# Estimating the human health risk from possible BSE infection of the British sheep flock

**N. M. Ferguson, A. C. Ghani, C. A. Donnelly, T. J. Hagenaars & R. M. Anderson**

*Department of Infectious Disease Epidemiology, Faculty of Medicine, Imperial College of Science, Technology and Medicine, St Mary's Campus, Norfolk Place, London W2 1PG, UK*

**Following the controversial failure of a recent study[1] and the small numbers of animals yet screened for infection[2], it remains uncertain whether bovine spongiform encephalopathy (BSE) was transmitted to sheep in the past via feed supplements and whether it is still present. Well grounded mathematical and statistical models are therefore essential to integrate the limited and disparate data, to explore uncertainty, and to define data-collection priorities. We analysed the implications of different scenarios of BSE spread in sheep for relative human exposure levels and variant Creutzfeldt–Jakob disease (vCJD) incidence. Here we show that, if BSE entered the sheep population and a degree of transmission occurred, then ongoing public health risks from ovine BSE are likely to be greater than those from cattle, but that any such risk could be reduced by up to 90% through additional restrictions on sheep products entering the food supply. Extending the analysis to consider absolute risk, we estimate the 95% confidence interval for future vCJD mortality to be 50 to 50,000 human deaths considering exposure to bovine BSE alone, with the upper bound increasing to 150,000 once we include exposure from the worst-case ovine BSE scenario examined.**

The aim of this study was not to evaluate the probability that BSE has entered the sheep flock, but rather, given the pessimistic assumption that infection has occurred, to explore its potential extent and pattern of spread. In this, we used epidemiological parameter estimates from experimental BSE infections of sheep, and, where data are unavailable, assumed (given the observed similarities in BSE and scrapie pathogenesis in sheep) that other aspects of disease epidemiology resemble those of scrapie. Analyses were constrained to be consistent with the failure to detect the BSE agent in a small sample of 180 brains[2] collected between 1996 and 2000 from sheep diagnosed with scrapie (giving an upper bound for BSE prevalence within apparently scrapie-affected sheep of 2%; Fig. 1a), and are also broadly consistent with an assessment of historical exposure of the ovine population to meat and bonemeal (MBM)[3].

Key to our analysis are estimates of the infectivity in animal tissues during disease incubation. Data are limited for BSE in sheep acquired by oral challenge, but using new experimental results and published data from studies of both scrapie[4–7] and sheep BSE[8,9] pathogenesis, we constructed an infectiousness profile. This profile was based on temporal changes in the density of the agent in different tissues, weighted by the proportion of such tissue in the host's body (Fig. 1b). This profile differs from that of BSE in cattle[10,11], with a more rapid rise in overall infectivity early in the incubation period in a wide range of tissues (for example, spleen and lymph nodes). The sheep–human infectiousness profiles (Fig. 1b) adjust for tissue-specific usage in food[12] and the effect of the 1997 specified risk materials (SRM) ban in sheep.

The distribution of the BSE incubation period in sheep is not well characterized, but on the basis of the limited available data, we used

