LETTER

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A dynamic model of bovine tuberculosis spread and control in Great Britain

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Bovine tuberculosis (TB) is one of the most complex, persistent and controversial problems facing the British cattle industry, costing the country an estimated £100 million per year[1]. The low sensitivity of the standard diagnostic test leads to considerable ambiguity in determining the main transmission routes of infection, which exacerbates the continuing scientific debate[2–6]. In turn this uncertainty fuels the fierce public and political disputes on the necessity of controlling badgers to limit the spread of infection. Here we present a dynamic stochastic spatial model for bovine TB in Great Britain that combines within-farm and between-farm transmission. At the farm scale the model incorporates stochastic transmission of infection, maintenance of infection in the environment and a testing protocol that mimics historical government policy. Between-farm transmission has a short-range environmental component and is explicitly driven by movements of individual cattle between farms, as recorded in the Cattle Tracing System[2]. The resultant model replicates the observed annual increase of infection over time as well as the spread of infection into new areas. Given that our model is mechanistic, it can ascribe transmission pathways to each new case; the majority of newly detected cases involve several transmission routes with moving infected cattle, reinfection from an environmental reservoir and poor sensitivity of the diagnostic test all having substantive roles. This underpins our findings on the implications of control measures. Very few of the control options tested have the potential to reverse the observed annual increase, with only intensive strategies such as whole-herd culling or additional national testing proving highly effective, whereas controls focused on a single transmission route are unlikely to be highly effective.

Bovine tuberculosis (TB) has been a long-standing problem in Britain. In the first half of the 20th century, 40% of British cattle were suspected to be infected, with contaminated milk being a major transmission route to humans[3]. This route was eliminated with the pasteurization of milk, and a 'test-and-slaughter' scheme was started in the 1950s to eradicate infection among cattle. Incidence fell markedly and in the 1970s only 0.22% of tests revealed infected animals[4,5]. However, over the past 20 years incidence has been steadily increasing, most notably in the southwest and west of England and the southwest of Wales. The 2001 foot-and-mouth disease (FMD) epidemic exacerbated the problem, as a reduction in bovine TB testing was followed by atypical movements of cattle to replenish FMD-affected farms[6]. Since then, results of the randomized badger culling trial have been reported and analysed[7] and a variety of new legislation and controls have been introduced[8].

Present-day control measures have evolved from the original test-and-slaughter scheme, but are still based on the regular testing of herds, slaughter of positive animals and the imposition of movement restrictions following a failed test[5,8]. The most common method for detecting infected animals is the single intradermal comparative cervical tuberculin (SICCT) test (Extended Data Fig. 1), based on the measurement of the reactions produced to an antigen mixture (tuberculins) derived from *Mycobacterium bovis* and *Mycobacterium avium*[9]. The test sensitivity (proportion of infected animals successfully detected) is estimated to lie in the range 70–90%[10–12]; in addition, an animal is unlikely to test positive for a period of time following infection. Using such a test necessitates the use of multiple follow-up tests following a positive test on a herd to increase the chance of detecting all infected cattle. Movement restrictions are placed on herds until they pass one or two follow-up tests at approximately 60-day intervals, and once movement restrictions are lifted two further tests are required after 6 and 12 months. In 2010–2012 there was a marked expansion and consolidation of testing protocols in England, culminating in 2013 with the division of the country into annual testing counties in the south and west and four yearly testing counties in the east and north[8]. All herds in Wales were placed on annual testing in 2009. In 2013 over 8 million cattle were tested and over 32,000 cattle slaughtered to control this infection.

Bovine TB incidence can be measured in several different ways according to the results of the bovine TB testing policy. The number of reactors is defined as the total number of cattle testing positive. Failed tests are a herd-level measure and refer to any test on a farm (including routine, whole-herd and follow-up test) where at least one animal tests positive. Herd breakdowns (or Officially TB Free Withdrawn or Suspended, OTFW/S) are defined as a failed test on a herd not currently subjected to movement restrictions.

Mathematical modelling has formed an integral part in planning the control of livestock diseases such as FMD[13,14]. Dynamic mechanistic modelling of bovine TB has posed a challenge owing to the long timescales associated with the disease, the asymptomatic nature of infection, the ambiguity in the transmission pathways, the potential contribution from a local reservoir and the effect of complex and changing control policies[12,15,16]. However, the availability of data from the Cattle Tracing System has enabled detailed investigation of livestock infections that are spread by the movement of cattle[17,18]. Here we develop a mechanistic model of bovine TB transmission between the approximately 134,000 livestock premises in Great Britain that moved cattle between 1996 and 2011. Mechanistic models can be challenging to fit to observed data, as they are constrained by mechanistic transmission rules; however, they allow us to separate cause and effect and to determine the long-term consequences of alternative interventions.

A stochastic SEI (Susceptible, Exposed (or Latent), Infectious) process, the most relevant model formulation for tuberculosis[19], is used to capture the infection dynamics within each farm. Within-farm transmission is modelled as both direct cattle-to-cattle and indirect from the farm environment, which increases persistence of infection. This environment captures the effect of both contaminated pasture and infected wildlife, with the two being inseparable in our formulation. Spread between farms is captured by the daily movement of approximately 30,000 cattle that can potentially transport infection, and from the local regional environment that facilitates both short distance spread and persistence. This regional environment again corresponds to both contaminated pasture and wildlife, and allows transmission between farms within the same parish. A herd-level testing policy is incorporated that explicitly uses recorded routine test dates and generates follow-up tests in accordance with historical government policy. As the model is a herd-level model that does not distinguish between individual cattle on a farm, we included all herd-level tests but no individual cattle tests.

