

# Optimal reactive vaccination strategies for a foot-and-mouth outbreak in the UK

Michael J. Tildesley<sup>1</sup>, Nicholas J. Savill<sup>2,3</sup>, Darren J. Shaw<sup>4</sup>, Rob Deardon<sup>2,5</sup>, Stephen P. Brooks<sup>2</sup>, Mark E. J. Woolhouse<sup>3</sup>, Bryan T. Grenfell<sup>6,7</sup> & Matt J. Keeling<sup>1</sup>

**Foot-and-mouth disease (FMD) in the UK provides an ideal opportunity to explore optimal control measures for an infectious disease. The presence of fine-scale spatio-temporal data for the 2001 epidemic has allowed the development of epidemiological models that are more accurate than those generally created for other epidemics<sup>1–5</sup> and provide the opportunity to explore a variety of alternative control measures. Vaccination was not used during the 2001 epidemic; however, the recent DEFRA (Department for Environment Food and Rural Affairs) contingency plan<sup>6</sup> details how reactive vaccination would be considered in future. Here, using the data from the 2001 epidemic, we consider the optimal deployment of limited vaccination capacity in a complex heterogeneous environment. We use a model of FMD spread to investigate the optimal deployment of reactive ring vaccination of cattle constrained by logistical resources. The predicted optimal ring size is highly dependent upon logistical constraints but is more robust to epidemiological parameters. Other ways of targeting reactive vaccination can significantly reduce the epidemic size; in particular, ignoring the order in which infections are reported and vaccinating those farms closest to any previously reported case can substantially reduce the epidemic. This strategy has the advantage that it rapidly targets new foci of infection and that determining an optimal ring size is unnecessary.**

The control of infectious diseases is often a compromise between the desire for large-scale implementation of control measures and what is logistically or economically feasible. Therefore, it is important that control measures are optimally targeted so as to minimize the adverse population-level impact of a disease. Optimal targeting will in general depend in a complex nonlinear fashion on disease dynamics, host demography and logistical constraints. Well-parameterized mathematical models of infectious disease spread are therefore a necessary tool for determining optimal control strategies, because a vast range of policies can be rapidly tested by simulation. One important aspect of optimal control is the balance between maintaining local control of outbreaks while attacking new foci of infection.

During the course of the 2001 FMD epidemic a range of control measures were implemented to try to reduce the transmission of infection; these included movement restrictions preventing long-range transportation of livestock, increased farm bio-security, rapid culling of livestock on infected premises (IPs) to limit virus excretion, and the reactive culling of livestock on 'at risk' farms to eliminate potential new cases. Reactively culled farms fell into two main

categories (see Methods): dangerous contacts (DCs) and contiguous premises (CPs). Reactive vaccination was considered during the later stages of the 2001 epidemic but was dismissed for several reasons (detailed in ref. 7), including concerns that the limited vaccination campaign that was logistically feasible at the time would have little impact on the epidemic.

The recently published European Union Directive<sup>8</sup> suggests reactive vaccination as a preferred means of intervention should a foot-and-mouth disease outbreak occur in any member state. This is reflected in the UK by the new FMD contingency plan published by DEFRA<sup>6</sup>. However, neither document suggests a specific design for reactive vaccination programmes. Here, we concentrate on developing an optimal reactive and responsive vaccination programme based on the 2001 UK epidemic, assuming vaccination-to-live so that vaccinated animals do not have to be culled. Vaccination of cattle is combined with localized culling (following EU and DEFRA recommendations<sup>6,8</sup>) in which all livestock on infected premises are culled within 24 hours of reporting and farms considered by epidemiological investigation to be at increased risk (DCs) are culled within 48 hours. By default, simulations do not include CP culling. The model closely follows that developed in refs 1 and 2; we use the farm census database from June 2000 to incorporate farm-level heterogeneities into our model while the epidemiological parameters are obtained by fitting to the 2001 spatio-temporal epidemic profile (see Methods and Supplementary Information).