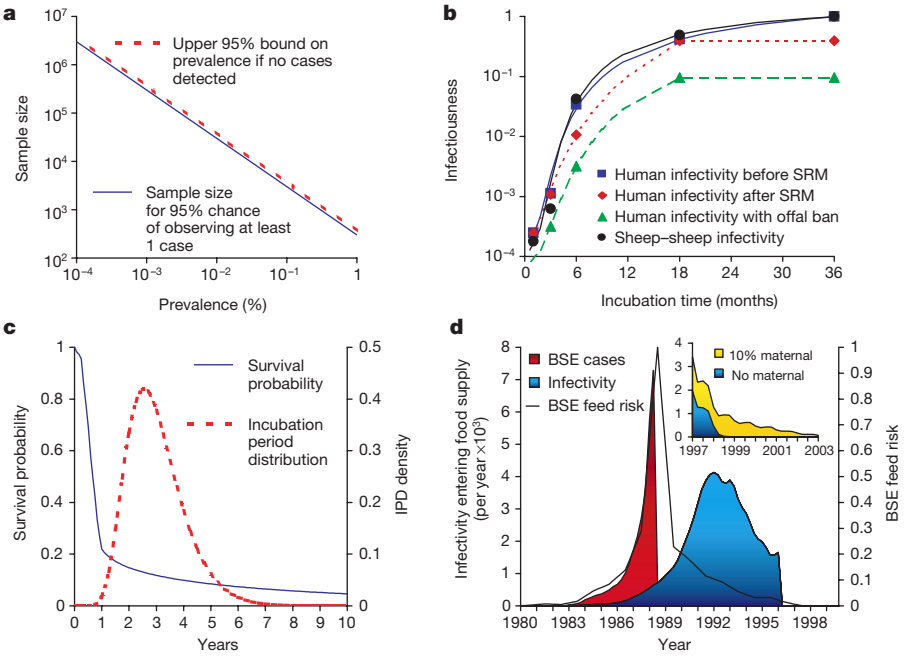


**Figure 1** Epidemiological inputs to transmission model. **a**, Relationship between sample size and detectable prevalence in screening studies. **b**, Infectiousness of sheep as a function of time from infection (see Methods). Sheep and human profiles are separately normalized to give maxima of 1. **c**, Survival probability of sheep as a function of age, and assumed incubation period distribution (IPD) of BSE in sheep. The survivorship function was estimated from annual data from the June census, slaughter, export and disappearance statistics, and data on the seasonality of lamb slaughter. **d**, Before mid-1988, both reported and unreported clinical BSE cases could be used for food (red-shaded curve). After that time, BSE was made notifiable and cases were destroyed, so we assume none entered food. The blue-shaded curve represents the rate of slaughter (per year) of pre-clinical infected cattle weighted by infectiousness relative to disease onset, assuming infectiousness grows at the exponential rate of 4 per year. The over-30-month scheme ended most bovine exposure in 1996, with estimates of residual levels (inset) being dependent on the extent of maternal transmission of BSE. The solid black curve represents the estimated infection hazard to cattle and sheep posed by infectivity in contaminated feed, relative to the maximum level reached in 1988.

an offset gamma distribution with a mean of 3 years (Fig. 1c) and substantial variance (intended to capture variation caused by dose dependency and host genotype) both for sheep infected by feed and those infected horizontally. Pathogenesis and susceptibility are dependent on the genetic background of the host[13–15], and genotype frequencies of the key polymorphisms vary considerably within and between flocks of different breeds[16,17]. Collation of limited available data suggests that roughly one-third of sheep in Great Britain (England, Scotland and Wales) have BSE-susceptible genotypes (see Supplementary Information). Exposure of the sheep flock to the BSE agent via contaminated feed (Fig. 1d) is assumed to mirror (albeit at a much lower level) that of British cattle, as estimated in back-calculation analyses of the BSE epidemic[18,19]. Exposure is likely to have occurred as far back as the early 1980s, before the disease was identified in cattle[18,19]. As for BSE in cattle[20], host survivorship is important given the long incubation period of the disease. Best estimates (see Supplementary Information) are presented in Fig. 1c (giving a mean life expectancy of 1.5 years), although more precise data are urgently required, perhaps based on a sheep equivalent of the British Cattle Tracing System (http://www.bcms.gov.uk).

Capturing the information in Fig. 1 requires a framework that integrates the temporal evolution of BSE pathogenesis in the individual host (incorporating age-dependent susceptibility and exposure) into a mathematical model of transmission within (including seeding and spread) and between flocks. This model builds on previous analyses of within- and between-flock transmission of scrapie[21,22], and consists of a set of nonlinear partial differential equations detailing the transmission dynamics of the agent and the demography of the sheep flock under time-dependent exposure to BSE-contaminated feed. The dynamics of disease transmission within the sheep population are determined by the magnitude of the respective basic reproduction numbers of the agent within a flock ($R_0^A$) and between flocks ($R_0^F$). The reproduction numbers define the average number of secondary cases or flocks generated by one primary case or infected flock in a susceptible flock or population of flocks. We considered three representative scenarios: (I) $R_0^A > 1$, $R_0^F < 1$—self-sustaining transmission within a flock but not between flocks; (II) $R_0^A > 1$, $R_0^F > 1$—the worst-case scenario for future spread, with spread within and between flocks inducing an expanding epidemic; and (III) $R_0^A < 1$, $R_0^F < 1$—the best-case scenario, with non-self-sustaining transmission both within and between flocks (see Fig. 2 for precise parameter values).