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This model unifies within- and between-herd transmission; it is this and the combination of several key features that distinguishes this model from previous work[12,18,20–22]. First, it is dynamic rather than statistical, such that the behaviour one day is carried forward and affects future events. Such an approach is vital in predicting the effects of alternative control measures rather than simply associating risks. Second, it deals with the infection dynamics at several spatial scales, incorporating within-farm behaviour into a national model of bovine TB spread. This level of detail is necessary, given that the transmission of infection within farms is slow and often only a few cattle are infected. In addition, the movement of cattle is modelled explicitly, such that susceptible, latent and infectious animals can all be moved on or off a farm, in contrast to traditional network-based models of disease transmission. The model includes a testing regime that approximately captures changing government policy. Throughout we make the important distinction between infected herds and herds where infection has been detected, which enables the investigation of realistic control measures.

The model is parameterized using sequential Monte Carlo approximate Bayesian computation[23,24] (SMC-ABC), in which the posterior distributions of parameters are generated by repeated stochastic simulation of the model (see Methods, Supplementary Information, Extended Data Fig. 2 and Extended Data Table 1). We fit the model to the number of reactors and number of failed herd tests per county per year between 1997 and 2007. ABC offers a flexible method for inferring parameters, as standard likelihood-based approaches are infeasible because of the model complexity and the uncertainty of test results. Some key implications arise from this parameter inference. First, the test sensitivity is estimated to be 72% (credible interval 63–81%). This indicates that farms with a low number of infected animals may escape detection; at least four animals on a farm need to be infectious and tested to correctly identify a breakdown with 99% certainty. In addition, even when the farm is correctly detected individual animals may escape; on a farm with four infectious cattle there is only a 26% (12–49%) chance of detecting all four animals at the first test. Second, our inferred parameters indicate that the majority of within-farm transmission is through the environment rather than direct transmission (Extended Data Table 1), where this environment captures the effect of both contaminated pasture or infected wildlife. These localized environmental reservoirs also allow infection to persist between tests after the infectious animals have been removed. The level of infection in the environment is predicted to decay with a half-life of 34 days (credible interval 20–71 days) (Extended Data Table 1), and although this is rapid it is sufficient to allow infection to arise months after infectious cattle are removed.

The model, initialized to capture the detected cases in 1996–1998, is iterated forwards and captures many aspects of the spatio-temporal spread of bovine TB (Fig. 1, Extended Data Figs 3, 4). Although the fitting procedure operates at the county scale there is good agreement with the national observations, capturing steady rise in the annual number of reactors (cattle failing the test) (Fig. 1a), which have increased by on average 10% each year between 2004 and 2010. At the county scale we find an extremely strong correlations (Pearson correlation coefficient = 0.993, $P < 2 \times 10^{-16}$) between predictions and observations for both numbers of failed tests and numbers of reactors (Extended Data Fig. 3). In particular, we can visually compare the predicted and observed spatial spread of infection as it has expanded and intensified from 1998 to 2010 (Fig. 1b, Extended Data Fig. 4). Additionally, predictive models such as this can be used to extrapolate future behaviour, we do this here by reusing the historical cattle movements from 2007–2010 to predict infection up to 2015. Although individual movements vary from year to year, the overall pattern is largely consistent[20], suggesting that this replaying of annual patterns is a reasonable approximation. In the absence of additional controls, the recent trend is predicted to continue, with numbers of reactors continuing to grow exponentially; this increase tends to be concentrated within South Western counties with limited spatial increase in the five years from 2010 to 2015.

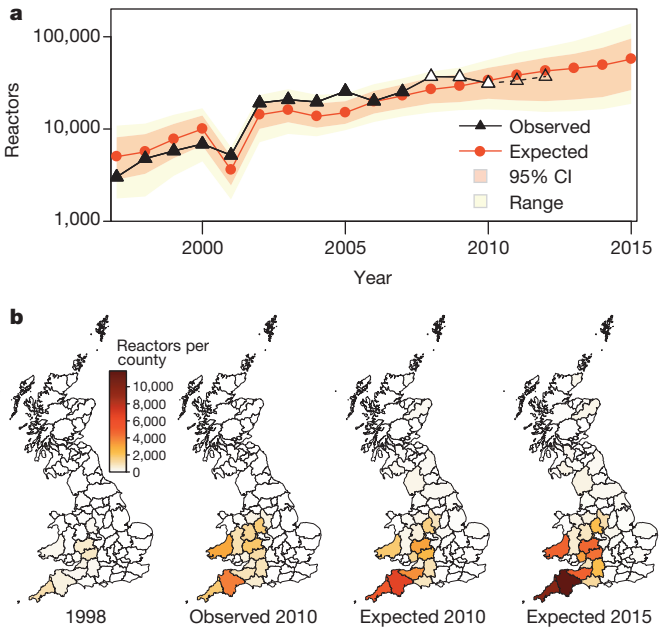

Figure 1 | Spatio-temporal comparison of model and data. **a**, Total number of reactors (cattle failing a test) per year. Triangles show the recorded data (filled black, years used for inference; filled white, years when detailed records are available; empty, years where only aggregate data are available). Red dots are the mean of 5,000 simulations; red shaded region is the combined 95% credible interval, whereas the yellow region is the range from 5,000 simulations. **b**, Spatial distribution of reactors at the county scale—showing observations from 1998 (initial conditions) and 2010; and mean of model replicates for 2010 and 2015.

We now use the model to investigate the driving mechanisms of transmission (Fig. 2). The farm-to-farm reproductive number measures the number of new secondary farms infected by each farm during its time harbouring infected animals (Fig. 2a). Transmission between farms occurs by two basic routes: either through the movement of infected cattle, or infection spread via the regional environment; we present these two separately. Movement is responsible for the majority (84%) of newly infected farms, with an over-dispersed distribution—where some farms are predicted to generate many secondary cases whereas around 90% of farms do not generate any secondary cases while harbouring infection. A similar pattern is predicted for transmission through the regional environment. This suggests that a small minority of farms act as superspreaders of infection, and therefore represents a more extreme version of the 80–20 rule (where 20% of farms are responsible for 80% of infection) reported for infection spread by cattle movements[17].