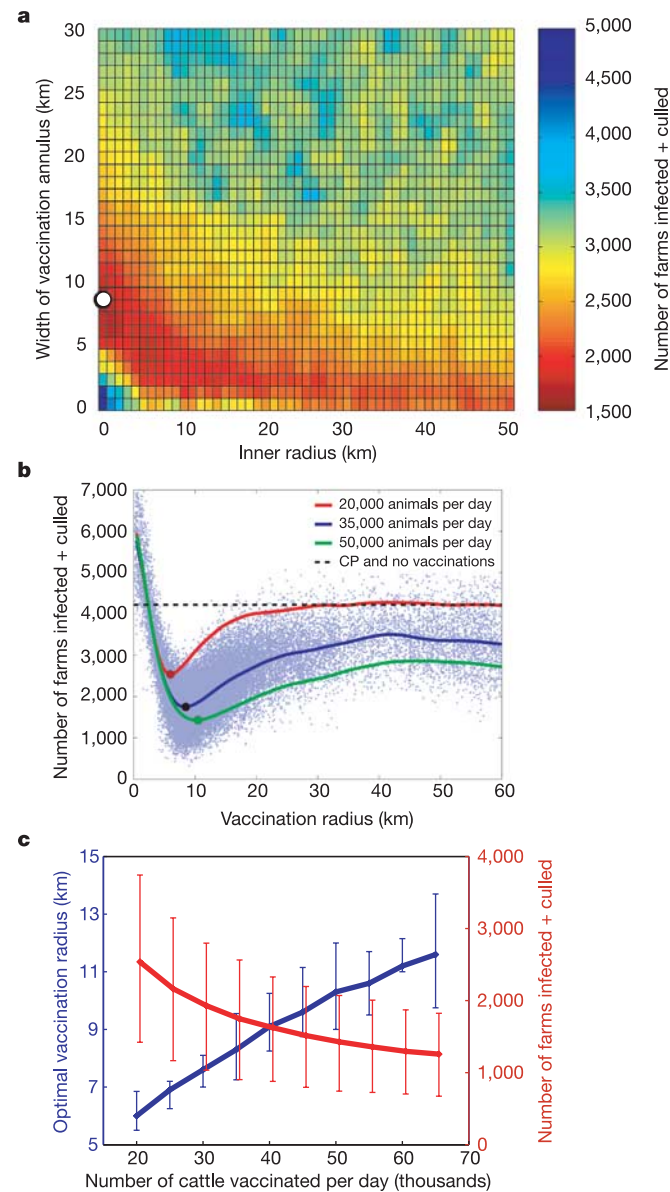
We begin by assuming that vaccination (of cattle only) takes place within an annulus (defined by an inner and outer radius,  $R_{\text{inner}}$  and  $R_{\text{outer}}$ ) around each IP<sup>3,9</sup> such that all farms within a given distance of every IP will be identified for vaccination (see Methods). Vaccination of these farms is then prioritized in the order that the associated IPs were reported and, for those farms identified on the same day, priority is given to those furthest from the IP. Thus vaccination within each annulus is performed from the outside in. Protection of cattle is influenced by several factors. We assume a vaccine efficacy of 90% so that 10% of vaccinated cattle remain susceptible<sup>10,11</sup>; in addition there is a four-day delay between vaccination and protection. Finally, although farms within an annulus are targeted for vaccination two days after the IP is reported, it may take longer before they are vaccinated owing to the logistical constraint that only a limited number of cattle can be vaccinated per day.

Varying  $R_{\text{inner}}$  and  $R_{\text{outer}}$ , we seek the vaccination annulus that minimizes the epidemic impact—defined as the number of farms that are infected (IPs) or culled as part of the control (DCs + CPs if appropriate). For a plausible vaccination capacity (defined as the

<sup>1</sup>Department of Biological Sciences and Mathematics Institute, University of Warwick, Gibbet Hill Road, Coventry CV4 7AL, UK. <sup>2</sup>Statistical Laboratory, Centre for Mathematical Sciences, University of Cambridge, Wilberforce Road, Cambridge CB3 0WB, UK. <sup>3</sup>Epidemiology Group, Centre for Infectious Diseases, University of Edinburgh, Ashworth Laboratories, Kings Buildings, West Mains Road, Edinburgh EH9 3JF, UK. <sup>4</sup>Veterinary Clinical Studies, Royal (Dick) School of Veterinary Studies, University of Edinburgh, Easter Bush Veterinary Centre, Roslin, Midlothian EH25 9RG, UK. <sup>5</sup>Cambridge Infectious Diseases Consortium, Centre for Veterinary Science, University of Cambridge, Madingley Road, Cambridge CB3 0ES, UK. <sup>6</sup>Center for Infectious Diseases Dynamics, Biology Department 208, Mueller Laboratory, Pennsylvania State University, University Park, Pennsylvania 16802, USA. <sup>7</sup>Fogarty International Center, National Institutes of Health, Bethesda, Maryland 20892, USA.