For each scenario, the level of flock infection due to MBM exposure was adjusted to give BSE prevalence below 2% of scrapie prevalence at present (consistent with the results of ongoing studies screening sheep brains). Judgements of scenario consistency therefore depend on the estimated prevalence of scrapie in British sheep, with such estimates being based on limited data from detailed surveys of specific flocks (using clinical criteria for diagnosis) and a postal survey of farmers intended to characterize national historical patterns of scrapie incidence[23,24]. The uncertainties in interpreting these data (giving estimates of infection prevalence anywhere between 0.1% and 1%, see Supplementary Information) make large-scale (Fig. 1a) screening of the national flock for transmissible spongiform encephalopathies (TSEs) a priority. In constructing the scenarios, we assumed a scrapie prevalence of about 0.3%, with scenarios II and III then corresponding to a BSE prevalence of 0.5% that of scrapie, and scenario I to a prevalence of about 2% that of scrapie. Scenario I was thus intended to represent something of a worst case in terms of the numbers of animals infected to date, although we cannot exclude the possibility of even larger epidemics given the limited data currently available.

Figure 2 displays the epidemiological characteristics of these scenarios in terms of within-flock and overall prevalence (Fig. 2a–c), and their implications for human exposure via food (Fig. 2d–f). The estimates of exposure incorporate data on human

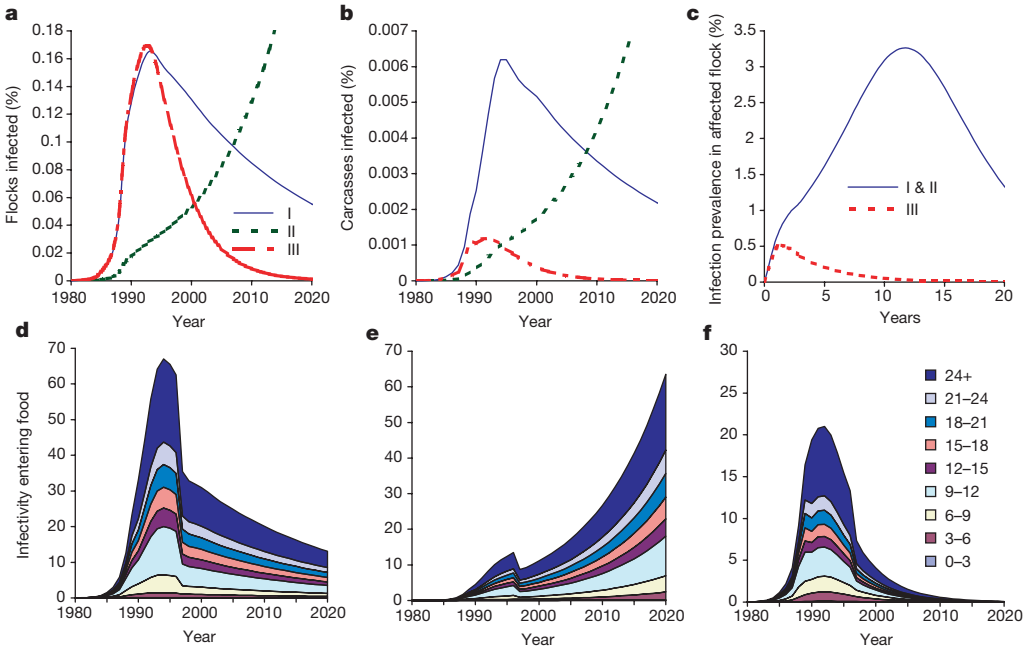


**Figure 2** Epidemiological characteristics of BSE transmission scenarios in sheep. $R_0^A = 2$, $R_0^F = 0.8$ and $\beta_B = 0.2\%$ per year for scenario I; $R_0^A = 2$, $R_0^F = 1.5$ and $\beta_B = 0.025\%$ per year for scenario II; and $R_0^A = 0.8$, $R_0^F = 0.5$ and $\beta_B = 0.2\%$ per year for scenario III; where $\beta_B$ is the assumed flock infection incidence rate per unit of feed risk profile shown in Fig. 1c. By comparison, $\beta_B$ values of 0.2% and 0.025% represent per-animal infection hazards about 50- and 400-fold less than that experienced by cattle. **a**, Proportion of flocks affected through time for scenarios I–III. **b**, Proportion of carcasses entering the food supply infected (at any incubation stage) with BSE. **c**, Prevalence in affected flock as a function of time since initial entry of infection into the flock. **d**–**f**, Estimated infectivity (in units of maximally infectious carcasses) entering the food supply under scenarios I, II and III, respectively, derived from the infectiousness profiles shown in Fig. 1a. Varying the proportion of flocks affected with BSE (shown in **a**, and determined by $\beta_B$) scales the exposure curves in **d**–**f** proportionately.