From our model results, we are also able to identify the three contributing causes of each herd breakdown (Fig. 2b): (1) movement of an infected animal onto the farm has occurred since the last clear test (red), (2) transmission of infection from the environment (including both the local farm and regional environment) has occurred since the last clear test (green), (3) where the last clear test missed (failed to detect) infected animals that have remained on the farm (blue), and combinations of these three. We predict that no single cause dominates: 40% of herd breakdowns have infections due to all three causes, and only 29% of herd breakdowns are attributable a single cause. Although transmission from the environment is the single largest contributing factor, even removing this route completely would only eliminate 15% of breakdowns. This multifactorial nature of transmission contributes to the difficulties of controlling bovine TB.

We now use the model to go beyond a retrospective analysis of the past, to consider the effect of alternative control mechanisms, as though they had been implemented in 2005 and run for six years until the end of 2010 (Fig. 3, Extended Data Table 2, Extended Data Fig. 5). We investigated

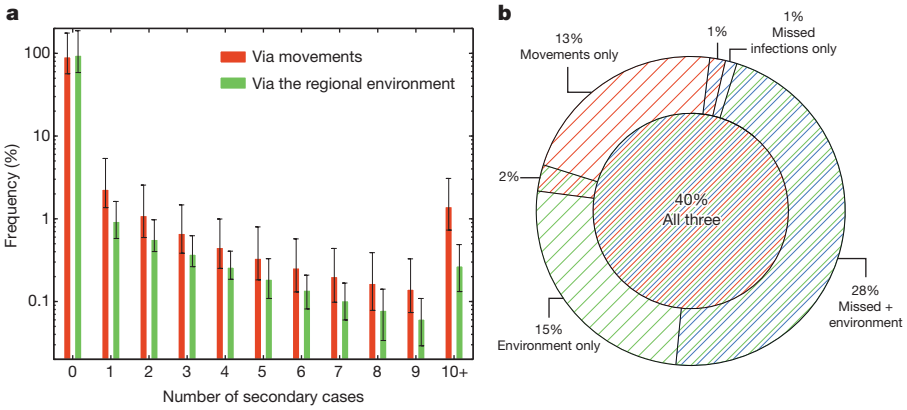

Figure 2 | Mechanisms driving transmission. **a**, Frequency distribution for infected farms generating a particular number of secondary infected farms (red, generated through movements; green, through local regional environment); note frequency is plotted on a logarithmic scale. **b**, Predicted causes of herd breakdowns (HBDs) in 2010. The area of each section corresponds to the proportion attributable to each cause (red, movements; green, local regional environment; blue, infected animals remain on a farm after testing). When multiple causes exist the area is shaded appropriately.

several control strategies (see Supplementary Material, Extended Data Table 2), but highlight here only those that have a substantial effect on the patterns of infection. Given that the cost of any control strategy is multifactorial, we show four distinct measures: the number of reactors, the number of cattle slaughtered, the number of herds tested and the number of herds under movement restrictions. Any strategy that can simultaneously lower all four of these is clearly beneficial.

Culling the entire herd if an animal tests positive (red bar) has by far the greatest effect, reducing the numbers of reactors, cattle slaughtered and farms under movement restrictions by over 80% compared to baseline in 2010 after 6 years of implementation. However, this strategy would necessitate a huge increase (approximately 20 fold) in the number of cattle slaughtered in the first year of operation; although this might be an acceptable cost if one is prepared to take a sufficiently long-term view. Vaccination of cattle which acts to slow the progression of infection (yellow), has a marked effect on all measures of bovine TB, but given that the vaccine offers only limited protection it does not have the effect that we usually associate with mass-vaccination campaigns; in particular even assuming 100% uptake and ignoring interference with the SICTT, vaccination is just sufficient to overturn the observed annual increase. A single additional mass testing program in 2005 (pale green), comparable to what was performed in Wales in 2008-09, obviously generates more tests but also identifies more cases and therefore places more farms under movement restrictions in the first three years. However, in later years this period of increased testing proves beneficial reducing all four measures below baseline.

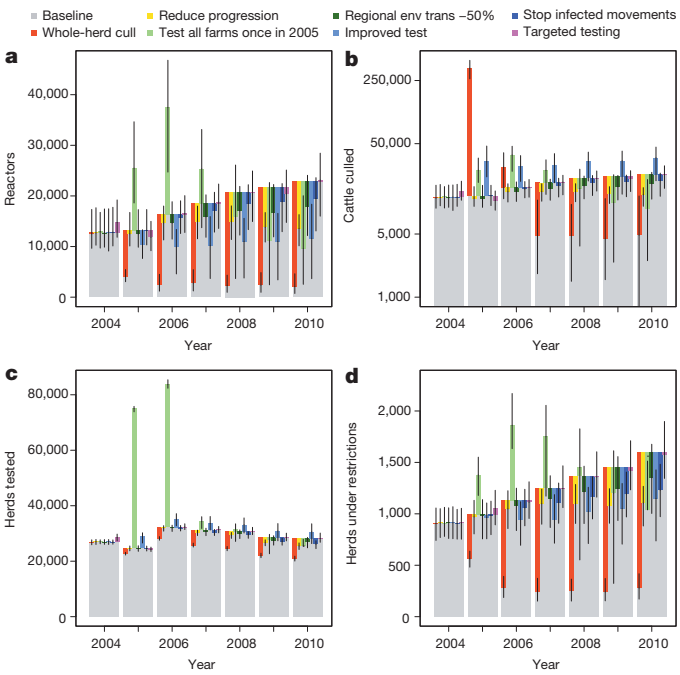

Figure 3 | Effect of different interventions assumed to begin in 2005 compared to a baseline of standard testing. **a–d**, Number of reactors in each year (**a**), number of slaughtered cattle (plotted on a logarithmic scale) (**b**), number of herds tested (**c**), number of herds under movement restrictions (**d**). Coloured bars show the mean deviation from the baseline scenarios; large grey bars show the baseline. The error bars represent the 95% combined prediction and credible interval from 1,000 simulations.

