keeling MJ, Woolhouse MEJ, Shaw DJ, Matthews L, Chase-Topping M, Haydon DT, Cornell SJ, Kappey J, Wilesmith J, Grenfell BT. Dynamics of the 2001 UK foot and mouth epidemic: Stochastic dispersal in a heterogeneous landscape. *Science* 294, 813-817, 2001.

November 2000

Howard SC and Donnelly CA. The importance of immediate destruction in epidemics of foot and mouth disease. *Research in Veterinary Science* 69(2), 189-196, 2000.