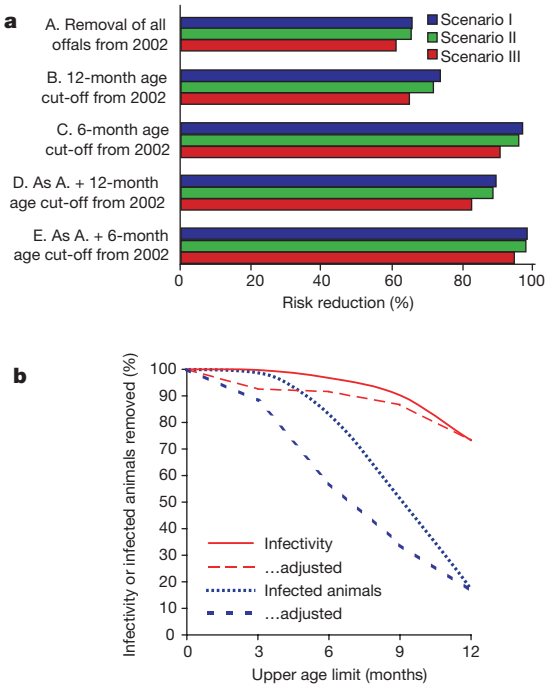


**Figure 3** Impact of risk-reduction measures. **a**, Estimated relative impact of various measures on current exposure to BSE infectivity in sheep food products for scenarios I–III. 'Removal of all offals' corresponds to a ban on all internal organs and central nervous system tissue of sheep entering the human food supply, but does not assume removal of lymph nodes. Estimates presented were calculated assuming that age restrictions would not change slaughter patterns. **b**, Estimated impact of imposing age restrictions as a function of the upper age limit imposed for scenario I. Effects on infectivity and total number of infected animals entering the food supply are shown, with dashed curves showing how the impact is reduced if slaughter patterns are adjusted after such a measure, such that all animals currently slaughtered under 12 months old are then slaughtered under the upper age limit imposed.

consumption of ovine material (see Supplementary Information), which indicate that 67% of lambs and 83% of sheep older than 12 months slaughtered for consumption in 1999 were consumed domestically in the UK. Very few live sheep are imported into Great Britain, and most imported lamb meat originates from New Zealand, which has never detected signs of BSE or scrapie infection in either its bovine or ovine populations. Thus the potential risk from BSE-infected sheep arises from home-bred animals.

The sudden drop in human exposure in the late 1990s (Fig. 2d–f) is due to the SRM ban for sheep (banning the consumption of the skull, tonsils and spinal column of animals older than 12 months and the spleen of all animals). In the worst-case scenario (II), the degree of risk is still rising steeply, whereas for the other scenarios risk is falling, approaching very low levels in the best case (III). Critically, even in the worst-case scenario, the great majority of past exposure of the human population to BSE arose from cattle (Fig. 1d). However, for all three scenarios considered (and therefore assuming BSE did enter the sheep flock), the number of maximally infectious sheep entering the food supply in Great Britain at present is estimated to be greater than the number of maximally infectious cattle[18,19] (Fig. 1d, inset). This comparison equates the risk from one maximally infectious sheep with that of a cow, despite the difference in body mass, an assumption motivated by the evidence of more widespread distribution of infectivity in sheep.

Potential risk-reduction strategies include restrictions on the age of sheep slaughtered for consumption and enhanced tissue-based controls to reduce the amount of infectivity entering the food supply; additional measures based on flock history or ram genotype might also be possible but are not considered here. Combined tissue- and age-based restrictions are estimated to reduce current and future risk by at least 80% for all three sheep BSE scenarios considered (Fig. 3a). This is encouraging, but the precise values shown depend on the accuracy of the data on the development of infectivity in different tissues of BSE-infected sheep. Furthermore, verifying the age of sheep is difficult without an identification scheme, so in the short term it would be feasible only to exploit seasonal birthing patterns and dental indicators to impose approximate age restrictions. How the impact of 12-month age restrictions might be reduced by compensatory changes in slaughter patterns is shown in Fig. 3b.