Other intervention strategies are aimed at particular transmission routes but their effectiveness is limited as no single route dominates the spread of infection. Decreasing local regional environmental transmission between farms by 50% (dark green), which may represent the potential ffect of a large-scale badger cull, has a relatively little effect – we still predict a sustained rise in reactors and farms under restrictions over the entire six years. Similarly, even preventing the movement of all infected animals (dark blue), thereby containing the spread of infection has limited benefit. The introduction of an improved test (light blue), which has higher sensitivity but lower specificity as a follow-up test after a herd breakdown may be compared to the use of gamma-interferon based testing. While reducing the number of herds under restrictions, such a test increases the number of slaughtered animals as more infected animals are detected by this additional test. Finally, although we have identified farms selling many animals as responsible for the majority of onward transmission, targeting such farms with additional standard skin (SICCT) tests is largely ineffective.

Our model highlights the mixture of transmission routes and range of spatial scales involved in the dynamics of bovine TB in Great Britain, and the consequent challenges of eradication. The multifactorial nature of transmission is reflected in our predictions for different interventions; only generic measures such as more national testing, whole herd culling or vaccination that affect all routes of transmission are effective at controlling the spread of bovine TB.

The role of badgers in the maintenance and spread of bovine TB is a matter of considerable scientific, political and public interest[5,25,26]. Owing to the absence of necessary spatial and population level data on badgers, our model does not explicitly include their role in transmission. The environmental reservoirs play a comparable function, although the contribution of reservoir species and contaminated pasture cannot be separated. The environment is essential in maintaining local infection and may be implicated in up to 80% of all herd breakdowns (Fig. 2b, green hashed area). However, we predict that the environment only contributes weakly to generation of new cases (Fig. 2a), and its effect decays fairly rapidly in the absence of infected cattle (Extended Data Table 1). Therefore, we predict that control of local badger populations and hence control of environmental transmission (Fig. 3, dark green bars) will have a relatively limited effect on all measures of bovine TB incidence.

Online Content Methods, along with any additional Extended Data display items and Source Data, are available in the online version of the paper; references unique to these sections appear only in the online paper.

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Supplementary Information is available in the online version of the paper.

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Author Contributions M.J.K. and E.B.-P. developed the model structure; E.B.-P. and G.O.R. developed the statistical methodology; all authors contributed to the writing of the manuscript.

Author Information Reprints and permissions information is available at www.nature.com/reprints. The authors declare no competing financial interests. Readers are welcome to comment on the online version of the paper. Correspondence and requests for materials should be addressed to M.J.K. (M.J.Keeling@warwick.ac.uk).