number of cattle that can be vaccinated per day), the model predicts that the optimal policy is to vaccinate in a complete ring with the inner radius set to zero (Fig. 1a). Extensive simulations have shown that this is true for all the situations examined here, indicating that—despite the delays involved—vaccination is still in general a locally effective control measure. This finding could be refined using predictive vaccination<sup>2</sup>, where (on a case-by-case basis) the use of predictive simulations indicates that it may be optimal to ignore some local farms if they are likely to become infected before vaccination would confer immunity.

We focus on the behaviour of the model when the inner radius is fixed at zero (Fig. 1b and c), and observe several important patterns.

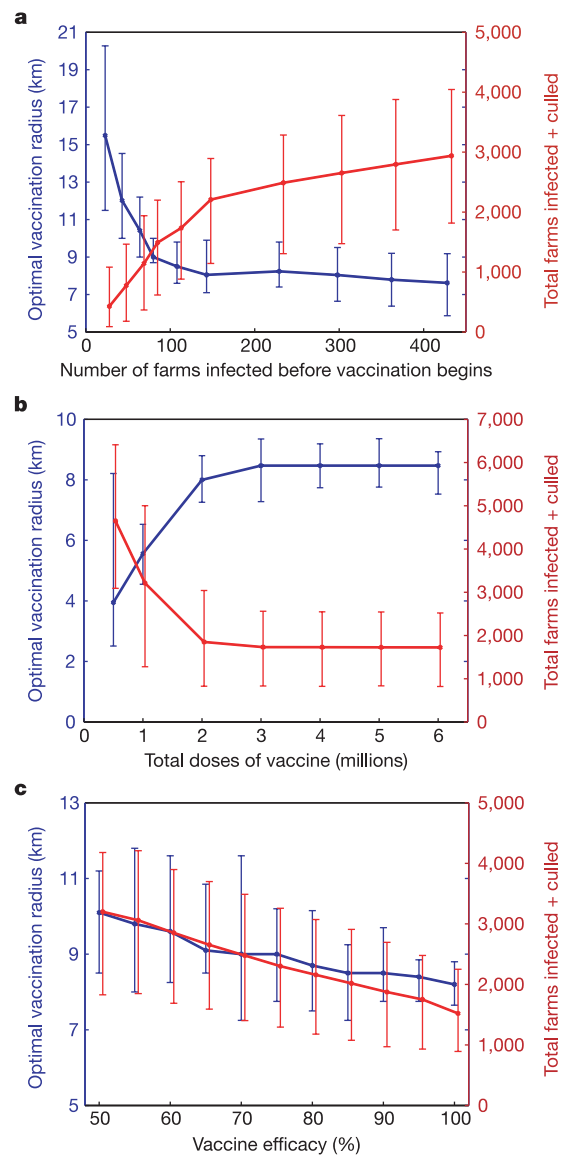


**Figure 1 | Epidemic impact (number of farms infected and culled).**

**a**, Epidemic impact as inner vaccination radius ( $R_{inner}$ ) and width of the vaccination annulus ( $R_{outer} - R_{inner}$ ) vary. The white dot marks the optimal strategy. **b**, Epidemic impact for various outer radii ( $R_{inner} = 0$ ); points represent individual simulations, lines give a smoothed average for different vaccination capacities with large dots marking the optimal ring size. The dashed black line gives the average epidemic impact with prompt CP and DC culling but no vaccination. **c**, Epidemic impact (red) and optimal radius (blue) as the daily vaccination capacity is varied (with 95% confidence intervals for each point).

Increasing the vaccination capacity reduces the average epidemic impact (Fig. 1b and c), although there is considerable variation between simulations. The optimal vaccination ring increases with vaccination capacity. However, the number of animals within the optimal ring is not proportional to the number that can be vaccinated per day; instead it increases more rapidly, compensating for overlapping vaccination rings. This highlights the fact that calculation of the optimal ring size is a complex nonlinear problem that requires detailed spatial models. Finally, we note that optimal reactive ring vaccination at 35,000 animals per day (together with IP and DC culling) is a far better strategy, in terms of reducing the total number of farms lost, than a policy of CP culling (together with IP and DC culling but no vaccination) even if all the culls are performed promptly (Fig. 1b).