Translation of the patterns of relative exposure through time into measures of absolute risk requires estimation of potential vCJD mortality in the human population of Great Britain. Given the uncertainty in the parameters determining such predictions (in particular, the incubation period distribution and human susceptibility), analyses must be based on the best available estimates of temporal changes in human exposure to infected material. The confidence bounds on vCJD mortality shown in Table 1 characterize human exposure by infectivity-weighted estimates of the numbers of BSE-infected cattle (Fig. 1d) and sheep (Fig. 2) slaughtered for consumption through time (correcting for early under-reporting of cattle BSE incidence). We modelled the vCJD epidemic solely in the 40% of the population that are methionine homozygous at prion protein (PrP) codon 129, assuming no other genetic variation in susceptibility. Currently no case data exist with which to constrain epidemic scenarios for other genotypes, but if future cases are diagnosed then upper bounds on epidemic size will increase. Compared with our previous estimates[25], upper bounds on epidemic size

**Table 1 95% confidence intervals for future vCJD deaths**

| Cattle only* | 2001–2002 | 2001–2005 | 2001–2010 | 2001–2020 | 2001–2040 | 2001–2080 |
|---|---|---|---|---|---|---|
| A | 20–100 | 40–400 | 40–1,200 | 40–5,000 | 40–20,000 | 50–50,000 |
| B | 20–100 | 40–400 | 40–1,200 | 40–5,000 | 40–20,000 | 40–40,000 |
| C | 20–100 | 30–400 | 40–1,400 | 40–7,000 | 40–40,000 | 40–90,000 |
| D | 20–100 | 30–400 | 30–1,300 | 40–7,000 | 40–40,000 | 40–100,000 |
| E | 20–100 | 40–350 | 40–1,100 | 40–5,000 | 40–20,000 | 50–35,000 |
| Cattle and sheep† | | Sheep:cattle infectivity ratio | | 2001–2020 | 2001–2040 | 2001–2080 |
| Scenario I | | 1:1 | | 40–5,000 | 40–20,000 | 40–60,000 |
| | | 10:1 | | 40–5,000 | 50–30,000 | 50–70,000 |
| Scenario II | | 1:1 | | 20–5,000 | 20–20,000 | 20–70,000 |
| | | 10:1 | | 40–5,000 | 70–30,000 | 110–150,000 |
| Scenario III | | 1:1 | | 40–5,000 | 40–20,000 | 40–50,000 |
| | | 10:1 | | 40–5,000 | 40–20,000 | 40–50,000 |

* Cattle-only calculations assume: A, BSE exposure in humans was proportional to the BSE cases before the mid-1988 in addition to infected animal slaughter rates shown in Fig. 1c; B, as A but excluding exposure to reported BSE cases; C, as A but additionally fitting to at least three vCJD deaths reported before 2001 being infected before 1986, as suggested by analysis of the Queniborough cluster; D, as A but assuming the 1989 specified bovine offal ban reduced human exposure by at least 80%; E, as A but restricting the mean incubation period to be no longer than 60 years.
† Calculations for cattle and sheep assume exposure as A from cattle plus exposure from sheep as in Fig. 2d–f from scenarios I–III, assuming sheep are equally or 10 times as infectious as cattle. Short-term predictions for these scenarios are similar to those excluding sheep.

in the absence of BSE in sheep have reduced (largely as a result of a change in statistical methods), being in the range 50,000–100,000 depending on the assumptions made. These values are substantially greater than recently published estimates derived assuming a cruder representation of past trends in human exposure to BSE infectivity[26,27]. Best-fit estimates associated with 2001–2080 confidence bounds generally lie in the range 100–1,000, but the fits of the model vary little for fewer than 10,000 deaths. It should be noted (Table 1, E) that large epidemics are still possible even if the mean incubation period is less than 60 years. In the presence of BSE in sheep, the upper bound is substantially increased only if BSE is capable of becoming endemic in the national flock (scenario II).