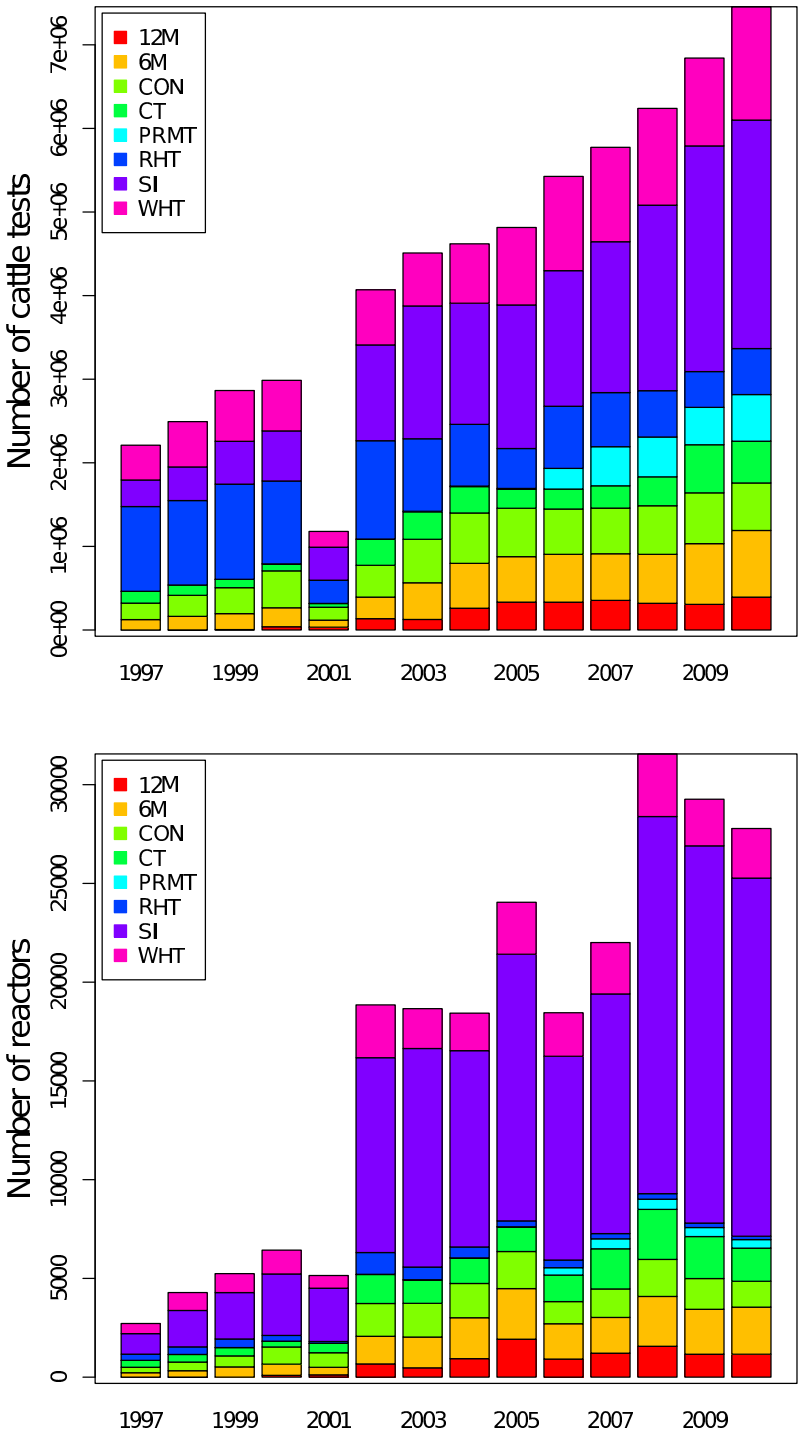
METHODS

All results presented here are derived from a stochastic model that captures the within farm dynamics across the GB cattle industry. Explicit mathematical formulae are given in the Supplementary Information, but the process can be described as follows. The number of cattle on each farm (labelled as an Agricultural Holding (AH) in the Cattle Tracing System) is updated by movements from the Cattle Tracing System, which includes the daily number of births, deaths (which are captured as movements off) and movements on and off. Routine testing occurs on days defined by the bovine TB test data. On testing, infectious and latent cattle are detected as reactors with probabilities ρ and $\rho\rho_E$ respectively. Detected animals are removed and the farm is placed under movement restrictions and re-tested in accordance with historical government policy.

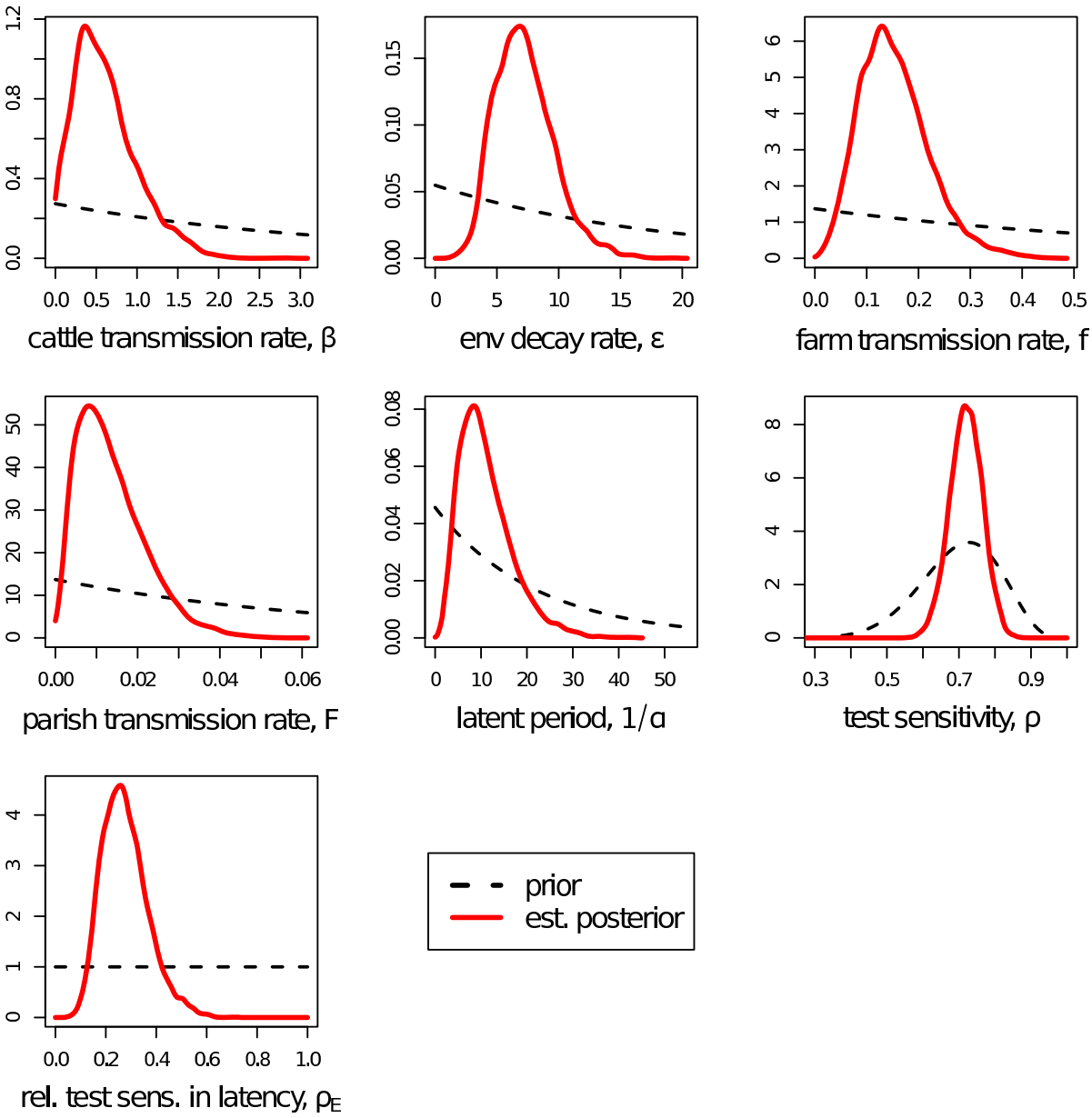
The force of infection experienced by cattle on a given farm on a given day is a composition of within-herd frequency-dependent transmission and transmission from the farm and local regional (parish) environment. This is governed by three parameters: β is the cattle-to-cattle transmission rate within a farm, while f and F are the levels of transmission from the immediate farm environment and local regional environment. The level of infection in the two localized environments is increased by infection on farms and decreased deterministically due to the natural decay of the pathogen. We stress that while the level of infectivity in the environment is modelled deterministically, all transmission events are stochastic.

Sequential Monte Carlo approximate Bayesian computation[23,24] (SMC ABC) was used to estimate the parameters of the model. SMC-ABC combines a particle filtering method with summary statistics and is ideal for stochastic models when the likelihood is difficult to define. Initial parameter sets are sampled from a multivariate prior distribution, and then from subsequent SMC rounds with a perturbation kernel. After each model replicate (where a replicate involves picking one sample of parameters and one stochastic simulation), model and data are compared using two summary statistics, chosen to reflect different epidemiological characteristics. A parameter set is accepted if the distance between the data summary statistic and model summary statistic is less than a threshold defined by the previous SMC round. The accepted parameter sets from the final SMC round approximate the posterior distribution from which point estimates and credible intervals were obtained. We chose two summary statistics: the number of infected farms per county per year and the number of reactors per county per year. The fitting procedure was done for the years 1998 to 2006, allowing three years (2007–2010) for unconstrained validation. Initial conditions were simulated using testing data between 1996 and 1998. We note that alternative methods of matching model to data, such as least squared errors and an approximate likelihood method produced comparable parameters.