Armed with these insights, we then explore the effect of varying



**Figure 2 | The optimal vaccination radius and the associated epidemic impact.** Results were determined (together with 95% confidence intervals) using an outside-in vaccination strategy and vaccination capacity of 35,000 cattle per day. **a**, The number of farms infected before vaccination begins is varied—capturing early or late detection and start of vaccination. **b**, The total number of doses of vaccine available is varied. **c**, The efficacy of the vaccine is varied.  $R_{inner}$  is zero in all simulations. Each point represents the results of 40,000 epidemic simulations. Similar results for the shortest-distance prioritization are given in the Supplementary Information.

**Table 1 | Effect of strain variation on optimal vaccination radius**

Risk factor	Optimal ring size (km)	
	Halved	Doubled
Sheep transmissibility	8.5 (7.3–0.8)	7.5 (6.8–8.1)
Cattle transmissibility	7.0 (6.0–8.5)	7.0 (6.3–7.5)
Sheep susceptibility	7.5 (6.5–8.4)	8.0 (6.5–10.0)
Cattle susceptibility	8.0 (6.3–11.0)	6.5 (5.8–7.6)
Kernel width (keeping total transmission constant)	6.0 (4.5–7.5)	8.0 (7.0–9.3)

The effect of varying epidemiological parameters, mimicking variation due to alternative strains, upon the optimal position of the outer vaccination ring. 95% confidence intervals are shown in parentheses.

other logistical and biological factors on the optimal vaccination radius and corresponding epidemic impact (Fig. 2). Figure 2a measures the delay before the disease is first detected combined with the delay before the onset of vaccination in terms of the average number of farms infected before vaccination begins. Prompt detection of the epidemic and a rapid decision to vaccinate allows larger vaccination rings to be implemented around each IP and substantially reduces the epidemic size, echoing more general principles<sup>1,12</sup>. Any supply of vaccine will be limited because of the impracticality of storing large amounts of vaccine for each virus type; also, vaccine efficacy will vary between strains and may be considerably reduced if there is a discrepancy between the invading strain and the closest available vaccine. Both of these have implications for the success of any vaccination campaign<sup>13–15</sup>. When the supply of vaccine is below three million doses, the vaccine ring must be reduced in size to prevent premature exhaustion of this supply, which in turn increases the epidemic impact (Fig. 2b). In contrast, although a reduction in vaccine efficacy (which may act as a surrogate for the farm-level effects of vaccination) also leads to a greater epidemic impact, it has a more limited effect on the optimal ring size (Fig. 2c).

The epidemiological characteristics within the model have been parameterized using the data from the 2001 epidemic. However, should foot-and-mouth disease enter the UK in future, it will not necessarily be the same strain and so its epidemiological characteristics could be substantially different. We therefore calculate the optimal vaccination ring (for the simple outside-in prioritization) while varying the susceptibility and transmissibility of cattle and sheep, and the width of the dispersal kernel, by a factor of two (Table 1). Although the average epidemic size is highly dependent upon these epidemiological parameters, the effect on the optimal radius,  $R_{\text{outer}}$ , is very small. We stress that these results are illustrative, because the true variation in strain characteristics has yet to be quantified, but do reflect the general robustness of the optimal ring size. We note, however, that strains that are effectively transmitted as air-borne plumes may give rise to dramatic changes to the

transmission kernel, and thus could invalidate the use of localized vaccination.

Ring vaccination is a form of targeted control that uses spatial proximity as a risk factor, but other refinements to the targeting could be used<sup>16,17</sup>. Table 2 shows that whether vaccination is prioritized outside-in or inside-out within each day has very little effect on the optimal ring size or the associated epidemic impact. Surprisingly, if all prioritization is completely ignored and farms within a given radius are vaccinated at random there is a slight improvement over outside-in. This is because local herd-immunity (the threshold population level of immunity needed to prevent disease spread) around each IP is reached more quickly as it does not require the vaccination of all cattle. Identifying farms within a given radius, but prioritizing vaccination towards those farms with the largest numbers of cattle or livestock (rather than prioritizing in chronological order) again increases the optimal ring size and decreases the epidemic impact. This improvement mirrors the general epidemiological tenet that targeting of control measures can provide a substantial increase in effectiveness.