Although the risk analysis presented here incorporates a wide variety of available information into a single integrated framework, its reliability depends on the quality and volume of data available for parameter estimation. The limited data highlight the need for further studies to measure: (1) scrapie and BSE prevalence in sheep (stratified by age), employing sample sizes sufficiently large to detect low prevalence; (2) sheep survivorship more precisely; (3) BSE infectivity in sheep quantitatively, by stage of incubation, tissue and sheep genotype; (4) age-dependent susceptibility to TSE infection in a variety of species, including sheep and cattle; and (5) historical trends in bovine and ovine tissue consumption. Molecular typing methods giving rapid results[28,29] are clearly valuable for prevalence screening and strain typing (whether for BSE or scrapie), but study design should take account of test sensitivity and therefore consider which tissue should be tested (brain not necessarily being optimal). Given the uncertainty regarding the presence of BSE in the British sheep flock, such large-scale testing is a priority. In the interim, this analysis informs prevalence survey design and policy consideration of the potential benefits of additional risk-reduction measures. □

## Methods

Additional detail is provided as Supplementary Information.

### Modelling transmission of BSE in sheep

Infectiousness of a BSE-infected sheep as a function of time $\tau$ since infection (relative to the incubation period $T$) was estimated by fitting the parametric form $\rho(\tau/T) = \exp(a(\tau/T)^b/((\tau/T)^b + c))$ to tissue-specific infectivity data from studies of pathogenesis of ovine BSE[8,9] and scrapie[4–7]. The data were weighted by total tissue mass when estimating sheep-to-sheep infectiousness, and by the proportion of tissue mass entering food when estimating human exposure to infectivity (Fig. 1b). This approach captures the impact on overall infectiousness of between-tissue variation in PrP accumulation during pathogenesis of ovine BSE—namely, that some tissues (for example, lymph nodes) rapidly develop detectable infectivity, the growth of which later slows and/or saturates, whereas others (for example, brain) only exhibit high levels of infectivity close to clinical onset.

Because mass-action models cannot capture the observed clustering of cases[20], we developed a model of TSE transmission in sheep that incorporated three relevant tiers: (1) the individual animal—capturing age-dependent susceptibility and exposure, and pathogenesis of disease; (2) the individual flock—capturing within-flock sheep-to-sheep transmission; and (3) the national population of flocks—capturing between-flock transmission and exposure to contaminated feed.

Assuming homogenous mixing within a flock, the deterministic susceptible-infected model is:

$$\frac{\partial x}{\partial t} + \frac{\partial x}{\partial a} = -(\Lambda(t)\kappa(a) + \mu(a))x \qquad x(t,0) = B \qquad \mu(a) = -\frac{1}{S}\frac{\mathrm{d}S}{\mathrm{d}a}$$

$$\frac{\partial y}{\partial t} + \frac{\partial y}{\partial a} + \frac{\partial y}{\partial \tau} = -(F_A(\tau) + \mu(a))y \qquad F_A(\tau) = \frac{f_A(\tau)}{1 - \int_0^\tau f_A(\tau')\mathrm{d}\tau'}$$

$$y(t,a,0) = \Lambda(t)\kappa(a)x(t,a)$$

$$\Lambda(t) = \beta_A \int_{\tau=0}^{t}\int_{T=\tau}^{\infty} F_A(T)\rho(\tau/T)y(t,a,\tau)\mathrm{d}T\mathrm{d}\tau \qquad y(0,a,0) = \frac{\kappa(a)Y_0}{\int \kappa(a)\mathrm{d}a}$$

where we denote the densities of susceptible and infected animals of age $a$ at time $t$ by $x(t, a)$ and $y(t,a,\tau)$; time from infection by $\tau$; the incubation period distribution by $f_A(\tau)$ (see Fig. 1c); the force of infection by $\Lambda(t)$; the transmission coefficient for horizontal spread by $\beta_A$; the fixed birth rate by $B$; the mortality rate by $\mu(a)$; and age-dependent susceptibility by $\kappa(a)$ (conservatively assumed to be constant for the first 12 months of life and zero thereafter). The number of animals infected at the start of a flock outbreak is $Y_0$.