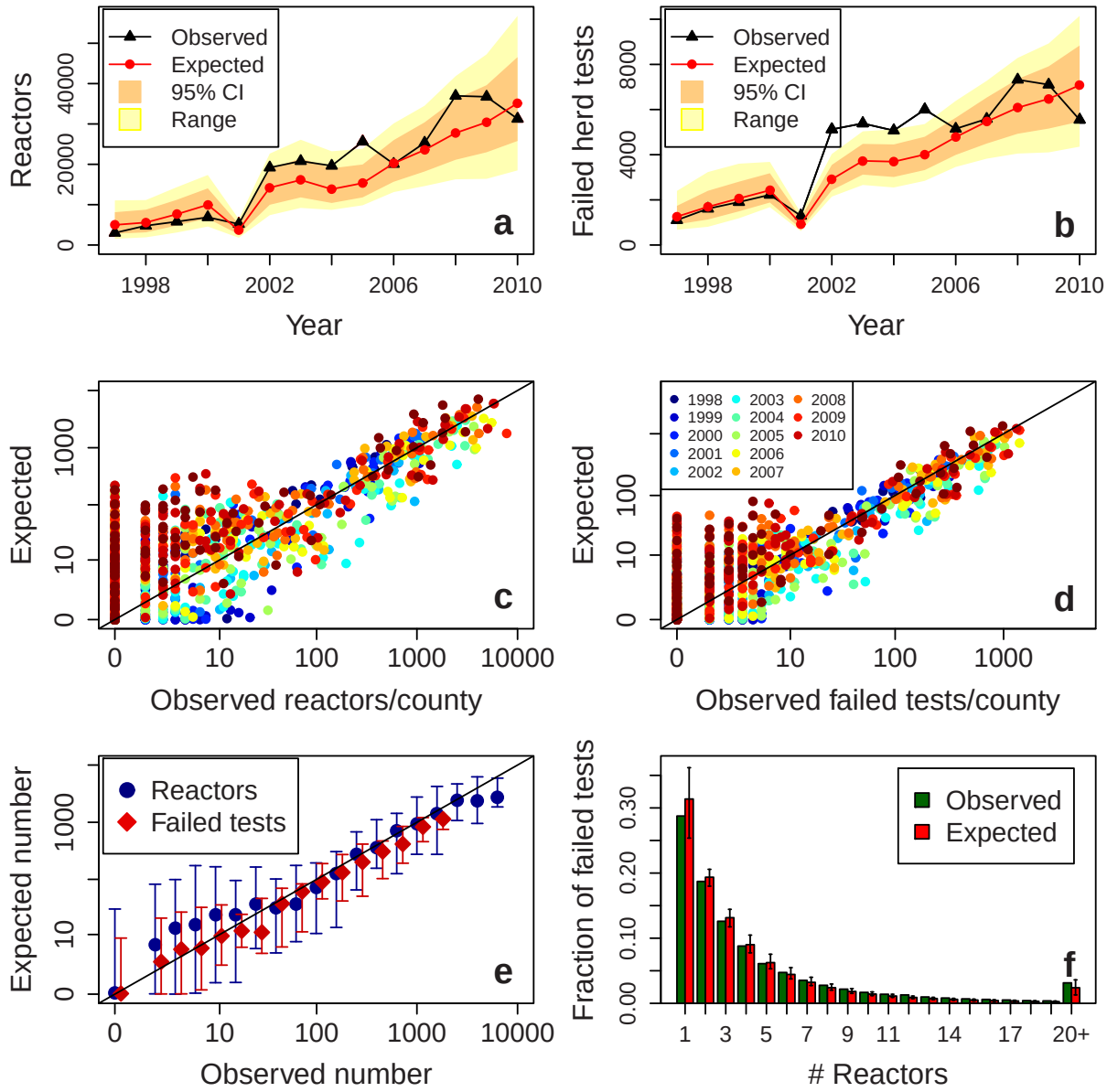
All results presented show the mean value and the 95% credible interval. The mean value represents the average over multiple stochastic simulations and over several accepted parameter sets from the SMC-ABC with choice of parameters weighted appropriately. The 95% credible interval is the range that contains 95% of all simulated epidemics, and therefore represents both parameter uncertainty and model stochasticity, showing how variable an individual simulation can be. Note that traditional confidence intervals on the mean are not shown as these can be reduced to zero by performing many simulations.