A variety of previous models have shown the success of CP culling in the absence of vaccination<sup>1,4,5</sup> and this is confirmed by our simulations. However, for all vaccination priorities investigated here the inclusion of additional CP culling leads to the total loss of more farms (though not necessarily more livestock). We postulate that this loss of efficiency is because a high proportion of farms that are CP culled are (at least partially) protected by vaccination, and therefore the effect of CP culling on the spread of the infection is diminished compared to a situation with no vaccination. This means that the reduction in cases owing to CP culling is smaller than the number of additional culls performed, and we therefore conclude that CP culling is not advantageous when combined with vaccination.

We next turned to new strategies for optimizing the balance between managing existing and new foci of infection. A simple and very successful strategy is that of prioritizing farms for vaccination purely by their proximity to any previously infected premises, while vaccinating at capacity every day. The resultant epidemic impact is smaller than for all other prioritizations investigated (Table 2). This strategy has two main advantages. Firstly, an optimal ring size does not have to be determined, because this strategy utilises the full logistical resources that are available on any day. Therefore any change in logistical constraints does not necessitate a change in the vaccination policy. Secondly, vaccination in the immediate vicinity of a new IP is rapid, thus focusing control on those farms that are at the most immediate risk. The benefits gained from this targeting approach are not particularly sensitive to the precise ordering of vaccination, the number of cattle that can be vaccinated per day or the initial seeding of the epidemic. A further improvement is achieved if the prioritization is in terms of the shortest distance to

**Table 2 | Effect of control strategies on optimal vaccination radius**

Vaccination priority	Optimal ring size (km)	IPs + DCs + CPs	Total animals culled (millions)
Earliest IP reporting date (outside-in)	8.5 (7.8–9.6)	1,752 (928–2544)	2.07 (1.04–3.23)
Earliest IP reporting date (inside-out)	8.6 (8.0–0.5)	1,791 (994–2469)	2.10 (1.04–3.30)
Random order	9.0 (7.8–11.2)	1,688 (883–2475)	2.02 (0.94–3.13)
Largest cattle farms	10.5 (8.8–11.9)	1,535 (745–2339)	1.74 (0.71–2.85)
Largest mixed farms	12.5 (10.3–15.4)	1,343 (696–2025)	1.42 (0.61–2.28)
Shortest distance to any IP	NA	1,254 (664–1954)	1.50 (0.67–2.46)
Shortest distance to any IP or DC	NA	1,192 (626–1860)	1.42 (0.65–2.35)
Shortest distance to any IP or DC identified within previous ten days	NA	1,088 (582–1726)	1.28 (0.60–2.17)
No vaccination (+CP culling)	NA	4,220 (2149–6431)	3.58 (2.32–5.02)
Earliest IP reporting date (+CP culling)	8.0 (6.6–9.8)	1,955 (1176–2803)	1.65 (0.80–2.54)
Largest mixed farms (+CP culling)	11.3 (9.7–22.5)	1,607 (1033–2277)	1.27 (0.72–1.93)
Shortest distance to IP (+CP culling)	NA	1,528 (895–2272)	1.69 (0.73–2.70)

The effect of vaccination priority and additional control strategies upon the optimal position of the outer vaccination ring together with the associated epidemic impact (IPs, and also DCs and CPs if appropriate) and the total number of animals culled. 95% confidence intervals are shown in parentheses.

NA, not applicable.

any IP or DC identified within the past ten days, as this also targets vaccination around DCs that are suspected of being infected and ignores regions of the country that no longer pose any risk.

We have shown that reactive vaccination could be a very powerful tool for combating FMD, and potentially other locally transmitted pathogens, when combined with efficient IP and DC culling and animal movement restrictions. As ever, rapid implementation is essential. A policy that prioritizes vaccination in terms of the shortest distance to any reported infection or DC has strong epidemiological benefits over traditional fixed-radius policies, especially in terms of balancing local and regional control and making full use of the daily vaccination capacity. It would also be easy to achieve practically, because optimization for a particular set of logistical constraints is unnecessary. This specific result echoes a more general trend, that detailed data-driven models are becoming an increasingly important tool in determining optimal epidemic control policies.