Assuming that the infectiousness at time $t$ of a flock infected at $t = 0$ to other flocks is proportional to the within-flock force of infection $\Lambda(t)$, we modelled transmission within a population of 100,000 flocks of 400 animals each. Genetic heterogeneity in susceptibility to infection was modelled at the flock level, with 33,000 flocks assumed to have all animals susceptible and the remainder completely resistant. The introduction of infection into a flock from an external source (contaminated feed or other sheep) was modelled as a rare event, initially infecting 1% of animals.

The infection dynamics of flocks were modelled using an SIRS framework, whereby flocks are initially 'susceptible' to infection, enter an 'infected' state of extended duration, 'recover' and become resistant to further infection (for a period of 20 years), then revert to the 'susceptible' state. The flock-level 'recovery' process approximates flock outbreak extinction mechanisms, such as demographic stochasticity (likely to be critical[30] given the low reported prevalence of scrapie), control measures and selection for scrapie-resistant genotypes.

Denoting the number of susceptible flocks at time $t$ by $s(t)$, flocks infected time $\theta$ ago by $h(t, \theta)$ (with infectivity $\Lambda(\theta)$ from the within-flock model) and recovered/resistant flocks by $r(t)$, model dynamics are described by:

$$\frac{\mathrm{d}s}{\mathrm{d}t} = \xi r - \Omega(t)s \qquad \Omega(t) = \beta_F \int_{\theta=0}^{\infty} \Lambda(\theta)h(t,\theta)\mathrm{d}\theta + \beta_B\phi(t)$$

$$\frac{\partial h}{\partial t} + \frac{\partial h}{\partial \theta} = -F_F(\theta)h \qquad F_F(\theta) = \frac{f_F(\theta)}{1 - \int_0^\theta f_F(\theta')\mathrm{d}\theta'}$$

$$\frac{\mathrm{d}r}{\mathrm{d}t} = \int F_F(\theta)h(t,\theta)\mathrm{d}\theta - \xi r \qquad s(0) = N \quad h(t,0) = \Omega(t)x \quad h(0,\theta) = 0$$

Here, $f_F(\theta)$ is the 'incubation period' distribution for flocks (gamma distributed with mean 6 years; see Supplementary Information); $\Omega(t)$ the force of infection for flocks at time $t$; $\beta_F$ and $\beta_B$ the coefficients for between-flock transmission and exposure of flocks to contaminated feed; $\phi(t)$ the relative risk from contaminated feed at time $t$ (estimates from refs 18, 19); and $\xi$ (= 0.05 per year) the rate at which recovered flocks re-enter the susceptible pool. The values of $\beta_A$ and $\beta_F$ corresponding to required values of $R_0^A$ and $R_0^F$ were determined numerically.

Exposure of the human population to BSE infectivity in sheep was represented by the number of infected animals slaughtered for food (stratified by age and incubation stage, weighted by infectivity; Fig. 2d–f). The effectiveness of risk-reduction measures was evaluated by examining the distribution of exposure as a function of animal age, and by comparing results obtained from the infectivity profiles corresponding to current SRM controls and a ban on all offal.

It should be noted that this model framework reproduces observed within-flock and overall scrapie incidence patterns well if run to endemicity (results not shown).

### Prediction of vCJD incidence

As in earlier work[25], the probability density that an individual develops clinical disease at time $t$ and age $a$ is

$$p(t,a) = S_H(t,a)\int_{t-a}^{t} f(t-u)I(u,a-t+u)\exp\left[-\int_0^u I(u', a-t+u')\mathrm{d}u'\right]\mathrm{d}u$$

where $S_H(t,a)$ is the probability that someone born at time $t-a$ will survive to age $a$ (derived from census data) and $f(t-u)$ is the incubation period distribution (modified lambda distribution). The infection hazard is given by

$$I(t,a) = \beta g(a)\left(\nu_c(t)\int \Omega_c(z)\omega_c(z,t)\mathrm{d}z + \nu_s(t)\int \Omega_s(z)\omega_s(z,t)\mathrm{d}z\right)$$

where $\beta$ is the transmission coefficient and $g(a)$ an age-dependent susceptibility/exposure function (uniform with gamma-distributed tails). For each infectious species $i$ (C for cattle, S for sheep), $\Omega_i(z)$ is the relative infectiousness of an animal time $z$ from disease onset, $\nu_i(t)$ is the time-dependent effectiveness of risk-reduction measures (for cattle, this is parameterized as a step reduction in 1989 due to the specified bovine offal ban), and $\omega_i(z,t)$ is the number of animals slaughtered for consumption stratified by time and incubation stage. (Values for sheep were obtained from the above model, and those for cattle used updated back-calculation estimates[18,19], with $\int\Omega_c(z)\omega_c(z,t)\mathrm{d}z$ plotted in Fig. 1d.)