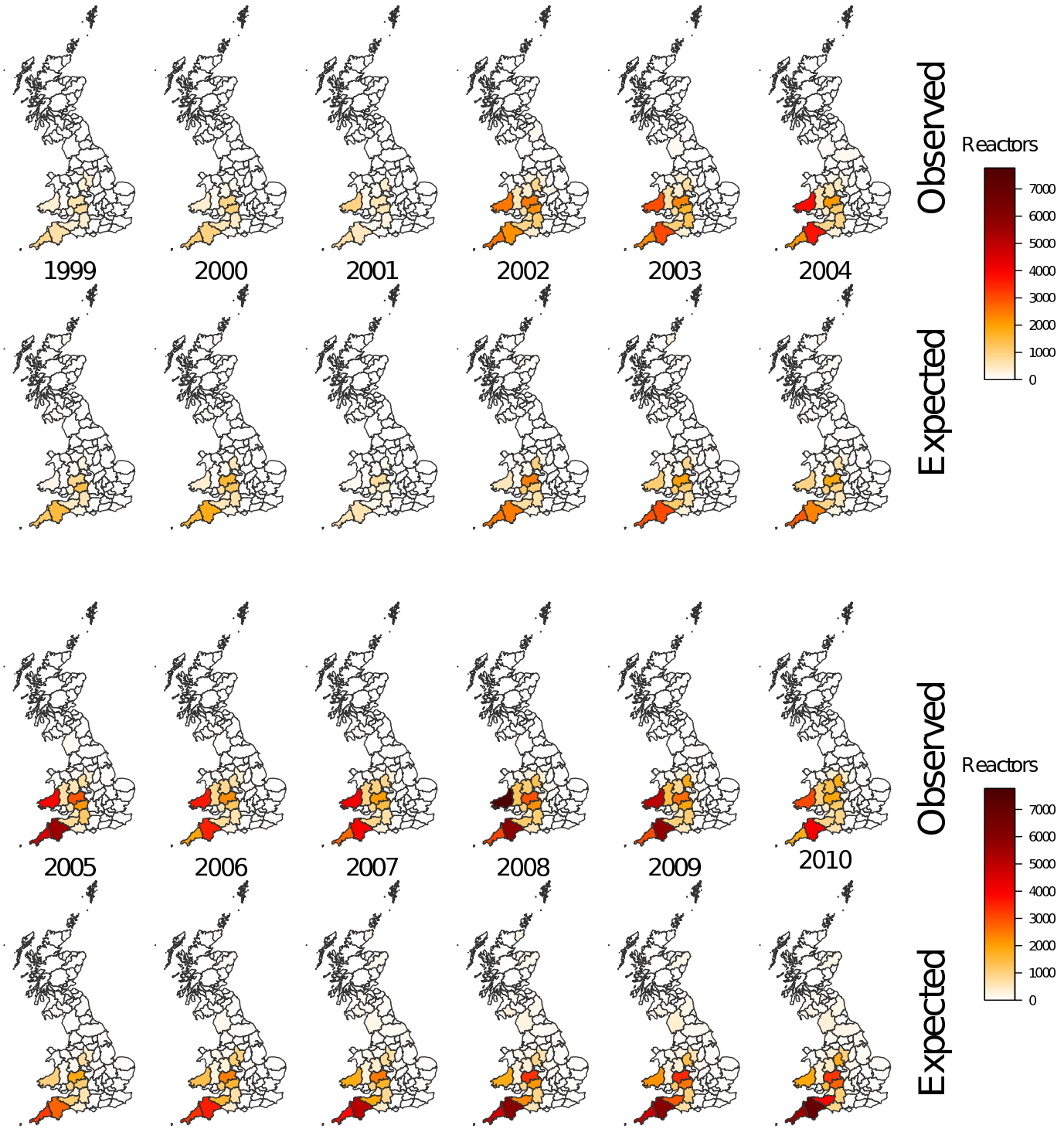
Extended Data Figure 1 | Historic testing patterns and identification of infected cattle. **a**, Number of single intradermal comparative cervical tuberculin (SICCT) tests carried out on cattle according to the reason for the test (test type). **b**, Number of reactors (cattle testing positive) by test type. Tests shown are: 12 month follow-up test (12M), 6 month follow-up test (6M), contiguous test (CON), check test (CT), pre-movement testing (PRMT), routine herd test (RHT), follow-up tests at sixty-day intervals (SI) and whole-herd tests (WHT).



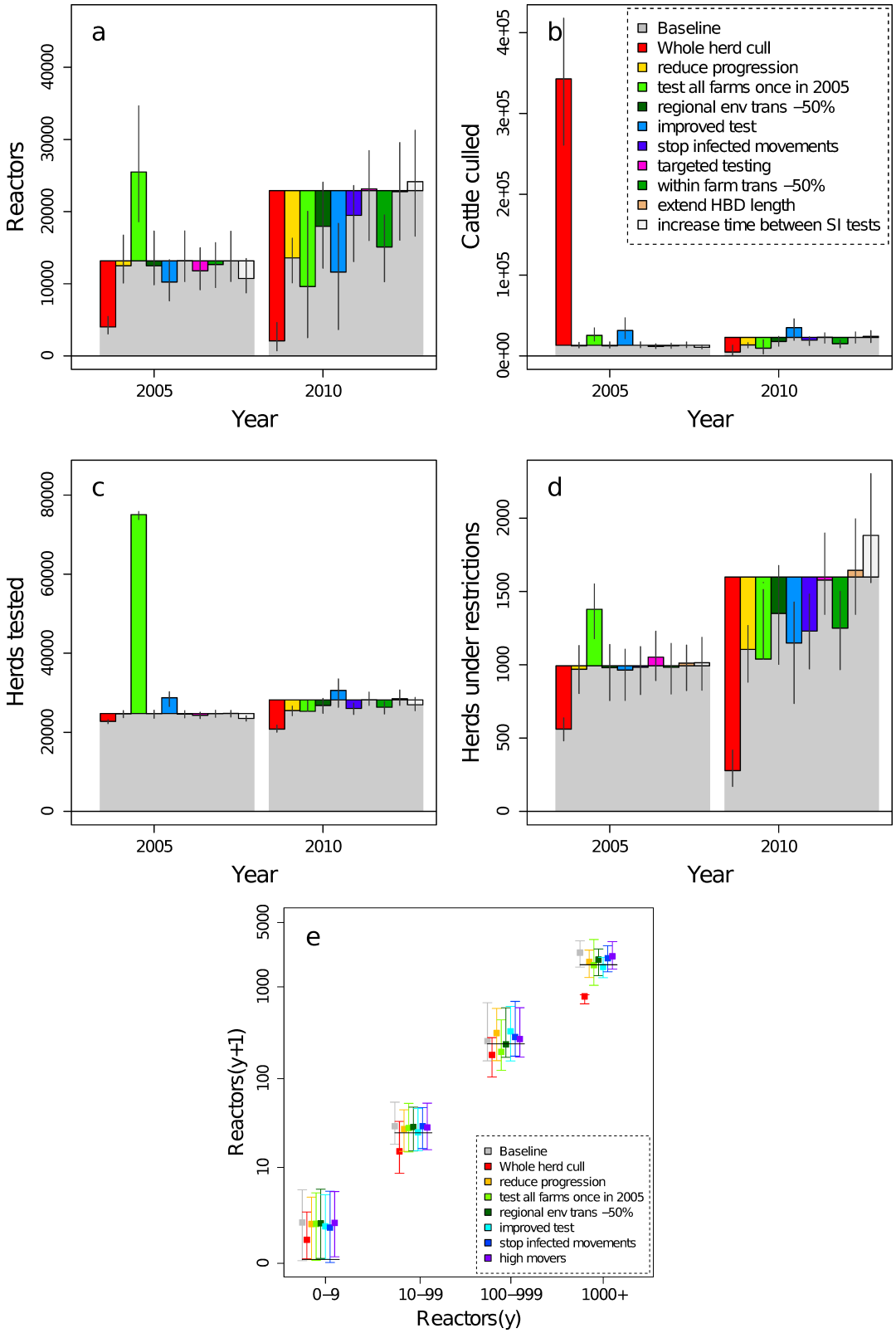
Extended Data Figure 2 | Prior and posterior distributions for the model parameters. Prior distributions (dashed lines) reflect captures uncertainty in the seven different parameters; only the test sensitivity, ρ, has a relatively informative prior based on estimates in the literature. Red curves show the posterior distribution as given by the ABC-SMC algorithm (see Supplementary Material).