## METHODS

**The Model.** The probability that a susceptible farm  $i$  is infected on a given day,  $D$ , is given by the equation:

$$P_{i,D} = 1 - \exp\left(-S^{(i)} \sum_{j \in \text{Infectious}(D)} T^{(j)} K(d_{ij})\right) \quad (1)$$

$$S^{(i)} = s_{\text{cow}} n_{\text{cow}}^{(i)} + s_{\text{sheep}} n_{\text{sheep}}^{(i)} \quad T^{(j)} = t_{\text{cow}} n_{\text{cow}}^{(j)} + t_{\text{sheep}} n_{\text{sheep}}^{(j)}$$

where  $S^{(i)}$  and  $T^{(j)}$  refer to the susceptibility and transmissibility of uninfected farm  $i$  and infectious farm  $j$ , respectively. These farm-level measures are in turn calculated from species-level parameters where  $s_A$  and  $t_A$  refer to the susceptibility and transmissibility of species  $A$ , and  $n_A^{(i)}$  is the number of species  $A$  on farm  $i$ . These animal-level parameters are estimated from the 2001 data by matching to the cumulative number of cases and culls in five distinct regions (Cumbria, Devon, Wales, Scotland and the rest of England). The best-fit parameters for Cumbria exemplify the general pattern:  $t_{\text{cow}} = 7.7 \times 10^{-7}$ ,  $t_{\text{sheep}} = 5.1 \times 10^{-7}$ ,  $s_{\text{cow}} = 10.5$ ,  $s_{\text{sheep}} = 1$  (see Supplementary Information for full parameters and confidence intervals). Pigs have been ignored in this model for simplicity because there is insufficient data from the 2001 epidemic to determine precise parameter values or even to show that the parameters are significantly different from zero.  $K$  is the infection kernel and  $d_{ij}$  is the distance between susceptible farm  $i$  and infectious farm  $j$ . The kernel is calculated from the contact tracing performed by DEFRA during 2001 after movement restrictions, which provides a distribution of distances between infecting farms<sup>2</sup>. We note that at present in the UK, only the residential position of the owner of the farm is recorded, which could be separate from the farm itself and also distant from where livestock is kept. However, large discrepancies in position affect only a small fraction of the total data and sensitivity analysis shows that the general results are unaffected by small errors in the positional data.

This epidemiological framework is coupled with the prompt culling of livestock on IPs (within 24 hours) and on DCs (within 48 hours). The model therefore mimics the rapid speed and significant levels of local control that were attained during the latter part of the 2001 outbreak, representing what it is hoped could be achieved from the detection of an epidemic in the future. The simulations are initialized with the exact conditions of 23 February 2001 (including infected, infectious and reported farms); in any future outbreak it is hoped that the disease will be detected earlier so that the spread is less disseminated (Fig. 2a).

**Calculation of dangerous contacts and contiguous premises.** In practice, DCs are identified for each IP on a case-by-case basis, and are based on veterinarian judgement of risk factors and known activities, such as the movement of vehicles. In our model, DCs are determined stochastically, accounting for infection risk factors and known transmission events (see Supplementary Information) and parameterized to match the best sustainable levels achieved during 2001.

CPs are determined by a comprehensive knowledge of the farm geography and are defined as farms that share a common boundary—in practice, this is again determined on a case-by-case basis using local maps and knowledge. However, the data on farms within the UK only identifies the location of the owner of the farm. We approximate CPs by tessellating around each point location, taking into account the known area of each farm, to obtain a surrogate set of adjacent farms. Clearly this set of farms will not necessarily be the set of true CPs<sup>1,2</sup>, but this approximation will capture many of the elements of local proximity.

**Vaccination assumptions.** There are a set of standard assumptions that are made

throughout the paper about the characteristics of vaccination. First, we assume that only cattle are vaccinated—vaccination of other species, such as sheep, would substantially limit the number of farms that could be vaccinated per day and therefore limit the effect of vaccination (see Supplementary Information). Unless otherwise stated, the vaccine efficacy is taken to be 90%, and a four-day delay from vaccination to immunity is assumed. Therefore, after four days, 90% of cattle on a given farm become totally immune and the remainder are totally susceptible. We make the pessimistic assumption that during the four days between vaccination and immunity, all cattle are completely susceptible and if infected, the disease progresses in the same way as for non-vaccinated cattle. A farm in which 90% of the cattle are immune has the same transmission and susceptibility properties as a farm with 10% of the number of cattle. In general, we assume that 35,000 animals can be vaccinated per day (unless otherwise stated) and there is no limit on the number of farms that can be vaccinated per day. This assumption results in vaccination of 260 farms per day (on average) for shortest-distance ring vaccination. The latest DEFRA estimates suggest that a maximum of 300 farms could be vaccinated per day, so our limit of 35,000 animals per day is reasonable. Vaccination is assumed to begin five days after the disease is first detected, in agreement with the DEFRA contingency plan<sup>6</sup>.