The relative infectiousness of cattle by incubation stage was assumed to increase exponentially from a baseline level to a maximum value before onset of clinical signs[25]. We restricted analysis to the 40% of the population that are methionine homozygous at PrP codon 129, assuming no other genetic variation in susceptibility.

Through numerical solution of the inverse problem (see Supplementary Information for further details), $\beta$ was calculated as a function of case incidence, allowing incidence of vCJD deaths in any time interval to be treated as a model parameter. This enabled nonlinear optimization techniques to be used to obtain likelihood profiles by fitting the model to the joint age- and time-stratified mortality data to the end of 2000. We obtained 95% confidence bounds from the one-dimensional likelihood profiles. Infection prevalence is poorly constrained by the observed incidence data, and can range from being equal to mortality to 100-fold larger, with little effect on model fit.

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The authors declare that they have no competing financial interests.

Correspondence and requests for materials should be addressed to N.M.F. (e-mail: neil.ferguson@ic.ac.uk).

# Reputation helps solve the 'tragedy of the commons'

**Manfred Milinski, Dirk Semmann & Hans-Jürgen Krambeck**

*Department of Evolutionary Ecology, Max Planck Institute of Limnology, 24306 Plön, Postfach 165, Germany*

**The problem of sustaining a public resource that everybody is free to overuse—the 'tragedy of the commons'[1–7]—emerges in many social dilemmas, such as our inability to sustain the global climate. Public goods experiments[4], which are used to study this type of problem, usually confirm that the collective benefit will not be produced. Because individuals and countries often participate in several social games simultaneously, the interaction of these games may provide a sophisticated way by which to maintain the public resource. Indirect reciprocity[8], 'give and you shall receive', is built on reputation and can sustain a high level of cooperation, as shown by game theorists[9–11]. Here we show, through alternating rounds of public goods and indirect reciprocity games, that the need to maintain reputation for indirect reciprocity maintains contributions to the public good at an unexpectedly high level. But if rounds of indirect reciprocation are not expected, then contributions to the public good drop quickly to zero. Alternating the games leads to higher profits for all players. As reputation may be a currency that is valid in many social games, our approach could be used to test social dilemmas for their solubility.**

Since Hardin[1] first described the 'tragedy of the commons', this type of social dilemma has been studied extensively by political and social scientists, economists and evolutionary theorists (see refs 2–7). Many of the experiments that have been carried out are a variant of the standard design[4]. In this model, four students seated at a table are each given an endowment of £5. They are then told that they can each choose to invest some or all of their £5 in a group project by putting, without discussion, an amount between £0 and £5 in an envelope. The experimenter will collect the 'contributions', total them up, double the amount, and then divide this money among the group.

The economic/game-theory prediction is that no one will ever contribute anything because each £1 contributed yields only £0.50 to its contributor, no matter what the others do. This is a public goods problem because the group would be best off (taking home £10 each) if all contributed £5. But individual self-interest is at odds with group interest. Usually people cooperate more than is predicted by standard economic theory[4]; however, observed cooperation is heterogeneous and declines over time (for example, see ref. 12). It has been shown that direct punishment of non-cooperators can cause a rise in the level of the average contribution to the public good[13–15], and cooperators are even prepared to pay a cost for punishing ('altruistic punishment')[16].

We present an alternative way to maintain potentially a high level of contribution to the public good. It can be achieved through interaction with a second game that promises rewards for those with a good reputation in the public goods game. Theorists have shown that cooperation through indirect reciprocity can evolve[9–11]. For indirect reciprocity, individuals who have helped others are given support, whereby the supporter builds up reputation[8,17] or a positive image score[9,10]. Experimental studies have confirmed that human subjects preferentially help others who have a positive image score[18–20]. As players would risk their reputation if they would not cooperate in a public goods game that is alternated with the indirect reciprocity game, we predicted that alternating rounds of these two games would induce continuous cooperation in the public goods game, in contrast to a situation in which all public goods rounds were played first.