Extended Data Figure 3 | Data–model comparisons. **a**, The number of reactors per year; **b**, the number of failed herd tests; **c**, observed and expected number of reactors per county and year; **d**, the observed and expected number of failed tests (at the herd level, per county and year); **e**, the observed and expected number of reactors and failed tests using logarithmic binning; **f**, the number of reactor cattle found per failed test. The error bars and red shaded regions denote the 95% prediction intervals; the yellow region in **a** and **b** shows the range from 5,000 simulations.



Extended Data Figure 4 | Observed and expected number of reactors per county per year. The expected value for each county and year is calculated as the (weighted) mean number of reactors produced by simulations using the posterior parameter sets, from 5,000 simulations.



Extended Data Figure 5 | A comparison of testing strategies using the stochastic model. **a**–**d**, The predicted model output compared to baseline predictions at the start (2005) and end (2010) of the implementation, for the ten controls listed in the Supplementary information and Extended Data Table 2, for reactors (**a**), cattle culled (**b**), herds tested (**c**) and herds under restrictions (**d**). **e**, For the baseline case and seven control measures listed in the main paper, the change in number of reactors at a county scale. Counties are aggregated into four bins (*x* axis) based on the number of reactors one year, and the expected number of reactors in the next year is shown on the *y* axis. Error bars denote the 95% prediction intervals.

Extended Data Table 1 | The biological meanings, prior distributions, point estimates (expected value from the posterior) and 95% intervals calculated from the marginal posterior distributions

Parameter: meaning	Prior	Posterior estimate (CI)
β: cattle-to-cattle transmission rate (years^{-1})	$\Gamma(1,3.65)$	0.61 (0.0503, 1.54)
Γ^{1}: average latent period (years)	$\Gamma(1,22)$	11.1 (3.29, 25.7)
$\varepsilon\Gamma$environmental decay rate (years^{-1})	$\Gamma(1,18.25)$	7.23 (3.57, 12.6)
f: farm environment-to-cattle transmission rate (years^{-1})	$\Gamma(1,0.73)$	0.154 (0.0488,0.309)
F: parish environment-to-cattle transmission rate (years^{-1})	$\Gamma(1,0.073)$	0.0136 (0.00288,0.0337)
ρ: test sensitivity (%)	$\beta(11.5,5)$	72 (63.3, 80.6)
ρ_E: relative sensitivity for latent cattle	U(0,1)	0.276 (0.136,0.488)

Note that given the scale of the values involved we quote all rates in terms of yearly timescales, although in practice the model operates using daily time steps.

Extended Data Table 2 | The estimated effect of control measures

Control	Reactors (CI)	Cattle slaughtered (CI)	Herd tests (CI)	Restricted herds (CI)
Baseline	22902 (16264, 29379)	22902 (16264, 29379)	28186 (26628, 29891)	1598 (1263, 1869)
Whole herd cull	2087 (728, 4624)	4849 (728, 13173)	20808 (20048, 21809)	278 (171, 418)
Reduced progression (vaccination)	13588 (10141, 16311)	13588 (10141, 16311)	25480 (24212, 26593)	1105 (882, 1268)
Additional test in 2005	9612 (2534, 20039)	9612 (2534, 20039)	25310 (25474, 27915)	1038 (1561, 1513)
Reduce parish transmission by 50%	17962 (12164, 24075)	17962 (12164, 24075)	26790 (24824, 28550)	1350 (1004, 1677)
Improved testing	11614 (3654, 18362)	34920 (19426, 45836)	30600 (26340, 33484)	1148 (736, 1427)
Stop movement of infected animals	19477 (13079, 23606)	19477 (13079, 23606)	26030 (24525, 27379)	1230 (972, 1482)
Target testing to larger farms	23146 (16004, 28446)	23146 (16004, 28446)	28234 (26821, 30143)	1578 (1344, 1898)
Reduce transmission on farms by 50%	15102 (10290, 19534)	15102 (10290, 19534)	26332 (24654, 27775)	1250 (967, 1500)
Longer movement restrictions	22763 (16049, 29561)	22763 (16049, 29561)	28476 (26818, 30690)	1645 (1344, 1995)
Extra delay between follow-up tests	24159 (16617, 31267)	24159 (16617, 31267)	26963 (25474, 28793)	1882 (1561, 2303)

The rows corresponds to the number of reactors, number of cattle culled, number of herd tests and number of herds under movement restrictions in 2010, assuming that control measures began in 2005 and continue until the end of 2010. The point estimates and 95% prediction intervals are from 100 iterations. Full descriptions of all strategies are given in the Supplementary Information, the first seven follow those described in the main text.