Received 16 June; accepted 29 September 2005.

- Keeling, M. J. *et al.* Dynamics of the 2001 UK foot and mouth epidemic: stochastic dispersal in a heterogeneous landscape. *Science* **294**, 813–817 (2001).
- Keeling, M. J., Woolhouse, M. E. J., May, R. M., Davies, G. & Grenfell, B. T. Modelling vaccination strategies against foot-and-mouth disease. *Nature* **421**, 136–142 (2003).
- Ferguson, N. M., Donnelly, C. S. & Anderson, R. M. The foot-and-mouth epidemic in Great Britain: pattern of spread and impact of interventions. *Science* **292**, 1155–1160 (2001).
- Ferguson, N. M., Donnelly, C. S. & Anderson, R. M. Transmission intensity and impact of control policies on the foot and mouth epidemic in Great Britain. *Nature* **413**, 542–548 (2001).
- Morris, R. S., Wilesmith, J. W., Stern, M. W., Sanson, R. L. & Stevenson, M. A. Predictive spatial modelling of alternative control strategies for the foot-and-mouth disease epidemic in Great Britain, 2001. *Vet Record* **149**, 137–144 (2001).
- DEFRA Foot and Mouth Disease Contingency Plan (<http://www.defra.gov.uk/footandmouth/contingency/index.htm>) (2004).
- Anderson, I. *Foot and Mouth Disease 2001: Lessons to be Learned Inquiry* (The Stationery Office, London, 2002).
- Council Directive 2003/85/EC. *Official J. Eur. Union* **L306**, 46, 1–87 (2003).
- Muller, J., Schonfisch, B. & Kirkilionis, M. Ring vaccination. *Math. Biol.* **41**, 143–171 (2000).
- Barnett, P. V. & Carabin, H. A review of emergency foot-and-mouth disease (FMD) vaccines. *Vaccine* **20**, 1505–1514 (2002).
- Woolhouse, M. E. J., Haydon, D. T., Pearson, A. & Kitching, R. P. Failure of vaccination to prevent outbreaks of foot-and-mouth disease. *Epidem. Infect.* **116**, 363–371 (1996).
- Ferguson, N. M. *et al.* Planning for smallpox outbreaks. *Nature* **425**, 681–685 (2003).
- McLean, A. R. & Blower, S. M. Modelling HIV vaccination. *Trends Microbiol.* **3**, 458–463 (1995).
- Williams, J. R., Nokes, D. J. & Anderson, R. M. Targeted hepatitis B vaccination—a cost effective immunisation strategy for the UK? *J. Epidemiol. Comm. Health* **50**, 667–673 (1996).
- Woolhouse, M. E. J., Haydon, D. T. & Bundy, D. A. P. The design of veterinary vaccination programmes. *Vet. J.* **153**, 41–47 (1997).
- Woolhouse, M. E. J. *et al.* Heterogeneities in the transmission of infectious agents: implications for the design of control programs. *Proc. Natl Acad. Sci. USA* **94**, 338–342 (1997).
- Matthews, L. *et al.* Neighbourhood control policies and the spread of infectious disease. *Proc. R. Soc. Lond. Ser. B* **270**, 1659–1666 (2003).

**Supplementary Information** is linked to the online version of the paper at [www.nature.com/nature](http://www.nature.com/nature).

**Acknowledgements** This research was supported by the Wellcome Trust.

**Author Contributions** M.J.T. and M.J.K. were responsible for the model formulation and analysis of results; N.J.S. provided helpful discussions throughout; D.J.S. generated cleaned demographic and epidemic data; R.D. and S.P.B. provided vital statistical input; M.E.J.W. and B.T.G. were instrumental in the initial development of the project. All authors contributed to the writing of the manuscript.

**Author Information** Reprints and permissions information is available at [npg.nature.com/reprintsandpermissions](http://npg.nature.com/reprintsandpermissions). The authors declare no competing financial interests. Correspondence and requests for materials should be addressed to M.J.K. ([m.j.keeling@warwick.ac.uk](mailto:m.j.keeling@warwick.ac.uk)).